QUESTA E' LA VERSIONE REFERATA DI QUELLA PUBBLICATA IL 21/11/2014; https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-0034-1379550

Regioselective Formation of 5-Methylene-6-methoxy-1,4,5,6-tetrahydropyridazines from the

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Abstract: A regioselective inverse electron demand hetero-Diels−Alder (IEDDA) reactions of in situ-generated 1,2-diaza-1,3-dienes with methoxyallene is reported. These Lewis and Brønsted acid-free reactions benefits from operational simplicity, and allows access to synthetically valuable 5-methylene-6-methoxy-1,4,5,6-tetrahydropyridazines in high yields.

Key Words: IEDDA / [4+2] cycloaddition / methoxyallene / 1,2-diaza-1,3-dienes / tetrahydropyridazines

The development of new and practical synthetic strategies offering selectivity, atom- and step-economy is an important goal in modern organic chemistry. Since the first studies of the IEDDA reaction of 3,6-disubstituted 1,2,4,5-tetrazines were reported in 1959,[1] hetero Diels−Alder reactions with inverse electron-demand have gradually gained in interest because of their powerful applications in convergent synthesis of heterocyclic compounds from simpler starting materials.[2,3]

Over the years, 1,2-diaza-1,3-dienes[4] (DDs) have been shown to be fruitful synthetic intermediates for the preparation of an impressive number of heterocycles. They not only reacted as Michael acceptors in conjugated 1,4 additions with nucleophiles but also frequently applied in cycloaddition reactions with a wide variety of partners. In particular, short-lived and highly reactive C-4 unsubstituted *N*-EWG 1,2-diaza-1,3-dienes, usually generated from α-halo *N*-EWG hydrazones and intercepted in situ, serve as electron-deficient dienes (C2N2 components) in [4+1], [4+2] and [4+3] cycloaddition to generate highly complex five-, six- and seven-membered rings[4–7] (Figure 1, equations 1−3). For example, Bolm et al. developed the first enantioselective synthesis of dihydropyrazoles by formal [4+1] cycloaddition of in situ-derived azoenes and sulfur ylides[5] (equation 1). Most recently, Wang et al. disclosed a catalytic asymmetric synthesis of [2,3]-fused indoline heterocycles through inverse electron demand aza-Diels-Alder reaction of indoles with azoenes[6] (equation 2). Also, Chen, Xiao et al. reported a [4+3] cycloaddition of the same azoenes with C,N-cyclic azomethine imines leading to 1,2,4,5-tetrazepine derivatives[7] (equation 3).

