Convenient Synthesis of 3,7-Diazabicyclo[3.3.1]nonane (Bispidine)

Yuji Miyahara,* Kenta Goto, Takahiko Inazu*

Department of Chemistry, Faculty of Science, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan
Fax +81(92)6422607; E-mail: miyahscc@mbox.nc.kyushu-u.ac.jp

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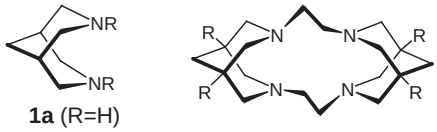
Abstract: Bispidine **1a** is conveniently synthesized via a route involving double Mannich reaction of 1-allylpiperidin-4-one to *N*,*N*′-diallylbispidinone, Wolff–Kishner reduction of the bispidinone, and deallylation of the resulting *N*,*N*′-diallylbispidine by treatment with ethyl chloroformate in the presence of NaI, followed by alkaline hydrolysis.

Key words: bicyclic compounds, Dieckman condensation, double Mannich reaction, deallylation



1a (R=H)
1b (R=CH_2Ph)
1c (R=$CH_2CH{=}CH_2$)
1d (R=CO_2Et)
1e (R=Me)

2a (R=H)
2b (R=Ph)

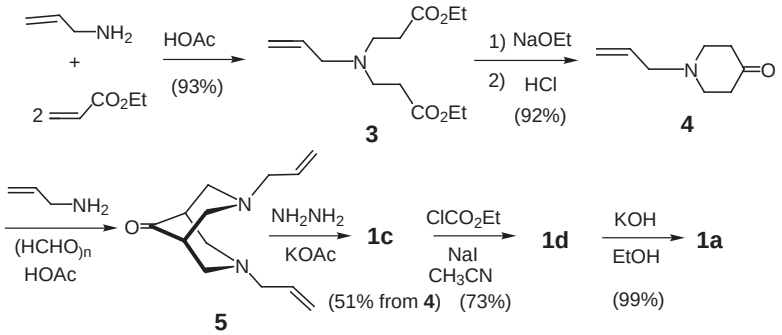
Since 1950s when several competing research groups developed several synthetic routes for 3,7-diazabicyclo[3.3.1]nonane (**1a**) (commonly known as bispidine) using pyridine-3,5-dicarboxylic acid as the common starting material,[1] many *N*-alkyl derivatives of bispidine have been synthesized,[2] in particular, because of their resemblance to useful chiral diamine (−)-sparteine.[3] In our search for systems where many nitrogen lone pairs are accumulated in a small molecular space, we have synthesized a macrocyclic tetramine with two 1,5-diphenylbispidine units **2b**.[4]

Although the molecule showed very interesting properties, the four phenyl groups in the molecule were found to have deleterious, rather than beneficial, effect on its solubility, which made further studies difficult. Therefore, we decided to synthesize the parent ring system **2a**.[5] Since pyridine-3,5-dicarboxylic acid originally used is expensive and tedious to prepare and the route starting from readily available tetraethyl propane-1,1,3,3-tetracarboxylate is too inefficient in the last cyclization,[6] we first tried a more recently developed route involving double Mannich reaction of 1-benzyl-4-pyridinone.[7] However, the hydrogenolysis of the resulting *N*,*N*′-dibenzylbispidine **1b** using 10% Pd-C under strongly acidic conditions at 60 °C not only required long reaction times, but often led to total recovery in larger scale reactions. We tried also 1-chloroethyl chloroformate[8] and Na in liquid NH_3[9] for the debenzylation without success.

In view of the recent advances in deallylation utilizing Rh[10] or Pd[11] catalysts, we turned to the use of allyl groups as the protective groups for the nitrogens. However, after all the synthetic route is as shown in the Scheme for the reasons described below.

Bis(carbethoxyethyl)allylamine (**3**), obtained in 93% yield by Michael addition of ethyl acrylate on allylamine in the presence of HOAc, was cyclized by Dieckman condensation using NaOEt. Acidic hydrolysis and decarboxylation of the condensation product readily provided 1-allylpiperidin-4-one (**4**) in 92% yield.

