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BENZOTRIAZOLE-ASSISTED SYNTHESIS OF NOVEL MANNICH BASES FROM KETONES AND DIVERSE ALDEHYDES

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Abstract: *A wide variety of β-amino ketones are prepared in moderate to good yields by the reaction of the lithium enolates of cyclohexanone, acetophenone, α-tetralone and camphor with the readily available adducts from an aldehyde or ketone, an amine and benzotriazole. Some diastereoselectivity is observed when the benzotriazole adduct is derived from benzaldehyde.*

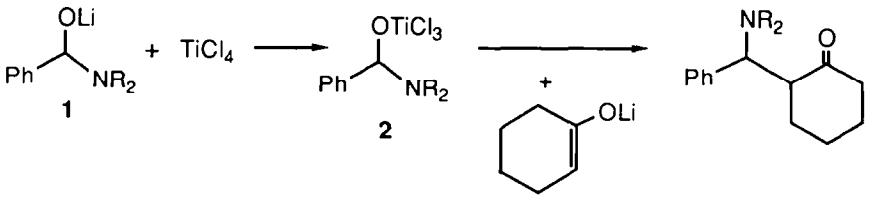
The Mannich reaction, an imino analogue of the aldol condensation, has been extensively studied by organic chemists and has been the subject of numerous reviews.[1-4] In the classical condensation, a single carbon atom is attached to an active methylene or methine group, using formaldehyde and an amine, to generate β-amino carbonyl compounds (Mannich bases).

The extension of the reaction to include aldehydes other than formaldehyde has not been well documented, and, as yet, no general procedure exists. Among the limited range of aldehydes studied, acetaldehyde and benzaldehyde or other aromatics predominate, as in the formation of piperidones from acetonedicarboxylic acid and its esters,[5] and in the Mannich condensation of Lawsone (2-hydroxy-1,4-naphthoquinone).[6] With only a few exceptions,[6,7] these extended Mannich reactions appear to be limited to the use of ammonia or primary amines.

Preformed imines (Schiff base) have been used to prepare Mannich bases by their reaction with ketones in the presence of a Lewis acid catalyst. In this way, Mannich bases derived from benzaldehyde can be prepared from cyclohexanone,[8] acetophenone,[9] α- and β-tetralone,[10,11] indanone[10] and 1-acetylnaphthalene,[9] whereas attempts to obtain these products in three component reactions (ketone, aldehyde and amine) were unsuccessful.[10]

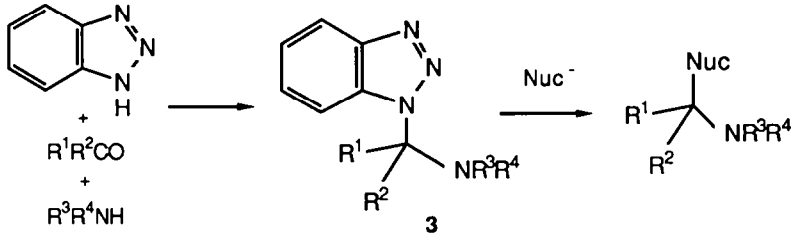
Recently, a diastereoselective Mannich reaction was reported by Seebach *et al.*[12] Lithium dialkylamines were added to non-enolisable aldehydes to form lithium dialkylamino-alkoxides **1** which, on conversion to the corresponding trichlorotitanium dialkylamino-alkoxides **2** and subsequent reaction with a lithium enolate, gave Mannich bases. Mannich bases were prepared in this way from benzaldehyde, cyclohexanone enolate, and various amines, with a diastereoselectivity ranging from 66-84% (see Scheme 1).

Scheme 1



Despite the above mentioned works, the preparation of ketone Mannich bases utilizing aldehydes other than formaldehyde remains a rarely attempted transformation compared to the frequent use of ketone Mannich bases derived from formaldehyde. Our group has been involved in the preparation of a large range of Mannich type adducts **3** obtained from condensation of benzotriazole with a carbonyl compound (formaldehyde, an aldehyde or a ketone) and a N-H substrate (amines,[13-15] amides,[16] or carbamates[17]). These N-(aminoalkyl)benzotriazoles can be regarded as masked imines (or iminium cations) and are reactive towards nucleophiles such as Grignard reagents (see Scheme 2). We have investigated their reaction with lithium enolates prepared from readily available silyl enol ethers and now report that this allows a general synthesis of a wide variety of Mannich bases.

Scheme 2



Preparation of Mannich Bases

The lithium enolate of cyclohexanone was generated by cleavage of the corresponding silyl enol ether with methyllithium in tetrahydrofuran.[18] Subsequent addition of the N-(alkylamino)benzotriazole derivatives **3**, easily available in previously described one-pot reactions,[13-17,19-21] gave the expected Mannich bases **4** (see Table 1). Removal of the benzotriazole by-product with aqueous base, followed by extraction into dilute acid and recovery, gave in most cases a clean crude product. Benzotriazole can be recovered from the alkali and reused. The β-substituted Mannich bases, derived from aldehydes other than formaldehyde, could be extracted into dilute acid, but underwent elimination of the amine component on chromatography, with either silica gel or alumina, to give the corresponding α,β-unsaturated ketones.

