Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Florence Souquet , Thierry Martens & Maurice-Bernard Fleury (1993) Use of Methylene Chloride as a C1 Unit in N,N-Dialkylaminomethylation Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 23:6, 817-828

To link to this article: http://dx.doi.org/10.1080/00397919308009843

SYNTHETIC COMMUNICATIONS, 23(6), 817-828 (1993)

USE OF METHYLENE CHLORIDE AS A C1 UNIT IN N,N-DIALKYLAMINOMETHYLATION REACTION

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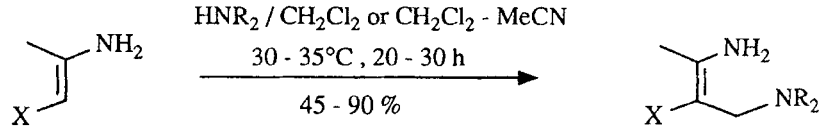
Abstract. Mannich products have been isolated in good yields with methylene chloride as a C1 unit, instead of formaldehyde. It is evidenced that, contrary to previous understanding, a high pressure procedure is not necessary required and that the methylene bisamines function as intermediates.

In the literature, accumulation of evidence has proved that methylene chloride can behave both as solvent and reactant. Then, the formation of MANNICH products required high pressure procedure, as observed in the reaction of ketones (acetophenone, cyclohexanone) or esters (malonate, n-butylacetate) with methylene chloride and secondary amines[1,2]. In such a reaction, it has been evidenced that the corresponding methylene-bisamines (aminals) function as intermediates. More recently, the MILLS group presented convincing evidence for the rapid reaction of methylene chloride and secondary amines to form aminals at room temperature and atmospheric pressure, in basic conditions[3-5]. In return, to the best of our knowledge, none of MANNICH products have been obtained at atmospheric pressure, even after extended reaction times[3].

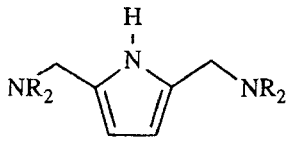
In this context, we report herein some preparative results providing additional evidence for the rapid reaction of methylene chloride with diethylamine or heterocyclic secondary amines (piperidine or morpholine), to form MANNICH adducts at atmospheric pressure.

The general reaction can be demonstrated using eneamines **1** and **2** (scheme 1). In a typical experiment, treatment of **1** or **2** (1 mmol) with an excess

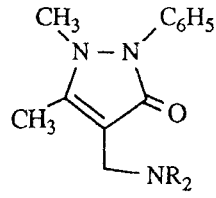


1 - 2 **1a -c** **2a -c**

1	X	R_2	2	X	R_2
a	CN	Et_2	**a**	$COOCH_3$	Et_2
b	CN		**b**	$COOCH_3$	
c	CN		**c**	$COOCH_3$	



3 a - c



4 a - c

3 - 4	R_2
a	Et_2
b	
c	

Scheme 1

Table 1. MANNICH Bases **1a-4c** and **7c** prepared.

Product	Reaction Conditions			mp	Yield [b] (%)	
	Temp. (°C)	Time (h)	Solvent [a]	(°C)	found	reported
1 a	35	30	A	oil	90	68 [6]
1 b	30	20	A	73	75[c]	75 [6]
1 c	30	20	B	115	45[c]	93 [6]
2 a	35	30	A	oil[d]	90	60 [7]
2 b	30	30	A	oil[d]	70	55 [7]
2 c	30	30	B	oil[d]	50[e]	50 [7]
3 a	40	60	A	oil	78	30 [8]
3 b	40	60	A	95	75	89 [8]
3 c	50	60	B	75	75	96 [8]
4 a	40	72	A	73	85	n.g.
4 b	40	72	A	95	78	n.g.
4 c	50	72	B	130	90	70 [9]
7c	40	72	C	oil	63	0 [10]

[a] Solvent: A: methylene chloride; B: 1:1 v/v methylene chloride/acetonitrile mixture; C: 1:1 v/v methylene chloride/acetic acid mixture.

[b] Yield of isolated product (our work). Yield reported in ref., using the classical MANNICH reaction.

[c] The by-products **5b** (15% yield); **5c** (45% yield) were also isolated.

