CHEMICAL REVIEWS

Review

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Triazolinediones as Highly Enabling Synthetic Tools

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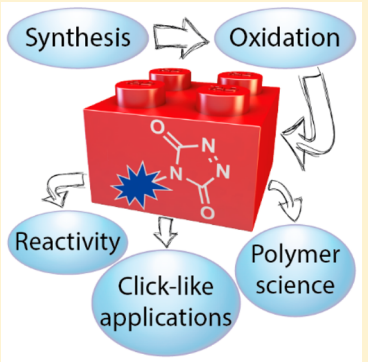
ABSTRACT: Triazolinediones (TADs) are unique reagents in organic synthesis that have also found wide applications in different research disciplines, in spite of their somewhat "exotic" reputation. In this review, we offer two case studies that demonstrate the possibilities of these versatile and reliable synthetic tools, namely, in the field of polymer science as well as in more recently emerging applications in the field of click chemistry. As the general use of triazolinediones has always been hampered by the limited commercial and synthetic availability of such reagents, we also offer a review of the available TAD reagents, together with a detailed discussion of their synthesis and reactivity. This review thus aims to serve as a practical guide for researchers that are interested in exploiting and further developing the exceptional click-like reactivity of triazolinediones in various applications.



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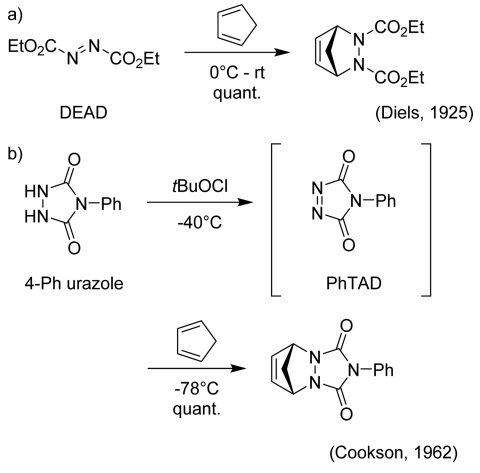
1. INTRODUCTION

The remarkable bond-forming reactivity of azodicarbonyl derivatives toward normally "unreactive" unsaturated hydrocarbon substrates was first recognized in the pioneering 1920s work by Diels et al.[1] This seminal finding would lead to the development of the famous and transformative Diels–Alder reaction, as reagents such as diethyl azodicarboxylate (DEAD) were found to spontaneously form a quantitative 1:1 adduct with cyclopentadiene at room temperature without the need for additives or catalysts (Scheme 1a).[1,2] The even more reactive *cis*- or cyclic azodicarbonyl analogues, however, were excluded from these initial studies, although a 4-substituted 1,2,4-triazoline-3,5-dione ("triazolinedione" or TAD) was reported as early as 1894 by Thiele and Stange.[3] In fact, as a result of the problematic synthesis and purification of TAD compounds, their use as a dienophile in the Diels–Alder reaction was not established before the 1960s, when Cookson et al. obtained pure crystalline 4-phenyl-TAD (Cookson's reagent) for the first time (Scheme 1b).[4,5] Cookson's procedure is now properly considered as a major breakthrough in the field of TAD chemistry, as it was followed by a wide range of investigations into the unique reactivity and many synthetic applications of TAD-bearing compounds, which have continued to grow to this day.

Scheme 1. (a) Initial Observation of Azodicarbonyl Reactivity with Hydrocarbon Substrates[1] and (b) First Useful Transformation of a (in situ prepared) TAD Reagent[4]



With a Diels–Alder-type reactivity that is, respectively, 30 000 and 1000 times faster than that of DEAD[6−8] and tetracyanoethylene,[9,10] triazolinediones are generally considered as the most reactive bench-stable dienophiles[6,11] and enophiles.[12] Moreover, as their reactivity depends to a certain extent on the nature of the 4-substituent, electron-poor 4-aryl substituents can even further increase the electrophilicity up to the point that TAD reagents, for example, 4-(4-nitrophenyl)-TAD, become too reactive to be isolated.[13−15] Nevertheless, once isolated, most triazolinediones are generally easy to handle and are stable for prolonged periods when stored in a cold environment (i.e., −18 °C) in the absence of light and moisture.[4,16,17]

The most recent review of TAD chemistry was published by Radl almost 2 decades ago (1997),[18] which gives an instructive overview of known TAD reactions with diverse substrates, with examples mainly limited to simple and commercially available reagents, such as 4-phenyl-TAD (PhTAD) and 4-methyl-TAD (MeTAD). Similarly, in 1983, the chemistry of 4-phenyl-TAD was reviewed by Korobitsyna et al.[19] In 1982, on the other hand, Moody reviewed the fascinating chemistry of azodicarbonyl compounds in general.[20] In 1980, Butler reviewed the use of simple TAD reagents to modify and synthesize polymers.[7,12]

Although the synthesis and chemistry of simple TAD reagents is well-understood,[18,19] in more recent applications, as in click chemistry and/or modern polymer chemistry (vide infra), functional or "tailored" TAD reagents are often required to harness the full potential of the exceptional TAD reactivity. Although the use of such functional TAD compounds enables unprecedented applications, research into this area is hampered by the limited synthetic accessibility of these compounds, even by today's high standards.

The main objective of the current review is therefore 2-fold. On the one hand, we wish to give an overview of the synthesis of various TAD reagents, with a brief overview on their general modes of reactivity, as a guide for the design and synthesis of novel functional TAD reagents (sections 2–4). On the other hand, we will discuss interesting applications of TAD chemistry that have emerged in more recent years, with a focus on developments in polymer science as well as on specific applications in which the click chemistry characteristics of the TAD-based conjugations are showcased (sections 5 and 6).

A survey of known practical synthesis methods for TAD compounds reveals that these almost invariably involve the oxidation of the corresponding 1,2,4-triazolidine-3,5-dione ("urazole"), as in Cookson's original procedure (Scheme 1b).[4] For the assembly of these heterocyclic precursor urazoles, a large variety of methods is now available, using a number of simple starting materials. Likewise, many different oxidation methods for urazoles have been explored, with varying degrees of efficiency and chemoselectivity. Despite all of these methodological developments, the "tailored" synthesis of triazolinediones is still no trivial matter and often involves critical strategic choices, as there are no "general" methods. The

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limited commercial availability of TAD reagents and the synthetic challenges encountered in preparing (functional) TAD compounds thus continue to serve as a major bottleneck for TAD-chemistry-based research and applications. For this, we provide an informative overview of urazole syntheses (section 2) and of urazole oxidation methods (section 3).

Rather than providing a full reference library on TAD compound syntheses and chemistries in sections 2 and 3, we aim to offer a conceptual framework that can guide synthetic decisions. It is our hope that these sections will allow the reader to be able to select the most suitable synthetic scheme for the specific triazolinedione and application of interest, while also serving as a source of inspiration for novel applications based on synthetic TAD reagents.

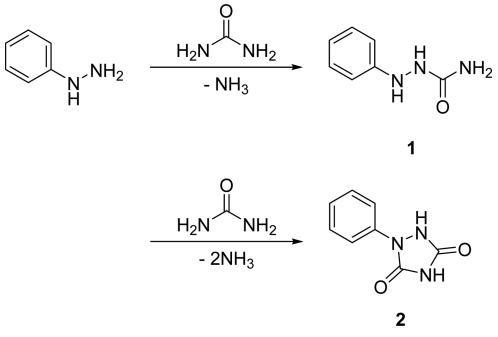
In the three last sections of this review (sections 4–6), we aim to provide an instructive overview of the reactivity of triazolinediones, illustrated by various applications. While TADs are highly activated species and can actually participate in a large variety of reactions, depending on conditions and reaction partners, only a brief discussion of the most important reaction partners and possible side reactions will be provided herein (section 4), while referring the interested readers to previous reviews.[7,12,18−20] In the next sections, two distinct case studies of TAD's reactivity in practical applications are presented. A first case study is a comprehensive overview of the use of triazolinediones in the field of polymer science (section 5), while a second case study will discuss the use of these reagents in click chemistry applications (section 6). This final section will highlight the enormous potential of TADs in an expanding synthetic chemistry field that, today, already pervades almost all of the natural sciences.

In summary, the goal of this review is to serve as a guide for readers that are interested in harnessing and further developing the exceptional click-like reactivity of 4-substituted triazolinediones. This survey will also provide the reader with a perspective on what kind of "general" or modular TAD reagents would be most useful for the development of future applications, pointing toward challenges in the field of organic synthesis.

2. SYNTHESIS OF FUNCTIONALIZED URAZOLE PRECURSORS

The first report on the synthesis of a 1,2,4-triazolidine-3,5-dione (urazole) dates back to 1887, when Pinner noted a peculiar reaction between phenylhydrazine and urea, the outcome of which depends on the ratio of the reactants (Scheme 2).[21] If only 1 equiv of urea is used, 1-phenyl-semicarbazide (**1**) is obtained, while an excess of urea leads to a cyclic compound (**2**). Since Pinner envisioned that other analogues of 1-phenyl-1,2,4-triazolidine-3,5-dione can be synthesized as well, he introduced the name "urazole" for this class of five-membered heterocyclic compounds.

Scheme 2. Reaction of Urea with Phenylhydrazine, As Reported by Pinner[21]



Because a 4-substituted 1,2,4-triazoline-3,5-dione is mostly obtained through oxidation of the corresponding 1*H*,2*H*-1,2,4-triazolidine-3,5-dione (vide supra), this section will discuss the possible synthetic pathways to produce such urazoles, as functional precursors to various TAD compounds. Figure 1 provides a brief overview of the possible synthetic strategies. These various assembly routes can be logically categorized according to the different "retrosynthetic disconnections", but in this text we have made a more practical subdivision of routes based on the nature of the required starting materials, building blocks, and intermediates.

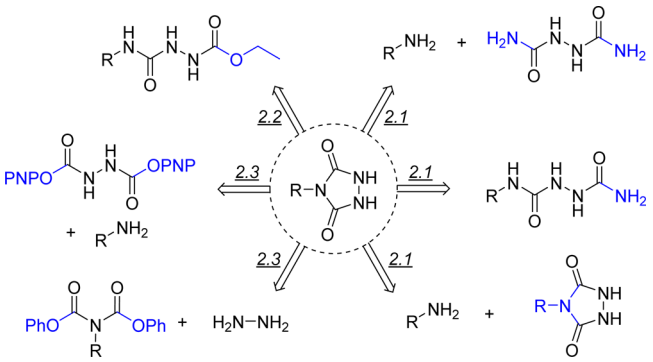


Figure 1. Brief overview of the possible synthetic strategies to obtain 4-substituted 1,2,4-triazolidine-3,5-diones (urazoles), with indication of the sections in which they will be discussed in detail (PNP = *p*-nitrophenyl).

The oldest synthetic routes for 4-substituted urazoles,[3,22] used before the second half of the 20th century, were all based on hydrazodicarboxamide intermediates or derivatives thereof. The first section (section 2.1) will describe the scope and limitations of these older syntheses, which often compare unfavorably to more recent strategies in terms of reaction conditions and isolated yield. The more efficient modern methods are distinguished by the use of 1-alkoxycarbonyl semicarbazides as alternative (and more activated) urazole precursors. These key intermediates for urazole synthesis are commonly referred to as "semicarbazides" in this context. As semicarbazides themselves can be assembled in a number of efficient ways, these alternative routes will be discussed within section 2.2, which is devoted to the synthesis and cyclization of semicarbazide intermediates.

Apart from semicarbazides and hydrazodicarboxamides, some alternative urazole precursors have also been explored. These less common synthetic schemes, which are usually limited in scope, are gathered in section 2.3.

While there is a vast choice of routes and starting materials to prepare "functional" urazoles, certain chemical functionalities are incompatible with all of them. In this case, an alternative can be found in procedures that transform available simple 4-substituted urazoles into more elaborate ones. Therefore, section 2.4 will provide the reader with examples and possibilities in the chemoselective modification of 4-substituted urazoles.

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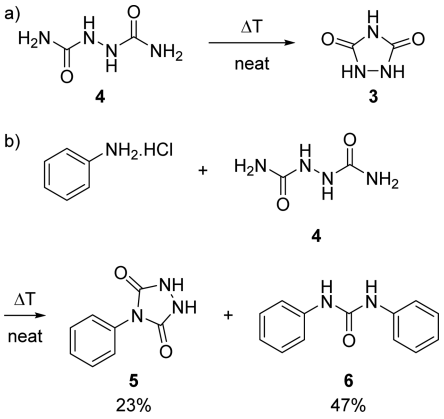
Finally, this section will be concluded by a brief summary of the many synthetic schemes available for urazoles (presented in sections 2.1−2.4), with a focus on the practical ease, robustness, and scalability of the different methods. The aim of section 2.5 is to serve as a guide for the reader to quickly identify the most viable synthetic route for the intended application.

Unless noted otherwise, all the described urazole syntheses in the following sections have also been successfully oxidized to the corresponding TAD compounds (cf. Scheme 1b; see also dedicated section 3).

2.1. 4-Substituted Urazoles from Hydrazodicarboxamide Derivatives

Following the earliest report of the synthesis of a urazole by Pinner in 1887,[21] i.e., 1-phenyl-1,2,4-triazolidine-3,5-dione (**2**), it took until 1894 before the somewhat elusive "parent" heterocycle, unsubstituted urazole, was prepared and isolated, in independent studies by Thiele and Stange[3] and Pellizzari and Cuneo.[23] Both approaches acquired urazole (**3**) by heating hydrazodicarboxamide (**4**, biurea[24]) to 200 °C in the absence of solvent (Scheme 3a). Thiele further found that adding aniline

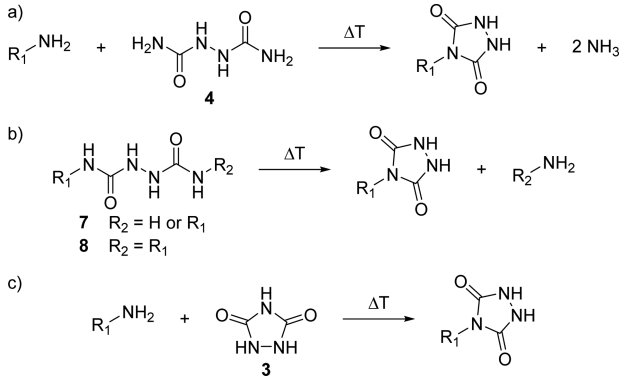
Scheme 3. Original Synthesis of (a) 1,2,4-Triazolidine-3,5-dione (Urazole) and (b) 4-Phenylurazole As Reported by Thiele[3,23]



hydrochloride to the original reaction mixture gave 4-phenylurazole (**5**), a positional isomer of the previously reported 1-phenylurazole (Scheme 3b). The mechanism of this latter reaction is of interest to the current report (vide infra) and is believed to proceed via the formation of a 1-arylbiurea, which expels ammonia, followed by cyclization and release of another equivalent of ammonia.[25−28]

While Thiele was the first to report on the synthesis of 4-substituted urazoles, this procedure mostly gives poor isolated yields because of competitive formation of diphenylurea (**6**) and the difficult separation of products from unreacted or excess starting materials.[3,25,29−31] Multiple variations of this original Thiele procedure have been reported in order to optimize the yield of 4-substituted urazoles. The overall efficiency is improved by using an excess of biurea,[3,29] by performing the reaction in a high-boiling solvent such as sulfolane or *N*-methylpyrrolidone,[25,30] or by physical removal of ammonia (Scheme 4a) using a slight vacuum.[25−27,30] Use of the hydrochloride salt rather than the neutral amine starting material, to allow acid-catalyzed cyclization,[3] is absolutely required in the case of anilines, since the presence of free aniline rapidly results in the formation of unreactive diarylurea.[3,29] This factor seems less crucial for the synthesis of 4-

Scheme 4. Synthesis of 4-Substituted Urazoles from Hydrazodicarboxamide Derivatives: (a) Direct Condensation of an Amine with Biurea; (b) Cyclization of 1-Substituted or 1,6-Disubstituted Biurea, Obtained by the Reaction of an Isocyanate with Semicarbazide (7) or Hydrazine (8), Respectively[a]; and (c) Direct Condensation of an Amine with Urazole 3, Obtained from the Thermal Cyclization of Biurea, either Neat[3] or in the Presence of a Solvent[30,32,33] [b]



[a] $R_1 = NH_2/R_2 = H$,[35,37,39] $R_1 = R_2 = NH_2$,[35,38] $R_1 = R_2 = Me$,[22] $R_1 = Ar/R_2 = H$.[26,29] [b] R_1 = cyclohexyl[26] or 4-aminocyclohexyl.[25,27]

alkylurazoles, where these side products are not isolated.[29] So for these targets, neutral amines can also be used.[25−27]

Suitable experimental conditions have been developed for a range of 4-aryl-[5,22,29] and 4-alkyl-substituted[26,28,29,32,33] urazoles, including polyurazoles derived from aliphatic polyamines (Scheme 4a).[25,27,32,33] In the case of 4-(4-alkyl)-phenylurazoles, it should be noted that the yield decreases with increasing carbon number of the alkylaniline,[29] an issue that is not apparent in the case of aliphatic amines.[28] Also, hydrazine can be used as starting material, resulting in the expected 4-aminourazole (Scheme 4a, $R_1 = NH_2$).[34−36]

As described earlier, the competitive formation of unsubstituted urazole can be problematic in the biurea-based synthesis of urazoles (Scheme 4a), if cyclization precedes intermolecular amine substitution. This problem can be avoided or circumvented by first preparing the 1-substituted or 1,6-disubstituted biurea (**7** or **8**, respectively) via an alternative route, which is then cyclized to the urazole (Scheme 4b). This approach thus constitutes a second strategy to obtain 4-substituted urazoles. However, in most cases this alternative two-step synthesis is not a solution. Efficient examples of this approach are mostly limited to the synthesis of 4-aminourazoles,[35,37−39] 4-methylurazoles,[22,26] and a few arylurazoles.[25−27,29] Furdik et al. have reported a general synthesis of 4-alkylurazoles in moderate to high yields (52−94%) from 1,6-dialkylbiureas,[40] but the reported yields have been found to be hard to reproduce in later studies.[31,41] Relying on similar reactivity, amines have also been directly condensated with 1,2,4-triazolidine-3,5-dione (**3**) at elevated temperatures, thus giving the corresponding 4-substituted urazoles (Scheme 4c). For most substrates, the isolated yield of 4-alkylurazoles in this transimidation approach is lower than in the corresponding amine−biurea condensation−cyclization.[26] The efficiency of the reaction might be hampered by the relative thermodynamic stability of urazole **3** compared to open-chain substrates.[25−27] Apart from the synthesis of simple 4-alkylurazoles, this strategy

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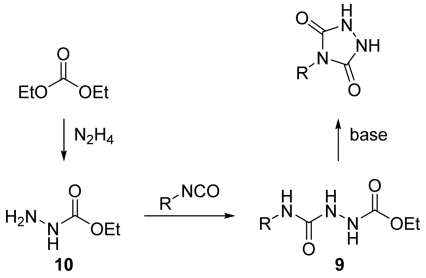
was also successfully applied for the synthesis of a bis-urazole compound derived from 1,4-cyclohexanediamine.[25,27]

In conclusion, 4-substituted urazoles can be synthesized from azodicarboxamide (biurea) derivatives. However, the optimization of reaction conditions can be very tedious. In terms of yield and efficiency, the direct condensation of an amine with biurea is the most robust method. Nevertheless, as a result of the required harsh reaction conditions, the overall substrate scope for this high-temperature process remains fairly limited.

2.2. Urazoles via Semicarbazides

In 1961, more than 7 decades after Thiele's original synthesis, Zinner and Deucker were the first to propose a synthetic scheme for urazoles that actually improved upon the methods based on Thiele's original approach.[42] Rather than using biurea starting materials, they synthesized 4-phenyl- and 4-butylurazole (R = Ph and Bu, respectively) through cyclization of the corresponding 4-substituted (ethoxycarbonyl)semicarbazide (**9**, Scheme 5), which only requires mild reaction conditions. In the

Scheme 5. Cookson/Zinner–Deucker Synthesis of Urazoles

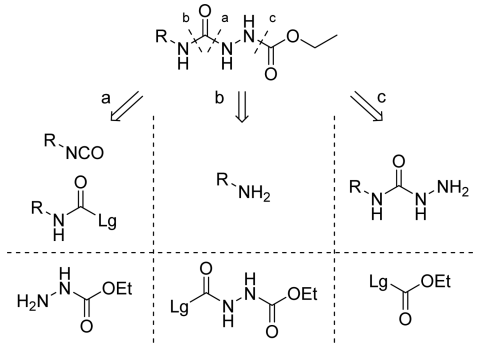


context of urazole synthesis, these more reactive urazole precursors are often simply referred to as "semicarbazides", as will also be done in this review. Significantly, semicarbazides can be generated by plainly mixing an isocyanate with ethyl carbazate (in itself a readily available condensation product of cheap hydrazine and diethyl carbonate) and is thus a very convenient approach.

While the isocyanate-based two-step approach is characterized by significantly higher overall yields and much milder reaction conditions compared to the original urazole synthesis (vide infra), it took 10 years for this strategy to gain the attention of the wider scientific community. Cookson and coworkers were the first to publish an efficient synthetic procedure for 4-phenyl-1,2,4-triazoline-3,5-dione starting from hydrazine, diethyl carbonate, and phenyl isocyanate in 1971 (Scheme 5).[41] This procedure includes the generation of ethyl carbazate (**10**), the subsequent reaction with phenyl isocyanate and cyclization to obtain 4-phenylurazole—according to the method of Zinner and Deucker—and the final oxidation to the triazolinedione. As this sequence was widely adopted thereafter, it became generally known as the Cookson method,[43] and triazolinediones became regularly referred to as Cookson reagents.[4,44,45]

The Cookson method for urazole synthesis (or Zinner–Deucker synthesis) has found many applications, where the main differences are found in synthetic strategies to obtain the semicarbazides (vide infra). Thus, these will be discussed in more detail in this section before a final discussion of the semicarbazide cyclization step itself. Scheme 6 provides a summary of the alternative semicarbazide syntheses, based on three different strategic bond disconnections. For the purposes

Scheme 6. Summary of the Possible (Ethoxycarbonyl)semicarbazide Synthetic Strategies with the Corresponding Starting Materials



of this review, the different semicarbazide syntheses will be discussed according to the class of readily available starting materials that can be used to introduce the R-group on the 4-position: isocyanates, carboxylic acids, or amines. The modification or derivatization of R-groups on the semicarbazide stage will also be briefly discussed.

It should be noted that in the discussed syntheses, ethyl carbazate can generally be substituted by methyl carbazate, as demonstrated by Bausch et al. as well as by Little et al.[46,47] The resulting 1-(methoxycarbonyl)semicarbazides can be processed in the same way as the regular 1-(ethoxycarbonyl)-semicarbazides, so a further distinction between both will not be made for the purposes of this review.

2.2.1. Semicarbazides from Isocyanates. As a result of the high reactivity of isocyanates, these readily react at room temperature with ethyl carbazate (**10**) to give the corresponding semicarbazide adducts (Scheme 5) in excellent yields (up to 100%), typically after stirring overnight. If the reaction mixture is heated, complete conversions can be achieved in a matter of hours. The role of the solvent is not critical, but as the semicarbazide products tend to precipitate from hydrophobic solvents such as toluene, the use of such solvents vastly simplifies the workup to the point that after collecting and drying the solids, there is generally no need for a further purification step.

Although the original Cookson method was mainly used for the synthesis of 4-phenylsemicarbazides (and urazoles) from phenyl isocyanate,[41,42,48,49] the substrate scope was quickly expanded to include a wide range of isocyanates as well. An analysis of Table 1 reveals that the structural variations in the obtained semicarbazides are only limited by the availability and reactivity of the isocyanates themselves.[50] This means semicarbazides bearing a chemical functionality for further modifications are not easily accessible by this strategy because of the general incompatibility with isocyanates. However, Yamada and Shimizu did report a synthesis of (3-chloropropyl)semicarbazide **11** (Figure 2),[51,52] in which the alkyl chloride can be used as a functional handle to introduce various nucleophilic groups, while Read and Richardson reported on the synthesis of a semicarbazide bearing a carboxybenzyl-protected amine (**12**), which—after deprotection—can be derivatized by various electrophilic groups.[14] On the matter of (industrial) scalability, Chandrasekhar et al. prepared nearly 4 kg of 4-phenylurazole in one batch with an overall yield exceeding 90%.[31]

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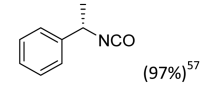
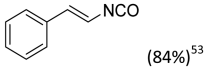
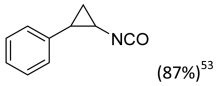
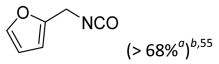
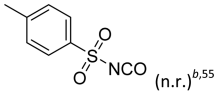
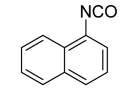
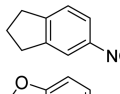
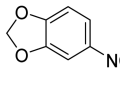
Table 1. Substrate Scope with Corresponding Yields for the Synthesis of Semicarbazides from Isocyanates (Cookson Method)[d]

R–NCO	Ar–NCO
Aliphatic isocyanates with R:	*Substituted phenyl isocyanate with R:*
Me (90-100%)[13,48,53]	4-Me (n.r.)[58]
Et (92-100%)[13,53]	4-Ac (90%)[59-60]
*n*Pr (96%)[53-54]	4-MeO(CO) (98-100%)[61-62]
*i*Pr (93%)[53]	4-EtO(CO) (86-94%)[51,63-64]
*n*Bu (90-96%)[42,48,53]	3-CF_3 (n.r.)[58]
*t*Bu (n.r.)[13,55]	3-NO_2 (> 27%[a])[55]
Cyclohexyl (n.r.)[48,55]	4-NO_2 (92-98%)[13,48,51,58,65]
1*H*,1*H*,2*H*,2*H*-perfluorodecyl (95%)[56]	3-MeO (> 88%[a])[55]
	4-MeO (90-98%)[13,48,53,66]
Unsaturated isocyanates	4-TMSO (94%)[c,67]
Allyl isocyanate (96%)[53]	4-F (> 91%[a])[55]
Benzyl isocyanate (85-97%)[13,53,55]	3-Cl (n.r.)[68]
 (97%)[57]	4-Cl (92%)[55,59]
 (84%)[53]	2,4,6-Me (73%)[69]
 (87%)[53]	2,6-*i*Pr (80-90%)[69-70]
 (> 68%[a])[b,55]	3,4,5-MeO (94%)[53]
 (n.r.)[b,55]	3,5-Cl (n.r.)[71]
	Other aromatic isocyanates
	 (98%)[55,72-73]
	 (> 92%[a])[55]
	 (> 37%[a])[55]

[a]These yields are estimates based on the overall urazole yields found in the original references. [b]The corresponding TAD compound could not be isolated after oxidation. [c]The alcohol is released from its silyl ether during cyclization. [d]n.r.: not reported.

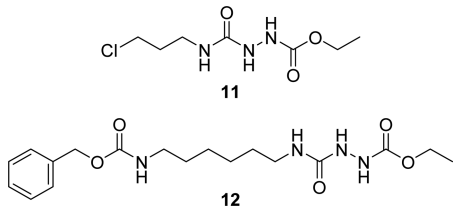


Figure 2. Examples of semicarbazides bearing a latent functionality. The urazole derived from **12** was modified (see section 2.4.2) prior to oxidation.

The Cookson method can also be used for the preparation of bis-semicarbazides when the corresponding diisocyanate is used. The possibility to convert bulk chemicals used in polyurethane synthesis, such as 4,4′-methylenediphenyl diisocyanate (MDI),[74] into the corresponding bivalent triazolinedione (bisTAD) reagents obviously attracted the interest of polymer chemists. Early reports by Wald and Wamhoff as well as Butler and co-workers triggered the development of a wide range of difunctional semicarbazides (and TAD reagents), as depicted in Figure 3 (compounds **13** to **20**).[75−79] These bivalent compounds also attracted attention in the patent literature, with reports on the transformation of some of the industrially relevant diisocyanates.[28] Recently, Du Prez and co-workers synthesized a novel divalent semicarbazide (and bisTAD reagent) based on isophorone diisocyanate (**21**, Figure 3).[80]

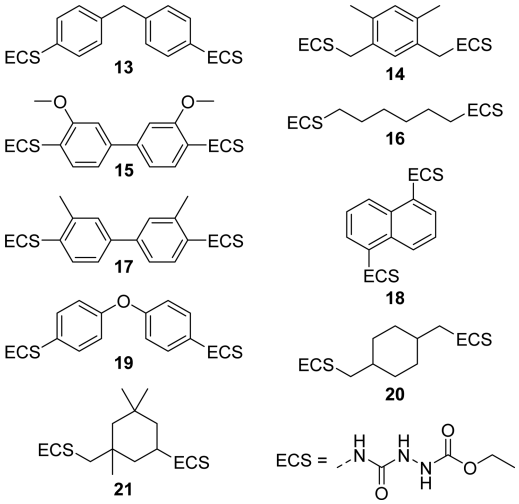
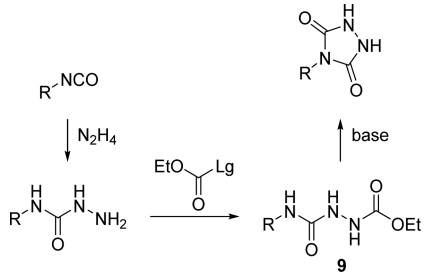


Figure 3. Reported divalent semicarbazides created by combining ethyl carbazate with the corresponding diisocyanate. ECS = (ethoxycarbonyl)semicarbazide.

Finally, a couple of examples are known in the literature to prepare the target 1-(ethoxycarbonyl)semicarbazides from the corresponding isocyanates in a sequence where the order of bond-forming steps is altered,[29,42] i.e., via 4-substituted semicarbazides (Scheme 7). A first example was already

Scheme 7. Alternative Synthesis of 4-Substituted Urazoles from Isocyanates, in Which the Order of Bond Forming Steps Is Altered Compared to the Common Cookson Method



provided by Zinner and Deucker, who reacted 4-phenylsemicarbazide with ethyl chloroformate (Scheme 7, R = Ph and Lg = Cl) to obtain 1-(ethoxycarbonyl)-4-phenylsemicarbazide.[42] Later, Pesson and Dupin substituted ethyl chloroformate by diethyl carbonate (Lg = OEt) to perform the same reaction.[81] Since the decreased reactivity of diethyl carbonate required harsher (alkaline) reaction conditions, the product is also immediately cyclized to the urazole under these conditions (vide infra). However, overall, this strategy is usually less practical with regard to isolation of compounds, generally being lower-yielding and, in the case where ethyl choloformate is used, more costly than the Cookson method.[31,42]

2.2.2. Semicarbazides from Carboxylic Acids. Despite the ease and versatility of the Cookson method, typically accompanied by a high yield of the overall synthesis, the method is limited by the structural variety in commercially available isocyanates (see section 2.2.1). Therefore, a lot of research has been performed to obtain semicarbazides from alternative starting materials. As in fact isocyanate-free synthetic schemes have been developed (vide infra), most "alternative"

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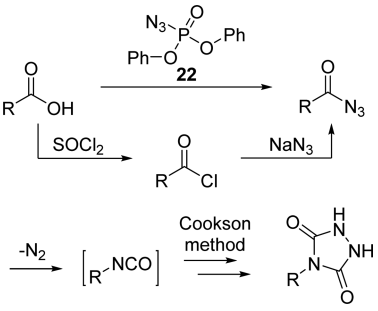
procedures are actually based on the Cookson method, where an isocyanate is prepared in situ, avoiding the isolation or purification of hazardous intermediates. Thus, the Cookson method has been extended to the preparation of semicarbazides from simple carboxylic acids.

A carboxylic acid can easily be converted into an acyl azide, which upon heating will readily rearrange into an isocyanate with the expulsion of nitrogen gas. The well-known Curtius rearrangement is a classical 19th century organic reaction,[82−84] but its first application for the synthesis of urazoles was only reported in 1990.[85] The acyl azide intermediates can be prepared in one step from carboxylic acids using an azidating agent, such as diphenylphosphoryl azide (DPPA, **22**, Scheme 8), or via an intermediate acid chloride that can be reacted with sodium azide (Scheme 8, bottom). While acyl azide intermediates can be isolated, the crude product or reaction mixture can be directly used for the Curtius rearrangement to the corresponding isocyanate. Again, toluene is a favored solvent for this thermal reaction, which demonstrates the compatibility with the Cookson method. Thus, upon completion of the Curtius rearrangement, ethyl carbazate can simply be added to the reaction mixture, from which the desired semicarbazide will precipitate.

