Monatshefte für Chemie 115, 581—585 (1984)

Monatshefte für Chemie
Chemical Monthly

A Study on the Double *Mannich* Reaction with 1,3-Diphenylacetone

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(Received 23 August 1983. Accepted 3 October 1983)

Double *Mannich* reaction of the title compound **1** with morpholine acetate in ethanol gave the symmetrical bis-base **2**, whereas such reaction in acetic acid afforded the vinyl-ketonic base **3**. Reactions of **3** with morpholine, piperidine, thiophenol and dimethyl phosphite were investigated. *Mannich* reaction of **2** with primary amines gave di-basically substituted γ-piperidones **6a–b**. Compound **1** reacts with ethylenediamine and formaldehyde to give the diazatricyclic system **7**.

(Keywords: Symmetrical bis-Mannich bases; Bis(morpholinomethyl-γ-piperidones; 3,6-Diazatricyclo[4.3.1.1^{3,8}]undecanone; Nitrogen heterocycles)

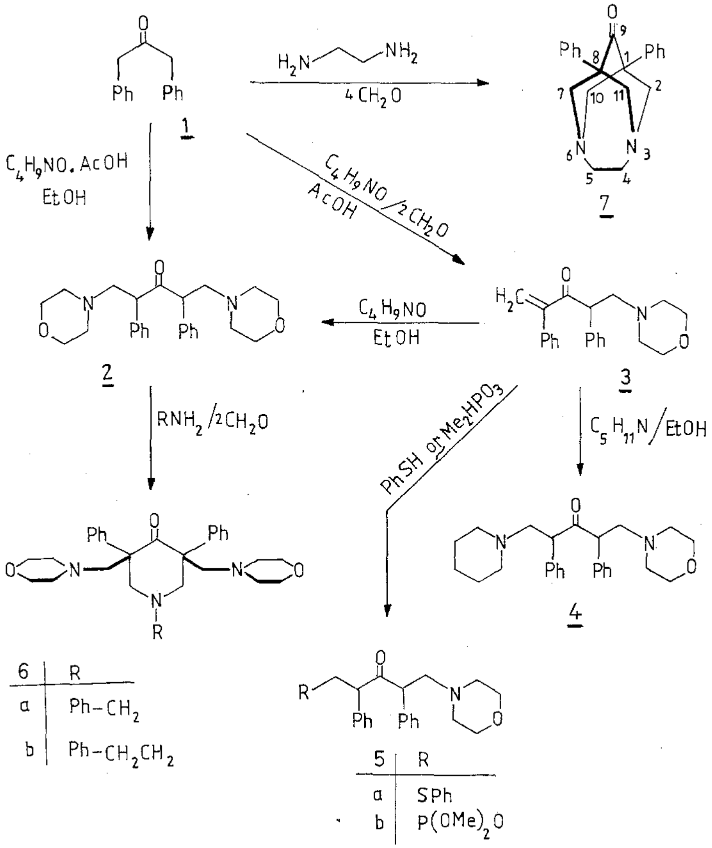
Untersuchungen zur doppelten Mannich-Reaktion mit 1,3-Diphenylaceton

Die Doppel-*Mannich*reaktion der Titelverbindung **1** ergab mit Morpholin-acetat in Ethanol die symmetrische Bis-Base **2**, in Essigsäure erhielt man jedoch die Vinyl-keton-base **3**. Die Reaktionen von **3** mit Morpholin, Piperidin, Thiophenol und Dimethylphosphit wurden untersucht. Die *Mannich*-Reaktion von **2** mit primären Aminen ergab di-basisch substituierte γ-piperidone **6a—b**. Verbindung **1** reagiert mit Ethylendiamin und Formaldehyd unter Ausbildung eines Diaza-tricyclischen Systems **7**.

Although many investigations of the *Mannich* reaction of 1,3-diphenylacetone with primary amines have been reported as a route to bis-pidinones[1–4], no attention has been paid to the similar reaction with secondary amines.