[d] Not cristallized owing to the slow dimethyl-1,4-dihydro-2,6-dimethyl-3, 5-pyridine dicarboxylates formation.

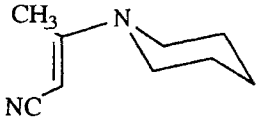
[e] Recovery starting materials **2**.

n.g. Not given.

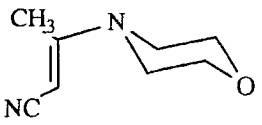
of diethylamine or piperidine (10 mmol) in methylene chloride (10 mL) gave, the corresponding N,N-dialkylaminomethyl derivatives **1a**, **1b**, or **2a**, **2b**, in satisfactory yields (scheme 1) as indicated in Table 1. The others π excessive compounds, pyrrole (**3**) and antipyrine (**4**), were similarly treated with secondary amines to afford the corresponding MANNICH bases **3a**, **3b** and **4a**, **4b** (scheme 1, Table 1).

The attempted reaction between compounds **1-4** and morpholine did not yield MANNICH products **1c**, **2c**, **3c** and **4c**, but these were again produced when acetonitrile was added to methylene chloride in a 1:1 v/v ratio.

With piperidine and morpholine, **1** afforded respectively 3-piperidino-crotonitrile **5b** and 3-morpholinocrotonitrile **5c** as by-products.



5b



5c

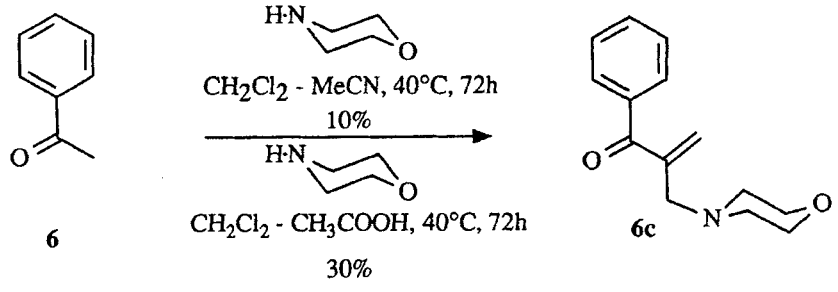
A nucleophilic attack at the C-3 position by piperidine or morpholine is consistent with the formation of **5b** and **5c**. In addition, it has been evidenced that this side-reaction was seriously influenced by the temperature; to minimize it, the more appropriate temperature was found to be 30°C.

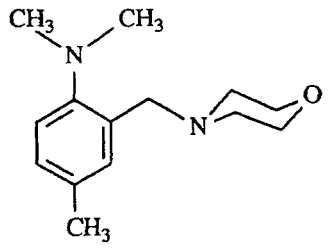
Contrary to **1**, **2** did not afford by-products, but MANNICH bases **2a**, **2b** and **2c** were slowly changed to Hantzch dihydropyridines upon storage at room temperature: the spectral data are in agreement with dimethyl-1,4-dihydro-2,6-dimethyl -3,5-pyridine dicarboxylates[11]. The reaction proceed from cyclocondensation of two MANNICH bases **2a**, **2b** or **2c** ; the exposure to acidic conditions accelerate the change involved. Accordingly, only chromatography on silicagel using a 2% diethylamine eluent permitted isolation of **2a-2c**. It is noteworthy that there is no comment about this reaction in ref.7.

Furthermore, the reaction can be carried out using substrates regarded hitherto as unreactive at atmospheric pressure[3]. For example, acetophenone **6** reacted with morpholine under our experimental conditions affording, after 72 h, 2-methylene-3-morpholino propiophenone **6c** in 10% yield (scheme 2), arising from decomposition of 2,2 bis(N-morpholinyl methyl) acetophenone[11]. The addition of acetic acid after 48 h resulted in an increasing of yield that was then found to be 30%.

In a more striking manner, using the same method as for **1-4**, N,N-dimethyl-p-toluidine **7** and morpholine did not result in MANNICH base (**7c**)(scheme 2) production, but this was produced in 65% yield when the medium was supplemented with acetic acid after 48 h (see experimental).