The Mannich base **4a** was obtained with a diastereoselectivity of 80% as observed from ^{1}H NMR analysis of the benzylic protons. Benzylidenecyclohexanone **5** was obtained as a minor secondary product (25%). The same Mannich base **4a** was also obtained by Seebach from titanium alkoxides[22] in 78% diastereo-purity and also with a 48% yield. In the present work, the isolation of benzylidenecyclohexanone suggests that the observed diastereoselectivity may be due to the preferential elimination of piperidine from one of the diastereoisomers formed.

In an extension of the reaction to include the preparation of β-amido ketones, treatment of the benzotriazole adduct **3g** with 1.1 equivalent of the lithium enolate gave a mixture of **4g** (14%) and the α,α-di-substituted cyclohexanone **6** (35%). Selective formation of **4g** in high yield (85%) was achieved by using a two fold equivalence of the cyclohexanone enolate.

Table 1 Reaction of Benzotriazole Adducts 3 with Cyclohexanone Enolate

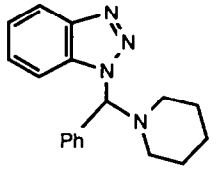
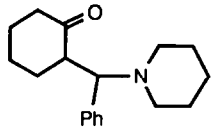
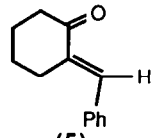
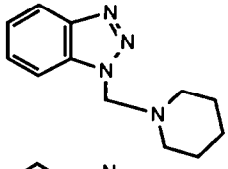
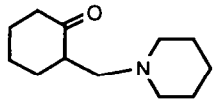
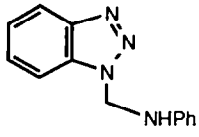
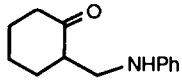
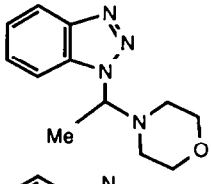
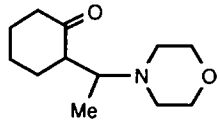
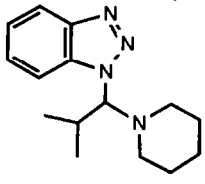
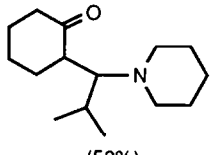
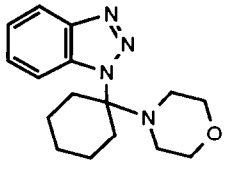
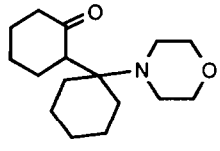
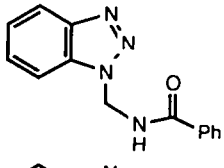
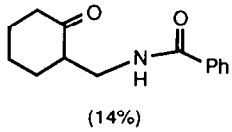
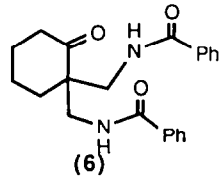
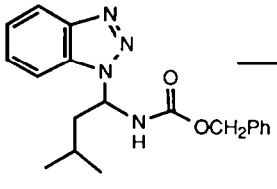
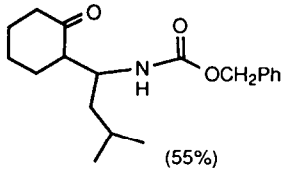
Entry	Benzotriazole Adduct 3	β-Amino Ketone 4	Additional Product
a		 (48%)	 (5)
b		 (67%)	
c		 (85%)	
d		 (15%)	
e		 (52%)	
f		 (66%)	
g		 (14%)	 (6) (35%)
h		 (55%)	

Table 2. Preparation of β-Amino-Ketones 4.

Product	Mol. Formula	Yield [a] (%)	m.p.(°C)	Calcd (found)		
				C	H	N
4a	$C_{18}H_{25}NO$	48	100-110 [b]	79.66 (80.01)	9.28 (9.47)	5.16 (5.13)
4b	$C_{12}H_{21}NO$	67	oil [c]		—	
4c	$C_{13}H_{17}NO$	85	90-92 [d]	76.81 (76.90)	8.43 (8.60)	6.89 (6.76)
4d	$C_{12}H_{21}NO_2$	15 [e]	oil [f]		—	
4e	$C_{15}H_{27}NO$	52	oil [f]		—	
4f	$C_{16}H_{27}NO_2$	66	oil [f]		—	
4g	$C_{14}H_{17}NO_2$	85 [g]	77.5-79	72.70 (72.48)	7.41 (7.51)	6.06 (5.87)
4h	$C_{19}H_{28}NO_3$	55 [g]	oil [f]		—	

