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Utility of sec-Mannich Bases of Cycloalkanones in Synthesis of Mixed Mannich Bases and Fused Heterocycles with Ring Junction Nitrogen Atom

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ABSTRACT

Treatment of cycloalkanones **1a-c** with benzalaniline or dibenzal-*p*-phenylenediamine gave the corresponding cycloalkanone *sec*-Mannich bases **2a-c** and **4**.Whereas, the reaction of **1a** or **b** with benzal-1-naphthylamine afforded the condensed systems **7** and **8**. 2,6-di(*p*-anisal)cyclohexanone (**10**) was obtained from **1b** and *N,N'*-bis(*p*-anisal)ethylenediamine **9**.On the other hand, treatment of the bis-(Mannich base) **12** with benzalaniline gave the mixed Mannich base **13**. The tetra-base **14** was obtained by treating **2b** with ammonium chloride and formaldehyde, or from the tris-(Mannich base) **15** and benzalaniline.Schmidt reaction of **2a-c** and **4** gave *N*-phenyl-α-aminobenzyl derivatives of piperidin-2-one **16**, azepan-2-one **17**, azocan-2-one **18** and the bis-(azepan-2-one) derivative **19**, respectively. The potential of compounds **16** and **17** as precursors to fused heterocycles containing a nitrogen atom at a ring-junction was investigated. The 1,2,4-triazepine derivatives **25** and **26** were obtained by treating **2a**,**b** with hydrazine and formaldehyde.

Key words: Mixed Mannich Bases, Schmidt reaction, Rin-junction nitrogen, 1,2,4-Triazepines

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INTRODUCTION

There is currently a great deal of interest in the chemistry of Mannich bases due to their wide range of biological and pharmacological activities. Several Mannich bases derived from cycloalkanones were prepared and studied from the pharmacological point of view [1-7]. Chemotherapeutically valuable compounds in this class are a series of Mannich bases, such as spiractin "respiratory stimulant" [8], oxazidione "anticoagulant" [9], Be-2254 "antihypertensive" [10, 11], and moban "neuroleptic" [12, 13]. In addition, tert-Mannich bases of cycloalkanones are of considerable importance as intermediates in the synthesis of condensed heterocyclic systems [3, 14-17], and of heterocycles of alkaloidal nature [18-23]. However, the use of sec-Mannich bases as synthetic intermediates has been reported in a limited number of cases [24, 25].

In connection with our studies in the area of Mannich bases and related compounds [16, 17, 20-23, 26, 27], the synthetic potential cycloalkanone sec-Mannich bases of the type 2 as intermediates for the synthesis of the title compounds was investigated,

MATERIALS AND METHODS

Experimental Section

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental microanalyses were carried out at the Microanalytical Unit, Faculty of Science, Cairo University. Infrared spectra were measured on a Mattson 5000 FTIR spectrometer. ^{1}H and ^{13}C NMR data were obtained in $CDCl_3$ or [D_6] DMSO solution on a Varian XL 300 MHz instrument using TMS as internal standard. Chemical shifts are reported in ppm (δ) downfield from internal TMS. Mass spectra were recorded on a GC-MS QP –1000 EX Shimadzu instrument. The course of the reaction and the purity of the synthesized compounds were monitored by TLC using EM science silica gel coated plates with visualization by irradiation with an ultraviolet lamp. Compounds **14**, **16** and **19** are of limited solubility in common ^{1}H NMR solvents.

N, N'-Bis [α-(cyclohexanon-2-ly) benzyl]-p-phenylenediamine (4)

A solution of **1b** (2.15 g, 22 mmol) and dibenzal-p-phenylenediamine (2.84 g, 10 mmol) in ethanol (40 mL) and two drops of conc. HCl was heated on a water bath at 45-50 ^{o}C for 3 min. After standing at r. t. for 12 h and neutralization with NH_4OH, the product was filtered and crystallized from ethanol to give **4**. M. p. 166 ºC. – Yield 67 % (colorless crystals). – IR (KBr): ν = 3377 (NH), 1687 (CO), 1611, 1315, 1225, 1110, 775 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.56-169 (m, 8H, 2 x CH_2CH_2), 1.67-1.82 (m, 4H, 2 x CH_2), 2.22-2.35 (m, 4H, 2 x CH_2CO), 2.84-2.88 (m, 2H, 2 x CHCO), 4.45 (br. s, 2H, 2 x NH), 5.11 (d, 2H, 2 x Ph-CH), 7.19-7.73 (m, 14H, aromatic). – MS (EI, 70 eV): m/z (%) = 480 (14) $[M]^+$, 481 (3) $[M+1]^+$, 482 (4) $[M+2]^+$, 383 (33) [M-cyclohexanone

unit]$^+$, 293 (22), 287 (24) [M-2 x cyclohexanone unit]$^+$, 97 (13), 77 (100). – $C_{32}H_{36}N_2O_2$ (480.64): calcd. C 79.96, H 7.55, N 5.83; found C 79.93, H 7.51, N 5.80.

