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ADDITION OF CARBOXYLIC ACIDS AND CYCLIC 1,3-DIKETONES TO 2-DIMETHYLAMINO-3,3-DIMETHYL-1-AZIRINE

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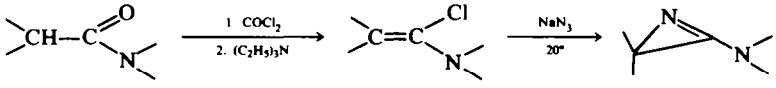
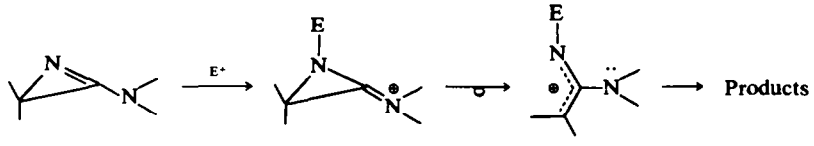
Abstract—The reaction of 2 - dimethylamino - 3,3 - dimethyl - 1 - azirine **1** with carboxylic acids **2a–e** at room temperature in inert solvents generates rearranged 1 : 1 adducts in 65–92% yields. These adducts are N-acyl derivatives of 2-amino, -N,N dimethyl-isobutyramide **3a–e** resulting from 1,2 addition of the acid followed by 1,2 ring cleavage and transfer of an acyl group. Cyclic enolizable 1,3 diketones **4a–c** react similarly with **1** to yield the corresponding rearranged 1 : 1 adducts **5a–c**, whereas acyclic diketones or ethyl acetoacetate are inert under comparable experimental conditions.

INTRODUCTION

2-Amino-1-azirines were first synthesized[1] in 1970 from the reaction of sodium azide with α-chloroenamines which, in turn, can be readily prepared from tertiary amides.[2] The method has been used for the synthesis of 2-dialkylamino-1-azirines bearing alkyl, aryl or alkenyl substituents at position – 3.[1,3]



An interesting property of this new class of cyclic amidines is their ability to react with electrophilic reagents to form 2-amino-1-azirinium cations which undergo a 1,3 ring opening to yield products derived from 2 - amino - 1 - aza - allyl cations.[1,3]



In contrast with the above results, we now wish to report that the reaction of 2 - dimethylamino - 3,3 - dimethyl - 1 - azirine **1** with carboxylic acids and enolizable cyclic 1,3 diketones yields adducts resulting from a 1,2 opening of the three-membered ring.

RESULTS AND DISCUSSION

Reactions with carboxylic acids. The reaction of **1** with carboxylic acids **2a–c** in solvents such as pentane, xylene, methylene chloride or dimethylformamide at room temperature results in the rapid formation of 1 : 1 crystalline adducts (Table 1) as indicated by elemental analysis, mass spectra and NMR integration. Structures **3a–e** were unequivocally established on the basis of spectroscopic evidence (Experimental for details): the IR spectra showed two different amide I absorption bands as well as NH peaks in the 3260–3340 cm^{-1} region. The NMR spectra featured a broad signal (from 5 to 8 ppm, depending on the solvent) which disappeared on addition of D_2O and, thus, was assigned to the proton of the NH–CO-functional group. The sharp singlets appearing at ~1·6 δ and 3·05 δ are consistent with the presence of $\begin{matrix}C\\C\end{matrix}\!>\!CMe_2$ and –$CONMe_2$ groups respectively.

