Unusual Transformations of Heterocyclic Azomethine Ylides Including an Unsymmetrical Dimerization and MO Calculations

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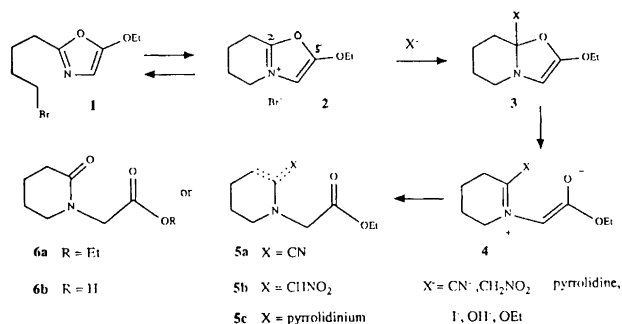
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2-(4-Bromobutyl)-5-ethoxyoxazole 1 reacts with ethyl carbazate and isocyanate nucleophiles in an unexpected manner to give N-substituted piperidines and an unsymmetrical dimer. A likely interpretation involves the intermediacy of an intramolecularly formed oxazolium salt and azomethine ylides, which undergo neutralization either by group migration or by an as yet unobserved, unsymmetrical dimerization. MO calculations indicate that in the oxazolium-derived azomethine ylide intermediate the ethoxycarbonyl group deviates from planarity with the ylide and prefers an S-conformation. Nevertheless, calculations indicate possible bonding in the U-conformer of the oxazolium ylide that can lead to group migration.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Recently, we reported that 2-(4-bromobutyl)-5-ethoxyoxazole 1 when subjected to reaction with nucleophiles such as PhS⁻, (MeCO₂)₂CH⁻ and SCN⁻ undergo bromide displacement, while other nucleophiles such as NO₂CH₂⁻, CN⁻, OH⁻, pyrrolidine, EtO⁻, I⁻ give rise unexpectedly to piperidines bearing the nucleophile at C-2 (5a–c) or to 2-piperidinones (6a–b).[1,2] It was shown that the first step involved intramolecular alkylation of 1 to form the bicyclic oxazolium salt 2, which added the nucleophile onto the immonium carbon to yield a 4-oxazoline 3. The latter underwent spontaneous valence tautomerization to the corresponding azomethine ylide 4.[3] The formation of products 5 and 6 was explained by neutralization of this short-lived intermediate[4] by proton transfer. In general, azomethine ylides are reactive intermediates which, although not isolated, have proved useful in synthesis.[4] In the reaction of 1 to 5, we succeeded in trapping the azomethine ylide 4 with either electron rich or electron poor dipolarophiles.[1,2]
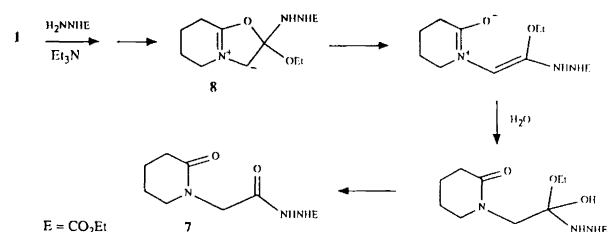
In this paper we wish to report new routes of neutralization of the reactive azomethine ylide 4, leading to unexpected products, together with the calculated geometries of 4, which shed more light on the chemistry of such ylides.

When 2-(4-bromobutyl)-5-ethoxyoxazole 1 was heated with ethyl carbazate as a nucleophile in the presence of NaI and Et₃N an unexpected product 7 was isolated in 51 % yield. The expected N-methylenepiperidine skeleton was indicated by ¹H NMR and ¹³C NMR spectroscopy and the nucleophilic moiety (CO–NH–NCO₂Et) was revealed by IR as well as by the carbonyl signals in the ¹³C NMR spectrum. A piperidone carbonyl signal appeared at 171.5 ppm. However, in this case, in contrast with piperidine derivatives 5, the nucleophilic moiety appeared at the end of the piperidine side chain on a carbon which was formerly C-5 of oxazole 1.

Three likely pathways may lead to 7. (1) Attack of the carbazate at C-5 of the oxazolium salt 2, followed by ring opening of intermediate 8 and subsequent hydrolysis to give 7. Although nucleophilic attack at C-5 of oxazolium salts has not been encountered yet (but rather at C-2), it is a feasible pathway because the ethoxy substituent in
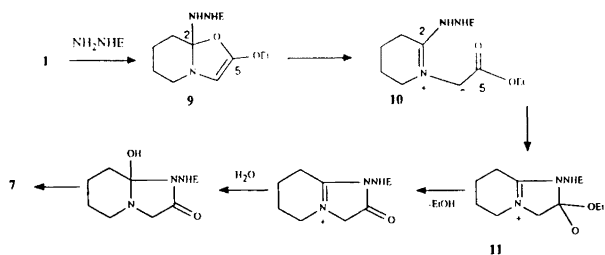

Scheme 1.

