ISSN 1070-4280, Russian Journal of Organic Chemistry, 2009, Vol. 45, No. 3, pp. 472–474. © Pleiades Publishing, Ltd., 2009.
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SHORT COMMUNICATIONS

Synthesis of *N*-Arylmethyl-3-azabicyclo[3.3.1]nonan-9-ones

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Received February 13, 2008

DOI: 10.1134/S1070428009030257

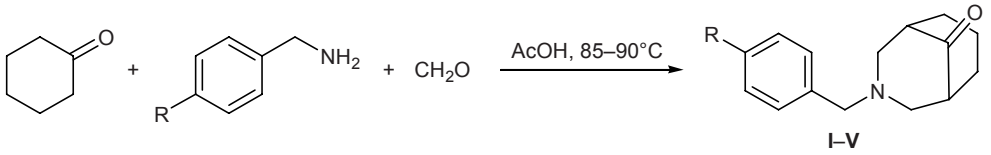
Interest in nitrogen-containing bicyclic compounds is related to the fact that they constitute structural fragments of a number of alkaloids [1] such as atropine and cocaine, which are used in medicine as spasmolytics and anesthetics [2]. N-Substituted 3-azabicyclo-[3.3.1]nonan-9-ones also belong to the above class of compounds; however, they have been poorly studied, presumably because of the lack of convenient methods for their preparation. The procedures reported in [3, 4] for the synthesis of *N*-benzyl-3-azabicyclo[3.3.1]-nonan-9-one (**I**) ensured only ~8% yield of the target product.

In the present communication we describe an improved procedure for the synthesis of compound **I**, which was also used to obtain new 3-azabicyclo-[3.3.1]nonan-9-one derivatives **II**–**V**. Compounds **I**–**V** were synthesized according to Mannich via double aminomethylation with substituted benzylamines in the presence of formaldehyde on heating in acetic acid (Scheme 1). Optimization of the reaction conditions and isolation procedure allowed us to raise the yield of target products **I**–**V** to 30–35%. No appreciable effect of the substituent R on the yield of **I**–**V** was observed.

Catalytic reductive dealkylation of compounds **I**–**V** with ammonium formate in the presence of 10% Pd/C in boiling ethanol afforded 3-azabicyclo[3.3.1]nonan-9-one (**VI**) in high yield, and the latter was subjected (without isaolation) to acylation with di-*tert*-butyl dicarbonate (Boc_2O). We thus isolated stable *tert*-butyl 9-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate (**VII**) (Scheme 2).

***N*-Benzyl-3-azabicyclo[3.3.1]nonan-9-one (I).** Benzylamine, 47 g (0.44 mol), was cooled with cold water, 37 ml of concentrated hydrochloric acid, 35.3 g (0.36 mol) of cyclohexanone, 90 ml of a formaldehyde solution, and 500 ml of glacial acetic acid were added in succession on cooling, and the mixture was stirred for 2.5 h at 85–90°C under argon and was left overnight at room temperature. The mixture was evaporated at 80°C, the oily residue was treated with 200 ml of water, and the resulting solution was extracted with diethyl ether (2×200 ml). The aqueous phase was made alkaline by adding in small portions under stirring 160–170 g of sodium carbonate, and the product was extracted into methylene chloride (3×150 ml); the extract was washed with water, dried over anhydrous sodium sulfate, and evaporated, 100 ml of ethanol was added to the oily residue, 35 ml of acetic anhydride was added in portions under stirring, and the mixture was stirred for 2 h. The mixture was treated with 37 ml of concentrated hydrochloric acid, stirred for 2 h, and evaporated at 60°C, 400 ml of water was added to the residue, the mixture was extracted with methylene chloride (2×100 ml), the yellow aqueous phase was made alkaline by adding sodium carbonate and extracted again with methylene chloride (3×100 ml), the extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was distilled

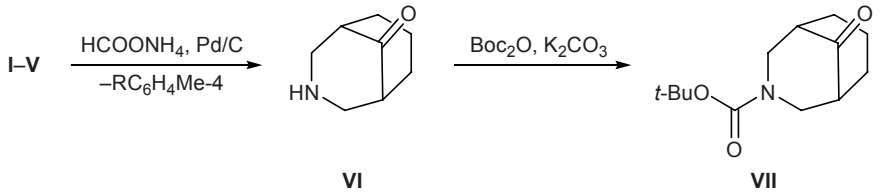
Scheme 1.



I–**V**

I, R = H; **II**, R = Me; **III**, R = F; **IV**, R = Br; **V**, R = MeO.

Scheme 2.



VI **VII**

under reduced pressure in a stream of argon, a fraction boiling in the temperature range from 148 to 155°C (0.8 mm) being collected. The light yellow oily distillate crystallized on cooling in several hours. The product was finally purified by chromatography on silica gel using hexane as eluent. Yield 26.21 g (32%). Light yellow crystals, mp 49–50°C [4], R_f 0.49. IR spectrum: ν 1720 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.47–2.12 m (6H, CH_2), 2.30–2.35 m (2H, CH), 2.85 d (2H, NCH_2), 2.96 d (2H, NCH_2), 3.44 s (2H, PhC**H**$_2$N), 7.2–7.4 m (5H, C_6H_5). Mass spectrum: *m*/*z* 230 $[M + H]^+$. Found, %: C 78.56; H 8.28; N 6.15. $C_{15}H_{19}NO$. Calculated, %: C 78.67; H 8.30; N 6.11.

Compounds **II**–**V** were synthesized according to a similar procedure.

