HETEROCYCLES, Vol. 55, No. 2, 2001, pp. 243 - 248, Received, 24th November, 2000

CYCLOADDITION OF SYNTHETIC EQUIVALENT OF NON-STABILIZED AMINONITRILE YLIDES: A NEW ROUTE TO AMINO-SUBSTITUTED Δ^2-IMIDAZOLINES AND Δ^3-1,2,4-TRIAZOLINES

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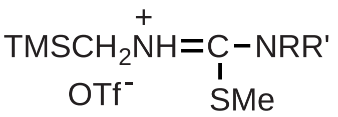
Abstract - The *N*-unsubstituted nonstabilized azomethine ylides generated from the desilylation of *N*-[(trimethylsilyl)methyl]iminium triflates undergo successful cycloaddition to strongly polarized sulfonylimines and diethyl azodicarboxylate to produce the corresponding Δ^2-imidazolines and Δ^3-1,2,4-triazolines together with the initial cycloadducts. The initial cycloadducts are converted to the corresponding aminonitrile ylide cycloadducts. Thus the present process provides a new route to amino-substituted Δ^2-imidazolines and Δ^3-1,2,4-triazolines that are otherwise relatively inaccessible.

The 1,3-dipolar cycloaddition of azomethine ylides to dipolarophiles is an important method for the construction of five-membered ring nitrogen heterocycles.[1] We recently reported[2] the generation of nonstabilized *N*-unsubstituted azomethine ylides (**A**) from the desilylation of *N*-[(trimethylsilyl)methyl]-iminium triflates (**1**) and their 1,3-dipolar cycloaddition reactions with electron-deficient alkenes, alkynes and aldehydes in which 2-amino-substituted pyrrolines, pyrroles and 2-oxazolines are formed, respectively: thus, **A** can be synthetic equivalents of nonstabilized aminonitrile ylides (**B**) that are otherwise relatively inaccessible.


$\mathrm{TMSCH_2\overset{+}{N}H{=}\underset{SMe}{C}{-}NRR'}\quad \mathrm{OTf^-}$

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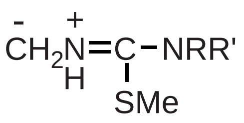

$\mathrm{\overset{-}{C}H_2\underset{H}{\overset{+}{N}}{=}\underset{SMe}{C}{-}NRR'}$

A


$\mathrm{\overset{-}{C}H_2\overset{+}{N}{\equiv}CNRR'}$

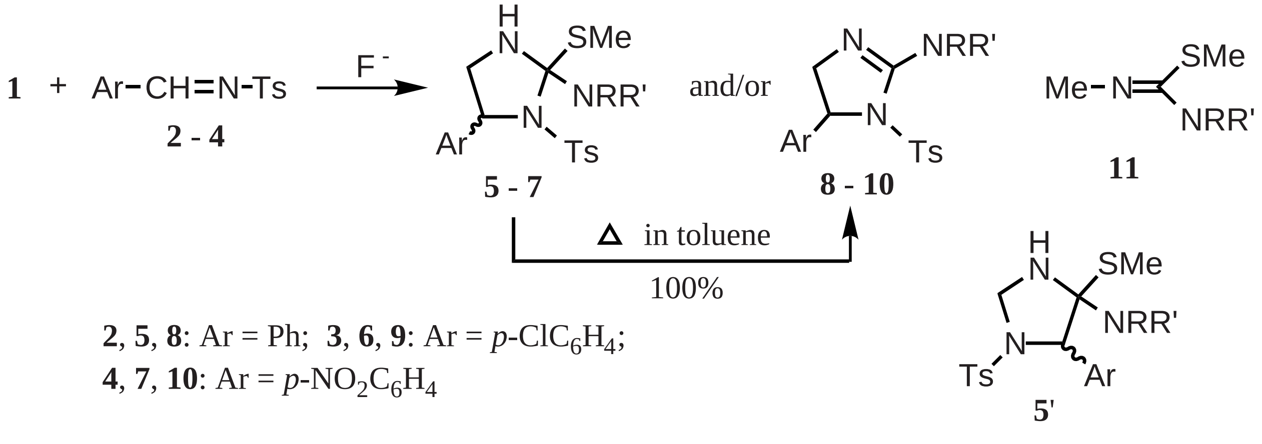
B

Nitrile ylides are also one of the interesting members of 1,3-dipole family.[3] Although the cycloaddition of aryl-substituted nitrile ylides ArC=NCHR has been widely studied, nitrile ylides without aromatic substitution are rare.[4-6] Particularly, the generation and cycloaddition of nonstabilized aminonitrile ylides such as **B** are little known.[7] Thus, in an effort to expand the synthetic utility of nonstabilized azomethine ylides (**A**) that are synthetic equivalent of aminonitrile ylides (**B**), we have investigated on cycloaddition reactions of **A** with 1,3-dipolarophiles other than electron-deficient alkenes, alkynes and aldehydes. The present communication describes the cycloaddition of **A** to imines and azo compounds.

