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Two approaches to α,α-bis-Mannich salts of *N*-monosubstituted amides

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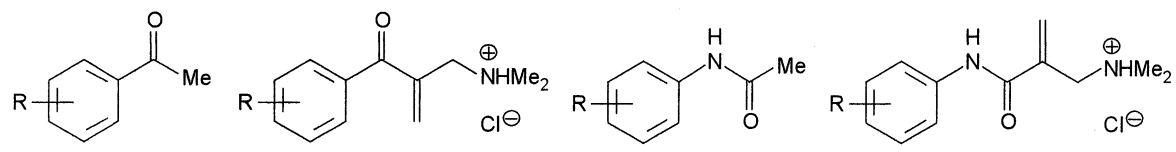
Abstract—Two generally applicable syntheses of 2-bis-(dimethylaminomethyl)acetamides **9** are described. The first one involves reaction of *N*-mono substituted acetamides **3** with dimethyl(methylene)ammonium chloride in the presence of phosphorus oxychloride using diethyl ether as a solvent. Starting from ketoximes, the amines **9** are obtained under the same reaction conditions via Beckmann rearrangement. *C*-Aminomethylation observed in all cases may be the result of the formation of imidoyl chlorides **5** as intermediates.

Recently, we disclosed that the aminoalkylation of aromatic methyl ketones **1** with paraformaldehyde and dimethylamine as well as with dimethyl-(methylene)ammonium chloride in dimethylformamide is an efficient method for the synthesis of 1-aryl-2-dimethylaminomethylprop-2-en-1-ones **2**.[1] These experimental results prompted us to investigate the general applicability of dimethylformamide as a solvent for the Mannich reaction of acetanilides **3** to give the corresponding 2-dimethylaminomethyl-propenoic acid anilides **4** (see Fig. 1). The first attempts to aminomethylate acetanilide using dimethyl-(methylene)ammonium chloride[2] in DMF or other solvents failed. Under standard conditions described earlier by us,[1] we isolated only starting materials. Therefore, we decided to activate acetanilide through formation of its imidoyl chloride to be generated in situ using phosphorus oxychloride as reagent and solvent. Later on, we used diethyl ether as a solvent reducing thereby the excess of phosphorus oxychloride to a necessary minimum (see Scheme 1). In a typical one-pot procedure, the *N*-mono substituted amide **3** was treated together with phosphorus oxychloride using diethyl ether as a solvent for 2 hours at ambient temperature. Then, the Mannich reaction was initiated by addition of two molar equivalents of dimethyl-(methylene)ammonium chloride to the solution, which is then stirred overnight at room temperature. Of course standard conditions[3,4] cannot be used because phosphorus oxychloride and dimethylamine hydrochloride would react to form phosphoric acid amide. In order to get rid of the excess of phosphorus oxychloride as well as to avoid the isolation of moisture sensitive hydrochlorides, diethyl ether is removed and the resulting crude product mixture dissolved in isopropanol followed by treatment with perchloric acid at 0°C. Under these conditions the perchlorates of the bis-Mannich products **9** are formed in up to 40% yield analyti-



1 **2** **3** **4**

R = H, 4-Me, 4-Br, 4-OMe, 3,4-Cl_2, 3,4-$(OMe)_2$

Figure 1.

Keywords: amides; ketoximes; bis-dimethylaminomethylacetamides; Mannich reaction; Beckmann rearrangement.

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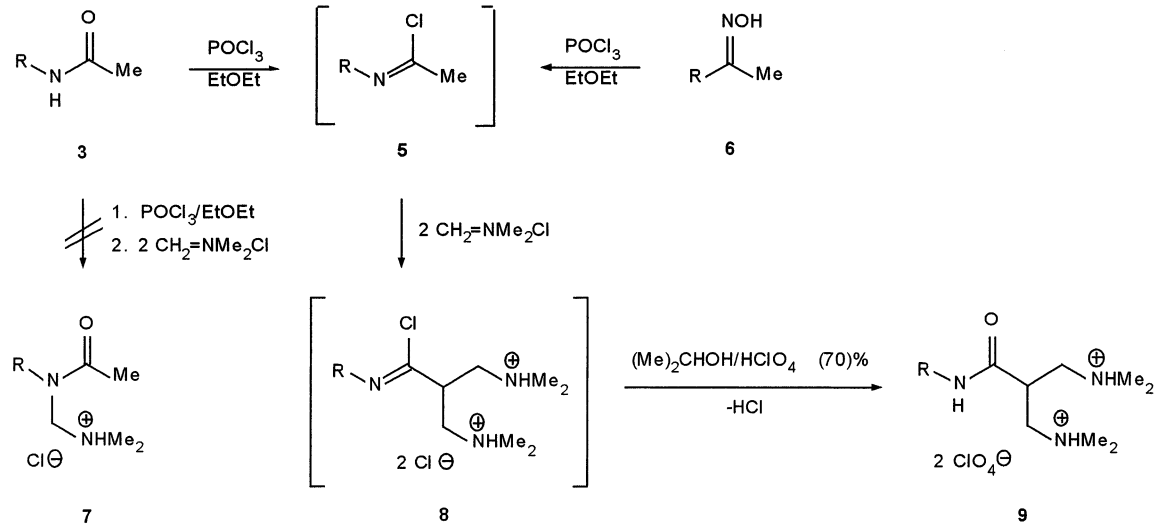

