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Regiospecific synthesis of N2-aryl 1,2,3-triazoles from 2,5-disubstituted
tetrazoles via photochemically generated nitrile imine intermediates.
Synlett, 25 (17). pp. 2480-2484. ISSN 0936-5214 ,
<http://dx.doi.org/10.1055/s-0034-1379010>**

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Regiospecific Synthesis of N2-aryl 1,2,3-Triazoles from 2,5-disubstituted Tetrazoles via Photochemically Generated Nitrile Imine Intermediates

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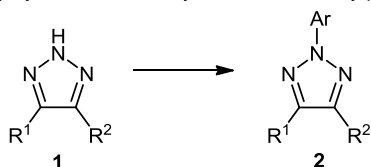
Received: The date will be inserted once the manuscript is accepted.

Abstract: The synthesis of N2-aryl 1,2,3-triazoles from 2,5-disubstituted tetrazoles was achieved under photochemical conditions. This simple and mild one step reaction provides regiospecific access to 2,4,5-substituted 1,2,3-triazoles via a nitrile imine intermediate. Syntheses of alkyl and heterocyclic derivatives were also investigated.

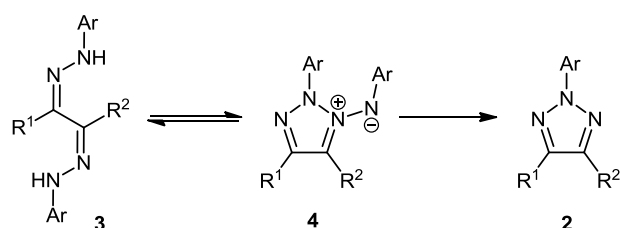
Key words: Photochemistry, Regioselectivity, Hydrazoneyl Chloride, Triazole, Indazole

1,2,3-triazoles are an important class of heterocycles due to a number of useful properties. N2-alkyl and acyl 1,2,3-triazoles act as PPAR agonists¹ and as selective CB1 receptor antagonists.² N2-aryl 1,2,3-triazoles have application as β_3 -Adrenergic receptor agonists,³ but more uniquely, have photonic properties which make them suitable as biocompatible UV/blue-light emitting dyes⁴ and inhibitors of polymer degradation.⁵ However, issues of regioselectivity between the N1 and N2 position means that the synthesis of N2-substituted 1,2,3-triazoles remains a challenge. Herein, we will focus on synthesis of N2-aryl 1,2,3-triazoles.

A) Synthesis of N2-aryl 1,2,3-triazoles by post-triazole arylation



B) Synthesis of N2-aryl 1,2,3-triazoles via bis(arylhydrazones)



Scheme 1 Common routes to N2-aryl 1,2,3-triazoles

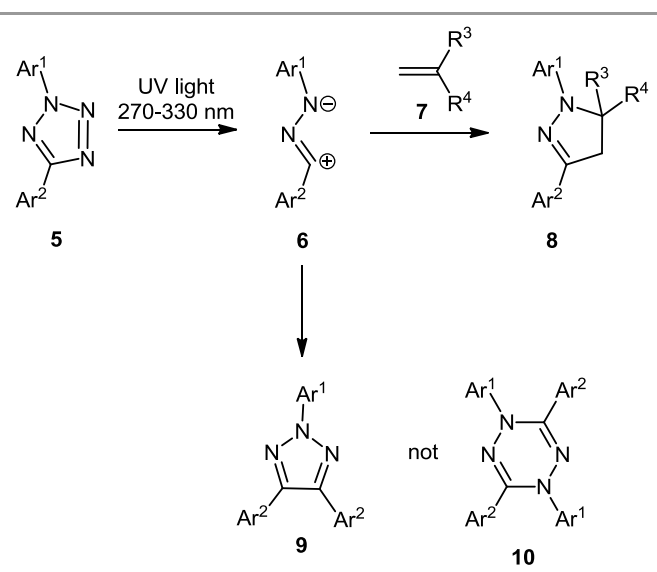
N2-aryl 1,2,3-triazoles **2** are synthesized via two main pathways: A) arylation of NH-1,2,3-triazoles **1** or B) rearrangement of bis(arylhydrazones) **3** via 1,2,3-triazolium 1-aminides **4** (Scheme 1).