Scheme 8. Extension to the Cookson Method by in Situ Generation of an Isocyanate via the Curtius Rearrangement of an Acyl Azide[a]



[a]The latter compound can be obtained in one step using diphenylphosphoryl azide (**22**) or in two steps via an activated carbonyl derivative such as an acid chloride[44,86−90] or a mixed anhydride (not shown).[91,92]

Shimada et al. first applied the one-step procedure—using DPPA—to obtain the corresponding acyl azides of a range of interesting fluorescent (**23** and **24**) or chromophoric carboxylic acids (**25**, Figure 4).[45,85] Likewise, Yamada and co-workers reported the synthesis of a highly fluorogenic semicarbazide, starting from quinoxalinone 2-propionic acid (**26**).[51,63,93] Later, Little et al. claimed that this synthetic scheme is also applicable to a wide range of carboxylic acids.[47] The main advantage of using (relatively expensive) DPPA to generate the acyl azide, as compared to the acyl chloride/sodium azide route, is that sequential one-pot reactions are possible that afford the semicarbazide from the corresponding carboxylic acid without the need of any intermediate workup or solvent switch. For instance, Read and Richardson applied such a one-pot procedure to synthesize a pyrene derived with a longer spacer (**27**).[14]

Mallakpour and co-workers developed an efficient three-step procedure, using activated carboxylic acids (**28**−**32**, Figure 4), by first transforming them in an acid chloride or a mixed anhydride with thionyl chloride[44,86−90] or ethyl chloroformate,[91,92] respectively. The resulting acyl derivative can then be reacted with sodium azide to obtain the acyl azide in high to excellent yields by a simple precipitation from the reaction mixture (76−96%). Since the Curtius rearrangement itself is a clean reaction, with only nitrogen gas as a side product, heating a pure acyl azide basically yields the pure isocyanate, which explains why the semicarbazides in this three-step process can be acquired in much higher yields than the corresponding one-pot procedure, up to the level of those obtained from pure isocyanates (96−98%). However, the substrate scope for this acyl azide isolation-based sequence seems limited to benzoic acid derivatives (**28**−**31**), as no examples of aliphatic carboxylic acids have been reported so far. Thus, the strength of this protocol critically relies on the ease of purification of the acyl azide intermediates.

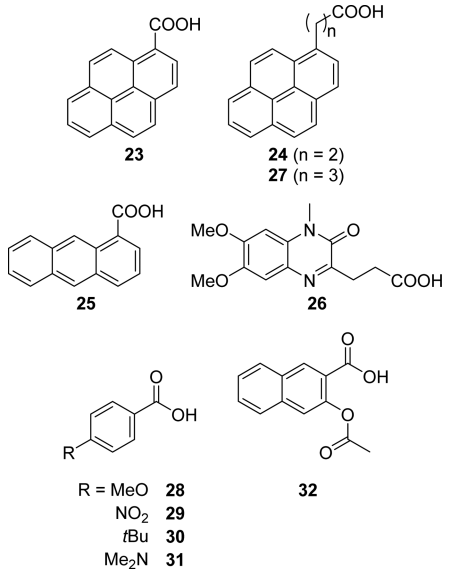


Figure 4. Carboxylic acids used for the synthesis of semicarbazides by generating an isocyanate in situ via the Curtius rearrangement. The acetyl ester is hydrolyzed during cyclization of the semicarbazide derived from **32** (see section 2.4.1).[89]

In conclusion, the one-pot procedure to convert carboxylic acids into the corresponding semicarbazides using DPPA not only stands out in operational practicality but it also has the widest possible substrate scope.

2.2.3. Semicarbazides from Amines. In analogy with the synthesis of semicarbazides from carboxylic acids using a Curtius rearrangement (section 2.2.2), isocyanates can be readily obtained in situ by combining an amine, or its hydrochloride salt, with phosgene. After removal of gaseous hydrochloric acid, addition of ethyl carbazate to the resulting reaction mixture thus leads to the formation of semicarbazides, as demonstrated by Paquette and co-workers for the synthesis of chiral semicarbazides from optically pure amines (**33**−**35**, Figure 5).[16,17] Later, the use of safer alternatives to the gaseous phosgene were demonstrated as well, i.e., trichloromethyl chloroformate (diphosgene)[14] and bis(trichloromethyl) carbonate (triphosgene).[94,95]

The reaction of an amine with (di- or tri)phosgene results only in the formation of the desired isocyanate and hydrochloric acid. In the absence of acid-sensitive moieties, this gas is easily removed and the isocyanate is obtained in essentially pure form, resulting in high yields of the target semicarbazide.[17] However, as a result of safety issues with regard to the use of

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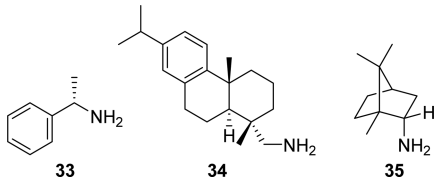
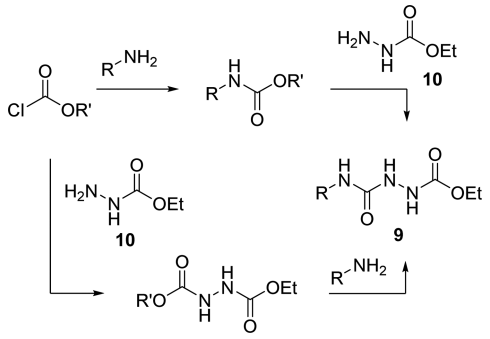


Figure 5. Treatment of enantiomerically pure amines, i.e., *S*-(−)-α-methylbenzylamine (**33**), (+)-dehydroabietylamine (**34**), and (+)-endobornylamine (**35**), with phosgene and ethyl carbazate (**10**) gave the corresponding semicarbazides in quantitative yield.

isocyanates and especially phosgene, alternative isocyanate-free methods have been developed for the production of semicarbazides from amines that altogether avoid the use and even intermediate formation of hazardous and less readily available isocyanates (as compared to amines and anilines).[96] Two distinct methods to perform this truly isocyanate-free semicarbazide synthesis can be found in the literature (Scheme 9).

Scheme 9. Different Synthetic Strategies To Produce a Semicarbazide (9) in an Isocyanate-Free Manner from Amines[a]



[a]R′ = *p*-NO_2Ph,[96−98] Ph,[43] or Et.[99]

The most straightforward strategy for the isocyanate-free production of semicarbazides closely follows the Cookson method (synthetic strategy a in Scheme 6), wherein activated carbamates are used as synthetic equivalents to isocyanates (Scheme 9, top). In the first step, the amine is reacted with a chloroformate, resulting in the generation of a carbamate, which is subsequently reacted with ethyl carbazate to obtain the corresponding semicarbazide. Mallakpour and co-workers, who were the first to develop this synthetic route, reported multiple procedures with different reactive carbamate intermediates. The reactivity of these carbamates toward ethyl carbazate is determined by the chloroformate reagent used in the first step.

The reaction of substituted anilines with *p*-nitrophenyl chloroformate gives a quite reactive carbamate (R′ = *p*-nitrophenyl, Scheme 9).[96] In fact, the intermediate carbamate can be considered as a "blocked" isocyanate, since *p*-nitrophenol is readily released upon refluxing in toluene, yielding the corresponding isocyanate. Apart from the synthesis of already known semicarbazides, this blocked isocyanate approach appears to be advantageous compared to the Curtius rearrangement for certain substrates, as, for example, 4-(2-nitrophenyl)semicarbazide could not be synthesized from 2-nitrobenzoic acid, while it was obtained from 2-nitroaniline in high yield.[96,99] Nevertheless, the yield of the different semicarbazides varies from 36% up to 85% and is therefore highly dependent on the substituents of the aniline. While Mallakpour's original procedure includes isolation of the carbamate, Barbas and co-workers recently developed a one-pot procedure using an excess of chloroformate and ethyl carbazate, directly giving semicarbazides, with varying success.[100−102] Nevertheless, good to quantitative yields (63−100%) were achieved for very interesting "clickable" semicarbazide products with a pending azide (**36**−**38**) or alkyne moiety (**39**) (Figure 6).[97,100,102−104] Lower yields resulted when 4-ethynylaniline or 4-aminoacetophenone were used as starting compounds.[97,101,102]

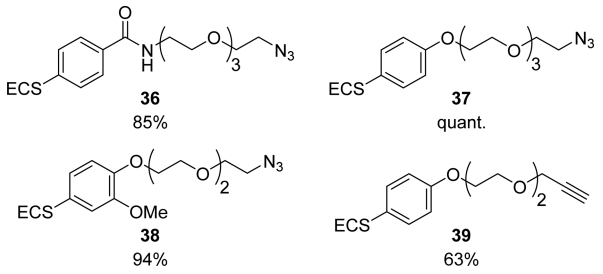


Figure 6. Semicarbazides with a pending azide or alkyne moiety obtained in good yields via the corresponding *p*-nitrophenyl carbamate.[97,100,103,104] The urazole derived from **37** was modified (see sections 2.4.2 and 2.4.5) prior to oxidation. ECS = (ethoxycarbonyl)semicarbazide.

The use of ethyl chloroformate and subsequent transformation of the less reactive ethyl carbamates (R′ = Et, Scheme 9) derived from substituted anilines were also studied by Mallakpour and Rafiee.[99] On the basis of this less reactive carbamate intermediate, a successful one-pot procedure was developed starting from anilines that can also give the urazole compound directly by a spontaneous in situ cyclization reaction (see section 2.2.5), without intermediate purification and using mild reaction conditions. The yields of the isolated urazoles are very similar compared to the analogous *p*-nitrophenyl chloroformate protocol (vide supra), but the overall process is clearly more efficient, cheaper, and less hazardous. Possible substrates include nitroaniline isomers, *p*-chloroaniline, and *p*-toluidine.

An alternative strategy to obtain semicarbazides in an isocyanate-free manner from the corresponding amines encompasses the synthesis of a reactive intermediate out of ethyl carbazate to which the amine is added (Scheme 9, bottom). A first example of such a reactive intermediate is reported by Breton and Turlington, who used phenyl chloroformate to obtain ethyl phenyl hydrazine-1,2-dicarboxylate (R′ = Ph).[43] This reactive hydrazine dicarboxylate can be used to transform aliphatic amines under very mild conditions with a high yield (76−93%). Nevertheless, no reaction was observed when aniline was used, even at elevated temperatures, which is explained by its decreased nucleophilicity compared to the alkyl amines. In a similar synthesis, Adamo and co-workers used *p*-nitrophenyl chloroformate (R′ = *p*-nitrophenyl) to obtain a more reactive ethyl carbazate derivative, which was subsequently reacted in situ with a range of structurally diverse aliphatic amines (Figure 7) to obtain the corresponding semicarbazide in acceptable yields (54−71%).[97,98] Both protocols use an excess of amine and therefore require a purification step in which the produced semicarbazide is separated from the unreacted amine.

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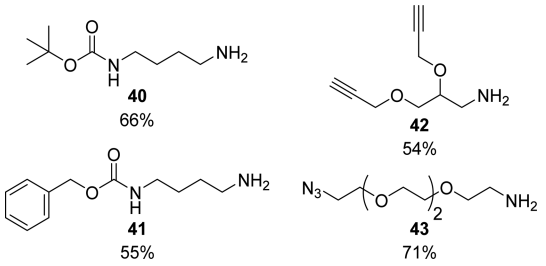
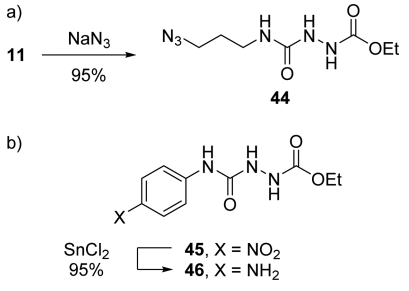


Figure 7. Overview of the aliphatic amines that are successfully reacted with a reactive hydrazine dicarboxylate to produce the corresponding semicarbazides in acceptable yields:[97,98] *N*-Boc-1,4-butanediamine (**40**), *N*-Cbz-1,4-butanediamine (**41**), bis(prop-2-ynyloxy)propan-1-amine (**42**), and 11-azido-3,6,9-trioxaundecan-1-amine (**43**). The urazole derived from **41** was modified (see section 2.4.2) prior to oxidation.

Little et al. introduced the use of carbonyldiimidazole to transform a carbazate in the corresponding activated carbonyl compound (Scheme 9, bottom).[47] The resulting intermediate is sufficiently reactive to transform both aliphatic amines and anilines. This synthetic scheme can also be applied for the synthesis of semicarbazides with azide and alkyne residues as well.[101,102] Similarly, phosgene can also be used to generate the reactive 2-ethoxycarbonylhydrazinecarbonyl chloride from ethyl carbazate (OR′ = Cl, Scheme 9, bottom). While this reactive intermediate is very sensitive to water, it can be purified and isolated as a white, crystalline solid.[105,106] It readily reacts with both aliphatic amines and fluorinated anilines;[107−109] however, since phosgene is required to produce this intermediate, this procedure is much more hazardous than other "isocyanate-free" protocols, while phosgene-mediated isocyanate-based routes tend to be higher yielding (vide supra).

2.2.4. Modification of Semicarbazides. The synthesis of semicarbazides (vide supra) does not tolerate too many chemical functionalities, so functional urazoles and TAD reagents are more challenging synthetic targets. One way around this problem is the chemoselective modification of semicarbazide or urazole intermediates. While plenty of methods are available to modify urazoles (see section 2.4), only a few modifications on the semicarbazide intermediates have been reported. For instance Yamada and Shimizu reacted **11** (vide supra) with sodium azide to produce the corresponding azide-bearing semicarbazide **44** (Scheme 10a) with a yield of 95%.[51] Mallakpour and Nasr-Isfahani reported the efficient reduction of 4-(4-nitrophenyl) semicarbazide (**45**, Scheme 10b) to the corresponding amine (**46**) using tin(II) chloride as a reductant, thus providing a reliable synthetic handle for further transformations using electrophilic reagents (e.g., amide bond formation).[87]

Scheme 10. Examples of Semicarbazide Modification by (a) S_N2 Substitution[51] or (b) Reduction[87]

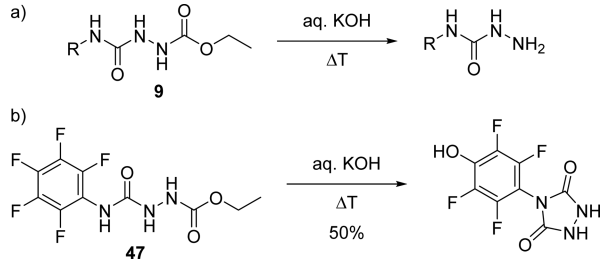


2.2.5. Cyclization. Most semicarbazides discussed above can be readily cyclized to the corresponding urazole. Thus, only a limited amount of protocols can be found throughout all reported syntheses. A clear rationale to why a certain method should be preferred over another one is rarely provided. In general, however, the cyclization of a semicarbazide is achieved using mildly basic conditions in a protic solvent.[17,42,48,108,110]

The original Cookson method reports a simple treatment of the semicarbazide with an aqueous potassium hydroxide solution at reflux temperature to effect cyclization of the semicarbazide to the urazole. When the cyclization is completed, as a result of the acidity of the formed urazole,[8,46] the urazole is obtained as a water-soluble potassium salt (solvated urazolyl anion), which, upon acidification of the solution to pH ≈ 1−2, precipitates from the aqueous medium as a neutral compound.

While Cookson's method for urazole synthesis is very practical and the cyclization is typically finished in 2−3 h, with a nearly quantitative yield, the reaction conditions can lead to obvious side reactions. Hydrolysis of the hydrazine carboxylate itself, followed by decarboxylation (Scheme 11a), is usually not a problem, except when the R-group is extremely electron withdrawing and/or severely sterically encumbering.[13,47] Hydroxide-mediated hydrolysis is more likely to occur in the R-groups, as was noticed by Gilbertson and Ryan, in the partial displacement of the 4′-fluorine atom when these reaction conditions were used to cyclize 1-(ethoxycarbonyl)-4-(pentafluorophenyl)semicarbazide (**47**, Scheme 11b).[108] Nevertheless, despite these possible (but predictable) side reactions, this cyclization is often the method of choice for urazoles that easily crystallize from the acidic aqueous solution, in particular those with an aromatic 4-substituent.[59]

Scheme 11. Two Examples of Possible Side Reactions during the Cyclization of Semicarbazides in a Refluxing Aqueous Potassium Hydroxide Solution: (a) Hydrolysis of an Ethoxycarbonyl Semicarbazide (9), Followed by Decarboxylation, Results in the Corresponding Semicarbazide,[47] While (b) the Base Might Participate in Nucleophilic Substitution Reactions[108]



A somewhat milder alternative to an aqueous potassium hydroxide solution is represented by sodium ethoxide in refluxing ethanol. This widely adopted method also allows for the isolation of urazoles in high yields, but longer reaction times of up to 24 h have to be taken into account. Often, these reaction conditions are the best choice if the substituent on the urazole, such as an aliphatic residue, prevents it from precipitating from an acidified aqueous solution.[47,59] This is mainly because this procedure is compatible with a nonaqueous workup to isolate the urazoles as an oil.

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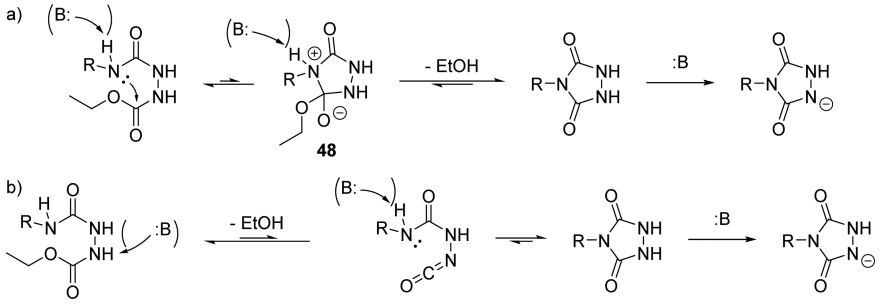
Scheme 12. Two Plausible Mechanisms for the Cyclization of Semicarbazides, Consistent with the Experimental Observations: Elimination of Ethanol Can Occur either (a) after or (b) prior to the Intramolecular Addition of the 4-Semicarbazide Nitrogen to the 1-Semicarbazide Carbonyl



Potassium carbonate can also be used as a base, rather than the much stronger ones applied in the previous systems. As a result of these milder conditions, higher yields can be obtained with some problematic substrates, although longer reaction times are necessary.[107,108] This protocol can be used in both water as well as in alcoholic solvents.[47,63,108] Mallakpour's previously mentioned elegant one-pot urazole synthesis (vide supra) uses triethylamine to mediate the cyclization of semicarbazides, in acetone as solvent.[99] Finally, semicarbazides can also be cyclized under neutral but high temperature (pyrolysis) conditions. In analogy to Thiele-type procedures (vide supra), heating the neat semicarbazide to 200−250 °C produces the corresponding urazole in good yields (65−75%).[17,67,111] Such pyrolysis conditions are only applied on the rare occasion that a semicarbazide is resistant to either of the conventional base-mediated cyclizations[17] or if a concurrent urazole modification is desired (see section 2.4).[67]

To the best of our knowledge, the mechanism of the cyclization of semicarbazides has not been extensively studied or considered in much detail. For this, we would like to propose herein two possible mechanisms, which are both consistent with experimental observations and account for the rate-enhancing effects of added base (Scheme 12).[95,112]

The first mechanism, shown in Scheme 12a, is based on the proposal by Ghorbani-Choghamarani et al.[95] and consists of the intramolecular addition of the 4-semicarbazide nitrogen to the 1-semicarbazide carbonyl with the formation of a charged intermediate (**48**). Consequent elimination of ethanol yields the corresponding urazole. Since both the addition and the elimination are reversible processes, the equilibrium can be shifted to the urazole by physical removal of the produced ethanol, cf. pyrolysis conditions. The presence of a base can increase the efficiency of the reaction at different stages. First, it can assist the addition step by proton abstraction, either before or after formation of the charged intermediate. Next, the elimination step can also be assisted by an alkaline environment, since this will result in an increased population of the charged alkoxide intermediate **48** compared to the corresponding protonated species. Finally, as a result of the relatively low pK_a value (≈ 5) of the urazole protons,[8,46] the product will be deprotonated by the base, which results in an irreversible step in the mechanism.

An alternative mechanism is shown in Scheme 12b and is very similar to the first proposal. However, in this case, ethanol is eliminated first with the formation of a neutral isocyanate-type intermediate, after which the urazole is formed as a result of an intramolecular addition. The existence of a similar transient isocyanate has been demonstrated earlier by pyrolysis of a hydrazinecarbonyl chloride in toluene with the elimination of hydrochloric acid.[105]

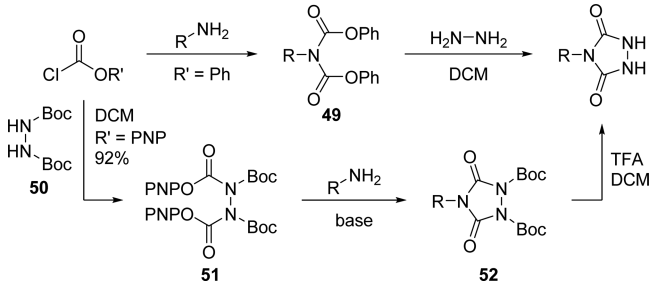
The cyclization step in the fragmentation−addition mechanism shown in Scheme 12b is favored over the acylation-type cyclization step on stereoelectronic grounds when the tendency for side reactions as a function of the utilized base is taken into account. At this time, we find no evidence to favor one pathway over the other, but a systematic investigation of different *N*-alkylated semicarbazides might lead to further insight into this matter.

2.3. Other Syntheses

Apart from the aforementioned and widely adopted strategies to produce 4-substituted urazoles, a number of other synthetic procedures have been reported as well. The protocols discussed in this section were mainly developed for a very specific purpose, such as the ability to synthesize urazoles bearing certain functionalities that are not tolerated by the more conventional methods. In selecting examples for this section, a number of alternative approaches were found that are either very low-yielding, limited to only one substrate, or have been simply reported as an unexpected side reaction.[22,35,38,39,113−115] These types of reports were thus not included in this section.

Buynak and co-workers proposed a general approach to obtain 4-substituted urazoles from amines in two steps (Scheme 13, top).[116] The first step comprises of the reaction of the amine with 2 equiv of phenyl chloroformate with the formation of an *N*,*N*-disubstituted diphenyl imidodicarbonate (**49**). This product can be subsequently cyclized to the urazole

Scheme 13. Alternative Syntheses for 4-Substituted Urazoles Reported by Chai et al.:[116,117] (a) Mild, Two-Step Protocol via a Diphenyl Imidodicarbonate Intermediate (49) and (b) Reaction of an Amine with the Isolated Hydrazine Derivative 51[a] Yields a Protected Urazole (52), Which Is Readily Deprotected in Acidic Medium



[a]PNP = *p*-nitrophenyl.

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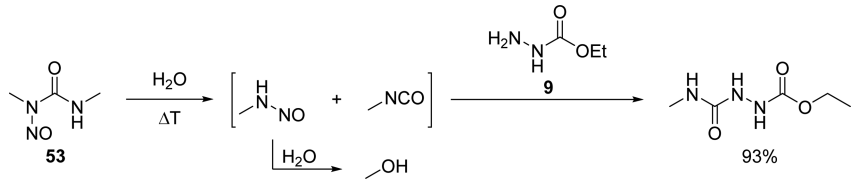
Scheme 14. Thermal Decomposition of 1,3-Dimethyl-1-nitrosourea (52) in Aqueous Conditions Generates Methyl Isocyanate, Which Can Be Trapped in Situ by Ethyl Carbazate (9) To Produce the Corresponding Semicarbazide



by reaction with hydrazine at room temperature. As a result of the general insolubility of 4-substituted urazoles in dichloromethane, separation of the product from the phenol byproduct was achieved by simple filtration. These mild reaction conditions, which do not require heating or base additives to produce the urazole, also allow for the generation of 4-alkoxyurazoles. However, the yields of these alkoxy-amine-derived urazoles are rather low (20−28%) and apparently have not been oxidized to the corresponding TAD reagents. Acceptable yields are reported for more conventional urazoles obtained via this synthetic scheme (55−64%).

Buynak and co-workers also reported an alternative procedure in which the amine is introduced in the final stage of the sequence (Scheme 13, bottom).[117] This approach requires more reactive *p*-nitrophenyl chloroformate, and a protected form of hydrazine, i.e., di-*tert*-butyl hydrazodicarboxylate (**50**). This yields a crystalline hydrazine derivative (**51**). This intermediate was subsequently reacted with an amine in the presence of *n*-butyllithium or pyridine to isolate di-Boc-protected urazoles (**52**) in low to moderate isolated yields (21−42%). However, direct conversion into the urazole by acidic removal of the Boc protecting groups without intermediate purification gave improved yields up to 71%.

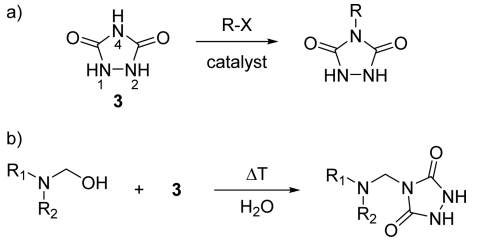
A final approach of interest to urazoles starts from 1,3-dimethyl-1-nitrosourea (**53**), which is known to decompose in aqueous conditions to generate methyl isocyanate in situ (Scheme 14), which can be trapped by ethyl carbazate, as evidenced by Breton and Turlington.[43] This reaction, followed by cyclization, can thus be used to produce 4-methylurazole on a multigram scale with satisfactory yields (68%), without having to handle or isolate highly toxic methyl isocyanate. This method is especially of interest in light of the ceased commercial availability of methyl isocyanate, which resulted in a discontinuation of commercial 4-methylurazole and 4-methyl-TAD as well. No other substituted nitrosourea compounds have been investigated.

2.4. Urazole Modification

Despite the fact that the aforementioned synthetic procedures can already accommodate for a large structural variety in the synthesized urazoles, these syntheses are often not compatible with a lot of sensitive chemical functionalities. When desired, these functionalities should thus be introduced in a postcyclization step in which either a latent functionality is transformed or a protecting group is removed (cf. semicarbazide modifications in section 2.2.4). From a strategic point of view, having a "reactive" urazole for the introduction of more elaborate 4-substituents avoids the cumbersome optimizations that are often required to obtain an efficient urazole synthesis.

In principle, unsubstituted urazole **3** can be transformed into various 4-substituted urazoles through a chemoselective reaction that can discriminate between the nucleophilic 4- and 1- (or 2-)nitrogen sites (Scheme 15a). In literature, however, to the best of our knowledge, only one such reaction

Scheme 15. Modification of Unsubstituted Urazole (3): (a) General Scheme for the Chemoselective Reaction of the Nucleophilic 4-Nitrogen Site and (b) An Example of Such a Modification in Which Methylolamine Acts as the Electrophile[32,33]



has been reported, using methylolamines at neutral or slightly alkaline pH (Scheme 15b).[32,33] While this strategy has apparently been successfully applied for the synthesis of multivalent urazoles in patent literature, no further examples could be found. Moreover, systematic studies by Arndt et al. on the regioselectivity of reactions of urazoles[22] seem to contradict the reported regioselectivity in this aminal-forming reaction. Taking into account that the hydrazide NH-moieties are not only more nucleophilic but also much more acidic ($pK_a \approx 5$) than the imide NH ($pK_a \approx 7.5$),[46] we propose that the aminal formation with urazole **3** actually gives a mixture of 1- and 4-substituted regioisomers. Thus, urazole **3** cannot be used as a starting material to efficiently prepare 4-substituted urazoles (and the corresponding TAD reagents).

In the remainder of this section, an overview of the chemical transformations of 4-substituted urazoles is provided, together with various urazole building blocks that can be orthogonally functionalized. Examples have been selected to offer the reader some broad synthetic considerations and insights in reaction conditions that are compatible with urazole moieties and to allow a chemoselective modification of the urazole substrates.

2.4.1. Modification during Semicarbazide Cyclization.

Under the standard semicarbazide cyclization conditions, it can be possible to concomitantly transform other functional groups in certain urazole substrates, which can release a useful synthetic handle. For example, ester hydrolysis readily occurs in aqueous base conditions, giving a urazole with a carboxylic acid functionality (**55**, R = H, Scheme 16a) starting from ester-functionalized semicarbazides (**54**).[61,64] The same cyclization in ethanol or methanol as solvent gives a transesterification of the alcohol part (R = Me).[64,118] More interestingly, urazoles with hydroxyl functions can be obtained in the same way from ester hydrolysis, where the semicarbazide is part of the alcohol moiety.[89] Burgert and Stadler developed a purely thermal cyclization protocol in which volatile ethoxytrimethylsilane is released from semicarbazide **56** (Scheme 16b) to give (4-hydroxyphenyl)urazole **57**.[67]

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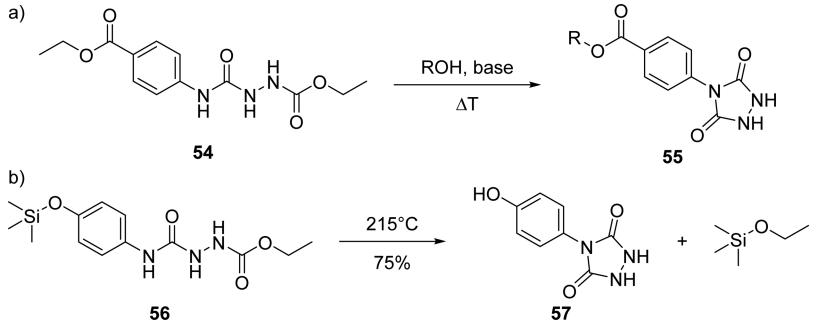
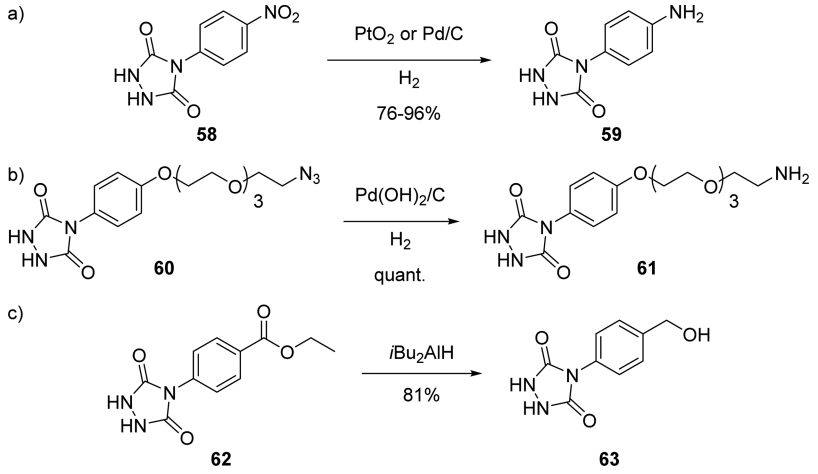
Scheme 16. Chemical Modification of a Functional Group during the Cyclization of the Semicarbazide: (a) Depending on the Solvent, either Transesterification or Hydrolysis Can Occur, Yielding Urazole 55 with R = Et (94%),[64] Me (91%),[118] or H (78-95%),[61,64] and (b) Trimethylsilyl Ethers Were Demonstrated To Cleave during a Purely Thermal Cyclization Protocol[67]

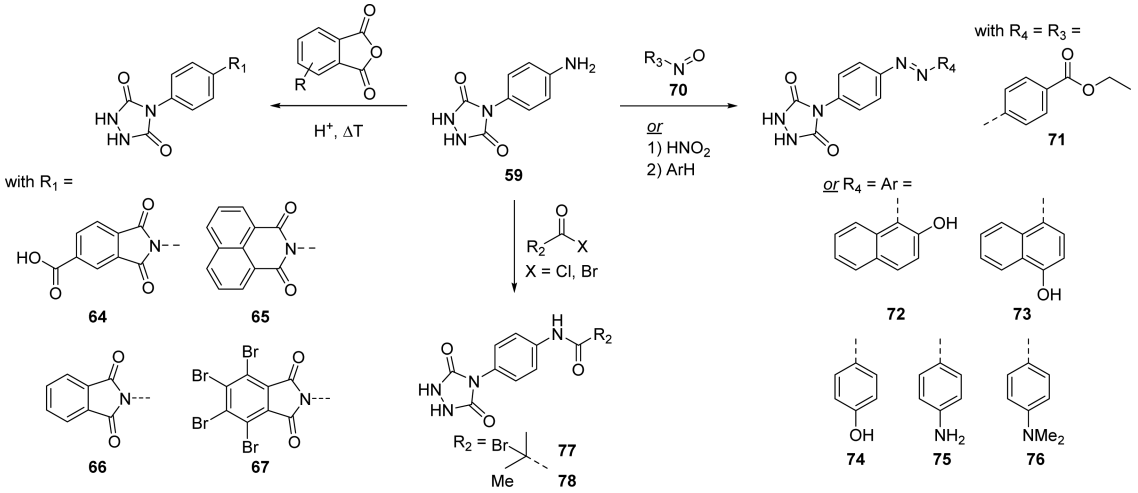


Scheme 17. Examples of Reductive Urazole Modifications: Amines Can Be Obtained by a Catalytic Hydrogenation of (a) a Nitro Group or (b) an Azide and (c) Selective Hydride Reduction of the Ester in Urazole 62 is Possible as Well[a]



[a]Due to reactivity reasons (see section 4), only the hydrochloride salt of 4-(4-aminophenyl)urazole (**59**) can be oxidized to the corresponding triazolinedione.[119,120] To the best of our knowledge, products **61** and **63** were never oxidized, but are further modified using electrophilic reagents (section 2.4.3).

Scheme 18. Reactions of 4-(4-Aminophenyl)urazole (59)[a]



[a]Except for urazoles **71** and **77**, none of the given compounds were oxidized to their corresponding triazolinediones.