Table 1. Adducts from **1** and carboxylic acids

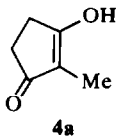
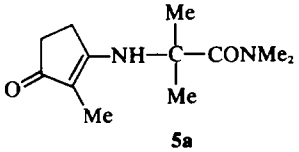
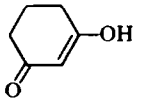
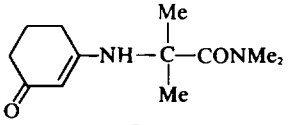
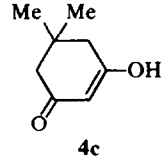
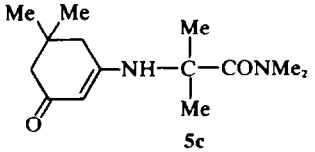
Acid		Product		% yield	m.p. °C
$H-CO_2H$	**2a**	$H-CO-NH-C(CH_3)_2-CON(CH_3)_2$	**3a**	82	59–61
CH_3CO_2H	**2b**	$CH_3-CONH-C(CH_3)_2-CON(CH_3)_2$	**3b**	85–90	140
$C_6H_5CO_2H$	**2c**	$C_6H_5-CO-NH-C(CH_3)_2-CON(CH_3)_2$	**3c**	85	163–4
$C_6H_{11}CO_2H$	**2d**	$C_6H_{11}-CO-NH-C(CH_3)_2-CON(CH_3)_2$	**3d**	92	175
$CH_3-CH-CO_2H$ $CH_3-CH-CO_2H$	**2e**	$CH_3-CH-CO-NH-C(CH_3)_2-CON(CH_3)_2$ $CH_3-CH-CO-NH-C(CH_3)_2-CON(CH_3)_2$	**3e**	65	230

Reactions with 1,3 *diketones.* Cyclic enolizable 1,3 diketones **4a–c** (pK_a of the corresponding enols ~ **5**) behave like carboxylic acids toward **1** and yield adducts (Table 2) which showed analytic and spectral properties supporting structures **5a–c** (Experimental). In particular the UV spectrum showed the expected absorption for the $\diagdown N-C=C-CO-\diagup$ chromophore (**4**) whereas the NMR spectrum featured the resonances at ~ 1·55 δ^1 and 3·05 δ^1 for the $\diagdown CMe_2$ and $CONMe_2$ groups.

Mechanistic proposal

The nature of the products demonstrates that a 1,2 opening of the 2 - amino - 1 - azirine has occurred in contrast with the 1,3 opening which was observed when **1** was exposed to aqueous HCl or $HClO_4$. In all these reactions the first step is most likely the formation of an aminoazirinium cation **6** which, with Cl^- or ClO_4^- as gegenions in the absence of a good nucleophile rearranges to the 2 - amino - 1 - aza - allyl cation **7** by breaking of the N–C(3) bond. On the other hand, **6** is expected to be unstable toward the nucleophilic carboxylate or

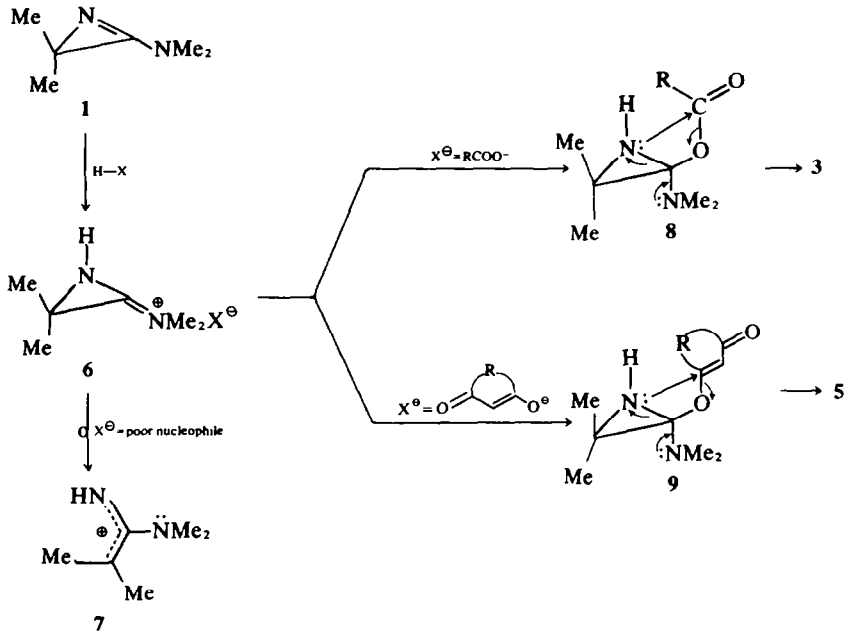
Table 2. Adducts from cyclic 1,3 diketones and **1**