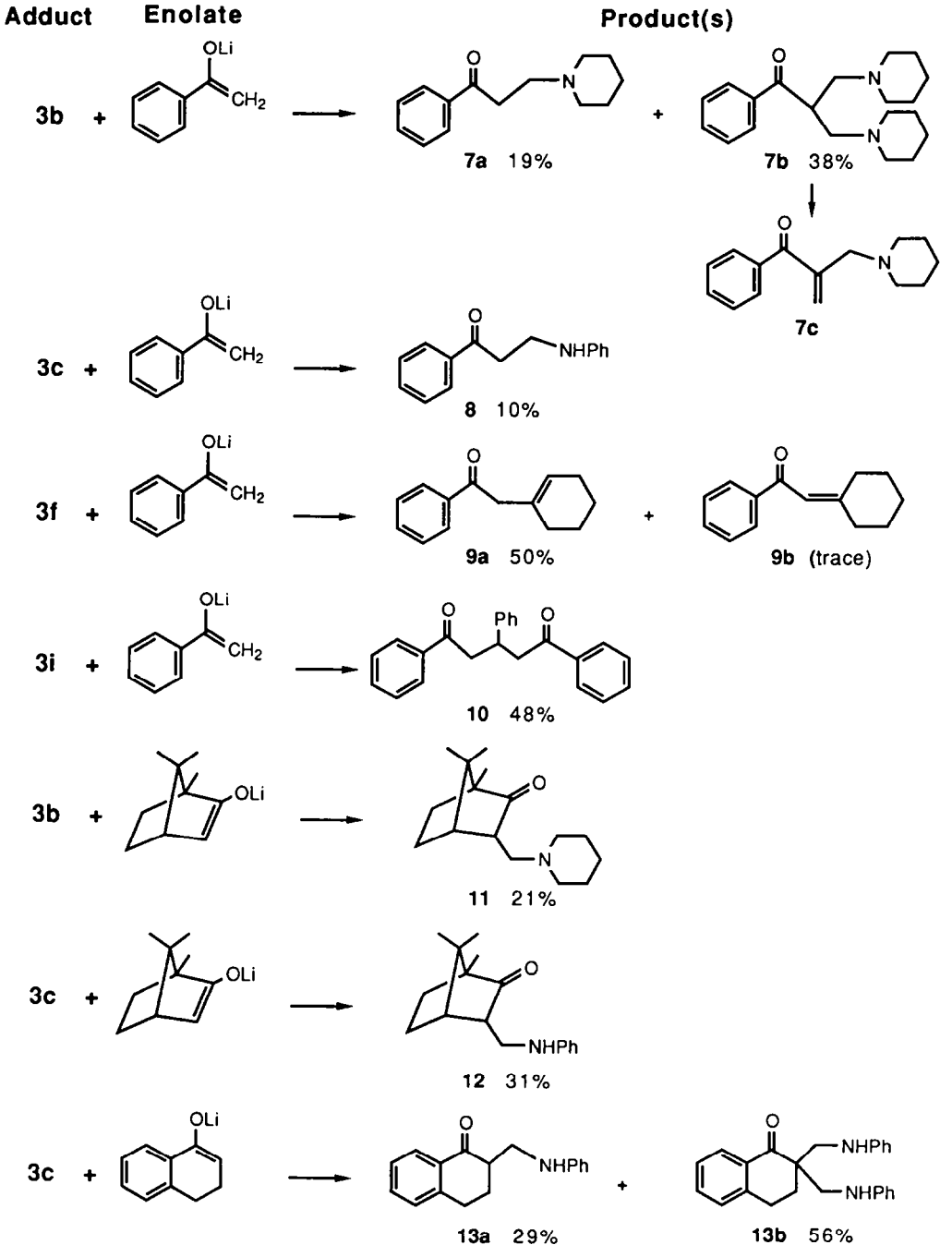
[a] Yields are based on the benzotriazole adduct **3** used.
[b] lit. m.p. 99-102°C[12] and for pure diastereoisomer 109-110°C.[22]
[c] Spectroscopic data identical to that of sample prepared by Mannich procedure.[23] [d] lit. m.p. 89-90°C.[24]
[e] Yield based on the isolation of 2-(1-propenyl)-cyclohexanone after column chromatography of the crude product.
[f] Products isolated as pure oils (by NMR analysis), and characterized by their reduction (see Table 4).
[g] Yield obtained after **3g** was reacted with 2.1 equiv. of lithium enolate.

To establish the generality of the reaction with regard to the ketone component, several other silyl enol ethers were prepared, converted to the corresponding lithium enolates, and treated with benzotriazole adducts **3**. The addition of benzotriazole adduct **3b** to the enolate of acetophenone gave an equimolar mixture of the expected Mannich base **7a** and the disubstituted bis-amino ketone **7b**. (Under standard Mannich conditions, the β-amino ketone **7a** is known to undergo further reaction; a three-fold excess of both formaldehyde and piperidine gave the bis-amino ketone **7b** exclusively).[25] Column chromatography of the mixture resulted in decomposition of **7b** to the α-piperidinylmethyl unsaturated ketone **7c**. The Mannich reaction cannot be used to prepare β-anilinopropiophenone **8**;[26] however, **8** could be obtained by reaction of acetophenone enolate with adduct **3c**, although in low yield. Treatment of the same enolate with adduct **3f** gave ω-(cyclohexen-1-yl)acetophenone[27] **9a** without isolation of the intermediate β-amino ketone, (a trace of the isomer 2-cyclohexyldiene-acetophenone[28] **9b** was detected by NMR in the product). Interestingly, the reaction of the benzotriazole adduct **3i**, derived from benzaldehyde and morpholine, with acetophenone enolate resulted in elimination of both benzotriazole and morpholine to give 1,3,5-triphenyl-1,5-pentanedione **10**. Such 1,5-dicarbonyl compounds are obtained by catalyzed Michael addition of silyl enol ethers to α,β-unsaturated ketones.[29]

This method was successfully applied to the α-aminomethylation of camphor to give previously unreported Mannich bases. Thus, the silyl enol ether of camphor, on conversion to its lithium enolate and subsequent treatment with benzotriazole adducts **3b** and **3c**, gave the β-amino ketones **11** and **12** as mixtures of their exo and endo isomers. The lower yields compared to the α-aminomethylation of cyclohexanone presumably reflect a greater steric hinderance at the reactive enolate sites.