6-Phenyl-6,7,8,9-tetrahydro-5H-benzo[h]cyclopenta[c]quinoline (7)

This compound was obtained by treating **1a** (1.01 g, 12 mmol) with benzal-1-naphthylamine (2.31 g, 10 mmol) and two drops of conc. HCl, following the procedure described above for the synthesis of **4**. The product was purified by crystallization from benzene-ethanol (1:2) to give **7**. M. p. 275 ºC. – Yield 62 % (pale-brown powder). – IR (KBr): ν = 3345 (NH), 1577, 1514, 1377, 1270, 801, 770 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.56-1.64 (m, 2H, 8-H_2), 2.29-2.32 (m, 2H, 9-H_2), 2.78-2.90 (m, 2H, 7-H_2), 4.85 (s, 1H, 6-H), 7.22-7.75 (m, 11H, aromatic), 9.44 (s, 1H, NH). – MS (EI, 70 eV): m/z (%) = 297 (4) [M]$^+$, 298 (2) [M+1]$^+$, 299 (1) [M+2]$^+$, 295 (17), 294 (100), 255 (13), 220 (26) [M-Ph]$^+$, 77 (11). – $C_{22}H_{19}N$ (297.39): calcd. C 88.85, H 6.44, N 4.71; found C 88.80, H 6.41, N 4.68.

6-Phenyl-5,6,7,8,9,10-hexahydro-benzo[c]phenanthridine (8)

This compound was obtained in the same manner as described for **7**, but using **1b** (1.17 g, 12 mmol) instead of **1a**. The product was purified by crystallization from benzene-ethanol (1:2) to give **8**. M. p. 260 ºC. – Yield 55 % (pale-brown powder). – IR (KBr): ν = 3360 (NH), 1572, 1516, 1400, 1341, 798, 768 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.58-1.63 (m, 4H, 8-H_2, 9-H_2), 2.75-2.77 (m, 2H, 10-H_2), 2.79-2.90 (m, 2H, 7-H_2), 5.13 (s, 1H, 6-H), 7.35-7.76 (m, 11H, aromatic), 9.30 (s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 20.22 (C-9), 24.19 (C-8), 25.34 (C-7), 27.18 (C-10), 59.66 (C-6), 127.36 (C-10a), 128.15 (C-6a), 116.20, 117.45, 118.67, 124.60, 127.77, 127.96, 128.37, 128.66, 139.51, 143.52 (all Ar-C). – MS (EI, 70 eV): m/z (%) = 311 (3) [M]$^+$, 312 (1) [M+1]$^+$, 283 (13), 255 (21), 234 (12) [M-Ph]$^+$, 77 (28). – $C_{23}H_{21}N$ (311.42): calcd. C 88.71, H 6.80, N 4.50; found C 88.69, H 6.77, N 4.46.

2,6-Di(p-methoxybenzal)cyclohexanone (10)

This compound was obtained from **1b** (1.17 g, 12 mmol) and N,N'-bis(p-methoxybenzylidene)ethylenediamine (1.77 g, 6 mmol), following the same procedure described above for the synthesis of **4**. The product was purified by crystallization from ethanol to give **10**. M. p. 150 ºC. – Yield 77 % (yellow crystals). – IR (KBr): ν = 1644 (C=O), 1522, 1412, 1310, 1222, 1112, 790 cm^{-1}. – $C_{22}H_{22}O_3$ (334.41): calcd. C 79.02, H 6.63; found C 79.00, H 6.60.

The structure of **10** was confirmed by a comparison of IR data, m. p. and TLC with an authentic sample obtained from **1b** (1.17 g, 12 mmol) and p-anisaldehyde (3.26 g, 24 mmol) in ethanol (40 mL) containing (2 mL) of 20% NaOH solution.

N,N-Bis[3-(α-phenylaminobenzyl)-2-oxocyclohexylmethyl]methylamine (13)

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A solution of **12** (1.88 g, 7.5 mmol) and benzalaniline (2.71 g, 15 mmol) in ethanol (30 mL) and 0.2 mL of conc. HCl was heated on a water bath at 45-50 ^{o}C for 2-3 min. After standing at r. t. for 12 h and neutralization with NH_4OH, the product was filtered and crystallized from ethyl acetate to give **13**. M. p. 162 ºC. – Yield 73 % (white powder). – IR (KBr): ν =3397 (NH), 1736, 1461, 1382, 1122, 881 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.55-1.74 (m, 12H, 4-H_2, 5-H_2, 6-H_2, 4'-H_2, 5'-H_2, 6'-H_2), 2.22 (3H, NMe), 2.30 (m, 2H, 1-H, 1'-H), 2.42-2.55 (m, 4H, 2 x NCH_2), 2.80-2.86 (m, 2H, 3-H, 3'-H), 4.42 (br. s, 2H, 2 x NH), 3.88 (d, 2H, 2 x Ph-CH), 7.19-7.73 (m, 20H, aromatic). – ^{13}C NMR ($CDCl_3$): δ = 21.83 (C-5 and C-5'), 25.13 (C-4), 25.73 (C-4'), 29.75 (C-6), 29.94 (C-6'), 40.05 (NCH_3), 46.84 (C-1 and C-1'), 56.04 (C-3 and C-3'), 58.14 (C-Ph), 59.87 (CH_2N), 113.66, 118.22, 125.76, 128.84, 130.12, 139.39, 145.87 (all Ar-C), 213.20 (C=O). – MS (EI, 70 eV): m/z (%) = 612 (7) $[M-1]^+$, 611 (3) $[M-2]^+$, 430 (13), 250 (22), 181 (16), 169 (100), 92 (30), 77 (35). – $C_{41}H_{47}N_3O_2$ (613.83): calcd. C 80.22, H 7.72, N 6.85; found C 80.19, H 7.70, N 6.79.