3 5 6 7 8 9

3,6,9	R	3,9	R	6,9	R
a	C_6H_5	**g**	$C_6H_5CH_2$	**f**	4-$H_3COC_6H_4$
b	4-$NO_2C_6H_4$	**h**	$C_6H_5(CH_2)_4$	**k**	CH_3
c	4-BrC_6H_4	**i**	C_6H_{11}		
d	3,4-$Cl_2C_6H_3$	**j**	n-C_4H_9		
e	4-$CH_3C_6H_4$	**l**	i-C_3H_7		

Scheme 1.

cally pure by recrystallization from isopropanol, no fractionated crystallization is necessary.[5] Although the yields are scarcely satisfying, the low-cost materials make the present synthetic route for the preparation of bis-dimethylaminomethylacetamides **9** useful, in particular considering that compounds of this type are otherwise only obtained via multistep reactions. It is noteworthy to point out that mono-Mannich compounds are not obtained even after addition of only equimolar amounts of the iminium chloride. The structure of **9** was unambiguously deduced from their IR, ^1H and ^{13}C NMR spectra and elemental analyses (Table 1).

The replacement of the amide **3** by the ketoxime **6** in the aminomethylation leading to the same experimental results would be an important evidence for the reaction mechanism (see Scheme 1) provided that the imidoyl chloride **5** is formed via the Beckmann rearrangement. Indeed, according to the above described procedure, the ketoxime **6** reacted in the same manner as reported above. The analytically pure perchlorates of the bis-Mannich products **9** are formed in up to 55% yield by recrystallization from isopropanol, no fractionated crystallization is necessary. Thus, the scope of the reaction is broad because any aryl- or alkylmethylketone

Table 1. Mannich reaction of *N*-mono substituted acetamides **3** and ketoximes **6** using dimethyl(methylene)ammonium chloride in the presence of phosphorus oxychloride under ethereal media to give bis-dimethylaminomethyl-acetamides **9**[5]

Entry	Starting materials		Products **9**	R	Mp (°C)	Yield (%) from **3** and (**6**)	
	Amides **3**	Ketoximes **6**					
1	**3a**	**6a**	**9a**	C_6H_5	182	40	(51)
2	**3b**	**6b**	**9b**	4-$NO_2C_6H_4$	178	41	(53)
3	**3c**	**6c**	**9c**	4-BrC_6H_4	187	35	(48)
4	**3d**	**6d**	**9d**	3,4-$Cl_2C_6H_3$	163	31	(55)
5	**3e**	**6e**	**9e**	4-$CH_3C_6H_4$	155	32	(51)
6		**6f**	**9f**	4-$H_3COC_6H_4$	149		(42)
7	**3g**		**9g**	$C_6H_5CH_2$	118	34	
8	**3h**		**9h**	$C_6H_5(CH_2)_4$	149	26	
9	**3i**		**9i**	C_6H_{11}	183	45	
10	**3j**		**9j**	*n*-C_4H_9	162	36	
11		**6k**	**9k**	CH_3	192		(45)
12	**3l**		**9l**	*i*-C_3H_7	155	42	

All new compounds gave satisfactory microanalyses: C, H, N ±0.40.

can be converted into an α,α-bis-Mannich base performing a simple and convenient two-pot synthesis.

The *N*-aminomethylation of **3** to form **7** was not observed (see Scheme 1). This alternative pathway is largely documented in the literature.[6] Since the imidoyl chloride **5** is the crucial intermediate of the Beckmann rearrangement we suggest that this compound is also involved in the activation of the amide **3** and therefore the formation of dimethylaminomethylamides **7** is prevented. *C*-Mono-Mannich bases derived from acetanilides were accessible through aminomethylation of ketones and subsequent Beckmann rearrangement of the respective ketoxime[7] or by the preparation of 3-chloropropionic acid anilide followed by nucleophilic substitution of the halogen by dimethylamine under pressure.[8] Starting from 3-bromo-2-bromomethylpropionic acid chloride an analogous procedure is described for the synthesis of fiber-reactive dyes with the partial structure of 2-bis-(dimethylaminomethyl)-acetamide.[9]

In summary, treatment of *N*-mono substituted acetamides as well as aryl/alkyl-methylketoximes with dimethyl(methylene)ammonium chloride in the presence of phosphorus oxychloride offers two promising, straigthforward and generally applicable routes to 2-bis-(dimethylaminomethyl)-acetamides **9**. They are interesting targets themselves characterized by the classical pharmacophoric structure with an aromatic nucleus, a side chain, and a basic center.