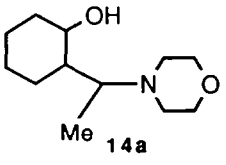
Similarly, α-tetralone, which is known to undergo the standard Mannich reaction only with secondary amines[30] or Schiff bases,[10] gave the Mannich base **13a** by the same procedure. The bis-substituted tetralone **13b** was also isolated under these conditions as the major product.

Table 3 Reaction of Acetophenone, Camphor and α-Tetralone Enolates

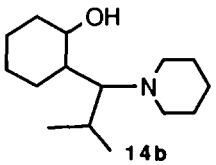


Reduction of the β-Amino Ketones

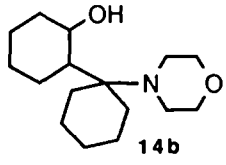
The β-substituted Mannich bases **4d-4f**, and **4h** were too unstable to allow analysis by mass spectrometry and attempted formation of derivatives such as picrates resulted in amine elimination. To obtain a more stable type of compound they were reduced with lithium aluminium hydride[31] to the β-amino alcohols **14a-c** in near quantitative yields. Reduction of the carbamate **4h** resulted in cyclization to the bicyclic 1,3-oxazine-2-one **14d**. The reductions were carried out in a one pot sequence, without isolation of the β-amino ketones, to give the corresponding alcohols as a mixture of diastereoisomers.



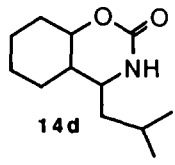
14a



14b



14b



14d

Table 4. Preparation of β-Amino-Alcohols 14a-c and 1,3-Oxazine-2-one 14d

Starting Material	Product	Mol. Formula	Yield [a] (%)	m.p.(°C)	Calcd (found) C	H	N
4d	14a	$C_{12}H_{23}NO_2$	15	oil	HRMS 213.1729 (213.1729).[b]		
4e	14b	$C_{15}H_{29}NO$	51	oil	HRMS 239.2249 (239.2247).[b]		
4g	14c	$C_{16}H_{29}NO$	66	180.5-182.5 [c]	53.22 (53.54)	6.50 (6.56)	11.28 (11.19) [c]
4h	14d	$C_{12}H_{21}NO_2$	55	170 [d]	68.25 (68.03)	10.30 (10.00)	6.63 (6.54)

[a] Yield based on quantity of benzotriazole adduct **3** used.
[b] High resolution mass spectroscopy (HRMS) measurement of molecular ion obtained.
[c] Picrate ($C_{22}H_{32}N_4O_9$).
[d] Sublimation temperature.

Table 5. ^{13}C-NMR Chemical Shifts (δ) for β-Amino-Ketones 4 ($CDCl_3$)

Product	Cyclohexanone $\underline{C}H_2$	$\underline{C}H$	$\underline{C}O$	$\underline{C}$-N	R ^{1}R^2-C-N	Amine R^3R^4
4a	20.5 24.5 29.0 39.1	51.8	213.1	69.4	134.5 129.1 128.0 127.4	50.4 28.0 26.3
4b	24.1 24.5 27.9 32.9	58.0	212.6	54.7	—	48.5 25.7 27.9
4c	25.2 28.1 32.4 42.6	50.1	213.5	44.1	—	113.2 117.6 129.6 148.4
4d[a]	20.8 23.3 27.1 28.7 28.3 30.4 39.4 44.6	56.5 57.3	212.0 212.4	54.2 54.4	9.7 10.2	45.6 47.9 66.5 67.1
4e[a]	25.0 26.9 27.1 27.7 29.6 30.5 40.3 41.4	67.7 67.0	212.6 214.2	51.9 52.0	20.4 20.8 21.0 21.9 23.0 24.8	26.5 26.9 27.1 27.7 49.9 50.6
4f	21.4 28.2 29.6 44.0	56.4	213.8	59.1	21.4 25.3 26.1 30.4 31.1	46.5 68.3
4g	24.6 27.6 31.6 39.5	50.6	213.7	42.0	—	126.7 128.3 131.2 134.3
4h[a]	24.5 24.8 30.6 32.0 39.2 40.0 43.1 42.2	49.8 50.6	212.1 212.8	54.6 54.9	21.2 21.7 22.4 23.1 23.5 24.9	66.3 64.8 126.7 127.1 127.7 127.8 128.2 128.3 136.5 141.0

[a] mixture of 2 diastereoisomers

In conclusion, this reaction displays a remarkable flexibility in the variety of Mannich bases that can be prepared. We have demonstrated that all three components (ketone, aldehyde and amine) can be successfully varied in this system. The wide range of benzotriazole adducts now known, combined with the extensive chemistry on the preparation of silyl enol ethers, indicates that many β-amino ketones, previously unobtainable under standard Mannich conditions, are now accessible.

Experimental Section

General: Column chromatography was carried out on MCB silica gel (230-400 mesh). Melting points were determined with a Kofler hot stage apparatus and are uncorrected. ^1H and, ^{13}C NMR spectra were recorded on a Varian VXR 300 MHz spectrometer in $CDCl_3$ (unless otherwise stated) using TMS as an internal reference for ^1H spectra and $CDCl_3$ for ^{13}C NMR spectra (abbreviations used: s singlet; d doublet; t triplet; q quartet; m multiplet; bs broad singlet and dd doublet of doublets). Elemental analyses were performed on a Carlo Erba-1106 instrument under the supervision of Dr.D.Powell. High resolution mass measurement were recorded on an AEI MS-30 mass spectrometer. Tetrahydrofuran and diethyl ether were predried and distilled from sodium.