Since the reportedly best method for the double Mannich reaction requires long reaction times (15 days) at room temperature,[7] we searched for better reaction conditions by changing reagents, solvents, reaction temperature and time. Thus, we found that when paraformaldehyde (2.2 mol), **4** (1 mol), allylamine (1.1 mol), and HOAc (2.1 mol) in EtOH were heated at 55–60 °C, the condensation reaction proceeded smoothly as paraformaldehyde dissolved gradually. Although *N*,*N*′-diallylbispidin-9-one **5** appeared to be the only product apart from the baseline materials as judged by TLC, it was unstable and decom-



Scheme

posed on attempts at its isolation and purification.[12] Therefore, the crude product obtained by evaporation was immediately subjected to the Wolff−Kishner reduction. Thus, KOH was added to the crude product in an amount just enough to neutralize the HOAc initially used and then KOAc, hydrazine monohydrate, and diethylene glycol. The higher the concentration of KOAc, the better was the yield. Eventually, we could obtain *N*,*N*′-diallylbispidine **1c** in 51% yield from **4**. When KOH was used in this reaction, the yield of **1c** dropped to 32% as a result of reduction of **5** to *N*,*N*′-diallylbispidin-9-ol. This unusual carbonyl reactivity has been attributed to σ-coupling between the nitrogens and the carbonyl group in the bicyclo[3.3.1]nonane framework,[13] and NaOAc has been recommended to avoid this side reaction.[14]

The present procedure can also be applied efficiently to the preparation of other *N*,*N*-dialkylbispidines. Thus, when *N*-methylpiperidin-4-one and methylamine were used instead, *N*,*N*′-dimethylbispidine, **1e** was readily obtained in 25% overall yield.[15]

In order to remove the allyl groups in **1c**, we first tried 8 mol% of Pd catalyst with 2-mercaptobenzoic acid as an allyl scavenger.[11] The reaction, however, stopped on the half way, possibly due to deactivation of the catalyst by the strongly coordinating product diamine.

Therefore, we turned to the more conventional methods. Although allyl groups on nitrogens are usually inert toward acylating agents, it has been reported recently that addition of NaI greatly enhanced the reactivity of acylating agents.[16] When **1c** was treated with 6 equivalents each of ethyl chloroformate and NaI in acetonitrile at reflux temperature, bis(ethyl carbamate) **1d** was found to form in 73% yield. The biscarbamate **1d** in turn was readily hydrolyzed with 10 N KOH to give, after removal of H_2O as an azeotrope with benzene, bispidine **1a** in an overall yield of 37% from **4**.

The present method is very efficient and allowed us to make multigram quantities of bispidine **1a** from simple starting materials in short time and achieve the synthesis of **2a**.[17]

Bis(carbethoxyethyl)allylamine (3)

A mixture of allylamine (91.9 g, 1.61 mol), ethyl acrylate (617.2 g, 6.17 mol), and HOAc (1.8 mL, 0.03 mol) was refluxed for 3 days. After distilling off excess ethyl acrylate, a colorless oil (383.8 g, 93%) was collected at bp 150−154 °C / 7 Torr.

IR (neat): ν = 3078, 2982, 2824, 1740, 1732, 1643, 1447, 1419, 1371, 1252, 1184, 1119, 1043, 922, 856, 791, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.76−5.86 (m, 1H, olefinic CH), 5.11−5.20 (m, 2H, olefinic CH_2), 4.13 [q, 4H, *J* = 7.0 Hz, $C(O)OCH_2C$], 3.11 (d, 2H, *J* = 6.0 Hz, allyl CH_2), 2.79 (t, 4H, *J* = 7.0 Hz, NCH_2), 2.44 [t, 4H, *J* = 7.0 Hz, $CCH_2C(O)$], 1.25 (t, 6H, *J* = 7.0 Hz, CCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.51 [C(O) = O], 135.49 (olefinic CH), 117.41 (olefinic CH_2), 60.30 (CCH_2O), 57.02 (allyl CH_2), 49.00 (NCH_2C), 32.76 [$CCH_2C(O)$], 14.23 (CCH_3).

Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.00; N, 5.44. Found: C, 60.69; H, 8.94; N, 5.44.

