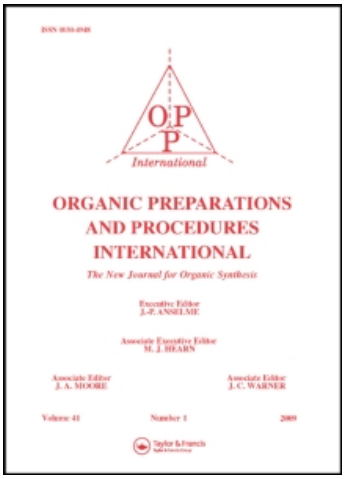

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IMPROVED SYNTHESIS OF 8-METHYL-3, 8-DIAZABICYCLO [3.2.1] OCTANE

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IMPROVED SYNTHESIS OF 8-METHYL-3,8-DIAZABICYCLO[3.2.1]OCTANE

Submitted by (08/10/06)

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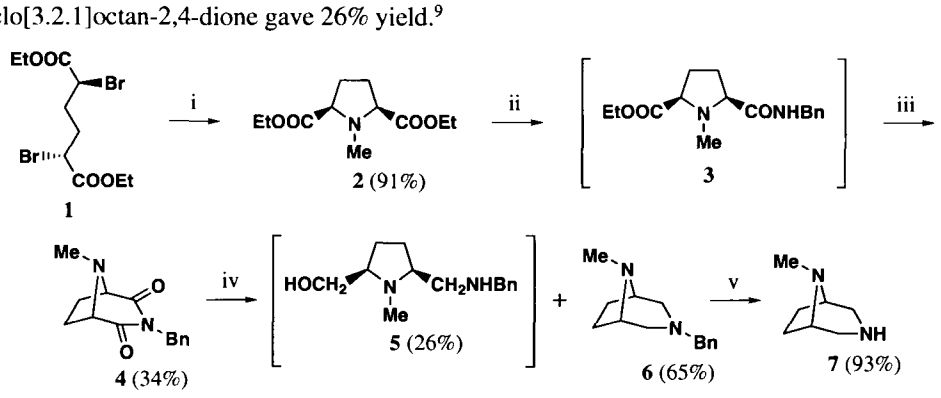
Although monosubstituted 3,8-diazabicyclo[3.2.1]octanes are important starting materials for the preparation of compounds possessing analgesic activity,[1-4] methods for their synthesis remain poorly investigated. 8-Methyl-3,8-diazabicyclo[3.2.1]octane (**7**) has previously been prepared in seven-[5,6] or eight-step[7] procedures from diethyl *meso*-2,5-dibromoadipoate (**1**) in about 13% and 12% overall yield, respectively. We now describe the preparation of **7** from the same starting material by a four-step procedure in 19% overall yield.

Our procedure starts from the preparation of diethyl *cis*-1-methylpyrrolidine dicarboxylate (**2**), which was previously obtained in 35% yield by heating diethyl *meso*-2,5-dibromoadipoate with methylamine in benzene followed by fractional distillation.[8] We found that compound **2** can be easily synthesized in a similar manner with significantly higher yield (91%) if the reaction is carried out in THF instead of benzene. The second and most difficult step of the synthetic route was the cyclization leading to the novel intermediate 3-benzyl-8-methyl-3,8-diazabicyclo[3.2.1]octan-2,4-dione (**4**). A solution of compound **2** and benzylamine in xylene was refluxed for 16 hours. Amide **3** was identified as the main reaction intermediate. After evaporation of the solvent, the temperature was raised to 210°C. After 18 h of heating, the reaction mixture was allowed to cool to room temperature. The crude product was distilled under vacuum (0.1 mbar, 180°C) using a Büchi oven. The material obtained solidified and was recrystallized from ethyl acetate-hexane to afford 3-benzyl-8-methyl-3,8-diazabicyclo[3.2.1]octan-2,4-dione (**4**) in 34% yield. A similar procedure for the synthesis of 3-benzyl-8-ethyl-3,8-diazabicyclo[3.2.1]octan-2,4-dione gave 26% yield.[9]



i) methylamine, THF, 0 → 20°C, 18 h; ii) benzylamine, xylene, reflux, 16 h; iii) 210°C, 18 h; iv) $LiAlH_4$, dioxane, reflux, 18 h; v) H_2, Pd/C, methanol, 40°C, 3 h

Reduction of compound **4** was carried out with $LiAlH_4$ in boiling dioxane to afford **6** in 65% yield. The reaction gave side-product **5**, whose formation could be explained by cleavage of the carbon-nitrogen bond of the lactam at the stage of the tetrahedral intermediate after hydride attack. The synthesis of compound **6** by methylation of 3-benzyl-3,8-diazabicyclo[3.2.1]octane with formaldehyde in formic acid is described in the literature.[6] Hydrogenolysis of compound **6** in methanol (Pd/C) gave the target compound **7** in 93% yield.