The N,N-dialkylaminomethylation reaction rate was found very low (Table 1). To give evidence supporting the hypothesis that the aminal formation may constitute the rate determining step, aminals have been prepared (see experimental) from reaction of methylene chloride and secondary amine. The overall reaction yielding **8a-c** was:





7c

Scheme 2

$$CH_2Cl_2 + 4\,RNH_2 \longrightarrow R_2N - CH_2 - NR_2 + 2\,HNR_2 + 2\,HCl \quad (1)$$

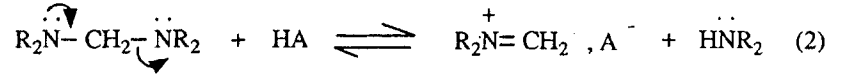
The observed yields (see experimental) are virtually good when taking into consideration that four moles of secondary amines are required for the production of aminal.

The aminals were consecutively used in modified MANNICH reactions[9,13,14] with compounds **1**,**3**,**4**. When **1** (1 mmol) was exposed for 2h at 25°C and atmospheric pressure to **8a-b** (1 mmol), in chloroform (10 mL), MANNICH products were produced in roughly quantitative yields, to the exclusion of the by-products **5b** or **5c**.

In contrast, the N,N-dialkylaminomethylation reaction of **3**-**4** using aminals **8a-b** was found less easy and required addition of ammonium salt, while **8c** was reactive only in acetonitrile. This finding justifies the use of a 1:1 v/v methylene chloride/acetonitrile mixture in the reaction between compounds **1**-**4** and morpholine.

From our results, it can be emphasized that, in the **1-4,7** studied series, the more labile the hydrogen atom of their eneamine moiety, and the greater the activity of compounds will be, according to the sequence **1** ≥ **2** >> **3** > **4** >> **7**.

Beside this structural feature, the effectiveness of the acid present in the experimental medium (hydrochloric acid yielded by the shift of equilibrium (1) towards the right handside, or acidic species added to the medium during the course of the reaction) jointly might determine the optimal conditions in order to maintain a useful rate. That aminals function as intermediates in the studied reaction provides an interpretation of these results. Indeed, the aminals can be considered as preformed Eschenmoser salts:



(2)

Accordingly, the reactivity of aminals should occur via an antecedent protonation, dependent on the effectiveness of the HA species present in promoting reaction.

From the data listed in Table 1, it is obvious: a) that methylene chloride can serve as a C-1 unit in N,N-dialkylaminomethylation reaction; b) that the high pressure conditions reported by MATSUMOTO and confirmed by MILLS are not necessarily required; c) that MANNICH products were generally afforded in better yields compared to the literature procedures using formaldehyde as a C-1 unit. Further explorative work will show if this reaction can be found synthetically useful for the N,N-dialkylaminomethylation of an electron-rich carbon atom, because of the density, low toxicity and low boiling point of methylene chloride.

EXPERIMENTAL

All reagents were purchased from MERCK and were used without further purification. The solvents were obtained from S.D.S.. Chromatography was performed using silica gel grade 60, purchased from MERCK. Melting points (m.p.) were determined on a Köfler block and were uncorrected. ^{1}H NMR (300 MHz) spectra were recorded on a Bruker WM-300 spectrometer using $CDCl_3$ as solvent. $SiMe_4$ was used as internal standard. The various splitting patterns were designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; bs:

broad signal. Chemical shifts were expressed in units (ppm) and coupling constants were given in Hz. Chemical ionisation (CI; NH_3) mass spectrometry (MS) was carried out on a Nermag R 10-10 C instrument.

MANNICH bases 1a-4c formation; General Procedure:

A solution of compound **1-4** (1 mmol) and secondary amine (10 mmol) in CH_2Cl_2 (10 mL) or in a mixture of CH_2Cl_2/ MeCN 1:1 v/v (10 mL) was stirred (see Table 1 for specific conditions). The resulting suspension was washed with water (25 mL). The aqueous phase was extracted with CH_2Cl_2 (25 mL) and the combined organic layers were dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave the crude product. The final purification of the MANNICH bases (except for **1a** and **2a** which were analysed without further purification) was accomplished by column chromatography.