Tri[3-(α-phenylaminobenzyl)-2-oxocyclohexylmethyl]amine (14)

Procedure A: A mixture of **2b** (8.37 g, 30 mmol), ammonium chloride (0.53 g, 10 mmol) and formalin (37%, 3.25 mL, 40 mmol) was heated until the mixture became homogeneous. After cooling to r. t., the reaction mixture was diluted with water (60 mL) and extracted with ether (2 x 30 mL). The aqueous layer was basified with NH_4OH and extracted with ethyl acetate (2 x 30 mL), dried over sodium sulfate and concentrated to give **14**. M. p. 159 ºC. – Yield 67 % (yellow powder). – IR (KBr): ν = 3413 (NH), 1671, 1606, 1448, 1311, 1261 1155, 754 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 891 (14) $[M]^+$, 890 (23) $[M-1]^+$, 889 (22) $[M-2]^+$, 506 (21), 293 (27), 198 (18), 182 (36), 109 (27), 106 (100), 92 (50) 77 (13). – $C_{60}H_{66}N_4O_3$ (891.19): calcd. C 80.86, H 7.46, N 6.29; found C 80.82, H 7.40, N 6.20.

Procedure B: A solution of **15** (1.74 g, 5 mmol) and benzalaniline (2.71 g, 15 mmol) in ethanol (30 mL) and 0.2 mL of conc. HCl was heated on a water bath at 45-50 ^{o}C for 3 min. After standing at r. t. for 24 h and neutralization with NH_4OH, the product was filtered and crystallized from ethyl acetate to give **14**. M. p. 160 ºC. – Yield 54 %. The structure was confirmed by a comparison of IR data, m.p. and TLC with that from procedure A.

Schmidt reaction with 2a-c: Synthesis of compounds 16-18

To a solution of **2a**-**c** (10 mmol) in chloroform (50 mL) containing 90 % sulfuric acid (4 mL) at 0 ºC, there was added sodium azide (0.72 g, 11 mmol). After stirring for 1 h at 0 ºC and 4 h at 25 ºC, the reaction mixture was diluted with ice water (50 mL) and basified with NH_4OH. The product was filtered and crystallized from ethyl acetate – ethanol (2 : 1).

6-[(N-Phenylamino)benzyl]piperidin-2-one (16)

M. p. 180 ºC. Yield 58 % (colorless crystals). – IR (KBr): ν = 3327, 3181, 1640, 1331, 1312, 1260, 828 cm^{-1}. – MS (EI, 70 eV): m/z (%) = 280 (3) $[M]^+$, 279 (1) $[M-1]^+$,

188 (4) $[M-PhNH]^+$, 187 (20) $[M-PhNH_2]^+$, 182 (100) $[PhNHCHPh]^+$, 98 (9), 77 (2). – $C_{18}H_{20}N_2O$ (280.36): calcd. C 77.11, H 7.19, N 9.99; found C 77.04, H 7.16, N 9.91.

7-[(N-Phenylamino)benzyl]azepan-2-one (17)

M. p. 189 ºC. Yield 67 % (colorless crystals). – IR (KBr): ν = 3317, 3203, 1665, 1460, 1377, 1090, 746 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.46-1.53 (m, 2H, 5-H_2), 1.80-1.82 (m, 2H, 6-H_2), 1.83-1.92 (m, 2H, 4-H_2), 2.43-2.46 (m, 2H, 3-H_2), 3.59 (m, 1H, 7-H), 4.29 (m, 1H, Ph-CH), 4.53 (s, 1H, NH), 6.51 (s, 1H, CONH), 7.06-7.32 (m, 10H, aromatic). – ^{13}C NMR ($CDCl_3$): δ = 23.07 (C-4), 29.57 (C-5), 33.14 (C-6), 37.04 (C-3), 58.87 (C-7), 62.16 (Ph-CH), 114.04, 118.29, 127.28, 127.99, 129.02, 129.21, 140.32, 146.67 (all Ar-C), 178.04 (C-2). – $C_{19}H_{22}N_2O$ (294.39): calcd. C 77.52, H 7.53, N 9.52; found C 77.50, H 7.49, N 9.48.

8-[(N-Phenylamino)benzyl]azocan-2-one (18)

M. p. 222 ºC. Yield 63 % (colorless crystals). – IR (KBr): ν = 3381, 3273, 1660, 1450, 1315, 1152, 750 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.22-1.59 (m, 6H, 4-H_2, 5-H_2, 6-H_2), 1.69 (m, 2H, 7-H_2), 2.47 (m, 2H, 3-H_2), 3.80 (m, 1H, 8-H), 4.22 (m, 1H, Ph-CH), 4.51 (s, 1H, NH), 5.82 (s, 1H, CONH), 7.06-7.33 (m, 10H, aromatic). – MS (EI, 70 eV): m/z (%) = 308 (5) $[M]^+$, 182 (13) $[PhNHCHPh]^+$, 181 (100), 126 (2), 77 (1). – $C_{20}H_{24}N_2O$ (308.42): calcd. C 77.89, H 7.84, N 9.08; found C 77.84, H 7.81, N 8.98.

N,N'-Bis[α-(azepan-2-one-7-yl)benzyl]-p-phenylenediamine (19)

This compound was obtained from **4** (2.40 g, 5 mmol) and sodium azide (0.72 g, 11 mmol), following the same procedure described above for the synthesis of **16**-**18**. The product was purified by crystallization from ethyl acetate to give **19.** M. p. 190 ºC. – Yield 68 % (brown crystals). – IR (KBr): ν = 3358 (NH), 3222 (NH lactam), 1655, 1333, 1322, 1245, 758 cm^{-1}. – $C_{32}H_{38}N_4O_2$ (510.67): calcd. C 75.26, H 7.50, N 10.97; found C 75.21, H 7.48, N 10.90.