6a R = Et
6b R = H

5a X = CN
5b X = CH₂NO₂
5c X = pyrrolidinium

X⁻ = CN⁻, CH₂NO₂   pyrrolidine,
I⁻, OH⁻, OEt

E = CO₂Et   7

Scheme 2.

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oxazolium salt **2** increases the partial positive charge on C-5 both by inductive and resonance effects (Scheme 2). (2) Formation of the ester **6a** as a result of hydroxide attack at C-2 due to the presence of traces of water, followed by hydrazide–ester exchange to produce **7** (Scheme 3). (3) Initial attack of the carbazate at C-2 of
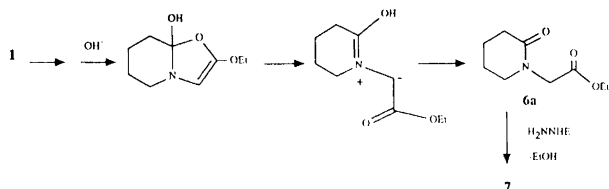
Scheme 3.

the oxazolium salt to give 4-oxazoline **9** followed by azomethine ylide **10** formation and carbazate transfer from 'C-2' to 'C-5' via the cyclic intermediate **11** with final hydrolysis by water to **7** (Scheme 4). Pathway (2)


Scheme 4.

was eliminated by subjecting the ester **6a** to the reaction conditions and determining that it was recovered unchanged. Pathway (1) is considered unlikely since Mulliken charges calculated by the STO-3G method[5, 6] for the oxazolium salt **2** indicated a considerably smaller positive charge at C-5 (+0.282) than at C-2 (+0.339). This and the behavior of cyanate toward 1, as discussed below, leads us tentatively to favor path (3) in which the nucleophilic moiety is transferred from 'C-2' of the oxazole to 'C-5' via a cyclic intermediate for the formation of **7**.

Similar behavior was observed for the cyanate ion. When oxazole **1** was refluxed in acetone with NaOCN and a catalytic amount of NaI, two products in nearly equal ratio were isolated in quantitative yield. One product revealed the presence of two amide functions

(171.3, 171.0 ppm), one of which was a primary amide (IR: 3316, 3182 cm^{-1}, ^{1}H NMR: two broad singlets at 6.53 and 5.81 ppm, one strongly hydrogen bonded). The rest of the spectrum revealed the typical 1-methylene-2-oxopiperidine skeleton which led to the structure assignment of **12**.

The same three pathways as discussed above for the reaction with ethyl carbazate were considered. Again the lack of reaction of ester **6a** with NaOCN under the reaction conditions eliminated path (2). Path (3) via the intermediacy of the azomethine ylide **13**, now involves formation of a 7-membered ring carbamate **14** (Scheme 5). This we first considered as a somewhat less likely scenario, and therefore decided to examine by MO calculations the preferred geometry of some azomethine ylides and the role of a methoxycarbonyl and cyano group in stabilizing these ylides. Four possible geometries [U, W, $S(E, Z)$ and $S(Z, E)$] can be visualized for unsymmetrically substituted azomethine ylides.[4] (See Fig. 1). So far the geometry of azomethine ylides was inferred from the geometry of their trapping products by dipolarophiles. Trapping experiments by Grigg,[7] Toth[8, 9] and Vedejs[10] suggested a preferred S-dipole (or E, Z) conformation **17a** for certain alkoxycarbonyl azomethine ylides. This preference the authors attributed to dipole-stabilizing interactions.

We carried out AM1[11] and STO-3G[5] calculations for the simplified model **17b** of our ylides **4**. Geometry optimizations were carried out using the GAUSSIAN 88 system of *ab initio* MO programs.[6] These indicated that the methoxycarbonyl group in **17b** deviated from the dipole plane by $-21.5°$ (AM-1) or $-20.5°$ (STO-3G), suggesting strong steric inhibition of resonance stabilization of the dipole by the ester groups in this conformation.