Diketone	Product	% yield	m.p. °C
 **4a**	 **5a**	65	197–8
 **4b**	 **5b**	60	190–1
 **4c**	 **5c**	88	226–7

Cyclic 1,2-diketones (cyclopentane - 1,2 - dione, pK_a of the enol = 9·1 or cyclohexane - 1,2 - dione, pK_a = 10·3) as well as open chain 1,3-diketones (acetylacetone, pK_a = 8·9) and acetoacetic ester (pK_a = 10·7) did not react with the 2 - amino - 1 - azirine **1** in xylene or DMF solution even at higher temperatures. Obviously the enols of the above mentioned compounds are not strong enough acids.

enolate anions, and, therefore, collapses readily to **8** or **9**. These aminoaziridines could readily undergo a 1,2 ring cleavage with simultaneous transfer of an aryl group or its vinylog counterpart to give **3** or **5** respectively. A similar pathway has been proposed by Sato *et al.*[5] to account for the behaviour of a 2 - phenyl - 1 - azirine with benzoic acid.

The present results further illustrate the reactiv-



ity of 2-amino-azirine and shed light on the factors governing 1,2 and 1,3 ring cleavage under the influence of electrophilic reagents.

EXPERIMENTAL

General. M.ps were taken on a Mettler FP-2 m.p. apparatus. Elemental analysis were performed by the micro-analytical laboratories of the Organic Chemistry Department, University of Zürich, and of A. Bernhardt, Mülheim.

Mass spectra were taken on a Consolidated Electronic Corporation 21-110 B mass spectrometer or an AEI MS 12 mass spectrometer at an ionizing voltage of 70 eV and data are expressed in *m/e* (rel. %).

NMR spectra were measured in deuterochloroform solution at 60 or 100 MHz using TMS as internal standard. Chemical shifts are expressed in ppm.

UV spectra were performed in 95% ethanol and data are given in nm (log ϵ).

Adducts from 1 *and carboxylic acids*

1. *Formic acid.* Formic acid (0·92 g, 20 mmoles) was added to a soln of **1** (2·24 g, 20 mmoles) in 7 ml of CH_2Cl_2 at room temp. After 30 min the solvent was evaporated and the residue was distilled (short path dist., bath temp 125°/0·5 Torr) to give **3a** (2·7 g, 82%) as colourless crystals, m.p. 59–61°; IR ($CHCl_3$, cm^{-1}) 3415 and 3350 (NH), 1685, 1630 (amide); NMR (60 MHz): δ 8·17 (2 AB doublets H–CONH), 8·06 (broad s, disappears on shaking with D_2O, N–H), 3·10 (s, $N(CH_3)_2$), 1·6 (s, $C(CH_3)_2$); *m/e*: 158 (M^+, 41), 86 (100), 72 (83). (Found: C, 53·31; H, 8·78; N, 17·50. Calcd. for $C_7H_{14}N_2O_2$ (158·20): C, 53·14; H, 8·92; N, 17·71; O, 20·23%).

2. *Acetic acid.* Acetic acid (0·140 g, 2·2 mmoles) was added to a solution of **1** (0·252 g, 2·2 mmoles) in 5 ml pentane. After 5 min the pentane was evaporated. The residue was practically pure **3b** as shown by NMR. Recrystallisation from CH_2Cl_2/ether or acetone/ether gave pure **3b** in 85–90% yield, m.p. 140°; IR (KBr, cm^{-1}): 3290 (NH), 1645, 1635 and 1545 (amide); NMR (60 MHz): δ 7·40 (broad s, disappears on shaking with D_2O, NH), 3·09 (s, $N(CH_3)_2$), 2·00 (s, CH_3CO), 1·60 (s, $C(CH_3)_2$); *m/e*: 172 (M^+, 0·8), 128 (4), 115 (5), 100 (25), 86 (4), 72 (10), 58 (100). (Found: C, 55·81; H, 9·59; N, 16·17. Calcd. for $C_8H_{16}N_2O_2$ (172·22): C, 55·79; H, 9·36; N, 16·26%).

