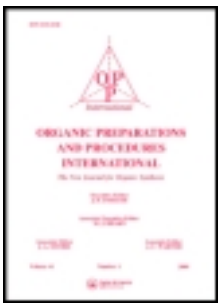

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IMPROVED PROCEDURE FOR THE PREPARATION OF 1-(2-PHENETHYL)-4-PIPERIDONE

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IMPROVED PROCEDURE FOR THE PREPARATION OF 1-(2-PHENETHYL)-4-PIPERIDONE

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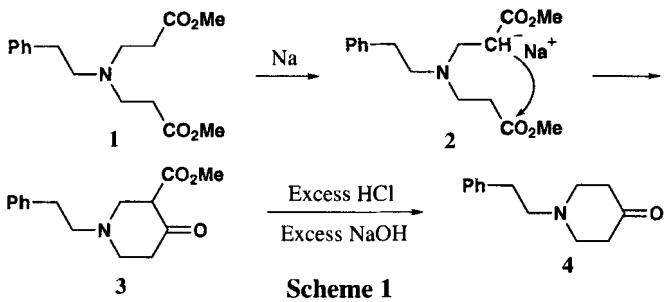
1-(2-Phenethyl)-4-piperidone (**4**) is a key intermediate for the preparation of *fentanyl* (analgesic),[1-5] its analogues[6] and other medicaments.[7,8] The most widely-used method for the synthesis of 4-piperidones is the Dieckmann cyclization of aminodicarboxylate esters which is a multi-steps procedure that occurs under equilibrium condition and is influenced by multiple parameters.[9] The general method of McElvain for the preparation of 4-piperidones consisting in the condensation of appropriate primary amine with two equivalents of methyl (or ethyl) acrylate, the cyclization of the resulting *bis*-ester (Dieckmann reaction) followed by hydrolysis and decarboxylation of the resulting cyclic product, is a well-known method (*Scheme 1*).[10]



Scheme 1

The first step of the Dieckmann condensation involves the base-catalyzed generation of the ester enolate anion (**2**). The rate determining-step is the ring-closure, the subsequent loss of the alkoxide being rapid.[9] The reversibility of the process means that cyclic 2-alkoxycarbonyl ketones such as **3** are liable to cleavage by alkoxide (*retro*-Dieckmann reaction), a process of synthetic significance. Thus careful control of non-equilibrium conditions and high dilution techniques (to prevent the dimerization of *bis*-ester) are often required. The work-up of the Dieckmann reaction must be performed very carefully.[11] The sodium salt of **3** generated during the reaction can be separated from the organic phase by slow filtration after addition of a filter aid or by dissolution in water. The addition of water and mild acidification of the aqueous phase (to regenerate **3**) are exothermic and the temperature must be controlled to prevent the *retro*-Dieckmann reaction. In the synthesis of **4** from **1**, varying final yields have been reported.[3-5,12,13] In a recent paper on the synthesis of *fentanyl* analogues,[6] product **4** was obtained after several steps producing intermediates which had to be separated prior to the next steps; in some cases, the procedure was further complicated by the formation of the diethyl ketal hydrochloride salt of **4**

before the final acidification step for the preparation of the target product.[12] Thus, in spite of the inexpensive starting materials (phenethylamine and methyl acrylate for the quantitative preparation of **1**[14]), commercial **4** is expensive, not very pure, and available only in gram quantities (98%, $ 50/g). In this contribution, we have reinvestigated different parameters such as reaction time, temperature, nature of the base, the rate of *bis*-ester addition, the amount and type of solvent that influence the yield of **4** through the Dieckmann condensation of *N,N-bis*-(carbomethoxyethyl)phenethylamine (**1**).

After the first step (formation of ester enolate), cyclization occurred followed by deprotonation of another acidic proton at the α-position of other carboxylic group, leading to the sodium salt of **3**. This explains the necessity of two-fold excess of base in the first step. In the second step, the sodium salt of **3** was dissolved in water and was thus separated from the unreacted and side-products left in the organic phase. If sodium is used as the base (in the form of fine shot), it is necessary to separate unreacted excess sodium before addition of water. The addition of water must be carried out at 2-3°C to prevent a rise in temperature and the *retro*-Dieckmann reaction. Acidification of the aqueous phase to pH 3-4 by carefully controlled addition of 37% aqueous HCl led to the separation of **3** as an upper oily layer. Hydrolysis and decarboxylation of **3** were performed by addition of excess concentrated HCl and refluxing the mixture. Finally, addition of an excess of sodium hydroxide provided the target product as an upper oily layer which was extracted with xylene, evaporation of which afforded pure crystals of **4** (98%).