1-Allylpiperdin-4-one (4)

To a suspension of NaH (31.7 g of 60% oil dispersion, 0.793 mol) in dry toluene (500 mL) was added absolute EtOH (46 mL) in dry toluene (300 mL). When H_2 evolution ceased, the mixture was refluxed with mechanical stirring under N_2 to ensure the conversion of NaH to NaOEt. A solution of **3** (201.6 g, 0.783 mol) in dry toluene (500 mL) was added to the stirred mixture within 15 min and the resulting mixture was refluxed for 4 h. Then, the solvent (approx. 900 mL) was distilled out under reduced pressure. After cooling, the reaction mixture was poured into 6 N HCl (500 mL), and the organic layer was extracted once with 6 N HCl (200 mL). The aqueous layers were combined and refluxed for 12 h. The cooled reaction mixture was made alkaline by addition of aqueous KOH. The oil liberated was extracted with EtOAc (1 × 200 mL, 2 × 100 mL), and the combined extract was dried (Na_2SO_4). The solvent was removed and the residue was distilled to give 100.7 g (92%) of a colorless oil, bp 75−76 °C / 9 Torr.

IR (neat): ν = 3078, 2964, 2910, 2793, 2754, 1720, 1717, 1643, 1474, 1418, 1385, 1340, 1288, 1240, 1202, 1126, 1084, 991, 920, 814, 762 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.85−5.96 (m, 1H, olefinic CH), 5.18−5.25 (m, 2H, olefinic CH_2), 3.12 (d, 2H, *J* = 6.5 Hz, allyl CH_2), 2.75 (t, 4H, *J* = 6.0 Hz, NCH_2C), 2.46 [t, 4H, *J* = 6.0 Hz, $CCH_2C(O)$].

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.81 (C = O), 134.93 (olefinic CH), 118.20 (olefinic CH_2), 60.66 (allyl CH_2), 52.89 (NCH_2C), 41.20 [$CCH_2C(O)$].

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.78; H, 9.41; N, 10.04.

3,7-Diallyl-3,7-diazabicyclo[3.3.1]nonane (1c)

A suspension of paraformaldehyde (10.74 g, 0.34 mol), allylamine (9.60 g, 0.17 mol), and **4** (22.12 g, 0.16 mol) in EtOH (1500 mL) was neutralized by addition of HOAc (18.6 mL, 0.34 mol) in an ice bath and gently heated at 55−60 °C with magnetic stirring under N_2. The progress of the reaction was monitored by analyzing aliquots of the reaction mixture, after treatment with aqueous NaOH, by TLC (silica gel, $CHCl_3$/MeOH, 1:1 with a small amount of aqueous NH_3). When the reaction was completed (5 h), the solvent was evaporated to give crude bispidinone **5** as an amber oil.

The oil was then dissolved in diethylene glycol (90 mL) and KOH (18.8 g, 0.34 mol) was added to neutralize the HOAc present. To this mixture were added KOAc (22.0 g, 0.224 mol) and hydrazine monohydrate (140 mL). After refluxing for 12 h, the reflux condenser was replaced with a Dean−Stark trap and the product was distilled out as an azeotrope with hydrazine in an oil bath at 160−180 °C. The top layer of the distillate was collected and the bottom layer was returned to the reaction flask. This procedure was repeated until no more oil came over. The combined distillate was extracted with hexane (3 × 30 mL), dried (Na_2SO_4), and evaporated. The residue was distilled to give 16.92 g (51% from **4**) of **1c** as a colorless oil (bp 70−74 °C / 0.7 Torr).

IR (neat): ν = 3075, 3004, 2899, 2777, 1836, 1643, 1460, 1437, 1419, 1376, 1341, 1320, 869, 848, 832, 804, 747 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.87−5.92 (m, 2H, olefinic CH), 5.07−5.20 (m, 4H, olefinic CH_2), 2.95 (d, 4H, *J* = 6.5 Hz, allyl NCH_2), 2.84 (d, 4H, *J* = 9.5 Hz, NCH_2C), 2.28 (dd, 4H, *J* = 4.0, 11.1 Hz, NCH_2C), 1.92 (s, 2H, bridgehead CH), 1.48 (s, 2H, CCH_2C).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.69 (olefinic CH), 117.01 (olefinic CH_2), 62.82 (allyl CH_2), 58.29 (NCH_2C), 31.03 (CCH_2C), 29.99 (bridgehead CH).

FAB MS: *m/z* = 207.21 (MH^+).

Treatment of **1c** with excess $HClO_4$ gave its mono $HClO_4$ salt as colorless plates (EtOH/CH_3CN), mp: 108.0−109.5 °C.

Anal. Calcd for $C_{13}H_{23}N_2O_4Cl$: C, 50.90; H, 7.56; N, 9.13. Found: C, 50.92; H, 7.58; N, 9.11.

