Enamines; 44[1]. 2-Acyl-1,1-diamino-ethenes. A New Source of Methylketones, β-Keto Amides and β-Keto Esters

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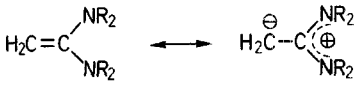
A general synthesis of 2-acyl-1,1-diamino-ethenes by reaction of 1,1-dimorpholino- and 1,1-dipiperidino-ethenes with aliphatic and aromatic acyl chlorides and their utilization as a source of methylketones, β-keto amides and β-keto esters is reported.

A simple system, potentially useful as synthon in organic reactions, is represented by 1,1-diaminoethenes **1**, which can react as a nucleophile to electrophilic substrates thus



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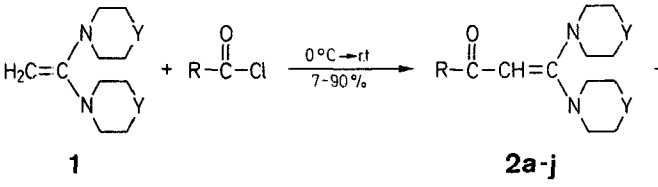
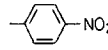
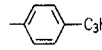
introducing a two-carbon unit. Some work on this subject have appeared in the literature[2,3], however, in our opinion the synthetic potential of **1** is worthy of further investigation.

In this paper we report the general synthesis of 2-acyl-1,1-diamino-ethenes **2** by reaction of 1,1-dimorpholino and 1,1-dipiperidino-ethenes[4] with aliphatic and aromatic acyl chlorides and their utilization as a source of methylketones, β-keto amides and β-keto esters.



1 **2a-j**

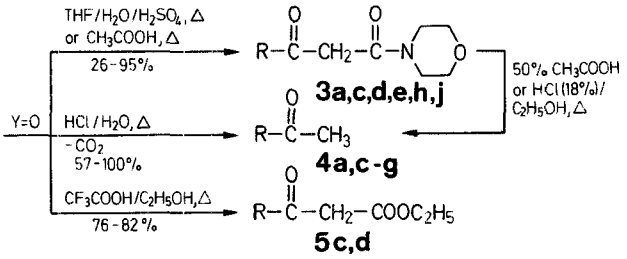
1-5	R	Y
a		O
b		CH_2
c		O
d		O
e		O

1-5	R	Y
f		O
g	$H_3C-(CH_2)_{14}-$	O
h	C_2H_5O-	O
i		O
j		O

Two examples of this kind of acylation have been reported till now, both on the preparation of acetyl derivatives: 2-acetyl-1,1-dimorpholino-ethene[5] and 2-acetyl-1,1-dipiperidino-ethene[6].

Although not related with our approach, other synthesis of 2-acyl-1,1-diamino-ethenes have been described starting from 1,1-dichloro-3-vinyl-ketones[7] or 1-bromo-ethynyl-ketones[8] and reacting them with primary or secondary amines.

The compounds prepared in this work are listed in Table 1 besides some physico-chemical properties. As evidenced from Table 1, better yields are obtained with aromatic acyl chlorides, while the method has poor preparative interest



3a,c,d,e,h,j **4a,c-g** **5c,d**

when aliphatic acyl chlorides are used. The low yields in the latter case are due to the competitive nucleophilic attack of the amine at the carbonyl of acyl chlorides affording the acyl morpholines or acyl piperidines as byproducts. Good yields are obtained with chlorocarbonates by directly mixing them with 1,1-dimorpholino-ethene. The 2-acyl-1,1-diamino-ethenes **2** afford by selective hydrolysis the corresponding β-keto amides. These can be further decarboxylated to methylketones. The selective hydrolytic process to β-keto amides has been attempted with several reagents. 18%