Shi et. al. reported regioselective copper catalysed, or S_NAr mediated, N2-arylation utilising bulky ligands or

bulky 4,5-substituents.⁶ Palladium catalysis has also been reported for this application.⁷ Chen et. al. have demonstrated the regioselective generation of 1,2,3-NH-triazoles followed by subsequent arylation using one-pot multicomponent reactions starting from a variety of molecules.^{8,9,10} However, the scope of these S_NAr reactions was limited to electron poor substrates.

Syntheses from bis(arylhydrazones) **3** can proceed via acid catalysed rearrangement to 1,2,3-triazolium-1-aminides. Subsequent photolysis or reduction with carbon disulfide¹¹ and hydrogen sulfide¹² yield the triazole. Butler et. al. favoured oxidation to 1,2,3-triazolium-1-aminides and subsequent reduction to triazoles using lead oxide and phosphorous trichloride respectively.¹³ Most recently, Guru et. al. have shown efficient and regiospecific copper catalysed formation of triaryl 1,2,3- or 1,2,4-triazoles from arylhydrazones under aerobic conditions.¹⁴

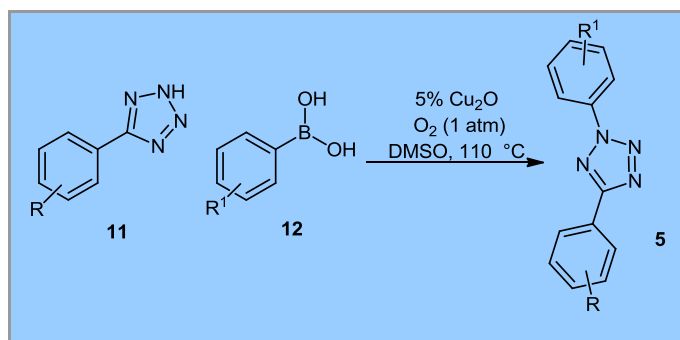
In an effort to synthesize pyrazoline adducts **8** to serve as probes for the intracellular visualisation of alkene-tagged systems **7**, we unexpectedly isolated 2,4,5-triaryl 1,2,3-triazoles **9** from 2,5-diaryl tetrazoles **5** (Scheme 2). Previous accounts had reported the formation of tetrazine **10** from the dimerisation of the nitrile imine intermediate **6**, in contrast to the triazoles isolated in the current study.^{15,16}



Scheme 2 Formation of 2,4,5-triaryl 1,2,3-triazoles as a by-product of photochemical pyrazoline synthesis

A survey of the literature revealed few examples of converting 2,5-diaryl tetrazoles to triazoles under photochemical conditions.^{17,18} Using recently developed methodology for the copper catalysed synthesis of 2,5-diaryl tetrazoles¹⁹ we decided to investigate the scope of this reaction. Accordingly, 2,5-diaryl tetrazoles **5a-q** were prepared from 5-aryl NH-tetrazoles **11** and aryl boronic acids **12** in 49-93% yield (Table 1) as substrates for the study.¹⁹

Table 1 Synthesis of 2,5-diaryl tetrazoles



Entry	R	R ¹	Yield/ %	Time/ h
5a	H	H	86	6
5b	p-Cl	H	64	72
5c	m-Cl	H	84	24
5d	o-Cl	H	85	24
5e	p-OMe	H	- ^a	-
5f	H	p-Me	93	6
5g	H	p-OMe	- ^a	-
5h	H	m-OMe	77	16
5i	H	o-OMe	49	16
5j	H	p-NH ₂	- ^b	-
5k	H	p-NH(CO)Me	- ^c	-
5l	H	p-CO ₂ Et	75	24
5m	H	m-CN	60	6
5n	H	p-NO ₂	55	24
5o	p-OMe	p-OMe	- ^a	-
5p	p-Cl	p-OMe	70	22
5q	p-SO ₂ NMe ₂	p-OMe	79	16

^aCommercially available

^bSynthesised by reduction of tetrazole 5n (86 %)

^cSynthesised by acetylation of tetrazole 5j (92%)