Cycloaddition Reactions with Imines. Although imines were first employed in cycloadditions with azomethine ylides as early as 1963,[8] there is only a limited number of reports concerning the imine cycloadditions. Azomethine ylides generated through 3,4-dihydroisoqunolinium salts,[8,9] and aziridines,[10,11] reacted with imines to give the corresponding imidazolidines. It would be no exaggeration to say that most imine cycloadditions have been discovered unexpectedly during investigations on the generation of azomethine ylides from imines.[12] In recent years,[13] it has been reported that the ester-stabilized imidate ylide, derived from the condensation of ethyl acetimidate with dimethyl aminomalonate, reacted with benzylidenealkylamines to give Δ^2-imidazolines with the loss of ethanol; thus the imidate ylide can be a synthetic equivalent of ester-stabilized nitrile ylide. To the best of our knowledge little has been investigated on the reaction of nonstabilized azomethine ylides with imines.

On the other hand, cycloadditions of nitrile ylides to imines are also little employed as useful routes of heterocyclic synthesis.[14-16]

If the cycloaddition of azomethine ylides (**A**) generated from iminium salts (**1**) to imines occurs in the similar manner to those with electron-deficient carbon-carbon multiple bonds and aldehydes,[2] a novel and general route to amino-substituted imidazolidines and/or imidazolines is offered through the cycloaddition and elimination sequence. Unfortunately the imines such as arylidenealkylamines and -arylamines were very sluggish to the azomethine ylides from **1**. However, we have eventually found that the strongly polarized sulfonylimines[17] such as benzylidene- (**2**), *p*-chlorobenzylidene- (**3**) and *p*-nitrobenzylidene-*p*-toluene-sulfonamide (**4**) are reactive to the intended cycloaddition reaction.



2, **5**, **8**: Ar = Ph; **3**, **6**, **9**: Ar = *p*-ClC_6H_4;
4, **7**, **10**: Ar = *p*-$NO_2C_6H_4$

a: R = H, R' = Ph; **b**: RR' = -$(CH_2)_5$-; **c**: RR' = -$(CH_2)_2O(CH_2)_2$-

Scheme 1

The reaction of anilino-substituted *N*-[(trimethylsilyl)methyl]iminium triflate (**1a**) with imine (**2**) in the presence of cesium fluoride (CsF) at room temperature gave a single product, whose molecular formula corresponded to that of initial cycloadducts, 2-anilino-2-methylthio- (**5a**) or 5-anilino-5-methylthio-4-phenyl-3-tosyl-imidazolidine (**5'a**). On the basis of chemical shifts and splitting pattern of methine and methylene protons of its imidazolidine ring in ^1H NMR spectrum, however, the product was concluded to be **5a**.

Similar reactions of **1a** with imines (**3**) and (**4**) afforded the corresponding initial cycloadducts, 2-anilino-2-methylthio-substituted 4-(*p*-chlorophenyl)- (**6a**) and 4-(*p*-nitrophenyl)-3-tosylimidazolidine (**7a**), although the aminonitrile cycloadduct, 2-anilino-5-(*p*-chlorophenyl)-1-tosyl-Δ^2-imidazoline (**9a**) was formed as a by-product in the reaction with **3** (Scheme 1, Table 1).[18] In the cycloaddition of azomethine ylides (**A**) to carbon-carbon and carbon-oxygen multiple bonds the initial cycloadducts could not be isolated, but instead the products that are one oxygen state higher than initial cycloadducts were directly obtained.[2] It is thus noteworthy that imidazolidines (**5a**, **6a** and **7a**) are the first example of stable initial cycloadducts of **A** to multiple bonds. The initial cycloadducts (**5a**, **6a** and **7a**) were quantitatively converted to the corresponding 2-anilino-4-aryl-1-tosyl-Δ^2-imidazolines (**8a**, **9a** and **10a**), when refluxed in toluene.

