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Azavinyl Azomethine Ylides from Thermal Ring Opening of α-Aziridinohydrazones: Unprecedented 1,5-Electrocyclization to Imidazoles

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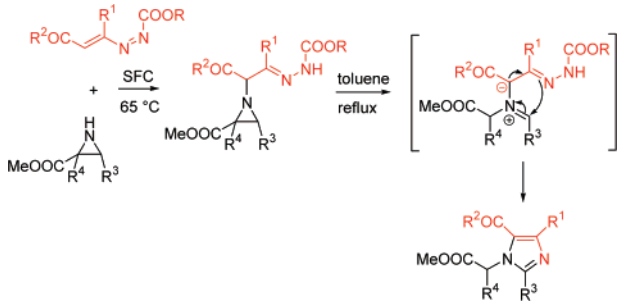
ABSTRACT



Michael-type addition of aziridinecarboxylates to 1,2-diaza-1,3-butadienes under solvent-free conditions (SFC) resulted in the formation of α-aziridinohydrazone adducts. In toluene under reflux, α-aziridinohydrazones gave imidazoles in moderate to good yields. Such a reactivity pattern is explained by 1,5-electrocyclization of azavinyl azomethine ylide generated through thermal ring opening of α-aziridinohydrazones.

In the charming panorama of ylides, azomethine ylides represent a particular case of useful intermediates in organic synthesis. Based on his pioneer studies, in 1963 Huisgen disclosed the existence of 1,3-dipoles and opened the route to 1,3-dipolar cycloadditions.[1] Both intra- and intermolecular 1,3-dipolar cycloadditions of simple azomethine ylides with dipolarophiles lead to five-membered heterocycles containing one nitrogen atom, namely pyrrolidine or pyrroline derivatives (Figure 1, eq 1).[2] When a double bond or a 1,3-diene system is conjugated with the azomethine ylide, five- (pyrroline) or seven-membered (dihydroazepine) heterocycles can be obtained by 1,5- or 1,7-electrocyclization, respectively (Figure 1, eqs 2 and 3).[3]

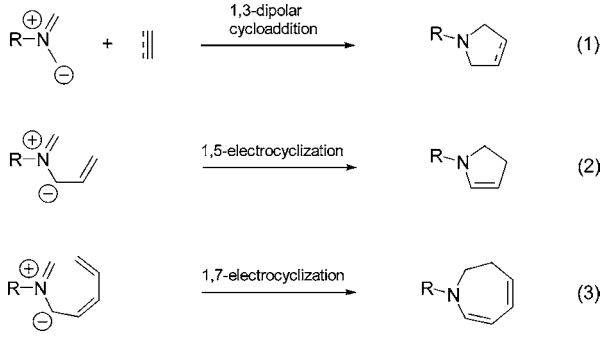


Figure 1. Typical reactivity patterns of azomethine ylides.

Azomethine ylides are usually generated in situ by a variety of methods, including photo- or thermolysis of aziridines.[2]

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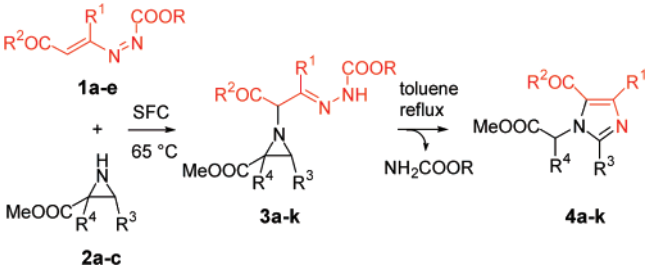
Indeed, aziridines represent a versatile class of building blocks for a wide range of synthetic applications.[4] Their chemistry is characterized by the relatively high ring strain, which results in the easy cleavage of the carbon−nitrogen bond by nucleophiles.[4f] However, aziridines are also known to react by thermal or photochemical electrocyclic ring-opening at the carbon−carbon bond to give azomethine ylides and represent useful precursors of such highly reactive species. Hence, aziridines can be considered as masked 1,3-dipoles that can undergo either inter- or intramolecular [3 + 2] cycloadditions with a range of dipolarophiles to yield five-membered nitrogen-containing heterocycles.[5−7]

On the other hand, 1,2-diaza-1,3-butadienes have been extensively investigated by several authors as building blocks in organic synthesis.[8] In fact, these compounds act as efficient regioselective Michael acceptors and give rise to a large variety of acyclic or heterocyclic products by means of various subsequent intramolecular cyclizations where three atoms (C−C═N) of the azo-ene system are frequently involved.

As part of our ongoing interest in this chemistry, we decided to investigate the Michael-type addition of aziridinecarboxylates **2a**−**c** to 1,2-diaza-1,3-butadienes **1a**−**e**. In particular, we expected that α-aziridinohydrazone adducts **3a**−**k** would undergo aziridine ring-opening and subsequent intramolecular ring-closing[4,9] to tetrahydropyrazines through a formal [3 + 3] intramolecular cycloaddition.

