An Approach to Azabicyclo[*n*.3.1]alkanes by Double Mannich Reaction

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Abstract: Chlorotrimethylsilane-promoted double Mannich annulation of ketones using *N*,*N*-bis(methoxymethyl)benzylamine has been explored. It has been shown that the structure of the substrate drastically influenced the outcome of the reaction. The method allows azabicyclo[*n*.3.1]alkane derivatives ($n = 2–5$) to be obtained in good yields.

Key words: annulation, Mannich bases, molecular rigidity, bicyclic compounds, chlorotrimethylsilane

Fragment-based drug design, which became a novel paradigm for drug discovery in the last decade,[1] appeared to require even more demanding and novel diverse building blocks than high-throughput screening; this has represented an ongoing challenge to synthetic chemists. Conformationally restricted and rigid building blocks exhibit some advantages in the design of drug candidates when compared to their flexible analogs, mainly due to the decrease in entropy of binding of the potential drug candidate with its biological target.[2] This concept is embodied in aza-substituted bicyclic scaffolds (Figure 1), which are widespread both in natural compounds [e.g. (+)-makomakine (**1**)[3] or atropine (**2**)] and in synthetic drugs [e.g. anti-HIV Maraviroc (**3**)[4] or 5-HT3 receptor antagonist Granisetron (**4**)[5]].

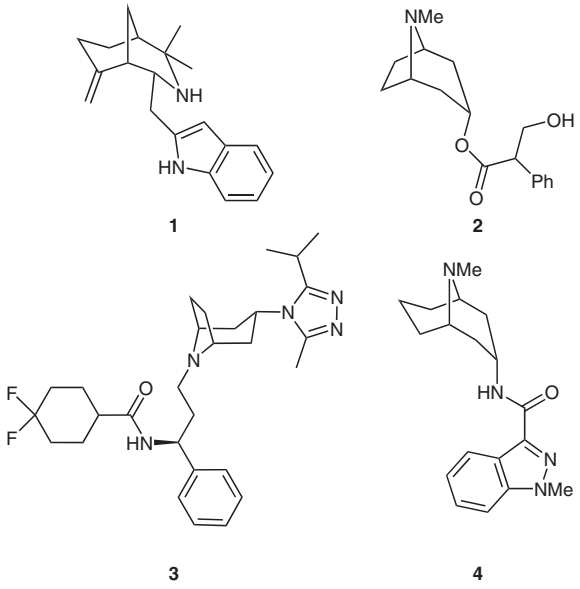
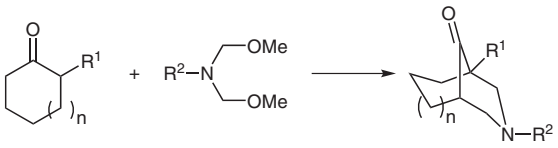


Figure 1

Over the last few years, several examples of double Mannich annulation of cyclic ketones using *N*,*N*-bis(alkoxymethyl)alkylamines have been reported (Scheme 1).[6] Most of these referred to cyclic β-keto esters; Mannich annulations of other cyclic ketones appeared to be more sensitive to the nature of the substrate.[6c]



Scheme 1

Recently, we started a project on the design and the synthesis of conformationally constrained and rigid bicyclic diamines as potential building blocks for drug design.[7] As a part of this project, we were interested in chlorotrimethylsilane-promoted double Mannich annulations of the substrates **5**–**11** using *N*,*N*-bis(alkoxymethyl)alkylamines (Figure 2). *N*,*N*-Bis(methoxymethyl)benzylamine (**12**) was used in all the annulations reported below in order to make further N-deprotection of azabicyclo[*n*.3.1]alkane derivatives possible.