2.4.2. Urazole Substrates in Hydrogenation or Hydride Addition Reactions. Urazole moieties seem to be highly resistant to reductive conditions, such as catalytic hydrogenations, opening up a number of strategies to introduce new functionalities. For example, the interesting 4-(4-aminophenyl)urazole (**59**) is readily obtained by hydrogenation of the nitro group in **58** using Adams' catalyst (PtO_2)[51] or palladium on carbon (Pd/C, Scheme 17a).[65,118] Alkene

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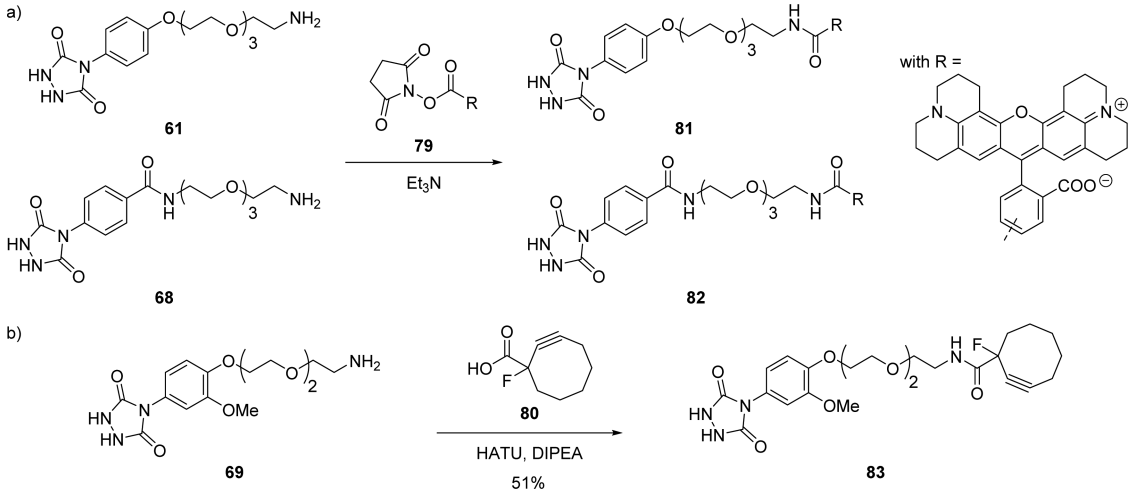
Scheme 19. Examples of Modifications on Urazoles with an Aliphatic Amine Using (a) an NHS-Activated Carboxy-X-rhodamine (79) or (b) a Combination of 1-Fluorocyclooct-2-ynecarboxylic Acid (80) and HATU as Coupling Reagent



hydrogenations in urazole substrates using PtO_2 have also been reported.[53] Aliphatic amines can be generated from the corresponding azides via simple hydrogenation using either palladium[51] or palladium(II) hydroxide[100,103] catalysts (Scheme 17b), the latter of which is reported to give the best yields. A carboxybenzyl (Cbz) group is also readily removed by catalytic (Pd/C) hydrogenation in urazoles with a Cbz-protected amine (cf. urazole derived from **41**, Figure 7).[14,97] These deprotections are helped by adding formic acid to the reaction mixture, thereby generating the formate salts rather than the free amines.[14]

Urazoles are also stable toward hydride reductions, as demonstrated by the transformation of the ester group in urazole **62** (Scheme 17c) to the corresponding benzylic alcohol (**63**), using an excess of diisobutylaluminum hydride (DiBAl-H), as reported by Shimizu et al.[51,63]

2.4.3. Derivatization of Amino-, Hydroxyl- and (Activated) Carboxyurazoles. Reactive chemical functionalities such as amines, hydroxyls, and (activated) carboxylic acids are incompatible with standard urazoles syntheses, but they can be introduced on urazole substrates in a number of straightforward ways (see sections 2.4.1 and 2.4.2). Thus, these reactive moieties can be used as synthetic handles for further derivatization of urazoles.

The use of 4-(4-aminophenyl)urazole (**59**) as a versatile intermediate to prepare a range of functional TAD reagents has been extensively explored (Scheme 18). Reaction with trimellitic anhydride gives the corresponding imide (**64**, Scheme 18, left).[121] In a fully analogous reaction, the aniline is transformed in imides with a 1,8-naphthalimidophenyl (**65**),[122,123] phthalimidophenyl (**66**),[124,125] or tetrabromophthalimidophenyl (**67**)[126] substituent by using the appropriate anhydride. These reactions all occur in a mildly acidic environment at elevated temperatures and provide the products in good yields (76−98%). Rather than using maleic anhydride, Bauer et al. used *N*-(methoxycarbonyl)maleimide to transform the aliphatic amine of urazole compounds **68** and **69** (Scheme 19) into a maleimide.[97,103] Good yields of 70−85% were obtained.

Starting from 4-(4-aminophenyl)urazole, azo compounds can also be readily obtained. Reaction of aniline **59** with nitrosobenzene derivative **70**, for example, produces azo compound **71** (Scheme 18, right).[118] An alternative route toward azo dyes comprises the diazotization of the same aniline using sodium nitrite in acidic medium.[87] Subsequent reaction of the diazonium salt with an electron-rich aromatic compound, either in acidic or basic media, yields the corresponding azo dye (**72**−**76**) in varying yields (66−97%).

Recently, Du Prez and co-workers reported a simple procedure using pyridine as a mildly basic solvent to couple aminourazole **59** with a functional acid bromide, giving a robust amide derivative (**77**, Scheme 18, bottom).[65,127] In fact, the amide is an initiator for copper-mediated polymerizations with a urazole moiety and was subsequently used for this exact purpose. An acylation with acetyl chloride has also been achieved in neutral dimethylacetamide (**78**).[128]

The use of hydroxyl functions in urazole substrates has been considerably less explored and also seems more problematic. A good illustration can be found in the work of Shimizu et al. toward the synthesis of fluorescent TAD reagents, wherein urazole **63** (Scheme 17) was reacted with an acid chloride.[51,63] However, this straightforward esterification proved to be rather difficult with problems pointing toward the typical basic reaction conditions used for such reactions. In fact, in the presence of a base, the acidic urazole ($pK_a \approx 5$) is readily deprotonated,[46] which will give an anion that can compete with the hydroxyl function as a nucleophile. Shimizu et al. solved this problem by running the reaction under acidic conditions in the absence of base at elevated temperatures. Read and Richardson reported similar issues when they tried to couple 4-(6-aminohexyl)urazole with dansyl chloride, where competitive urazole acylation led to low yields (25%).[14] However, under the amide bond forming conditions using the much less basic pyridine with aminourazole **59** (vide supra), the urazole acylation does not seem to be problematic.

On the basis of the above observations, it can be concluded that acylation reactions on urazoles should preferably not be performed in the presence of an excess of strong bases ($pK_a > 5$), as this will likely lead to competitive urazole acylations.

Activated carboxylic acid intermediates such as *N*-hydroxysuccinimide (NHS) esters have also been successfully coupled with amino-functional urazoles. These activated esters are reported to selectively react with the amines and do not give urazole acylation, even in the presence of a catalytic or

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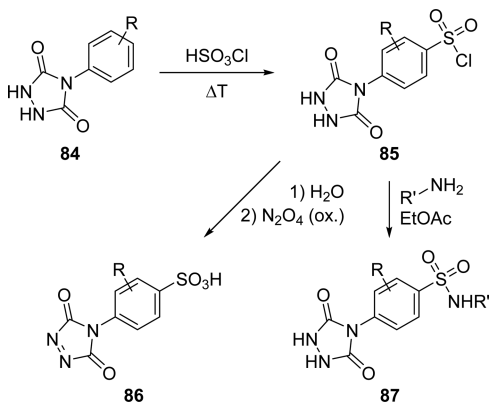
equimolar amount of base [triethylamine or diisopropylethylamine (DIPEA)]. Barbas and co-workers prepared two rhodamine-bearing urazoles by reacting NHS-activated carboxy-X-rhodamine (**79**) with the amine **61** or **68** (Scheme 19a). However, yields are not reported.[100,102] Similarly, Adamo et al. reported on the successful reaction of 4-(4-aminobutyl)-urazole with an NHS ester of poly(ethylene glycol) in 82% yield.[97] Modern amide coupling reagents have also been used to derivatize amino-functional urazoles. Bauer et al. demonstrated the use of HATU in the presence of DIPEA to attach 1-fluorocyclooct-2-ynecarboxylic acid (**80**) to a urazole with an amine functionality (**69**) in 51% yield (Scheme 19b).[103] In general, however, these coupling reagents are not always preferred because of the difficult removal of waste products from the urazole compound and the risk for urazole acylation in the presence of an excess of base.

The use of carboxylic acid derivatives as synthetic handles in urazoles has been very limited. This is likely because urazoles are expected to interfere with most reactions of carboxylic acids (as they are similar in acidity). Apart from the transesterification and hydrolysis examples shown in section 2.4.1, Seidel et al. have demonstrated the aminolysis of methyl ester **55** (Scheme 16, R = Me) with aqueous ammonia, resulting in 4-(4-urazolyl)benzamide.[118] While this reaction readily occurs at room temperature with an excellent yield (91%) in a matter of hours, it is reported to fail when other 4-(4-urazolyl)benzoic acid derivatives (**55**) are used.[118] Ketones have also been used to functionalize urazoles with limited success. Adamo et al. reacted 4-(4-acetylphenyl)urazole with *O*-benzylhydroxylamine and *O*-(prop-2-ynyl)hydroxylamine to obtain the corresponding Schiff base in very low yields (7−23%).[97] Dey and Purkayashtha obtained yields up to 65% for a similar derivatization.[60] In conclusion, carbonyl-type moieties seem less suitable as synthetic handles on urazole substrates.

2.4.4. Electrophilic Aromatic Substitution. In the case of PhTAD, the aromatic ring is electronically activated toward electrophilic aromatic substitutions. Indeed, Keana et al. reported the synthesis of water-soluble TAD reagents by reacting 4-arylurazoles (**84**, Scheme 20) with chlorosulfuric acid at elevated temperatures.[69] The obtained sulfonyl chloride **85** could be isolated and subsequently hydrolyzed in water to yield the corresponding sulfonic acid (**86**). The sulfonyl chloride **85** could also be immobilized on aminopropylsilylated silica gel via a sulfonamide link (**87**).

Scheme 20. Sulfonation of 4-Arylurazoles Allows for the Synthesis of Water-Soluble TAD Reagents and the Immobilization of Triazolinediones on Silica Gel[69]



2.4.5. "Click" Modification of Urazoles. By definition, click reactions are the most reliable methods to introduce covalent links between two moieties. For this, Barbas and co-workers developed azide-containing urazoles, using different synthetic approaches (see section 2.2.3). These azidourazoles were successfully reacted with an alkyne in a copper-catalyzed Huisgen 1,3-dipolar cycloaddition. Using this strategy, urazoles bearing a cyclic RGD peptide,[100,102] a poly(ethylene glycol) chain,[101] or aplaviroc,[101] i.e., a HIV entry inhibitor, were obtained in moderate to high yields (52−95%). Thus, the azidourazole compounds are probably the most versatile synthetic intermediates for functional TAD synthesis, although their synthesis is quite long and expensive (e.g., 11% overall yield over eight steps[102,129] from commercial materials for **60**, Figure 8), thereby prohibiting large-scale applications.

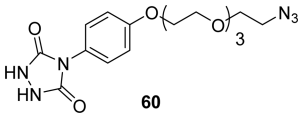


Figure 8. Urazole derived from **37** (Figure 6).

2.5. Concluding Remarks about Urazole Syntheses

Since a myriad of methods is available for the synthesis of urazole precursors for triazolinediones, the reader might encounter problems in the identification of viable routes for the envisioned application. Consequently, this section will provide guidelines for the swift identification of strategies that should afford the target urazole on a large scale.

The synthesis of urazoles via azodicarboxamide derivatives (section 2.1) requires harsh reaction conditions, resulting in a fairly limited overall substrate scope. Moreover, the optimization of the process can be tedious, since the optimal reaction conditions seem to be substrate-dependent. Nevertheless, this one-step procedure seems to be especially feasible in an industrial environment, where a single batch typically yields hundreds of grams of product without the need of intermediate purifications.

As a result of much milder reaction conditions compared to azodicarboxamide-based syntheses, the production of urazoles through cyclization of semicarbazides (section 2.2) is undoubtedly the most reliable lab-scale method to obtain urazoles. Semicarbazides can be most conveniently obtained by plainly mixing an isocyanate with ethyl carbazate (section 2.2.1). This Cookson method is still the most versatile and widely applied strategy, in which the urazole is generally produced on a scale of up to a few tens of grams.

If an isocyanate is not commercially available, the Cookson method can still be applied by generating the required isocyanate in situ. These extended Cookson methods allow for the use of carboxylic acids (section 2.2.2) and amines (section 2.2.3), offering a wealth of possible commercial starting materials. However, this expanded substrate scope, allowing for a larger structural variety in the resulting urazoles, is limited by the compatibility of the functional groups with the isocyanate-generating chemistry. For amines and carboxylic acids that are suitable for an isocyanate synthesis, the synthesis of the corresponding urazole can be easily scaled to multiple gram quantities, but it can also be performed without problem on a few tens of milligrams.

The remaining "isocyanate-free" strategies (sections 2.2.3 and 2.3) can be considered as much milder methods and are the

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preferred or indeed required methods to directly obtain urazoles that include more sensitive or exotic additional functional groups. The synthesis of such tailored urazoles is, however, more expensive, time-consuming, and typically limited to a scale of tens to hundreds of milligrams.

An alternative method for the synthesis of more diversely functionalized urazole substrates is offered by a range of derivatization reactions that have been demonstrated on synthetically simple urazoles (section 2.4). Urazoles do give rise to several chemoselectivity issues (related to their strong acidity), but generally speaking, urazoles seem to be quite compatible with reductive conditions and electrophilic aromatic substitution reactions (sections 2.4.2 and 2.4.4). Chemoselectivity problems can be expected with reactions involving nucleophiles, such as alcohols or amines. Most critically, a urazole is characterized by an acidity similar to that of a carboxylic acid and is proven to be a potent nucleophile as well in its deprotonated form (section 2.4.3). Therefore, the reaction conditions often have to be controlled or fine-tuned in order to minimize competition of the urazole moiety as a nucleophile. As this derivatization approach requires multiple (purification) steps, they are generally more expensive and time-consuming than direct methods.

3. OXIDATION OF 4-SUBSTITUTED URAZOLES TO THEIR CORRESPONDING 1,2,4-TRIAZOLINE-3,5-DIONES

The initial synthesis and isolation of 4-substituted urazole components dates back to experiments performed in the late 19th century (see section 2.1). At that time, reduction and oxidation reactions were commonly applied chemical analysis methods for structure elucidation. As a consequence, the first synthetic routes toward urazoles generally also encompassed a final oxidation experiment, in support of the successful conversion toward these target urazole components.[3,21,23] Many of the used routine "analytical oxidants" were observed to convert the urazole moieties into brightly colored azo compounds, affording a simple color test to confirm the formation of a urazole. Thus, although urazole oxidation was a standard analytical method, for which several oxidation methods were developed and fine-tuned throughout the years, these methods were not of much synthetic value. In fact, as described in section 1, pure triazolinediones could not be obtained, and their modes of reactivity could not be studied, before Cookson's seminal work in the 1960s. Until today, all practical methods to synthesize TAD reagents proceed via a final oxidation step of a urazole precursor.

An important remark in the context of TAD synthesis is that, although oxidation of urazoles is a very straightforward reaction, it can sometimes be a true bottleneck of triazolinedione synthesis. Although urazoles are in fact readily oxidized by most oxidants, these reactions are hard to perform because of two interrelated issues, i.e., the chemoselectivity of the oxidant and the reactivity of the resulting TAD compounds. Especially isolation of TAD reagents from reaction mixtures can be challenging. Ideal oxidation methods should thus be highly chemoselective, give one single triazolinedione reaction product, and generate no waste products or only waste products that are readily removed. Neither the oxidant nor its reduced forms should react with the TAD compound. Unfortunately, there are no generally successful approaches, and developing a successful protocol is often a question of trial and error, balancing the kinetics of several processes. For some applications, an "in situ" oxidation method is preferred, which avoids the isolation problem, but it usually exacerbates the chemoselectivity problem.

In this section, an overview is given of the widely applied and available procedures that enable the crucial final stage in triazolinedione synthesis to be carried out. In the following sections, the oxidation methods are divided into six subcategories, based on the chemical type of the oxidant used. Within these dedicated sections, some important aspects are highlighted, such as efficiency and ease of execution and compound isolation, as well as the compatibility of the applied reaction conditions to the presence of (functional) substituents and other chemical moieties. A brief overview of all different described procedures is listed within each subcategory. By identifying both the benefits and drawbacks of the different oxidation systems, this section aims to guide the reader in order to select the most suitable oxidation method for the specific application of interest. Finally, some general remarks and guidelines are described at the end of this section, with an emphasis on scalability of the most versatile oxidation procedures.

3.1. Nitrogen(IV) and Nitrogen(V) Oxide-Based Oxidations

3.1.1. Nitric Acid Oxidation: HNO_3. The first nitrogen(IV)-mediated oxidation was serendipitously observed by Thiele when he sought to dissolve a silver salt of an unsubstituted 4*H*-urazole in concentrated nitric acid, a common solvent for heavy metals and their salt derivatives.[3] However, instead of just observing a fast dissolution process, a bright red color also appeared, which was attributed to the formation of an azodicarbonamide oxidation product. Subsequently, *concentrated nitric acid* was also used to oxidize 4-phenylurazole, but the generated PhTAD has a limited lifetime under these conditions and could not be isolated from the reaction mixture (Scheme 21 and Table 2). In much later

Scheme 21. General Oxidation Scheme of Nitrogen(IV) and Nitrogen(V) Oxides, Affecting the Conversion of Urazoles toward Their Triazolinedione Counterparts

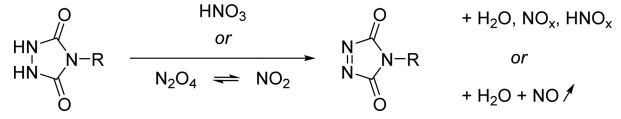
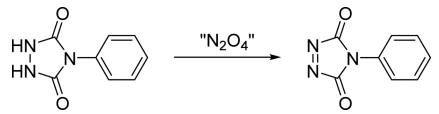


Table 2. Described Nitric Acid and Nitrogen(IV) Oxide Oxidation Procedures of 4-Phenylurazole to 4-Phenyltriazolinedione



oxidant	conditions[a] (time, min; temp, °C)	% yield	ref
concd HNO_3	$CHCl_3$ (nr; 0)	70	130
NO_2/N_2O_4(g)	CH_2Cl_2 (nr; 0)	86[b]	48
	CH_2Cl_2 (nr; 0−5)	80	131
	CH_2Cl_2 (90; −10)	94	132
N_2O_4 solution	EtOAc (12; RT)	95[c]	14

[a]nr: not reported. RT: room temperature [b]Yield after sublimation. [c]Determined spectroscopically.

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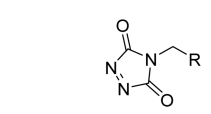
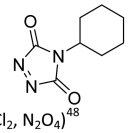
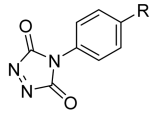
Table 3. Overview of Functional Triazolinediones Synthesized via N(IV)- and N(V)-Mediated Oxidation of Their Corresponding Urazole Precursors[b]



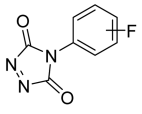
R = Pr
84% ($CHCl_3$, *fum.* HNO_3)[40]
R = H, Et, Pr
80-90% (CH_2Cl_2, N_2O_4)[48,54,131]



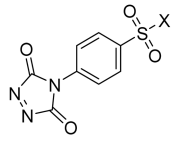
86% (CH_2Cl_2, N_2O_4)[48]



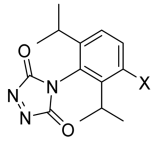
R = MeO
60% (CH_2Cl_2, N_2O_4)[48]
R = NO_2
20% (CH_2Cl_2, N_2O_4)[48]



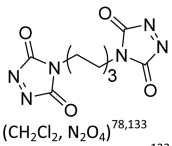
4-F
91% (EtOAc, N_2O_4)[108]
2,4,6-F_3
83% (EtOAc, N_2O_4)[108]
2,3,4,5,6-F_5
55% (EtOAc, N_2O_4)[108]



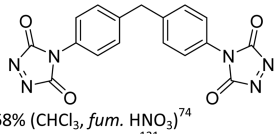
X = Cl
91% (CH_2Cl_2, N_2O_4)[69]
X = OH
> 28%[a] (CH_2Cl_2:THF 1:1, N_2O_4)[69]
X = NH-R (silica bound)
> 57%[a] (CH_2Cl_2, N_2O_4)[69]



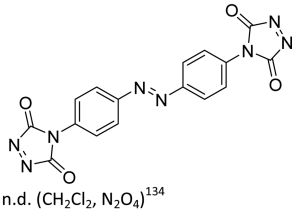
X = H
61% (CH_2Cl_2, *conc.* HNO_3)[70]
94% (CH_2Cl_2, N_2O_4)[69]
X = SO_3H
67% (CH_2Cl_2, N_2O_4)[69]
89% (Na-salt, CH_2Cl_2, N_2O_4)[69]



70-79% (CH_2Cl_2, N_2O_4)[78,133]
96% (Na-salt, CH_2Cl_2, N_2O_4)[133]



68% ($CHCl_3$, *fum.* HNO_3)[74]
80% (CH_2Cl_2, N_2O_4)[131]



n.d. (CH_2Cl_2, N_2O_4)[134]

[a]These yields are estimates based on efficiency data of subsequent reactions found in the original references. [b]n.d.: not determined.

studies, Furdik et al. managed to optimize this type of oxidation by adding 2 equiv of *fuming nitric acid* to a cooled chloroform suspension of 4-alkyl- and 4-benzylurazoles (Table 3).[40] The resulting purple reddish chloroform phase was separated from the aqueous layer, concentrated, and treated with a dry air stream to get rid of residual nitric acid. The generated TAD reagents were obtained in good yield, but they had a limited shelf life; thus, the labile product was subsequently used in a follow-up reaction. Finally, in 1973, Ried and Lim developed a more controlled procedure, in which 40 g of 4-phenylurazole could be oxidized by careful nitric acid addition, giving 70% of isolated and stable PhTAD as carmine red crystals.[130]

Saville screened a number of oxidation procedures to obtain MDI-derived divalent TAD reagents (vide supra).[74] For this transformation, Furdik's oxidation procedure with fuming nitric acid treatment of a suspension of urazole in chloroform proved to be the most effective one (Table 3). Saville further found the workup procedure to be of critical importance. Importantly, the crude residue obtained after extraction and evaporation of the reaction mixture was purified by redissolving in ethyl acetate and removing remaining solids (likely unreacted urazoles and/or hydrolysis products) by filtration. The filtrate was then slowly added to an excess of petroleum ether, resulting in the precipitation of the bivalent triazolinedione (bisTAD) reagent. Although isolated yields were somewhat lower in this procedure (68%), the obtained triazolinedione was found to be stable for weeks when stored in a dark environment, while other investigated oxidation methods only yielded a transient bisTAD species with a limited shelf life.

3.1.2. Nitrogen(IV) Oxides as Highly Effective Oxidants: NO_2/N_2O_4. Although nitric acid solutions are cheap and relatively easy to handle reagents, the obtained triazolinedione yields are rather moderate. Presumably, the presence of acidic protons, water, and oxidation waste products in these nitric acid-mediated procedures can lead to further reactions of the generated TAD compounds. Besides that, these strongly acidic and oxidizing conditions also clearly limit the substrate scope of this procedure. These side reactions were investigated by Williams using more elaborate substrates, such as 4-benzoic acid urazole and its ethyl ester derivative.[135] Finally, the use of an excess of nitric acid typically requires an aqueous workup procedure, while it is known that most TAD compounds only have limited stability toward hydrolysis.[70]

Stickler and Pirkle[48] developed a straightforward water- and acid-free protocol for the oxidation of urazoles by making use of gaseous *dinitrogen tetroxide* (N_2O_4), which is known to be in equilibrium with *nitrogen dioxide* [$NO_2(g)$],[136] which is a milder (reduced) and dehydrated form of nitric acid (Scheme 21).[137] The use of dinitrogen tetroxide, which is a liquid below 20 °C, can convert urazoles to their corresponding triazolinediones in an almost traceless manner, as the gaseous oxidant can be used in excess without compromising the straightforward isolation procedure. The residues obtained from simple evaporation of the reaction mixture thus contain little contaminants and pure, bench-stable TAD reagents can be obtained by a 2-fold sublimation of the residue. The toxic gas N_2O_4 can be handled in liquid form, but a solution of this gas in an inert solvent can also be employed to achieve less hazardous handling procedures.[14,69,114] This reaction can also be performed in more polar solvents, such as ethyl acetate, which broadens the scope of the classical nitric acid procedure considerably, which is typically limited to (hydrophobic) chloroform- or dichloromethane-soluble TAD reagents (Table 2).[64]

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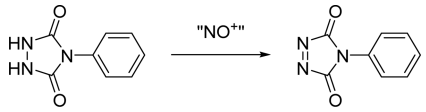
Table 4. Heterogeneous Alternatives To Oxidize 4-Phenylurazole by in Situ Generation of a Nitrosonium Ion[a]



oxidant	conditions[b] (time)	% yield	ref
$[NO^+ \cdot crown \cdot H(NO_3)_2^-]$	CH_2Cl_2 (instantaneously)	quant.	141
Kryptofix−N_2O_4	CH_2Cl_2 (1−3 min)	78−82	142
PEG−N_2O_4	CH_2Cl_2 (30 min)	95	143
$NaNO_2$/oxalic acid dihydrate	CH_2Cl_2 (1 h)	80	144
$NaNO_2/NaHSO_4$	CH_2Cl_2 (1−3 h)	90−96	145, 146
$NaNO_2/Mg(HSO_4)_2$	CH_2Cl_2 (1 h)	94	145
$NaNO_2/KHSO_5$(oxone)	CH_2Cl_2 (1.5 h)	94	147
$NaNO_2/H_5IO_6$	CH_2Cl_2 (1 h)	80	148
$NaNO_2/HIO_3$	CH_2Cl_2 (1.5 h)	86	148
$NaNO_2$/TTSA	CH_2Cl_2 (0.5 h)	99	149
$NaNO_2$/sulfamic acid	CH_2Cl_2 (2 h)	80	150
$NaNO_2$/isocyanuric acid	CH_2Cl_2 (0.5 h)	95	150
$NaNO_2$/AcOH	EtOAc (5 min)	>98	151
$NaNO_2/SiO_2-H_2SO_4$	CH_2Cl_2 (2 h)	84−96	145, 152
$NaNO_2/SiO_2-HNO_3$	CH_2Cl_2 (1.5 h)	56−68	145
$NaNO_2/SiO_2-H_3PO_4$	CH_2Cl_2 (2 h)	79	145
$NaNO_2/SiO_2$−Cl	CH_2Cl_2 (3 h)	98	153
$NaNO_2$/sulfonated polystyrene	CH_2Cl_2 (0.5−1 h)	91−95	150
$NaNO_2$/poly(4-vinylpyridinium)−HNO_3	CH_2Cl_2 (1.5 h)	98	154
PVP−HNO_3	CH_2Cl_2 (1 h)	75	155
SiO_2-HNO_3	CH_2Cl_2 (1 h)	72−73	145
	CH_2Cl_2 (35 min)	99	155
$(NH_4)_2[Ce(NO_3)_6]$	CH_2Cl_2 (2 h)	84	145
$NH_4NO_3/Al(HSO_4)_3$	CH_2Cl_2 (40 min)	98	156
NH_4NO_3/SiO_2-OSO_3H	CH_2Cl_2 (40 min)	98	157
$Al(NO_3)_3 \cdot 9H_2O/SiO_2-OSO_3H$	CH_2Cl_2 (2 h)	98	158
guanidinium nitrate/SiO_2-OSO_3H	CH_2Cl_2 (45 min)	98	159
$BnPh_3P^+NO_3^-/AlCl_3$	CH_2Cl_2 (30 min)	96	160

[a]PEG: poly(ethylene glycol). TTSA: 1,3,5-triazine-2,4,6-triyltrisulfamic acid. PVP: poly(vinylpyrrolidone). [b]All reactions are carried out at RT.

The generally high yields and relative operational ease prompted a wide adoption of the N_2O_4/NO_2-mediated procedure for the oxidation of various urazole substrates, including 4-alkyl-substituted[114] and fluorinated[107,108] or sulfonated[69] 4-arylurazoles, as well as for a range of bifunctional urazoles based on aliphatic,[78,138] aromatic,[131,138,139] and azobenzene[134] backbones (Table 3). Also solid-supported urazoles[69] are readily converted into their highly reactive TAD counterparts by this convenient method. The reaction can even be run in basic medium, as urazole sodium salt derivatives are also effectively oxidized this way.[54,78,133] Gardlik and Paquette,[16,17] and later Mallakpour,[57] were also able to oxidize different urazoles containing a chiral 4-subtituent to their optically active triazolinedione counterparts (vide supra, Figure 5).

Although the N_2O_4/NO_2 method seems to be widely applicable to many urazole substrates, some electron-rich aryl groups tend to give competitive electrophilic aromatic nitration reactions, as evidenced during the attempted oxidation of 4-(4-hydroxyphenyl)urazole (see also section 3.2.2).[67] As TAD reagents themselves also react with electron-rich aryls (see section 4.3), this does not always affect the effective substrate scope of the method. Another disadvantage is the formation of 1 equiv of water and possible acidic byproducts, which might interfere with the obtained triazolinediones. However, such problems can greatly be excluded by the simple addition of an appropriate desiccant, such as anhydrous NaOAc or Na_2SO_4.[48,114]

Today, the N_2O_4-based oxidation is still one of the most effective and reliable methods to obtain TAD reagents of a high analytical quality, owing to the straightforward workup (removing of volatiles). However, this highly effective method also has several unfavorable aspects, such as stringent shipping procedures for commercial dinitrogen tetroxide, relatively high cost of the reagent (in pure form), and the sometimes unreliable quality. As a result, Mallakpour developed a convenient lab-scale procedure for the controlled generation of small amounts of neat N_2O_4.[132] In this setup, based on the popular student lab demonstration of the chemical equilibria with freshly generated dinitrogen tetroxide, dried lead nitrate is heated with a Bunsen burner and the resulting gas mixture of N_2O_4 and NO_2 can be collected through condensation or can be directly guided through the cooled urazole suspension. Besides lead nitrate, also arsenious oxide can be used as a precursor to generate nitrogen(IV) oxides in situ when treated with concentrated nitric acid. However, both procedures result in highly toxic waste.[140]

3.1.3. Heterogeneous Alternatives for in Situ Generation of N(IV) Oxide Species. Despite the ease and versatility of the in situ generation of N_2O_4 gas in a closed setup, this procedure remains somewhat laborious and hazardous, because of the use of large amounts of a highly

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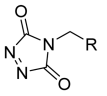
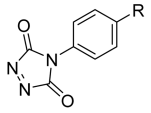
Table 5. Representation of the Substrate Scope for Heterogeneous in Situ Nitrosonium Oxidations



R = Et
95% (CH_2Cl_2, [NO^+.crown.H(NO_3)$_2^-$])[141]
56-99% (CH_2Cl_2, $NaNO_2/H^+$)[144-150,152-153,161]

R = H, Me, Pr
80-100% (CH_2Cl_2, $NaNO_2/H^+$)[144-150,152-153,161]

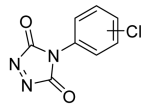
R = H, Me, Et, Pr
86-100% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
78-87% (CH_2Cl_2, PEG-N_2O_4)[143]
74-100% (CH_2Cl_2, NO_3^-/H^+ or $AlCl_3$)[154-160]



R = tBu
75-80% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
82% (CH_2Cl_2, PEG-N_2O_4)[143]
94-98% (CH_2Cl_2, $NaNO_2/H^+$)[149-150]

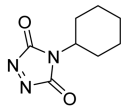
R = MeO
83-87% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
85% (CH_2Cl_2, PEG-N_2O_4)[143]
70-93% (CH_2Cl_2, $NaNO_2/H^+$)[149-150]
93-99% (CH_2Cl_2, NO_3^-/H^+ or $AlCl_3$) [155-160]

R = NO_2
67-70% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
90% (CH_2Cl_2, PEG-N_2O_4)[143]
77-100% (CH_2Cl_2, $NaNO_2/H^+$)[145-150,152-153,161]
>99% (EtOAc, $NaNO_2/H^+$)[151]
85-99% (CH_2Cl_2, NO_3^-/H^+ or $AlCl_3$)[154-160]

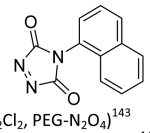


4-Cl
85-87% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
97% (CH_2Cl_2, PEG-N_2O_4)[143]
83-99% (CH_2Cl_2, $NaNO_2/H^+$)[145-150,152-153,161]
73-99% (CH_2Cl_2, NO_3^-/H^+ or $AlCl_3$)[154-160]

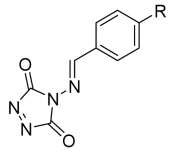
3,4-Cl_2
85-90% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
85% (CH_2Cl_2, PEG-N_2O_4)[143]
67-99% (CH_2Cl_2, $NaNO_2/H^+$)[149-150,152-153,161]
90-98% (CH_2Cl_2, NO_3^-/H^+ or $AlCl_3$)[154-159]



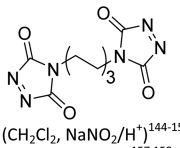
86-90% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
90% (CH_2Cl_2, PEG-N_2O_4)[143]
80-99% (CH_2Cl_2, $NaNO_2/H^+$)[144-150,152-153,161]
91-99% (CH_2Cl_2, NO_3^-/H^+ or $AlCl_3$)[154-160]



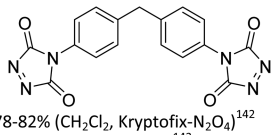
81% (CH_2Cl_2, PEG-N_2O_4)[143]
80-96% (CH_2Cl_2, $NaNO_2/H^+$)[149-150]
91-99% (CH_2Cl_2, NO_3^-/H^+)[154-156,158]



R = H, MeO
>98% (EtOAc, $NaNO_2/H^+$)[151]



70-98% (CH_2Cl_2, $NaNO_2/H^+$)[144-150,152-153,161]
86-97% (CH_2Cl_2, NO_3^-/H^+)[157,159]



78-82% (CH_2Cl_2, Kryptofix-N_2O_4)[142]
82% (CH_2Cl_2, PEG-N_2O_4)[143]
63-99% (CH_2Cl_2, $NaNO_2/H^+$)[144-150,152-153,161]
81-93% (CH_2Cl_2, NO_3^-/H^+ or $AlCl_3$)[159-160]

toxic gas and the generation of toxic waste (lead and arsenic oxides). Thus, Zolfigol, Mallakpour, and co-workers systematically explored alternative heterogeneous oxidation procedures that avoid the use of gas by exploring solid supports for nitrogen(IV) oxide species or also insoluble inorganic salts that can generate nitrogen(IV) oxides in situ (Table 4). In the case of completely insoluble reagents and waste products, a similar easy workup could be achieved (filtration and removal of volatiles).