1,4-Conjugate addition of aziridines **2a**−**c** to the azo-ene system of 1,2-diaza-1,3-butadienes **1a**−**e** under solvent free conditions (SFC) at 65 °C afforded the corresponding α-aziridinohydrazones **3a**−**k** in excellent yields (Scheme 1, Table 1). Surprisingly, however, treatment of adducts **3a**−**k** in toluene under reflux resulted in the unexpected formation of imidazoles **4a**−**k**[10,11] in good yields (Scheme 1, Table 1).

Scheme 1. Synthesis of α-Aziridinohydrazones **3a**−**k** and Subsequent 1,5-Electrocyclization to Imidazoles **4a**−**k**



The formation of the imidazole ring can be rationalized as shown in Scheme 2. Thermolytic cleavage of the aziridine C−C bond in adducts **3a**−**k** affords azomethine ylide **A**, whose formation is favored by the stabilizing effect of the

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(10) A representative procedure is the preparation of 3-methoxycarbonylmethyl-5-methyl-2-phenyl-3*H*-4-imidazolecarboxylic acid methyl ester (**4a**). A mixture of 1,2-diaza-1,3-butadiene **1a** (204 mg, 1.1 mmol) and aziridine **2a** (177 mg, 1.0 mmol) was stirred under solvent-free conditions at 65 °C. After disappearance of aziridine **2a** (3.5 h, monitored by TLC), the crude mixture was purified by column chromatography on silica gel using cyclohexane−ethyl acetate (30:70 v/v) as the eluant to afford adduct **3a** as a mixture of inseparable isomers in (97%); white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 and 1.99 (s, 3H), 2.73 and 3.30 (s, 1H), 2.98 and 3.61 (d, J = 2.4 Hz, 1H), 3.66−3.82 (m, 9H), 4.44 and 4.74 (s, 1H), 7.23−7.35 (m, 5H), 7.70 and 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.0, 42.6 and 45.3, 46.5 and 47.8, 52.4, 52.6, 53.0, 68.3 and 68.5, 126.1, 126.6 and 127.8, 128.4 and 128.5, 137.3, 147.8 and 148.4, 154.1, 169.2 and 169.6; IR (Nujol) ν 3295, 1750, 1727, 1717 cm^{-1}; MS (EI) *m/z* 363 (M^+, 6), 289 (80), 257 (25), 176 (48), 116 (100). Anal. Calcd for $C_{17}H_{21}N_3O_6$: C, 56.19; H, 5.83; N, 11.56. Found: C, 56.03; H, 5.89; N, 11.41. A solution of α-aziridinohydrazone **3a** (182 mg, 0.5 mmol) in toluene (25 mL) was heated at reflux until disappearance of the starting material (6.5 h, monitored by TLC). After evaporation under reduced pressure, purification by silica gel chromatography (cyclohexane−ethyl acetate 55:45 v/v) yielded imidazole **4a** as a white solid (60%): mp 85−89 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.92 (s, 2H), 7.44−7.55 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.7, 48.4, 51.4, 52.6, 119.6, 128.9, 129.1, 129.3, 130.0, 147.7, 151.5, 161.9, 168.9; IR (Nujol) ν = 1743, 1692 cm^{-1}; MS (EI) *m/z* 288 (M^+, 100), 256 (30), 229 (62), 198 (21), 169 (16). Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.35; H, 5.68; N, 9.57.

(11) The structure of compounds **4a**−**k** was confirmed by mono- (^{1}H, ^{13}C) and bidimensional (COSY, HMQC, HMBC) NMR analysis and by mass spectroscopy (see the Supporting Information).

Table 1. Synthesis of α-Aziridinohydrazones **3a−k** and Imidazoles **4a−k**

	1,2-diaza-1,3-butadiene **1**				aziridine **2**			α-aziridinohydrazone **3**			imidazole **4**		
entry	**1**	R	R^1	R^2	**2**	R^3	R^4	**3**	time (h)	yield[a,c] (%)	**4**	time (h)	yield[b,c] (%)
1	**1a**	Me	Me	OMe	**2a**[d]	Ph	H	**3a**	3.5	97	**4a**	6.5	60
2	**1a**	Me	Me	OMe	**2b**	H	CO_2Me	**3b**	7	92	**4b**	21	56
3	**1b**	Et	Me	OEt	**2a**[d]	Ph	H	**3c**	8	85	**4c**	19	82
4	**1b**	Et	Me	OEt	**2b**	H	CO_2Me	**3d**	5	76	**4d**	12.5	42
5	**1b**	Et	Me	OEt	**2c**	H	Ph	**3e**	2.5	96	**4e**	19	57
6	**1c**	*t*-Bu	Me	NEt_2	**2a**[d]	Ph	H	**3f**	5	81	**4f**	12	57
7	**1c**	*t*-Bu	Me	NEt_2	**2b**	H	CO_2Me	**3g**	4	75	**4g**	12	61
8	**1c**	*t*-Bu	Me	NEt_2	**2c**	H	Ph	**3h**	3	78	**4h**	10	58
9	**1d**	Me	Et	OMe	**2a**[d]	Ph	H	**3i**	3	97	**4i**	17	52
10	**1e**	Et	Et	OMe	**2b**	H	CO_2Me	**3j**	3	71	**4j**	11	41
11	**1e**	Et	Et	OMe	**2c**	H	Ph	**3k**	2.5	94	**4k**	11	53