***N*-(4-Methylphenylmethyl)-3-azabicyclo[3.3.1]-nonan-9-one (II).** Yield 31%, mp 54–55°C, R_f 0.58. IR spectrum: ν 1722 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.46–2.09 m (6H, CH_2), 2.24 s (3H, CH_3), 2.30–2.34 m (2H, CH), 2.85 d (2H, NCH_2), 2.98 d (2H, NCH_2), 3.42 s (2H, ArC**H**$_2$N), 7.10 d and 7.22 d (2H each, C_6H_4, J = 8 Hz). Mass spectrum: *m*/*z* 244 $[M + H]^+$. Found, %: C 79.08; H 8.73; N 5.69. $C_{16}H_{21}NO$. Calculated, %: C 79.03; H 8.64; N 5.76.

***N*-(4-Fluorophenylmethyl)-3-azabicyclo[3.3.1]-nonan-9-one (III).** Yield 35%, mp 48–49°C, R_f 0.46. IR spectrum: ν 1720 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.48–2.11 m (6H, CH_2), 2.32–2.36 m (2H, CH), 2.89 d (2H, NCH_2), 3.01 d (2H, NCH_2), 3.58 s (2H, ArC**H**$_2$N), 7.18–7.35 m (4H, C_6H_4). Mass spectrum: *m*/*z* 248 $[M + H]^+$. Found, %: C 72.76; H 7.31; N 5.64. $C_{15}H_{18}FNO$. Calculated, %: C 72.89; H 7.28; N 5.66.

***N*-(4-Bromophenylmethyl)-3-azabicyclo[3.3.1]-nonan-9-one (IV).** Yield 33%, mp 62–63°C, R_f 0.48. IR spectrum: ν 1719 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.47–2.10 m (6H, CH_2), 2.30–2.37 m (2H, CH), 2.89 d (2H, NCH_2), 3.00 d (2H, NCH_2), 3.61 s (2H, ArC**H**$_2$N), 7.15 d and 7.60 d (2H each, C_6H_4, J = 8 Hz). Mass spectrum: *m*/*z* 309 $[M + H]^+$. Found, %: C 58.57; H 5.75; N 4.48. $C_{15}H_{18}BrNO$. Calculated, %: C 58.46; H 5.84; N 4.54.

***N*-(4-Methoxyphenylmethyl)-3-azabicyclo[3.3.1]-nonan-9-one (V).** Yield 31%, mp 71–72°C, R_f 0.39. IR spectrum: ν 1721 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.46–2.08 m (6H, CH_2), 2.31–2.36 m (2H, CH), 2.91 d (2H, NCH_2), 3.02 d (2H, NCH_2), 3.60 s (2H, ArC**H**$_2$N), 3.80 s (3H, CH_3O), 7.42 d and 7.80 d (2H each, C_6H_4, J = 7.6 Hz). Mass spectrum: *m*/*z* 260 $[M + H]^+$. Found, %: C 74.12; H 8.04; N 5.48. $C_{16}H_{21}NO_2$. Calculated, %: C 74.15; H 8.10; N 5.40.

***tert*-Butyl 9-oxo-3-azabicyclo[3.3.1]nonane-3-carboxylate (VII).** Compound **I**–**V**, 0.05 mol, was dissolved in 100 ml of ethanol, 12.6 g (0.2 mol) of ammonium formate and 10 g of 10% Pd/C were added, and the mixture was heated for 6–7 h under reflux on stirring in an argon atmosphere. During the reaction, additional amount of ammonium formate (10 g, 0.16 mol) and the catalyst (8 g) were added. The mixture was cooled and filtered through a layer of zeolite, the filtrate was evaporated at 60°C, the oily residue was dissolved in 200 ml of methylene chloride, the solution was washed with water, 150 ml of 10% aqueous sodium hydrogen carbonate was added, and a solution of 13.1 g (0.06 mol) of di-*tert*-butyl dicarbonate in 80 ml of methylene chloride was then gradually added under stirring. The mixture was stirred for 12 h, the organic phase was separated, dried over anhydrous sodium sulfate, and evaporated, and the oily residue was subjected to chromatography on silica gel using hexane–ethyl acetate (9:1) as eluent. The product was additionally recrystallized from hexane on cooling. Yield 9.32 g (78%), mp 89–90°C. IR spectrum, ν, cm^{-1}: 1721, 1682 (C=O). ^1H NMR spectrum, δ, ppm: 1.31 s (9H, *t*-Bu), 1.47–2.09 m (6H, CH_2), 2.38–2.44 m (2H, CH), 3.42 d (2H, NCH_2), 3.64 d (2H, NCH_2). Mass spectrum, *m*/*z*: $[M + H]^+$ 240, $[M - 57 + H]^+$ 183, $[M - 101 + H]^+$ 139. Found, %: C 65.18; H 8.72; N 5.87. $C_{13}H_{21}NO_3$. Calculated, %: C 65.29; H 8.78; N 5.85.

The IR spectra were recorded on a Specord 75IR spectrometer from thin films. The ^1H NMR spectra were measured on a Varian Mercury Plus-400 spectrometer (400 MHz) from solutions in $CDCl_3$ using HMDS as internal reference. The mass spectra (atmospheric pressure chemical ionization) were obtained on

a Thermo Finnigan Surveyor MSQ instrument (USA). The purity of the products was checked by TLC on Silufol UV-254 plates using hexane–ethyl acetate (10 : 1) as eluent; spots were visualized under UV light.

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