The adsorption and chemical complexation of gaseous N_2O_4 to a heterogeneous carrier gives a reagent that is safer to handle and can be easily stored. Thus, a range of suitable complexation agents for nitrogen(IV) oxide was investigated (Table 5). It was shown that a combination of N_2O_4 and 18-crown-6-ethers gives a relatively stable crystalline ionic complex with nitrosonium (NO^+) bound in the cavity of the macrocyclic ethers (with a nitrate counterion).[141] Once added to a urazole suspension, the active nitrosonium species is released in situ, which rapidly gives triazolinediones in high yields. However, the resulting solution is contaminated by the crown ether, which can dissolve in the utilized solvent. Therefore, the same strategy was applied using silica-supported functional crown ethers, such as the commercially available Kryptofix 21 and Kryptofix 22, making the oxidation system heterogeneous.[142] The biggest advantage of this solid-supported oxidant is the easy workup by filtration, the enhanced stability of the active species, and the possibility to recover the solid support and retreat it with a N_2O_4 gas stream. The main drawback is the excessive cost of these tailored reagents. Chemisorption of N_2O_4(g) by metal nitrate complexes [$M(NO_3)_x$] (M = Cu, Fe, Cr) can also be effected, but these were found to be unsuitable to oxidize urazoles to their corresponding triazolinediones.[145,146] Nitrogen(IV) oxide can also be complexed to a simple (and cheap) poly(ethylene glycol) support, without losing its oxidative properties.[143] The impregnation is performed by simply bubbling the gaseous oxidant through a cold solution of PEG in dichloromethane. PEG-supported dinitrogen tetroxide thus provides a low-cost, bench-stable oxidant with minimal hazards, although removal of the PEG-support from reaction mixtures is not always straightforward.

Several (in)organic salts and/or acids can be used to generate nitrogen(IV) oxides.[144] As is well-known, *sodium nitrite ($NaNO_2$)* will generate nitrosonium ions, via protonation and dehydration, in the presence of strong *organic and inorganic acids*, such as oxalic acid,[144] $NaHSO_4$,[145,146] $Mg(HSO_4)_2$,[145] $KHSO_5$ (oxone),[147] H_5IO_6 or HIO_3,[148] 1,3,5-triazine-2,4,6-triyltrisulfamic acid (TTSA),[149] sulfamic or isocyanuric acid,[150] $H_3[P(Mo_3O_{10})_4]$,[161] and acetic acid.[151] Shorter reaction times

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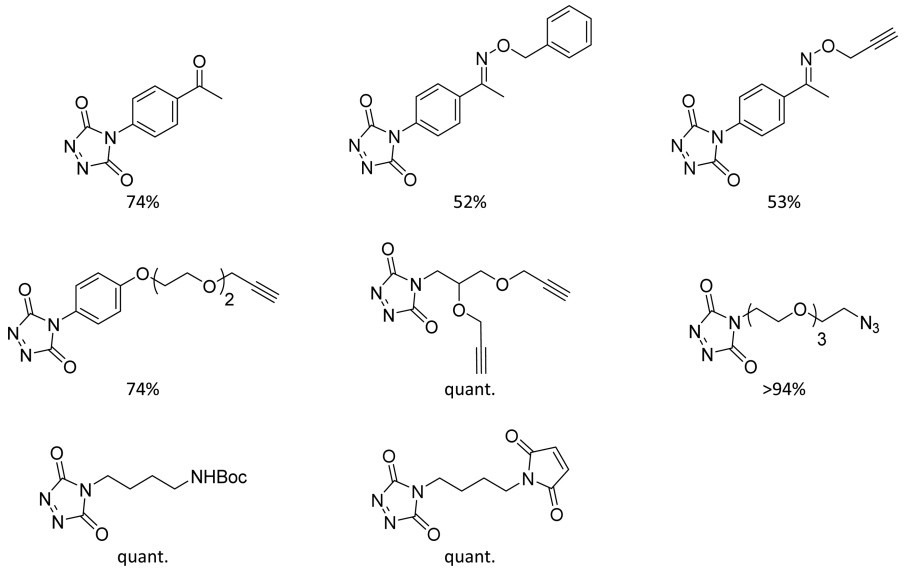
Table 6. Bifunctional Triazolinediones Compatible with a Silica-Supported Nitric Acid (SiO_2–HNO_3) Oxidation of Their Urazole Precursors in Dichloromethane at Room Temperature[97,98,162]



have been obtained when wet silica is added to the reaction mixture. More heterogeneous reaction conditions, and easier workups, have been achieved by using solid-supported acids, such as sulfuric, nitric and phosphoric acid adsorbed on silica,[145,152,155] silica chloride in combination with wet silica (liberating HCl),[153,155] and sulfonated polystyrenes[150] and nitric acid on poly(4-vinylpyridinium)[154] and poly-(vinylpyrrolidone) (PVP–HNO_3).[155] The PVP-supported nitric acid and the silica-supported analogue (SiO_2–HNO_3) also generate triazolinediones from urazoles in the absence of sodium nitrite because of the nitric acid autoionization process. The *HNO_3–PVP* system was found to be an interesting reagent for the successful chemoselective conversion of the electron-rich 4-(4-methoxyphenyl)urazoles, pointing to mild reaction conditions and a wider substrate scope.[155] *SiO_2–HNO_3*, on the other hand, has been shown to be compatible with a wide range of functionalities, such as carbamate-protected primary amines, maleimides, oximes, alkyl azides, and propargyl ethers (Table 6).[97]

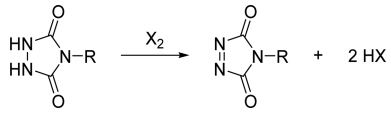
For the generation of nitrogen(IV) oxides, other nitrite ion sources besides the typical $NaNO_2$ were addressed in the form of nitrate salts. One of these alternative systems comprises the use of (ceric)[145] ammonium nitrate, which was investigated in the presence of different metal hydrogen sulfates [$M_x(HSO_4)_y$, M = Al, Na, K, Zr, Zn, Ca], of which $Al(HSO_4)_3$ was shown to be most effective.[156] However, when a catalytic amount of silica-bound sulfuric acid was used in combination with ammonium nitrate, a variety of urazoles were converted with near quantitative yields while reaction times were only slightly prolonged.[157] Similar results were obtained when aluminum nitrate,[158] urea nitrate,[163] and guanidinium nitrate[159] were examined as alternative nitrate source. When oxidation reactions were carried out in the absence of silica-bound sulfuric acid, no conversion of 4-phenylurazole was detected after several hours.

On the basis of the same principle, also benzyltriphenyl-phosphonium salts with nitrate counterions effectively carry out oxidations of urazoles in the presence of $AlCl_3$.[160] Again the active species generated in situ is believed to be a nitrosonium ion. Yet, the heterogeneous character is lost due to the solubility of benzyltriphenylphosphonium salts in organic media.

3.2. Halogen-Mediated Oxidations

Besides N(IV) and N(V) oxide-based reagents, a second major chemical class of oxidants used to convert urazoles into triazolinediones comprises halogens and their derivatives (Scheme 22). The development of these types of oxidation

Scheme 22. General Representation of a Halogen-Mediated Urazole Oxidation



procedures can again be traced back to the work of Thiele, who was able to generate a red solution of unsubstituted 4*H*-TAD with *hypochlorous acid* and *aqueous bromine*.[3] Stollé also had an early report on the oxidation of 4*H*-, 4-amino-, 4-phenyl-, and 4-benzilydeneamidourazoles with an ethereal *iodine solution*.[164] However, the corresponding urazoles need to be converted to their silver salts to enable this weaker iodine oxidant to be effective. In general, then, iodine cannot be used to oxidize urazoles, but bromine and chlorine can.

3.2.1. Chlorine and Bromine. The oxidation of urazoles by the action of *chlorine* is reported as being particularly fast and high yielding.[14,62] Interestingly, even treatment with submolar amounts of chlorine gas have also been found to lead to complete urazole oxidation, implicating the involvement of molecular oxygen in a radical chain oxidation process.[14] Chlorine can either be applied as a gas stream bubbled through the urazole suspension or added as a solution in tetrachloro-methane. The use of gaseous chlorine gives slightly higher yields and faster reaction times, but these differences remain very limited (Table 7).

Also *bromine* is a useful reagent for triazolinedione generation. The first use of bromine as an oxidant for 4-phenylurazole was reported by Sauer and Schröder.[165] By simply treating the urazole in a mixture of an aqueous buffer

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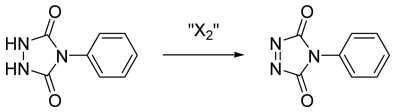
Table 7. Overview of All Applied Halogen-Mediated Oxidants for the Conversion of 4-Phenylurazole[a]



oxidant	conditions[b] (time, temp)	% yield	ref.
Cl_2(g)	EtOAc (0.5 min, RT)	100	14
Cl_2 in CCl_4	EtOAc (1.2 min, RT)	97	14
Br_2	benzene (1 min, RT)	49	165
*t*BuOCl	acetone (30 min, −50 to −78 °C)	78−80	4, 5
	dioxane (30 min, RT)	100	5
	EtOAc (20−40 min, RT)	62−97	14, 41
	EtOAc (40−60 min; 5−20 °C)	98−100	166, 167
$Ca(OCl)_2$	EtOAc (20 min, RT)	40	14
	CH_2Cl_2 (15 min, RT)	92	168, 169
SiO_2−ICl	CH_2Cl_2 (10 min, RT)	98	170
NBS	CH_2Cl_2 (15 min, 0 °C)	78	171
	EtOAc (10 min, RT)	50−71	14
trichloroisocyanuric acid	CH_2Cl_2 (30 min, RT)	74	120
	neat (15 min, RT)	70	120
1,3-dichloro-5,5-dimethylhydantoin	CH_2Cl_2 (2 h, RT)	80	10
	neat (6 h, RT)	96	10
1,3-dibromo-5,5-dimethylhydantoin	CH_2Cl_2 (2 h, RT)	97	10
	neat (2 h, RT)	80	10
trichloromelamine	CH_2Cl_2 (3 h, RT)	87	172
N,*N*,2,3,4,5,6-heptachloroaniline	CH_2Cl_2 (1 h, RT)	100	173
iodogen	CH_2Cl_2 (1 h, RT)	96	174
N,*N*,*N*′,*N*′-tetrabromobenzene-1,3-disulfonamide	CH_2Cl_2 (2 h, RT)	83	172
hexamethylenetetramine-bromine	CH_2Cl_2 (1 h, RT)	91	90
1,2-(dipyridiniumditribromide) ethane	CH_2Cl_2 (30 min, RT)	95	90
tribromoisocyanuric acid	CH_2Cl_2 (50 min, RT)	93	90
DABCO−Br	CH_2Cl_2 (2 h, RT)	80	90
periodic acid/KBr (cat.)	CH_2Cl_2 (20 min, RT)	95	15
oxone/KBr (cat.)	CH_2Cl_2 (20−25 min, RT)	>48−60	15, 175
oxone/SiO_2−Cl	CH_2Cl_2 (17 min, RT)	99	176
benzyltriphenylphosphonium peroxymonosulfate/$AlCl_3$ (cat.)	neat (10 min, RT)	94	177
benzyltriphenylphosphonium chlorate/$AlCl_3$ (cat.)	CH_2Cl_2 (15 min, RT)	97	178
	neat (10 min, RT)	94	178
UHP/MCl_n (M = Al, Zr, W)	CH_2Cl_2 (3.5 h, RT)	0	173
DABCO−DNOP/MCl_n (M = Al, Zr)	CH_2Cl_2 (1 h, RT)	95	179
PVP−H_2O_2/MCl_n (M = Zr)	CH_2Cl_2 (1.5 h, RT)	98	180

[a]NBS: *N*-bromosuccinimide. DABCO−Br: 1,4-diazabicyclo[2.2.2]octane and bromine. UHP: urea−hydrogen peroxide. DNOP: 1,4-bis(oxide)-bis(hydrogen peroxide). PVP: poly(vinyl pyrrolidone). [b]RT: room temperature.

and benzene in a separation funnel with an excess of bromine, followed by 1 min of vigorous shaking, 4-phenyl-TAD was obtained in 50% yield after sublimation. As expected, the chemoselectivity and substrate scope of these rather harsh oxidants, which generate hydrochloric or hydrobromic acid, is rather limited due to electrophilic and/or acid-mediated reactions.

3.2.2. Hypochlorites. Elemental chlorine and bromine often give low yields for urazole oxidations, presumably due to their limited chemoselectivity and because of the acid sensitivity of the formed TAD compounds. Cookson achieved a more controlled oxidation process by using *tert-butyl hypochlorite* for the oxidation of 4-phenylurazole in dry acetone at low temperatures (−50 to −78 °C).[4] The low temperature most likely prevents side reactions with acetone, which is not a completely inert solvent for triazolinediones.[7,58] Although isolation gave the resulting TADs in 80% yield, which can be directly used in a subsequent reaction, the obtained product was unstable, even after sublimation.[41]

A few years later, quantitative yields were made feasible at room temperature by changing the solvent to dioxane, which allowed for a relative stable crystalline product to be isolated.[5] Ethyl acetate gave even better results because of the higher solubility of the urazole precursor (Table 7).[41] Dichloromethane can also be used at room temperature, although urazoles are mostly insoluble in this solvent.[181] An important aspect in these optimized room-temperature procedures is to avoid overheating of the reaction mixture by adding the oxidant slowly over a certain period of time (20 min to 1 h), maintaining the reaction mixture around room temperature or—for very reactive TADs—at slightly lower temperatures (ca. 5 °C) (Table 7).[167] Bench-stable TAD reagents can generally be obtained through sublimation, although this is not always possible[13] and can give very low yields in some cases.[41] High yields of triazolinediones were also obtained under heteroge-

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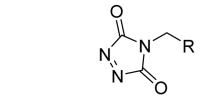
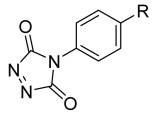
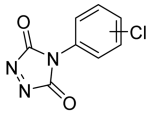
Table 8. Different Functional Urazoles Capable of Being Oxidized with Hypochlorites and Chlorates to Their Corresponding Triazolinediones



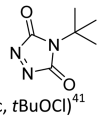
R = H
85% (EtOAc, *t*BuOCl)[41]
R = Et
82% (CH_2Cl_2, CaOCl)[168-169]
R = Me, Ph
65-85% (EtOAc, *t*BuOCl)[13]
R = H, Me, Pr
85-100% (CH_2Cl_2, CaOCl)[168-169]
R = CH_2-C_8F_{17}
51% (EtOAc, *t*BuOCl)[56]



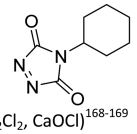
R = MeO
>62%[a] (EtOAc, *t*BuOCl)[67]
R = MeO
79% (EtOAc, *t*BuOCl)[13]
R = NO_2
25% (EtOAc, *t*BuOCl)[41]
70% (CH_2Cl_2, CaOCl)[168-169]



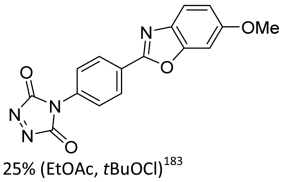
4-Cl
98% (CH_2Cl_2, CaOCl)[168-169]
3,4-Cl_2
90% (CH_2Cl_2, CaOCl)[168-169]



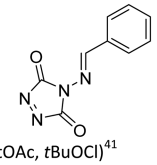
80% (EtOAc, *t*BuOCl)[41]



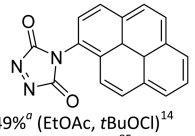
85% (CH_2Cl_2, CaOCl)[168-169]



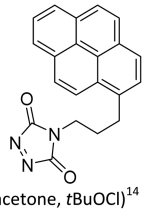
25% (EtOAc, *t*BuOCl)[183]



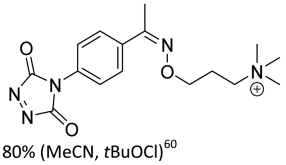
75% (EtOAc, *t*BuOCl)[41]



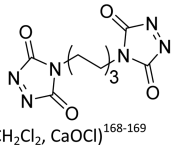
>25-49%[a] (EtOAc, *t*BuOCl)[14]
77% (EtOAc, *t*BuOCl)[85]



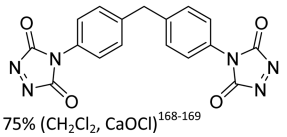
>53%[a] (acetone, *t*BuOCl)[14]



80% (MeCN, *t*BuOCl)[60]



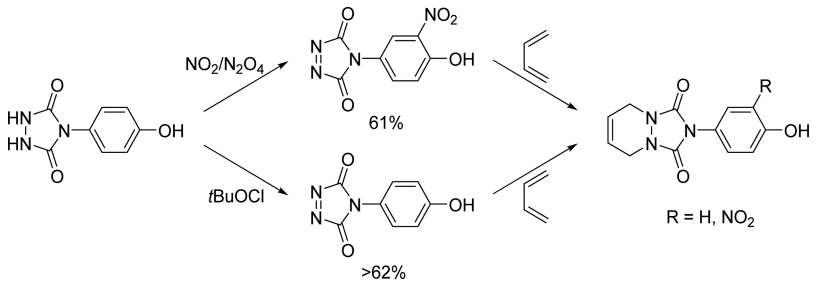
98% (CH_2Cl_2, CaOCl)[168-169]



75% (CH_2Cl_2, CaOCl)[168-169]

[a]These yields are estimates based on efficiency data of subsequent reactions found in the original references.

Scheme 23. Oxidation of 4-(4-Hydroxyphenyl)urazole, Illustrating the Advantageous Use of *t*BuOCl over Electrophilic Oxidants for Electron-Rich Aromatic Substrates[67]



neous conditions by the use of *calcium hypochlorite*,[168,169,182] which can be more conveniently removed by filtration because of its insolubility in dichloromethane.

The Cookson oxidation method, using *t*BuOCl, remains a well-established oxidation procedure that can be carried out on a large scale and in the presence of a broad range of known 4-substituents. Indeed, besides the traditional 4-fluorinated-alkyl-,[56] 4-benzyl-, and 4-aryl-substituted substrates,[13] also quaternary ammonium urazole salts[60] and the more elaborate 4-(1-pyrenyl)-,[85] 4-(methoxy-2-benzoxazolyl)-,[183] and (*S*)-4-(phenylethyl)urazole[184] components are readily converted into their corresponding triazolinediones, despite a more difficult sublimation process (Table 8). Especially the ability to oxidize urazoles containing electron-rich substituents is of advantage compared to the previously discussed more electrophilic reagents [nitrogen(IV) oxides and halogens], as was illustrated by Burgert and Stadler for the oxidation of a sensitive—4-(4-hydroxyphenyl)—urazole (Scheme 23).[67] Another notable difference with nitrogen(IV) oxides, as well as with chlorine- and bromine-mediated oxidations, is the absence of an induction period for this Cookson method.

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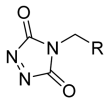
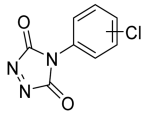
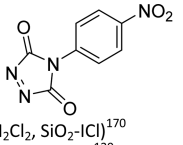
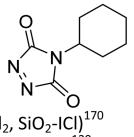
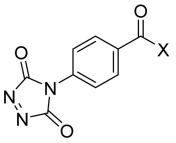
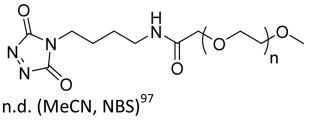
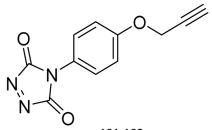
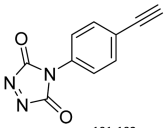
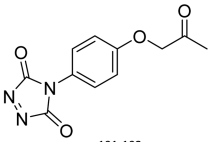
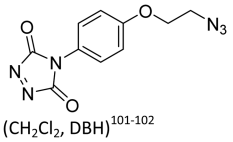
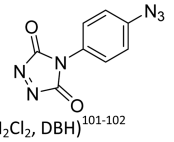
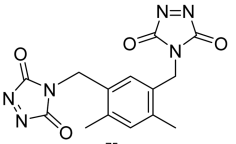
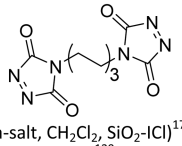
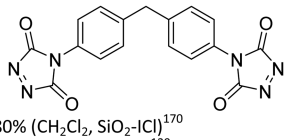
Table 9. An Overview of Reported Oxidations of Functionalized 4-Substituted Urazoles, Using in Situ Generated Halogen Species[b]

 *R = H, Et, Pr* 80-96% (CH_2Cl_2, SiO_2-ICl)[170] *R = H, Me, Et, Pr* 98-100% (CH_2Cl_2, TCICA)[120] 93-100% (CH_2Cl_2, DCH or DBH)[10] *R = Ph* 84% (CH_2Cl_2, NBS)[171]	 *4-Cl* 97% (CH_2Cl_2, SiO_2-ICl)[170] 73% (CH_2Cl_2, NBS)[171] 96% (CH_2Cl_2, TCICA)[120] 98% (CH_2Cl_2, DCH or DBH)[10] *3,4-Cl_2* 75% (CH_2Cl_2, NBS)[171] 98% (CH_2Cl_2, TCICA)[120] 89-98% (CH_2Cl_2, DCH or DBH)[10]	 95% (CH_2Cl_2, SiO_2-ICl)[170] 63% (CH_2Cl_2, TCICA)[120] 95-98% (CH_2Cl_2, DCH or DBH)[10]
 84% (CH_2Cl_2, SiO_2-ICl)[170] 99% (CH_2Cl_2, TCICA)[120] 98-99% (CH_2Cl_2, DCH or DBH)[10]	 *X = OH, NH-R (solid support)* n.d. (DMF/CH_2Cl_2, NBS)[139]	 n.d. (MeCN, NBS)[97]
 85% (CH_2Cl_2, DBH)[101-102]	 >67%[a] (CH_2Cl_2, DBH)[101-102]	 81% (CH_2Cl_2, DBH)[101-102]
 81% (CH_2Cl_2, DBH)[101-102]	 86% (CH_2Cl_2, DBH)[101-102]	 66% (CH_2Cl_2, NBS)[75]
 80% (Na-salt, CH_2Cl_2, SiO_2-ICl)[170] 90% (CH_2Cl_2, TCICA)[120] 97-99% (CH_2Cl_2, DCH or DBH)[10]	 80% (CH_2Cl_2, SiO_2-ICl)[170] 90% (CH_2Cl_2, TCICA)[120] 99-100% (CH_2Cl_2, DCH or DBH)[10]	

[a]These yields are estimates based on efficiency data of subsequent reactions found in the original references. [b]n.d.: not determined. NBS: *N*-bromosuccinimide. TCICA: trichloroisocyanuric acid. DCH: 1,3-dichloro-5,5-dimethylhydantoin. DBH: 1,3-dibromo-5,5-dimethylhydantoin.

3.2.3. In Situ Generation of Active Halogen Species. In order to avoid the use and handling of hazardous (and harsh) elemental bromine and chlorine, a number of alternative reagents and procedures have been developed that rely on the slow generation of halogen-based oxidants. Moreover, a heterogeneous character of an oxidation procedure can be achieved by simply using a solid-supported reagent. This usually gives shorter reaction times and a more efficient removal of salts by filtration, as exemplified by Karami et al., who reported a convenient oxidation procedure with *silica-supported iodinemonochloride (ICl)*.[170]

As a well-known alternative reagent for bromine, *N-bromosuccinimide (NBS)* has also been used to oxidize a variety of urazole derivatives,[171,182,185] with efficiencies for (chlorinated) phenyl and benzyl substrates comparable to those obtained by the Stickler (N_2O_4) and Cookson (*t*BuOCl) methods. The similarity between these methods was also illustrated by the oxidation of urazole-functionalized solid supports[139] and divalent TAD reagents (Table 9).[75] Furthermore, NBS was shown to be a suitable oxidant for poly(ethylene glycol) bearing a urazole end group.[97] However, since an extensive extraction workup procedure is generally needed to remove the resulting succinimide oxidation byproduct, this NBS procedure is less suitable for water-sensitive TAD compounds. Alternatively, this workup can be omitted by using the crude reaction mixture for further reactions.[97,103]

More recently, Zolfigol, Mallakpour, and co-workers, searched for heterogeneous halogen-generating reagents that can be easily used in excess and allow a straightforward workup procedure by simple filtration and subsequent evaporation of the resulting reaction mixture. Thus, *trichloroisocyanuric acid* was found to be a convenient and cheap in situ source for the active chlorine species capable of converting a wide variety of urazoles to the triazolinedione counterparts in excellent yields

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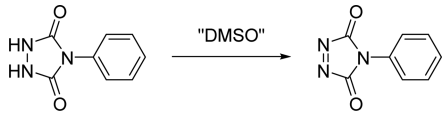
Table 10. Overview of the Different Chalcogen-Mediated Homogeneous Oxidation Procedures



oxidant	conditions[a] (time, temp)	% yield	ref
trichloroacetyl isocyanate	DMSO (15 min, RT)	98[b] (~20[c])	187
p-toluenesulfonyl isocyanate	DMSO (15 min, RT)	98[b]	187
benzoyl isocyanate	DMSO (15 min, RT)	88[b]	187
phenyl isocyanate	DMSO (15 min, RT)	< 10[b]	187
n-butyl isocyanate	DMSO (15 min, RT)	< 10[b]	187
DCC−H_3PO_4	DMSO (30 min; nr)	33[b]	187
Ac_2O	DMSO (2 h; nr)	86[b]	187
P_2O_5	DMSO (10 min; nr)	-[d]	187
benzeneseleninic anhydride	EtOAc (10 min, RT)	59−62[b]	14
	EtOAc (30 min, RT)	45−47[b]	14
	THF (3−10 min, RT)	72−78[e]	188, 189
	THF (2 h, RT)	96[e]	181
phenylseleninic acid	THF (2 h, RT)	98[e]	181
diphenylselenoxide	nr	81[e]	181
di(*p*-methoxyphenyl)telluroxide	nr	98[e]	181

[a]nr: not reported. RT: room temperature. [b]Determined spectroscopically. [c]Yield after sublimation. [d]Not reported due to unknown experimental uncertainty. [e]Yield of the Diels−Alder adduct after preparative layer chromatography (plc).

in both dichloromethane as well as under solvent-free conditions (Table 7).[120] This method was found to be exceptionally mild, as it can be used for notoriously sensitive urazole substrates, such as the hydrochloride salt of 4-(4-aminophenyl)urazole.

Zolfigol, Mallakpour, and co-workers reported *1,3-dichloro-*[10] and *1,3-dibromo-5,5-dimethylhydantoin*[10] as suitable oxidants for a wide variety of urazoles, including divalent ones (Table 9). 1,3-Dibromo-5,5-dimethylhydantoin (DBH) in dichloromethane proved to be the best oxidant in terms of isolated yield. The workup can be further facilitated by running the reaction in the presence of silica-supported sulfuric acid to absorb hydantoin byproducts.[10,101] Quite recently, the mildness of this oxidation procedure was demonstrated by the Barbas group in the synthesis of several PhTAD-derived labeling reagents for bioconjugation purposes.[101,102] Among these 4-phenylurazole precursors, a variety of functionalities, such as propargyl ethers, azides, and ketones proved to be highly compatible with the mild 1,3-dibromo-5,5-dimethylhydantoin-mediated oxidation method (Table 9).

In related work toward heterogeneous oxidation procedures, Zolfigol, Mallakpour, and co-workers also reported on the use of *trichloromelamine*,[172] *N,N,2,3,4,5,6-heptachloroaniline*,[173] and *1,3,4,6-tetrachloro-3a,6a-diphenylglycoluril (iodogen)*[174] as a source for active chlorine species and *N,N,N′,N′-tetrabromobenzene-1,3-disulfonamide*,[172] *hexamethylenetetramine−bromine*,[90] *1,2-(dipyridiniumditribromide)ethane*,[90] and *tribromoisocyanuric acid*[90] to generate active bromine species in situ.[90] The tetrameric complex of *1,4-diazabicyclo[2.2.2]octane* and *bromine (DABCO−Br)*[90] has been found to be a particularly useful heterogeneous reagent that does not require the addition of silica gel to remove excess reagents and byproducts. Besides the mild conversion of low molecular weight (divalent) urazole components, this bromine complex was also found to be suitable for the heterogeneous oxidation of polymers bearing urazole end groups, which has very recently been demonstrated by Du Prez and co-workers.[65]

3.2.4. Catalytic Procedures Involving Generation of Active Halogen Species. The exceptionally fast reaction of urazoles with active chlorine- or bromine-type reagents has prompted investigations into catalytic procedures using a simple and more convenient stoichiometric oxidant. As noted above, urazoles can be oxidized to some extent by air in the presence of chlorine gas.[14] A more convenient approach uses a catalytic amount of a halide salt in combination with an inorganic oxidant, which results in an in situ formation of active halogen species such as transient dihalogens (X_2) or halogen radicals (X°).[15] These active species are responsible for the oxidation of urazoles toward triazolinediones with the concomitant formation of the corresponding halide ions (X^-), which are then again oxidized by the stoichiometric oxidant.

A screening of various insoluble (heterogeneous) reagents for the in situ oxidation of halide ions revealed *periodic acid and oxone* as low-cost and convenient reagents for bromine- and chlorine-catalyzed urazole oxidation. Several salts have been explored as halide source, but *potassium bromide* (20 mol % per mole of urazole moiety) was shown to be more efficient than KCl and NaCl.[15,175] Similarly, an $AlCl_3$-catalyzed oxidation of urazoles has been reported using *benzyltriphenylphosphonium peroxymonosulfate* as terminal oxidant,[177] as well as a mixture of *silica chloride and oxone*.[176] Also *benzyltriphenylphosphonium chlorate* was used as a mild and stable reagent in the presence of a catalytic amount of $AlCl_3$.[178] This oxidant can be regarded as a nonaqueous substitute of sodium perchlorate (cf. section 3.2.2) that shows good solubility in organic solvents. Moreover, the homogeneous reaction conditions enable fast reaction times (Table 7). Solvent-free oxidation procedures were carried out successfully with this latter oxidant as well.

Although hydrogen peroxide was found to be unable to oxidize urazoles to triazolinediones, even in the presence of sulfuric and phosphoric acid,[173] the combination of *hydrochloric acid* and *hydrogen peroxide* can generate active halogen species in situ to oxidize urazoles. Likewise, the use of hydrogen chloride in combination with a *urea−hydrogen peroxide (UHP)*

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complex gives a rapid reaction with urazoles, but the resulting TAD compounds immediately decompose under these conditions. The use of *chloride salts*, such as $AlCl_3$, $ZrCl_4$, and WCl_6, in the presence of wet silica-supported UHP gave markedly better results.[173] However, this procedure shows a remarkable substrate specificity, wherein 4-alkylurazoles are readily oxidized to the corresponding TADs, whereas 4-arylurazole derivatives are unaffected. Besides UHP, also *1,4-diazabicyclo[2.2.2]octane−1,4-bis(oxide)-bis(hydrogen peroxide) (DABCO−DNOP)*[179] and *poly(vinylpyrrolidone)-supported* H_2O_2[180] methods were developed later on, which, in contrast to UHP, are also capable of oxidizing 4-aryl-substituted analogues.