1,2-Diphenylhexahydroimidazo[1,5-a]pyridine-5(1H)-one (20)

A solution of **16** (1.12 g, 4 mmol) and formalin (37 %, 0.33 mL, 4 mmol) in ethanol (40 mL) was heated on a steam bath for 2 h. After standing at r. t. for 48 h, the product was filtered and crystallized from ethanol to give **20**. M. p. 110 ºC. – Yield 52 % (yellow crystals). – IR (KBr): ν = 1644 (CO), 1513, 1452, 1369, 1326, 1180, 700 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.55-1.62 (m, 2H, 8-H_2), 1.98-2.10 (m, 2H, 7-H_2), 2.34-2.38 (m, 2H, 6-H_2), 3.58-3.60 (m, 1H, 8a-H), 4.21 (d, 1H, 1-H), 5.16 (s, 2H, 3-H_2), 6.88-7.39 (m, 10H, aromatic). – ^{13}C NMR ($CDCl_3$): δ = 20.58 (C-8), 25.58 (C-7), 31.27 (C-6), 65.62 (C-8a), 65.96 (C-3), 70.27 (C-1), 114.61, 118.69, 126.39, 128.21, 128.95, 129.24, 139.46, 144.58 (all Ar-C), 167.39 (C-5). – MS (EI, 70 eV): m/z (%) = 293 (8) $[M+1]^+$, 292 (34) $[M]^+$, 291 (24) $[M-1]^+$, 290 (16), 195 (64), 194 (100), 193 (65), 162 (19), 104 (31), 92 (15), 77 (54). – $C_{19}H_{20}N_2O$ (292.37): calcd. C 78.05, H 6.89, N 9.58; found C 77.95, H 6.81, N 9.38.

4-Cyclohexyl-1,2-diphenyloctahydropyrido[1,2-e][1,3,5]triazepin-7(1H)-one (21)

A solution of **16** (1.12 g, 4 mmol), cyclohexylamine (0.4 g, 4 mmol) and formalin (37 %, 0.65 mL, 8 mmol) in ethanol (50 mL) was heated on a steam bath for 3 h. After standing at r. t. for 48 h, the product was filtered and crystallized from ethanol to give **21**. M. p. 184 ºC. – Yield 48 % (pale-yellow crystals). – IR (KBr): ν = 1656 (CO), 1600, 1494, 1402, 1315, 1259, 746 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.61-1.65 (m, 6H, 3 x CH_2 of cyclohexane), 1.66-1.70 [m, 4H, $(CH_2)_2CHN$], 1.71-1.74 (m, 4H, 9-H_2, 10-H_2), 1.92 (m, 2H, 8-H_2), 2.39-2.41 [m, 1H, $(CH_2)_2CHN$], 3.74 **(**m, 1H, 10a-H), 4.35 (m, 1H, 1-H), 4.38 (s, 2H, 5-H_2), 6.33 (s, 2H, 3-H_2), 6.75-7.36 (m, 10H, aromatic). – $C_{26}H_{33}N_3O$ (403.56): calcd. C 77.38, H 8.24, N 10.41; found C 77.31, H 8.22, N 10.38.

4,4-Diethyl-1,2-diphenylhexahydropyrido[1,2-a][1,4]diazepine-3,5,7-(4H)-trione (22)

A solution of **16** (1.12 g, 4 mmol), and diethyl diethylmalonate (0.86 g, 4 mmol) in absolute ethanol (20 mL) was added to a solution of sodium ethoxide (prepared by dissolving 0.2 g sodium in 20 mL absolute ethanol). The reaction mixture was refluxed for 3 h, cooled and acidified with acetic acid to give **22**. M. p. 295 ºC (washed with boiling ethanol). – Yield 67 % (white powder). – IR (KBr): ν = 1659 (CO), 1637 (CO), 1461, 1315, 1260, 1202, 1069, 775 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.22 (t, 3H, CH_3CH_2), 1.65 (q, 2H, CH_3CH_2), 2.19-2.24 (m, 4H, 9-H_2, 10-H_2), 2.49 (m, 2H, 8-H_2), 3.72 **(**m, 1H, 10a-H), 4.39 (m, 1H, 1-H), 6.75-7.36 (m, 10H, aromatic). – MS (EI, 70 eV): m/z (%) = 375 (40) $[M\text{-}Et]^+$, 271(26), 228 (33), 211 (33), 181 (100), 121 (13), 77 (22). – $C_{25}H_{28}N_2O_3$ (404.50): calcd. C 74.23, H 6.98, N 6.93; found C 74.19, H 6.91, N 6.89.

6-Methylene-1,2-diphenylhexahydro-1H-imidazo[1,5-a]azepin-5(6H)one (23)

This compound was obtained by treating **17** (2.06 g, 7 mmol) with formalin (37 %, 0.65 mL, 8 mmol) in ethanol (60 mL) following the procedure described above for the synthesis of **20**. The product was purified by crystallization from ethanol to give **23**. M. p. 90 ºC. – Yield 72 % (brown powder). – IR (KBr): ν = 1637 (CO), 1515, 1448, 1384, 1228, 1187 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.46-1.54 (m, 4H, 8-H_2, 9-H_2), 2.00-2.13 (m, 2H, 7-H_2), 4.32 (m, 1H, 9a-H), 4.43 (m, 1H, 1-H), 4.73 (d, 2H, 3-H_2), 5.47-5.51 (m, 2H, =CH_2), 6.88-7.47 (m, 10H, aromatic). – MS (EI, 70 eV): m/z (%) = 319 (16) $[M+1]^+$, 320 (19) $[M+2]^+$, 235(19), 194 (36), 182 (32), 167 (100), 119 (29), 77 (61). – $C_{21}H_{22}N_2O$ (318.41): calcd. C 79.21, H 6.96, N 8.80; found C 79.19, H 6.91, N 8.75.