The benzotriazole adducts **3a**,[13] **3b**,[14] **3c**,[15] **3f**,[19] **3g**,[16] **3h**,[17] and **3i**[13] were prepared according to the previously described methods. The compound **3d** was obtained by the procedure using diethyl ether as solvent[20] and adduct **3e** was prepared as previously reported for the synthesis of its pyrrolidine analogue.[21] The trimethylsilyl enol ethers were obtained from their corresponding ketones by the methods of House[32] (from cyclohexanone), Duboudin[33] (from acetophenone), Hellberg[34] (from α-tetralone) and Joshi and Pande[35] (from 3-endo bromocamphor).

Reaction with Lithium Enolates; A Typical Procedure

Methyl lithium (2.7 mL, 3.8 mmol) was added to the trimethyl silyl enol ether of cyclohexanone (640 mg, 3.8 mmol) in predried THF (50 mL) under nitrogen and the solution stirred for 1h at 25°C. The benzotriazole adduct **3a** (1.0 g, 3.4 mmol) in THF (25 mL) was added in one portion and stirring continued overnight (approx. 16h). The THF was removed under reduced pressure and the resulting oil dissolved in CH_2Cl_2 (100 mL) and washed with dilute NaOH solution (50mL) to remove the benzotriazole by-product. The organic layer was dried with $MgSO_4$ and evaporation at reduced pressure gave the crude product (740 mg), as a mixture of 2-(α-piperidinobenzyl)cyclohexanone **4a** and benzylidenecyclohexanone **5** . The mixture was dissolved in ether (100 mL) and the Mannich base **4a** separated by extraction into dilute HCl acid (50 mL). On basification of the aqueous phase and extraction with CH_2Cl_2 (2 x 100 mL) **4a** (450 mg, 48%) was obtained on removal of the solvent.

For the preparation of non-basic compounds **4g**, **4h**, **6**, **19a**, and **10**, the same procedure was followed except no acid extraction was employed in the work-up.

2-(α-Piperidinobenzyl)cyclohexanone 4a: ^1H NMR 1.0-2.70 (m, 18H, aliphatic ^1H's), 3.18 (m, 1H, C<u>H</u>-CO), 4.08 (d, J=6Hz, 1H, C<u>H</u>-Ph), 7.0-7.4 (m, 5H, Ph). The minor diastereoisomer could be indentified by a signal at 3.95 (d, J=6Hz, C<u>H</u>-Ph), the other signals overlapping with the major isomer.

2-(Phenylaminomethyl)cyclohexanone 4c: ^1H NMR 1.4-2.3 (m, 8H, $(C\underline{H}_2)_4$), 3.02 (dd, J=4.6,13.5Hz, 1H, C<u>H</u>-N), 3.34 (dd, J=7.6,13.5Hz, 1H, C<u>H</u>-N), 4.08 (bs, 1H, N<u>H</u>), 6.50 (m, 2H, <u>o</u>-Ph), 6.60 (m, 1H, <u>p</u>-Ph), 7.08 (m, 2H, <u>m</u>-Ph).

2-(1-Morpholinoethyl)cyclohexanone 4d: (2 diastereoisomers) ^1H NMR 0.91 (d, J=7.5Hz, 3H, Me), 0.98 (d, J=7.5Hz, 3H, Me), 1.5-3.5 (m, 18H), 2.86 (m, 4H, $C\underline{H}_2$-N-$C\underline{H}_2$), 3.66 (m, 4H, $C\underline{H}_2$-O-$C\underline{H}_2$).

2-(1-Propenyl)cyclohexanone: Obtained as an oil in 15% yield after the crude product **4d** was column chromatographed (silica gel/dichloromethane). ^1H NMR 1.7(m, 3H, Me), 1.65 (m, 2H, $C\underline{H}_2$), 1.85 (m, 2H, $C\underline{H}_2$), 2.4 (m, 2H, $C\underline{H}_2$), 2.5 (m, 2H, $C\underline{H}_2$), 6.7 (m, 1H, C=C<u>H</u>). ^{13}C NMR 13.1, 23.0, 23.2, 25.6, 39.7, 133.7, 136.8, 200.3. Mass spectrum, *m/z* (relative intensity) 124 (100, M^+), 109 (30), 96 (24), 81(39), 67(81); HRMS, 124.0877 ($C_8H_{12}O$ requires 124.0889).

2-(1-Piperidinoisobutyl)cyclohexanone 4e: (2 diastereoisomers) ^1H NMR 0.86 (d, J=6.81Hz, 3H, Me), 0.87 (d, J=6.81Hz, 3H, Me), 0.91 (d, J=6.89Hz, 3H, Me), 0.99 (d, J=6.84Hz, 3H, Me), 1.4-2.6 (m, 18H), 2.79 (dd, J=5.5,7.9Hz, 1H, C<u>H</u>-Me), 2.93 (dd, J=5.86,7.3Hz, 1H, C<u>H</u>-N), 3.16 (m, 1H, C<u>H</u>-CO).

2-(1-Morpholinocyclohexyl)cyclohexanone 4f: ^{1}H NMR 1.1-2.6 (m, 18H, C$\underline{H}_2$) ^{1}H's), 2.67 (m, 4H, C$\underline{H}_2$-N-C$\underline{H}_2$), 3.64 (m, 4H, C$\underline{H}_2$-O-C$\underline{H}_2$).