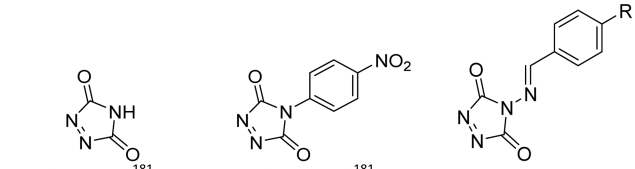
3.3. Activated DMSO- and Seleninic Acid-Mediated Oxidations

A third group of oxidants for urazoles comprises the well-known "activated DMSO"-type oxidations, which are actually part of the more general classification of oxidation methods using chalcogen-containing oxoacid compounds. The rapid oxidation of urazoles by activated DMSO was serendipitously discovered in the reaction of 4-phenylurazole with *trichloroacetyl isocyanate in DMSO*, which instantaneously gave a bright red color.[186,187] After optimization of the procedure and careful control of the reaction conditions—to avoid overheating—4-phenyltriazolinedione was obtained with an excellent yield of 98%, as determined by spectrophotometry. However, isolation by sublimation only afforded 20% of pure 4-PhTAD. Thus, this method is mostly suited as a mild in situ generation of triazolinediones, and it has been used to generate the highly labile 4-[4-(dimethylamino)phenyl]-TAD reagent in neutral form.[135] Moore et al. found that a wide range of isocyanates can be used, but they need to be activated by a strong electron-withdrawing substituent (Table 10). Moore's method was also compared to other known activating systems for DMSO-mediated oxidations, such as DCC−H_3PO_4, Ac_2O, and P_2O_5, but these were shown to be less effective.

Shortly following Moore's report on DMSO-mediated oxidation of urazoles, Barton and co-workers found another very mild chalcogen-mediated oxidation procedure. This method is based on their work for the mild synthesis of ketones from N-containing precursors with *benzeneseleninic anhydride* in dry THF.[190] Among the N-substrates, 4-phenylurazole was investigated in an in situ oxidation experiment, giving over 78% of ergosterol-trapped PhTAD in less than 10 min.[188,189] The best results were obtained when the urazole is oxidized in the presence of a complementary reaction partner, since the formed PhTAD tends to be gradually lost over time in the oxidation mixture.[7,14,191,192] The chemoselectivity of this oxidation method toward the normal reaction partners of TAD compounds, i.e. dienes and alkenes, is quite exceptional. Generally, oxidations of urazoles to triazolinediones cannot be carried out in the presence of a diene reaction partner.[193] This unique feature of the oxidation method encouraged Barton to optimize the benzeneseleninic anhydride procedure, giving nearly quantitative conversions of (substituted) 4-phenylurazoles with only $^1/_3$ equiv of oxidant (Tables 10 and 11).[181] *Phenylseleninic acid* itself was also found to give in situ triazolinediones in excellent yield, as well as *diphenyl selenoxide* and *di(p-methoxyphenyl)telluroxide*.

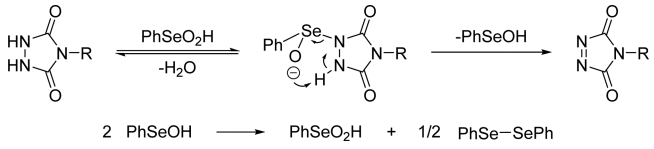
A plausible mechanism for the oxidation of urazoles with benzeneseleninic anhydride can be suggested on the basis of the unusual substoichiometric amounts of the anhydride (1/3 equiv) and seleninic acid (2/3 equiv) that are required. Because of the disproportionation of selenenic acid (R−Se−OH) to seleninic acid (R−SeO_2H) and a diselenide, 1 equiv of seleninic anhydride will ultimately generate more than three "active" seleninic acids (Scheme 24).[194]

Table 11. Overview of the Different Chalcogen-Mediated Homogeneous Oxidation Procedures[a]



[a]Yields reported are those of the trapped Diels−Alder adduct after isolation via preparative layer chromatography. BSA: benzeneseleninic anhydride. PSA: phenylseleninic acid.

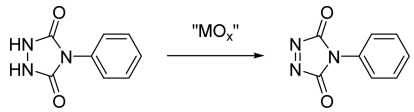
Scheme 24. Plausible Mechanism for Benzeneseleninic Anhydride Oxidation of Urazoles to Triazolinediones



3.4. Metal Ion/Metal Oxide-Mediated Oxidation

Various reducing metal ions can also be used as direct oxidants for the generation of triazolinedione compounds from urazoles (Table 12). Again, Thiele initially encountered this type of transformation when he treated a 4-phenylurazole mixture in diluted sulfuric acid with 2 equiv of *lead(II) oxide*.[3] Although he reported this oxidation method to be the best one of those investigated, no pure 4-phenyltriazolinedione could be isolated.

Table 12. Overview of the Reported Oxidation Methods of 4-Phenylurazole with Metal Ion/Metal Oxides



oxidant	conditions[a] (time, temp)	% yield[b]	ref
PbO	dil H_2SO_4 (nr, nr)	nd	3
(powdered) $BaMnO_4$	EtOAc (2.5 min, RT, dark)	51−100[c]	14
MnO_2	EtOAc (10 min, RT)	54[c]	14
AgO_2	EtOAc (15 min, RT)	0	14
	EtOAc (18 h, RT)	78[c]	14
$KMnO_4$	neat (15 min, RT)	74	119
$KMnO_4$/alumina	neat (8 min, RT)	90	119
$K_2Cr_2O_7/AlCl_3$	neat (3 min, RT)	95[d]	196
CrO_2 (Magtrieve)	ionic liq (90 min, RT)	96	197
$Pb(OAc)_4$	CH_2Cl_2 (1−2 h, 0−5 °C)	>81[e]	198
Ph_3BiCO_3	CH_2Cl_2 (2 h, RT)	>84[e]	199

[a]nr: not reported. RT: room temperature. [b]nd: not determined. [c]Determined spectroscopically. [d]After sublimation. [e]These yields are estimates based on efficiency data of subsequent reactions found in the original references.

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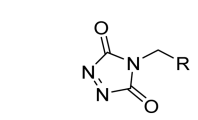
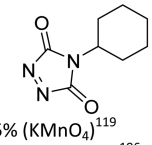
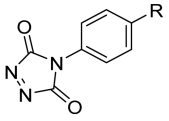
Table 13. Representation of Compatible Functionalities with Metal Ion/Metal Oxide-Mediated Oxidation Procedures of 4-Substituted Urazole Components[b]



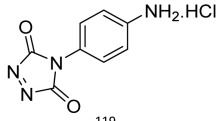
R = H
> 91%[a] (CH_2Cl_2, Ph_3BiCO_3)[199]
R = Pr
75-80% ($KMnO_4$)[119]
94% (ionic liq., CrO_2)[197]
R = Me, Et
93-95% ($K_2Cr_2O_7/AlCl_3$)[196]



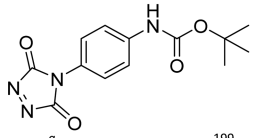
80-85% ($KMnO_4$)[119]
98% ($K_2Cr_2O_7/AlCl_3$)[196]



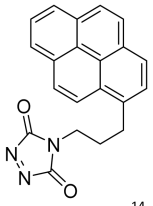
R = Cl, NO_2
70-86% ($KMnO_4$)[119]
90% ($K_2Cr_2O_7/AlCl_3$)[196]
R = Cl
91% (ionic liq., CrO_2)[197]
R = MeO
> 90%[a] (CH_2Cl_2, $Pb(OAc)_4$)[53]



70% ($KMnO_4$)[119]
80% ($KMnO_4/Al_2O_3$)[119]



> 84%[a] (CH_2Cl_2, Ph_3BiCO_3)[199]



94% (EtOAc, $BaMnO_4$)[14]

[a]These yields are estimates based on efficiency data of subsequent reactions found in the original references. [b]n.d.: not determined.

Only one other claim, over a century later, can be found of a lead(IV) oxide-mediated urazole oxidation.[195] Most likely, the presence of redox-active metal ions is actually expected to contribute to a rapid decomposition of TAD compounds, which explains why these methods are much less popular than the preceding three types (sections 3.1−3.3).

Read and Richardson briefly explored metal ion or metal oxide oxidants for a sensitive, fluorescent pyrenyl-TAD compound.[14] They found finely powdered, high-quality *barium manganate* in ethyl acetate suspension to be of particular use in this case. A number of other metal oxides were tested as well, including *silver(I) oxide* and *manganese(II) oxide*,[182] but these showed much lower efficiencies with lower isolated yields (Table 12). Urazoles were found to be inert to suspensions of silver(I) carbonate. In later work, also *potassium permanganate* was reported to be a relative fast oxidant, giving moderate yields for some standard triazolinediones.[119] However, when carried out in the presence of an alumina support, higher yields can be obtained in shortened reaction times. A comparable system based on *potassium dichromate* gave similar results, although in this case an equimolar amount of $AlCl_3$ is required to activate the oxidation process.[196] Finally, *chromium(IV) oxide* has also been explored as a urazole oxidant, the waste products of which can be removed by magnetically assisted decantation.[197] Although several metal oxides are clearly capable of converting urazoles to TADs under mild and heterogeneous conditions (Table 13), much less is known about substrate scope.

The use of *lead tetraacetate* ($PbOAc_4$) to oxidize urazoles is considered as a modified procedure of the method of Clement for the synthesis of phtalazine-1,4-diones, a six-membered analogue of TAD.[200] In this modification, developed by Gillis and Hagarty, $Pb(OAc)_4$ was shown to oxidize a cold suspension of 4-phenylurazole in dichloromethane to its triazolinedione counterpart.[198] Prior to the addition of the cold oxidant solution, a diene was added to the reaction mixture to trap the formed PhTAD in situ. To date, no isolation of triazolinediones have been reported when applying this oxidant, although a wide variety of 4-substituted urazoles can be oxidized efficiently to TAD compounds, which are trapped in situ.[53] Although lead tetraacetate is a quite chemoselective oxidant, it has been known to give rise to overoxidation hydrolysis products.[200]

Another effective in situ metal-based oxidant is *triphenylbismuth carbonate* (Ph_3BiCO_3).[199] This mild reagent also allows oxidation of urazoles in the presence of dienes. The wide scope of this procedure was demonstrated by carrying out the oxidation reaction in the presence of different functionalities, such as alcohols, esters, Boc-protected amines, and ethers, present on both the diene as well as on the urazole substrate (Table 13). Secondary amines are also compatible with this procedure, but primary amines needed to be protected because they are known substrates for the bismuth complex. Besides, the presence of primary amines is known to have a detrimental effect on triazolinedione stability (vide infra). Although high yields are obtained in a moderate time window, the removal of triphenylbismuth-related byproducts makes purification of the resulting TAD adducts difficult, prohibiting "click chemistry"-type applications.[201]

A catalytic version of a metal-mediated urazole oxidation has been developed, using *tetralin hydroperoxide* as stoichiometric oxidant in the presence of a trace amount of vanadyl acetylacetonate [$VO(acac)_2$].[14] The peroxide generates a vanadium(V) species that effects the oxidation reaction of urazoles. However, this method is not very practical, as only 15% conversion to the triazolinedione was obtained after 18 h, especially when compared to the halogen-mediated catalytic methods (vide supra).

The swift reaction between reducing metal ions and urazoles is sometimes exploited to quantify rare metal ions in samples, such as *tantalium(III) ions*.[202,203] The rapid oxidation reaction of urazoles induced by Tl(III) species in aqueous medium actually gives a quantitative colorimetric test for this metal by measuring the characteristic triazolinedione absorbance, similar to the standard phorensic detection of traces of blood with solutions of luminol.

3.5. Electrochemical Oxidation

As with many redox reactions, urazole oxidation can also be achieved by using an *electrochemical oxidation*. From a

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fundamental point of view, these methods represent the ultimate traceless method. However, so far, practical applications of electrochemical methods are very limited. For a detailed discussion of these methods, we would like to point out the work of Alstanei et al.,[204] who reported on the properties of 4-methyl- and 4-phenyl-substituted urazole−TAD redox systems and characterized the intermediate species involved by coupled electron paramagnetic resonance (ESR) and visible-light absorption spectrometry.

Wamhoff and Kunz were the first to report on the straightforward preparative electrolysis of an unsubstituted urazole suspension at a platina electrode to give low yields of the unsubstituted 4*H*-triazolinedione.[205] With the same method, the synthesis of 4-methyl-, 4-phenyl-, (3,)4-(di)-chlorophenyl- as well as hexamethylene diisocyanate-based triazolinediones has been claimed. The method has been used to prepare solutions of TAD reagents and for the in situ oxidation in the presence of a suitable reaction partner for the TAD compounds (dienes).

Bausch and David[68] studied urazoles in cyclovoltammetry (CV) experiments. Reduction potentials of a variety of 4-substituted TAD components were determined by CV and rationalized with regard to the pK_a values of the corresponding parent urazoles.

In a unique kinetic trapping experiment, the electrosynthesis of TADs was exploited by Lorans et al. as a tool to investigate the decomposition products of ferrocenenium cations.[206] The experimental setup included an elegant flow-cell anodic co-oxidation of a mixture of ferrocene and 4-phenylurazole at a graphite felt porous electrode. The decomposition of ferrocenium cationic species into the cyclopentadiene ligand (minor) and cyclopentadien-5-ol (major) products was monitored by efficiently trapping these transient products by the controlled electrochemical cogeneration of TAD compounds, allowing for a complete characterization of the resulting Diels−Alder adducts. Successful in situ electrochemical oxidations of 4-methyl-, 4-phenyl-, and 4-*m*-tolylurazole were also performed in methanol and even in aqueous solution.[207] The aqueous method, however, suffered from solubility issues of both the urazole substrates as well as the diene reaction partners.

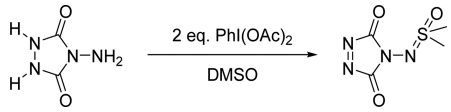
Recently, attention to the electrochemical generation of triazolinediones from their urazole precursor was reinvigorated by Varmaghani, Mallakpour and co-workers.[208] The electrochemical oxidation of 4-*n*-propyl- and 4-*n*-butyl-substituted urazoles at a glassy carbon electrode in an aqueous buffer solution was investigated by means of CV, showing a quasi-reversible redox process under controlled conditions. A minor side reaction, an oxidative ring cleavage involving addition of water at one of the TAD carbonyl carbons, was later elucidated by CV experiments of 4-phenylurazole as a model component.[209] Oxidative ring cleavage is faster in electron-poor TAD reagents. In situ trapping of electrochemically generated TAD compounds can be effected by addition of 4-arylsulfinic acids as a nucleophile. In this way, the electrogenerated TADs could be trapped via a nucleophilic addition of the sulfur component onto the generated electron deficient azo moiety, giving 4-arylsulfonamides in high yield (80−90%), thus avoiding or minimizing oxidative ring cleavage.[210]

3.6. Miscellaneous Oxidation Methods

The oxidation of urazoles can be performed with *2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)* in reasonable yield.[14] This method is quite mild and selective but is not very practical, because of long reaction times (65% yield after 18 h).

Triazolinediones can be readily obtained from the corresponding urazoles by treatment with typical hypervalent iodine compounds. These mild and nonacidic reagents were first introduced by Moriarty et al., who used *iodobenzene diacetate (IBD)* and *pentafluoroiodobenzene bistrifluoroacetate* to synthesize methyl- and phenyl-substituted triazolinediones.[211] The reaction proceeds readily at room temperature within 15 min and gives a homogeneous reaction mixture with mostly inert byproducts. After evaporation, the TAD compounds can be crystallized from hexane in high yields. An IBD oxidation was further reported by Shimuzu and co-workers in the oxidation of urazoles substituted with a fluorescent group.[63,93] Meehan and Little used 2 equiv of IBD to oxidize the sensitive 4-aminourazole via a concomitant oxidative deactivation of the amine (Scheme 25).[212] This procedure gives the interesting 4-

Scheme 25. Hypervalent Iodine Oxidation of 4-Aminourazole toward the Highly Labile S-TAD



S,S-dimethylsulfoxyimino-TAD ("S-TAD"), a bifunctional TAD reagent that cannot be isolated but can be directly used in subsequent reactions.

Next to hypervalent iodine, chlorate has also been used to oxidize urazoles; i.e., a combination of *potassium chlorate* ($KClO_3$) and silica sulfuric acid yielded triazolinediones under mild and heterogeneous conditions.[176]

3.7. Concluding Remarks about Urazole Oxidation Procedures

Despite the vast number of methods to convert urazoles to their triazolinedione counterparts, the majority of oxidants have only been reported in small-scale proof-of-concept studies on a limited substrate scope. Consequently, this concluding section will provide the reader with some informative guidelines to quickly identify a suitable oxidation protocol that also has a proven track record in applied research.

The most widely applied procedures to generate TADs are based on N-containing oxidants. In early work, nitric acid was used as a general large-scale oxidant (i.e., a few tens of grams) for nonfunctional urazole components. However, only moderate yields are obtained under these strongly acidic and oxidative conditions, which also have a severe impact on the stability of the generated TADs. Later, gaseous NO_2/N_2O_4 quickly gained popularity as a heterogeneous acid-free alternative to effect urazole oxidations. Consequently, this protocol can nowadays be regarded as the method of choice to convert a wide range of (functional) urazole substrates in a traceless manner. Nevertheless, practical and safety considerations must be made when handling this gaseous and toxic reagent, especially in a lab environment.

As a result of possible competitive electrophilic aromatic substitution, N_2O_4-based oxidation methods should not be used in the presence of electron-rich aromatic substrates (see Scheme 23) or other nucleophilic species. *t*BuOCl is a milder oxidant that does not affect nucleophilic arenes, and was shown to be a valid alternative on a multiple gram scale.

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In order to greatly facilitate the workup, heterogeneous oxidants such as NO_2/N_2O_4 are highly preferred from a practical point of view. Nevertheless, the laborious handling of this toxic and gaseous reagent led to the development of solid-based heterogeneous systems. For example, silica-supported nitric acid can be used as a heterogeneous N(IV) oxide alternative for oxidations on a scale of hundreds of milligrams, but it has the ability to oxidize a broad substrate scope. DABCO−Br, on the other hand, generates a mild active halogen species in situ and is typically used on a multigram scale. Therefore, both methods represent a viable alternative to NO_2/N_2O_4 or *t*BuOCl for lab-scale oxidations.

Finally, for highly sensitive (functionalized) urazoles, in situ oxidation in the presence of or just prior to adding the TAD coupling partner is recommended. Here, the choice for a mild oxidant such as NBS or DBH (section 3.2.3) that is compatible with the present functions can also be required, and isolation of the desired TAD reagents can prove very difficult. Nevertheless, such "one-pot" approaches can be very efficient for many applications (vide infra).

4. OVERVIEW OF THE REACTIVITY OF TRIAZOLINEDIONES

TAD reagents have an overall resemblance in chemical structure with the more widely known maleimides (Figure 9),

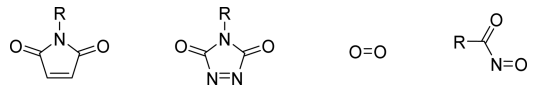


Figure 9. TAD reagents and related reactive compounds: maleimides, triazolinediones, singlet oxygen, and nitrosocarbonyls.

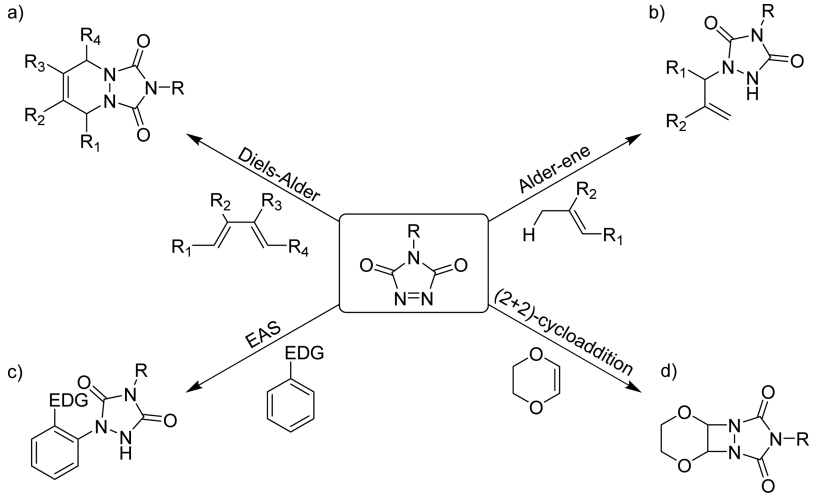
which are a well-established class of important synthetic tools for a wide range of applications, including click chemistry.[213−215] Indeed, also their modes of reactivity show some important similarities. Nevertheless, TAD compounds react much faster than maleimides and can also participate in a larger variety of pericyclic reactions with a much wider range of substrates and with simple olefins, in particular.[9,70,216] TAD reagents also have a higher intrinsic thermodynamic driving force than maleimides. Thus, whereas many maleimide-based conjugation reactions are reversible processes, most TAD-based reactions are completely irreversible. An important difference is the relative lack of (controlled) reactivity that TAD reagents show toward typical nucleophiles, such as amines and thiols.

In terms of reactivity, TAD compounds have often been compared with singlet oxygen (Figure 9).[217−219] Indeed, both singlet oxygen and TADs show a great preference for Diels−Alder, ene-type, and (2 + 2)-cycloaddition reactions for more or less the same range of substrates (electron-rich or nonpolarized olefins). This similarity in reactivity can also be related to a correspondence in the particular arrangement and energies of the frontier orbitals (HOMO and LUMO), with a filled and an empty π-type orbital of very similar energy.[220]

In essence, TAD and singlet oxygen have a strong preference for orbital-controlled reactions and favor delocalized π-cloud type substrates over typical localized or ionic nucleophiles. A major difference in terms of practicality between singlet oxygen and TAD reagents, however, is their lifetime. Many TAD compounds can be isolated and stored for prolonged periods (vide supra), while singlet oxygen only has a half-life of a few microseconds in most organic solvents. Moreover, TAD reagents offer the possibility to introduce a wide range of functionality (R-groups), instead of just effecting oxygenations. A reagent that is—in more than one way—a kind of hybrid of TADs and singlet oxygen, are the nitrosocarbonyl compounds (Figure 9).[220,221] These also have very limited lifetimes and need to be generated in situ just like singlet oxygen, but they can be used to introduce different substituents. Recently, nitroso compounds have received a renewed interest as versatile synthetic tools for various applications.[222]

The preferred reaction partners and reactivity modes of TAD reagents are outlined in Scheme 26. Each of these reaction types will be briefly discussed below, in dedicated sections (sections 4.1−4.4).[18] Apart from these very fast conjugation reactions, in which carbon−nitrogen bonds are formed, TAD reagents can engage in a wide range of other reactions. These secondary reaction modes are often much less selective but also much slower than the ones shown in Scheme 26. Nevertheless,

Scheme 26. Four Most Relevant Reactions Involving TAD Molecules: (a) Diels−Alder Reaction, (b) Alder−Ene Reaction, (c) Electrophilic Aromatic Substitution (EAS) with an Activated Aromatic System,[a] and (d) (2 + 2)-Cycloaddition



[a]EDG = electron-donating group.

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these reactions can be observed as undesired side reactions and will also be briefly discussed in section 4.5. For a more detailed overview of the reactivity of TAD molecules, we refer the reader to previous review articles.[7,12,18−20]

4.1. Diels−Alder Reaction

The original discovery of the Diels−Alder (DA) reaction is actually closely linked to the chemistry of azodicarbonyl compounds (vide supra, Scheme 1). Since its discovery, the DA reaction has been developed into one of the most efficient and widely applicable organic bond-forming reactions. The DA reaction allows the introduction of two new carbon−carbon σ-bonds and up to four new stereocenters,[223] with very pronounced and predictable levels of chemo-, stereo-, and regioselectivity. Generally, the reaction requires elevated temperatures, but many DA reactions can also be effected at low temperature by using simple catalysts.[224] The DA reaction is a highly atom economical process, and at least in theory, the bond-forming process can be reversed, giving a retro-Diels−Alder (rDA) reaction that releases the original reaction partners.[225] This dynamic feature of the DA/rDA reaction has been used in a range of interesting applications in organic synthesis, such as temporary protection of dienes,[151,226] scavenging of dienes from complex reaction mixtures,[227] and capturing and releasing transient reaction intermediates.[228] In polymer chemistry, the rDA reaction has been used to design covalently adaptable materials that show interesting properties, such as healing[229] and remendability.[230]

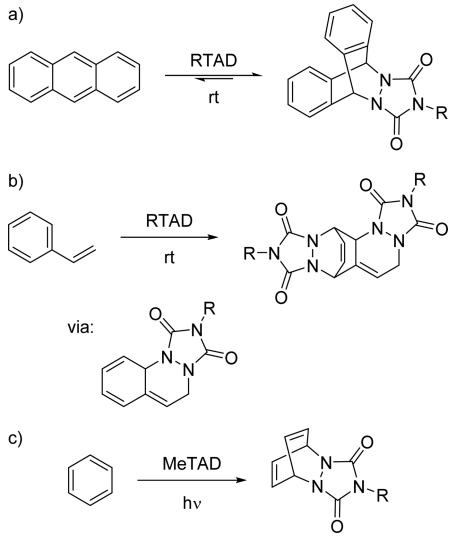
The DA reaction has an enormous substrate scope, but TAD compounds were relatively late entries to the Diels−Alder toolbox. However, since Cookson's original report of an instantaneous reaction between PhTAD and cyclopentadiene at −78 °C,[4] TADs have become an intensively studied class of DA substrates, acquiring the reputation of being the fastest dienophile that can be isolated.[18,220] The exceptional reactivity of triazolinediones can be appreciated by the fact that their reaction with "good" Diels−Alder dienes is almost instantaneous and quantitative even at quite low temperatures (−78 to −50 °C, e.g., Scheme 1).

Reactions with less reactive dienes, such as anthracene or styrene, still proceed smoothly at room temperature (Scheme 27a,b). The reaction between anthracene and TAD is very fast at room temperature, but it is also one of the few DA reactions that shows reversibility at room temperature,[70] related to the aromatic stability of the diene. In the case of styrene, which does normally not react with dienophiles even at elevated temperatures, a 1:2 adduct is quantitatively formed via a highly reactive diene intermediate that cannot be isolated (Scheme 27b).[5] Reaction of styrene with just 1 equiv of a TAD compound thus leads to a clean conversion of half of the styrene into the bis-adduct with TAD. Sheridan and co-workers found that while benzene, naphtalene, and phenantrene do not readily react with TAD compounds, Diels−Alder adducts of these can be obtained by a photochemical Diels−Alder reaction[231−235] or with the aid of an acid catalyst.[236]

4.2. Alder−Ene Reaction

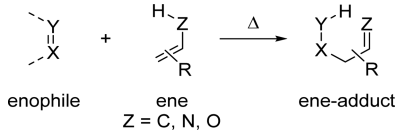
The Alder−Ene (AE) reaction (also referred to as ene reaction) can be defined as the reaction of an alkene bearing an allylic hydrogen (the ene) with a double bond (*enophile*), and it was first described by Alder et al. in 1943 (Scheme 28).[237] During Alder's Nobel lecture in 1950 it was classified as an "*indirect substitution addition*" or "*ene synthesis*".[238] It belongs to a general class of pericyclic reactions and comprises the migration of a σ-bonded hydrogen atom, the formation of a new C−C σ-bond at the expense of a C−C π-bond, and the displacement of the initial π-bond.[239]

Scheme 27. (a) 1:1 Adduct of TAD and Anthracene,[a] (b) 1:2 Adduct of TAD and Styrene,[b] and (c) Photochemical Adduct of Benzene and TAD



[a]Reversible at room temperature. [b]TAD and styrene react to form a diene that reacts in situ with another TAD moiety.

Scheme 28. General Reaction Scheme of an Alder−Ene Reaction



Despite the great potential in organic synthesis of the ene reaction,[240] the applications of the AE reaction have been rather limited as compared to the DA reaction. One reason for this is the unfavorable activation entropy and enthalpy, related to the highly ordered transition state with relatively poor orbital overlap, which results in much slower reaction rates.[241] Indeed, the AE reaction often requires extreme conditions (high pressure and temperature close to or above 200 °C), especially in the case of intermolecular ene reactions. The use of Lewis acid catalysts can lead to much enhanced reaction rates at lower temperature, but the issue of regioselectivity, in the common case where more than one allylic hydrogen is present in the ene substrate, has limited such methods mostly to intramolecular applications (ene cyclizations).[242] The introduction of highly reactive enophiles such as TAD compounds, however, has opened the door to quite reliable and even selective intermolecular ene reactions (Scheme 29). Just a few years following Cookson's isolation of TAD compounds, its use as a potent enophile was found in room temperature reactions with simple alkene substrates, giving *N*-allylurazole adducts in quantitative yields.[6] A number of more recent illustrative TAD-based AE reactions are shown in Scheme 30.

The mechanism of the TAD-based ene reactions has been a matter of some debate in the literature, where a six-electron concerted pericyclic process has been discarded in favor of a stepwise route involving the formation of the zwitterion

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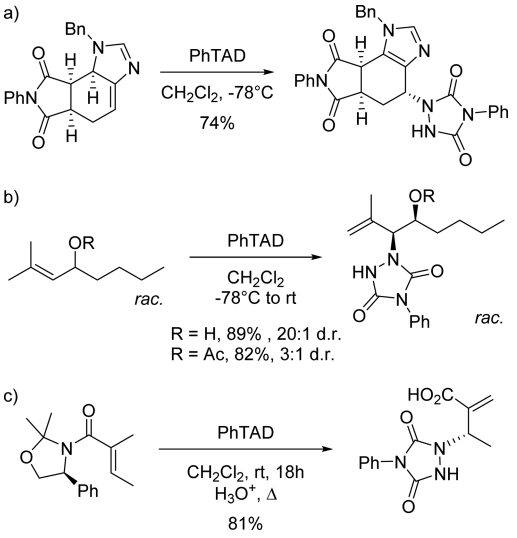
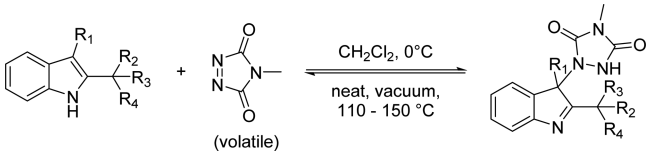
Scheme 29. (a) DA Cycloadducts of 4-Vinylimidazoles Are Viable Substrates for High-Yielding and Highly Diastereoselective Ene Reactions with TAD,[243] (b) Regio- and Diastereoselective Ene Reaction of 4-Phenyl-TAD with Chiral Allylic Alcohols,[244] and (c) Reaction between 2,2-Dimethyloxazolidines and PhTAD[245]



aziridinium imide (AI, Scheme 30).[246,247] The exact mechanism for subsequent hydrogen transfer is unclear, but studies by Squillacote and co-workers suggest the involvement of an open form polarized diradical (PD) intermediate and also that this mechanism might actually be solvent-dependent.[248,249]

Because of the (very) high activation barriers for typical ene reactions, it is not unexpected that the retro-Alder−ene (rAE) reaction has only rarely been observed in comparison to the retro-DA reaction.[240,250] Most of the described thermoreversible AE reactions require pyrolysis-type conditions and are thus of limited value in synthetic applications.[240,251] On the basis of the much higher kinetic reactivity of TAD compounds as enophiles, one might expect to find ene reactions with these reagents that can be reversible in reasonable temperature intervals. However, so far only one example has been reported in the literature. Baran et al. described in 2003 the possibility to thermoreversibly protect an indole functionality.[217] Indoles readily and selectively form ene adducts, even at 0 °C. By simply heating the adduct, a rAE reaction will take place, which allows removal of a volatile TAD reagent and gives the indole moiety (Scheme 31).

Scheme 31. 2,3-π-Bond of Certain Indoles Can Be Protected via the Ene Reaction with a TAD Compound[a]

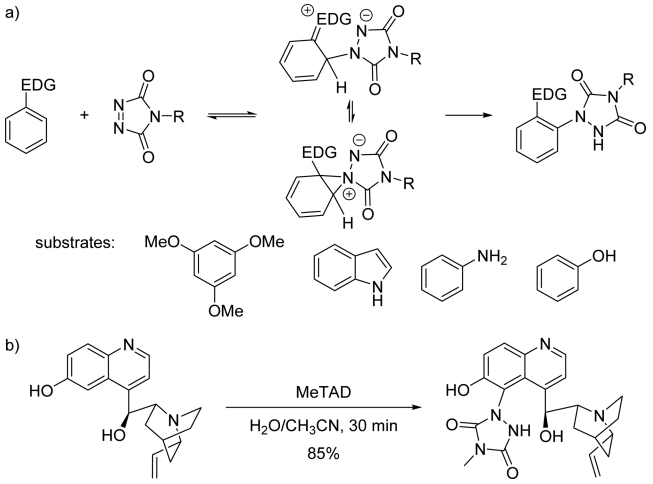


[a]Heating the adduct under vacuum allows for deprotection by removal of the volatile MeTAD.

