Search for a Nonelectrocyclic Cyclization of Nitrosostyrene: Rearrangements of Michael Adducts from DMAD and α-Dialkylamino Oximes

Necdet COŞKUN[*] and Nevin ARIKAN
Uludağ University, Department of Chemistry,
16059 Görükle, Bursa-TURKEY

The aza-Claisen rearrangement product of the Michael adducts **2** from α-dialkylaminoacetophenone oximes and DMAD underwent fragmentation to give dialkylaminomaleate, and benzonitrile at reflux in acetonitrile. The fragmentation was assumed to proceed through an unstable $4H$-1,2-oxazete **6**. The same reaction performed at room temperature, in addition to the nitrile and maleate, gave the corresponding 2-(2-dialkylamino-1-phenylethylideneaminooxy)-but-2-enedioic acid dimethyl esters **8** and **9**. Compounds **9** isomerized to **8** on heating in acetonitrile.

Introduction

Wieser and Berndt reported the first examples of sterically stabilized $4H$-1,2-oxazete N-oxides[1] and $4H$-1,2-oxazetes.[2] 1,1-di-*tert*-butylallenes react with N_2O_4 to give 4,4-di-*tert*-butyl-$4H$-1,2-oxazete N-oxides via an α,β-unsaturated nitroalkene.[1] The same authors synthesized 4,4-di-*tert*-butyl-$4H$-1,2-oxazete from the thermal intramolecular cyclization of the corresponding nitrosoalkene.[2] (Z)-3,3-dimethyl-1,1-di(methylthio)-2-butanone oxime was converted into the corresponding $4H$-1,2-oxazete by treating it with MCPBA at room temperature. The formation of the oxazete ring was assumed to proceed via an electrocyclic ring closure of the corresponding nitrosoalkene[3]. The $4H$-1,2-oxazete N-oxides have been reported as reactive intermediates in the thermal[4] and photochemical[5] cleavage of α,β-unsaturated nitro group containing compounds to form carbonyl compounds and nitrile oxides. The oxazete ring itself was shown to cleave in a similar manner on heating to give the corresponding nitrile and carbonyl compound[2,3]. The pyrolysis of α-chloroacetaldehyde oxime to HCN and formaldehyde was also proposed to proceed via $4H$-1,2-oxazete formed from the electrocyclization of nitrosoethylene[6]. Attempts to prepare $4H$-1,2-oxazetes having sterically less demanding substituents were unsuccessful.[2] Azirine 1-oxides and 1,2-oxazetes are still the subject of theoretical investigations[7−8].

To prepare a 4-unsubstituted $4H$-1,2-oxazete ring at mild conditions we planned a nonelectrocyclic route involving uncatalysed Michael addition of aminooximes **1** to DMAD. The aza-Claisen rearrangement

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[*]Corresponding author

of adduct $\mathbf{2}^2$ would give a zwitterion **3**, which in turn was expected to undergo synchronous intramolecular cyclization and fragmentation to give the azirine oxide **5** or oxazete **6** and the corresponding dialkylamino-maleate (see Scheme 1).

Here we report the rearrangement of adducts **2** from α-dialkylaminoketone oximes **1** and DMAD in acetonitrile at reflux leading to benzonitrile and dialkylaminomaleate probably via an unstable $4H$-1,2-oxazete **6** (Scheme 1) and the formation of 2-(2-dialkylamino-1-phenylethylideneaminooxy)-but-2-enedioic acid dimethyl esters **8** and **9** (Scheme 2) when the reaction is performed at room temperature.
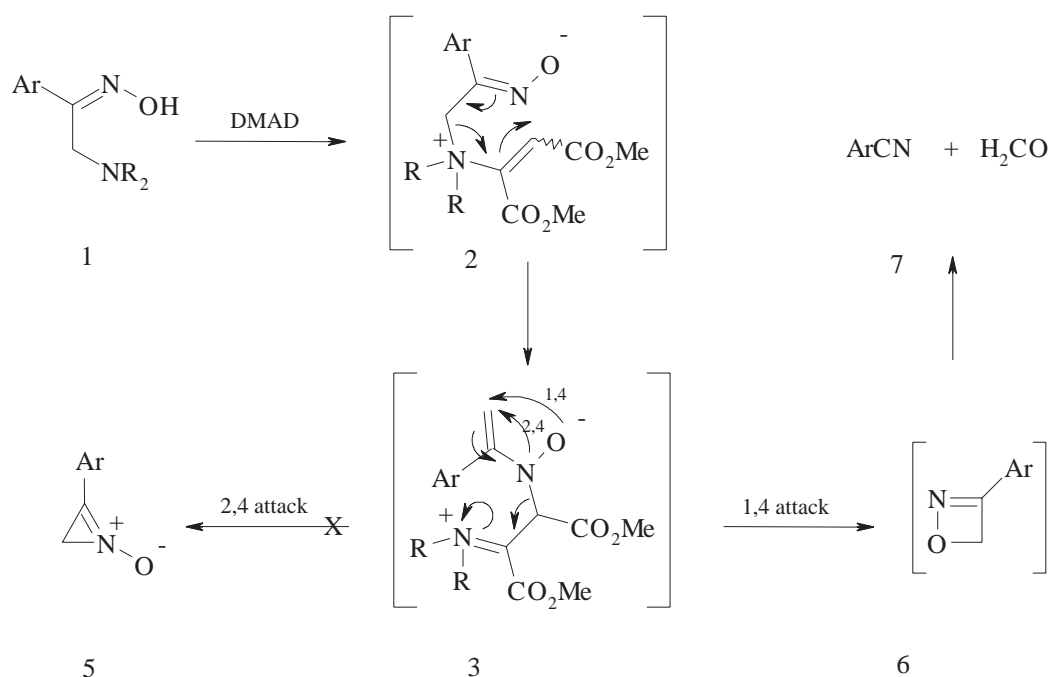
Scheme 1