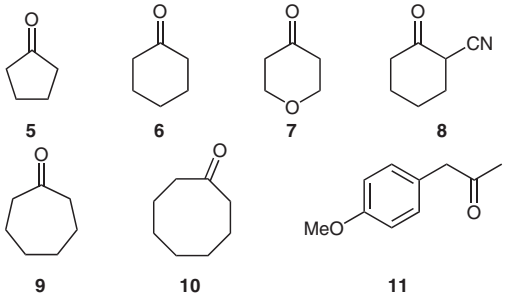


Figure 2

The structure of the substrate appeared to influence drastically the outcome of the double Mannich annulations of cyclic ketones using amine **12**. In particular, reaction of **12** with cyclopentanone **5** and cyclohexanone **6** resulted in the formation of ketals **15** (18%) and **16** (80%), respec-

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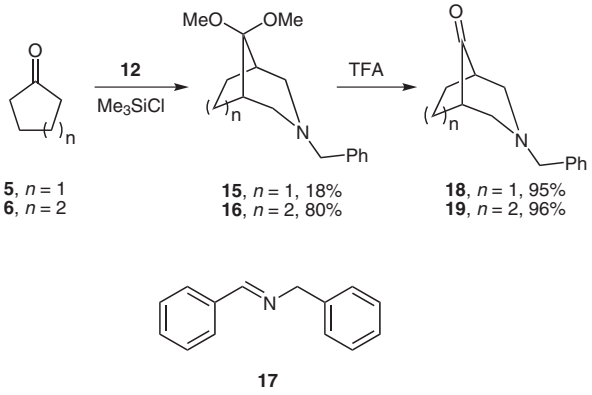
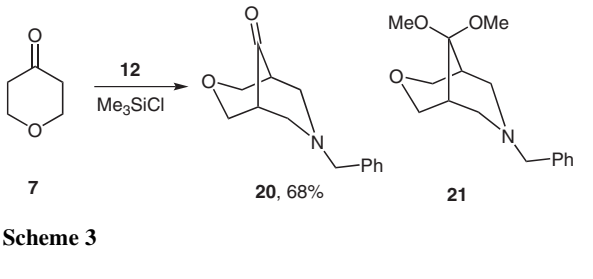
tively. In the case of ketone **5**, *N*-benzylidenebenzylamine (**17**) was also isolated in 23% yield (Scheme 2). The mechanism of the formation of **17** is unclear; however it is certain that partial oxidation of benzylamine to benzaldehyde is one of the steps of the reaction. Compounds **15** and **16** were transformed into the corresponding amino ketones **18** and **19**, respectively, by treatment with trifluoroacetic acid. We believe that ring constraints in the bicyclic systems of ketones **18** and **19** lead to the enhanced reactivity of their carbonyl group, thus resulting in acid-catalysed formation of ketals **15** and **16** under the anhydrous conditions of the double Mannich condensation.



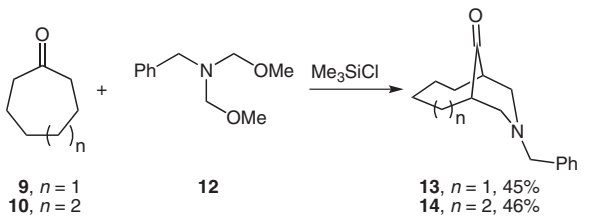
Scheme 2

This effect appeared to be very sensitive to the structure of the substrate, for example, reaction of **12** and γ-pyranone (**7**) resulted in the direct formation of ketone **20**; no ketal product **21** was isolated (Scheme 3). Analogously, in the case of cycloheptanone (**9**) and cyclooctanone (**10**), the corresponding amino ketones **13** and **14** were obtained in 45 and 46% yields, respectively (Scheme 4). These results are in accordance with literature data reported for other *N*,*N*-bis(alkoxymethyl)alkylamines.[6c]

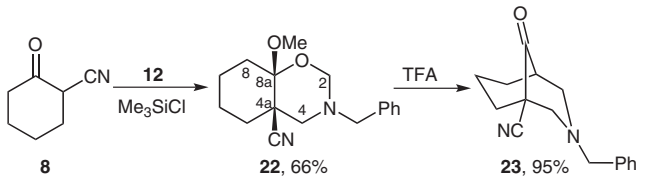
When benzylamine derivative **12** was allowed to react with 2-cyanocyclohexanone (**8**), the octahydro-2*H*-1,3-benzoxazine derivative **22** was isolated in 66% yield (Scheme 5). The structure of compound **22** was confirmed by 2D NMR (HMBC) spectroscopy and X-ray crystal structure analysis (Figure 3). Formation of compounds with a related tricyclic core in Mannich-type reactions has been reported previously.[8] It is interesting to note that the *cis*-isomer of **22**, which is expected to be thermodynamically less stable, was also formed in the reaction. Compound **22** was transformed into the target bicyclo[3.3.1]nonane **23** in 95% yield by treatment with trifluoroacetic acid (Scheme 5).