The reaction of 30 mg (0·5 mmole) of AcOH and 56 mg (0·5 mmole) of **1** in 1·5 ml of DMF gave the same **3b** in 91% yield.

3. *Benzoic acid.* Benzoic acid (86 mg, 0·7 mmole) was added to a solution of **1** (79 mg, 0·7 mmole) in 5 ml pentane. Evaporation of the solvent gave practically pure **3c** as controlled by NMR. Recrystallisation from CH_2Cl_2/ether or acetone/ether gave pure **3c** (85%), m.p. 163–4°; IR (KBr, cm^{-1}): 3290 (NH), 1650, 1620 and 1528 (amide); NMR (60 MHz): δ 7·9–7·25 (m, C_6H_5CONH), 3·07 (s, $N(CH_3)_2$) and 1·78 (s, $C(CH_3)_2$; *m/e*: 234 (M^+, 3), 190 (25), 162 (100), 105 (100), 77 (66), 72 (7). (Found: C, 66·54; H, 7·70; N, 11·83. Calcd. for $C_{13}H_{18}N_2O_2$ (234·29): C, 66·64; H, 7·74; N, 11·95%).

4. *Cyclohexanecarboxylic acid.* A soln of cyclohexanecarboxylic acid (0·2 g, 1·56 mmole) in 1 ml xylene was treated with **1** (0·18 g, 1·6 mmole). The adduct **3d**, which crystallised immediately, was filtered, washed with ether and recrystallised from acetone/ether. The colourless crystals (0·345 g, 92%) melted at 175°; IR (KBr, cm^{-1}): 3295 (NH), 1670, 1628 and 1540 (amide); NMR (60 MHz): δ 6·80 (broad s, disappears on shaking with D_2O, NH), 3·04 (s, $N(CH_3)_2$), 2·1–1·0 (m, 11H of the cyclohexyl ring), 1·63 (s, $C(CH_3)_2$), *m/e*: 240 (M^+, 3), 196 (14), 168 (36), 157 (14), 114 (7), 83 (36), 72 (7), 58 (100). (Found: C, 64·68; H, 10·16; N, 11·42. Calcd for $C_{13}H_{24}N_2O_2$ (240·34): C, 64·96; H, 10·06; N, 11·65%).

5. *Rac.-2,3 dimethylsuccinic acid.* A soln of 2,3-dimethylsuccinic acid (0·2 g, 1·35 mmole) in 1 ml xylene was reacted with **1** (0·3 g, 2·7 mmoles). After 30 min, the crystals were filtered, washed with ether to give pure

colourless **3e** (0·24 g, 65%), m.p. 230°; IR (KBr, cm^{-1}): 3310 (NH), 1649, 1628 and 1550 (amide); NMR (100 MHz): δ 7·11 (broad s, disappears on shaking with D_2O, 2NH), 3·03 (s, 2 $N(CH_3)_2$), 2·65–2·4 (m, H_3C–CH–CH–CH_3), 1·55 (s, 2 $C(CH_3)_2$), 1·19 (d, J = 6·5 Hz, H_3C–CH–CH–CH_3); *m/e*: 370 (M^-, 2), 326 (4), 298 (5), 281 (3), 253 (4), 241 (100), 196 (5), 168 (58), 114 (40), 86 (20), 72 (17), 58 (51). (Found: C, 58·18; H, 9·46; N, 15·05. Calcd. for $C_{18}H_{34}N_4O_4$ (370·49): C, 58·35; H, 9·25; N, 15·12%).