EXPERIMENTAL SECTION

Mps were determined in open capillary tubes on a Büchi B-540 melting point apparatus and are uncorrected. Infrared spectra were recorded as KBr pellets in a Perkin Elmer FT-IR Spectrum GX spectrometer. ^1H NMR spectra were obtained at 300 MHz on a Variant Inova spectrometer; ^{13}C NMR spectra were determined at 75.4 MHz. Chemical shifts are expressed in δ ppm, relative to TMS. Vacuum distillations were performed using a Büchi Model B580 GKR oven.

Diethyl *cis*-1-Methylpyrrolidine-2,5-dicarboxylate (2).- Diethyl *meso*-2,5-dibromoadipoate (**1**) (203.4 g, 0.566 mol) was placed into a three necked round bottom flask (2000 mL) fitted with a reflux condenser, a thermometer and a dropping funnel and dissolved in absolute THF (600 mL) at 0°C under argon. A precooled (0°C) solution of methylamine (54.6 g, 1.76 mol) in absolute THF (300 mL) was added dropwise to the solution of **1** maintaining the reaction temperature below 20°C with the ice bath. Then the reaction mixture was stirred at room temperature for 18 h, the separated methylammonium bromide was removed by filtration and washed thoroughly with THF. The filtrate was concentrated on a rotary evaporator under reduced pressure and the residue was purified on a silica gel chromatographic column with hexane-ethyl acetate (4:1) as eluent. The collected eluate (4 L) was concentrated under reduced pressure, and the residue was dried with stirring at room temperature *in vacuo* for 1 h to yield 117.8 g (91%) of a colorless oil. The product, when stored below 4°C, crystallized fully, while at 12°C it is in equilibrium with a liquid phase.

^1H NMR ($CDCl_3$): δ 1.15 (t, J = 7.2 Hz, 6H, 2 x CH_2CH_3), 1.90-2.10 (m, 4H, H-3, H-4), 2.43 (s, 3H, NCH_3), 3.00-3.10 (m, 2H, H-2, H-5), 4.13 (q, J = 7.2 Hz, 4H, 2 x CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 14.06 (CH_2CH_3), 27.79 (C-3, C-4), 40.96 (NCH_3), 60.57 (CH_2CH_3), 68.15 (C-2, C-5), 172.48 (C=O).

3-Benzyl-8-methyl-3,8-diazabicyclo[3.2.1]octane-2,4-dione (4).- A solution of diethyl *cis*-1-methylpyrrolydine-2,5-carboxylate (85.3 g, 0.372 mol) and benzylamine (41.0 g, 0.383 mol) in xylene (150 mL) was refluxed in a round-bottomed flask (250 mL) for 16 h. The latter was equipped with a vertical air condenser (15 cm) followed by a Liebig condenser, allowing removal of ethanol from the reaction mixture. The xylene was removed under reduced pressure through the Liebig condenser, then the oil bath temperature was raised to 210°C and the residue was heated under argon for 18 h. The product obtained was distilled in three portions (about 35 g each) using a Büchi oven *in vacuo* (0.1 mbar) at 180°C (average distillation time - 1 h) collecting

the fraction from the terminal (third) oven flask. The three combined third fractions were dissolved by boiling in a mixture of ethyl acetate-hexane 1:1 and allowed to crystallize at room temperature for 3 days. The crystalline material was collected, washed with a small amount of ethyl acetate and dried *in vacuo* to afford 28.3 g of the target product as a white crystalline solid. The filtrate was concentrated and the residue crystallized from ethyl acetate (50 mL) at 4°C for 2 days to yield 2.6 g of the same product. The total yield of compound **4** was 30.9 g (34%), mp. 104-105°C. IR (KBr): 1724, 1673 cm^{-1} (C=O, imides); ^1H NMR ($CDCl_3$): δ 1.84-1.92 (m, 2H, H-6, H-7), 2.30-2.40 (m, 2H, H-6, H-7), 2.42 (s, 3H, NCH_3), 3.78-3.83 (m, 2H, H-1, H-5), 4.88 (s, 2H, CH_2Ph), 7.22-7.40 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$): δ 26.69 (C-6, C-7), 35.82 (NCH_3), 41.26 (CH_2Ph), 65.72 (C-1, C-5), 127.42, 128.36 (2C), 128.62 (2C), 136.91 (C-Ph), 173.26 (C-2, C-4).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.73; H, 6.68; N, 11.31.

