Sargis S. Hayotsyan*, Gevorg G. Mkryan, Asya A. Aghekyan and Gagik S. Melikyan

Synthesis of perhydro-N-(2,2-disubstituted-3-aminopropyl) heterocycles as potentially bioactive compounds and fragments for combinatorial chemistry

Abstract: A new method for the preparation of perhydro-N-(2,2-disubstituted-3-aminopropyl) heterocycles that allows to obtain a large variety of corresponding derivatives with high to moderate yields using simple procedures is described.

Keywords: 2,2-disubstituted-1,3-diaminopropane; ethyl cyanoacetate; perhydroheterocycles.

Introduction

The 2,2-disubstituted-1,3-diaminopropane fragment is a fairly common moiety in several biologically active compounds. N-Cyclohexyl-1,3-diaminopropane acts as a spermine synthase inhibitor, thus suppressing cancer (particularly human breast cancer) cell growth (Huber et al., 1995). Other types of 1,3-diamino fragments are contained in several pharmaceutical substances, such as apridine, desipiramine, ethylmemazine, and many other analogous compounds.

The common way for the construction of N,N-disubstituted-2,2-disubstituted-1,3-diaminopropanes is through the hydrogenation of corresponding α,α-disubstituted-β-aminonitriles or oximes with lithium aluminum hydride (Zaugg et al., 1953; Hine et al., 1975). Sodium in ethanol (Faust et al., 1959) can also be used for the hydrogenation of the oximes. 1,3-Dinitropropanes have also been reduced with hydrogen over a Raney nickel at 20°C and elevated pressures (Lamm et al., 1970).

Results and discussion

In the current report, a new way for the synthesis of N-(3-amino-2,2-disubstituted) perhydroheterocycles 3a–x starting from a cyanoacetic ester is described. In the first step, the reaction between ethyl cyanoacetate and the corresponding perhydro-NH heterocycles furnished the amides of cyanoacetic acid 1. These products 1 were converted into the corresponding α,α-disubstituted amides 2 by alkylation with appropriate alkyl halides. Then the amides 2 were reduced with lithium aluminum hydride (LAH) (Mndzhoyan et al., 1971) to give the desired N-(3-amino-2,2-dialkyl)-perhydroheterocycles 3a–x in yields of about 70% (Scheme 1). Some of the obtained compounds (3b,c,h,i,k) are highly reactive toward carbon dioxide from the air. Accordingly, after distillation, they were converted into stable oxalates and further characterized in that form.

Conclusions

A new, inexpensive, and highly convenient method for the synthesis of N-substituted perhydroheterocycles is described. These compounds are interesting as individual substances as well as the fragments for the combinatorial chemistry.

Experimental section

All initial compounds were of commercial grade and used without further purification. Yields refer to the isolated compounds. Melting points were determined on SMP-10 melting point apparatus. Infra-red spectra were recorded in KBr pellets on a Nicolet Avatar 330 spectrometer. 1H NMR spectra were obtained in a DMSO-d6 solution.
at 30 °C, at 300 MHz, on a Varian Mercury 300 VX spectrometer, with TMS as internal standard.

General procedure for the synthesis of \( N \)-\((3\text{-amino-2,2-disubstituted-3-aminopropyl})\) perhydroheterocycles \(3a-x\)

A mixture of ethyl cyanoacetate (10.7 mL, 0.1 mol) and corresponding perhydroheterocycle (0.1 mol) was stirred for 2 h at room temperature and afterward kept at room temperature for 2 days. The resultant crystals of 1 (yield 70–80%) were filtered and washed with diethyl ether.

Further, a solution of corresponding amide \(1\) (0.05 mol) in DMSO (100 mL) was treated with NaOH (8 g, 0.2 mol), and the mixture was treated dropwise with methyl iodide (7 mL, 0.11 mol) at 15–20 °C or (100 mL) was treated with NaOH (8 g, 0.2 mol), and the mixture was heated under reflux for 12 h and quenched with \(\text{HCl} \). The mixture was then treated with water and dried with anhydrous sodium sulfate. After the removal of the solvent, the residue was distilled under reduced pressure. In the case when the amine was unstable in a free form, the distillate was treated with oxalic acid, and the resultant oxalate was crystallized from water and dried at 50–60°C/20 mm Hg.