Results and Discussion

The reaction of dialkylaminoacetophenone oximes **1,** readily available from the reaction of two moles of the corresponding secondary amine and one mole of halooxime in ethanol, with DMAD in acetonitrile at reflux for 3 h gives dialkylaminomaleates[10,12], and benzonitrile[13]. The mechanism of the reaction leading to dialkylaminomaleate and benzonitrile probably involves a Michael addition of compounds **1** to DMAD leading to ammonium species **2**. The conversion of **2** to iminium species **3** is a new example of aza-Claisen rearrangement involving azaallyl instead of an allyl group. Of the possible competing reactions, 2,4-intramolecular attack, which (see Scheme 1) could lead to azirine 1-oxide **5**, and 1,4-intramolecular attack, which could lead to 1,2-oxazete **6,** only the latter was observed.
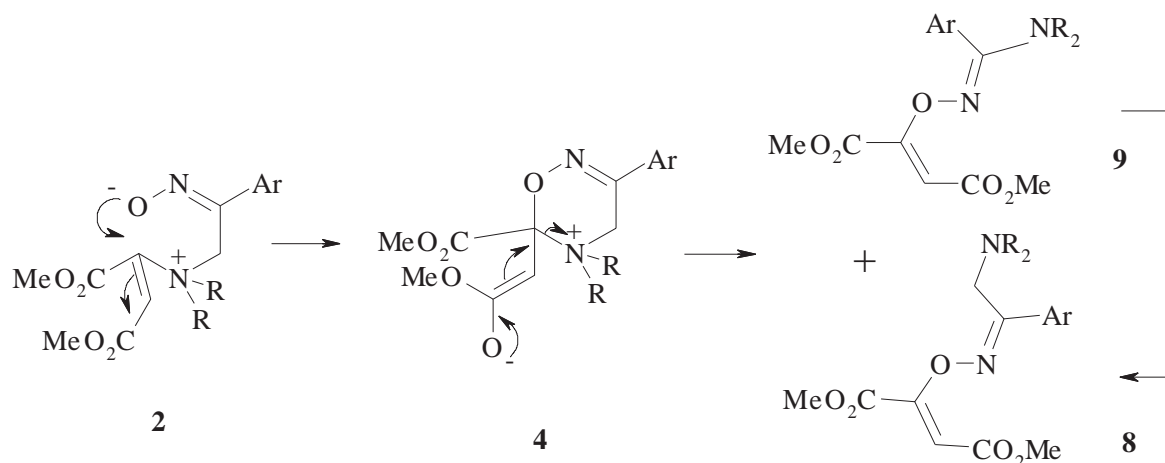
Scheme 2

Table. The reaction of α-dialkylaminooximes with DMAD in acetonitrile.

Entry	R	Ar	reflux		room temperature			
		Yields (%)	7	DAM[1]	7	DAM	8	9
a	Me	Ph	82	80	51	50	15	17
b	Et	Ph	80	79	50	50	14	16
c	Et	4-MeOC$_6$H$_4$	81	80	52	51	17	16
d	Me	4-MeOC$_6$H$_4$	79	80				
e	-(CH$_2$)$_5$-	Ph	81	80				

