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TWO-STEP PROTIC SOLVENT-CATALYZED REACTION OF PHENYLETHYLAMINE WITH METHYL ACRYLATE

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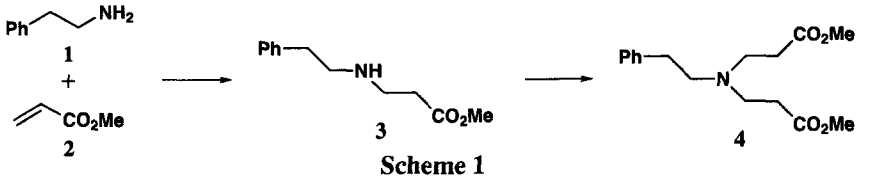
The reaction of phenylethylamine (**1**) with methyl acrylate (**2**), performed in two steps, led to *N*-(β-carbomethoxyethyl)phenethylamine (**3**) and *N,N-bis*-(β-carbomethoxyethyl)phenethylamine (**4**). Compounds **3** and **4** are useful for the preparation of important and valuable compounds, *e. g.* 1-(2-phenethyl)piperidine-4-one and its derivatives, utilized in the synthesis of analgesics such as *fentanyl,*[1-8] *carfentanyl,*[9] *3-methylfentanyl,*[10-13] and lactam analogues of *fentanyl.*[14]



Scheme 1

Several investigations of the reaction of phenethylamine (**1**) with acrylate derivatives have been undertaken.[3-5,14-19] Mc Elvain *et al.* studied the reaction of benzylamine with methyl acrylate and obtained the benzyl analogues of **3** and **4** in 87% and 84% yields, respectively.[19] The reaction of **1** with ethyl acrylate (300 mol%) in ethanol at reflux temperature for 48 h afforded the ethyl analogue of **4**.[17] The generation of **3** from equimolar amount of **1** and **2** in methanol and at room temperature has been reported in yields of 76% (after 4 h)[15] and 83% (after 48 h).[14] In all the cited reports, compounds **3** and **4** were obtained in pure form only after distillation of the crude products. The major reasons that make the distillation step indispensable are the simultaneous presence of **3** and **4** in the crude product and the polymerization of the acrylate that rendered the color of the solution dark red. It was mentioned that the *bis* addition of **2** to **1** (to afford **4**) is strongly catalyzed by polar solvents. On the other hand, it was stated that in less polar solvent such as toluene or CH_2Cl_2 (or solventless conditions), mono addition predominates to give **3** as the major product.[18] A quantitative yield was reported for the preparation of **4** *via* the reaction of **1** with **2** in methanol at reflux temperature for 8 h.[18]

In spite of the importance of **3** and **4** in the preparation of interesting compounds, adequate attention has not been paid to the experimental details of the reaction between **1** and **2**. In the present contribution, the two-step reaction of **1** with **2** was reexamined and optimal conditions to separate the two steps and to obtain the highest yields of the pure products (**3** and **4**), without the need of further distillation, were investigated. Special attention was paid to determine the nature of the catalytic effect of the solvent. The composition of the reaction mixture was determined using ^{1}H NMR spectroscopy.

The addition of equimolar amounts of **2** to **1** in $CHCl_3$ at RT led to the formation of **3** in 5%, 35%, 68% and 85% after 5 min, 1 h, 4 h, and 22 h respectively. The total conversion of **1** to **3** required 50 h. The use of methanol as solvent increased the reaction rate considerably. Thus the first step reaction in methanol at RT proceeds in 15 min leading to **3** greater than 95% purity after evaporation of the solvent. A purer product (> 98%) was obtained by the dropwise addition of **2** to **1**. A solventless mixture of **1** and **2** (400 mol% excess) at RT showed the rapid formation of **3** followed by a progressive appearance of **4** in 10%, 30%, 60% and 90% after 6 h, 30 h, 150 h, and 220 h respectively.

The formation of **4** by the reaction of **1** with excess amounts of **2** (400 mol%) was studied at different temperatures (RT, reflux and 120°C) under solventless conditions and in solvents such as $CHCl_3$, CH_2Cl_2, dioxane, dimethylformamide, acetonitrile and methanol (*Table 1*). Nearly quantitative yields of pure product were obtained in all experiments performed at RT and at 120°C (in a glass autoclave) after vacuum stripping of the solvent and excess methyl acrylate. Under reflux conditions, some precautions must be taken, otherwise polymerization of methyl acrylate occurs to some extent. The reaction times differed according to the temperatures and the solvents used (*Table 1*) and required 3 h for quantitative