2,2-Dimethyl-3-pyrrolidinopropan-1-amine (3a) Yield 77%; bp 59–60°C/2 mm Hg; IR: 3417, 3387, 3329 cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 0.81 (s, 6H, \(2\text{CH}_3\)), 1.42 (dd, \(J = 11\) Hz and 6 Hz, 4H, \(\text{C}_2\text{H}_2\text{N}\)), 1.60 (td, \(J = 11\) Hz and 6 Hz, 2H, \(\text{CH}_2\text{CH}_2\text{NH}\)), 2.39 (s, 2H, \(\text{C}_2\text{H}_2\text{N}\)), 2.52–2.57 (m, 4H, \(\text{C}_2\text{H}_2\text{N}\)). Anal. Calcd for \(\text{C}_{10}\text{H}_{23}\text{N}_3\): C, 64.81; H, 12.51; N, 22.68. Found: C, 64.98; H, 12.39; N, 22.57.

2,2-Dimethyl-3-piperidinopropan-1-amine (3b) Yield 75%; bp 61–62°C/3 mm Hg; (mp of oxalate 143–145°C); IR: 3431, 3392, 3342 cm\(^{-1}\); \(^1\)H NMR of oxalate: \(\delta\) 0.98 (s, 6H, \(2\text{CH}_3\)), 1.42 (dd, \(J = 11\) Hz and 6 Hz, 4H, \(\text{C}_2\text{H}_2\text{N}\)), 2.39 (s, 2H, \(\text{C}_2\text{H}_2\text{N}\)), 2.53–2.63 (m, 4H, \(\text{C}_2\text{H}_2\text{N}\)). Anal. Calcd for \(\text{C}_{13}\text{H}_{26}\text{N}_2\text{O}_4\): C, 70.53; H, 12.02; N, 16.45. Found: C, 70.30; H, 12.93; N, 16.30.

3-Azepano-2,2-dimethylpropan-1-amine (3c) Yield 73%; bp 65–67°C/2 mm Hg; (mp of oxalate 140–142°C); IR: 3419, 3389, 3332 cm\(^{-1}\); \(^1\)H NMR of oxalate: \(\delta\) 1.16 (s, 6H, \(2\text{CH}_2\)), 1.68 (br, 2H, \(\text{CH}_2\text{CH}_2\text{NH}\)), 2.94 (br, 2H, \(\text{CH}_2\text{N}\)), 3.23 (br, 2H, \(\text{CH}_2\text{NH}\)), 3.68 (br, 2H, \(\text{NCH}_2\)), 5.04–6.99 (br, 4H, \(\text{NH} + \text{H}_2\text{CO}_4\)). Anal. Calcd for \(\text{C}_{11}\text{H}_{23}\text{N}_4\): C, 70.53; H, 13.02; N, 16.45. Found: C, 70.30; H, 12.93; N, 16.30.

2,2-Dimethyl-3-(4-methylpiperazino)propan-1-amine (3d) Yield 85%; bp 85–90°C/2 mm Hg; IR: 3425, 3393, 3341 cm\(^{-1}\); \(^1\)H NMR: \(\delta\) 0.78 (s, 6H, \(2\text{CH}_3\)), 0.90–1.30 (br, 2H, \(\text{NH}\)), 2.11 (s, 2H, \(\text{CH}_2\text{N}\)), 2.15 (s, 3H, \(\text{CH}_3\)), 2.25–2.30 (m, 2H, \(\text{CH}_2\text{N}\)), 2.39 (br, 2H, \(\text{CH}_2\text{NH}\)), 2.44–2.50 (m, 4H, \(\text{CH}_2\text{N}\)). Anal. Calcd for \(\text{C}_{13}\text{H}_{27}\text{N}_4\): C, 64.81; H, 12.51; N, 22.68. Found: C, 64.98; H, 12.39; N, 22.57.
3-(3,4-dihydroisoquinolin-2(1H)-yl)-2,2-dimethylpropan-1-amine (3e) Yield 69%; bp 148–150°C/2 mm Hg: IR: 3427, 3381, 3341 cm⁻¹; 1H NMR: δ 0.85 (s, 6H, 2CH₃), 1.35–1.56 (m, 6H, 2CH₂), 2.18–2.47 (m, 4H, 2CH₂N), 2.99–3.27 (m, 2H, 2CH₂N), 3.53–3.61 (m, 4H, 2CH₂O), 5.62–6.07 (br, 4H, NH + H₂C₂O). Anal. Calcd for C₁₃H₂₆N₂O: C, 67.42; H, 12.66; N, 13.22. Found: C, 67.38; H, 12.64; N, 13.24.