2-(Phenylamidomethyl)cyclohexanone 4g: ^{1}H NMR 1.3-2.4 (m, 8H, (C$\underline{H}_2$)$_4$), 2.66 (m, 1H, C$\underline{H}$-CO), 3.38 (m, 1H, C$\underline{H}$-CN), 3.68 (m, 1H, C$\underline{H}$-CN), 7.0 (bs, 1H, N$\underline{H}$), 7.40 (m, 3H, m,p-Ph), 7.74 (m, 2H, o-Ph).

2-[(1-Benzyloxycarbonylamino)isopentyl]cyclohexanone 4h: (2 diastereoisomers) ^{1}H NMR 0.85 (m, 6H, Me), 1.1-2.5 (m, 13H, aliphatic ^{1}H's), 5.06 (s, 2H, C$\underline{H}_2$-Ph), 7.3 (m, 5H, Ph).

2-[Bis-(Phenylamido)methyl]cyclohexanone 6: The obtained mixture of **4g** and **6** (see footnote, Table 1) was repeatedly recrystallized from toluene to isolate the major product **6** as colorless needles, m.p. 111-116°C. ^{1}H NMR 1.63 (m, 2H, C$\underline{H}_2$), 1.92 (m, 2H, C$\underline{H}_2$), 2.05 (m, 2H, C$\underline{H}_2$), 2.52 (m, 2H, C$\underline{H}_2$), 3.08 (dd, 2H, J=4.15,13.92Hz, C$\underline{H}$-N), 4.15 (dd, 2H, J=9.28,13.92Hz, C$\underline{H}$-N), 7.5 (m, 6H, o,p-Ph), 7.8 (bs, 2H, N$\underline{H}$), 7.93 (m, 4H, o-Ph). ^{13}C NMR 20.7, 27.6, 32.7, 39.8, 40.8, 55.0, 127.1, 128.5, 131.7, 133.6, 168.1, 215.9. Anal. $C_{22}H_{24}N_2O_3$ calcd (found) C 72.51 (72.59) H 6.64 (6.73) N 7.69 (7.55).

β-Piperidinopropiophenone 7a: Obtained as an oil after crude product (a mixture of **8a** and **8b**) was column chromatographed (silica gel/chloroform), yield 19%. ^{1}H NMR 1.35 (m, 2H, p-piperidine), 1.5 (m, 4H, m-piperidine), 2.35 (m, 4H, o-piperidine), 2.7 (t, J=7.5Hz, 2H, C$\underline{H}_2$-N), 3.1 (t, J=7.5Hz, 2H, C$\underline{H}_2$-CO), 7.35 (m, 2H, m-Ph), 7.45 (m, 1H, p-Ph) 7.9 (m, 2H, o-Ph). ^{13}C NMR 24.0, 25.6, 36.0, 53.6, 54.3, 127.7, 128.3, 132.7, 136.7, 199.0. Mass spectrum, *m/z* (relative intensity) 217 (6, M^+), 105 (15), 98 (100), 77 (27); HRMS, 217.1470 ($C_{14}H_{19}NO$ requires 217.1466).

β-Piperidino-(α-piperidinomethyl)propiophenone 7b: Obtained as a mixture with **7a**, estimated yield 38% by ^{1}H NMR analysis of the mixture (**7b** decomposed to **7c** on column chromatography). ^{1}H NMR 1.3-1.5 (m, 6H, piperidine), 2.3-2.45 (m, 4H, piperidine) 2.7 (dd, J=8,12Hz, 2H, C$\underline{H}_2$-CN), 2.47 (dd, J=5.5,12Hz, 2H, C$\underline{H}_2$-CN), 3.93 (m, 1H, C$\underline{H}$-CO), 7.4-7.6 (m, 3H, p,m-Ph), 7.95 (m, 2H, o-Ph). ^{13}C NMR 24.3, 25.9, 43.5, 54.6, 60.5, 128.1, 128.3, 128.5, 132.3, 204.0.

1-Phenyl-2-(1-piperidinomethyl)-2-propen-1-one 7c: Obtained by decomposition of **7b** on column chromatography (silica gel/chloroform) as an oil. ^{1}H NMR 1.55 (m, 6H, m,p-piperidine), 2.45 (m, 4H, o-piperidine), 3.36 (s, 2H, C$\underline{H}_2$-N), 5.7 (s, 1H, C=C$\underline{H}_2$), 6.0 (s, 1H, C=C$\underline{H}_2$), 7.4-7.6 (m, 3H, m,p-Ph) 7.8 (m, 2H, o-Ph). ^{13}C NMR 24.1, 25.9, 54.4, 59.7, 126.5, 128.0, 129.4, 132.2, 137.4, 144.8, 197.6. Mass spectrum, *m/z* (relative intensity) 229 (13, M^+), 212 (61) 105 (44), 98 (100), 84 (92), 77 (67); HRMS, 229.1467 ($C_{15}H_{19}NO$ requires 229.1467).