Scheme 3



Scheme 4



Scheme 5

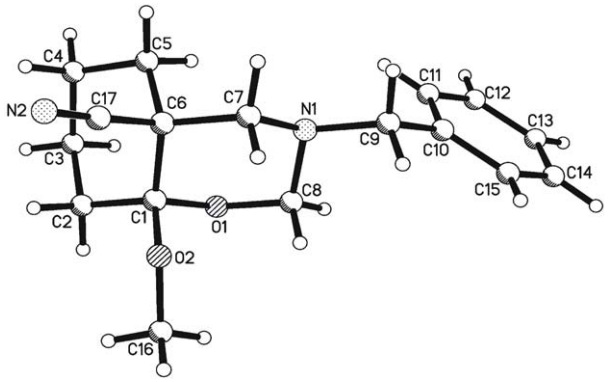
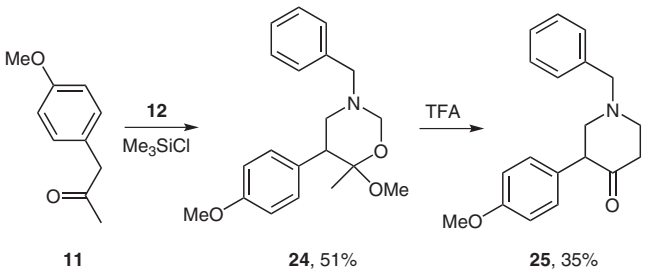


Figure 3 Molecular structure of compound **22**

An analogous reaction of **12** with (4-methoxyphenyl)acetone (**11**) led to the formation of 1,3-oxazinane derivative **24** (51%; Scheme 6). As in the case of **22**, compound **24** was transformed into piperidone **25** in 35% yield by treatment with trifluoroacetic acid.



Scheme 6

To conclude, chlorotrimethylsilane-promoted double Mannich annulation of ketones using *N*,*N*-bis(methoxymethyl)benzylamine is an efficient method for the construction of azabicyclo[*n*.3.1]alkane systems (*n* = 2–5). The structure of the substrate is crucial for the outcome of the process: whereas classical Mannich bases are formed

in the case of higher cycloalkanones and γ-pyranone, the reaction of cyclopentanone, cyclohexanone and 4-methoxyphenylacetone is complicated by ketal or 1,3-oxazinane formation.

Solvents were purified according to standard procedures. All starting materials were purchased from Acros, Merck or Fluka. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H, ^{13}C NMR, and all 2D NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (499.9 MHz for ^{1}H, 124.9 MHz for ^{13}C). Chemical shifts (δ) are reported in ppm downfield from TMS (^{1}H, ^{13}C) as an internal standard. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (CI) and Agilent 5890 Series II 5972 GCMS instrument (EI). Elemental analyses were performed on an Elementar Vario MICRO Cube CHNS/O analyzer. Flash chromatography was performed using a Buchi Fraction Collector C-660 (5–6 bar, 460 × 36 mm column, silica gel).

2-Cyanocyclohexanone (8)

Heptanedinitrile (70 g) was added to a suspension of NaH (25 g) in anhydrous THF (1.2 L). The resulting mixture was refluxed for 10 h (reaction monitored by TLC), cooled to r.t., quenched with MeOH (60 mL), stirred for 30 min, and evaporated in vacuo. The residue was dissolved in a mixture of H_2SO_4 (90 g) and H_2O (550 mL) and the solution was stirred at r.t. for 30 min, then extracted with Et_2O (3 × 350 mL). The combined organic extracts were evaporated under reduced pressure and the residue was distilled in vacuo (81–83 °C/1 mmHg) to give 2-cyanocyclohexanone (**8**; 51.5 g, 73%) as a pale-yellow oil. The spectral and physical data were in agreement with those previously reported.[9]

***N*,*N*-Bis(methoxymethyl)benzylamine (12)**

The procedure used was essentially the same as that reported for the synthesis of *N*,*N*-bis(ethoxymethyl)benzylamine.[6b] Anhydrous K_2CO_3 (387 g) was added to a mixture of anhydrous MeOH (675 g) and paraformaldehyde (273 g). Then benzylamine (300 g) was added over a period of 1.5 h, and the resulting mixture was stirred for 48 h. The crude reaction mixture was filtered to remove all the solids and evaporated in vacuo. The residue was suspended in anhydrous CH_2Cl_2 (1 L) and filtered. The combined filtrates were evaporated, and the residue was distilled in vacuo (102–103 °C/1 mmHg) to give amine **12**.