3-amino-2-(N,N-diethylaminomethyl) crotonitrile (1a).

General procedure with **1** (82 mg) and diethylamine (730 mg) produced a pale yellow oil **1a** (150 mg, 90% yield) which was analysed without further purification. ^1H NMR, δ: 0.95 (t, 6H, $CH_3\times$ 2, ethyl); 2.02 (s, 3H, CH_3); 2.45 (q, 4H, $CH_2\times$ 2, ethyl); 3.10 (s, 2H, CH_2); 5.62 (bs, 2H, NH_2). MS, m/z 168 (MH^+).

3-amino-2-(N-piperidinylmethyl) crotonitrile (1b) and 3-piperidino crotonitrile (5b).

General procedure with **1** (82 mg) and piperidine (850 mg) yielded a mixture of products. Chromatography (CH_2Cl_2/ MeOH, 90:10) provided a white solid **1b** (135 mg, 75% yield, m.p. 73°C) and a pale yellow oil **5b** (24 mg, 15% yield). Spectral data for **1b** are as follows: ^1H NMR, δ: 1.45 (m, 2H, CH_2-4', piperidinyl); 1.55 (m, 4H, CH_2-3' and CH_2-5', piperidinyl); 2.05 (s, 3H, CH_3); 2.35 (m, 4H, CH_2-2' and CH_2-6', piperidinyl); 3.05 (s, 2H, CH_2); 5.70 (bs, 2H, NH_2). MS, m/z 180 (MH^+). Spectral data for **5b** are as follows: ^1H NMR, δ: 1.60 (m, 6H, CH_2-3', CH_2-4' and CH_2-5', piperidinyl); 2.15 (s, 3H, CH_3); 3.21 (m, 4H, CH_2-2' and CH_2-6', piperidinyl); 3.91 (s, 1H, H-2). MS, m/z 151 (MH^+)

3-amino-2-(N-morpholinylmethyl) crotonitrile (1c) and 3-morpholino crotonitrile (5c).

General procedure was perfomed using a methylene chloride/acetonitrile mixture 1:1 v/v with **1** (82 mg) and morpholine (870 mg). Chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 95:5:0.5) permitted isolation of two products: a white solid **1c**

(80 mg, 45% yield, m.p. 115°C) and a yellow oil **5c** (70 mg, 45% yield). Spectral data for **1c** are as follows: ^{1}H NMR, δ: 2.10 (s, 3H, CH_3); 2.45 (m, 4H, CH_2-3' and CH_2-5', morpholinyl); 3.10 (s, 2H, CH_2); 3.70 (m, 4H, CH_2-2' and CH_2-6', morpholinyl); 5.65 (bs, 2H, NH_2). MS, m/z 182 (MH^+). Spectral data for **5c** are as follows: ^{1}H NMR, δ: 2.20 (s, 3H, CH_3); 3.18 (m, 4H, CH_2-3' and CH_2-5', morpholinyl); 3.75 (m, 4H, CH_2-2' and CH_2-6', morpholinyl); 4.00 (s, 1H, H-2). MS, m/z 155 (MH^+).

3-amino-2-(N,N-diethylaminomethyl) crotonate methyl ester (2a).

General procedure with **2** (115 mg) and diethylamine (730 mg) produced a pale yellow oil **2a** (181 mg, 90% yield) which was analysed without further purification. ^{1}H NMR, δ: 1.00 (dt, 6H, $CH_3\times$ 2, ethyl); 2.02, 2.12[a] (s, 3H, CH_3); 2.44 (dq, 4H, $CH_2\times$ 2, ethyl); 3.12, 3.35[a] (s, 2H, CH_2); 3.62[a], 3.64 (s, 3H, $COOCH_3$)(signals of the minor isomer are designated by [a]). MS, m/z 201 (MH^+)

3-amino-2-(N-piperidinylmethyl) crotonate methyl ester (2b)

General procedure with **2** (82 mg) and piperidine (850 mg) yielded, after Chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 95:5:0.2), **2b** as an oil (148 mg, 75% yield). ^{1}H NMR, δ: 1.40 (m, 2H, CH_2-4', piperidinyl); 1.50 (m, 4H, CH_2-3' and CH_2-5', piperidinyl); 2.10, 2.27[a] (s, 3H, CH_3); 2.37 (m, 4H, CH_2-2' and CH_2-6', piperidinyl); 3.10, 3.30[a] (s, 2H, CH_2); 3.62[a], 3.66 (s, 3H, $COOCH_3$)(signals of the minor isomer are designated by [a]).MS, m/z 213 (MH^+).