Ethyl *cis*-5-[(Benzylamino)carbonyl]-1-methylpyrrolidine-2-carboxylate (3) was obtained by removal of a sample of the above reaction mixture (0.5 g) after 16 h of heating and evaporation of xylene (see the synthesis of compound **4** described above). Purification of the sample on a silica gel column with ethyl acetate-hexane 1:1 as eluent, afforded 0.24 g of compound **3** as a yellowish oil.

^1H NMR ($CDCl_3$): δ 1.14 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.70-2.30 (m, 4H, H-3, H-4), 2.41 (s, 3H, NCH_3), 3.20-3.35 (m, 2H, H-2, H-5), 4.08 (q, J = 7.0 Hz, 2H, CH_2CH_3), 4.44 (d, J = 6.2 Hz, 2H, $NHCH_2$), 7.16-7.32 (m, 5H, ArH), 8.23 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.73 (CH_2CH_3), 29.60, 30.02 (C-3, C-4), 40.70, 42.43 (CH_2NH, NCH_3), 60.51 (CH_2CH_3), 68.02, 69.32 (C-2, C-5), 126.76 (2C), 126.92 (2C), 128.17, 138.32 (C-Ph), 173.63, 173.72 (COO, CONH).

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.02; H, 7.52; N, 9.75.

Methyl *cis*-1-Benzyl-5-[(benzylamino)carbonyl]pyrrolidine-2-carboxylate (5) and 3-Benzyl-8-methyl-3,8-diazabicyclo[3.2.1]octane (6).- To a solution of compound **4** (28.3 g, 0.116 mol) in 1,4-dioxane (200 mL) in a three-necked round bottom flask (500 mL), was added $LiAlH_4$ (7.6 g, 0.2 mol) in small portions and the mixture refluxed under argon for 18 h. The reaction mixture was cooled to 80°C and a mixture of water (7.5 mL) and 1,4-dioxane (40 mL) was dropped carefully into reaction flask (CAUTION: vigorous hydrogen evolution). A finely suspended solid was filtered off using a fritted glass Büchner funnel, the solid material was washed with 1,4-dioxane and the combined filtrate was concentrated under reduced pressure. The residue was distilled using a Büchi oven *in vacuo* (0.1 mbar) at 120°C. The third collection flask contained 3,8-diazabicyclo[3.2.1]octane **6** (16.3 g, 65%) as a viscous colorless oil (dipicrate mp. 223-226°C, *lit.*[9] dipicrate mp. 228-230°C), while the second collection flask furnished the side-product **5** as a viscous colorless oil (7.1 g, 26%).

Compound **6**. ^1H NMR ($CDCl_3$): δ 1.80-1.98 (m, 4H, 6-H, 7-H), 2.28 (s, 3H, CH_3), 2.34 (d, J = 9.5 Hz, 2H, 2-H, 4-H), 2.58 (dd, J_1= 11.1 Hz, J_2 = 3.1 Hz, 2H, H-2, H-4), 3.05 (m, 2H, H-1, H-5), 3.48 (s, 2H, CH_2N), 7.20-7.36 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 25.56 (C-6, C-7), 40.65

(CH_3), 58.66 (C-2, C-4), 61.44, 61.69 (C-1, C-5, CH_2N), 126.58 (2C), 127.94 (2C), 128.44, 139.08 (C-Ph).

Anal. Calcd. for $C_{14}H_{20}N_2$: 77.73; H, 9.32; N, 12.95. Found: C, 77.64; H, 9.59; N, 13.05.