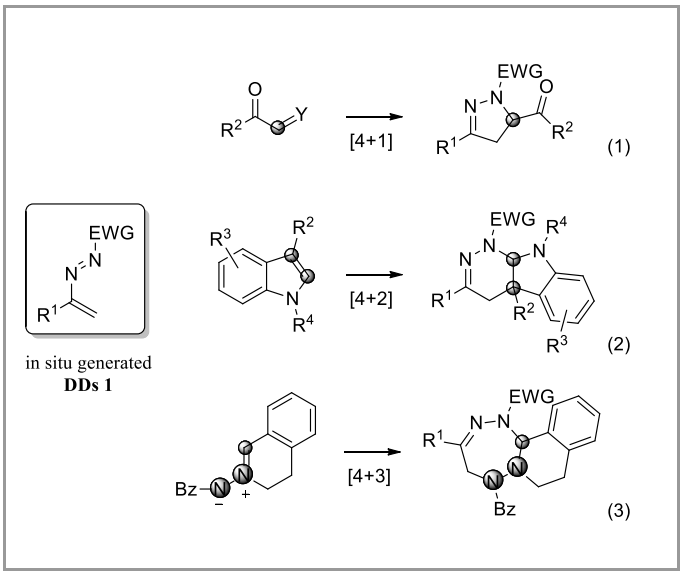


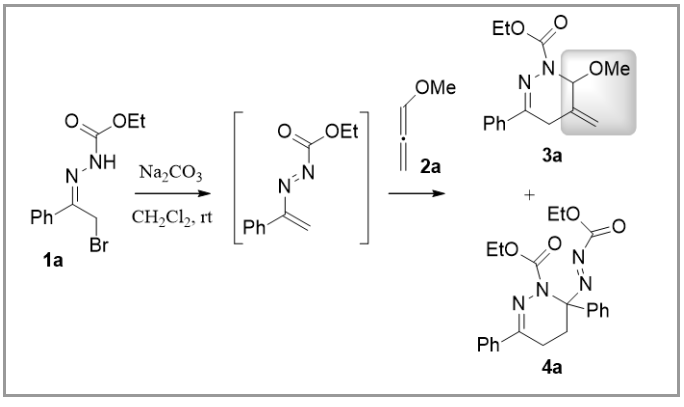
Figure 1. Use of in situ generated 1,2-diaza-1,3-dienes (DDs) **1** as C2N2 components in some recently reported annulation reactions.

On the other hand, the exceptional reactivity of easily accessible methoxyallene[8] with different classes of substrates has led to its use as convenient building block in a large number of diverse applications.[9] Among them, the Diels-Alder cycloaddition in which alkoxyallenes serve as dienophiles (C2 components) provides an attractive approach to the construction of various carbo- and heterocycles. For examples, alkoxyallenes reacts with α,β-unsaturated ketone/aldehyde, 1-aza-1,3-dienes, and phenanthroquinone to afford 3,4-dihydro-2*H*-pyranes, 1,2,3,4-tetrahydropyridazines and 1,4-dioxine, respectively, as reported by Boger,[10] Tietze,[11] Mattay,[12] and co-authors. Also, other papers of 2π partecipation of alkoxyallenes in [4+2] cycloaddition reactions with α-nitrosoalkenes to give 5,6-dihydro-4*H*-1,2-oxazines are described by Reisseg[13], and co-workers.

In an effort to expand the field of IEDDA chemistry, and taking cognizance of some recent examples of [4+2] azoene annulation reactions, we decided to investigate the use of methoxyallene as a productive C2 component in reactions with in situ-formed azoene compounds. Following this way, a facile regioselective access to synthetically valuable tetrahydropiridazine derivatives was realized. Indeed, 1,4,5,6-tetrahydropyridazine rings occur in a large number of pharmacologically active

molecules.[14] Despite the variety of synthetic approaches which are available for the construction of the pyridazine ring, partially saturated pyridazines[14d,15] such as tetrahydropyridazines **3a-o** (*vide infra*) bearing an exocyclic methylene group and a *N*,*O*-acetal carbon in two vicinal positions (C_5 and C_6 respectively) are as yet difficult to prepare. So far, only one example of such derivatives, namely 3-tetrazolyl-1,4,5,6-tetrahydropyridazine, has been described in the literature.[15c] These compounds could be used as precursors for further chemical transformations/postfunctionalizations, *e.g.* for the generation of electrophilic *N*-acyl iminium specie as an attractive dienophile in novel Diels−Alder cycloaddition.[16]

We started our investigation with readily available *N*-ethoxycarbonyl hydrazone **1a** and commercially available methoxyallene **2a**, as a representative model system (Table 1). 1.5 Equiv. of allene **2a** and 1 equiv. of Na_2CO_3 which is the most commonly used base for in situ generation of azoene compounds, were employed in initial experiments. TLC check of the reaction revealed that both the desired 1,4,5,6-tetrahydropyridazine **3a** (38% yield) as well as the pyridazine by-product **4a** (20% yield) were formed with slow consumption of the starting **1a**. It is well known that DDs bearing no substituents at the C-4 position show the tendency to self-condense giving cyclic dimers when no suitable or inefficient partners for cycloaddition reaction are present.[4c,17] Increasing the amount of metoxyallene (3 equiv.) and base (1.5 equiv.) seems to have considerable influence on the reaction profile and product **3a** was increased up to 64% (13% of **4a**). Thus, the side reaction could be completely suppressed when a 7 equiv. of methoxyallene **2a** and a 5 equiv. of base (Na_2CO_3) were used in this reaction and product **3a** was recovered in almost quantitative yield (98%).



Scheme 1. Reaction of ethoxycarbonyl hydrazone **1a** with methoxyallene **2a**.