Table 1. Physical Constants of Solvents[a,b] and Reaction Times for the Preparation of 4 *via* the Reaction of 1 and 2 (400 mol%) at Different Temperatures

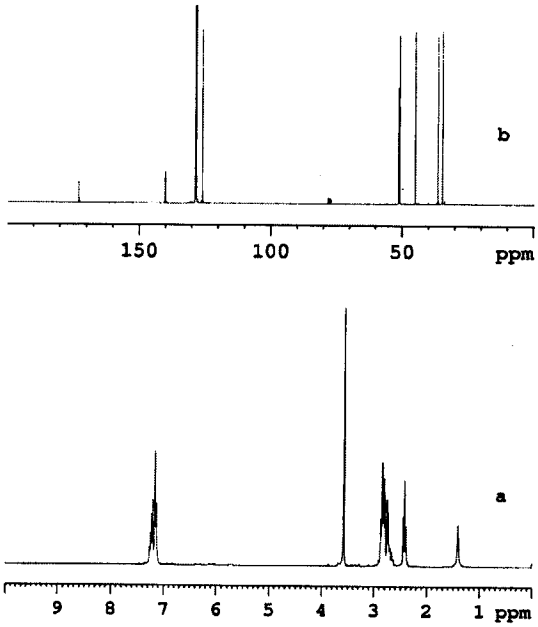
Dielectric constant[e]	Solubility parameter	Dipole moment (Debye)	Density (g/cm^3)	bp (°C)	Reaction time at different temps RT	Reflux	120°C[d]	Solvent[c]
----	----	----	----	----	20 h	Polymn.	9 days	solventless
37.5	----	3.92	0.7857	81.6	29 h	Polymn.	33 days	acetonitrile
36.7	12.1	3.82	0.9447	153	22 h	Polymn.	29 days	DMF
4.81	9.3	1.01	1.4832	61.7	15 h	51 h	32 days	$CHCl_3$
2.21	10.0	2.06	1.0836	94.1	8 h	37 h	25 days	dioxane
9.08	9.7	1.60	1.3266	40.0	5 h	12 h	11 days	CH_2Cl_2
32.63	14.5	1.70	0.7914	65.1	3 h	8 h	15 h	Methanol

a) From CRC Handbook of Chemistry and Physics (73rd Edition). b) Hildebrand solubility parameters (cal/cm^3) are cited from *Directory of Solvent* Edited by B. P. Whim and P. G. Johnson; Chapman & Hall, First Edition, 1996; p 28. c) The solvents were used to obtain 1.5 molar solutions. d) This reaction temperature was attained in a glass autoclave. e) The values of dielectric constants were given at 20°C for $CHCl_3$, dioxane and CH_2Cl_2 and at 25°C for methanol.

formation of **4** in methanol at 120°C (*Table 1*). Other solvents were not as successful as methanol. The dipole moment and the dielectric constant values of the solvents and the order of the reaction rates lead us to exclude the influence of these two parameters on the reaction rate. It appears that the protic character of methanol plays an important role, a fact confirmed by the use of small amount of acetic acid at RT which raised the reaction rate. Under solventless conditions, the reaction times differed greatly for stirred and non-stirred mixtures but in the presence of solvents, the reaction time was independent of the stirring.

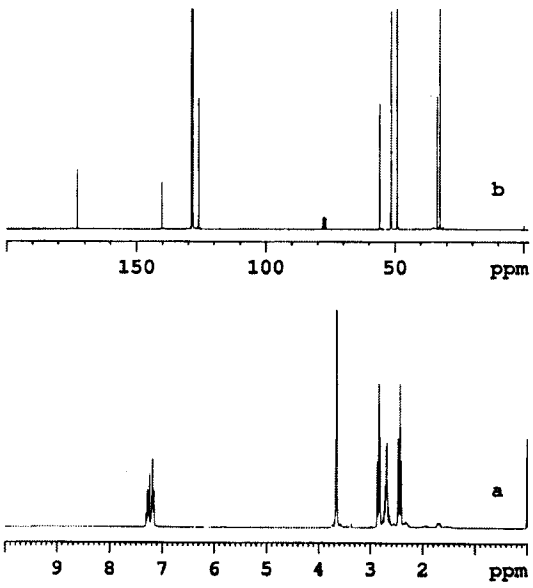
The ^1H NMR and ^{13}C NMR spectra of **3** and **4** (*Figs. 1 and 2)* showed notable differences in the chemical shifts of protons and carbons from those reported previously.[18] The ^1H NMR signals of the CH_2 groups protons adjacent to the carboxylate group appeared as two very distinct triplets in **4**. The chemical shift of one of these triplets in **3** could not be exactly specified and the signals appeared in conjunction with the signals of CH_2 group protons adjacent to the phenyl group that appeared from δ 2.6 to d 2.9.