Compound **5**. IR (KBr): 3400 (OH and NH); ^1H NMR ($CDCl_3$): δ 1.57-1.97 (m, 4H, H-3, H-4), 2.28 (s, 3H, C*H*$_3$), 2.52-2.68 (m, 3H, H-2, H-5, C*H*NHCH$_2$Ph), 2.70-2.80 (m, 1H, C*H*NHCH$_2$Ph), 3.43 (dd, J_1 = 11.0 Hz, J_2 = 2.6 Hz, 1H, CH*H*OH), 3.63 (dd, J_1 = 11.0 Hz, J_2 = 3.8 Hz, 1H, C*H*HOH), 3.79-3.88 (AB-q, J = 13.5 Hz, 2H, CH_2Ph), 7.22-7.39 (m, 5H, Ph). ^{13}C NMR ($CDCl_3$): δ 26.09 (C-3), 28.23 (C-4), 39.58 (CH_3), 52.38 (*C*H$_2$NHCH$_2$Ph), 54.16 (CH$_2$NH*C*H$_2$Ph), 61.67 (C-5), 66.58 (CH_2OH), 67.45 (C-2), 126.76 (2C), 127.88 (2C), 128.23, 140.32 (C-Ph).

Anal. Calcd. for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95. Found: C, 71.65; H, 9.34; N, 11.75.

8-Methyl-3,8-diazabicyclo[3.2.1]octane (7).- To a solution of compound **6** (16.3 g, 0.075 mol) in freshly distilled methanol (40 mL) was added 10% Pd/C catalyst (0.8 g) under argon. The solution was hydrogenated with H_2 at ambient pressure and 40°C for 3 h. The solution was filtered through a layer of Celite, and the filtrate was concentrated under reduced pressure on a rotary evaporator and the residue distilled on Büchi oven *in vacuo* (0.1 mbar) at 90°C to afford compound **7** (8.85 g, 93%) as a viscous colorless oil (dipicrate mp. 262-265°C, *lit.*[9] dipicrate mp. 247-250°C).

^1H NMR ($CDCl_3$): δ 1.49-1.57 (m, 2H, H-6, H-7), 1.68 (s, 1H, N*H*), 1.82-1.89 (m, 2H, H-6, H-7), 2.10 (s, 3H, C*H*$_3$), 2.42-2.49 (m, 2H, H-2, H-4), 2.81-2.88 (m, 4H, H-1, H-2, H-4, H-5). ^{13}C NMR ($CDCl_3$): δ 24.73 (C-6, C-7), 41.72 (CH_3), 52.10 (C-2, C-4), 62.08 (C-1, C-5).

Anal. Calcd. for $C_7H_{14}N_2$: C, 66.62; H, 11.18; N, 22.20. Found: C, 66.54; H, 11.13; N, 22.33.

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AN IMPROVED IODINATION OF 2-AMINO-5-NITROBENZONITRILE

Submitted by (08/18/06)

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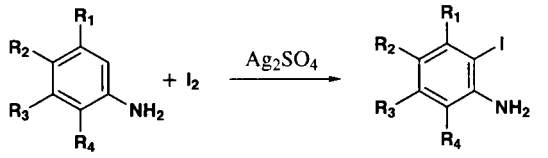
Aryl iodides are important intermediates in organic synthesis,[1-3] especially in the Heck reaction as well as the Stille and the Negishi cross-couplings. However, some of aryl iodides are not commercially available. Those that are available are too expensive for practical application. In the course of our current research program, we required several iodoaromatic amines as substrates for the Sonogashira cross-coupling reaction.[4]



1 2

a) $R_1 = R_3 = R_4 = H$, $R_2 = NO_2$
b) $R_1 = R_3 = H$, $R_2 = COOC_2H_5$, $R_4 = NO_2$
c) $R_1 = R_3 = H$, $R_2 = NO_2$, $R_4 = CN$
d) $R_1 = R_3 = R_4 = H$, $R_2 = COOC_2H_5$
e) $R_1 = R_4 = H$, $R_2 = COOCH_3$, $R_3 = Cl$
f) $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
g) $R_1 = R_2 = R_3 = R_4 = H$
h) $R_1 = R_3 = R_4 = H$, $R_2 = Cl$
i) $R_1 = R_3 = R_4 = H$, $R_2 = F$

Initially, we attempted the synthesis of these compounds by treatment of aromatic amines with iodine in the presence of silver sulfate.[5] Although ordinary iodoaromatic amines (**2a**, **2b** and **2d**) were obtained under the reported conditions,[5, 6] we could not obtain **2c** in greater than 29% yield and **2c** was contaminated with iodine. Attempts to modify this procedure using other catalysts such as silver nitrite[7] or adding more of silver salts and varying the reaction time were also unsuccessful. Finally, we found that yield of **2c** was dramatically improved (70%) by