Yield: 339 g (62%).

^{1}H NMR ($CDCl_3$): δ = 7.36 (m, 4 H, *o*-PhH and *m*-PhH), 7.28 (m, 1 H, *p*-PhH), 4.26 (s, 4 H, NCH_2OCH$_3$), 4.03 (s, 2 H, PhCH_2), 3.30 (s, 6 H, OCH_3).

^{13}C NMR ($CDCl_3$): δ = 138.6 (PhC-1), 128.6 (CH), 128.0 (CH), 126.8 (CH), 85.5 (NCH_2OCH$_3$), 54.6 (OCH_3), 52.4 (PhCH_2N).

MS: *m*/*z* = 195 [M$^+$], 164, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.95; H, 8.41; N, 6.92.

Reaction of *N*,*N*-Bis(methoxymethyl)benzylamine (12) with Ketones 5–11; Typical Procedure

Chlorotrimethylsilane (91 g, 0.83 mol) was added to a mixture of 2-cyanocyclohexanone (**8**; 51.5 g, 0.42 mol) and *N*,*N*-bis(methoxymethyl)benzylamine (**12**; 163g, 0.83 mol) in MeCN (660 mL). The mixture was stirred under an atmosphere of nitrogen at r.t. for 96 h, then quenched with sat. aq $NaHCO_3$ (450 mL). The aqueous layer was extracted with EtOAc (3 × 450 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product (145 g) was recrystallized twice from hexane to obtain **22**.

3-Benzyl-8a-methoxyoctahydro-1,3-benzoxazine-4a-carbonitrile (22)

Yield: 9 g (66%); white powder; mp 81–82 °C.

^{1}H NMR ($CDCl_3$): δ = 7.22 (m, 5 H, PhH), 4.06 (d, *J* = 7.6 Hz, 1 H, 2-C*H*H), 4.00 (d, *J* = 7.6 Hz, 1 H, 2-CH*H*), 3.52 (d, *J* = 13.1 Hz, 1 H, C*H*HPh), 3.34 (d, *J* = 13.1 Hz, 1 H, CH*H*Ph), 3.20 (s, 3 H, OCH_3), 2.97 (d, *J* = 12.0 Hz, 1 H, 4-C*H*H), 2.56 (m, 2 H, 8-CH_2), 2.13 (d, *J* = 12.0 Hz, 1 H, 4-CH*H*), 1.58–1.69 (m, 3 H), 1.49–1.58 (m, 2 H), 1.38–1.48 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 131.2 (*ipso*-PhC), 128.6 (CH), 127.6 (CH), 127.5 (CH), 121.5 (CN), 96.9 (8a-C), 78.0 (2-CH_2), 57.0 (CH_2Ph), 54.3 (4-CH_2), 47.8 (OCH_3), 42.3 (4a-C), 31.6 (CH_2), 31.1 (CH_2), 22.5 (CH_2), 21.9 (CH_2).

MS: *m*/*z* = 254 [M$^+$], 163, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 71.76; H, 7.63; N, 10.01.

8-Benzyl-8-azabicyclo[4.3.1]decan-10-one (13)

Prepared from cycloheptanone **9** and purified by flash chromatography ($CHCl_3$–EtOAc, 9:1).

Yield: 15.6 g (46%); mp 66 °C (hexane).

^{1}H NMR ($CDCl_3$): δ = 7.34 (m, 4 H, *o*-PhH and *m*-PhH), 7.25 (t, *J* = 6.8 Hz, 1 H, *p*-PhH), 3.49 (s, 2 H, NCH_2Ph), 2.82 [d, *J* = 11.2 Hz, 2 H, *endo*-7(9)-C*H*H], 2.60 (t, *J* = 3.4 Hz, 2 H, 1- and 6-CH), 2.41 [dd, *J* = 11.2, 3.4 Hz, 2 H, *exo*-7(9)-CH*H*], 2.05 (m, 2 H), 1.77 (m, 2 H), 1.58 (m, 2 H), 1.42 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 212.9 (C=O), 138.4 (PhC-1), 128.9 (CH), 128.2 (CH), 127.0 (CH), 62.7 (CH_2), 59.5 (CH_2), 48.6 (1-CH and 6-CH), 31.2 (CH_2), 26.7 (CH_2).