In summary, we have developed optimized conditions for near-complete separation of the two-step addition reaction of **1** with **2** to produce nearly quantitative yields of pure **3** and **4** *without* distillation. It seems that the reaction rates strongly depend on the protic character of the solvent. Thus, the first step, a rapid reaction of **1** with **2** in methanol, occurred in 15 min at RT and was well separated from the second step which required 3 h at 120°C.



^1H (a) and $\{1H\}^{13}C$ (b) NMR spectra (in $CDCl_3$) of 3

Fig. 1



^1H (a) and $\{1H\}^{13}C$ (b) NMR spectra (in $CDCl_3$) of 4

Fig. 2

EXPERIMENTAL SECTION

NMR spectra were obtained on a Bruker DPX-250 instrument (250 MHz for ^1H and 62.5 MHz for ^{13}C), and $CDCl_3$ was used as solvent; chemical shifts are reported in δ (ppm) from TMS. Electronic ionization GC-MS spectra were recorded on a Varian (SATURN 4D) spectrometer with capillary column (DB-5MS, 0.1 micron, 30 m x 0.250 mm). Only m/z values having intensities of more than 10% are given and retention times are reported for T_{col} of 200°C and He flow rate of 10 mL/min. IR spectra were determined on a Perkin-Elmer 783 instrument using neat samples.

Preparation of 3.- Methyl acrylate (8.6 g, 9 mL, 0.1 mol) was added dropwise (5 min) to a solution of phenylethylamine (12.1 g, 12.5 mL, 0.1 mol) in methanol (30 mL) in a 100 mL, one-necked flask equipped with a addition funnel and magnetic stirrer. The mixture was stirred at RT for 15 min. Vacuum stripping of the solvent led to 19.8 g (96%) of **3** as a pale yellow liquid; its bp. is reported to be 124-127°C/1.2mm Hg.[15]

^1H NMR ($CDCl_3$): δ 1.45 (s, 1H, NH), 2.49 (t, J_{H-H} = 6.7 Hz, 4H, CH_2), 2.6-2.9 (m, 8H, CH_2), 3.64 (s, 3H, CH_3), 7.10-7.25 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$): δ 34.6, 36.4, 45.0, 51.0, 51.3, 126.1, 128.5, 128.7, 140.1, 172.7. GC-MS: retention time = 3.6 min; m/z (intensity (%)): 42 (54), 84 (19), 105 (16), 116 (55), 208 (100), 209 (14), 220 (14). IR (neat sample): 691 (s), 740 (m), 1018 (m), 1110 (s), 1153 (s), 1182 (s), 1240 (m), 1340 (m), 1413 (s), 1430 (s), 1470 (m), 1575 (w), 1703 (vs), 2790 (m), 2900 (m), 2980 (m), 3010 (w), 3025 (vw) cm^{-1}.

Preparation of 4.- Phenylethylamine (12.1 g, 12.6 mL, 0.1 mol), methyl acrylate (35.2 g, 36 mL, 0.4 mol) and methanol (30 mL) were placed in a 100 mL glass autoclave equipped with a magnetic stirrer. The mixture was stirred at 120°C for 3 h. After vacuum stripping of solvent and excess methyl acrylate, 28.5 g (97%) of **4** was obtained as a pale orange liquid; its bp. has not been reported.

^1H NMR ($CDCl_3$): δ 2.44 (t, J_{H-H} = 7 Hz, 4H, CH_2), 2.65-2.75 (m, 4H, CH_2), 2.84 (t, J_{H-H} = 7 Hz, 4H, CH_2), 3.66 (s, 3H, CH_3), 7.15-7.25 (m, 5H, C_6H_5) ^{13}C NMR ($CDCl_3$): δ 32.5, 33.7, 49.2, 51.5, 55.7, 125.9, 128.3, 128.7, 140.3, 172.9. GC-MS: retention time: 8.5 min; m/z (intensity (%)): 42 (17), 105 (15), 130 (25), 160 (18), 202 (100), 220 (25), 294 (10). IR (neat sample): 703(s), 750 (m), 843 (w), 1000 (m), 1043 (m), 1120 (s), 1165 (s), 1192 (s), 1245 (m), 1315 (m), 1345 (m), 1423 (s), 1440 (s), 1481 (m), 1587 (w), 1715 (vs), 2800 (m), 2922 (m), 2998 (m), 3030 (w), 3050 (vw) cm^{-1}.

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