1,2-Diphenyldecahydroazepino[1,2-c][1,3,6]oxadiazepine (24)

A solution of **17** (2.06 g, 7 mmol) in tetrahydrofuran (20 mL) was added to (0.76 g, 20 mmol) in (20 mL) of the same solvent. The reaction mixture was refluxed for 6 h, cooled, poured into ice-water (200 mL), basified with NH_4OH and filtered. The filtrate was dried and evaporated under reduced pressure to give a thick oil, which was dissolved in ethanol (40 mL) and treated with formalin (37 %, 1.20 mL, 15 mmol) and 0.2 mL of dil. HCl (10 %). After standing at r. t. for 12 h, the reaction mixture was concentrated and the product was crystallized from ethyl acetate to give **24**. M. p. 176 ºC dec. – Yield 58 % (pale-yellow crystals). – IR (KBr): ν =

1602, 1500, 1468, 1342, 1252, 1132, 1069, 746 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.32-1.66 (m, 8H, 8-H_2, 9-H_2, 10-H_2, 11-H_2), 2.73 (m, 2H, 7-H_2), 2.85 (m, 1H, 11a-H), 4.70 (m, 1H, 1-H), 5.85 (s, 2H, 5-H_2), 6.05 (s, 2H, 3-H_2), 6.80-7.47 (m, 10H, aromatic). – ^{13}C NMR ($CDCl_3$): δ = 23.48 (C-10), 26.38 (C-9), 29.27 (C-11), 29.86 (C-8), 51.16 (C-7), 53.25 (C-3), 55.56 (C-11a), 62.12 (C-1), 85.13 (C-5) 114.31, 118.19, 128.27, 128.85, 129.24, 139.76, 147.38 (all Ar-C). – $C_{21}H_{26}N_2O$ (322.44): calcd. C 78.22, H 8.13, N 8.69; found C 78.19, H 8.10, N 8.61.

2,3,4,5,5a,6,7,8-Octahydro-4,5-diphenylcyclopenta[f][1,2,4]triazepine (25)

A solution of **2a** (2.65 g, 10 mmol) and hydrazine hydrate (0.5 g, 10 mmol) in ethanol (40 mL) was heated on a steam bath for 20 min, then formalin (37 %, 0.8 mL, 10 mmol) and acetic acid (0.1 mL) were added and the reaction mixture was heated for 5 min. After standing at r. t. for 12 h, the product was filtered and crystallized from ethanol to give **25**. M. p. 215 ºC. – Yield 42 % (colorless crystals). – IR (KBr): ν = 3376 (NH), 1616, 1504, 1346, 1199, 1093, 748 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 1.33-1.60 (m, 6H, 6-H_2, 7-H_2, 8-H_2), 2.88 (m, 1H, 5a-H), 3.46 (m, 1H, 5-H), 4.71 (s, 2H, 3-H_2), 7.8 (s, 1H, NH), 6.59-7.22 (m,10 H, aromatic). – MS (EI, 70 eV): m/z (%) = 291 (7) $[M]^+$, 292 (7) $[M+1]^+$, 280 (14), 192 (21), 182 (41) $[PhNHCHPh]^+$, 181 (90) $[PhN=CHPh]^+$, 180 (96), 150 (12), 121 (13), 104 (27), 77 (100). – $C_{19}H_{21}N_3$ (291.39): calcd. C 78.32, H 7.26, N 14.42; found C 78.29, H 7.20, N 14.39.

3,4,5,5a,6,7,8,9-Octahydro-4,5-diphenyl-2H-benzo[f][1,2,4]triazepine (26)

This compound was obtained in the same manner as described for **25**, but using **2b** (2.79 g, 10 mmol) instead of **2a**. The product was purified by crystallization from ethanol to give **26**. M. p. 240 ºC. – Yield 46 % (colorless crystals). – IR (KBr): ν = 3413 (NH), 1614, 1420, 1346, 1195, 1100, cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 1.22-1.64 (m, 8H, 6-H_2, 7-H_2, 8-H_2, 9-H_2), 3.11 (m, 1H, 5a-H), 3.60 (m, 1H, 5-H), 3.97 (s, 2H, 3-H_2), 8.42 (s, 1H, NH), 6.84-7.18 (m,10 H, aromatic). – MS (EI, 70 eV): m/z (%) = 306 (5) $[M+1]^+$, 307 (4) $[M+2]^+$, 182 (12), 181 (7), 131 (20), 123 (17), 104 (14), 92 (12), 77 (11), 56 (100). – $C_{20}H_{23}N_3$ (305.42): calcd. C 78.65, H 7.59, N 13.76; found C 78.60, H 7.52, N 13.71.