Table 1. Cycloaddition Reaction with Imines (**2** - **4**)[a]

Entry	Precursor	Imine	Molar ratio[b]	Products (yield, %)[c]
1	**1a**	**2**	1/1/1.2	**5a** (42), **11a** (31)
2	**1a**	**3**	1/1/1.2	**6a** (55), **9a** (7)
3	**1a**	**4**	1/1/1.2	**7a** (70)
4	**1b**	**3**	1/1/1.2	**9b** (50), **11b** (21)
5	**1b**	**3**	1/2/1.2	**9b** (66)
6	**1b**	**4**	1/1/1.2	**10b** (58)
7	**1c**	**3**	1/1/1.2	**9c** (31), **11c** (24)
8	**1c**	**4**	1/1/1.2	**10c** (32), **11c** (21)
9	**1c**	**4**	1/2/1.2	**10c** (52)

[a] The reactions were carried out in dry DME at room temperature for 6 h under argon. [b] Molar ratio of **1**/imine/CsF. [c] Isolated yield based on the precursor (**1**).

The reaction of *N*-[(trimethylsilyl)methyl]iminium triflates (**1b**) and (**1c**) bearing cyclic amine moiety with more reactive imines (**3**) and (**4**) was next investigated under similar conditions, since the reactions with **2** were very sluggish. Some selected runs are listed in Table 1 (Entries 4-9). The azomethine ylides generated from **1b** and **1c** were somewhat less reactive than that from **1a**. In contrast with **1a**, the corresponding initial cycloadducts (**6b**, **6c** or **7b**, **7c**) could not be isolated, but instead the formal aminonitrile ylide cycloadducts (**9b**, **9c** or **10b**, **10c**) were directly obtained, respectively.

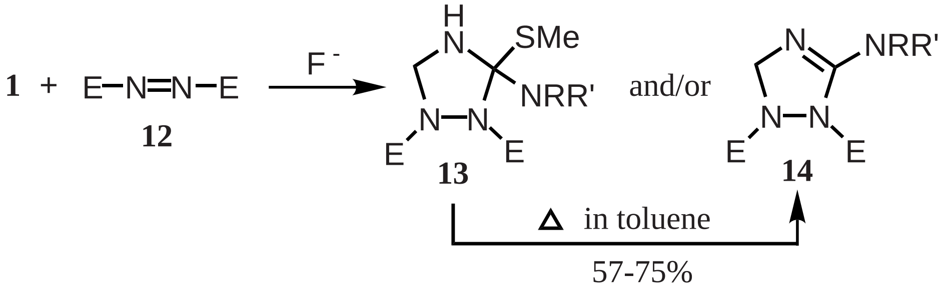
In the reaction between rather inactive two reagents, imine (**11**) which was probably derived from the azomethine ylide through a 1,2-proton migration was obtained as the by-product.[19]

Cycloaddition Reaction with Diethyl Azodicarboxylate. Although only limited examples are known, the electron-deficient nitrogen-nitrogen double bond of azodicarboxylates is also reactive to azomethine ylides and nitrile ylides. Azomethine ylides generated through the aziridine,[20] tautomerization[21] and decarboxylation routes[22] are captured as the corresponding triazolidine cycloadducts. A variety of nitrile ylides generated from the photolysis of 2*H*-azirines,[23] and thermolysis of 2,3-dihydro-1,4,$2\lambda^5$-oxazaphospholes[24] have been found to react with diethyl azodicarboxylate to yield the corresponding Δ^3-1,2,4-triazolines. It has also been reported that azobenzene reacted with nitrilio hexafluoro-2-propanides to yield the Δ^3-1,2,4-triazolines.[25]

The reaction of azomethine ylides generated from **1** was thus investigated with the electron-deficient nitrogen-nitrogen double bond of diethyl azodicarboxylate (**12**). This reaction was particularly interesting, since isolation of the initial cycloadducts, 1,2,4-triazolidines, might be expected in analogy with the reaction of imines (**2-4**) described above.