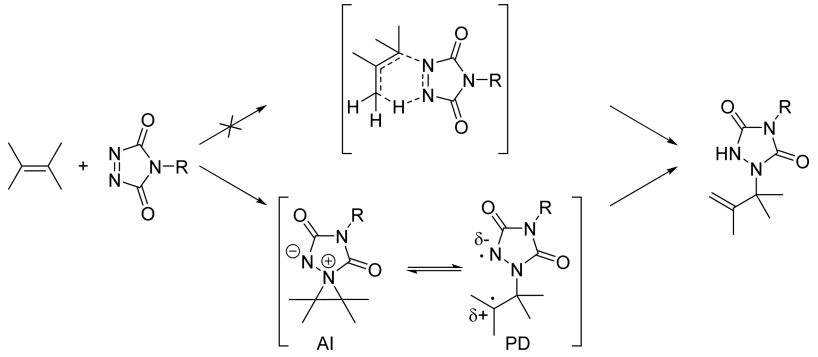
4.3. Electrophilic Aromatic Substitution

In electrophilic aromatic substitution (EAS) reactions, TAD compounds can act as suitable electrophiles for highly activated aryl systems. Because TAD compounds are neutral, the expected carbocationic intermediates are actually zwitterions that can also exist as an aziridinium imide (AI) intermediate (Scheme 32a). This initial addition intermediate needs to

Scheme 32. (a) Electrophilic Aromatic Substitution between an Electron-Enriched Aromatic System and a TAD Molecule and (b) an Example of Selective Formation of an Elaborate 1-Aryl-4-methylurazole under Aqueous Conditions[102]



Scheme 30. Two Mechanisms Considered for the Alder−Ene Reaction between a Mono-Olefin and a TAD Molecule: (a) a Concerted Pericyclic Process via a Six-Membered Ring Transition State and (b) a Stepwise Route[a]



[a]Via an open zwitterion (OZ) or an aziridinium (AI) transition state.

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undergo a proton transfer that yields a 1-aryl-substituted urazole compound. Although this mode of reactivity of TAD compounds can be quite pronounced, surprisingly, only a handful of studies have been reported on this reaction.[18,100,101,252−255] Suitable substrates include dialkoxy- and trialkoxy-substituted aryls, as well as electron-rich nitrogen-containing aryls, such as various aniline derivatives and indoles. The formation of charge-transfer complexes has also been observed in these reactions, although it is unclear if they are involved in the reaction pathway.[256] Quite recently Breton was able to expand the substrate range for less-activated aryl substrates (including some dialkyl-substituted benzenes) by using trifluoroacetic acid[257] as a catalyst or by simply shining visible light[256] on the reactions.

The reaction of 2,3-disubstituted indoles has been discussed under ene reactions, but it can also be considered as an "aborted" or shunted EAS reaction of TAD with an indole substrate, wherein the rearomatization step is prevented. Likewise, the reaction of phenols with TAD compounds can be considered as an ene reaction,[258] followed by a keto−enol tautomerization to restore aromaticity. The phenolic proton indeed seems to be implicated in the EAS reaction with TAD, as simple monoalkoxyaryls are much less reactive substrates,[256,257] while phenols are excellent substrates, especially in an aqueous medium, that give selective and rapid formation of arylurazoles (Scheme 32b).[100−102]

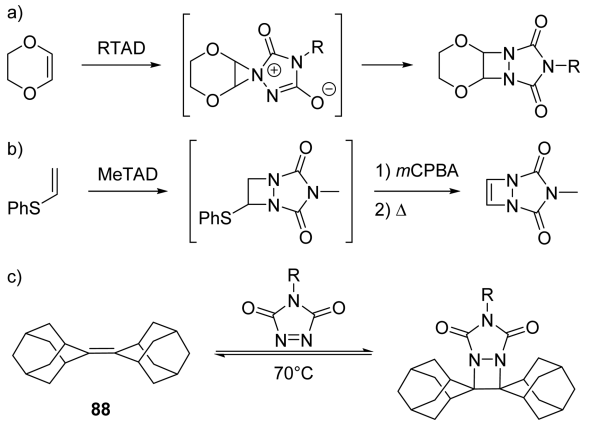
4.4. (2 + 2)-Cycloaddition

In classical pericyclic reactions, (2 + 2)-cycloadditions usually constitute thermally forbidden processes that require photochemical conditions, because of the requirement for both π-bonds to approach each other in an antarafacial way, which is sterically impossible. However, for sterically more accessible two-electron π-systems, such as ketenes,[259,260] an antarafacial addition mode is possible and orbital symmetry-allowed thermal concerted (2 + 2)-cycloadditions can occur. Indeed, also with TAD reagents a thermal, antarafacial (2 + 2)-cycloaddition is geometrically possible. Although a concerted thermal (2 + 2)-cycloaddition cannot be excluded for reasons of orbital symmetry, Seymour et al. showed that the cycloaddition reaction actually proceeds via a stepwise aziridinium imide (AI) intermediate that rearranges to the neutral diazetidine ring (Scheme 33a).[261] Especially, electron-rich alkenes are good substrates for this TAD (2 + 2)-cycloaddition, but these should not possess allylic hydrogens that can be transferred to give the thermodynamically preferred ene-type adducts. Indeed, the resulting diazetidine rings are highly strained compounds. Using this exceptional reactivity of TAD compounds, Breton and co-workers even managed to prepare a highly strained Δ-1,2-diazetine, which was also shown to be an excellent dienophile and thus a valuable intermediate for diazetidine syntheses (Scheme 33b).[262,263] Seymour studied the reaction of adamantylideneadamantane (**88**), which does not have any transferable allylic hydrogens, and found that the (2 + 2)-cycloaddition is actually reversible at slightly elevated temperatures (Scheme 33c).[261]

4.5. Secondary Reaction Modes of TADs and Important Side Reactions

As was proven in the previous sections, TAD compounds are highly reactive toward electron-rich delocalized π-cloud-type substrates, including simple alkenes. A qualitative empirical reactivity scale is provided in Figure 10, and some illustrative experimentally determined reaction rate constants are summarized in Table 14. In the case where there are no such suitable reaction partners available, TAD compounds can undergo a whole range of other reactions, albeit with slower kinetics. Thus, these reactions are often observed as undesired side reactions or as decomposition reactions. The main types of these "slow" TAD reactions are summarized in Scheme 34.

Scheme 33. Examples of (2 + 2)-Cycloadditions with TAD Compounds: (a) Reaction with 1,4-Dioxene Proceeds According to Seymour et al. via an Aziridinium Intermediate State,[261] (b) Synthesis of a Diazetine via the Reaction of MeTAD with Phenyl Vinyl Sulfide, followed by Oxidation and Pyrolysis of the Labile Adduct,[262] and (c) Reaction of TAD with Adamantylideneadamantane (88) is Reversible at Elevated Temperature[261]



As already mentioned, some TAD molecules are not stable enough (or are too reactive) to be isolated. However, in crystalline form, reagents such as PhTAD are relatively stable up to 160 °C and can be stored for several months in a dark, cold environment without significant decomposition.[5] However, when PhTAD is exposed to UV irradiation (for a longer period of time) or to temperatures above 160 °C, dimerization through self-condensation occurs (Scheme 34a).[192] Thus, this dimerization process—actually the loss of nitrogen gas—puts an upper limit on reaction temperatures that can be employed when working with TAD reagents.

Although quite a few reactions of TAD compounds are actually conducted in water as solvent,[100,101] hydrolysis of TAD is a feasible process.[70] When stored in water for longer times, TAD compounds will slowly hydrolyze, giving the corresponding urazole and amine as final decomposition products (Scheme 34b). This problem can usually be avoided by storing TAD compounds in a dry medium and container. The presence of acid or base can accelerate the hydrolysis, which needs to be taken into account when working in non-neutral media.

As can be expected from section 3, TAD compounds are also redox-active compounds, acting as oxidants for substrates such as thiols,[268] leading to disulfide formation (Scheme 34c). Also alcohols[269] can be oxidized (Scheme 34d). In some cases, these mild oxidation reactions are actually synthetically useful, giving a clean oxidation under relatively neutral conditions.

Besides the secondary reaction modes described in Scheme 34, there are some other types of reactivity that are worth highlighting. TAD compounds can react with strained double bonds (e.g., quadricyclane[270] or bicyclo[1.1.0]butane[271]), act as a potential spin trap,[263,272] abstract hydrogens,[192,256,273] and even play an important role in the synthesis of strained molecules.[233,274]

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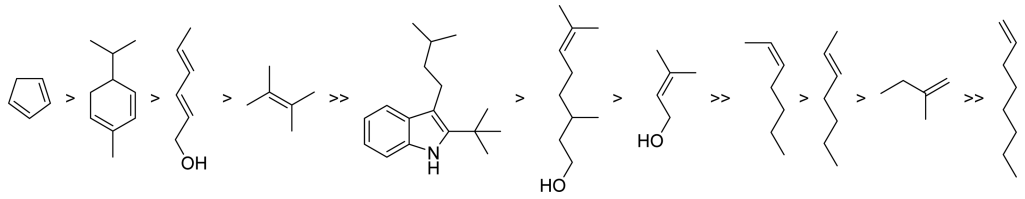
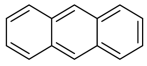
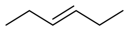


Figure 10. Relative reaction rates as observed in a head-to-head analysis (in DMSO-d_6) of different representative reaction partners for triazolinediones. The symbol ">" indicates that a selectivity for the left substrate is observed (>50% adduct formation), while the symbol "≫" indicates a complete selectivity.

Table 14. Experimental Rate Constants (k_2) for a Variety of Substrates in Their Reaction with PhTAD

Substrate	k_2 ($M^{-1}s^{-1}$)
	160000[a]
	333[b]
	6.92[c]
	6.5[b]
	0.89[b]
	0.33[a]
	0.15[b]
	0.01[b]
	0.000733[b]

[a]Toluene. [b]Dichloromethane. [c]Benzene.[264−267]

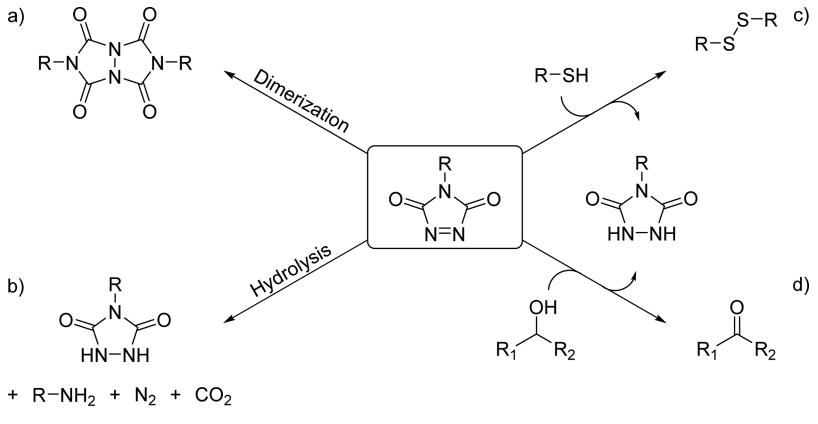
In spite of all the different modes of reactivity that are available to TAD compounds, most TAD reactions of the type described in sections 4.1−4.4 are surprisingly chemo-, regio-, and even stereoselective, even in the presence of competing reaction partners. This is because of the very pronounced kinetic selectivity TAD reagents have (cf. Figure 10). Another feature that contributes to this orthogonal behavior of a TAD reagent is the fact that although it is a highly electrophilic species, it reacts only very slowly with classical (ionic) nucleophiles with "localized" electron density.

A notable chemoselectivity issue in TAD reactions can arise in the presence of basic amines. The reaction of TADs with basic amines depends on a number of factors, and also a distinction has to be made between primary, secondary, and tertiary amines. In combination with primary and secondary amines, TAD compounds can promote an acylation-type reaction of the amine, ultimately giving a urea derivative (Scheme 35a).[104] The reaction proceeds via a nucleophilic attack of the amine, which leads to the ring-opened species, which quickly expels N_2 and CO gas with the formation of a urea. In the case of tertiary amines, the reaction follows a different course after initial ring opening and can react with another TAD molecule. The original amine is then expelled to form the dimer, as can be seen in Scheme 35b, and thus acts as a TAD-dimerization catalyst.[275,276] These side reactions can be suppressed by prior protonation of the amines (e.g., by adjusting the pH of the reaction medium) or by using substrates that are (much) more reactive than amines (such as Diels−Alder-type dienes). Anilines are usually less problematic and mostly give EAS reaction with TAD, without significant urea formation or TAD dimerization.

5. USE OF TRIAZOLINEDIONES IN POLYMER SCIENCE

Following the introduction of TAD compounds as versatile reagents in organic synthesis in the 1960s, the polymer community also developed an interest for the unique reactivity of TADs. Most of the early literature appeared in the 1970s and mainly dealt with the modification of polydienes. This particular subject has already been covered in two dedicated reviews by Butler in the early 1980s.[7,12] Nevertheless, the use of TADs in polymer chemistry has been further explored in various other macromolecular applications. Below, we offer a comprehensive overview of this work as an illustrative case study for the application scope of TAD chemistry.

Scheme 34. Important Side Reactions Involving TAD: (a) Dimerization of TAD under UV Irradiation or When Heated above 160 °C, (b) Hydrolysis of TAD, (c) Oxidation of Thiols, and (d) Oxidation of Alcohols to Aldehydes or Ketones



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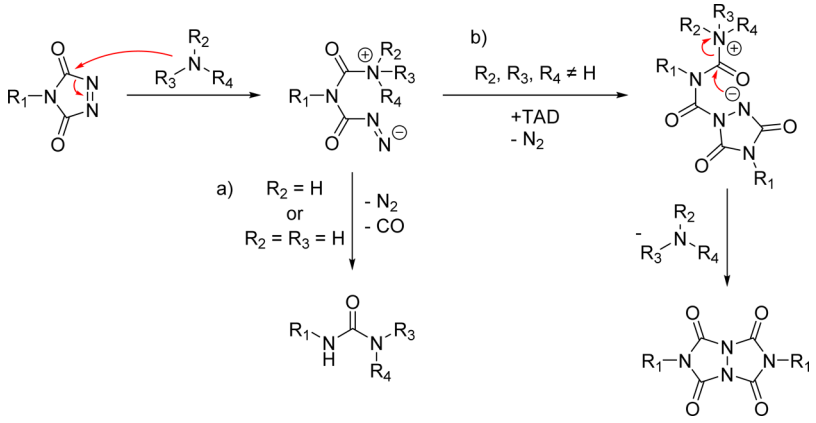
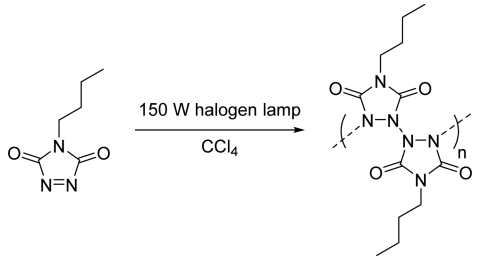
Scheme 35. Reaction Mechanism of the Unwanted Side Reaction between TAD and (a) Primary/Secondary Amines and (b) Tertiary Amines[104,275,276]



5.1. Homopolymerization of TAD-Based Monomers

In 1970, Pirkle and Stickler investigated a direct polymerization reaction of TAD-based molecules, to obtain polymers with an exotic all-nitrogen backbone (Scheme 36).[277] In this report, a

Scheme 36. Homopolymerization of BuTAD ($n \approx 10$)



0.3 M carbon tetrachloride solution of 4-butyl-1,2,4-triazoline-3,5-dione (BuTAD) was irradiated with a halogen lamp for 8 min, giving a colorless polymer with an average molecular weight of 4200 g/mol (around 20 monomer units). However, the obtained polymer had a very limited lifetime in the original CCl_4 solution, i.e., depolymerization slowly occurs within a time frame of 30 min to a few days. Moreover, the polymer is fully degraded within minutes in the presence of trace amounts of pyridine. The same experiments did not give polymers when aromatic TAD components were used.

In an alternative approach to directly polymerize TAD compounds, Turner et al.[131] attempted the polymerization of bifunctional TAD molecules with the aid of sodium cyanide as catalyst, but no polymers were formed. It was not until Butler et al. studied the peculiar decomposition behavior of (bifunctional) TAD molecules that homopolymerization of bisTADs was detected in 1985.[79] Indeed, in the presence of catalytic amounts of pyridine, a solution of a bifunctional TAD molecule in 1,2-dichloroethane can be gradually converted to a polymeric structure over the course of 30 min to 1 h. The polymerization reaction, as judged by the disappearance of the characteristic TAD color, was also found to be slower when it was conducted in the dark. The obtained polymers were fully characterized by IR and NMR to support their assigned structure, shown in Figure 11, and were also shown to have a remarkable thermal stability (decomposition around 300 °C). Up to now, this remains the only successful homopolymerization of TAD-containing molecules.

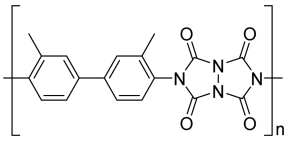


Figure 11. Assigned structure of the obtained product of the polymerization of 3,3′-dimethyl-4,4′-bis(1,2,4-triazoline-3,5-dione) diphenyl with the aid of catalytic amounts of pyridine (adapted from ref 79).

5.2. Copolymerization of Monofunctional TAD Monomers

TAD molecules possess a very intriguing reactivity toward a wide range of relatively simple reaction partners, supplying a range of different mechanisms as possible tools for a copolymerization. An interesting feature of TAD is its powerful electron-acceptor activity. On the basis of this, shortly following the work of Pirkle and Stickler,[277] Butler et al. showed that 4-phenyl-1,2,4-triazoline-3,5-dione (PhTAD) could react with a variety of electron-donating alkenes to yield alternating copolymers. A first example was the combination with vinyl ethers.[278] The reaction of PhTAD with ethyl vinyl ether in dichloromethane (DCM) resulted in a copolymer with a rather low M_n (up to 2400 g/mol), via a coupling of 1,4-dipolar intermediates (Figure 12a) most likely involving a cationic ring-opening-type polymerization of the initially formed zwitterionic aziridinium-type adducts. When using a divinyl ether, a mixture of the expected copolymer and a (2 + 2)-cycloaddition adduct was observed. The yield for the copolymer could be increased by raising the temperature or switching to DMF as a solvent.

In a follow-up study, Butler et al. investigated the copolymerization of PhTAD with *N*-vinylcarbamates.[279] More specifically, *tert*-butyl *N*-vinylcarbamate reacted spontaneously with PhTAD in DCM to form a low molar mass copolymer (M_n = 1 000 g/mol). However, in contrast to the results with vinyl ethers, this time proof was obtained that the reaction proceeded through the −N═N− bond rather than through the −N═N−C═O− system (Figure 12b), as was previously stated. Similar results were obtained for reaction with *N*-vinylcarbazole.[279]

A final example of a polyaddition using monofunctional TAD monomers was presented by Endo and co-workers, who copolymerized PhTAD with isobutoxyallene.[280] This highly exothermic reaction was performed at lower temperature (−40 to −20 °C), resulting in polymers with M_n up to 10 000 g/mol ($Đ \leq 1.72$; Figure 12c). These authors also studied the reaction

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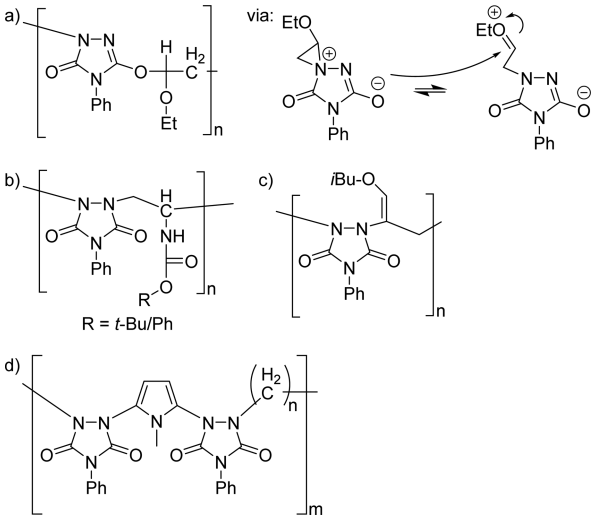


Figure 12. Assigned structure of the obtained products via the polymerization of 4-phenyl-1,2,4-triazoline-3,5-dione with (a) vinyl ethers, (b) *N*-vinylcarbamates, (c) isobutoxyallene, or (d) alkyl dihalides.

mechanism, which can be either a classical free radical polyaddition process or a stepwise ring-opening-type mechanism involving zwitterionic intermediates. It was shown that the active species of the copolymerization was in fact a zwitterion and not a diradical. In case of using polar and donative solvents, the zwitterion is effectively stabilized, resulting in a higher yield and M_n as compared to polymers prepared in DCM. However, when the polymerization is performed in bulk, the role of diradical active species could not be excluded in this work.

In a variation on the above-described strategy, Mallakpour et al. first reacted two PhTAD molecules with *N*-methylpyrrole.[281] The expected 2:1 adduct, obtained via a double EAS, was then deprotonated to its potassium dianion salt. A polycondensation of this dianion salt with alkyl dihalides (1,2-dibromoethane, 1,2-diiodoethane, and 1,4-diiodobutane) was performed in DMSO at room temperature and resulted in novel polymers with pyrrole and urazole linkages (Figure 12d).

5.3. Copolymerization of Bifunctional TAD Monomers

Most research on TAD compounds focuses on their ability to be used as very reactive dienophiles and/or enophiles.[18,19] This very pronounced reactivity immediately suggests opportunities for the formation of polymers in a stepwise manner via an AA–BB monomer approach with the aid of bisTAD molecules such as 4,4′-methylenebis(1,4-phenylene)-di-1,2,4-triazoline-3,5-dione (MDI-TAD, **89**, Figure 13a).[282] Kuhrau and Stadler started research on this type of polymer in the early 1990s. Various bisTAD molecules were combined with respectively ditropyl (**90**),[283] bis(cyclohepta-2,4,6-trien-1-yl) sulfide (**91**),[284] and divalent dihydrophthalimides (such as **92**)[285] as useful bis-dienes (Figure 13b). The obtained polymers contained a rather rigid main-chain structure with M_n up to 18 000 g/mol. A Diels–Alder reaction under nonstoichiometric conditions offered the opportunity to prepare rigid rod telechelics with TAD end groups. In a later stage, these telechelics have been used as cross-linkers for polydienes (see section 5.4).[286]

Besides the combination of bifunctional TAD compounds with bis-dienes, other complementary partners are also suitable for polymerization. Indeed, while the work of Kuhrau and

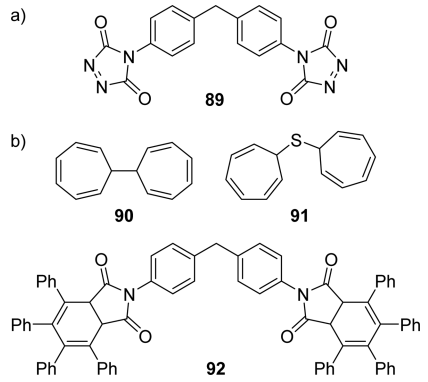
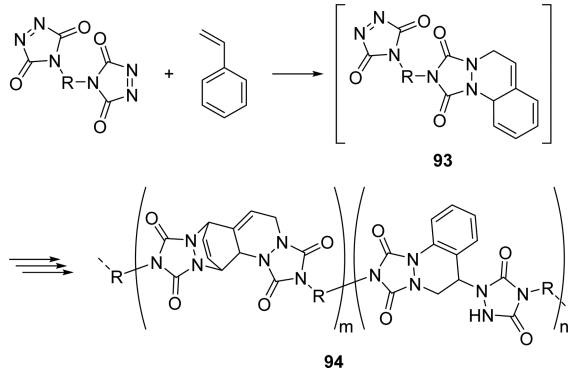


Figure 13. (a) Example of a divalent TAD, i.e. 4,4′-methylene-bis(1,4-phenylene)-di-1,2,4-triazoline-3,5-dione (**89**), and (b) bis-dienes used for polymerization via Diels–Alder, i.e., ditropyl (**90**), bis(cyclohepta-2,4,6-trien-1-yl) sulfide (**91**), and a divalent dihydrophthalimide (**92**).

Stadler focused on consecutive Diels–Alder reactions, Alder–ene reactions have also been explored.[287] A very interesting example can be found in the work of Butler and co-workers, in which bifunctional TAD molecules have been combined with styrene as a comonomer.[78] TAD can react with styrene in an initial slow Diels–Alder reaction, in which the aromaticity of styrene is lost (cf. Scheme 27b). The resulting 1:1 adduct (**93**), however, undergoes a faster second reaction. Careful investigations showed that, in this second reaction, a 1:2 ratio is obtained for respectively the Diels–Alder and the Alder–ene adduct. This cascade-type reaction of styrene with TAD has been used as a propagation mechanism in the copolymerization of styrene and (aromatic and aliphatic) bisTAD molecules (Scheme 37), leading to polymers with molar masses up to 36 000 g/mol (**94**, $Đ$ = 3.34).

Scheme 37. Polymerization of bisTAD and Styrene: The First (Diels–Alder) Reaction Leads to a 1:1 Adduct (93) That Is Prone to a Second TAD Reaction[a]



[a] m:n ≈ 1:2, corresponding to a ratio of the double Diels–Alder and the Diels–Alder–ene adduct, respectively.

Following their interesting results with styrene, the group of Butler studied the behavior of monofunctional TAD molecules in combination with a range of monofunctional components.[76,77,287,288] Those experiments resulted in a class of reactions that showed that TAD undergoes an initial reaction with vinyl esters to generate (2 + 2)-cycloadducts (**95**) or rearranged derivatives thereof (**96**, Figure 14a).[287,288] In an attempt to apply this reaction in polymer context, an adipate-based diester (**97**, Figure 14b) was chosen (because of the

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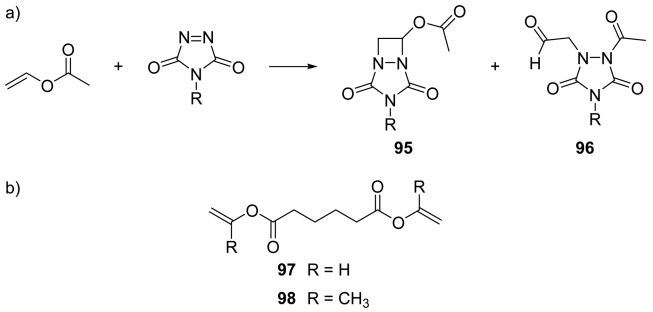

Figure 14. (a) Initial reaction between TAD and a vinyl ester leads to a mixture of (2 + 2)-cycloadducts (**95**) and rearranged products thereof (**96**). (b) Adipate-based diesters (**97** and **98**) used for polymer synthesis in combination with a bisTAD.

small steric hindrance).[76] Low molecular weight polymers were isolated via this route, most likely due to the degradation of the obtained polymers. An attempt was made to solve this degradation by replacing the starting monomer with diisopropenyl adipate (**98**).[77] In practice, however, different fractions were obtained that were not well characterized, leading to the conclusion that vinyl esters are not ideal partners for TAD molecules due to the instability of the obtained adducts.

Inspired by the previous work, Williams and Butler studied the reactivity of TAD molecules toward β-dicarbonyl components.[9] As these compounds were found to react with two TADs via two consecutive ene reactions on the enol (vinylogous carboxylic acid) form, they can be used as monomers in a copolymerization reaction with bisTAD compounds (**99**−**102**, Figure 15).[289] Although the low molecular weight model studies for this double ene reaction showed promising results, all acquired polymers had very low molar masses as a result of precipitation of oligomers in the reaction medium.[9]

Starting from the original work of Butler with styrene (Scheme 37), Mallakpour et al. attempted in 1996 a step-growth polymerization of bivalent triazolinediones with 1,1-diphenylethylene.[290] The reaction was performed in DMF and proceeded very fast, i.e., 4 min compared to 30 min for styrene.[78] The structural and physical properties of the resulting polymers were studied and reported. A much slower reaction was obtained when the same bifunctional molecules were combined with *trans*-stilbene (reaction completed in several hours).[291] Mallakpour et al. continued this concept of tandem ene and Diels−Alder reactions by combining bisTAD moieties with (cheap) 1,4-cyclohexadiene.[292] In this case, an initial Alder−ene reaction leads to an intermediately formed 1,3-hexadiene. This diene is very reactive and will react in situ with another TAD molecule, leading to the formation of polymer chains. In order to make the obtained polymers more useful, Mallakpour et al. attempted to add flame-resistant properties by using *trans*-3,3-dichloro-1-phenyl-1-propene.[293] The reaction at room temperature proceeded rather slowly (30 h), but the reaction time could be reduced to 18 h by refluxing the starting materials in DCM. Finally, also optically active polymers (containing isoeugenol[294,295] and naphthalene[296] groups) were prepared via the same polymerization technique.

Apart from its application in polycondensations with monofunctional TAD compounds (see section 5.2), Mallakpour and Butler used *N*-methylpyrrole with a range of bifunctional TAD molecules (Scheme 38) to obtain polymers via a polyaddition approach.[297] Pyrroles can undergo two consecutive electrophilic aromatic substitution reactions that are extremely fast at room temperature (much faster than the substitution reaction at the pyrrole 3-position). The properties of the obtained polymers could be altered by varying the nature of the bifunctional TAD molecule. Similar results were obtained with other electron-rich aromatic compounds that have two reactive hydrogens, such as *N*,*N*,*N*′,*N*′-tetramethyl-*m*-phenylenediamine.[298] This highly activated aromatic ring showed an exceptionally fast EAS reaction with TAD, affording the *p*-substituted aromatic polymer derivatives.

5.4. Triazolinedione Modification of Polydienes

The major application of triazolinediones in polymer science, so far, lies in the low-temperature modification of polydienes, both in academic[12] and industrial context.[299−303] The alkene−TAD ene reaction is very versatile and gives an atom-efficient and site-selective way to functionalize substrates that are otherwise quite hard to chemically modify in a reliable way (Scheme 39).[7]

TAD-based modification of polydienes was introduced in the early 1970s by Saville[74] using natural rubbers and was later on more extensively studied by Williams and Butler.[9,50] A wide range of polydienes (polybutadiene, polyisoprene, random styrene−butadiene copolymer, and a 1:1 alternating copolymer of furan and maleic anhydride) were modified with monofunctional TAD molecules. Although, theoretically, it is possible to add 4 mol of reactant per repeating unit (i.e., four "active" C−H bonds), the solubility of the obtained polymers plays a

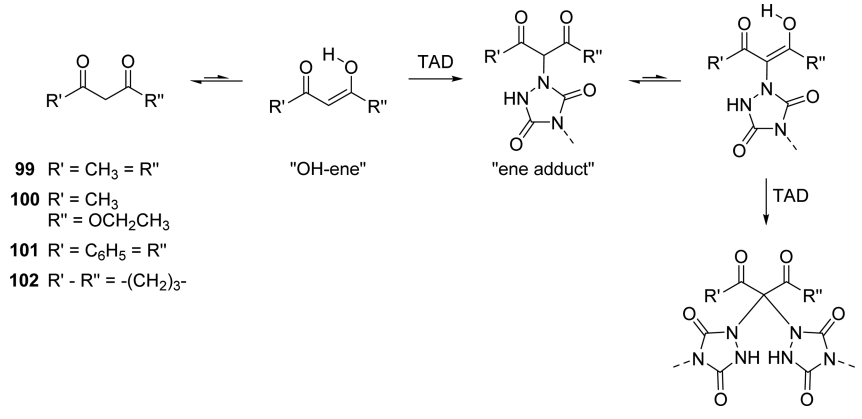

Figure 15. β-Dicarbonyl components can polymerize when combined with bisTADs via a double-ene reaction on the enol form.

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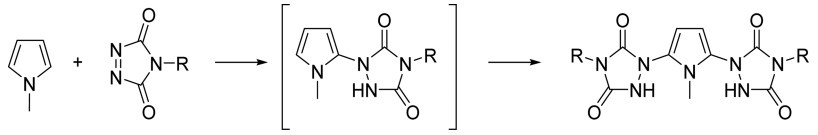
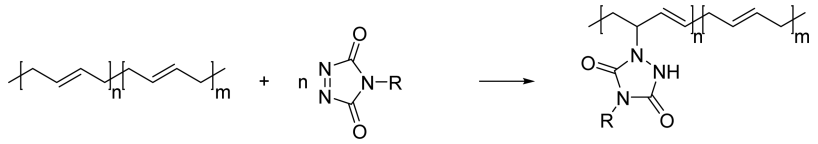
Scheme 38. Reaction between *N*-Methylpyrrole and TAD Selectively Gives a 2,5-Difunctionalized Pyrrole



Scheme 39. Reaction between Polybutadiene and TAD



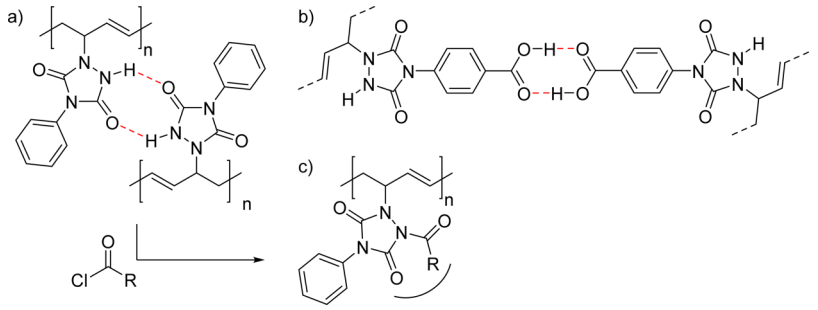


Figure 16. (a) Secondary cross-linking of a polybutadiene functionalized with PhTAD and (b) extra secondary cross-linking of polybutadiene functionalized with a 4-carboxy derivative of PhTAD. (c) The acidic urazole proton can be (partially) acylated, thereby blocking the self-associating behavior.

significant role, and the subsequent reactions are usually kinetically disfavored. Polymers with modification degrees ranging from 5 to 100% can be obtained, in which the polymers with lowest conversion demonstrated elasticity, which was an indication for possible secondary—supramolecular—cross-linking reactions (higher conversion led to rigid amorphous polymers with high T_g).