[1]DAM = dialkylaminomaleate

The reaction of DMAD with **1a-c** at room temperature in dry acetonitrile gives benzonitrile, maleate and a mixture of the corresponding aminooxybutenedioic acid esters **8** and **9** in a nearly 1:1 ratio (Scheme 2, Table). Assuming that adducts **8** and **9** could be formed from **2**, a mechanism involving an intramolecular nucleophilic substitution at the carbon linked to the ammonium nitrogen would be reasonable (Scheme 2). However, direct addition of the aminooxime to DMAD probably facilitated by the internal base on the oxime should also be considered as another possible mechanism for the formation of compounds **8** and **9**. It is clear from the Table that the yields of benzonitrile **7** and dialkylaminomaleate are influenced significantly by temperature, and at reflux the dialkylaminomaleates and nitriles are formed at the expense of the adducts **8** and **9**. It seems that the temperature favours the rearrangement of **2** to **3** rather than the conversion of **2** to **8** and **9** or the direct addition of aminooximes to DMAD if the latter mechanism is operative.

The IR spectra of compounds **8** show carbonyl absorption at 1730 cm^{-1} and C=N absorption at 1651 cm^{-1}. Singlets in the ^{1}H NMR spectra at δ 3.91 (2H) and 6.07 (1H) were assigned to the methylene α to the C=N and vinylic protons respectively. The ortho protons' peaks at nearly 7.75 are indicative for the acetophenone oximes. The same ortho protons appear at nearly 8.50 ppm when the oxime nitrogen is involved in a cyclic nitrone.[14] The IR spectra of compounds **9** show absorptions at 1751, 1719 and 1640

cm^{-1}. The singlets for the methylene and vinylic protons appear at nearly 3.69 (2H) and 5.95 (1H). ^{1}H NMR data for the vinylic proton in a similar environment reported in the literature allows us to assume that the double bond's configuration of compounds **8** and **9** is probably (*Z*).[15] (*Z*)-1-phenyl-2-piperidin-1-ylethanone oxime and (*E*)-1-phenyl-2-piperidin-1-ylethanone oximes' methylene protons α to the oxime C=N have absorptions at 3.74 and 3.33 ppm respectively[16]. Analogously we assumed that **8** with methylene protons having a chemical shift at a lower field may have (*Z*) configuration at the C=N while **9** have (*E*) configurations[16]. The reflux of compound **9b** in acetonitrile led to the formation of **8b**, which seems to be thermodynamically the more stable isomer.

To prove the structure of compounds **8** and **9** in an independent way we planned their synthesis by the reaction of dialkylamines with the adduct of α-haloketone oximes with DMAD. However, attempts to prepare such an addition product between phenacyl bromide oxime and DMAD in dry acetonitrile or DME-water (7:1) failed, although 1,2-quinone monooximes were reported to react with DMAD on heating in DME-water to give the corresponding 1,2-addition products (*Z*) and (*E*)-1,2-benzoquinone 1-*O*-[1,2-bis(methoxycarbonyl)ethenyl]oximes.[17]The same authors reported in another work the reaction of DMAD with pyrazole-4,5-dione-4-oxime in DME-H_2O at room temperature to give addition product via the oxime's nitrogen[18]. The ^{1}H NMR spectra of both types of adducts reported show nearly the same chemical shifts for the vinylic (6.44 and 6.52) and the same shifts for the methoxys' protons. It is likely that the adducts reported in reference 17 are of the same type as in reference 18.

Experimental

Infrared spectra were recorded on a Mattson 1000 FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Dpx 400 MHz spectrometer. All spectra were taken in deuteriochloroform. Mass spectra were routinely recorded at 70 eV by electron impact on a Fisons VG Platform II instrument.

2-(2-Dialkylamino-1-phenyl-ethylideneaminooxy)-but-2-enedioic acid dimethyl ester General Procedure. To a solution of the secondary amine (2 mmol) in ethanol (5 mL) was added phenacyl bromide oxime (1 mmol) dissolved in ethanol (5 mL) and the mixture stirred for 2 h[19]. Water (30 mL) was added an the mixture extracted with chloroform (2 x 15). The combined extracts were dried over anhydrous $Na_2SO_4$and filtered. The organic solvent was removed under vacuum and the residue dissolved in acetonitrile (10 mL). Dimethyl acetylenedicarboxylate (1 mmol, 0.142 g) was added and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue subjected to a silica gel packed column and eluted with ethylacetate-petroleum ether.