With this satisfactory result in hand, various substituted α-halo *N*-acyl hydrazones as the azoene precursors, were then investigate to demonstrate the feasibility of the IEDDA cycloaddition with respect to metoxyallene.[18]

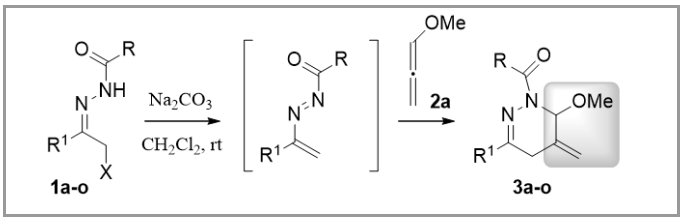
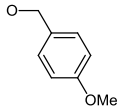
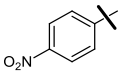
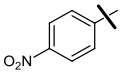
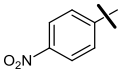
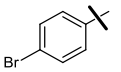
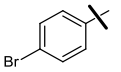
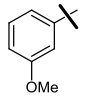
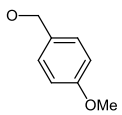


Table 1. Substrate scope of the IEDDA reaction of methoxyallene **2a** with various α-halo *N*-acyl hydrazones **1a–o**.[a]

Entry	**1**	X	R	R^1	**3**	%[b]
1	**1a**	Br	OEt	Ph	**3a**	98
2	**1b**	Br	O*t*-Bu	Ph	**3b**	41
3	**1c**	Br		Ph	**3c**	77
4	**1d**	Br	NHPh	Ph	**3d**	54
5	**1e**	Br	OMe		**3e**	88
6	**1f**	Br	OEt		**3f**	93
7	**1g**	Br	O*t*-Bu		**3g**	83
8	**1h**	Br	OMe		**3h**	77
9	**1i**	Br	OEt		**3i**	88
10	**1j**	Br	OEt		**3j**	74
11	**1k**	Cl	NHPh	CH_3	**3k**	26
12	**1l**	Br	OMe	CO_2Et	**3l**	60
13	**1m**	Br	O*t*-Bu	CO_2Et	**3m**	58
14	**1n**	Br		CO_2Et	**3n**	61
15	**1o**	Br	NHPh	CO_2Et	**3o**	71

[a] All reactions were carried out in CH_2Cl_2 (3 mL) at room temperature using α-halo *N*-acyl hydrazone **1** (0.5 mmol), methoxyallene **2a** (3.5 mmol) and Na_2CO_3 (2.5 mmol) until complete disappearance of **1** (TLC check, 24h-7d). [b] Yields of isolated products.

As shown in Table 1, different *N*-carboalkoxy and carboamido α-halo hydrazones resulted compatible with the reaction. Besides, it was found that a wide range of α-bromo *N*-acyl hydrazones **1a–j** with electron-neutral, -poor and -rich groups, (variously substituted at 3- or 4-positions of the aromatic ring,) were well tolerated, and the corresponding cyclized products were produced in high yields (Table 1, entries 5−10). In contrast, aliphatic hydrazone such as 4-phenylsemicarbazone **1k** derived from chloroacetone only gave a modest yield of the cyclization product **3k** (Table 1, entry 11). Notably, ester-substitued *N*-acyl hydrazones **1l–o** can be successfully employed in the cycloaddition reaction, leading to the relative products with good yields (Table 1, entries 12−15).

The structure of the products **3a**–**o** has been established by a consideration of spectroscopic properties of **3a**.[19] In particular, ^{1}H and ^{13}C NMR spectrum of **3a** in $CDCl_3$ exhibit some peculiarities: (i) one singlet at 5.79 ppm attributed to the downshielded proton of the tertiary *N*,*O*-acetal carbon; (ii) two distinctive doublets at 5.26 and 5.12 ppm ascribable to methylene (=CH_2) exocyclic group where geminal (^{2}J = 2.8 Hz) coupling was observed; one double triplets (^{2}J = 19.6 Hz and ^{4}J = 2.8 Hz) at 3.52 ppm and one doublet (^{2}J = 19.6 Hz) at 3.30 ppm attributed to the diastereotopic CH_2 protons of the pyridazine nucleus; (iii) the presence of two distinctive C-sp^3 signals at 28.9 ppm and 82.6 ppm attributed to aliphatic methylene (CH_2) and tertiary (CH) *N*,*O*-acetal carbon, respectively. (iv) the presence of two diagnostic C-sp^2 signals (113.4 and 134.5 ppm) assignable to the C=CH_2 double bond fragment. The six-membered cyclic structure was further confirmed by ^{1}H-^{1}H homonuclear and ^{13}C-^{1}H heteronuclear correlations (direct and long-range) for compound **3a**. In addition the mass spectrum of **3a** displayed a molecular ion peak at *m/z* = 274 [M^+].