Follow-up studies on TAD-functionalized polydienes[304,305] ruled out covalent cross-linking and supported the hypothesis that the highly polar pendant urazole groups have pronounced inter- and intramolecular hydrogen-bonding interactions (Figure 16a), which can be related to properties such as elasticity, changes in solubility character, thermal behavior, and tensile strength. However, since this urazole-based association behavior is physical in nature, the polymer remains soluble. Stadler et al. studied this hydrogen bond network formation in detail using star-shaped polybutadienes.[306,307]

Many studies report a combination of polybutadiene (or copolymers with isoprene[308,309]) with PhTAD. The profound influence of the hydrogen bonding on the properties of elastomers was extensively studied by a range of different characterization methods: on the solid material (or a solution thereof) (SEC,[310] rheology,[311,312] IR,[313,314] birefringence,[315] light scattering,[316,317] DMA[318] and broadband dielectric spectroscopy[319]), in melt,[320,321] and in silico.[322,323] Because the attached urazole groups contain a quite acidic proton ($pK_a \approx 5$), further modifications of this strong hydrogen bond donor are relatively straightforward. Following a simple acylation reaction that "caps" this acidic N−H group, polymers with a wider range of properties can be obtained by using different acid chloride modifiers, while the supramolecular self-associating behavior is also blocked.[324] The degree of modification can be easily controlled by the amount of PhTAD, and the type of modification can be controlled by the choice of the acylating group. In this way, also optically active acid chlorides can be introduced on polydienes.[325]

Extending upon the concept of urazole-based hydrogen-bonding networks (cf. Figure 16a), Stadler and co-workers explored a range of TAD reagents that would enhance this supramolecular behavior, including hydroxyl, nitro, and carboxyl functional TAD molecules.[326] It was shown that the addition of a hydroxyl group as an extra hydrogen bond donor resulted in the formation of extended "junction zones" instead of pointlike linkages. The use of a nitro-functionalized TAD moiety showed a similar hydrogen-bonding behavior as the original PhTAD complexes, and they were used to convert the polybutadienes into ionomers.[327] The modification of polydienes with the 4-carboxy derivative of PhTAD (PhTAD−COOH) was first described in patent literature,[61,328,329] and later Hilger and Stadler studied the hydrogen-bonding behavior in these materials, which was found to be similar to that of a covalently cross-linked material up to 80 °C (Figure 16b).[330] The mechanical properties were superior to those of PhTAD-based H-bonded networks and actually comparable to those of thermoplastic elastomers of the covalent multiblock copolymers type, with high modulus and tensile strength.[64,331−336]

The PhTAD−COOH-functionalized "H-bond cross-linked" polydienes have been studied quite extensively as materials. Although experiments were conducted to determine the best position of the carboxyl group on the aromatic system, the original para-positioned group gives the most satisfactory results, as proven by DSC, birefringence, DMA, stress−strain experiments, SAXS, crystallography, and deuterated NMR.[337] In addition to simple polybutadienes, different matrices have also been successfully modified into networks using PhTAD−COOH,[62] including copolymers of butadiene and isoprene,[338] oligo-[339] and polyisobutylene,[340] and polystyrene−polybutadiene block copolymers.[341] Similar results have been obtained

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using a range of PhTAD−COOH derivatives, such as 5-isopthalic acid,[342−344] benzamide,[118] or phenylazobenzoic acid.[118]

Not only modification with monofunctional components was attempted but also reaction of bisTAD molecules with the aforementioned polydienes, resulting in highly cross-linked polymer networks.[50,345] Stadler and co-workers studied the characteristics of the network formation in the reaction of polybutadiene and MDI-TAD (**89**, Figure 13). This reaction was studied in solution as a model system, which allowed monitoring of the cross-linking kinetics, as a function of the gelation process[346,347] and the primary molecular weight of the polymer matrix.[348] In later studies, a variety of cross-linkers [containing azo dyes[134] or poly(ethylene glycol) chains[349,350]] and matrices[302,303] were used to obtain different network properties. In a very recent study, van der Heijden et al. showed that the properties of styrene−butadiene−styrene (SBS) electrospun fibers could be tuned by their reaction with PhTAD and TAD cross-linkers.[351]

Given the extremely reactive nature of TAD toward enes, the cross-linking kinetics of polydienes is often hard to control in order to achieve homogeneous material properties, especially under solvent-free bulk conditions. For this, in line with the concept of blocked isocyanates, attempts have been made to temporarily "block" the TAD functionality in order to release it at a higher temperature, giving a controlled cross-linking reaction. Greene and co-workers have shown that adamantylideneadamantane (**88**, Scheme 33), which reacts with TAD at room temperature to give a (2 + 2)-cyclocadduct,[261,264] can undergo the reversed reaction above 70 °C, which gives a thermally triggered TAD-generating reaction. This "blocked TAD" approach was used for the controlled cross-linking of polydienes in bulk (without solvent). Heating a mixture of polydiene and a blocked bisTAD reagent at 100−120 °C in a vacuum oven results in homogeneous network formation.[352]

Very recently, Zhao et al. introduced triazolinediones as an efficient postpolymerization tool for ring-opening metathesis polymerization (ROMP) derived polymers. The TAD-based Alder−ene reaction was used to efficiently postfunctionalize well-defined ROMP polymers. Both monofunctional and bifunctional TAD molecules were employed to functionalize and cross-link poly(*N*-propyl-5-norbornene-*exo*-2,3-dicarboximide).[353]

5.5. Cross-Linking and Functionalization of Other Polymer Matrices with TAD Reagents

Next to alkenes, electron-rich aromatic rings can also be included in simple linear polymers as reaction partners for TAD. On the one hand, vinyl-type (co)monomers, having an activated aromatic ring, can be easily synthesized and incorporated into linear polymer chains (Figure 17), which can then be functionalized or cross-linked with suitable TAD reagents.[354] Poly(2,4,6-trimethoxystyrene) (PTMS, **103**) reacts only very slowly with PhTAD (10 days at room temperature, 2 days in boiling DCM) while the reactions with poly(4-(*N*,*N*-dimethylamino)styrene) (PDMAS, **104**) and poly(*N*-methyl-2-vinylpyrrole) (PMVP, **105**) were much faster. For the latter two materials, the TAD functionalization reactions proceed readily at room temperature and resulted in, respectively, 90% and 97% incorporation of PhTAD. Stock et al. found that PhTAD-functionalized PDMAS (and related copolymers) shows a weak hydrogen bond between the urazole proton and the DMA group.[355]

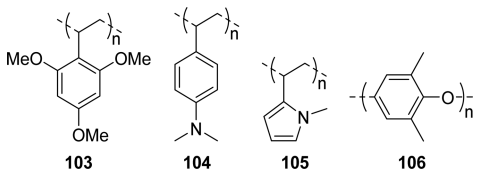

Figure 17. Synthesized polymers for modification with TAD via EAS: poly(2,4,6-trimethoxystyrene) (**103**), poly[4-(*N*,*N*-dimethylamino)-styrene] (**104**), poly(*N*-methyl-2-vinylpyrrole) (**105**), and poly(oxy-2,6-dimethyl-1,4-phenylene) (**106**).

On the other hand, a whole range of new polymer blends containing poly(oxy-2,6-dimethyl-1,4-phenylene) (PPE, **106**, Figure 17) were investigated for different applications at the end of the 1980s. As the repeating unit in these materials is actually a rather activated aromatic ring, these polymers can be directly modified using the EAS reaction with TAD. Indeed, Stadler et al. showed that PPE can be functionalized with TAD compounds at room temperature.[356,357] By addition of the highly polar urazole groups, physical linkages to other polymers and improved adhesion were achieved. With the goal to modify commercial blends, mixtures of polystyrene (PS) and PPE were functionalized with TAD to various extents. It was shown that PS and PPE, modified with up to 10% PhTAD, were still miscible, making this a valuable synthesis route for the modification of PPE blends.

5.6. Surface Modification

Shortly after the first publications concerning TAD chemistry with unsaturated polydienes, investigations started on polymer surface modification. Cutts et al. has been treating surfaces of elastomers with TAD components (both mono- and bifunctional).[358] In this way not only the adhesion could be improved but also resistance to peeling with flexible paints was improved while the surface tack of the elastomers was reduced. This proved to be an advantageous method over the prior one (chlorination and halogen donor techniques), particularly because the applied triazolinediones are relatively mild and noncorrosive.

Triazolinedione chemistry could also be used to verify the successful incorporation of diene (ene) moieties in polymers. In this context, Gleason and co-workers reacted PhTAD on a poly(furfuryl methacrylate) (PFMA) film.[359] This PFMA film is actually a furan-ring-functionalized solid surface, achieved by chemical vapor deposition. By analysis of the FT-IR and XPS spectra, obtained before and after the reaction with PhTAD, proof of the successful modification of the furan moiety was given.

5.7. Other Uses of Triazolinediones in Macromolecular Context

Besides the already mentioned categories, there are also some isolated publications involving triazolinediones in polymer science. One of these examples is the synthesis of macrocyclizations described by Banert and Schumann.[360] In this work, the authors use a combination of bifunctional TAD and sorbic acid (or sorbyl derived) molecules in high dilution. The formation of the macrocycles consists of two steps: first an intermolecular Diels−Alder reaction of the bifunctional diene with bisTAD, followed by an intramolecular ring closure (Scheme 40). Via this procedure, larger cycles up to 21-membered rings could be obtained.

Very recently, Craig and co-workers reported another use of TAD molecules, more specifically, in the area of mechano-

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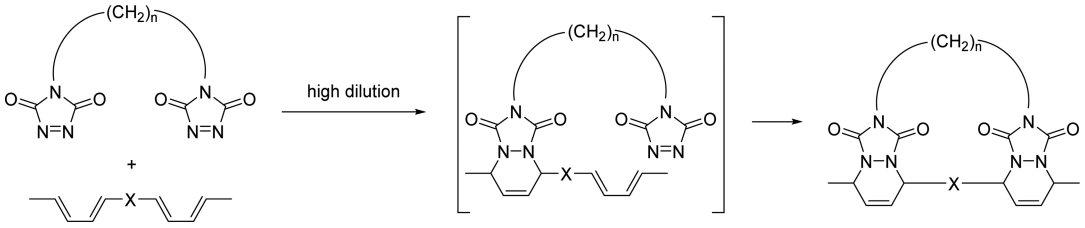
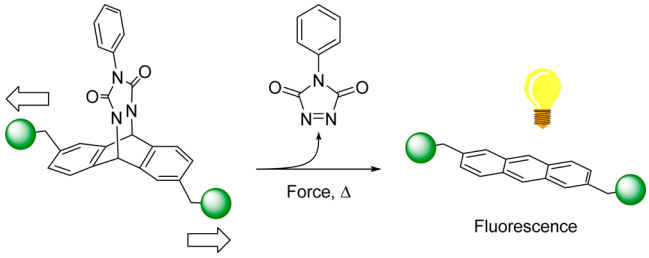
Scheme 40. Formation of Macrocycles by Combining bisTAD Molecules (n = 2 or 6) with a Bis-diene



chemistry.[361] In this work, embedding mechanophores into a poly(dimethylsiloxane) (PDMS) network allowed for covalent bond activation under mechanical stress. This has been shown by applying a mechanical force onto PDMS-containing PhTAD−anthracene cross-links. When sufficient stress was applied, the retro-Diels−Alder reaction occurred, leading to the release of PhTAD and unveiling the fluorescent behavior of the anthracene moiety (Scheme 41).

Scheme 41. Application of Mechanical Force on a PDMS Network Induced a Retro-Diels−Alder Reaction in the PhTAD−Anthracene Cross-Links, Thereby Unveiling Fluorescent Behavior of the Released Anthracene



6. USE OF TRIAZOLINEDIONES IN CLICK-LIKE APPLICATIONS

The concept of "click chemistry" was introduced in 2001 by Finn, Fokin, and Sharpless,[362,363] and it has made a huge impact on the scientific community,[364] despite the fact that click chemistry is often just focused on repurposing long-known reactions for new applications. The simple but visionary act to define a set of characteristics that a synthetic bond-forming reaction should ideally meet [be *modular, wide in scope, high yielding, chemoselective*, give no offensive byproducts (or be *atom-economic*), and have an intrinsic driving force to follow a *single* reaction *trajectory*] offers a highly subjective but at the same time quite useful conceptual framework to consider chemical reactivity in terms of the possible applications a reaction may have. In short, the introduction of click chemistry was a strong encouragement for chemists to focus on reactions that work in almost any context and are user-friendly to the point where also nonchemists can benefit from the power of chemical synthesis.[364]

The above list of click criteria are now regarded as the minimum set that "new" click reactions should have.[365] The initial introduction of the click chemistry concept was tailored for the example of the development of new medicines but—as anticipated in the original report—has also been adopted outside this specific area of human endeavor. For biology-oriented applications, compatibility with water and the physiological stability of adducts have been identified as additional desirable characteristics. For other areas of research that were quick to adopt click chemistry principles, such as polymer science,[366] the concepts and criteria have also been customized and expanded to fit the largest possible number of applications. In fact, for macromolecular substrates, three additional requirements have been defined by Barner-Kowollik et al., in addition to the original Sharpless−Finn criteria of "click" chemistry, namely, *equimolarity*, *scalability* (and scalable purification), and a stronger emphasis on *rapid reaction rates*.[367]

Although hetero-Diels−Alder reactions have been called "beautiful representatives of click chemistry ideals" by Sharpless and Finn, TAD-based chemistry has not been discussed in the context of click chemistry for almost a decade after the initial report.[100] Indeed, apart from having a reputation as the "most reactive" dienophiles, TAD compounds also have a reputation of being "exotic" reagents and have been generally regarded as highly unstable species. Nevertheless, as is shown in the previous sections, the synthesis of TAD reagents can be straightforward and mostly involves steps that are high-yielding and do not require a purification step, at least when chemoselectivity issues are carefully considered in the choice of starting materials and reagents. We believe that this "lag" for triazolinediones to emerge as versatile click chemistry tools is reminiscent of the similar lag in its initial adoption as a useful dienophile and enophile in organic synthesis (see section 1).

Although many of the examples discussed in sections 4 and 5 can in some way or another be considered as click reactions, those sections mainly focus on well-known simple TAD compounds that have no other functional moieties and provide a good illustration of the reactivity of TADs, but they do not readily showcase the potential of triazolinediones in click chemistry, because of the often highly specific (i.e., non-modular) nature of the application.

Below, we offer an overview of applications of TAD reagents that are closer to what is generally expected of truly modular click chemistry tools. We believe this selection shows the way forward for TAD chemistry in click applications, which brings some unprecedented features to click chemistry, such as dynamic but highly controlled bond formation.

6.1. Click Bioconjugation of Peptides and Proteins

Barbas and co-workers were the first to explicitly report on TAD reagents as useful tools for click chemistry, in their 2010 paper on a "*click-like*" conjugation strategy for natural peptide and protein substrates. Herein, Barbas explored the use of triazolinediones as an efficient tyrosine bioconjugation strategy.[100,102] Although TAD molecules are known to react slowly with phenol substrates via an EAS pathway (see section 4.3), Barbas serendipitously observed that this reaction is greatly accelerated in aqueous medium. Conversely, a similar EAS or ene-type reaction with tryptophane side chains (indole core) is not accelerated, offering a way to site-selectively label tyrosine residues in natural peptide and protein substrates (Scheme 42).

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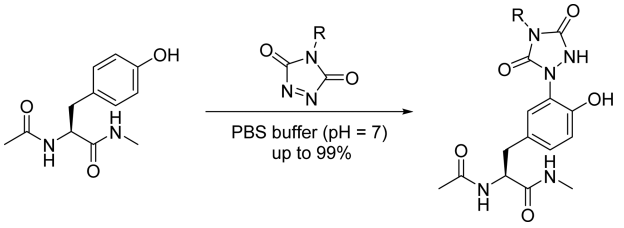
Scheme 42. Model Reaction of the Tyrosine Bioconjugation (R = Ph or Me)



Following the initial report, Barbas and co-workers showed the true potential of this tyrosine bioconjugation with a range of additional experiments and a systematic study of TAD orthogonality toward different amino acid side chains.[101] For this, they used a synthetic decapeptide with unprotected side chains, containing all of the potentially reactive amino acids, Trp, Ser, Glu, Lys, Arg, and His, as a stringent chemoselectivity test. Even when 3 equiv of a TAD reagent was applied, this peptide was site-selectively functionalized at the tyrosine residue (Scheme 43). As reactions with primary amines are typically hard to avoid (see section 4.5), the success of this click-like tyrosine conjugation method can also be explained by the use of a buffered medium (pH 7 phosphate buffer), which will keep most of the free amines (on the lysine and N-terminal residue) in their unreactive protonated form. Purification by using reversed-phase HPLC yielded pure labeled peptides in approximately 60% yield.

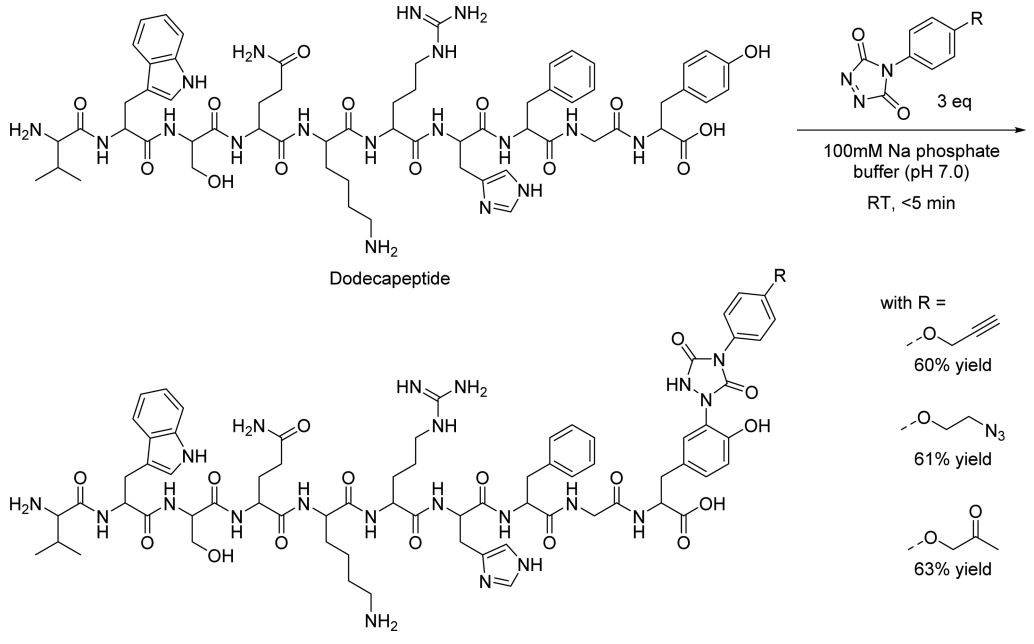
To expand this tyrosine-selective click modification even further, Barbas' group also implemented it for site-selective and orthogonal protein multifunctionalizations.[101] In this case, orthogonal trifunctionalization at tyrosine, cysteine, and lysine residues of bovine serum albumin (BSA) and human serum albumin (HSA) was achieved. Cysteine and lysine were modified with a fluorescein maleimide and 11-(dansylamino)-undecanoic acid, respectively, while the tyrosine units were successfully reacted with TAD derivatives.

In a related study by Barbas and co-workers,[101] PEGylation of proteins was studied, which is one of the most important protein conjugation reactions for pharmaceutical applications. For this, a 5 kDa poly(ethylene glycol) chain with a TAD end group was prepared through CuAAC reaction by using an azide-functionalized urazole (Scheme 44). After oxidation, the macromolecular TAD reagent was directly coupled to chymotrypsinogen A (which contains four tyrosine units). Reactions were performed in buffer solutions (pH 7.4) with 10 equiv of the PEG-TAD compound. After removal of the excess of PEG, predominant formation of mono-PEG addition products was observed, pointing toward a site-selective modification.

In another biomedical application, Barbas and co-workers used the TAD−tyrosine click conjugation to couple the anti-HIV drug aplaviroc with a monoclonal antibody.[101] The targeted delivery of drugs through antibody−drug conjugates can be of use for many therapeutic applications. As a model monoclonal antibody, the well-characterized trastuzumab was used. An alkyne-containing derivative of aplaviroc was coupled to an azidourazole by using a CuAAC reaction. This precursor was oxidized to yield the TAD derivative, which was immediately used for labeling of trastuzumab (Scheme 45). Again, the obtained protein mostly showed the incorporation of a single drug molecule. This drug−antibody conjugate was further shown to retain both its antiviral as well as its antigen-binding activity.

Bauer et al. used the tyrosine−TAD click reaction to prepare DNA−protein conjugates, making use of a range of interesting heterobifunctional cross-linkers (Figure 18).[103] These bifunctional cross-linkers incorporate a TAD moiety to ensure the fast and selective reaction with tyrosines and another functionality to couple a DNA strand. For this last coupling, a variety of different "click" reactions was tested, i.e., maleimide−thiol Michael addition (**107** and **108**), CuAAC reaction (**109**), and strain-promoted copper-free AAC reaction (**110**). All three orthogonal click strategies gave conjugates that outperformed

Scheme 43. Tyrosine Click Reaction of a Model Decapeptide, Including All Possible TAD-Reactive Side Chain Residues, Demonstrating the Chemoselectivity and Efficiency of the Reaction



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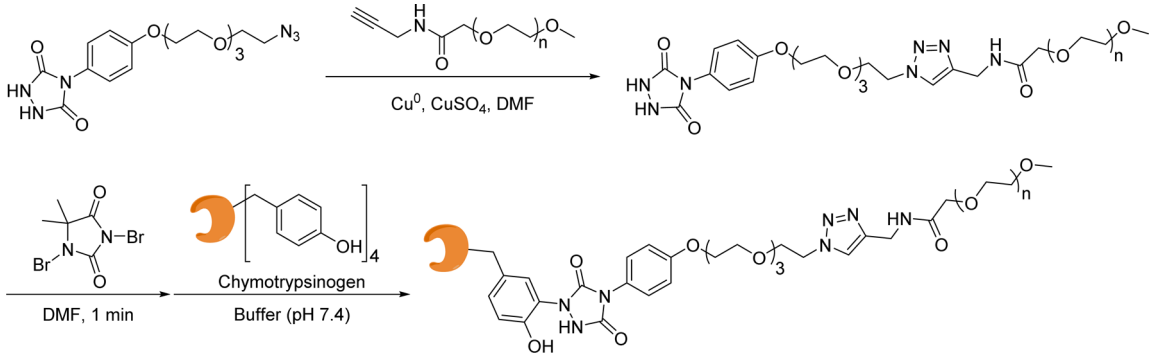
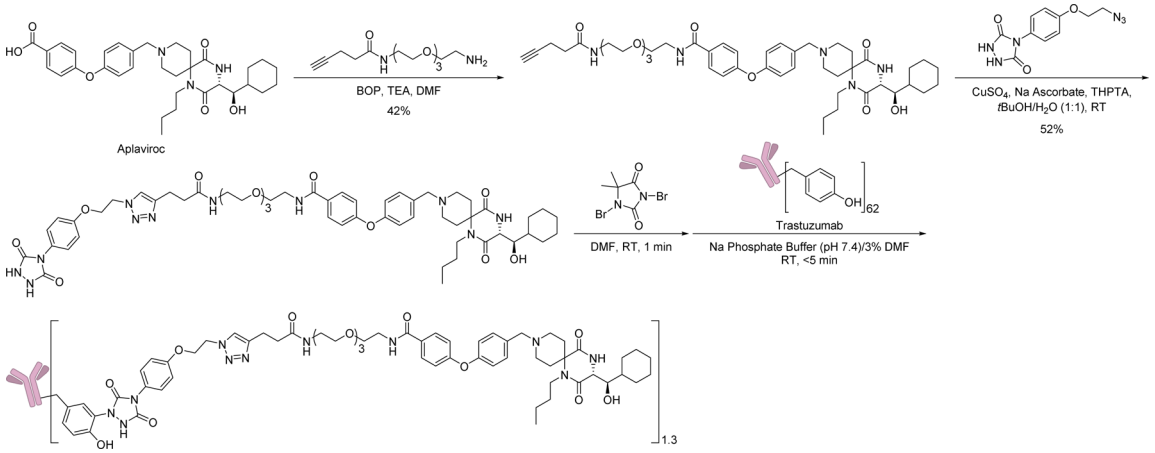
Scheme 44. Treatment of a Buffered Aqueous Solution of Chymotrypsinogen with an Excess (10 equiv) of a Freshly Oxidized Solution of PEG-TAD in DMF Leads to Selective Mono-PEGylation of the Protein Substrate



Scheme 45. Drug–Antibody Conjugation by Using Tyrosine Click Bioconjugation of Trastuzumab with a Small Molecule HIV Entry Inhibitor



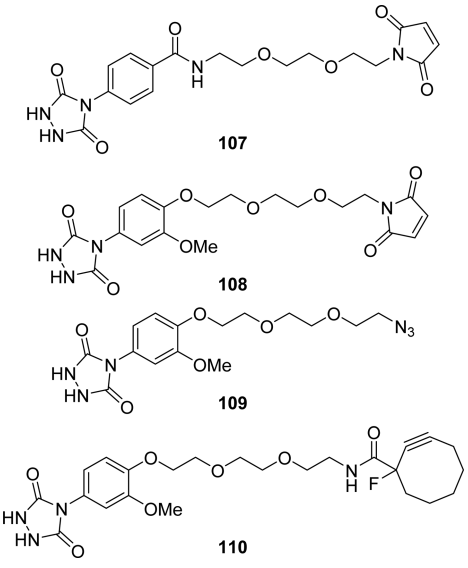


Figure 18. Urazole precursors for TAD-based heterobifunctional cross-linkers useful in sequential orthogonal click reactions.

those obtained through more classical lysine-based protein ligation.

In a recent paper from a pharmaceutical industry group, Hu et al. report the use of the tyrosine–TAD click reaction to tackle a challenging protein substrate of considerable pharmaceutical interest.[104] CRM_{197} is a nontoxic mutant diphtheria toxin that has been extensively used as the protein carrier in many licensed vaccines and has well-proven safety and efficacy. As this substrate apparently has some very reactive lysine residues that compete for the usually more reactive tyrosine side chains, the group undertook a systematic study of TAD site-selectivity for several proteins and examined the influence of reaction conditions. They found the use of an amine-based buffer to be helpful to suppress lysine conjugation, as it may also act as a scavenger for isocyanates. They also found that the amount of TAD reagent has to be varied in the range of 1.1–30 equiv, depending on the substrate, to achieve a complete conjugation, reflecting the varying "availability" of tyrosine residues in different proteins.

As can be expected, a clear correlation was observed between the labeling efficiency of tyrosine residues and their relative exposure to the protein surface in the X-ray structure. Similarly, for CRM_{197}, which forms homodimers in solution, the tyrosine residues involved in the dimerization were found to be unreactive toward TAD. When CRM_{197} is treated with an excess of TAD linker, a reproducible labeling of the same four specific tyrosine residues was observed, out of a possible 18. Using an alkyne-functionalized TAD reagent, a well-defined glycosylated CRM_{197} conjugate was obtained through sequential tyrosine–TAD click and CuAAC reactions (Scheme 46).[104] Such glycoconjugates can be used as vaccines, and the overall strategy seems applicable for the synthesis of many well-defined protein conjugates.

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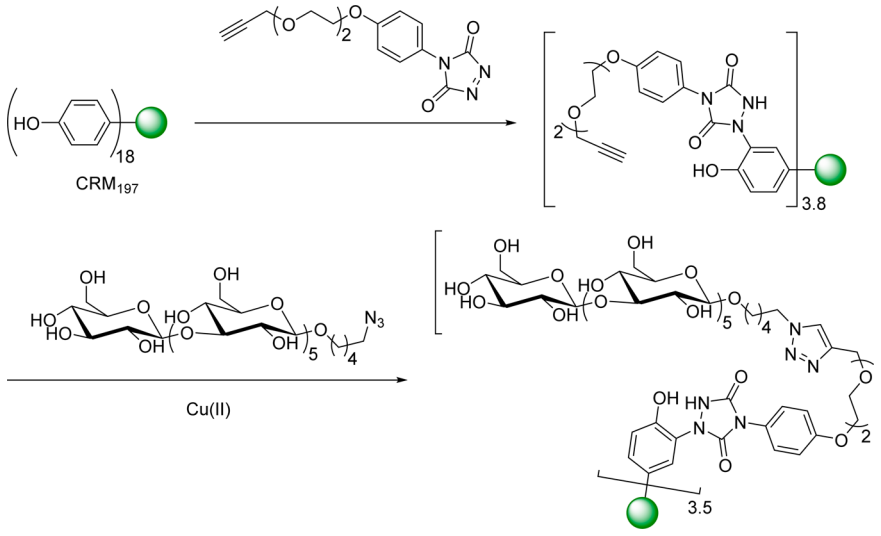
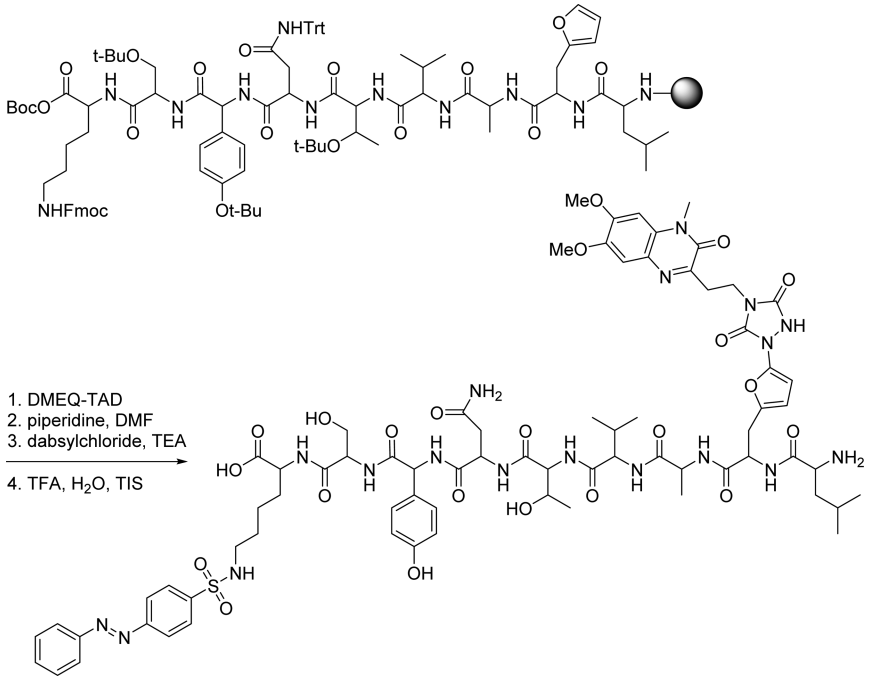
Scheme 46. Tyrosine-Click-Mediated Glycosylation of CRM_{197} for Use as an Anti-Candidiasis Vaccine[a]



[a]Reactions are performed in an aqueous buffer.

Scheme 47. "On Resin" Orthogonal Peptide Labeling though Furan–TAD EAS[a]



[a]The peptide was synthesized via a standard Fmoc/*t*Bu strategy using HBTU/DIPEA couplings on a Rink amide resin.