2-(2-Dimethylamino-1-phenyl-ethylideneaminooxy)-but-2-enedioic acid dimethyl ester (8a) IR (neat) $\nu_{C=O}$ 1730, $\nu_{C=N}$ 1651 cm^{-1}; ^{1}H NMR CDCl$_3$$\delta$ 2.30 (6 H, s), 3.69 (3 H, s), 3.87 (3 H, s), 3.91 (2 H, s), 6.05 (1 H, s), 7.38 (3 H, m), 7.74 (2 H, m); Anal. Calcd for $C_{16}H_{20}N_2O_5$: (320.35) C, 59.99; H, 6.29; N, 8.74. Found C, 59.87; H, 6.35; N, 8.70. m/z 320 (M$^+$) **(9a)** IR (neat) $\nu_{C=O}$ 1752, 1720, $\nu_{C=N}$ 1640 cm^{-1}; [1]H NMR CDCl$_3$$\delta$ 2.28 (6 H, s), 3.69 (2 H, s), 3.74 (3 H, s), 3.96 (3 H, s), 5.95 (1 H, s), 7.45 (3 H, m), 7.79-7.82 (2 H, m); Anal. Calcd for $C_{16}H_{20}N_2O_5$: (320.35) C, 59.99; H, 6.29; N, 8.74. Found C, 59.90; H, 6.37; N, 8.71. m/z 320 (M$^+$)

2-(2-Diethylamino-1-phenyl-ethylideneaminooxy)-but-2-enedioic acid dimethyl ester (8b) IR (neat) $\nu_{C=O}$ 1730, $\nu_{C=N}$ 1651 cm^{-1}; ^{1}H NMR CDCl$_3$$\delta$ 1.03 (6 H, t, J = 7.10), 2.57 (4 H, q, J = 7.10),

3.69 (3 H, s), 3.87 (3 H, s), 3.91 (2 H, s), 6.07 (1 H, s), 7.38 (3 H, m), 7.74 - 7.76 (2 H, m);^{13}C NMR CDCl$_3$$\delta$ 11.98; 48.05, 48.74, 52.53, 53.55, 106.83, 128.85, 129.35, 131.16, 133.38, 135.01, 154.38, 164.0, 166.51. Anal. Calcd for C$_{18}$H$_{24}$N$_2$O$_5$ (348.40) C, 62.05; H, 6.94; N, 8.04. C, 62.15; H, 6.90; N, 8.00. m/z 228 (M$^+$ - 120) **(9b)** IR (neat) $\nu_{C=O}$ 1752, 1720, $\nu_{C=N}$ 1640 cm^{-1}; ^{1}H NMR CDCl$_3$$\delta$ 1.00 (6 H, t, J = 7.11), 2.52 (4 H, q, J = 7.11), 3.74 (3 H, s), 3.80 (2 H, s), 3.95 (3 H, s), 5.94 (1 H, s), 7.43 (3 H, m), 7.79 - 7.82 (2 H, m); ^{13}C NMR CDCl$_3$$\delta$ 11.85; 47.95, 48.78, 52.39, 53.75, 96.66, 128.95, 129.49, 131.64, 134.68, 161.87, 164.41, 165.07, 167.91. Anal. Calcd for C$_{18}$H$_{24}$N$_2$O$_5$ (348.40) C, 62.05; H, 6.94; N, 8.04. C, 62.10; H, 6.90; N, 8.08. m/z 281 (M$^+$ - 67)

2-[2-Diethylamino-1-(4-methoxy-phenyl)-ethylideneaminooxy]-but-2-enedioic acid dimethyl ester (8c) IR (neat) $\nu_{C=O}$ 1730, $\nu_{C=N}$ 1651 cm^{-1}; ^{1}H NMR CDCl$_3$$\delta$ 1.03 (6 H, t, J = 7.10), 2.57 (4 H, q, J = 7.10), 3.69 (3 H, s), 3.87 (3 H, s), 3.91 (2 H, s), 3.93 (3 H, s), 6.05 (1 H, s), 6.94 (2 H, d, J = 8.95), 7.58 (2 H, d, J = 8.95); Anal. Calcd for C$_{19}$H$_{26}$N$_2$O$_6$ (378.43) C, 60.31; H, 6.93; N, 7.40. Found C, 60.30; H, 6.90; N, 7.40. m/z 378 (M$^+$) **(9c)** IR (neat) $\nu_{C=O}$ 1752, 1720, $\nu_{C=N}$ 1640 cm^{-1}; ^{1}H NMR CDCl$_3$$\delta$ 1.00 (6 H, t, J = 7.11), 2.52 (4 H, q, J = 7.11), 3.71(3 H,s), 3.75 (2 H, s), 3.83 (3 H, s), 3.95 (3 H, s), 5.90 (1 H, s), 6.94 (2 H, d, J = 8.95), 7.58 (2 H, d, J = 8.95); Anal. Calcd for C$_{19}$H$_{26}$N$_2$O$_6$ (378.43) C, 60.31; H, 6.93; N, 7.40. Found C, 60.37; H, 6.95; N, 7.45. m/z 378 (M$^+$)

Acknowledgement

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19. Some of the aminooximes were isolated and their structures proved by spectral means as well as by comparing their melting points with those in the literature[16].