All attempts to vary the allene failed. As expected, the employment of not activated ~~alkyl~~ substituted allenes *i.e.* methylallene **2b**, cyclohexylallene **2c**, 4-hydroxy-buta-1,2-diene **2d** and ethyl 2,3-butadienoate **2e** resulted in no formation of tetrahydropyridazine derivatives and only cyclodimerization product were observed (Figure 2).

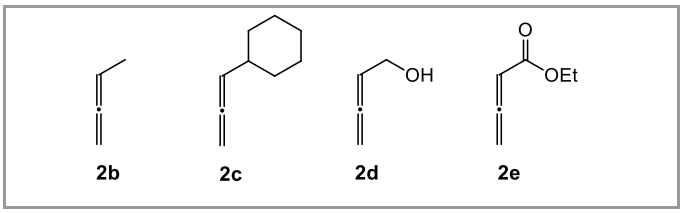


Figure 2. Other allenes texted in [4+2] cycloaddition of azoenes.

In this intermolecular [4+2] cycloaddition the methoxy group is located at C-6 of the pyridazine ring since the enol ether double bond of the methoxyallene results exclusively attacked by the azoene partner.

In summary, we have developed a regioselective inverse electron demand hetero-Diels-Alder reaction of in situ-generated 1,2-diaza-1,3-dienes with methoxyallene. The reaction provides a facile access to intriguing 1,4,5,6-tetrahydropyridazines containing vicinal exocyclic methylene double bond and cyclic *N*,*O*-acetal center (C_5 and C_6 respectively) in good to excellent yields. We are currently investigating the expansion of the reaction scope of this [4+2] cycloaddition as well as its synthetic application.

Acknowledgements: This work was supported by financial assistance from the Ministero dell'Università, dell'Istruzione e della Ricerca (MIUR) – Rome, and Università degli Studi di Urbino "Carlo Bo", Italy.

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18. In a typical procedure, to a CH_2Cl_2 solution (4 mL) of *N*-acyl hydrazone **1a** (0.150 g, 0.5 mmol) were added methoxyallene **2a** (0.258 g, 3.5 mmol) and Na_2CO_3 (0.265 g, 2.5 mmol) at 25 °C until complete disappearance of **1a** (TLC check, 30h). After removal the solvent, the residue was purified directly by flash column chromatography (silica gel, cyclohexane:EtOAc = 90:10) to give the corresponding 1,4,5,6-tetrahydropyridazine **3a** as a pale yellow oil (0.134 g, 98%).
19. **Ethyl 6-methoxy-5-methylene-3-phenyl-5,6-dihydropyridazine-1(4*H*)-carboxylate (3a)** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (t, *J* = 7.2 Hz, 3H), 3.30 (d, ^2J = 19.6 Hz, 1H), 3.39 (s, 3H), 3.52 (dt, ^2J = 19.6 Hz, ^4J = 2.8 Hz, 1H), 4.30−4.41 (m, 2H), 5.12 (d, ^2J = 2.8 Hz, 1H), 5.26 (d, ^2J = 2.8 Hz, 1H), 5.79 (s, 1H), 7.35−7.41 (m, 3H), and 7.77−7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.5 (q), 28.9 (t), 54.9 (q), 62.8 (t), 82.6 (d), 113.5 (t), 125.6 (d), 128.3 (d), 129.4 (d), 134.5 (s), 136.4 (s), 147.5 (s), 155.0 (s). IR (nujol): ν_{max} = 1714. MS *m/z* (%): 274 (88), 257 (91), 249 (100), 235 (45); anal. calcd. for $C_{15}H_{18}N_2O_3$ (274.32): C 65.68, H 6.61, N 10.21; found: C 65.55, H 6.58, N 10.30.

Regioselective Formation of 5-methylene-6-methoxy-1,4,5,6-tetrahydropyridazines from the [4+2] cycloaddition reaction of in Situ-Generated 1,2-Diaza-1,3-dienes with Methoxyallene.

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