[a] The reaction was conducted under solvent-free conditions (SFC) using 1.1 mmol of 1,2-diaza-1,3-butadienes and 1.0 mmol of aziridines at 65 °C (bath temperature). [b] The reaction was carried out in refluxing toluene on a 0.5 mmol scale. [c] Isolated yield after silica gel chromatography. [d] Trans isomer.

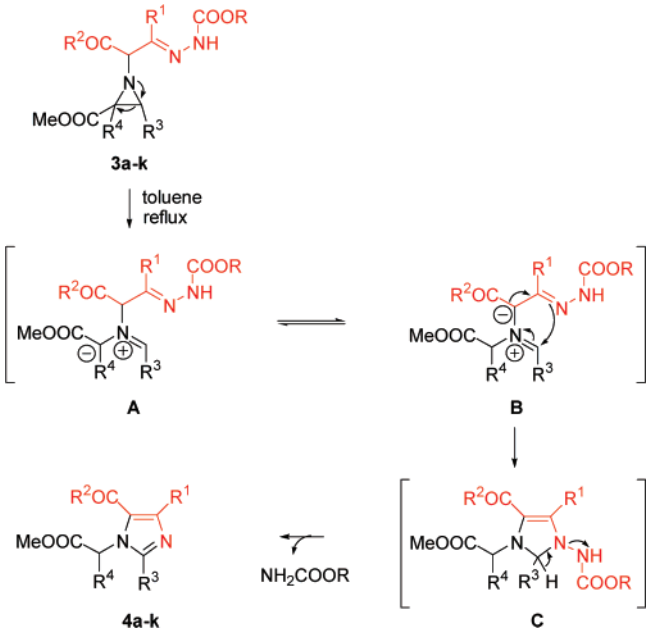
adjacent electron-withdrawing methoxycarbonyl group(s).[12] The latter would also assist tautomeric equilibration of ylide **A** to azavinyl azomethine ylide **B**, which is also stabilized by the adjacent carbonyl group. Subsequently, 1,5-electrocyclic ring closure of conjugated ylide **B** results in the formation of 2,3-dihydroimidazole **C**. In turn, aromatization with concomitant loss of a carbamate residue by cleavage of the N−N bond affords imidazoles **4a−k** (Scheme 2).

Thermolytic C−C bond cleavage of aziridines to azomethine ylides has been utilized for the preparation of five-membered nitrogen-containing rings by either inter- or intramolecular [3 + 2] cycloadditions of 1,3-dipoles with dipolarophiles.[5−7] In such reactions, all three atoms of the parent aziridine ring are incorporated in the final cycloaddition product. In this case, by contrast, aziridine-derived azomethine ylides participate only with two ring atoms (C−N) in the 1,5-electrocyclization, while the 1,2-diaza-1,3-butadiene partner provides the remaining three heteroring atoms (C−C−N) to the final imidazole.

To the best of our knowledge, such a reactivity of aziridine-derived azomethine ylides is unprecedented and represents the first example of 1,5-electrocyclization of azavinyl azomethine ylides where direct C−N bond formation occurs, instead of the observed C−C bond formation in 1,5-electrocyclizations of vinyl azomethine ylides.[3] This particular behavior permits a new and original access to substituted imidazoles.

Indeed, imidazole rings occur in a large number of natural products[13] and pharmacologically active molecules.[14] They also behave as ligands in metalloenzymes[15] and nonnatural metal complexes.[16] Furthermore, DL-1-(1-arylalkyl)imidazole-5-carboxylic acid esters were shown to possess strong hypnotic properties.[17] Despite the variety of synthetic ap-

Scheme 2. Postulated Mechanism for the Formation of Imidazoles **4a−k** via 1,5-Electrocyclization of Azavinyl Azomethine Ylide **B**



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proaches which are available for the construction of the imidazole ring,[18,19] imidazoles such as **4a**−**k** bearing *N*-acetate or -malonate appendages are as yet difficult to prepare. Such derivatives can be useful for the preparation of imidazo[5,1-*c*]-1,4-oxazines.[17b]

In conclusion, a simple and versatile approach to richly substituted imidazoles from easily available aziridinecarboxylates and 1,2-diaza-1,3-butadienes has been developed. Further investigations in order to extend the scope and applications of this reaction are currently in progress.

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Supporting Information Available: Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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