3-amino-2-(N-morpholinylmethyl) crotonate methyl ester (2c).

General procedure was perfomed using a methylene chloride/acetonitrile mixture 1:1 v/v (10 mL) with **2** (115 mg) and morpholine (870 mg). Chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 95:5:0.2) permitted isolation of **2c** as an oil (108 mg, 50% yield). Spectral data for **2c** are as follows: ^{1}H NMR, δ: 2.14 (s, 3H, CH_3); 2.50 (m, 4H, CH_2-3' and CH_2-5', morpholinyl); 3.17 (s, 2H, CH_2); 3.70 (m, 7H, CH_2-2' and CH_2-6', morpholinyl and $COOCH_3$).MS, m/z 215.

2,5-bis(N,N-diethylaminomethyl) pyrrole (3a).

General procedure with **3** (65 mg) and diethylamine (730 mg) produced, after chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 90:10:1), a yellow oil **3a** (185 mg, 78% yield). ^{1}H NMR, δ: 1.02 (t, 12H, $CH_3\times$ 4, ethyl); 2.50 (q, 8H, $CH_2\times$ 4, ethyl); 3.60 (s, 4H, $CH_2\times$ 2); 5.85 (d, 2H, H-3 and H-4, J H_1-H_3= J H_1-H_4= 2.6 Hz); 8.65 (bs, 1H, NH, D_20 exchanged). MS, m/z 238 (MH^+).

2,5-bis(N-piperidinylmethyl) pyrrole (3b).

General procedure with **3** (65 mg) and piperidine (850 mg) produced after chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 90:10:1), a yellow solid **3b** (198 mg,

76% yield, m.p. 95°C). ^{1}H NMR, δ: 1.22 (m, 4H, CH_2-4' × 2 , piperidinyl); 1.35 (m, 8H, CH_2-3'× 2 and CH_2-5'× 2, piperidinyl); 2.35 (m, 8H, CH_2-2'× 2 and CH_2-6'× 2, piperidinyl); 3.42 (s, 4H, CH_2× 2); 5.90 (d, 2H, H-3 and H-4, J H_1-H_3= J H_1-H_4= 2.6 Hz); 8.80 (bs, 1H, NH, D_2O exchanged). MS, m/z 261 (MH^+).

2,5-bis(N-morpholinylmethyl) pyrrole (3c).

General procedure using methylene chloride/acetonitrile 1:1 v/v mixture with **3** (65 mg) and morpholine (870 mg) produced after chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 95:5:1), a solid **3c** (198 mg, 75% yield, m.p. 75°C). ^{1}H NMR, δ: 2.15 (m, 8H, CH_2-3'× 2 and CH_2-5'× 2, morpholinyl); 3.15 (s, 4H, CH_2× 2); 3.42 (m, 8H, CH_2-2'× 2 and CH_2-6'× 2, morpholinyl); 5.60 (d, 2H, H-3 and H-4, J H_1-H_3= J H_1-H_4= 2.6 Hz); 8.48 (bs, 1H, NH, D_2O exchanged). MS, m/z 266 (MH^+).

4-(N,N-diethylaminomethyl) antipyrine (4a).

General procedure with **4** (188 mg) and diethylamine (730 mg) produced after chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 80:20:1), a pale yellow solid **4a** (231 mg, 85% yield, m.p. 73°C). ^{1}H NMR, δ: 1.10 (t, 6H, CH_3× 2, ethyl); 2.30 (s, 3H, CH_3); 2.60 (q, 4H, CH_2× 2, ethyl); 3.00 (s, 3H, N-CH_3); 3.38 (s, 2H, CH_2); 7.40 (m, 5H, phenyl). MS, m/z 274 (MH^+).