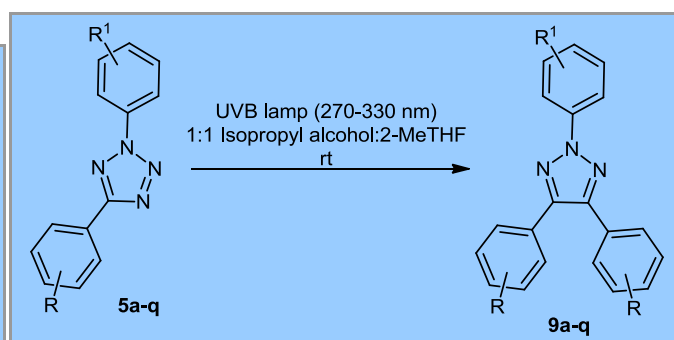
With a range of suitably functionalised tetrazole systems in hand, we conducted a solvent screen; a number of which were tolerated in the reaction, including: DCM, MeCN, TBME, 2-MeTHF, EtOAc, toluene and DMF. However, DMSO failed to produce any reaction due to inhibition of nitrile imine formation. Further experimentation revealed that a mixture of 2-MeTHF:isopropyl alcohol (1:1 v/v) was a suitable environmentally sustainable solvent system for the reaction.²⁰

Tetrazoles **5a-q** were irradiated with a UVB lamp (270-330 nm) in 2-MeTHF:isopropyl alcohol under atmospheric conditions, until all starting material had been consumed. The triazole products were isolated by chromatography and the results shown in Table 2 provide insight into the effects of substituents on the reaction.

Tetrazole **5a** was chosen as a baseline for comparison of substituent effects and gave triazole **9a** in 19% yield.

Initial substituent effects were investigated with C-aryl substitution (Entries **9b-9e**). Electron donating substituents appeared to improve yields slightly, relative to electronically neutral **9a**. Substitution in the meta and para positions were tolerated; however, o-Cl substitution failed to yield triazole **9d**. It was reasoned that this substitution was not tolerated due to steric effects in the nitrile imine intermediate.

Table 2 Photochemical synthesis of 2,4,5-triaryl 1,2,3-triazoles



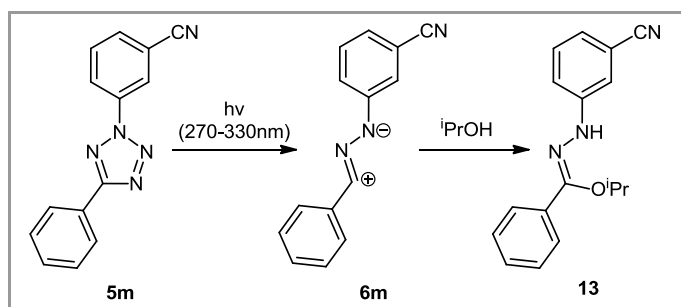
Entry	R	R ¹	Yield/ %	Time/ h
9a	H	H	19	24
9b	p-Cl	H	27	16
9c	m-Cl	H	28	31
9d	o-Cl	H	0	26
9e	p-OMe	H	38	30
9f	H	p-Me	47	19
9g	H	p-OMe	62	10
9h	H	m-OMe	25	35
9i	H	o-OMe	33	40
9j	H	p-NH ₂	17 (46) ^a	48 (7) ^a
9k	H	p-NH(CO)Me	41	6
9l	H	p-CO ₂ Et	14	23
9m	H	m-CN	0	24
9n	H	p-NO ₂	0	>100
9o	p-OMe	p-OMe	90	7
9p	p-Cl	p-OMe	67	16
9q	p-SO ₂ NMe ₂	p-OMe	0	6

^aIsopropyl alcohol:2-MeTHF solvent (5x volume)

We then investigated the electronic effect of substituents on the N-aryl ring (Entries **9f-9k**). In general, addition of electron donating groups favoured formation of the desired triazoles in significantly improved yields, particularly in the para position. Interestingly, ortho substitution is also tolerated, albeit in moderate yield. **Substitution with p-NH₂ was expected to give excellent reactivity; however, triazole 9j could only be isolated in 17% yield. Conducting the reaction under more dilute conditions gave an improved yield of 46% due to reduced by-product formation and improved solubility of tetrazole 5j. However, the role of concentration was not explored further in the current study. Instead, the reactive aniline moiety was protected as an acetamide derivative to afford triazole 9k in an improved yield of 41%.**