As a part of our studies directed toward the use of symmetrical bis-*Mannich* bases in organic synthesis[5], we have found that 1,3-diphenylacetone (**1**) undergoes double *Mannich* reaction with morpholine acetate and paraformaldehyde in ethanol to give 1,5-bis(*N*-morpholino)-2,4-diphenylpentan-3-one (**2**); its NMR spectrum showed two (*Ph*·**CH**·CO) protons at δ 3.75. The bis-base **2** was again the sole product when the reaction conditions were modified in the hope of isolating a mono- or a tetrakis-base.

On the other hand, treatment of **1** with morpholine and formalin in acetic acid afforded 5-morpholino-2,4-diphenyl-1-penten-3-one (**3**), instead of **2**. The characteristic feature of the NMR spectrum of **3** is the presence of a doublet at 5.5 and 5.73 attributable to the vinylic protons. The formation of **3** finds support from some reported cases[2,6,7], in which vinylic products are obtained in the *Mannich* reaction, probably via a deamination reaction.



The structure of **3** was rigidly established by converting it to **2**, via treatment with morpholine. It is interesting in this connection that treatment of **3** with piperidine afforded the bis-base 1-(*N*-morpholino)-5-(*N*-piperidino)-2,4-diphenylpentan-3-one (**4**) with two different basic moieties. Furthermore, the vinyl-ketonic base **3** proved to be a potentially useful intermediate in the synthesis of the phenylthioetheryl and dimethylphosphoryl derivatives **5 a–b** via its reaction with thiophenol and dimethyl phosphite, respectively.

It was reported earlier[1] that attempts to prepare 3,5-diphenylpiperidin-4-ones via *Mannich* reaction of **1** with primary amines led to 9-keto-1,5-diphenylbispidines. However, *Mannich* reaction of the bis-base **2** with primary amines appeared to be a possible route to di-basically substituted γ-piperidones. Such reaction with benzylamine and 2-phenylethylamine afforded 3,5-bis(*N*-morpholinomethyl)-3,5-diphenylpiperidin-4-ones (**6 a–b**), respectively.

In a study of the possible synthesis of diazadamantane via *Mannich* synthesis, the reaction of 1,3-diarylacetones with ammonia and formaldehyde in a molar ratio of (1 : 2 : 5) has been reported[2,8] as a route to 1,3-diazaadamantan-6-ones. In the present work, when **1** was subjected to *Mannich* reaction using ethylenediamine and formaldehyde in a molar ratio of (1 : 1 : 4), it afforded 1,8-diphenyl-3,6-diazatricyclo[4.3.1.$1^{3,8}$]undecan-9-one (**7**). Our attempt to obtain **7** via treating 1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one[1] with dibromoethane failed.

Experimental

All melting points (°C) were uncorrected and were taken in a Gallenkamp electric melting point apparatus. IR spectra were performed on a Unicam SP 2000 Infrared Spectrophotometer using KBr. NMR spectra were obtained in $CDCl_3$ solution with a Varian model "A-60". Elementary analyses (C,H,N) of **2**, **3**, **4**, **5 a–b**, **6 a–b** and **7** were in good agreement with the proposed structures.

1,5-Bis(N-morpholino)-2,4-diphenylpentan-3-one (**2**)

A mixture of **1** (21 g; 0.01 mol), morpholine acetate (29.43 g; 0.2 mol) and paraformaldehyde (6 g; 0.2 mol) in ethanol (100 ml) was refluxed for 3 h. The crystalline product that separated was filtered and recrystallized from ethanol to give **2** in 76% yield. M.p. 160°. NMR ($CDCl_3$): δ 2.0–2.4 (m, 12 H, cyclic $2\,\mathbf{CH_2}{-}N{-}\mathbf{CH_2}$ and $2\,\mathbf{CH_2}{-}N$ of side-chains), 3.3 (m, 8 H, $2\,\mathbf{CH_2}{-}O{-}\mathbf{CH_2}$), 3.75 (m, 2 H, 2 *Ph*–**CH**–CO) and 7.0 (s, 10 H, aromatic protons).

The same compound was also obtained in 82% yield from **3** (1 g; 0.003 mol) and morpholine acetate (0.44 g; 0.003 mol) in boiling ethanol (25 ml) for 4 h. The product was purified as above.