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5. **General procedure**: To a solution of 50 mmol phosphorus oxychloride in 20 ml of diethyl ether, 10 mmol of **3** or **6** was added and the ensuing solution stirred at ambient temperature. Dimethyl(methylene)ammonium chloride (20 mmol) was added after 2 h to the yellow solution. The resultant suspension was allowed to react overnight at ambient temperature while stirring was continued. In order to isolate the product the following two procedures were used with the same result: (a) if a solution was formed overnight, 20 ml of isopropanol was added to get rid of the excess phosphorus oxychloride and 20 mmol of perchloric acid (70%, aqueous solution), usually at this point precipitation occurred. If this was not the case, the solvent was removed in vacuo and 20 ml of isopropanol added to the residue. (b) In case of a suspension the solid was separated from the ethereous phosphorus oxychloride solution and 20 ml of isopropanol followed by 20 mmol of perchloric acid (70%, aqueous solution) was added to the residue under stirring. Thereafter, the crystals were obtained by filtration and subsequent washing with diethyl ether. Recrystallization from isopropanol. Analytical and spectroscopic data of some new compounds: **9a**: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.87$ (br s, 12H, 2×N(CH_3)$_2$); 3.49 (br s, 4H, 2×CH_2); 3.68 (m, 1H, COCH); 7.13 (t, 1H arom, H-4); 7.36 (t, 1H arom, H-3, H-5); 7.70 (dd, 2H arom, H-2, H-6); 10.30 (br s, 2H, exchangeable with D_2O, 2×NH); 11.06 (s, 1H, exchangeable with D_2O, CONH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 38.4$ (CH), 42.7 (CH_2), 43.0 (CH_2), 56.1 (CH_3), 119.7, 124.1, 128.6, 138.3 (CH arom.), 167.4 (C=O). IR (KBr pellet, cm^{-1}): $\nu = 3353$ (br m), 3033 (w), 2976 (w), 2689 (br s), 1686 (s), 1602 (m), 1547 (s), 1446 (br m), 1087 (s), 763 (s), 626 (s). **9d**: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.87$ (br s, 12H, 2×N(CH_3)$_2$); 3.39 (m, 4H, 2×CH_2); 3.65 (m, 1H, COCH); 7.61 (m, 2H arom, H-2, H-6); 8.08 (d, 1H arom, H-5); 10.01 (br s, 2H, exchangeable with D_2O, 2×NH); 11.46 (s, 1H, exchangeable with D_2O, CONH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 38.5$ (CH), 43.0 (CH_2), 56.1 (CH_3), 119.8, 121.7, 125.6, 130.6, 130.8, 138.4 (CH arom.), 167.9 (C=O). IR (KBr pellet, cm^{-1}): $\nu = 3370$ (br m), 3020 (w), 2980 (w), 2670 (br s), 1679 (s), 1580 (s), 1540 (s), 1450 (br m), 1090 (s), 1030 (s), 740 (s), 640 (s). **9k**: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.66$ (d, 3H, NHCH_3); 2.80 (br s, 12H, 2×N(CH_3)$_2$); 3.38 (br m, 5H, CH(CH_2)$_2$); 8.12 (d, 1H, exchangeable with D_2O, CONH); 10.18 (br s; 2H, exchangeable with D_2O, 2×NH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 25.9$ (CH_3), 37.4 (CH), 42.4 (CH_2), 43.0 (CH_2), 56.1 (CH_3), 169.0 (C=O). IR (KBr pellet, cm^{-1}): $\nu = 3272$ (m), 2980 (w), 2670 (br s), 1660 (s), 1540 (m), 1441 (m), 1256 (w), 1070 (br s), 889 (w), 613 (s). **9l**: ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.09$ (d, 6H, 2×CH_3); 1.23 (m, 1H, CH); 2.80 (br s, 12H, 2×N(CH_3)$_2$); 3.31 (br m, 4H, 2×CH_2); 3.84 (m, 1H, COCH); 8.58 (d, 1H, exchangeable with D_2O, CONH); 10.16 (br s; 2H, exchangeable with D_2O, 2×NH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 21.9$ (CH_3), 37.6 (CH), 41.2 (CH), 42.1 (CH_2), 43.3 (CH_2), 56.1 (CH_3), 167.8 (C=O). IR (KBr pellet, cm^{-1}): $\nu = 3272$ (m), 2972 (m), 2686 (br s), 1656 (s), 1554 (m), 1464 (m), 1244 (w), 1088 (br s), 896 (w), 626 (s).
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