17a, X=H (S-dipole)
17b, X=CN (U-dipole)   U -dipole   S -dipole

4a, X=CN
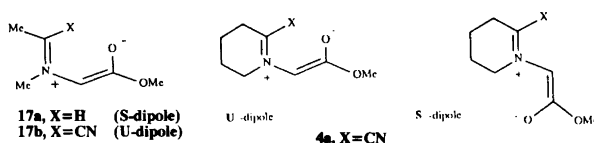
Calculations (STO-3G) on the complete dipole structure of **4a** both for the U-dipole ($\Delta H_f = -8.90$ kcal mol^{-1}) and the S-dipole ($\Delta H_f = -12.13$ kcal mol^{-1}) show a definite preference for the S-conformation. However, when we optimized the geometry of a possible U-shaped dipole **13** at the STO-3G level, we found that the bond distance between the O$^-$ and the isocyanate carbon was

priority of substituents : $R_1 > R_2$, $R_3 > R_4$

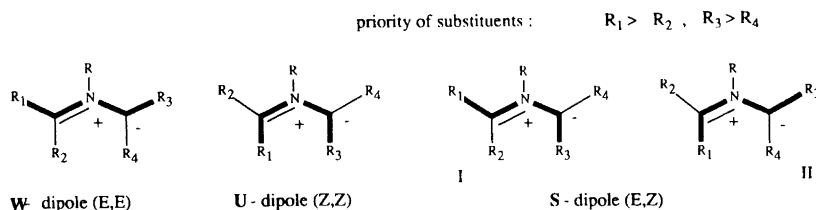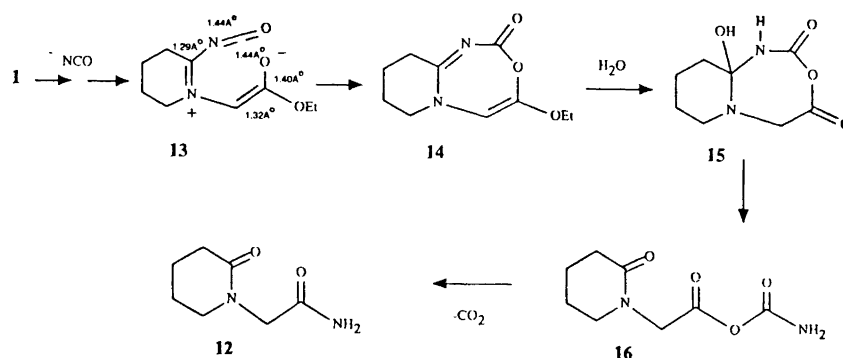W- dipole (E,E)   U - dipole (Z,Z)   S - dipole (E,Z)

Fig. 1.

Scheme 5.

calculated as 1.44 Å, indicative of bonding between these two atoms. (Description of bond lengths in ylide 13 is shown in Scheme 5). Mixed anhydrides of carboxylic acids and isocyanates, like intermediate 15 or 16, which can form upon hydrolysis of 14, are known to lose CO_2, easily forming amides.[12] The above calculations strengthened our hypothesis that neutralization of azomethine ylide 13 by group migration from 'C-2' to 'C-5' was involved in these transformations.

Unsymmetrical dimer of an azomethine ylide. The second product in the reaction of 1 with cyanate ion, obtained in 54% yield, had the entirely surprising structure 20. HRMS indicated a dimeric structure $C_{18}H_{26}N_2O_4$. The dimer contained two ethoxycarbonyl groups, one of which was α to an sp^3 carbon, the other being α,β-unsaturated. ^1H NMR spectroscopy was not very informative, but ^{13}C NMR spectroscopy indicated four quaternary carbons implying a pyrrole ring.[13] COSY and hetero COSY spectra unequivocally established the structure as 20, a non-symmetrical dimerization product of azomethine ylide 13.

Only few examples are known in the literature for dimerization of azomethine ylides. Huisgen observed symmetrical dimerization of mono and 2,3-diester aziridines during their thermolysis and explained it by a [3 + 3] cycloaddition of the derived azomethine ylides.[14] A symmetrical dimer was isolated in low yield from the thermolysis of a 1,2,3-triazoline.[15] Porter dismissed a [3 + 3] cycloaddition of the 1,1-diethoxycarbonylazomethine ylide intermediate as symmetry forbidden and proposed that the dimerization occurred via diradical intermediates.[15]