β-Anilino-propiophenone 8: Crude product was recrystallized from ethanol as colorless needles, m.p. 111-116°C (lit. m.p. 113-114°C),[27] yield 10%

2-(Cyclohexen-1-yl)acetophenone 9a: Obtained as an oil after crude product was column chromatographed (silica gel/chloroform), yield 50%. ^{1}H NMR 1.5-1.7 (m, 4H, C$\underline{H}_2$x2), 2.0 (m, 4H, C$\underline{H}_2$x2), 3.6 (s, 2H, C$\underline{H}_2$-CO), 5.6 (s, 1H, C=C$\underline{H}$), 7.4 (m, 2H, m-Ph), 7.55 (m, 1H, p-Ph) 7.95 (m, 2H, o-Ph). ^{13}C NMR 22.4, 23.1, 25.7, 29.1, 48.1, 126.3, 128.3, 128.7, 132.5, 133.2, 137.3, 198.0. Mass spectrum, *m/z* (relative intensity) 200 (9, M^+), 105 (100), 77 (24); HRMS, 200.1197 ($C_{14}H_{16}O$ requires 200.1201).

1,3,5-Triphenyl-1,5-Pentanedione 10: Obtained after crude product was column chromatographed (silica gel/toluene), yield 48%, m.p. 83-85°C (toluene/hexane), lit. m.p. 81-83°C.[36]

1,7,7-Trimethyl-3-(piperidinomethyl)-bicyclo (2.2.1) heptan-2-one 11: Crude product purified by column chromatography (silica gel/chloroform) to give mainly one isomer as an oil, yield 21%. ^{1}H NMR 0.88 (s, 3H, Me), 0.89 (s, 3H, Me), 1.0 (s, 3H, Me), 1.2-1.3 (m, 2H, C$\underline{H}_2$), 1.4-1.5 (m, 2H, C$\underline{H}_2$), 1.55-1.65 (m, 6H, piperidine), 1.65-1.85 (m, 2H), 2.3-2.5 5 (m, 6H, piperidine), 2.6-2.7 (m, 2H). ^{13}C NMR 9.6, 19.2, 19.5, 20.5, 24.3, 25.9, 25.9, 31.1, 47.0, 48.5, 54.7, 56.4, 220.3. Mass spectrum, *m/z* (relative intensity) 249 (4,M^+), 98 (100); HRMS, 249.2097 ($C_{16}H_{27}NO$ requires 249.2093).

1,7,7-Trimethyl-3-(phenylaminomethyl)-bicyclo (2.2.1) heptan-2-one 12: Crude product purified by column chromatography (silica gel/toluene) to give a mixture of exo and endo isomers as an oil, yield 31%. ^{1}H NMR 0.8-0.9 (m, 6H,2xMe), 1.2 (s, 3H, Me), 1.3-2.1 (m, 4H, C$\underline{H}_2$), 2.6-3.4 (m, 2H, C$\underline{H}$-C$\underline{H}$-CO), 3.7 (m, 2H, C$\underline{H}_2$-N), 6.55-6.7 (m, 3H, o,p-Ph), 7.0-7.15 (m, 2H, m-Ph). ^{13}C NMR 9.0, 9.2, 18.9, 19.2, 20.0, 20.2, 21.4, 28.7, 29.0, 29.4, 30.8, 42.1, 45.5, 45.7, 46.6, 46.7, 29.0, 29.4, 30.8, 42.1, 45.5, 45.7, 46.6, 46.7, 48.5, 53.4, 57.6, 58.6, 112.8, 129.0, 117.3, 118.2, 148.7, 148.9, 220.2, 220.5. Mass spectrum, *m/z* (relative intensity) 257 (12, M^+), 106 (100); HRMS, 257.1774 ($C_{17}H_{13}NO$ requires 257.1780).

3,4-Dihydro-2-(phenylaminomethyl)-1-naphthalenone 13a: Mixture of **13a** and **13b** separated by column chromatography (silica gel/toluene-hexane) to give **13a** in a 29% yield; m.p. 98-100°C (ethanol). ^{1}H NMR 1.8-1.95 (m, 1H, 3-H), 2.05-2.15 (m, 1H, 3-H), 2.6-2.7 (m, 1H, 2-H), 2.8-2.9 (m, 1H, 4-H), 3.2-3.3 (dd, J=6.6,13.3Hz, 1H, CH-N), 3.5-3.6 (dd, J=5.5,13.3Hz, 1H, CH-N), 4.2(bs, 1H, NH), 6.5-6.6 (m, 3H, Ph), 7.0-7.1 (m, 3H, Ph), 7.14-7.19(m, 1H, Ph), 7.90-7.92 (m, 1H, Ph). ^{13}C NMR 27.4, 28.5, 44.4, 46.8, 112.9, 117.3, 126.5, 127.1, 128.6, 129.1, 132.3, 133.4, 143.8, 148.0, 199.8. Mass spectrum, *m/z* (rel. int.) 251 (14,M^+), 146 (30), 106 (100). Anal. $C_{17}H_{17}NO$ calcd (found) C 81.27 (81.33), H 6.82 (6.86), N 5.57 (5.37).

3,4-Dihydro-2-bis-(phenylaminomethyl)-1-naphthalenone 13b: Obtained with **13a** and isolated in a 56% yield as an oil which on standing solidifies as yellow crystals; m.p. 91-92°C (isopropanol) ^{1}H NMR 2.25 (t, J=6.47Hz, 2H, 3-H), 3.15 (t, J=6.47Hz, 2H, 4-H), 3.4-3.6 (m, 4H, CH_2-N), 4.1(bs, 2H, NH), 6.6 (m, 6H, Ph), 7.1-7.5 (m, 7H, Ph), 8.05 (m, 1H, Ph). ^{13}C NMR 25.1, 29.3, 47.0, 50.3, 113.1, 117.7, 125.2, 126.9, 127.9, 128.2, 128.8, 129.0, 129.2, 129.3, 131.6, 133.9, 143.2, 148.4, 201.4. Mass spectrum, *m/z* (relative intensity) 356 (2,M^+), 250 (63), 106 (50), 93 (100). HRMS, 356.1877 ($C_{24}H_{24}N_2O$ requires 356.1888).).

