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An improved and scalable process for 3,8-diazabicyclo[3.2.1] octane analogues

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Abstract

An improved and scalable process for substituted 3,8-diazabicyclo[3.2.1]octane was developed. *N*-Benzyl-2,5-dicarbethoxypyrrolidine **2** was reduced to *N*-benzyl-2,5-dihydroxymethylpyrrolidine **9** and subsequently debenzylated to afford *N*-Boc-2,5-dihydroxymethylpyrrolidine **10**. After mesylation of the diol **10** and cyclization with benzylamine, a diversity of scaffold, 3,8-diazabicyclo[3.2.1]octane analogue **12** was obtained in a total yield of 42% in five steps.

Keywords: 3,8-Diazabicyclo[3.2.1]octane; Scaffold; Process development

The piperazine nucleus is often found embedded in chemotherapic agents exhibiting a wide range of biological activities [1,2]. As an analogue and alternative of piperizine in drug discovery, compounds based on 3,8-diazabicyclo[3.2.1]octanyl ring system received great interest for their biological acativities such as anti-tumor activity [3], antiarrhythmic activity [4], antinociceptive activity [5], analgetic activity [5,6], as μ-opioid receptor [7], neuronal nicotinic acetylcholine receptor [8] as well as novel amide CCR5 antagonist [9].

Cignarella et al. [10] first reported the synthesis of 3,8-diazabicyclo[3.2.1]octane derivatives. Several 3-substituted-8-methyl-3,8-diazabicyclo[3.2.1]octanes were synthesized starting from 2,5-dicarbethoxypyrrolidine, which was converted into *N*-carbobenzoxy-2,5-pyrrolidine dicarboxylic acid anhydride in three steps. The latter reacted with appropriate amines to give 3-substituted-8-carbobenzoxy-3,8-diazabicyclo[3.2.1]octanes-2,4-diones from which the corresponding bicyclic bases were obtained by reduction with lithium aluminium hydride. The process suffers from several disadvantages such as long steps, tedious and labrious isolation of intermediates and low overall yields. A more efficient synthesis of 3-benzyl-3,8-diazabicyclo[3.2.1]octanes was subsequently reported soon and has being used today (Scheme 1) [3,5,9,11]. The key intermediate, 2-benzylcarbamyl-5-carbethoxy pyrrolidine **4** was obtained in an overall yield of 87% based on the recovery of starting materials by refluxing **3** with benzylamine in xylene. **4** was then heated at 200–210 °C to afford intermediate **5** from which the 3-benzyl-3,8-diazabicyclo[3.2.1]octane was obtained by reduction with lithium aluminiun hydride. The modified synthesis is much shorter and efficient than the original one. But it still has some drawbacks. The intermediates need to be isolated in each step, which result in labrious work-up and isolation. The cyclization of the key intermediate **4** was carried out at high temperature. The total yield is only 17%

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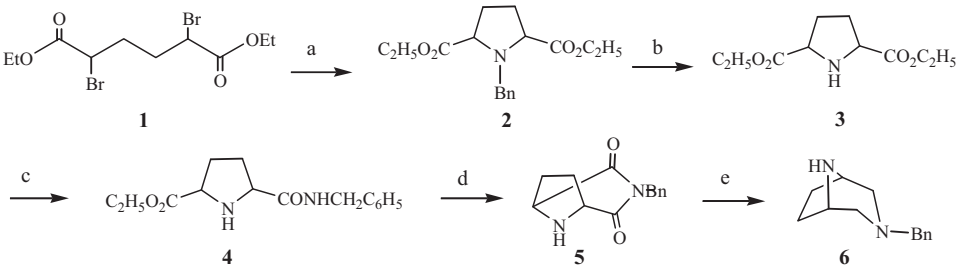


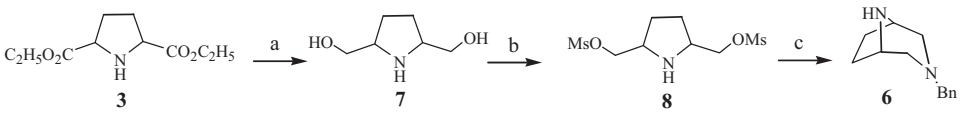
Scheme 1. Cignarella's synthesis of mono-substituted 3,8-diazabicyclo[3.2.1]octane. Reagents and conditions: (a) $BnNH_2$, benzene, reflux; (b) H_2, Pd/C, ethanol; (c) benzylamine, xylene, reflux; (d) 210 °C; (e) $LiAlH_4$, ether, 0 °C–r.t.