Dimer 20 possesses no symmetry elements which suggests a different mechanism for its formation than the

above-mentioned cases. A disconnection of the 2,3- and 4,5-bonds of the pyrrole core of dimer 20 reveals the dipole and the dipolarophile precursors. Our proposed mechanism involves formation of azomethine ylide 13, which in part undergoes a proton transfer to 18. The latter serves as a dipolarophile in a 1,3-dipolar cycloaddition to 13. The thus-formed intermediate 19 undergoes double elimination of HNCO to produce 20 as a single regioisomer (Scheme 6). FMO theory, which is commonly applied in the analyses of cycloadditions,[16-19] supplies an explanation for this fact which is in complete agreement with the regiochemistry found.
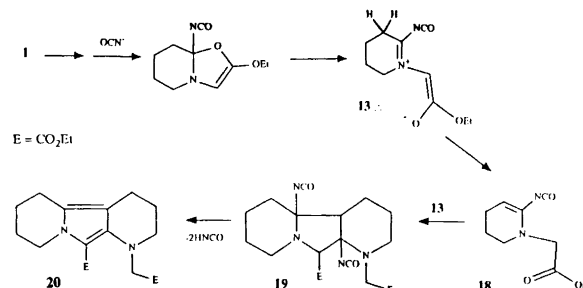
Scheme 6.

A schematic interaction diagram for the interaction between dipole 13 and dipolarophile 18 based on their FMO energies as calculated by the AM1 method, indicates that the reaction is just barely HOMO–dipole controlled (see Fig. 2). The preferred regiochemistry, in which the largest lobe in the HOMO of the electron donor dipole 13 interacts with the appropriate lobe in the LUMO of the electron acceptor 18 is indeed the one obtained experimentally (see Fig. 2).

In summary, 2-(4-bromobutyl)-5-ethoxyoxazole, 1, led
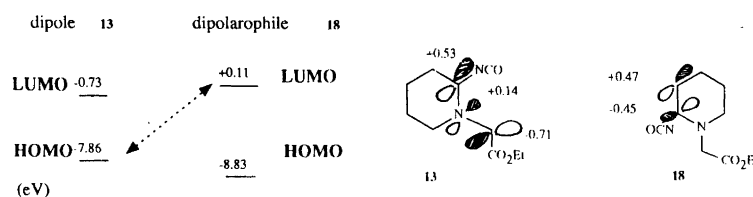
Fig. 2. Schematic interaction diagram from 13 and 18.

led upon reaction with ethyl carbazate and isocyanate ion to the piperidine derivatives **7** and **12** and to the dimer **20**. The suggested mechanism, which is supported by MO calculations, involves the intermediacy of the oxazolium salt **2** which, upon reaction with nucleophiles, undergoes spontaneous valence tautomerization to the azomethine ylides **10** and **13**. These reactive intermediates undergo neutralization either by group migration, to produce **7** and **12**, or by unsymmetrical dimerization, leading to **20**. The regiochemistry of the latter is explained based on FMO calculations.

Experimental

General. ^{1}H NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz on a Bruker AM-300 spectrometer using $CDCl_3$ as the solvent. IR spectra were recorded on Nicolet 60 SXB FT-IR spectrometer. Mass spectra were obtained on a Finnigan 4021 instrument. HRMS spectra were obtained on a Varian MAT-731 instrument. Silica gel (Merck Art. 9385) was used for chromatography. Melting points were determined on a Fisher-Johns block. Trivial vicinal coupling constants in ethoxy groups or aliphatic chains ($J = 7$ Hz) are not given in the ^{1}H NMR spectra.

2-(4-Bromobutyl)-5-ethoxyoxazole (**1**). To a mixture of 5-bromovaleronitrile (2 g, 12.3 mmol) and $BF_3 \cdot OEt_2$ (1.23 ml, 10 mmol) in a flame dried system under Ar, was added dropwise ethyl diazoacetate (1.14 g, 10 mmol) at 0–5°C. The mixture became dark red on stirring at room temperature for 12 h. An equivalent of triethylamine was added and this mixture was chromatographed on silica gel. Elution with EtOAc–hexane 1:3 yielded the product **1** as an orange oil, yield 0.74 g (30%). ^{1}H NMR: δ 5.91 (H-4, s, 1 H), 4.04 (OEt, q, 2 H), 3.38 (CH_2Br, t, *J* 7 Hz, 2 H), 2.64 (CH_2-oxazole, t, *J* 7 Hz, 2 H), 1.9 (CH_2CH_2, m, 4 H), 1.38 (OEt, t, 3 H). ^{13}C NMR δ: 159.30 (C-5), 154.52 (C-2), 98.69 (C-4), 67.80 (OCH_2), 32.86 (CH_2Br), 31.72 (CH_2-oxazole), 21.17, 25.19 (CH_2CH_2), 14.39 (CH_3). MS IP 70 eV; *m/z* 250, 248 (*M*H), 168 (*M*H − HBr). Anal. calc. for $C_9H_{14}BrNO_2$: C, 43.54; H, 5.65. Found: C, 43.80; H, 5.81.