As expected, electron deficient N-aryl substituents were poorly tolerated. Of these, only p-CO₂Et tetrazole **5l** yielded the desired triazole and in a lower yield than for electronically neutral tetrazole **5a**. Photo-activation of p-

NO_2 tetrazole **5n** was inefficient, with starting material predominating after irradiation for 100 hours, and no discernible product evident after this time. Incorporation of a *m*-CN in tetrazole **5m** group did not afford the expected triazole **9m**. Instead, isopropyl-N-(3-cyanophenyl) benzo-hydrazone **13**, formed by trapping of the nitrile imine **6m** with isopropyl alcohol, was isolated as the major product with a yield of 54% (Scheme 3). Such nucleophilic quenching reactions have been reported previously.^{21,22} Repeating the reaction in ethyl acetate also failed to yield the desired product, presumably due to poor reactivity resulting from the electron withdrawing CN substituent. It should be noted that trapping of the nitrile imine was not observed with the more reactive tetrazole substrates.



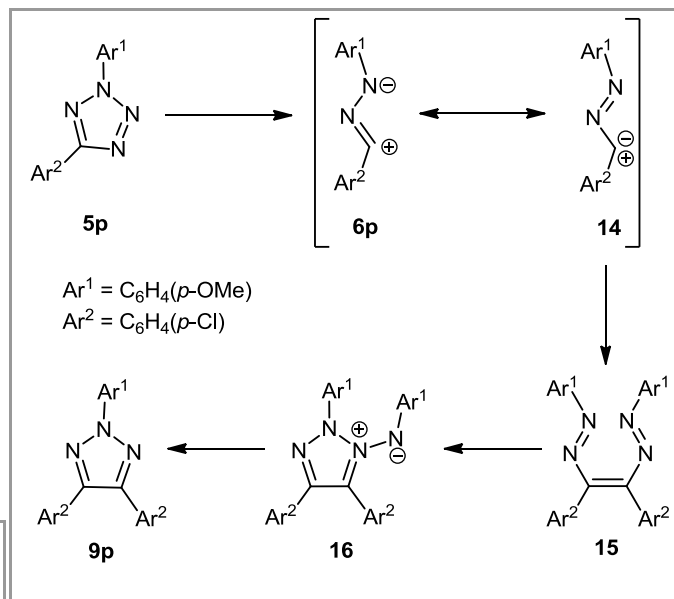
Scheme 3 Trapping of nitrile imine **13** by isopropyl alcohol

Finally, the observed trends in reactivity were combined when studying triazoles **9o-9q**. As predicted, combining an electron rich N-aryl ring with electron donating groups on the C-aryl ring gave significant improvements in yields. However, the electron withdrawing effects of a sulfonamide moiety could not be surmounted.

Interestingly, during the synthesis of triazole **9p** a precipitate was formed and, when isolated, Wanzlick dimer **15** was obtained in 57% yield instead of the expected triazole (Scheme 4). Previously, photochemical formation of this intermediate had only been observed spectroscopically.¹⁷ Further exposure to UV light yielded the desired product by rearrangement to 1,2,3-triazolium-1-aminide **16** and N-N bond cleavage.