Adducts from **1** *and cyclic* 1,3 *diketones*

1. 2 - *Methyl* - *cyclopentane* - 1,3 - *dione*. A soln of 2 - methyl - cyclopentane - 1,3 - dione (0·2 g, 1·79 mmole), and **1** (0·2 g, 1·79 mmole) in 2 ml xylene was allowed to stand at room temp for 5 h. The ppt was filtered and recrystallised from acetone–ether to give 0·26 g (65%) of **5a** as colourless crystals, m.p. 197–198°; UV: λ_{max} 283 mμ (log ϵ = 4·54); IR (cm^{-1}) 3295 (NH), 1642, 1608 and 1580 (C=O, C=C, amide); NMR (100 MHz): δ 5·0 (broad s, disappears on shaking with D_2O, NH), 3·11 (s, $N(CH_3)_2$), 2·6–2·3 (m, 2 CH_2 groups of the 5-ring), 1·64 (s, CH_3–C=C, $C(CH_3)_2$); *m/e*: 224 (M^+, 8), 152 (100), 110 (9), 72 (8), 58 (8). (Found: C, 64·21; H, 8·78; N, 12·17. Calcd. for $C_{12}H_{20}N_2O_2$ (224·30): C, 64·25; H, 8·98; N, 12·48%).

2. *Cyclohexane* - 1,3 - *dione*. Cyclohexane - 1,3 - dione (0·2 g, 1·79 mmole) and **1** (0·2 g, 1·79 mmole) dissolved in 1 ml xylene were allowed to react for 3 h at room temp. Filtration of the crystals and recrystallisation from acetone–ether gave 0·24 g (60%) of **5b** as colourless crystals, m.p. 190–191°; UV: λ_{max} 285 mμ (log ϵ = 4·43); IR (cm^{-1}) 3260 (NH), 1647, 1605, 1590 and 1543 (C=O, C=C, amide); NMR (100 MHz); δ 5·84 (s, disappears on shaking with D_2O, NH), 4·99 (s, C=CH), 3·02 (s, $C(CH_3)_2$), 2·5–1·8 (2m, 3 CH_2 of the 6-ring), 1·54 (s, $C(CH_3)_2$); *m/e* 224 (M^+, 8), 152 (100), 124 (2), 72 (8), 58 (13). (Found: C, 64·59; H, 9·07; N, 12·53. Calcd. for $C_{12}H_{20}N_2O_2$ (224·30): C, 64·25; H, 8·98; N, 12·48%).

3. *Dimedone*. Aminoazirine **1** (5·6 g, 0·05 mole) was slowly added to a soln of 7·0 g (0·05 mole dimedone in 30 ml xylene. After 1 h at room temp the adduct **5c** was filtered, washed with ether and recrystallised from acetone–ether, yield 11·1 g (88%), m.p. 226–227°; UV: λ_{max} 288 mμ (log ϵ = 4·14) IR (KBr, cm^{-1}): 3260 (NH), 1637, 1604, 1586, 1532 (C=O, C=C, amide); NMR (60 MHz): δ 5·89 (broad s, disappears on shaking with D_2O, NH), 5·00 (s, C=CH), 3·06 (s, $N(CH_3)_2$), 2·20 and 2·13 (2s, 2 CH_2 of the 6-ring), 1·56 (s, α-$C(CH_3)_2$), 1·06 (s, $C(CH_3)_2$ on the 6-ring); *m/e* 252 (M^+, 10), 180 (100), 83 (16), 72 (6), 67 (10), 58 (9). (Found: C, 66·72; H, 9·77; N, 10·85. Calcd. for $C_{14}H_{24}N_2O_2$ (252·35): C, 66·63; H, 9·58; N, 11·10%).

When the reaction of 140 mg (1 mmole) of dimedone and 112 mg (1 mmole) of **1** was conducted in 1·5 ml of dimethylformamide, the adduct **5c** which crystallised from the mixture was obtained in 84% yield.

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