N'-Ethoxycarbonyl(2-oxopiperidino)acetohydrazide (**7**). A solution of **1** (0.125 g, 0.5 mmol), ethyl carbazate (0.058 g, 0.5 mmol) and Et_3N (0.079 ml, 0.5 mmol) in THF (4 ml) was heated under reflux for 48 h. The solvent was evaporated off and the residue was chromatographed (EtOAc and then EtOAc–MeOH 8:1) to yield **7** as a yellowish oil which upon high vacuum drying formed a light yellow highly hygroscopic foam, yield 0.062 g (51%). ^{1}H NMR δ: 8.73 (NH, br s, 1 H), 7.05 (NH, br s, 1 H), 4.17 (OEt, q, 2 H), 4.04 (NCH_2CO, s, 2 H), 3.45 (CH_2N, br t, *J* 5.5 Hz, 2 H), 2.42 (CH_2CO, br t, *J* 6.3 Hz, 2 H), 1.85 (CH_2CH_2, m, 4 H), 1.25 (OEt, t, 3 H). ^{13}C NMR: δ 171.47 (NCO), 168.86 (NNCO), 156.25 (NCO_2Et), 62.09 (OEt), 50.05 (NCH_2), 49.80 (NCH_2),

32.10 (CH_2CO), 23.1, 22.1 (CH_2), 14.4 (OEt). IR (neat) v_{max}: 3245 (br, NH), 1730, 1695, 1617 (C=O) cm^{-1}. MS [CI; *m/z* (% rel. int.)]: 244 (*M*H, 3), 198 (*M*H − EtOH, 9), 140 (*M*H − H_2NNHCO_2Et, 100). HRMS: calc. for $C_7H_{10}NO_2$ (*M* − $NHHNCO_2Et$) 140.0709. Found: 140.0786.

2-Oxopiperidin-1-ylacetamide (**12**) *and ethyl 1-ethoxycarbonylmethyl-1,2,3,4,5,6,7,8-octahydropyrido[3,2-a]indolizine-10-carboxylate* (**20**). A solution of **1** (0.12 g, 0.48 mmol), NaOCN (0.032 g, 0.48 mmol) and a catalytic amount of NaI in dry acetone (3 ml) was heated under reflux for 13 h. The precipitate was removed by filtration and the filtrate was evaporated and chromatographed (EtOAc–hexane 1:1) to give the dimer **20** as a yellow oil, yield 0.044 g (54%). The eluent was changed to EtOAc–MeOH 4:1 to give **12** as a light brown oil, yield 0.035 g (45%).

12: ^{1}H NMR: δ 6.53 (br s, 1 H, NH), 5.81 (br s, 1 H, NH), 3.97 (s, 2 H, CH_2), 3.37 (m, 2 H, CH_2), 2.40 (m, 2 H, CH_2), 1.81 (m, 4 H, CH_2CH_2). ^{13}C NMR: δ 171.34, 170.99 (NCO), 51.44 (NCH_2), 49.62 (NCH_2), 32.42 (CH_2CO), 23.09, 21.10 (CH_2). IR (film): 3316, 3182 (NH_2), 1677, 1624 (NCO) cm^{-1}. MS [CI, NH_3; *m/z* (% rel. int.)]: 157 (*M*H, 100), 140 (*M*H − NH_3, 14). HRMS: calc. for $C_7H_{12}N_2O_2$: 156.0896. Found: 156.0908.

20: ^{1}H NMR: δ 4.21 (m, 6 H, 2 $CO_2Et + CH_2$), 4.00 (NCH_2E, s, 2 H), 3.17 (CH_2-pyrrole, m, 2 H), 2.57, 2.36 (CH_2, t, *J* 6.5 Hz), ca. 1.85 (2 CH_2CH_2, m, 8 H), 1.27 (2 CO_2Et, t, 6 H). ^{13}C NMR: δ 171.83 (CO_2Et), 160.71 (C=C–CO_2Et), 142.58, 132.49, 107.81, 107.26 (pyrrole carbons), 60.34, 59.09 (CO_2Et), 58.08 (CH_2N-pyrrole), 51.16 (NCH_2E), 45.81 (NCH_2), 23.84, 22.22, 19.76, 19.53, 19.48 (CH_2), 14.45, 14.25 (CO_2Et). IR (film): 1749, 1730 (CO_2Et), 1668, 1650 (C=C) cm^{-1}. MS [CI; *m/z* (% rel. int.)]: 335 (*M*H, 67), 249 (*M*H − CH_2CO_2Et, 100). HRMS: calc. for $C_{18}H_{26}N_2O_4$: 334.1891. Found: 334.1834.

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