4-(N-piperidinylmethyl) antipyrine (4b).

General procedure with **4** (188 mg) and piperidine (850 mg) produced after chromatography (CH_2Cl_2/ MeOH, 80:20), a pale yellow solid **4b** (224mg, 78% yield, m.p. 95°C). ^{1}H NMR, δ: 1.45 (m, 2H, CH_2-4', piperidinyl); 1.60 (m, 4H, CH_2-3' and CH_2-5', piperidinyl); 2.30 (s, 3H, CH_3); 2.50 (m, 4H, CH_2-2' and CH_2-6', piperidinyl); 3.10 (s, 3H, N-CH_3); 3.30 (s, 2H, CH_2); 7.20-7.50 (m, 5H, phenyl). MS, m/z 286 (MH^+).

4-(N-morpholinylmethyl) antipyrine (4c).

General procedure was performed using a mixture of methylene chloride/acetonitrile 1:1 v/v (10 mL) with **4** (188mg) and morpholine (870 mg). Chromatography (CH_2Cl_2/ MeOH/ Et_2NH, 90:10:1) permitted isolation of a white solid **4c** (262 mg, 90% yield, m.p. 130°C). ^{1}H NMR, δ: 2.25 (s, 3H, CH_3); 2.50 (m, 4H, CH_2-3' and CH_2-5', morpholinyl); 3.05 (s, 3H, N-CH_3); 3.30 (s, 2H, CH_2); 3.65 (m, 4H, CH_2-2' and CH_2-6', morpholinyl); 7.40 (m, 5H, phenyl). MS, m/z 288 (MH^+).

2-methylene-3-morpholino propiophenone (6c).

A solution of acetophenone **6** (120 mg, 1 mmol) and morpholine (0.87 mL, 870 mg, 10 mmol) in CH_2Cl_2 (10 mL) was stirred at 40°C. After 48h, acetic acid (10 mL) was added and the resulting solution was stirred at 40°C for 24h longer. The reaction mixture was poured into water (100 mL) and made alkaline and then extracted with ethylacetate (50 mL × 2). The combined organic layers were dried over anhydrous sodium sulphate and evaporated to dryness under reduced pressure. Chromatography (ethylacetate/ cyclohexane/ acetone, 50:50:1) provided 2-methylene-3-morpholino propiophenone **6c** as a white solid (72 mg, 31% yield, m.p. 62°C), (recovery starting material (**6**), 60 mg, 50% yield). ^{1}H NMR, δ: 2.50 (m, 4H, CH_2-3' and CH_2-5', morpholinyl); 3.40 (s, 2H, CH_2-N); 3.70 (m, 4H, CH_2-2' and CH_2-6', morpholinyl); 5.78 (d, 1H, H_A, methylene, J H_A-H_B= 1Hz); 6.02 (d, 1H, H_B, methylene, J H_A-H_B= 1Hz); 7.40-7.90 (m, 5H, phenyl). MS, m/z 232 (M^++ 1).

2-(N-morpholinylmethyl)-N,N-dimethyl-p-toluidine (7c).

Using the same method as for **6** with **7** (135 mg) and morpholine (870 mg), and after chromatography (ethylacetate/ cyclohexane/ acetone, 40:40:2), **7c** was obtained as a yellow oil (148 mg, 63% yield). ^{1}H NMR, δ: 2.30 (s, 3H, CH_3-4); 2.48 (m, 4H, CH_2-3' and CH_2-5', morpholinyl); 2.70 (s, 6H, N-$(CH_3)_2$); 3.55 (s, 2H, CH_2); 3.70 (m, 4H, CH_2-2' and CH_2-6', morpholinyl); 7.00 (s, 2H, H-5 and H-6); 7.26 (s, 1H, H-3). MS, m/z 235 (MH^+).

Synthesis of methylenebisamines 8a, 8b, 8c.