5-Morpholino-2,4-diphenyl-1-penten-3-one (**3**)

A solution of **1** (21 g; 0.1 mol), morpholine (17.4 g; 0.2 mol) and formalin (16 ml, 37%) in acetic acid (60 ml) was allowed to stand at room temperature for 24 h. The reaction mixture was diluted with ice water, basified with 40% ammonia to give a white solid which was crystallized from cold acetone to give colourless needles of **3** in 52% yield. M.p. 104°. Recrystallization from acetone raised the m.p. to 107°. NMR ($CDCl_3$): δ 2.2–2.55 (m, 6 H, cyclic $\mathbf{CH_2}-N-\mathbf{CH_2}$ and side-chain $\mathbf{CH_2}-N$), 3.5 (m, 4 H, $\mathbf{CH_2}-O-\mathbf{CH_2}$), 4.3 (m, 1 H, *Ph*—**CH**—CO), 5.5 and 5.7 (d, 2 H, vinylic protons) and 7.1 (s, 10 H, aromatic protons).

1-(N-Morpholino)-5-(N-piperidino)-2,4-diphenylpentan-3-one (**4**)

Piperidine acetate (0.43 g; 0.003 mol) was added to a solution of **3** (1 g; 0.003 mol) in ethanol (30 ml), and the reaction mixture was refluxed for 4 h. The product that obtained on cooling was crystallized from ethanol to give colourless crystals of **4** in 55% yield. M.p. 144°. NMR ($CDCl_3$): δ 1.5 (broad s, 6 H, 3 $\mathbf{CH_2}$ of positions 3, 4 and 5 of piperidine), 1.8–2.25 (m, 12 H, cyclic 2 $\mathbf{CH_2}-N-\mathbf{CH_2}$ and 2 $\mathbf{CH_2}-N$ of side chains), 3.15 (m, 4 H, $\mathbf{CH_2}-O-\mathbf{CH_2}$), 3.70 (m, 2 H, 2 *Ph*—**CH**—CO) and 7.10 (s, 10 H, aromatic protons).

1-(N-Morpholino)-5-(phenylthioetheryl)-2,4-diphenylpentan-3-one (**5a**)
1-(N-Morpholino)-5-(dimethylphosphoryl)-2,4-diphenylpentan-3-one (**5b**)

To a solution of **3** (1 g; 0.003 mol) in ethanol (40 ml) was added thiophenol (0.33 g; 0.003 mol) followed by two drops of piperidine or dimethyl phosphite (0.33 g; 0.003 mol) and three drops of methanolic Na*OMe* (5%). The reaction mixture was refluxed for 4 h, left to stand overnight and cooled. The product that separated was crystallized from methanol to give **5a–b** in 55–60% yield. M.p. 152° (**5a**), 168° (**5b**).

1-Benzyl-[3,5-bis(N-morpholinomethyl)]-3,5-diphenylpiperidin-4-one oxalate (**6a**) *and 1-(2-Phenylethyl)-[3,5-bis(N-morpholinomethyl)]-3,5-diphenylpiperidin-4-one oxalate* (**6b**)

A solution of **2** (1 g; 0.0025 mol), benzylamine or 2-phenylethylamine (0.0025 mol) and paraformaldehyde (0.15 g; 0.005 mol) in acetic acid (30 ml) was heated to the boiling point and then allowed to stand at room temperature for 12 h. The mixture was diluted with ice water, basified with 40% ammonia, extracted with ether, dried and ethereal oxalic acid was added to give the oxalate of **6a–b**, in 55–62% yield. Recrystallized from ethanol—ether, m.p. 180° (decomp.) (**6a**), 188° (decomp.) (**6b**).

1,8-Diphenyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-one (**7**)

Amixture of **1** (2.1 g; 0.01 mol), ethylenediamine acetate (1.8 g; 0.01 mol) and paraformaldehyde (1.2 g; 0.04 mol) in ethanol (30 ml) was refluxed for 4 h. The precipitated product was filtered and washed thoroughly with boiling ethanol to give **7** as a yellow powder in 68% yield. M.p. 262°. NMR ($CDCl_3$): δ 2.30–2.55 (m, 4 H, 4-H_2 and 5-H_2), 2.80–3.20 (broad s, 8 H, 2-H_2, 7-H_2, 10-H_2 and 11-H_2) and 7.0 (s, 10 H, aromatic protons).

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