The reaction of **1a** with **12** in DME at room temperature gave the expected initial cycloadducts, 3-anilino-1,2-bis(ethoxycarbonyl)-3-methylthio-1,2,4-triazolidines (**13a**) in good yields, but the same reaction in refluxing DME afforded a mixture of **13a** and the corresponding aminonitrile cycloadduct, 3-anilino-1,2-bis(ethoxycarbonyl)-Δ^3-1,2,4-triazoline (**14a**). Similarly, **1b** or **1c** reacted with **12** to give the corresponding initial cycloadduct (**13b**) or (**13c**) and/or Δ^3-1,2,4-triazoline (**14b**) or (**14c**), whose relative yields depended on the reaction temperature. Elimination of methanethiol from initial cycloadduct (**13**) was more sluggish than that from the imine-initial cycloadducts. When heated in refluxing toluene for 8 h, however, the initial cycloadducts (**13**) were converted into the corresponding Δ^3-1,2,4-triazolines (**14**) in 57-75% yields, together with recovery of **13**.

Table 2. Cycloaddition Reaction with Diethyl Azodicarboxylate (**12**)[a]



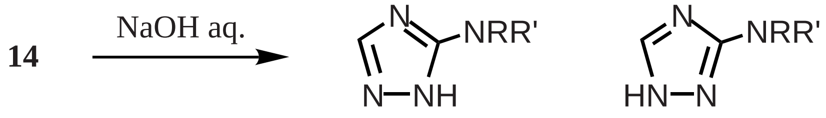
E = COOEt

a: R = H, R' = Ph; **b**: RR' = -$(CH_2)_5$-; **c**: RR' = -$(CH_2)_2O(CH_2)_2$-

Entry	Precursor	Temp.	Products (yield, %)[b]
1	**1a**	rt	**13a** (73)
2	**1a**	reflux	**13a** (8), **14a** (49)
3	**1b**	rt	**13b** (54)
4	**1b**	reflux	**13b** (20), **14b** (31)
5	**1c**	rt	**13c** (74)
6	**1c**	reflux	**13c** (51), **14c** (19)

[a] The reactions (molar ratio of **1**/**12**/CsF=1/1/1.2) were carried out in dry DME at room temperature or reflux for 8 h. [b] Isolated yield based on the precursor (**1**).

Hydrolysis of **14a-14c** with 10% aqueous sodium hydroxide in refluxing ethanol for 1 h afforded the corresponding amino-substituted 1,2,4-triazoles in good yields. On the basis of ^{1}H NMR spectra in which the proton at 5-position appeared as a singlet, the triazoles were assigned as 3-amino-2*H*-1,2,4-triazoles (**15a-15c**), but not 1*H* isomers (**15'**) (Scheme 2).



14

15a (78%)
15b (74%)
15c (79%)

15'

a: R = H, R' = Ph; **b**: RR' = -$(CH_2)_5$-; **c**: RR' = -$(CH_2)_2O(CH_2)_2$-

Scheme 2

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7. Recently, two research groups[6a,6b] reported that in the reactions of carbonyl compounds 2-azaallyl anions generated through the desilylation of certain *N*-(silylmethyl)isothioureas served as synthetic equivalents of aminonitrile ylides such as **B**.
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18. All the new compounds reported herein were characterized by spectroscopy and microanalysis. For example, **6a:** colorless needles ($CHCl_3$), mp 174-175 ˚C (decomp). IR 3412, 1584, 1334, 1162 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.10, 2.33 (each s, 3H), 3.25-3.46 (m, 2H), 4.58 (dd, *J* = 6.8, 13.5 Hz, 1H), 6.42 (br s, 1H), 6.58-6.61 (m, 2H), 6.90-6.96 (m, 1H), 7.17-7.32 (m. 8H), 7.56-7.60 (m, 2H), 8.31 (d, *J* = 6.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 13.15, 20.86, 47.42, 55.76, 121.99, 126.40, 127.83, 128.41, 128.64, 129.32, 131.53, 137.70, 139.39, 142.41, 149.52, 152.58; MS *m/z* (relative intensity) 475 (M^+, 0.5), 473 (M^+, 1), 427 (8), 425 (19), 272 (23), 270 (66), 152 (5), 150 (17), 133 (100). Anal. Calcd for $C_{23}H_{24}N_3O_2ClS_2$: C, 58.27; H, 5.10; N, 8.86. Found: C, 58.21; H, 5.11; N, 8.86. However, the stereochemisty of initial cycloadducts (**5a**, **6a** and **7a**) was not clear yet.
19. In the reaction of **1** with rather inactive aromatic aldehyde under similar conditions imine (**11**) was obtained as the by-product.[2]
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