RESULTS AND DISCUSSION

In the present study, the 2-[α-(*N*-phenylamino)benzyl]cycloalkanones **2a**-**c** were prepared by treating the appropriate cycloalkanone **1a**-**c** with benzalaniline in presence of hydrochloric acid as previously described [28-30]. The scope of this reaction has been broadened by treating **1b** with dibenzal-*p*-phenylenediamine (**3**) to give *N,N'*-bis[α-(cyclohexanon-2-ly)benzyl]-*p*-phenylenediamine (**4**). Whereas, the reaction of **1a** and **1b** with benzal-1-naphthylamine takes a different course. The reaction proceeded smoothly to give 6-phenyl-6,7,8,9-tetrahydro-5*H*-benzo[*h*]cyclopenta[*c*]quinoline (**7**) and 6-phenyl-5,6,7,8,9,10-hexahydro-benzo[*c*]phenanthridine (**8**), respectively, *via* the intermediacy of **6** (n = 1 or 2), which undergoes cyclization to give **7** and **8** as the end products (Scheme 1). The mass, IR and ^{1}H NMR spectra of compounds **4**, **7**, and **8** are consistent with their structures. The formation of

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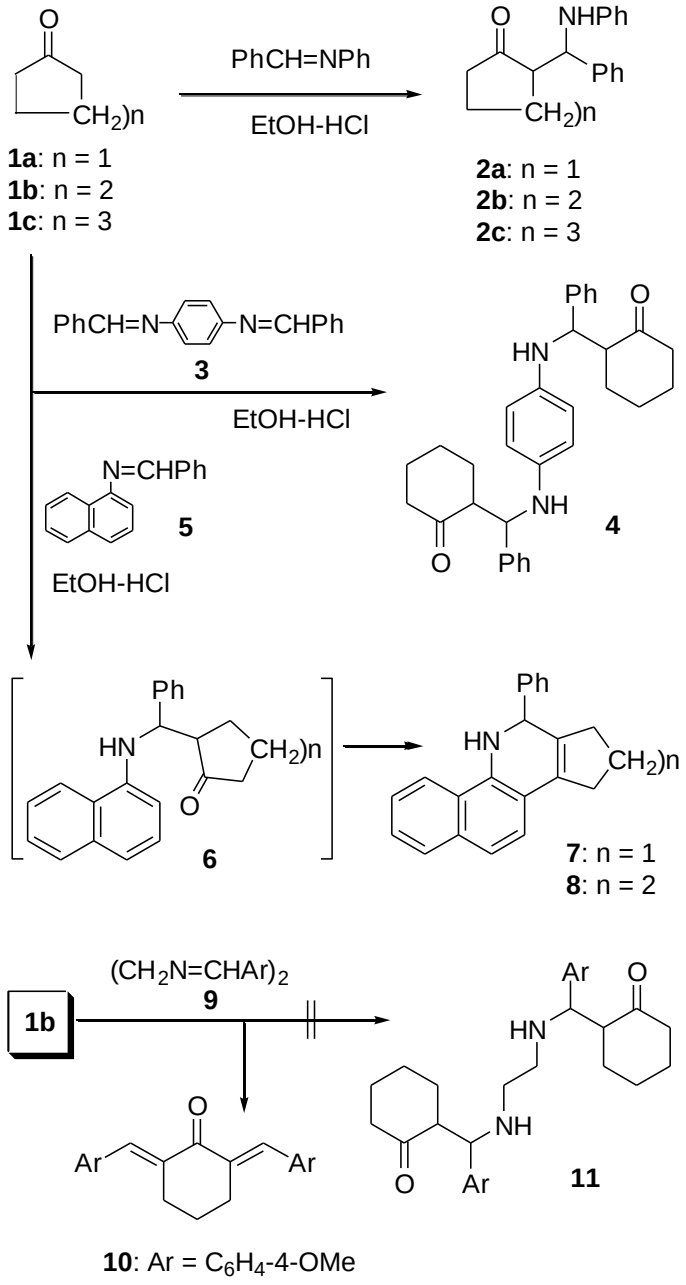
compounds **7** and **8** is in line with an earlier report [31] in which 2-phenyl-5,6-benzolepidine was obtained by the acid catalyzed condensation of benzal-2-naphthylamine with acetone. The IR spectra of **7** and **8** revealed the absence of carbonyl groups and showed strong bands at 3345 and 3360 (NH), respectively.



Scheme 1.

Treatment of **1b** with *N,N'*-bis(*p*-methoxybenzylidene)ethylenediamine (**9**) afforded 2,6-di(*p*-methoxybenzal)cyclohexanone (**10**). The formation of **10** rather than the expected bis-(*sec*-Mannich base) **11** may be attributed to the reaction of **1b** with *p*-anisaldehyde resulting from

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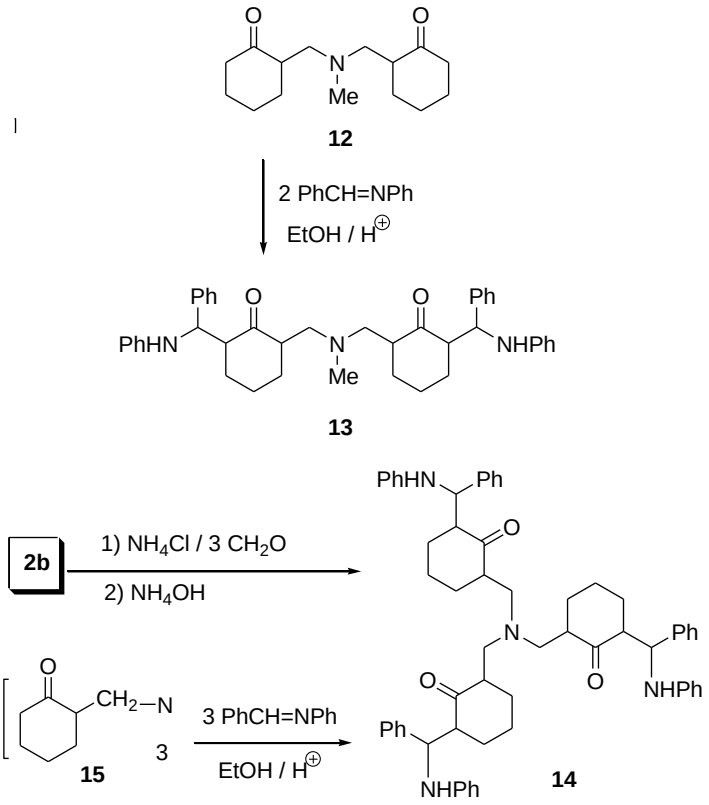
decomposition of **9**. This result parallel the reported formation of 2-(*p*-methoxybenzal)-1,3-indandione from **9** and 1,3- indandione [32].