In a follow-up study, the tyrosine click bioconjugation strategy was further developed toward the preparation of glycoconjugates.[98] Here, a heterobifunctional TAD-azide linker was first site-selectively clicked to a protein substrate, followed by a copper-free strain-promoted cycloaddition to cyclooctyne-modified carbohydrates. The synthesis was employed for vaccine antigens and was found to be very versatile and high-yielding.[97]

Madder and co-workers developed an alternative TAD-based strategy to functionalize peptides prepared through classical solid-phase synthesis.[368] Instead of relying on tyrosines, which react very sluggishly with TADs in nonaqueous media, a highly reactive furan residue was incorporated in a synthetic peptide, using the unnatural but commercially available amino acid furylalanine. A model peptide featuring a furylalanine was synthesized on a solid support. As a classical maleimide-furan Diels–Alder conjugation proved to be not very efficient, the more reactive triazolinediones were investigated. Indeed, by using only 3 equiv of PhTAD in dichloromethane, a complete reaction was observed with the solid-supported peptide in only 15 min at room temperature. However, detailed investigations showed that the expected Diels–Alder adduct was not observed, but instead the product of a clean furan–PhTAD electrophilic aromatic substitution (EAS) was found. The reaction proved to be a useful tool for quantitative and site-selective peptide labeling and was also used in a simple

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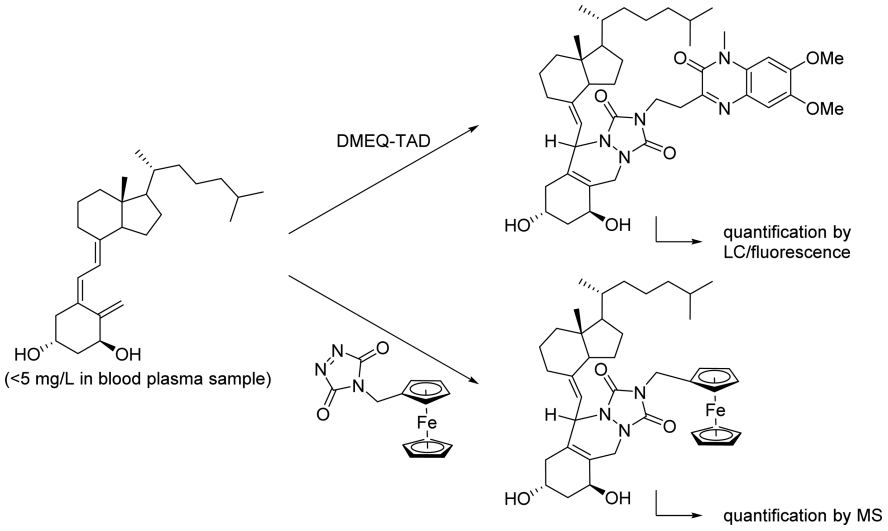
Scheme 48. Derivatization and Quantification of Vitamin D Metabolites with DMEQ–TAD or TAD–Ferrocene, Respectively, as Fluorescent Tags or MS Tags[373]



orthogonal peptide labeling protocol. In this case, a simple FRET probe could be synthesized by using the commercially available TAD-based compound DMEQ–TAD (Scheme 47).[368]

6.2. Click Derivatization of Low-Abundant Lipid Metabolites in Biological Samples

The quantification of lipid metabolites can be of great diagnostic value, but standard chromatographic and mass spectrometric methods are hampered by high detection limits. Yamada and co-workers reported in 1990 that triazolinediones are ideal reagents to derivatize conjugated dienes in natural lipids, even in complex and dilute biological samples. Yamada and co-workers synthesized the now commercially available fluorescent DMEQ–TAD reagent and used it to assay and quantify various hormonally active and important vitamin D metabolites.[63] The TAD–diene hetero-Diels–Alder click reaction is so fast and orthogonal that vitamin D metabolites, at a concentration as low as 10^{-8} M, could be reliably labeled and then quantified via HPLC with a fluorescence detector.[93] This technique has a detection limit for vitamin D-related metabolites down to 0.1 fmol. In a similar application, Shimada and Oe employed fluorescent TADs as a derivatization tool to quantify 7-dehydrochlolesterol, a steroid that also incorporates a diene.[85]

In later work, the determination of vitamin D metabolites with the aid of TADs was extensively studied (especially in mass spectrometry) and is a standard method in the field, reflected by the fact that DMEQ–TAD is commercially available.[369−372] In 2005, Murao et al. showed the unique combination of TAD as a powerful dienophile with an efficiently ionizable functionality (ferrocene group) (Scheme 48).[373] The TAD–ferrocene reagent was found to give the most sensitive detection method for vitamin D-like metabolites.

6.3. Triazolinediones as Tools in Modular Chemical Library Synthesis

For the parallel synthesis of structurally diverse libraries of chemical compounds, it is important that each reaction step proceeds with the maximum efficiency and that reaction workup and purification can be standardized to a point that allows for automated synthesis and purification steps. Click chemistry concepts are thus ideally suited for these needs. In practice, however, the number of truly diversity-generating click reactions is limited, and it is hard to build libraries using *only* click reactions.

The famous Diels–Alder reaction, which is arguably the most powerful construction reaction in organic synthesis, has a few drawbacks with regard to click chemistry ideals, despite the fact that it has been denoted earlier as a "click" reaction.[374] Although most Diels–Alder reactions have a high intrinsic driving force, obtained yields and conversions are often limited because of kinetic reasons, as they require considerable thermal activation. The most common and reliable way to achieve good yields in reasonable time frames for Diels–Alder reactions is the use of an excess of one of the reaction partners. However, this straightforward strategy typically requires a chromatographic separation of the desired cycloadduct from the excess of diene or dienophile as an "offensive byproduct". This chromatographic separation can be avoided if the excess diene or dienophile can be selectively derivatized with a secondary Diels–Alder reaction that does meet click chemistry ideals, if this gives nonoffensive cycloadducts that can be easily removed from reaction mixtures.

In 2003, Werner and Curran introduced the use of triazolinedione reagents in the field of fluorous tagging.[56] Their work in fluorous tagging focused on suitable diene scavengers. A range of highly fluorinated dienophiles, including maleimides and triazolinediones, was explored. These fluorous tags were used to treat Diels–Alder reaction mixtures containing an excess of diene as the only "side product", which would allow for removal of the initially nonreacted diene by a simple solid-phase extraction (Scheme 49). As expected, the TAD-based fluorous tags outperformed their maleimide counterparts. Furthermore, because of the characteristic color of TADs, a highly practical workup protocol was developed in which a simple titration of the reaction mixture with the TAD scavenger was performed, until the persistence of a pink color was observed.

In a patent application by a pharmaceutical industry group, Pieken et al. describe the use of a TAD-based solid-phase diene scavenger to separate reaction products from reagents in the solution-phase synthesis of oligonucleotides.[375] By using a

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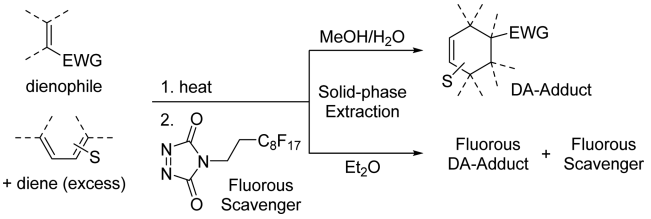
Scheme 49. Fluorous Tagging of Excess Dienes in Reaction Mixtures Facilitates Purification of a "Generic" Diels–Alder Adduct[56]



diene-functionalized protecting group during oligonucleotide synthesis, all compounds that incorporate this protecting group can be selectively removed from complex reaction mixtures and excess reagents with a TAD–resin-loaded column (Scheme 50). Using standard deprotection conditions, the desired compounds can then be eluted from this column, and oligonucleotide products can be obtained in pure form without the need for complicated chromatography. A simple TAD-functionalized scavenger resin was obtained by treating a diene-functionalized polystyrene column with a large excess of a bifunctional TAD reagent. For this, a sterically constrained bisTAD compound was chosen to minimize intraresin cross-linking. This strategy seems applicable for the temporary and highly selective immobilization of a wide range of products onto a solid phase, as long as suitable diene-functionalized protecting groups can be introduced into the substrate. A range of dienophiles was explored, but triazolinediones again emerged as the reagents of choice for this catch-and-release strategy.

Besides its use as a click-like cleanup tool for reaction mixtures, triazolinediones can also be used directly in the synthesis of libraries of diverse screening compounds. Porco and co-workers were the first to describe the systematic use of variously functionalized triazolinedione building blocks in a stereocontrolled synthesis of a complex library.[376] Similarly, Schreiber and co-workers developed a highly efficient protocol based on eneyne metathesis of simple olefin building blocks, resulting in 1,3-dienes that are then "rigidified" into a range of diverse polycyclic scaffolds (Scheme 51).[377]

6.4. Natural Plant Oils as a Versatile Feedstock Monomer for New Materials

One of the hallmarks of click chemistry is that it can bring the power of chemical synthesis to unprecedented or unsuspected applications in—at least for chemists—"unusual" contexts. The synthesis of organic polymer materials is a chemical process that typically requires precise control of reaction conditions, dedicated reaction vessels, and raw materials (monomers) of high chemical purity. As the use of TAD-based click chemistry was expanding,[65] Du Prez and co-workers showed interest in natural plant oils as complementary partners for TAD reagents. Although most plant oils contain a large number of olefinic bonds, only very limited chemical transformations can be effected on these natural synthetic handles, often requiring catalysts and/or harsh reactions conditions.

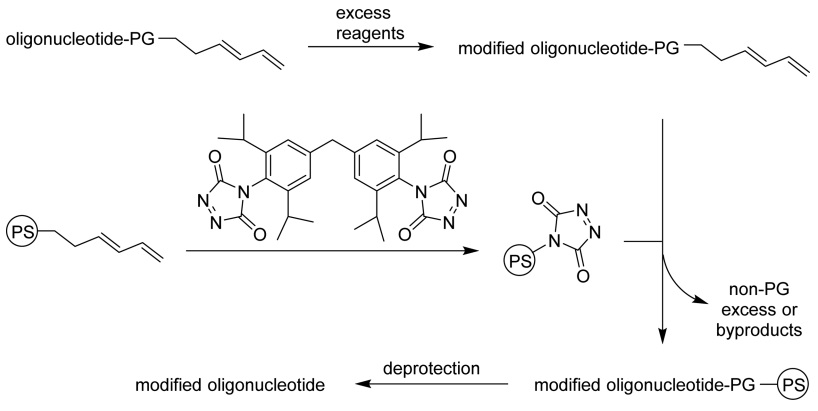
The initial study of simple unsaturated fatty acid methyl esters showed a specific and selective reactivity toward TAD reagents.[80] As a result of the nature of the Alder–ene reaction with isolated olefins, the fatty acid unsaturations actually remain present in the TAD-modified lipid tails and can even be used in a second, markedly slower ene reaction with a TAD reagent (Scheme 52). The versatility of this click reaction for unsaturated fatty acids was then demonstrated by cross-linking crude, readily available plant oils with bifunctional TAD molecules. By studying the gelation times (occurring within minutes at room temperature) and determining the thermal properties of the obtained cross-linked materials, a general trend in plant oil reactivity could be perceived, showing that a higher percentage of polyunsaturation resulted in both shorter gelation times and a higher T_g of the obtained plant oil network. Furthermore, by simply varying the amount of cross-linker or the structure thereof, a range of different materials, with T_g's varying in a range of more than 70 °C, could be obtained starting from the same plant oil. This preliminary work thus points to a versatile new class of renewable "monomers" for the design of polymer networks.

In a subsequent collaboration of the Du Prez group with the group of Tang, plant-oil-based triblock copolymers were prepared from monomers derived from soybean oil.[378] The TAD-based "fatty acid click coupling" strategy was employed to site-selectively create chemical junctions between the middle blocks of the triblock copolymers, improving tensile strength and resulting in excellent elastic recovery characteristics.

6.5. Clicking and Unclicking Protecting Groups in Organic Synthesis

TAD reagents can be used as protecting groups for dienes,[379] but the deprotection requires a hydrolysis in strongly alkaline medium at elevated temperatures. Thus, as is often the case in implementing protecting groups in organic synthesis, this

Scheme 50. A Diels–Alder Catch-and-Release Strategy for the Solution Phase Synthesis of Oligonucleotide Substrates, Based on Diene-Functionalized Protecting Groups and TAD-Functionalized Resins



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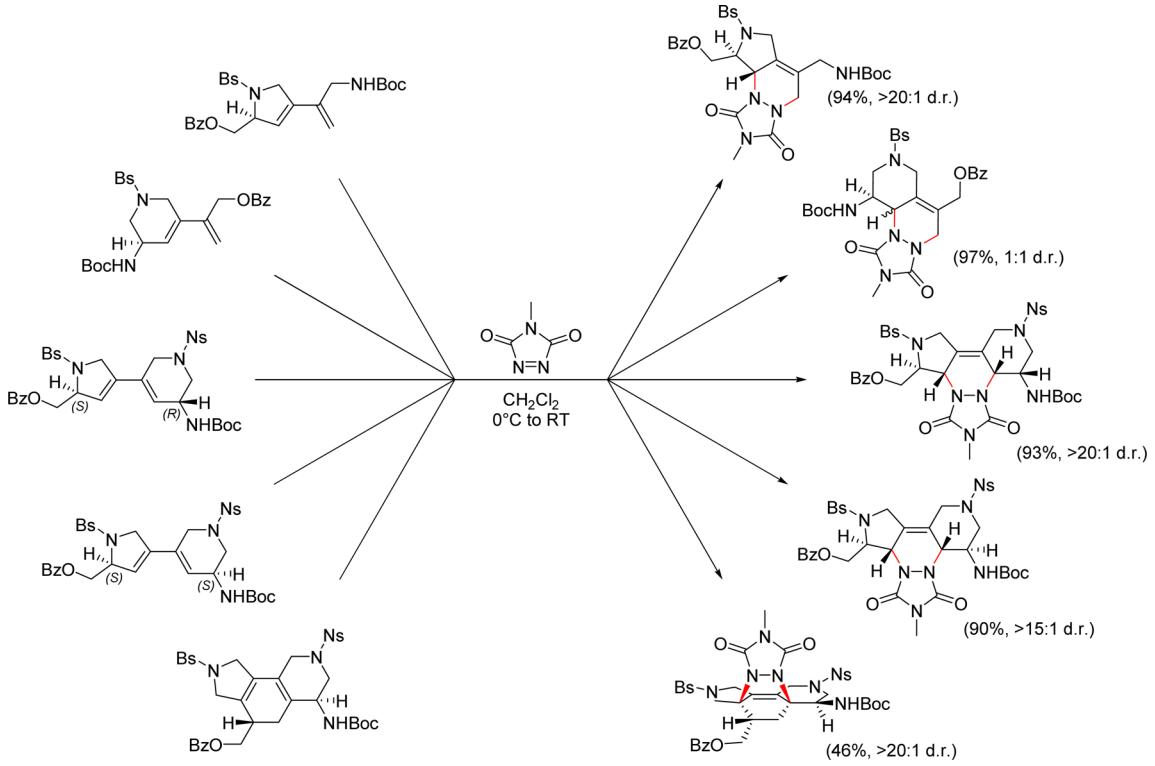
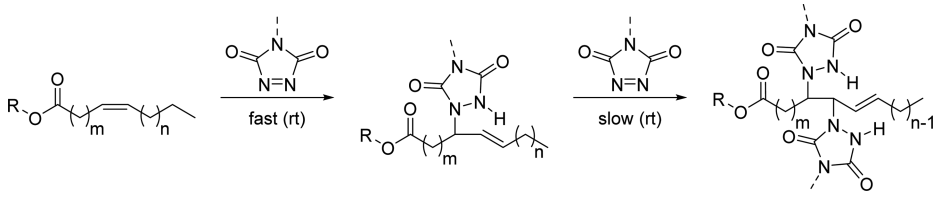
Chem. Rev. 2016, 116, 3919–3974

Scheme 51. Schreiber's Two-Step Synthesis of Diverse Scaffolds Using an Eneyne Metathesis from Simple Linear Polyeneyne Starting Materials, Giving Complex Tri- and Tetracyclic Scaffolds[a]



[a]Newly formed bonds are indicated in red.

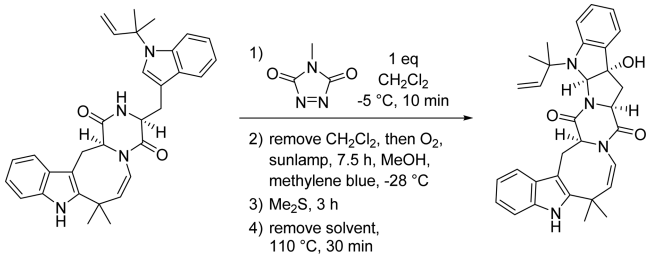
Scheme 52. Clicking Lipids: Unsaturated Fatty Acid Derivatives React Selectively and Specifically with Triazolinediones at Room Temperature; Moreover, Since the Unsaturation Remains Present, a Second Yet Markedly Slower Modification Is Possible



strategy adds a lot of practical difficulties to a synthesis, making it a less efficient process. In ideal synthetic routes, the use of protecting groups should be completely avoided.[380] However, protecting groups than can be installed and removed in a straightforward way, with regard to the click chemistry criteria, could be considered as "ideal" protecting groups.

In 2003, Baran et al. implemented triazolinediones as a highly efficient protecting group for the N−H and 2,3-π-bond of indoles.[381] During their total synthesis of okaramine N, a nucleophilic indole needed to be protected during an oxidation step of another (less reactive) indole. Inspired by the well-known similarity in reactivity between singlet oxygen and triazolinediones, the commercially available methyl-substituted TAD (MeTAD) was first reacted with this bis-indole. This resulted in a highly selective, atom-economic, and fast (10 min) reaction with MeTAD in dichloromethane at −5 °C to form exclusively the ene product at C(3) of the N-unsubstituted indole subunit (Scheme 53, also Scheme 31).[217,381] Simple evaporation gave the product that could be used in the oxidation step. The purified oxidation product could be cleanly converted to the free indole by simply heating the neat material

Scheme 53. Use of MeTAD as a Volatile Click/Unclick Protecting Group in the Final Steps of the Total Synthesis of Okaramine N[a]



[a]Also see Scheme 31 for the ene and retro-ene reaction between TAD and indoles.

in vacuo, which removed volatile MeTAD and directly gave the deprotected product.

In later work, the same group explored the potential of this "ideal" protecting group for indole N−Hs, and found a wide

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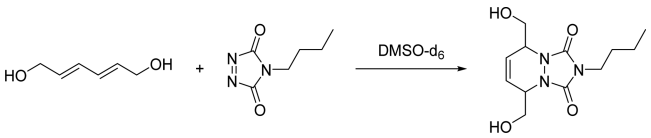
product range.[217] In most cases, the indole−TAD click-type ene reactions proceed within seconds or minutes at 0 °C and provide the urazole adducts in high yield without need of purification. A simple application of a vacuum and short heat treatment of the adducts return the original indole in excellent yields.

6.6. Ultrafast Macromolecular Click Derivatization and Conjugation

Du Prez, Winne, and co-workers were the first ones to formally investigate the click-like behavior of TAD chemistry with a range of simple olefin-type substrates.[65] The positive outcome of this study led to the introduction of a general click chemistry platform, based on hetero-Diels−Alder reactions of TAD reagents. These TAD-click reactions do not require additives or a catalyst and proceed readily at or even below room temperature. It was shown that the involved reactions were upscalable, quantitative (high yielding) under equimolar conditions, ultrafast (showing rate constants that go up to 160 000 L/mol s[267]), and resulted in a single reaction product.

A high degree of orthogonality was demonstrated by performing a TAD−diene reaction in the presence of a wide range of stoichiometric additives including various functional groups (Scheme 54). In this study, excellent chemoselectivity was observed, except in the case of free amines, which led to a somewhat reduced efficiency (only 95% adduct formation was observed in the presence of 1 equiv of butylamine or triethylamine). Even when a mixture of two reactive substrates is offered to 1 equiv of a TAD reagent, in many cases only one of the olefin-type substrates forms a TAD adduct selectively (Figure 10 and Table 14). To demonstrate the wide scope and modular nature of such TAD-based coupling reactions, macromolecular substrates were investigated in efficient polymer−small molecule and polymer−polymer couplings. For this purpose, linear polymers with a terminal cyclopentadiene moiety were synthesized and reacted with a low molecular weight TAD compound (4-BuTAD) or polymer-bound TAD reagent, respectively.

Scheme 54. Highly Orthogonal Diels−Alder Reaction of 4-BuTAD with a Conjugated Diene in the Presence of a Wide Range of Additives[a] [65]



[a]Such as acrylates, aldehydes, α-olefins, ketones, and thiols.

Recently, the research groups of Du Prez and Ravoo started exploring the use of triazolinediones for surface modification. In a first report, a layer-by-layer deposition of a polymer network was investigated.[382] The authors were able to assemble 58 covalently linked molecular layers in 20 min at room temperature on a silicon wafer. For this application, a divalent triazolinedione cross-linker and a specifically designed trivalent diene were utilized. Using ellipsometry, a linear increase of the layer thickness as a function of the layer number could be proven and further confirmed by AFM and XPS analyses (Scheme 55).

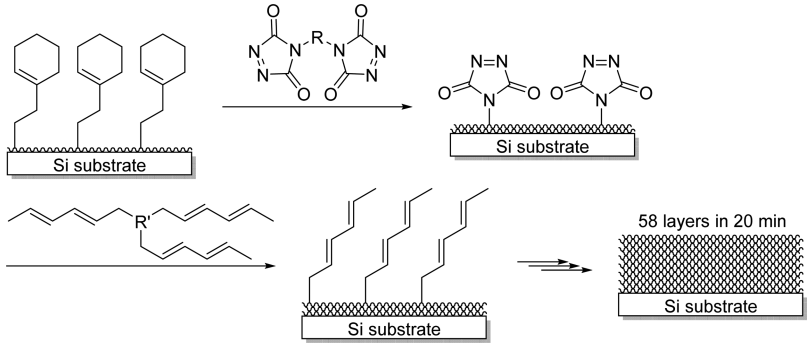
6.7. Clicking and Transclicking (Macromolecular) Substrates with TADs

Recently, Du Prez, Winne, and co-workers have explored TAD-based chemistry as a versatile platform for click chemistry applications, mainly in a macromolecular context.[65] A very wide range of ene-type reaction partners are available (simple olefins), which give reactions with the same click-like characteristics (Scheme 56a). On the basis of Baran et al.'s click−unclick TAD-based reaction for indoles (Scheme 56b),[217] Du Prez and co-workers described that the combination of a high thermodynamic forward driving force, as is required by click chemistry ideals, is only very rarely observed in combination with a kinetically feasible backward reaction. Such a dynamic feature usually goes hand-in-hand with either low "forward" yields or with hard-to-control free radical chemistry. Thus, this unique example of a dynamic TAD−indole reaction opened possibilities for unprecedented applications of TAD chemistry in a macromolecular context.

As an initial demonstration of dynamic TAD-click reactions, Du Prez and Winne reported a linear indole-functionalized polyurethane, making use of an indolediol, which was then cross-linked with a bifunctional TAD reagent. The resulting PU-network, containing TAD−indole cross-links, could be molded, recycled, and processed at elevated temperatures without loss of material properties. In one illustrative test, the stiff cross-linked material was broken into small fragments and then put into a mold under pressure for 30 min at 120 °C. A pristine sample was retrieved from the mold after cooling. While this last test was repeated seven times, a similar storage modulus was achieved each time.

Although the indole−TAD "unclick" reaction is an efficient and clean process, it is not practically feasible to fully "reverse" this click reaction in the case of nonvolatile reagents, because

Scheme 55. Layer-by-layer Synthesis: Alternatingly Dipping of an Alkene-Functionalized Silicon Substrate in, Respectively, a bisTAD and Trivalent Diene Solution Allows for the Assembly of 58 Layers in Merely 20 min



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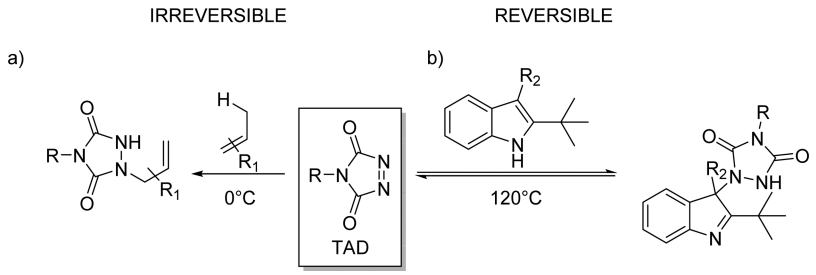
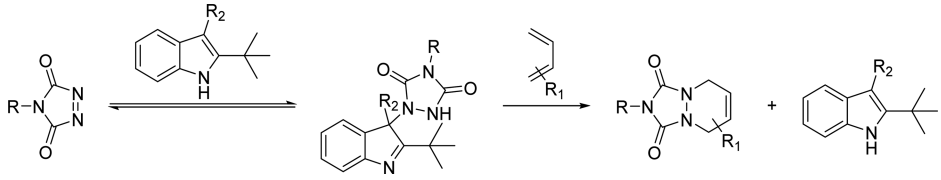
Scheme 56. (a) Irreversible Alder–Ene-Type Reaction with a 1,2,4-Triazoline-3,5-dione and (b) Reversible Alder–Ene Reaction by Replacement of the Alkene Derivative by a 1*H*-Indole

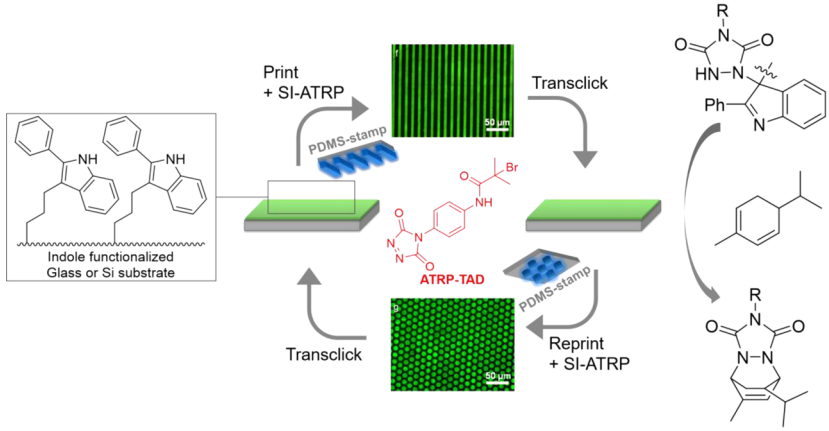


Scheme 57. Example of a Transclick Reaction: Reversible Alder–Ene Reaction between a 1,2,4-Triazoline-3,5-dione and a 1*H*-Indole, Followed by an Irreversible Diels–Alder Reaction[a]



[a]All reactions are under click conditions.

Scheme 58. Rewritable Surfaces: Heterogeneous Triazolinedione Click and Transclick Chemistry with Indole-Functionalized Substrates Enable Printing (Microcontact Chemistry) and Erasing (Transclick with α-Phellandrene) of Highly Defined Micropatterns[a]



[a]Adapted with permission from ref 127. Copyright 2015 John Wiley and Sons.

the indole and TAD reagents will re-form the adduct quantitatively at room temperature. However, by adding an alternative reaction partner for TAD, which is known to result in an irreversible adduct formation, the TAD–indole adduct can be completely unclicked, while another substrate is now clicked onto the TAD reagent. For this unprecedented concept in click chemistry applications, the term "*transclick reaction*" was introduced (Scheme 57) for "any covalent linking process that subsequently can be triggered to form a new bond with an alternative or orthogonal reaction partner and at the same time release one of the original binding partners, in which both bond-forming steps meet the usual requirements for click reactions".[65] Indeed, it was shown that a TAD and an indole react in an equimolar ratio to afford the TAD–indole Alder–ene adduct. When this adduct is heated in the presence of 1 equiv of a conjugated diene, the TAD molecule is completely and selectively transferred to this diene, resulting in a new Diels–Alder adduct and the release of the original indole compound without any side reactions.

In a very recent collaborative effort between the groups of Du Prez and Ravoo, the newly introduced "transclick" concept was used to develop rewritable polymer brush micropatterns.[127] For this, indole-functionalized surfaces were first patterned with a TAD-tagged atom transfer radical polymerization initiator, which was subsequently used in a surface-initiated polymerization. As a result of the dynamic nature of the TAD–indole connection at elevated temperature, (polymer) patterns could be erased, leaving the regenerated indole substrate ready for the printing of new patterns (Scheme 58). The robustness of this rewritable method was demonstrated by four repetitions on the same surface. In principle, this concept could be further expanded to selective and "programmed" transclick reactions from one substrate to another.

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7. CONCLUSIONS AND OUTLOOK

Triazolinediones are very reactive species that can participate in a whole range of reactions with specific classes of olefin-type substrates. Despite their high reactivity, many TAD reagents can be isolated in pure form and are bench-stable compounds, while more functionalized and/or sensitive TAD compounds can be easily generated in situ or used as a freshly prepared solution. This remarkable combination of stability and high reactivity can be appreciated by the vast body of literature on these reagents in the field of polymer synthesis and modification, which emphasizes its robustness, scalability, and relative safety when used under solvent-free conditions (50–100 g scale). Furthermore, 4-phenyl-TAD is a reagent that is commercially available in multigram scale.

TAD reactions are characterized by a very pronounced kinetic selectivity toward electron-rich π-systems, predominantly resulting in very fast hetero-Diels–Alder and hetero-Alder–ene type reactions. Importantly, many TAD-based reactions match all of the typical click chemistry requirements. The scope and modularity of such reactions have been demonstrated in this review by highlighting applications ranging from organic synthesis, polymer chemistry, and surface modification to site-selective labeling of natural proteins and peptides.

Moreover, the extraordinary kinetics of TAD-based reactions have also resulted in the development of unprecedented "dynamic" click reactions, including our introduction of the concept of "transclick" reactions as a means to program or direct successive and selective covalent exchange reactions. This resulted, for example, very recently in the development of rewritable polymer-based micropatterns onto surfaces.

The interest of using TAD reagents for various application has clearly known a renaissance in the past decade, partially related to the search for orthogonal, yet highly reactive, modular click chemistry tools. It can thus be expected that the further development of TAD-based click chemistry applications will be hampered by the limited availability of these reagents. Up to date, the oxidation of 4-functionalized urazoles is the only practical method to obtain useful TAD reagents. While chemoselectivity can be a major issue in this oxidation step, a vast amount of oxidation methods is available (see section 3), and—also in our experience—tuning of reaction conditions can lead to the desired TAD reagents in most cases.

The real issue in tailored TAD synthesis is the limited versatility and chemoselectivity in the assembly of urazole precursor compounds, related to highly reactive intermediates and/or harsh reaction conditions (see section 2). While common urazole substrates, such as 4-phenyl- or 4-butylurazole, and numerous bis-urazoles have been synthesized on (very) large scale and with high yields from cheap starting materials, many click-like applications require specific TAD reagents. However, urazoles bearing an additional functionality such as a functional handle, "clickable" group, fluorescent group, or bioactive molecule often require lengthy multistep procedures, with a moderate to low overall yield.

For niche applications that do not require large amounts of TAD reagents, such as in biomedical research, the cost of their synthesis is not an issue. Consequently, many heterobifunctional TAD reagents have been developed, some of which have been commercialized for small scale (milligram amount) use, either as the TAD reagent itself, i.e. DMEQ–TAD, or as the urazole precursor, i.e., alkyne–TADs and azide–TADs. For large-scale adoption and further developments in the field of TAD-based click chemistry, the chemical community is in need of short, scalable, and versatile synthesis methods for simple functionalized urazoles. We hope that interest in this particular topic might be sharpened by the current review and anticipate that a wide range of TAD- or urazole-based building blocks will become more readily available over time.

With this comprehensive overview of the existing syntheses and the reactivity of both urazoles and triazolinedione compounds, we do not only want to encourage researchers to develop novel synthetic strategies to produce TAD compounds on larger scale. As we expect that current applications of TAD chemistry have only scratched the surface of what these versatile synthetic tools can do, we also hope to inspire novel applications for the fascinating chemistry that surrounds triazolinediones, using the existing and already quite versatile TAD reagents that can be found in this review.

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Notes

The authors declare no competing financial interest.

Biographies

Kevin De Bruycker received his M.Sc. in chemistry from Ghent University, Ghent, Belgium, in 2013. His master thesis focused on reversible polymer systems based on the triazolinedione–indole ene reaction. Currently, he is pursuing his Ph.D. degree in the group of Prof. Filip Du Prez, conducting research on triazolinedione chemistry in interfacial systems.

Stijn Billiet obtained a M.Sc. in chemistry at Ghent University, Ghent, Belgium in 2011, performing his master thesis in the Polymer Chemistry Research Group working on self-healing polymers. His Ph.D. research dealt with the development of a new click chemistry platform making use of triazolinediones. After a stay in the research group of Prof. Craig Hawker (University of California—Santa Barbara) in 2015, he obtained his Ph.D. degree in the beginning of 2016.

Hannes A. Houck obtained both his B.Sc. (2012) and M.Sc. (2014) in chemistry from Ghent University, Ghent, Belgium. The subject of his master thesis revolved around the synthesis and modification of indole components and hence their tunable reversibility characteristics toward triazolinedione-based reactions. In 2015, he started post-graduate studies (Ph.D.) in a collaborative project under the supervision of Prof. Filip Du Prez at Ghent University and Prof. Christopher Barner-Kowollik at the Karlsruhe Institute of Technology, Karlsruhe, Germany.

Subrata Chattopadhyay obtained his M.Sc. in chemistry in 2009 at the Indian Institute of Technology Madras, Chennai, India, and received his Ph.D. degree in 2014 at RWTH Aachen University, Aachen, Germany. During his Ph.D. research, he studied the synthesis and antimicrobial studies of azetidinium-functionalized polymers in the group of Prof. Möller. Afterwards, he joined the group of Prof. Du Prez as a postdoctoral researcher. His research interest focuses on sustainable design of functional polymers and nanomaterials, which includes the use of click-like reactions, renewable starting materials, reactions in water, and enzyme-catalyzed reactions.

Johan M. Winne obtained a Ph.D. in chemistry from Ghent University in 2007, having studied cationic polyene cyclizations with Prof. Pierre

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De Clercq. He spent 2 years as a postdoctoral researcher with Prof. Gerald Pattenden at the University of Nottingham, Nottingham, UK, working on the total synthesis of terpenoid natural products. In 2009, he was appointed as doctor-assistant at Ghent University, and in 2015, he obtained a full-time independent faculty position. Besides maintaining active research interests in organic synthesis, aimed at biologically relevant applications, he has collaborated with the Polymer Chemistry Research Group to design and explore novel materials based on dynamic covalent chemistries.

Filip E. Du Prez has headed since 1999 the Polymer Chemistry Research Group (www.PCR.UGent.be) at Ghent University, in which about 30 researchers are dealing with the development of new polymer structures, exploration of powerful functionalization methods (e.g., TAD chemistry), and the design of dynamic/renewable polymer materials for specific applications, such as vitrimers. In 2008, he had a visiting professor position at the CAMD Research Center (University of New South Wales, Sydney, Australia). He is author of about 200 peer-reviewed publications, 11 patents, and 10 book chapters and has been (co)chairman of 10 (inter)national conferences on polymer chemistry related topics. Since 2008, he is one of the editors of *European Polymer Journal*.

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