Reduction of β-Amino Ketones

The Mannich bases **4d-f** and **4i** were prepared as described above and reduced without isolation by addition of one equivalent of lithium aluminium hydride and subsequent stirring of the THF solution for 5-6hrs. The resulting β-amino alcohols **14a-c** were obtained using the same acid-base work-up procedure described above, whereas the product **14d** was obtained without acid extraction. The diastereotopic mixtures were analyzed by G.C. (temperature range 70-250°C, rate 10°C per min.) to determine their ratios.

2-(1-Morpholinoethyl)cyclohexanol 14a: Purified by column chromatography (silica gel /dichloromethane) to give predominantly one diastereoisomer. ^{1}H NMR 0.97 (d, J=6.7Hz, 3H, Me), 1.24(m, 4H, CH_2 ^{1}H's), 1.71 (m, 4H, CH_2 ^{1}H's), 1.9(m, 1H, CH-CHOH), 2.45 (m, 2H, CH_2-N-CH_2), 2.6 (m, 1H, CH-N), 2.8 (m, 2H, CH_2-N-CH_2), 3.45 (m, 1H, CH-OH), 3.72 (m, 4H, CH_2-O-CH_2), 8.2 (bs, 1H, OH) (m, 2H, CH_2-N-CH_2). ^{13}C NMR 9.9, 24.4, 25.9, 27.0, 27.9, 34.8, 44.3, 66.5, 66.7, 67.1, 77.5. Mass spectrum, *m/z* (relative intensity) 213 (0.3, M^+), 198 (3, M-Me), 114 (100); HRMS, 213.1729 ($C_{12}H_{23}NO_2$ requires 213.1729).

2-(1-Piperidinoisobutyl)cyclohexanol 14b: (4 diastereoisomers in ratio 1:1.1:5.5:2.8). ^{1}H NMR 0.8-1.1 (m, 6H, Me), 1.1-3 (m, 21H), 3.45, 3.7, 3.85, 4.0 (m, 1H total, OH). ^{13}C 18.7, 19.6, 20.1, 20.3, 21.6, 21.6, 22.5, 22.7, 23.2, 23.4, 23.7, 24.2, 24.3, 24.4, 25.0, 25.1, 25.6, 25.9, 26.2, 26.3, 26.5, 26.7, 26.8, 27.2, 27.3, 27.3, 27.8, 29.0, 32.2, 33.6, 35.2, 35.8, 37.9, 42.0, 42.3, 48.3, 50.8, 53.0, 67.0, 69.9, 70.4, 71.3, 72.3, 75.7, 76.6, 76.8. Mass spectrum, *m/z* (relative intensity) 239 (0.7, M^+), 238 (0.8, M-1); HRMS, 239.2247 ($C_{15}H_{29}NO$ requires 239.2249).

2-(1-Morpholinocyclohexyl)cyclohexanol 14c: (2 diastereoisomers in ratio 4.8:1). ^{1}H NMR 1.1-2.3 (m, 18H, CH_2) ^{1}H's), 2.9-3.2 (m, 2H, CH_2-N-CH_2), 3.4-3.6 (m, 2H, CH_2-N-CH_2), 3.4-3.6 (m, 2H, CH_2-O-CH_2), 4.0-4.2 (m, 2H, CH_2-O-CH_2). ^{13}C NMR Major isomer: 19.1, 21.2, 21.7, 22.5, 26.8, 27.4, 30.8, 33.8, 39.9, 47.2, 50.6, 64.6, 65.6, 65.9, 73.4; minor isomer 20.9, 21.1, 23.0, 23.7, 25.3, 25.5, 27.3, 27.9, 35.4, 46.4, 47.2, 50.6, 65.5, 65.9, 71.5, 73.3.

Octahydro-2H-4-isobutyl-1,3-benzoxazin-2-one 14d: (2 diastereoisomers in ratio 2.5:1) ^{1}H NMR major isomer 0.9 (d, J=6.54Hz, 3H, Me), 0.95 (d, J=6.54Hz, 3H, Me), 1.2-1.5 (m, 6H), 1.6-2.0 (m, 5H), 2.1-2.2 (m, 1H, CH-CHO), 3.05- 3.2 (m, 1H, CH-N), 3.9 (m, 1H, CH-O), 5.6 (bs, 1H, N-H); minor isomer 3.4 (m, 1H, CH-N), 4.1 (m, 1H, CH-O), 6.4 (bs, 1H, N-H), the other signals overlapping with the major isomer. ^{13}C NMR major isomer: 21.1, 23.9, 24.6, 27.1, 31.4, 41.9, 42.8, 54.1, 79.2, 154.4, minor isomer: 20.8, 23.7, 24.1, 25.1, 26.2, 32.2, 39.9, 40.8, 50.4, 75.1, 154.3. IR 1694cm^{-1} (CO), 2900cm^{-1} (NH). Mass spectrum, *m/z* (relative intensity) 212 (15, M^++1), 154 (49, M-^{t}Bu), 110 (100).

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