MS: *m*/*z* = 243 [M$^+$], 152, 120, 106, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.35; H, 8.38; N, 6.01.

9-Benzyl-9-azabicyclo[5.3.1]undecan-11-one (14)

Prepared from cyclooctanone **10** and purified by flash chromatography (hexane–EtOAc, 9:1).

Yield: 11.2 g (45%); oil.

^{1}H NMR ($CDCl_3$): δ = 7.39 (d, *J* = 7.3 Hz, 2 H, *o*-PhH), 7.35 (t, *J* = 7.3 Hz, 2 H, *m*-PhH), 7.28 (t, *J* = 7.3 Hz, 1 H, *p*-PhH), 3.58 (s, 2 H, NCH_2Ph), 2.84 (d, *J* = 11.2 Hz, 2 H, 8- and 10-C*H*H), 2.44 (d, *J* = 11.2 Hz, 2 H, 8- and 10-CH*H*), 2.35 (m, 4 H), 1.89 (m, 2 H), 1.80 (m, 2 H), 1.67 (m, 1 H, 4-C*H*H), 1.33 (m, 1 H, 4-CH*H*), 1.25 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 217.6 (C=O), 138.9 (PhC-1), 128.9, 128.3, 127.2, 62.2 (NCH_2Ph), 58.5 (8- and 10-CH_2), 50.6 (1- and 7-CH), 31.3 (CH_2), 24.6 (CH_2).

MS: *m*/*z* = 257 [M$^+$], 166, 120, 106, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.61; H, 8.77; N, 5.50.

3-Benzyl-8,8-dimethoxy-3-azabicyclo[3.2.1]octane (15)

Prepared from cyclopentanone **5**.

Yield: 4.8 g (18%); mp 58 °C (hexane).

^{1}H NMR ($CDCl_3$): δ = 7.25 (d, *J* = 7.2 Hz, 2 H, *o*-PhH), 7.20 (t, *J* = 7.2 Hz, 2 H, *m*-PhH), 7.13 (t, *J* = 7.2 Hz, 1 H, *p*-PhH), 3.45 (s, 2 H, NCH_2Ph), 3.16 (s, 3 H, OCH_3), 3.10 (s, 3 H, OCH_3), 2.44 [dd, *J* = 10.4, 2.7 Hz, 2 H, *endo*-2(4)C*H*H], 2.35 [d, *J* = 10.4 Hz, 2 H, *exo*-2(4)C*H*H], 1.98 (s, 2 H, 1- and 5-CH), 1.63 (m, 4 H, 6- and 7-CH_2).

^{13}C NMR ($CDCl_3$): δ = 140.0 (PhC-1), 128.6 (CH), 128.1 (CH), 126.7 (CH), 108.2 (C-8), 61.6 (CH_2), 55.2 (CH_2), 49.2 (OCH_3), 47.4 (OCH_3), 38.2 (CH), 25.8 (CH_2).

MS: *m*/*z* = 261 [M^+], 230 [$M^+ - OCH_3$], 215, 198, 170, 134, 101, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.82; H, 8.69; N, 5.16.

3-Benzyl-9,9-dimethoxy-3-azabicyclo[3.3.1]nonane (16)
Prepared from cyclohexanone **6**.

Yield: 20.4 g (80%); mp 88 °C (hexane).

^{1}H NMR ($CDCl_3$): δ = 7.36 (m, 4 H, *o*-PhH and *m*-PhH), 7.27 (m, 1 H, *p*-PhH), 3.45 (s, 2 H, NCH_2Ph), 3.22 (s, 3 H, OCH_3), 3.21 (s, 3 H, OCH_3), 2.79 (d, *J* = 10.4 Hz, 2 H, 2- and 4-C*H*H), 2.74 (m, 1 H, 7-C*H*H), 2.55 (d, *J* = 10.4 Hz, 2 H, 2- and 4-CH*H*), 1.99 (s, 2 H, 1- and 5-CH), 1.92 (m, 2 H, 6- and 8-C*H*H), 1.70 (m, 2 H, 6- and 8-CH*H*), 1.50 (m, 1 H, 7-CH*H*).