The first step is critical in the determination of the yield of the Dieckmann reaction. Thus, using sodium as base in a dilute solution, rapid addition of **1** to mixture at 50 °C, and continuing the reaction at RT for 24h, has afforded pure **4** (98%) in 72% yield. Recrystalization from xylene or *n*-heptane by slow partial evaporation of solvent afforded very pure (>99%) **4** as yellow crystals. The inconvenience and danger of the use of sodium in large scale preparations led us to perform the first step with other bases such as NaH, NaO*t*Bu and NaOMe which afforded **4** with yields of 64, 61 and 40% respectively.

Cyclization of the ester enolate was time consuming. Thus performing the first step at RT using sodium as base for 6, 12, 24 and 72 h afforded 19, 44, 57 and 20% yield. After 24 h, the yield decreased perhaps due to the side-reaction of the product in the reaction mixture. Performing the first step at reflux temperature (or even an initial temperature of 50 °C for several minutes) decreased the yield.

Dilution had a remarkable effect on the yield and a three-fold increase of the solvent led to an approximately two-fold increase in the yield. Under the optimized conditions, a twelve-fold excess of solvent was necessary. The type of solvent also plays an important role on the yield: xylene, toluene and benzene gave yields of 72, 24 and 13% respectively. It appears that solvent with low boiling point do not favor intramolecular cyclization.

In summary, we have developed optimized conditions to obtain high yields of pure **4**.

EXPERIMENTAL SECTION

NMR spectra were obtained on a Bruker DPX-250 instrument (250 MHz for ^1H and 62.5 MHz for ^{13}C), in $CDCl_3$. Chemical shifts are reported in δ from TMS. Electronic ionization GC-MS spectra were recorded on a Varian (SATURN 4D) spectrometer with capillary column (DB-5MS, 0.1 m, 30 m x 0.250 mm). Only m/z values of intensities of more than 5% 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 as KBr pellets. Melting point was obtained on a Mettler FP61 apparatus. The solvents were previously dried on metallic sodium.

Preparation of 4.- Compound **1** (2.9 g, 0.01 mol), xylene (30 mL) and sodium *t*-butoxide (1.9 g, 0.02 mol) were placed in to a 100 mL, double-necked flask equipped with a magnetic stirrer, a condenser, a drying column and an addition funnel. The mixture was stirred for 24 h at room temperature. Then water (12 mL) was added dropwise at 2-3 °C. The aqueous phase (lower layer) was separated and acidified to pH 3-4 with 37% aqueous HCl. An oily liquid and some precipitate appeared and the aqueous phase was separated. Excess 20% aqueous HCl (12 mL) was added to the oily product and the mixture was refluxed for 2 h. By addition of 20% aqueous NaOH (15 mL), an oily layer reappeared. Removal of the aqueous phase followed by extraction of the oily layer with xylene (2 x 10 mL) afforded after drying ($CaCl_2$ (5 g)) and evaporation of solvent, 1.2 g (61%) of product containing 98% 1-(2-phenethyl)-4-piperidone (**4**) as yellow-orange crystals, mp 62-63 °C (*lit.*[12] 60.5-61.5°C, Merck product 98%, 56.5 °C). Following the same procedure with other bases such as Na, NaH and NaOMe led to **4** with yield of 72, 64 and 40% respectively.

^1H NMR ($CDCl_3$): δ 2.48 (t, J_{H-H} = 6.25, 4H, CH_2), 2.69-2.88 (m, 4H, CH_2), 2.81 (t, J_{H-H} = 6.25, 4H, CH_2), 7.21-7.34 (m, 5H, C_6H_6).^{13}C NMR ($CDCl_3$): δ 34.1, 41.2, 53.0, 59.3, 126.2, 128.4, 128.6, 139.9, 208.9. GC-MS: retention time: 4.3 min; m/z (intensity (%)): 42 (33), 112 (100), 113 (9), 204 (22). IR : 703(s),712(s), 753(s), 765(s), 1133(s), 1133(s), 1226(s), 1353(s), 1368(s), 1703(vs), 2765(s), 2796(s), 3933(s), 3958(s).

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