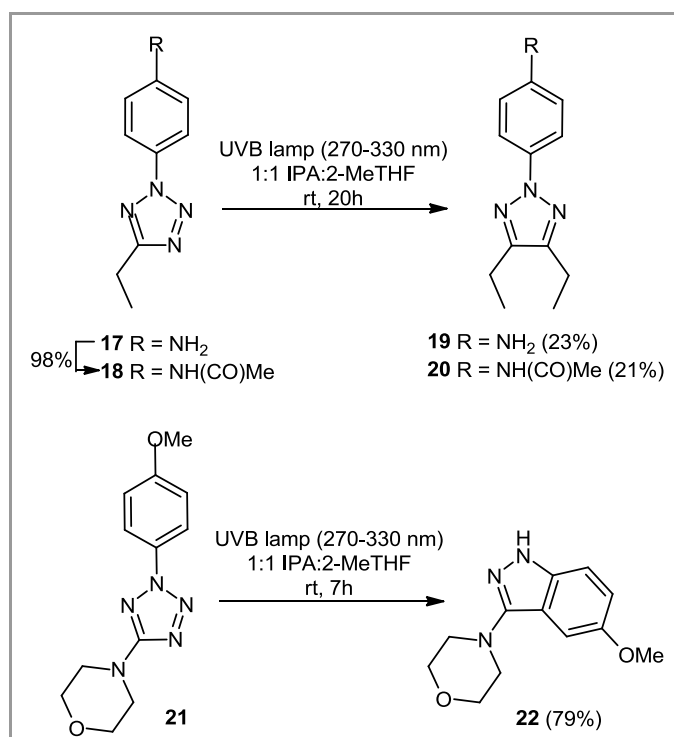
We suggest that formation of this Wanzlick dimer may occur through the carbenic resonance form **14** of the nitrile imine; which explains the tolerance of *o*-substituents on the N-aryl ring, but not the C-aryl ring.²³ Based on these observations, we also suggest that the tetrazine by-products previously reported during pyrazoline syntheses^{15,16} may have been Wanzlick dimers, as their NMR profile would appear similar. Furthermore, we did not observe tetrazine by-products during our syntheses of pyrazoline adducts.

Having investigated the synthesis of 2,4,5-triaryl 1,2,3-triazoles, we then sought to determine if C-heterocyclic or C-alkyl groups could be tolerated (Scheme 5).



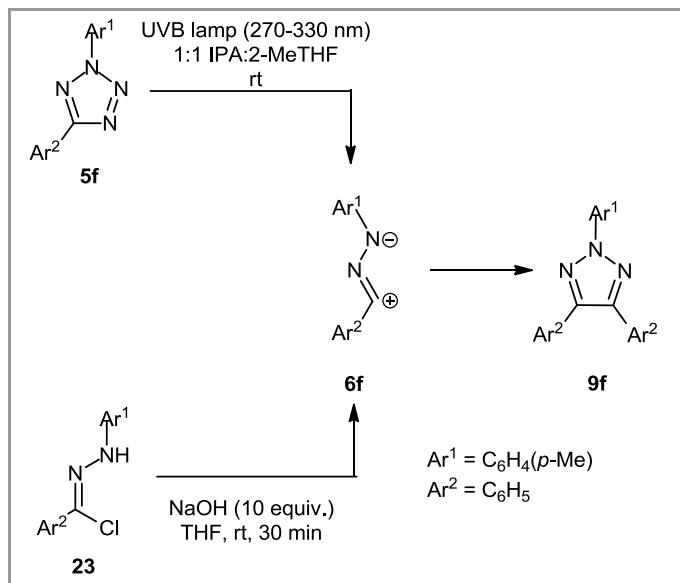
Scheme 4 Mechanism of N2-aryl 1,2,3-triazole formation

Commercially available 4-(5-ethyl-2H-tetrazol-2-yl)aniline **17** was irradiated to give triazole **19** in a modest 23% yield. In this case, masking the aniline with an acetamide moiety failed to improve the yield, indicating that C-alkyl groups are unfavourable. This could be attributed to a less stable carbocation in the nitrile imine intermediate, compared to C-aryl systems, resulting in a complex mixture of products. When irradiating C-morpholine tetrazole **21** we were surprised to observe efficient conversion to 3-morpholine indazole **22**. Such transformations have been observed previously using more forcing conditions such as high temperature.^{25,26}



Scheme 5 Synthesis of a N2-aryl 4,5-dialky 1,2,3-triazole and unexpected formation of substituted indazoles

Finally, we wished to investigate if other sources of nitrile imine intermediates could also yield 2,4,5-trisubstituted 1,2,3-triazoles. Interestingly, formation of tetrazine products via nitrile imine intermediates had been reported by Molteni et. al. from C-acyl, N-Aryl hydrazoneyl chlorides.²⁴ To determine if C-aryl substitution would instead yield triazole products we synthesised hydrazoneyl chloride **23** and generated nitrile imine **6f** using sodium hydroxide. Gratifyingly, the main product of the reaction was triazole **9f** (29% yield, unoptimised conditions) as confirmed by comparison to the previously obtained product (Scheme 6).



