Chemistry of Heterocyclic Compounds, Vol.35, No. 7, 1999

SYNTHESIS OF FUNCTIONALIZED 2,5-ETHANO-2-BENZAZEPINES

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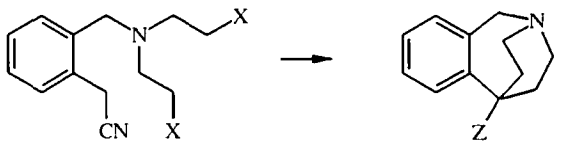
Cyclization of (un)substituted phenylacetonitriles by di(2-chloroethyl)amines is commonly used [1] to synthesize 4-arylpiperidinecarbonitriles, which are used as intermediates in the synthesis of CNS-active derivatives of pethidinic acid. In the present work, an intramolecular version of this reaction is proposed as a convenient method for synthesizing functionalized derivatives of the bridged 2,5-ethano-2-benzazepine system. Reports of this system are limited to a single communication [2] where exhaustive fluorination of perhydro-2,5-ethano-2-benzazepine (without synthesis method) is described in addition to other examples in order to synthesize blood substitutes and components of oxygen-transport systems.

A necessary intermediate for this method is 2-[di(2-chloroethyl)aminomethyl]phenylacetonitrile (Ib), which is synthesized in high yield in two steps by alkylation of diethanolamine with 2-(bromomethyl)-phenylacetonitrile with subsequent replacement of the hydroxyls in 2-[di-(2-hydroxyethyl)aminomethyl]-phenylacetonitrile (Ia) by chlorine using thionyl chloride.



I II

I a X = OH; b X = Cl; II a Z = CN; b Z = CO_2H

Compound Ia; mp 84°C (ethanol). IR spectrum (KBr): 3260-3150 (broad, O–H), 2240 cm^{-1} (C≡N). PMR spectrum (DMSO-d_6): 7.32 (4H, m, H_{arom}); 4.41 (2H, t, J = 5 Hz, OH); 4.25 (2H, s, Ar–CH_2–N); 3.67 (2H, s, CH_2CN); 3.44 (4H, m, CH_2OH); 2.53 ppm (4H, t, J = 7 Hz, CH_2–N–CH_2). Found, %: C 66.85; H 7.81; N 11.88. $C_{13}H_{18}N_2O_2$. Calculated, %: C 66.64; H 7.74; N 11.96.

Compound IIb; mp 58°C (petroleum ether). IR spectrum (KBr): 2240 cm^{-1} (C≡N). PMR spectrum ($CDCl_3$): 7.2-7.5 (4H, m, H_{arom}); 4.12 (2H, s, Ar–N–CH_2); 3.86 (2H, s, CH_2CN); 3.48 (4H, t, J = 7 Hz, CH_2Cl); 2.86 ppm (4H, t, J = 7 Hz, CH_2–N–CH_2). Found, %: C 57.41; H 5.83; N 10.20; Cl 26.31. $C_{13}H_{16}Cl_2N_2$. Calculated, %: C 57.58; H 5.95; N 10.33; Cl 26.15.

Intramolecular cycloalkylation of Ib was performed using sodium hydride in anhydrous DMF at room temperature for 2.5 h. The product 2,3,4,5-tetrahydro-2,5-ethano-1H-2-benzazepine-5-carbonitrile (IIa) was obtained in high yield.

IIa; mp 65-66°C (petroleum ether). IR spectrum (KBr): 2240 (C≡N), 2870, 2900, 2920 cm^{-1} (C–H). PMR spectrum ($CDCl_3$): 7.67 (1H, d, J = 8 Hz, 6-H); 7.23 (3H, 7-9-H); 4.28 (2H, s, 1-H); 3.11 (4H, m, 3-H, 11-H); 2.36 ppm (4H, t, J = 7 Hz, 4-H, 10-H). Found, %: C 78.83; H 7.15; N 14.12. $C_{13}H_{14}N_2$. Calculated, %: C 78.75; H 7.12; N 14.13.

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 0009-3122/99/3507-0880$22.00

Heating of the compound IIa in conc. HBr for 15 h produces 2,3,4,5-tetrahydro-2,5-ethano-1H-2-benzazepine-5-carboxylic acid hydrobromide (IIb·HBr); mp 309.5°C (water). The absence in the IR spectrum of the nitrile group bands and the presence of strong bands at 3500 and 1710 (O–H and C=O of the carboxyl group, respectively) and at 2600 cm^{-1} (N^+–H) are consistent with nitrile group hydrolysis.

IIb·HBr. PMR spectrum (DMSO-d_6): 10.65 (1H, br. s, CO_2H); 7.33 (3H, m, 7-9-H); 7.00 (1H, m, 6-H); 4.73 (2H, s, 1-H); 3.34 (4H, m, 3-H, 11-H); 2.28 ppm (4H, t, J = 7 Hz, 4-H, 10-H). Found, %: C 52.60; H 5.38; N 4.86; Br 27.03. $C_{13}H_{15}NO_2$·HBr. Calculated, %: C 52.37; H 5.41; N 4.70; Br 26.80.

The work was supported by the Ukraine State Foundation for Fundamental Research.

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