^{13}C NMR ($CDCl_3$): δ = 139.9 (PhC-1), 128.6 (CH), 128.2 (CH), 126.7 (CH), 100.2 (C-9), 63.2 (CH_2), 56.3 (CH_2), 46.7 (OCH_3), 46.4 (OCH_3), 34.8 (CH), 28.3 (CH_2), 21.0 (CH_2).

MS: *m*/*z* = 275 [M^+], 244 [$M^+ - OCH_3$], 212, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.98; H, 9.23; N, 4.87.

***N*-Benzylidenebenzylamine (17)**
Isolated as a by-product in the synthesis of **15** (4.5 g, 23%) by flash chromatography of the mother liquor obtained after recrystallization (hexane–EtOAc, 9:1). The spectral and physical data were in agreement with those previously reported.[10]

3-Benzyl-6-methoxy-5-(4-methoxyphenyl)-6-methyl[1,3]oxazinane (24)
Prepared from 1-(4-methoxyphenyl)propan-2-one (**11**) using **12** (2.2 equiv) and chlorotrimethylsilane (2.2 equiv) and purified by flash chromatography ($CHCl_3$–EtOAc, 4:1).

Yield: 16.4 g (51%); oil.

^{1}H NMR ($CDCl_3$): δ = 7.43 (d, *J* = 7.2 Hz, 2 H, *o*-PhH), 7.37 (t, *J* = 7.2 Hz, 2 H, *m*-PhH), 7.31 (m, 3 H), 6.88 (d, *J* = 8.6 Hz, 2 H, 3′-ArH and 5′-ArH), 4.70 (d, *J* = 9.2 Hz, 1 H, 2-C*H*H), 4.25 (d, *J* = 9.2 Hz, 1 H, 2-CH*H*), 4.05 (d, *J* = 13.2 Hz, 1 H, C*H*HPh), 3.72 (d, *J* = 13.2 Hz, 1 H, CH*H*Ph), 3.82 (s, 3 H, $ArOCH_3$), 3.51 (m, 1 H), 3.30 (s, 3 H, 6-OCH_3), 3.27 (m, 1 H), 2.78 (dd, *J* = 11.7, 1.7 Hz, 1 H), 1.31 (s, 3 H, 6-CH_3).

^{13}C NMR ($CDCl_3$): δ = 158.6 (4′-ArC), 138.7 (C), 131.7 (C), 130.6 (CH), 129.0 (CH), 128.4 (CH), 127.2 (CH), 113.4 (CH), 99.8 (C-6), 76.8 (2-CH_2), 56.0 (CH_2Ph), 55.2 ($ArOCH_3$), 51.2 (4-CH_2), 48.0 (6-OCH_3), 46.5 (5-CH), 21.8 (CH_3).

MS: *m*/*z* = 296 [$M^+ - OCH_3$], 176, 133, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found: C, 73.11; H, 8.01; N, 4.47.

3-Benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carbonitrile (23)
Nitrile **22** (53.7 g, 0.188 mol) was dissolved in TFA (160 g) and stirred overnight. The excess acid was removed in vacuo, and the residue was adjusted to pH 8 with sat. aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 250 mL) and the combined extracts were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (hexane–EtOAc, 9:1) to give ketone **23**.

Yield: 13.5 g (28%); mp 92–94 °C (hexane).

^{1}H NMR ($CDCl_3$): δ = 7.28 (m, 2 H, PhH), 7.22 (m, 3 H, PhH), 3.48 (d, *J* = 12.3 Hz, 1 H, C*H*HPh), 3.41 (d, *J* = 12.3 Hz, 1 H, CH*H*Ph), 3.33 (d, *J* = 11.4 Hz, 1 H, 2-C*H*H), 3.09 (d, *J* = 11.6 Hz, 1 H, 4-C*H*H), 2.92 (m, 1 H, 7-C*H*H), 2.71 (d, *J* = 11.4 Hz, 1 H, 2-CH*H*), 2.56 (d, *J* = 11.6 Hz, 1 H, 4-CH*H*), 2.45 (m, 2 H, 5-C*H* and 8-C*H*H), 2.23 (m, 1 H, 8-CH*H*), 2.08 (m, 1 H, 6-C*H*H), 1.99 (m, 1 H, 6-CH*H*), 1.55 (m, 1 H, 7-CH*H*).