A solution of appropriate secondary amine (100 mmol), diethylamine (7,3 g), piperidine (8,5 g) or morpholine (8,7 g), in methylene chloride (100 mL), was stirred and refluxed. After 65 h, the reaction mixture was washed with water (50 mL) and dried over anhydrous sodium sulphate. The solvent and the unreacted amine were removed under reduced pressure. The corresponding methylenebisamines **8a** (2,7 g, 17% yield), **8b** (3,3 g, 18% yield), **8c** (2,4 g, 13% yield) were isolated without further purification. The spectral data were in agreement with those previously described in the literature[2]. Note that, with morpholine (8,7 g), in methylene chloride/acetonitrile 1:1 v/v mixture (100 mL), **8c** was isolated in 25% yield (4,65 g)

Use of isolated methylenebisamines with 1.

A reaction mixture of compound **1** (82 mg, 1 mmol) and methylene bis diethylamine (158 mg, 1 mmol), methylene bis piperidine (182 mg, 1 mmol) in

chloroform (10 mL), or methylene bis morpholine (184 mg, 1 mmol) in acetonitrile (10 mL), was stirred at room temperature for 2h. The resulting solution was washed with water (20 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure to give **1a** (150 mg, 90% yield), **1b** (153 mg, 85% yield) or **1c** (146 mg, 80% yield) respectively.

Use of isolated methylenebisamines with 3.

A reaction mixture of compound **3** (188 mg), methylene bis diethylamine (474 mg, 3 mmol), methylene bis piperidine (546 mg, 3 mmol) in chloroform (10 mL), or methylene bis morpholine (558 mg, 3 mmol) in acetonitrile (10 mL) was stirred at 40°c for 24h after addition of the corresponding ammonium chloride (6 mmol).The resulting solution was washed with water (20 mL). The organic layer was dried over anhydrous sodium sulphate and the solvent removed under reduced pressure to give after chromatography respectively **3a** (154 mg, 65% yield), **3b** (182 mg, 70% yield), or **3c** (186 mg, 70% yield).

Use of isolated methylenebisamines with 4.

Using the same method as for **3**, a reaction of compound **4** (188 mg), methylene bis diethylamine (316 mg, 2 mmol), methylene bis piperidine (366 mg, 2 mmol) in chloroform (10 mL), or methylene bis morpholine (364 mg, 2 mmol) in acetonitrile (10 mL) with the corresponding ammonium chloride (4 mmol), gave **4a** (247 mg, 90% yield), **4b** (229 mg, 80% yield), or **4c** (273 mg, 95% yield).

REFERENCES

1. Matsumoto, K. *Angew. Chem.* **1982**, *94*, 937.

2. Matsumoto, K.; Hashimoto, S.; Ikemi, Y.; Otani, S. *Heterocycles.* **1984**, *22*, 1417.

3. Mills, J.E.; Maryanoff, C.A.; Cosgrove, R.M.; Scott, L.; Mc Comsey, D.F. *Org. Prep. Proc. Int.* **1984**, *16*, 99.

4. Mills, J.E.; Maryanoff, C.A.; Mc Comsey, D.F.; Stranzione, R.C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857.

5. Federsel, H.J.; Könberg, E.; Lilljequist, L.; Swahn, B.M. *J. Org. Chem.* **1990**, *55*, 2254.

6. Möhrle, H.; Reinhardt, H.W. *Pharmazie.* **1984**, *39*, 384.

7. Möhrle, H.; Reinhardt, H.W. *Arch. Pharm.* **1984**, *317*, 1017.

8. Bachman, G.B.; Heisey, L.V. *J. Am. Chem. Soc.* **1946**, *68*, 2496.
9. Lieberman, S.V.; Wagner, E.C. *J. Org. Chem.* **1949**, *14*, 1001.
10. Miocque, M.; Vierfond, J.M. *Bull. Soc. Chim. France.* **1970**, 1896-1910
11. Kurfûrst, A.; Trska, P.; Goljer, I. *Collection Czechoslovak Chem. Commun.* **1984**, *49*, 2393.
12. Jasor, Y.; Luche, M.J.; Gaudry, M.; Marquet, A. *J. Chem. Soc. Chem. Com.* **1974**, 253.
13. Hunt, W.C.; Wagner, E.C. *J. Org. Chem.* **1951**, *16*, 1792.
14. Wagner, E.C. *J. Org. Chem.* **1954**, *19*, 1862.

(Received in UK 5 October, 1992)