Scheme 6 Synthesis of triazole **9f** from 2,5-diaryl tetrazoles or hydrazoneyl chlorides

In conclusion, we have demonstrated the photochemical synthesis of a number of 2,4,5-triaryl 1,2,3-triazoles in two steps under mild conditions. Although the reaction shows strong dependence on substituent effects, with electron donating groups giving the best reactivity, we believe the current approach offers efficient access to this useful heterocyclic scaffold. This reaction is therefore complementary to other synthetic routes and alternative sources of nitrile imines can also be adopted. The synthesis of N2-aryl 4,5-dialkyl 1,2,3-triazole and 3-substituted indazole systems was also shown to be possible using this methodology.

Representative Example for the preparation of 2,5-diaryl tetrazoles: 5-phenyl-2-(p-tolyl)-2H-tetrazole (**5f**)

A solution of p-tolyl boronic acid (1.86 g, 13.7 mmol), 5-phenyl tetrazole (1.00 g, 6.84 mmol) and Copper(I) oxide (5 mol%, 0.049 g, 0.342 mmol) in DMSO (30 mL) was stirred under O₂ (1 atm) at 110 °C for 6 h. The reaction mixture was allowed to cool, diluted with ethyl acetate (200 mL) and washed successively with 1M HCl_(aq) solution (30 mL) and brine (30 mL) three times. The organic phase was separated, dried, and concentrat-

ed in vacuo. Purification by flash column chromatography (Si, 50 g, 0-10% EtOAc-cyclohexane, 60 mins) gave 5-phenyl-2-(p-tolyl)-2H-tetrazole **5f** (1.51 g, 93%) as a white solid. mp 103-104 °C. IR (cm⁻¹): 1507, 1448, 1212, 1012. ¹H NMR (400 MHz, CDCl₃): δ_H = 8.26 (dd, J = 2.0, 8.1 Hz, 2 H), 8.08 (d, J = 8.6 Hz, 2 H), 7.57 - 7.47 (m, 3 H), 7.38 (d, J = 8.6 Hz, 2 H), 2.46 (s, 3 H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ_C = 165.1, 139.9, 134.8, 130.5, 130.2, 128.9, 127.3, 127.0, 120.0, 119.8, 77.3, 77.2, 77.0, 76.7, 21.2 ppm. HRMS (ESI⁺): m/z calcd for C₁₄H₁₃N₄: 237.1135; found 237.1128.

Representative example for the preparation of 2,4,5-trisubstituted 1,2,3-triazoles: 4,5-diphenyl-2-(p-tolyl)-2H-1,2,3-triazole (**9f**)

A solution of 5-phenyl-2-(p-tolyl)-2H-tetrazole **5f** (200 mg, 0.85 mmol) in 1:1 Isopropyl alcohol:2-MeTHF (10 mL) was stirred under irradiation with a UVB lamp (270-330 nm) for 19 h. The reaction mixture was concentrated in vacuo and the residue purified by reverse phase chromatography (Si C₁₈, 50-95% MeCN:H₂O, HCO₂H modifier, 30 mins) to give 4,5-diphenyl-2-(p-tolyl)-2H-1,2,3-triazole **9f** (62 mg, 47%) as a brown gum. IR (cm⁻¹): 1510, 1441, 1268. ¹H NMR (400 MHz, CDCl₃): δ_H = 8.10 (d, J = 8.6 Hz, 2 H), 7.72 - 7.65 (m, 4 H), 7.43 (dd, J = 1.9, 4.9 Hz, 6 H), 7.33 (d, J = 8.6 Hz, 2 H), 2.45 (s, 3 H). ¹³C NMR (101 MHz, CDCl₃): δ_C = 145.7, 137.6, 137.3, 130.9, 129.8, 128.6, 128.6, 128.5, 127.1, 118.7, 21.1. HRMS (ESI⁺): m/z calcd for C₂₁H₁₈N₃: 312.1495; found 312.1496.

Acknowledgment

We would like to thank The University of Strathclyde and GlaxoSmithKline for the financial support of this project.

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