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SHORT COMMUNICATIONS

One-Pot Synthesis of 6,7-Dehydro-1-aza-3-oxabicyclo-[3.3.1]nonanes by Condensation of α-Methylstyrenes with Formaldehyde and Ammonia*

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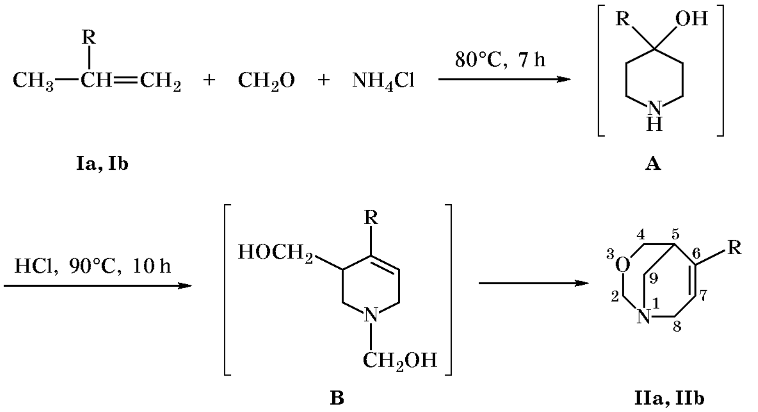
Acid-catalyzed reaction of α-methylstyrenes with formaldehyde and primary alkylamines at a ratio of 1:2:1 leads to formation of 4-aryl-4-hydroxypiperidines **A** [1], whose subsequent dehydration yields 1,2,3,6-tetrahydropyridines [2]. *N*-Alkyltetrahydropyridines can be converted into the corresponding 3-hydroxymethyl derivatives by treatment with formaldehyde according to Prins (with equimolar amounts of the reactants) [3, 4]. The present communication reports on our attempt to effect one-pot condensation of α-methylstyrenes **Ia** and **Ib** with formaldehyde and ammonium chloride, taken at a ratio of 1:4.5:1, with the goal of obtaining 1,3-bis(hydroxymethyl)tetrahydropyridines **B** (Scheme 1).

The initial three-component reactant mixture was first heated for 7 h at 80°C, 0.01 equiv of HCl was added, and the mixture was then heated for 10 h at 90°C. However, after conventional treatment of the reaction mixture and chromatographic separation, we isolated products of intramolecular etherification, 6,7-dehydro-1-aza-3-oxabicyclo[3.3.1]nonanes **IIa** and **IIb**, instead of the desired diols **B**. The unexpected extra heterocyclization stage is likely to be explained by high reactivity of the semiaminal NCH_2OH group.

6,7-Dehydro-6-phenyl-1-aza-3-oxabicyclo[3.3.1]-nonane (IIa). Yield 37%. Colorless thick oily substance. R_f 0.48 (acetone). ^1H NMR spectrum, δ, ppm: 2.52 br.s (1H, 5-H), 3.06 d.d (1H, 9-H, J = 7.8, 1.2 Hz), 3.39 br.d (1H, 8-H, J = 7.8 Hz), 3.55 d.d (1H, 8-H, J = 11.9, 1.9 Hz), 3.75–3.90 m (3H, 4-H, 9-H), 4.53 d and 4.59 d (1H each, 2-CH_2, J = 6.5 Hz), 6.40 t (1H, 7-H, J = 1.9 Hz), 7.25–7.4 m (5H, H_{arom}).

Scheme 1.



I, **II**, R = Ph (**a**), 4-MeC_6H_4 (**b**).

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Mass spectrum, *m*/*z* (I_{rel}, %): 201 (74) $[M]^+$, 171 (97) $[M-CH_2O]^{+\cdot}$, 142 (88), 128 (100), 115 (84), 91 (47), 77 (43). Found, %: C 77.48; H 7.68; N 6.71. $C_{13}H_{15}NO$. Calculated, %: C 77.61; H 7.53; N 6.97.

6,7-Dehydro-6-(4-tolyl)-1-aza-3-oxabicyclo[3.3.1]-nonane (IIb). Yield 31%. Colorless thick oily substance. R_f 0.5 (acetone). ^{1}H NMR spectrum, δ, ppm: 2.24 s (3H, Me), 2.47 br.s (1H, 5-H), 3.02 d.d (1H, 9-H, *J* = 7.8, 1.2 Hz), 3.33 br.d (1H, 8-H, *J* = 7.8 Hz), 3.59 d.d (1H, 8-H, *J* = 11.9, 1.9 Hz), 3.64–3.80 m (3H, 4-H, 9-H), 4.49 d and 4.58 d (1H each, 2-CH_2, *J* = 6.5 Hz), 6.24 t (1H, 7-H, *J* = 1.9 Hz), 7.0–7.25 m (4H, H_{arom}). Found, %: C 77.89; H 8.25; N 6.31. $C_{14}H_{17}NO$. Calculated, %: C 78.10; H 7.91; N 6.49.

The ^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer at 250 MHz using $CDCl_3$ as solvent and TMS as internal reference. The mass spectrum was obtained on an MKh-1321 instrument. Thin-layer chromatography was performed on Silufol UV-254 plates; development with iodine vapor.

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