3,7-Bis(carbethoxy)-3,7-diazabicyclo[3.3.1]nonane (1d)

To a stirred suspension of NaI (27.46 g, 0.183 mol) and ethyl chloroformate (17.5 mL, 0.183 mol) in dry CH_3CN (150 mL) was added a solution of **1c** (6.30 g, 0.0305 mol) in dry CH_3CN (20 mL) at r.t. The mixture was refluxed for 8 h and, after cooling to r.t., filtered. The filtrate was evaporated under reduced pressure and the residue was taken in EtOAc, washed with aqueous NaOH, dried (Na_2SO_4), and passed through a column of silica gel (hexane/EtOAc, 3:2) to give 6.03 g (73%) of **1d** as a colorless oil, which crystallized upon standing, mp: 58−60 °C.

IR (neat): ν = 2979, 2914, 2862, 1692, 1456, 1433, 1380, 1345, 1305, 1263, 1237, 877, 881, 834, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.29 (d, 2H, *J* = 13.1 Hz, NCH_2C), 4.21 (d, 2H, *J* = 13.1 Hz, NCH_2C), 4.07, 4.06 (two overlapping q, 4H, *J* = 7.0 Hz, OCH_2C), 3.07 (d, 2H, *J* = 13.1 Hz, NCH_2C), 3.01 (d, 2H, *J* = 13.1 Hz, NCH_2C), 1.83 (s, 2H, CCH_2C), 1.81 (s, 2H, bridgehead CH), 1.24 (t, 6H, *J* = 7.0 Hz, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.14 (C = O), 61.53 (OCH_2C), 48.80, 48.61 (NCH_2C), 31.48 (CCH_2C), 28.12 (bridgehead CH), 15.03 (CH_3).

Anal. Calcd for $C_{13}H_{22}N_2O_4$: C, 57.76; H, 8.20; N, 10.36. Found: C, 57.79; H, 8.20; N, 10.32.

FAB MS: *m/z* = 271.08 (MH^+).

3,7-Diazabicyclo[3.3.1]nonane (1a)

A solution of **1d** (5.52 g, 20.4 mmol) in EtOH (20 mL) and 10 N KOH (80 mL) was refluxed for 12 h. After distilling off all the EtOH present, the reaction mixture was refluxed for an additional 20 h. Then, the reflux condenser was replaced with a Dean−Stark trap and, after addition of benzene, heating was continued until the H_2O present was completely removed azeotropically. When cooled, the reaction mixture was filtered through a Celite pad. The solvent was evaporated and the residue was distilled at 175−178 °C / 27 Torr by means of a Kugelrohr apparatus to yield 2.55 g of **1a** (99%, 37% overall yield from **4**) as crystalline semisolid.

The crystals were extremely hygroscopic and quickly deliquesced in the air. Actually, first several papers did not report the mp of **1a**. Noting that the mp of **1a** was highly sensitive to the amount of H_2O absorbed, Galinovsky et al. first reported its mp, measured in a carefully sealed capillary, as 134−135 °C.[1f] Later, however, a mp as high as 203−205 °C was reported for a sample obtained by sublimation at 130−135 °C.[13] In our hands, crystals of **1a**, which sublimed at approx. 150 °C/1 atm and immediately sealed in a capillary under Ar, showed mp: 158−161 °C.

IR (neat): ν = 3300 (br), 2902, 2855, 2799, 2732, 1566, 1493, 1454, 1350, 1318, 1288, 1252, 1201, 834, 760 cm^{-1}. (Even a freshly distilled sample of **1a** showed very small bands at 2362 and 1644 cm^{-1} due to the hydrate of **1a**, which increased on standing in air.)

^1H NMR (400 MHz, C_6D_6): δ = 2.95 (d, 4H, *J* = 11.6 Hz, NCH_2C), 2.88 (d, 4H, *J* = 12.1 Hz, NCH_2C), 1.87 (br, 2H, NH), 1.60 (s, 2H, bridgehead CH), 1.18 (s, 2H, CCH_2C). (Strongly basic **1a** decomposes in $CDCl_3$ with abstracting D.)

^{13}C NMR (100 MHz, C_6D_6): δ = 53.09 (NCH_2C), 34.37 (CCH_2C), 30.20 (bridgehead CH).

FAB MS: *m/z* = 127.10 (MH^+)

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