(23% based on the conversion) in five steps. In our course to synthesize this intermediate, an improved and scalable process of diverse substituted 3,8-diazabicyclo [3.2.1]octane was developed. The synthetic route was illustrated as Scheme 3.

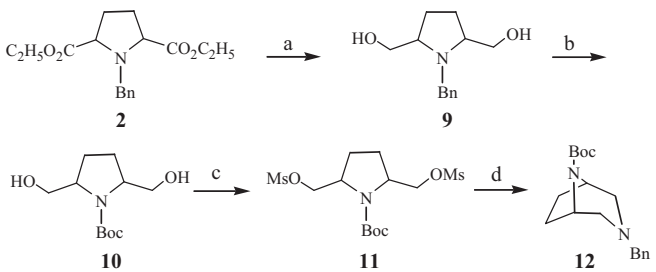
1. Results and discussion

In our effort to search for novel antitumor compounds in drug discovery, we need to synthesize this scaffold in kilogram quantities. We tried to use the same procedures as described by Cignarella [11a,b]. After mono-amidation of ethyl 2,5-pyrrolidine dicarboxylate **3,** the isolation of unreacted starting materials and product was difficult and the yield is unsatisfactory, the subsequent cyclization is also not worked well in our hand. After several attempts to the cyclization of the second ring, we found (Scheme 2) that when ethyl 2,5-pyrrolidine dicarboxylate **3** was reduced and mesylated, the dimesylate **8** could be cylizated smoothly by refluxing with primary amines. This process is much easer and the yield is reasonable. But it still has some drawbacks: the diol **7** was water soluble and hard to isolate, which also result in tedious work up. It is also necessary to isolate the intermediates **7** and **8**. The 3-benzyl-3,8-diazabicyclo[3.2.1]octane **6** needs to be distillated at high vacuum.

Inspired by this result, we examined the same strategy from **2** without debenzylation. The results are as well as expected. The yield of reduction of **2** is much better than that of reduction of **3** by lithium aluminium hydride. The reaction is easy to work up. Based on those results, we proposed a modified synthesis of the bicyclic ring system (Scheme 3). In order to maximize the diversity of the scaffold, we synthesized the di-substituted 3,8-diazabicyclo



Scheme 2. alternative synthesis of mono-substituted 3,8-diazabicyclo[3.2.1]octane. Reagents and conditions: (a) $LiAlH_4$, ether, 0 °C–r.t.; (b) MsCl, Et_3N, r.t. CH_2Cl_2; (c) $BnNH_2$, CH_3CN, reflux.



Scheme 3. Synthesis of substituted 3,8-diazabicyclo[3.2.1]octane. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C–r.t.; (b) H_2, Pd/C, Boc_2O, MeOH, 40 °C; (c) MsCl, Et_3N, r.t. CH_2Cl_2; (d) $BnNH_2$, CH_3CN, reflux.

[3.2.1]octane **12**, which could be either de-Boc to modify the amine in 3-position or debenzylated to modify the amine in 8-position and/or both.

The 2,5-dicarbethoxypyrrolidine **2** was synthesized from meso-α,α-dibromoadipate **1** by modifying the Braun and Seeman's method [12]. In our hand, starting with one kilogram of ethyl meso-α,α-dibromoadipate **1**, we obtained the 2,5-dicarbethoxypyrrolidine **2** (888 g) quantitively by refluxing with equimolar benzylamine in toluene for 4 h compared a yield of 82.5% in benzene for 24 h [12]. Reduction of **2** by lithium aluminium hydride in tetrahydrofuran gives *N*-benzyl-2,5-dihydroxymethylpyrrolidine **9**. Debenzylation of **9** in the mixture of di-*tert*-butyl dicarbonate and methanol by hydrogenation using Pd/C catalyst afford *N*-Boc-2,5-dihydroxymethylpyrrolidine **10**. Mesylation of the diol **10** with methanesulfonyl chloride in dichloromethane, we obtained *tert*-butyl 2,5-bis(((methylsulfonyl)oxy)methyl)pyrrolidine-1-carboxylate **11**. Refluxing **11** with benzylamine in acetonitrile afford the desired compound 3-benzyl-8-Boc-3,8-diazabicyclo[3.2.1]octane **12**. We also found by optimization that it is unnecessary to isolate the intermediates in each step. After regular work up, the intermediates (**2**, **9**, **10**, and **11**) were obtained and used in next step. The 3-benzyl-8-Boc-3,8-diazabicyclo[3.2.1]octane **12** (370 g) was obtained by recrystallization in petroleum ether [13–16]. The total yield is 42% in five steps.