Table 1. Compounds **2a–i** Prepared

Product No.	Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular Formula[c]	^{1}H-N.M.R. ($CDCl_3$/TMS) $\delta_{=CH}$ [ppm]	^{13}C-N.M.R. ($CDCl_3$/TMS) δ(O=C—CH=C) [ppm]		
					a	b	c
2a	60	142–144° (ethyl acetate)	$C_{17}H_{22}N_2O_3$ (302.4)	5.12	186.2	84.3	166.8
2b	30	74–77° (pentane)	$C_{19}H_{26}N_2O$ (298.4)	5.10	184.9	83.83	168.4
2c	90	190° (ethanol)	$C_{17}H_{21}N_3O_5$ (347.4)	5.10	182.76	84.2	167.26
2d	55	155–157° (ethyl acetate)	$C_{20}H_{28}N_2O_4$ (360.4)	5.10	185.73	84.37	160.00
2e	36	124–127° (diisopropyl ether)	$C_{16}H_{21}N_3O_3$ (303.4)	5.06	183.38	83.96	167.03
2f	16	111–113° (ethyl ether)	$C_{17}H_{28}N_2O_3$ (308.4)	4.50	198.56	85.45	165.54
2g	7	72–74° (pentane)	$C_{26}H_{48}N_2O_3$ (436.6)	4.50	195.59	86.91	165.13
2h	65	140–144° (ethyl ether)	$C_{13}H_{22}N_2O_4$ (270.3)	3.85	165.84 166.37	74.28	165.84 166.37
2i	60	111–114° (isopropanol)	$C_{17}H_{22}N_2O_4$ (318.4)	4.26	167.16 165.63	73.96	167.16 165.63
2j	75	138–140° (ethyl acetate)	$C_{18}H_{24}N_2O_4$ (332.4)	4.13	167.28 166.36	75.20	167.28 166.36

[a] Yield of isolated products.
[b] Uncorrected.
[c] The microanalyses were in good agreement with the calculated values: C ±0.31, H ±0.13, N ±0.15.

Table 2. β-Keto Amides **3a, c–e** and β-Alkoxycarbonyl Amides **3h, j** Prepared

Product No.	Reagent	Yield [%]	m.p. [°C][a] (solvent)	Molecular Formula[b] or Lit. m.p. [°C]
3a	$THF/H_2O/H_2SO_4$[c]	26	78° (diisopropylether)	77°[9]
3c	$THF/H_2O/H_2SO_4$[c]	50	156–158° (ethyl acetate)	$C_{13}H_{14}N_2O_5$ (278.3)
3d	$THF/H_2O/H_2SO_4$[c]	30	77–79° (ethyl acetate)	$C_{16}H_{21}NO_4$ (291.3)
3e	$THF/H_2O/H_2SO_4$[c]	30	106–108° (ethyl acetate)	108°[10]
3h	CH_3COOH (50%)	56	59–62° (ethyl ether)	$C_9H_{15}NO_4$ (201.2)
3j	CH_3COOH (50%)	95	oil	$C_{14}H_{17}NO_4$ (263.3)

[a] Uncorrected.
[b] The microanalyses were in good agreement with the calculated values: C ±0.30, H ±0.15, N ±0.20.
[c] Ratio: 30 : 10 : 1.

Table 3. Methylketones **4** Prepared

Educt	Reagent	Product[a]	Yield [%]
2a	CH_3COOH (50%)	Acetophenone **(4a)**	~100[b]
2c	CH_3COOH (50%)	4-Nitroacetophenone **(4c)**	73[c]
2d	CH_3COOH (50%)	4-Isopropylacetophenone **(4d)**	~100[b]
2e	EtOH/HCl (18%)	3-Acetylpyridine **(4e)**	57[c]
2f	CH_3COOH (50%)	Acetylcyclohexane **(4f)**	~100[b]
2g	CH_3COOH (50%)	Myristyl methyl ketone **(4g)**	~100[b]

[a] Compared with an authentic sample (I.R.).
[b] Determined by T.L.C.
[c] Yield of isolated product.