On the other hand, the reaction of the bis-(*tert*-Mannich base) **12** [33] with benzalaniline is of particular interest, because it offers access to the mixed Mannich base; *N,N*-bis[3-(*α*-phenylaminobenzyl)-2-oxocyclohexylmethyl]methylamine (**13**).



Scheme 2.

In connection with this study, the synthesis of tri-[3-(*α*-phenylaminobenzyl)-2-oxocyclohexylmethyl]amine (**14**) has been achieved by Mannich reaction of **2b** with ammonium chloride and formaldehyde. The unambiguous synthesis of the mixed Mannich base **14**, by treating the tris-(Mannich base) **15** [33] with benzalaniline confirmed its structure (Scheme 2). The mass spectra of **13** and **14** contain peaks of the respective molecular ions, and fragmentation patterns which supported their structures. The fragmentation pattern of **14** is depicted in Scheme 3.

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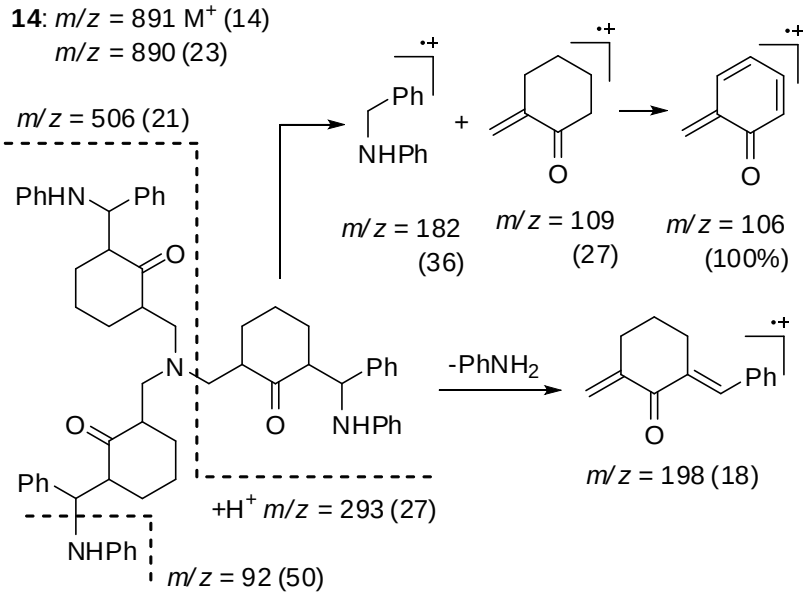
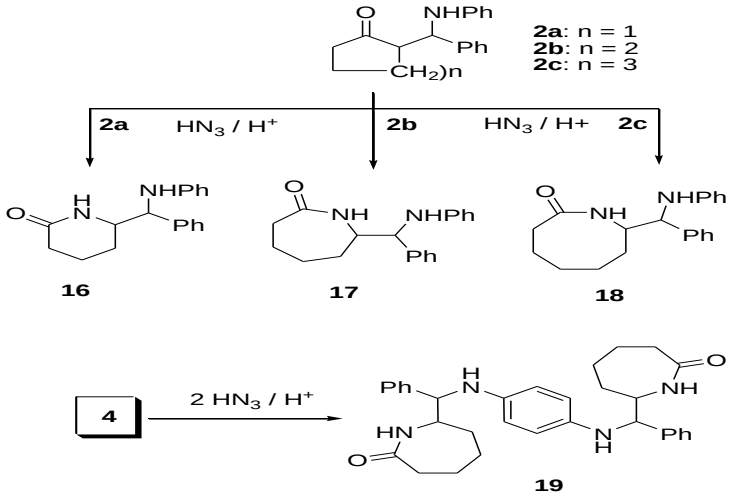


Scheme 3.

One of the specific objectives of this study was to investigate the possible synthesis of saturated NH-heterocycles from the cycloalkanone *sec*-Mannich bases **2a**-**c** and **4**, because the introduction of a cyclic NH group besides the *sec*-arylamino functionality, offers the possibility to form several fused heterocycles. The Schmidt reaction with **2a**-**c** and **4** constitutes an interesting and useful approach towards this goal. This has been realized by treating **2a-c** with one equivalent of hydrazoic acid to give the (*N*-phenylamino)benzyl derivatives of piperidin-2-one (**16**), azepan-2-one (**17**) and azocan-2-one (**18**), respectively. A similar reaction takes place on treating **4** with two equivalents of hydrazoic acid yielding *N,N'*-bis[α-(azepan-2-one-7-yl)benzyl]-*p*-phenylenediamine (**19**) (Scheme 4).



Scheme 4.