3-Aminomethyl-1-(azepanomethyl)cyclopentane (3l) Yield 62%; bp 195–198°C/2 mm Hg: IR: 3426, 3379, 3329 cm⁻¹; 1H NMR: δ 1.39–1.46 (m, 4H, 2CH₂), 2.46 (s, 2H, CH₂N), 2.68 (s, 2H, CH₂NH₂), 2.76–2.85 (m, 4H, NCH₂CH₂), 2.75–3.03 (br, 2H, NH₂), 3.52–3.75 (m, 4H, CH₂O), 3.68 (s, 2H, NCH₂Ar), 6.89–6.94 (m, 1H), and 6.99–7.04 (m, 3H, Ar). Anal. Calcd for C₁₄H₂₈N₂O: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.70; H, 9.65; N, 10.55.

3-Aminomethyl-1-(azepanomethyl)cyclopentane (3u) Yield 67%; bp 114–116°C/2 mm Hg: IR: 3409, 3382, 3331 cm⁻¹; 1H NMR: δ 1.33–1.44 (m, 4H, 2CH₂), 2.17–2.40 (m, 4H, 2CH₂N), 2.42 (s, 2H, CH₂N), 2.86–3.04 (m, 4H, 2CH₂O), 5.51–5.63 (m, 4H, CH₂N), 5.97–6.17 (m, 3H, 2NH₂). Anal. Calcd for C₁₃H₂₆N₂O: C, 67.54; H, 12.57; N, 18.03. Found: C, 67.52; H, 12.39; N, 18.01.
1.21–1.34 (m, 2H) and 1.42–1.59 (m, 6H, (CH₂)₄), 2.27 (s, 2H, CH₂N), 2.30–2.78 (br, 2H, NH₂), 2.41–2.45 (m, 4H, (CH₂)₂N), 2.50 (s, 2H, CH₂NH₂), 3.54–3.58 (m, 4H, (CH₂)₂O). Anal. Calcd for C₁₁H₂₂N₂O: C, 66.62; H, 11.18; N, 14.13. Found: C, 66.44; H, 11.38; N, 14.36.

1-Aminomethyl-1-(morpholinomethyl)cyclohexane (3v) Yield 60%; bp 120–122°C/3 mm Hg; IR: 3425, 3376, 3328 cm⁻¹; ¹H NMR: δ 1.10–1.50 (br, 2H, NH₂), 1.15–1.46 (m, 10H, (CH₂)₅), 2.18 (s, 2H, CH₂N), 2.43–2.48 (m, 4H, (CH₂)₂N), 2.54 (s, 2H, CH₂NH₂), 3.50–3.57 (m, 4H, (CH₂)₂O). Anal. Calcd for C₁₂H₂₄N₂O: C, 67.88; H, 11.39; N, 13.19. Found: C, 68.01; H, 11.16; N, 12.98.

1-Aminomethyl-4-morpholinomethyl-tetrahydro-4H-pyran (3w) Yield 70%; bp 152–153°C/2 mm Hg; IR: 3421, 3385, 3330 cm⁻¹; ¹H NMR: δ 1.32–1.40 (m, 4H, 2 CH₂), 2.16–2.40 (br, 2H, NH₂), 2.26 (s, 2H, CH₂N), 2.44–2.48 (m, 4H, (CH₂)₂N), 2.63 (s, 2H, CH₂NH₂), 3.47–3.57 (m, 8H, 2 (CH₂)₂O). Anal. Calcd for C₁₀H₁₈N₂O₂: C, 61.65; H, 10.35; N, 13.07. Found: C, 61.52; H, 10.46; N, 13.25.

1-Aminomethyl-1-(4-benzylpiperazinomethyl)cyclopentane (3x) Yield 52%; bp 155–156°C/3 mm Hg; IR: 3420, 3380, 3341 cm⁻¹; ¹H NMR: δ 1.20–1.32 (m, 2H) and 1.40–1.60 (m, 6H, (CH₂)₄), 1.86–2.12 (br, 2H, NH₂), 2.27 (s, 2H, NCH₂C), 2.33–2.43 (m, 4H, (CH₂)₂N), 2.43–2.50 (m, 4H, (CH₂)₂N), 2.47 (br, 2H, NH₂), 3.42 (s, 2H, PhCH₂), 7.13–7.28 (m, 5H, Ph). Anal. Calcd for C₁₈H₂₉N₃: C, 75.21; H, 10.17; N, 14.62. Found: C, 75.35; H, 10.02; N, 14.48.

Received June 7, 2012; accepted July 19, 2012; previously published online September 1, 2012

References