2. Conclusion

We developed an improved simple and scalable process for the synthesis of 3,8-diazabicyclo[3.2.1]octane analogues, which can be used in the synthesis of diverse 3,8-diazabicyclo[3.2.1]octane derivatives.

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[13] Spectral data of compound **2**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.27 (m, 2H), 7.23 (m, 1H), 4.05 (dd, 4H, J = 10.5 Hz, J = 7.5 Hz), 3.96 (s, 2H), 2.08 (m, 4H), 1.19 (t, 6H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4 (2C), 137.5, 129.5 (2C), 128.0 (2C), 127.2, 77.4 (2C), 60.6, 57.8 (2C), 28.7 (2C), 14.1 (2C); LRMS: MS (ES^+) m/z = 306.2 $(M+1)^+$.
[14] Spectral data of compound **6**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (m, 5H), 6.90 (br, 1H), 3.94 (s, 2H), 3.56 (s, 2H), 2.78 (d, 2H, J = 12.0 Hz), 2.71 (d, 2H, J = 12.5 Hz), 2.13 (m, 2H), 2.06 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 128.8 (2C), 128.4 (2C), 127.2, 65.0, 64.3 (2C), 58.8 (2C), 29.3 (2C); LRMS: MS (ES^+) m/z = 203.1 $(M+1)^+$.
[15] Spectral data of compound **10**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.94 (s, 2H), 3.82 (s, 4H), 3.51 (d, 2H, J = 7.5 Hz), 1.98 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (125 MHz,$CDCl_3$): δ 156.5, 80.7, 65.5, 64.4, 60.6 (2C), 28.4 (3C), 26.9 (2C); LRMS: MS (ES^+) m/z = 232.1 $(M+1)^+$.

[16] Typical procedure: To a suspension of $LiAlH_4$ (198 g, 5.21 mol) in THF (4000 mL), was added a solution of **2** (888 g, 2.912 mol) in THF (900 mL) at 0 °C dropwise. The mixture was stirred for five minutes. Then water (200 mL) and a solution of 10% NaOH (200 mL) were added dropwise at 0 °C. The mixture was filtered and the cake was washed with dichloromethane. The filtrate was combined and evaporated to obtain **9** (600 g, impure). It was dissolved in ethanol (3500 mL) and di-*tert*-butyl dicarbonate (600 g, 2.75 mol) and Pd/C (10 g) was added. The mixture was hydrogenated at 40 °C and 60 psi hydrogen pressure for four hours. The mixture was cooled and filtered. The filtrate was evaporated to obtain **10** (630 g, impure). It was dissolved in dichloromethane (1000 mL) and triethylamine (700 g, 6.92 mol) was added, then methanesulfonyl chloride (550 g, 4.80 mol) was added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stirred overnight. The mixture was washed sequentially with water, a solution of 10% citric acid and brine. The organic phase was dried over anhydrous sodium sulfate and evaporated to obtain **11** (800 g, impure). It was dissolved in acetonitrile (1000 mL) and benzylamine (762 g, 7.12 mol) was added. The mixture was heated to reflux overnight. The mixture was evaporated and the residue was dissolved in ethyl acetate, filtered through a silica pad, washed with water, a solution of 10% citric acid and brine. The organic phase was dried over anhydrous sodium sulfate and evaporated. The compound **12** was obtained by recrystallization from petroleum ether as white solid (370 g, 42.1% in five steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (m, 4H), 7.26 (m, 1H), 4.20 (s, 1H), 4.09 (s, 1H), 3.47 (s, 2H), 2.61 (d, 2H, J = 10.0 Hz), 2.31 (s, 1H), 2.24 (s, 1H), 1.90 (s, 2H), 1.83 (s, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7, 138.9, 128.7 (2C), 128.2 (2C), 127.0, 79.2, 61.9, 58.2, 57.7, 54.7, 53.8, 28.5 (3C), 27.8; LRMS: MS (ES^+) m/z = 303.2 $(M+1)^+$.