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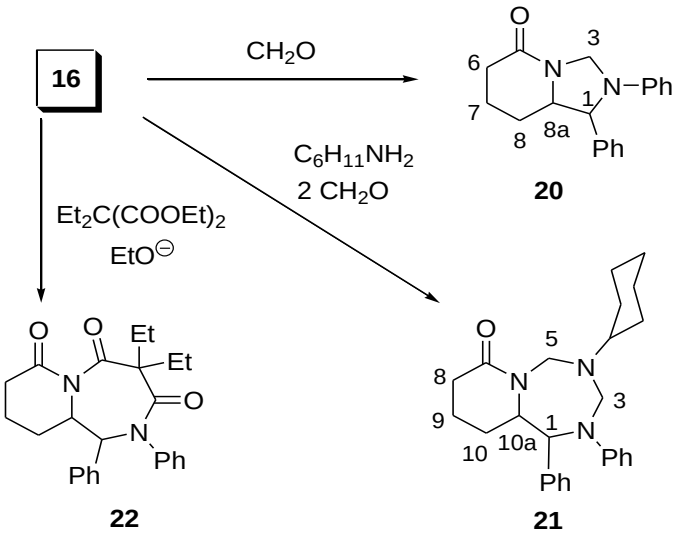
The assignment of the (NH) group between the (C=O) group and the substituted carbon atom of **16**-**19** is based on previous studies on the Schmidt reaction with *tert*-Mannich bases of cycloalkanones [17, 20, 34]. In addition, there is much evidence that bulky substituents at the *α*-position exert stereocontrol on the Schmidt reaction [21, 22, 35, 36].

In order to explore the synthetic potentialities of compounds **16**-**18** as intermediates for the synthesis of fused heterocycles containing a nitrogen atom at a ring junction, compound **16** was treated with formaldehyde to afford 1,2-diphenylhexahydroimidazo[1,5-*a*]pyridine-5(1*H*)-one (**20**). The double Mannich reaction of **16** with cyclohexylamine and formaldehyde provides a convenient access to the octahydropyrido[1,2-*e*][1,3,5]triazepin-7(1*H*)-one ring system (**21**). In addition, 4,4-diethyl-1,2-diphenylhexahydropyrido[1,2-*a*][1,4]diazepine-3,5,7-(4*H*)-trione (**22**) was obtained by treating **16** with diethyl diethylmalonate. The mass, IR and ^{1}H NMR spectra of compounds **19**-**21** are consistent with their structures (Scheme 5).



Scheme 5.

On the other hand, the reaction of **17** with formaldehyde afforded 6-methylene-1,2-diphenylhexahydro-1*H*-imidazo[1,5-*a*]azepin-5(6H)one (**23**). Whereas, the synthesis of the decahydroazepino[1,2-*c*][1,3,6]oxadiazepine ring system (**24**) has been achieved *via* a reaction sequence which involves reduction of **17** and subsequently treatment with excess formaldehyde under slightly acidic conditions (Scheme 6). The mass spectra of **23** and **24** revealed molecular ion peaks at *m/z* = 318 and 322, respectively. The main characteristic features of the ^{1}H NMR spectrum of **24** are two singlets at δ = 5.85 and 6.05 assignable to 5-H_2 and 3-H_2, respectively. The formation of **24** is in line with an earlier report [37], in which 4-alkyl-1,3,4,5-tetrahydro-1,3,6-oxadiazepino[3,4-*a*]benzimidazole is obtained from 2-alkylaminomethylbenzimidazole and formaldehyde.

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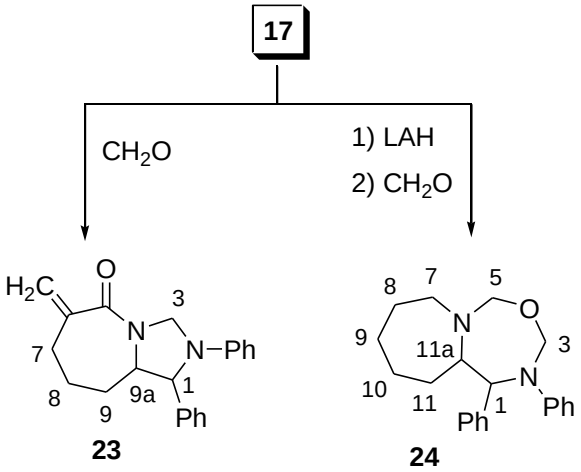
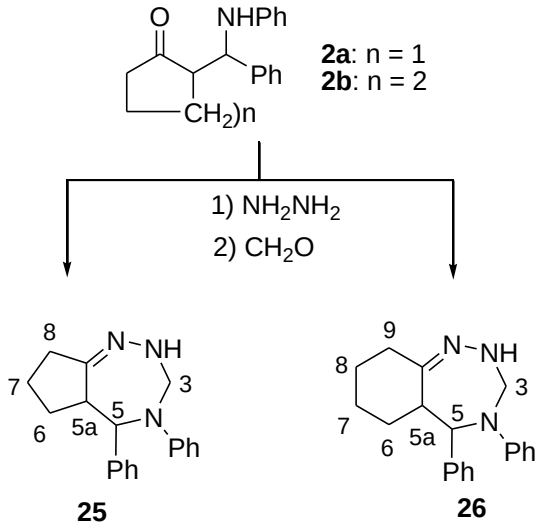


Scheme 6.

In an extension of this study, the ketonic *sec*-amine **2a** was treated with hydrazine and subsequently with formaldehyde under mild conditions to give 2,3,4,5,5a,6,7,8-octahydro-4,5-diphenylcyclopenta[*f*][1,2,4]triazepine (**25**). A similar reaction takes place on treating the hydrazone of **2b** with formaldehyde yielding octahydro-4,5-diphenyl-2*H*-benzo[*f*][1,2,4]triazepine (**26**) (Scheme 7). A practical advantage of the reactions leading to compounds **25** and **26** is that it is often unnecessary to isolate the intermediate hydrazones.



Scheme 7.

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