Hydrochloric acid, 10% sulfuric acid and aqueous trifluoroacetic acid afforded methylketones but only poor amount of β-keto amides, while a mixture of tetrahydrofure/aqueous sulfuric acid or 50% aqueous acetic acid allow the selective hydrolysis to β-keto amides. The ethoxycarbonyl and benzyloxycarbonyl groups remain unchanged during hydrolysis with acetic acid.

The alcoholysis performed in acidic ethanol on the acylethenes **2c** and **2d** gives the corresponding benzoylacetates in good yields.

2-Acyl-1,1-Diamino-ethenes (2a–g); General Procedure:
To a stirred solution of 1,1-diamino-ethene **1** (25 mmol) and triethylamine (2.83 g, 28 mmol) in chloroform (50 ml) cooled at 0 °C, acyl chloride (25 mmol) in chloroform (25 ml) is added dropwise over a period of 45 min. Stirring at room temperature is continued for 24 h, the reaction mixture is washed with a 10% sodium hydroxide solution (10 ml) and then with distilled water (10 ml). The organic layer, freed from the solvent by distillation under reduced pressure, gives a crude product which is purified by crystallization or by column chromatography on silica gel (ratio of silica gel/crude product = 40/1) (Table 1).

2-Alkoxycarbonyl-1,1-Diamino-ethenes (2h, j); 1,1-Diamino-2-phenoxycarbonyl-ethene (2i); General Procedure:
The chlorocarbonate (50 mmol) and 1,1-diamino-ethene **1** (25 mmol) are mixed with stirring until crystallization begins. The thick mass is washed with saturated sodium hydrogen carbonate solution (30 ml), and extracted with ethyl acetate (3 × 30 ml). The organic layer is work up as above to afford the pure products (Table 1).

Hydrolysis of 2-Acyl 1,1-Diaminoethenes to β-Keto amides and β-Alkoxycarbonylamides (3); General Procedure:
2-Acyl-1,1-diamino-ethenes **2** (2 mmol) are refluxed for 2 h in the acidic medium reported in Table 2. After neutralization with 10% sodium hydroxide the reaction mixture is extracted with ethyl acetate (2 × 10 ml). The organic phase is separated, dried with anhydrous sodium sulfate and freed from solvent under reduced pressure. The residue after purification affords β-keto amides.

Methylketones (4); General Procedure:
2-Acyl-1,1-diamino-ethenes **2** or β-keto amides **3** (2 mmol) are refluxed for 24 h in 50% aqueous acetic acid (20 ml) or in 18% ethanolic hydrogen chloride (20 ml). The reaction mixture is cooled and extracted several times with ethyl acetate (3 × 20 ml, for 4d, e) or chloroform (3 × 20, for 4a, c, f, g). The organic layer is dried with anhydrous sodium sulfate, the solvent is evaporated and the crude product purified (Table 3).

Ethyl 4-nitro-benzoylacetate (5c) and Ethyl 4-isopropylbenzoylacetate (5d):
2-Acyl-1,1-diamino-ethenes **2c** and **2d** (2 mmol) are refluxed for 30 h with ethanol (40 ml) in the presence of few drops of trifluoroacetic acid. The solvent is removed under reduced pressure and the crude residue is purified by crystallization or distillation at reduced pressure affording **5c** as yellow needles; yield: 0.36 g (76.6%); m.p. 68–69 °C (Lit.[11], 68–71 °C), and **5d** as an oil; yield: 0.41 g (81.9%); b.p. 78–80 °C/0.5 torr.

5d: $C_{14}H_{18}O_4$ (250.3) calc. C 67.17 H 7.24 found 67.08 7.18

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 1.15–1.50 (m, 9H, CH_3); 3.95 (s, 2H, CO—CH_2—O); 4.22 (q, 2H, J = 9.5 Hz, CH_2—CH_3); 4.70 (m, 1H, CH); 6.86–7.02, 7.86–8.02 ppm) AA'BB' system).

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