^{13}C NMR ($CDCl_3$): δ = 206.4 (C=O), 137.2 (PhC-1), 128.8, 128.7, 127.7, 118.2 (C≡N), 62.2 (2-CH_2), 61.5 (CH_2Ph), 59.5 (4-CH_2), 49.8 (1-CH), 46.2 (5-CH), 38.8 (8-CH_2), 33.6 (6-CH_2), 20.8 (7-CH_2).

MS: *m*/*z* = 254 [M^+], 163, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.69; H, 7.33; N, 10.78.

3-Benzyl-3-azabicyclo[3.2.1]octan-8-one (18)
Prepared from **15** analogously to 3-benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carbonitrile (**23**) and purified by flash chromatography (hexane–EtOAc, 9:1). The spectral and physical data were in agreement with those previously reported.[11]

Yield: 3.3 g (95%).

3-Benzyl-3-azabicyclo[3.3.1]nonan-9-one (19)
Prepared from **16** analogously to 3-benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carbonitrile (**23**) and purified by flash chromatography (hexane–EtOAc, 9:1). The spectral and physical data were in agreement with those previously reported.[11]

Yield: 9.4 g (96%); mp 51 °C (hexane).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.64; H, 8.06; N, 6.13.

7-Benzyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-one (20)
Prepared from **17** analogously to 3-benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carbonitrile (**23**) and purified by flash chromatography (hexane–EtOAc, 7:3). The spectral and physical data were in agreement with those previously reported.[12]

Yield: 10.3 g (68%)

1-Benzyl-3-(4-methoxyphenyl)piperidin-4-one (25)
Prepared from **24** analogously to 3-benzyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carbonitrile (**23**) and purified by flash chromatography (hexane–EtOAc, 4:1).

Yield: 3.7 g (35%); oil.

^{1}H NMR ($CDCl_3$): δ = 7.29–7.52 (m, 5 H, PhH), 7.26 (d, *J* = 8.6 Hz, 2 H, ArH), 6.97 (d, *J* = 8.6 Hz, 2 H, ArH), 3.85 (m, 1 H), 3.83 (s, 3 H, OCH_3), 3.73 (s, 2 H, NCH_2Ph), 3.24 (m, 1 H), 3.11 (m, 1 H), 2.85 (m, 1 H), 2.72 (m, 2 H), 2.58 (m, 1 H).

^{13}C NMR ($CDCl_3$): δ = 208.1 (C=O), 158.7 (4-ArCH), 138.2 (2 C), 130.0 (CH), 129.1 (CH), 128.6 (CH), 127.5 (CH), 114.0 (CH), 62.0 (CH_2), 60.2 (CH_2), 55.6 (3-CH), 55.3 (OCH_3), 53.6 (CH_2), 40.7 (5-CH_2).

MS: *m*/*z* = 295 [M^+], 134, 121, 91 [$C_7H_7^+$].

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.02; H, 6.98; N, 4.93.

X-ray Diffraction Data for 22
Crystals for X-ray diffraction studies were obtained by crystallization from MeCN. Empirical formula: $C_{17}H_{22}N_2O$; triclinic; 293 K; cell dimensions: *a* = 6.4829(5) Å, *b* = 10.9024(8) Å, *c* = 11.5044(8) Å, *α* = 74.398(6)°, *β* = 84.750(6)°, *γ* = 76.232(7)°; *V* = 760.3(1) Å^3; M_r = 286.37; *Z* = 2; space group $P\bar{1}$; D(calcd) = 1.251 g/cm^3; μ(MoK_α) = 0.082 mm^{-1}; *F*(000) = 308. Intensity of 7199 reflections (3478 independent, R_{int} = 0.017) were measured on an automatic Xcalibur 3 diffractometer (graphite

monochromated MoK_α radiation, CCD-detector, ω scanning, $2\Theta_{max} = 55°$).

The structure was solved by direct methods using the SHELX97 package.[13] Positions of hydrogen atoms were located from electron-density difference maps and refined using the isotropic model. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms was converged to $wR_2 = 0.091$ for 3430 reflections ($R_1 = 0.035$ for 2203 reflections with $I>4\sigma(I)$, $S = 0.892$). Final atomic coordinates, geometrical parameters and crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk] and are available on request quoting the deposition number CCDC 741371.

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