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SHORT COMMUNICATIONS

Role of Prins Reaction and Aminomethylation in the Synthesis of 1,3-Oxazinane from α-Methylstyrene

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Abstract—Study of the mechanism of formation of 1,3-oxazinane in the reaction of α-methylstyrene with formaldehyde and amines in aqueous medium has shown that 3,6-dimethyl-6-phenyl-1,3-oxazinane is formed as a result of transformations of 4-methyl-4-phenyl-1,3-dioxane which is the Prins reaction product.

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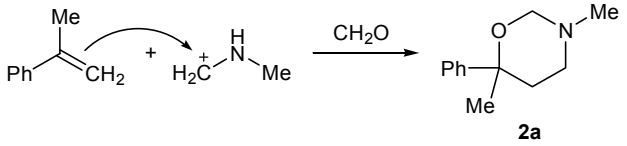
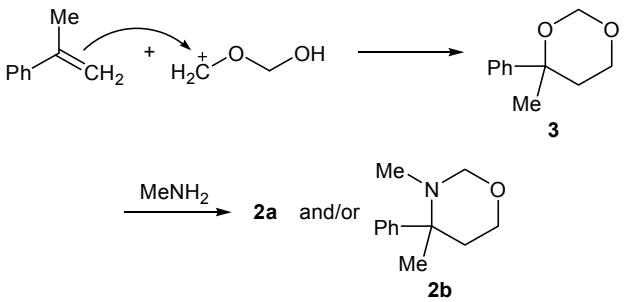
It is known that aminomethylation of alkenes underlies a promising method for the introduction of amino groups into organic molecules [1]. There are published examples of aminomethylation of alkenes with formaldehyde and amines in nonaqueous medium, which leads to the formation of open-chain compounds [2–4]. Analogous reactions in aqueous solution are interesting. In particular, phenyl-substituted alkenes were reported to react with formaldehyde and primary amines or ammonia in aqueous medium to produce 1,3-oxazinanes [5]. These products can be formed via both aminomethylation of alkene with an aminomethyl carbocation (Scheme 1) and transformation of the initially formed 1,3-dioxane (Prins reaction product) by the action of amine (Scheme 2). Taking into account that the question whether 1,3-oxazinanes are formed as a result of aminomethylation or Prins reaction remains open, we studied the reaction of α-methylstyrene (**1**) with formaldehyde and methylamine.

Scheme 1.



2a

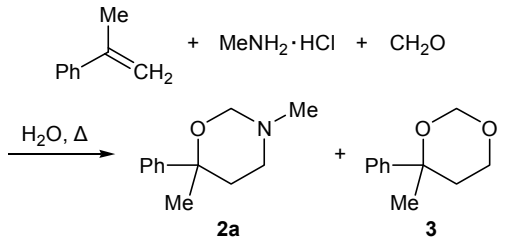
Scheme 2.



3 **2b**

The aminomethylation reaction could give 3,6-dimethyl-6-phenyl-1,3-oxazinane (**2a**) as the only product, whereas the formation of compound **2a** and/or isomeric 3,4-dimethyl-4-phenyl-1,3-oxazinane (**2b**) is possible in the transformation of 4-methyl-4-phenyl-1,3-dioxane (**3**). The structure of oxazinane obtained from alkene **1** was not studied in detail; therefore, we examined its structure using two-dimensional NMR techniques. For this purpose, compound **2a** was synthesized in 80% yield according to the procedure described in [5] (reaction time 20 h; Scheme 3). Its structure was proved by HMBC and HSQC two-dimensional NMR experiments (Fig. 1).

Scheme 3.



2a **3**

The formation of isomer **2a** rather than **2b** suggests that both mechanisms shown in Schemes 1 and 2 are possible. Unlike the data of [5], when the reaction time

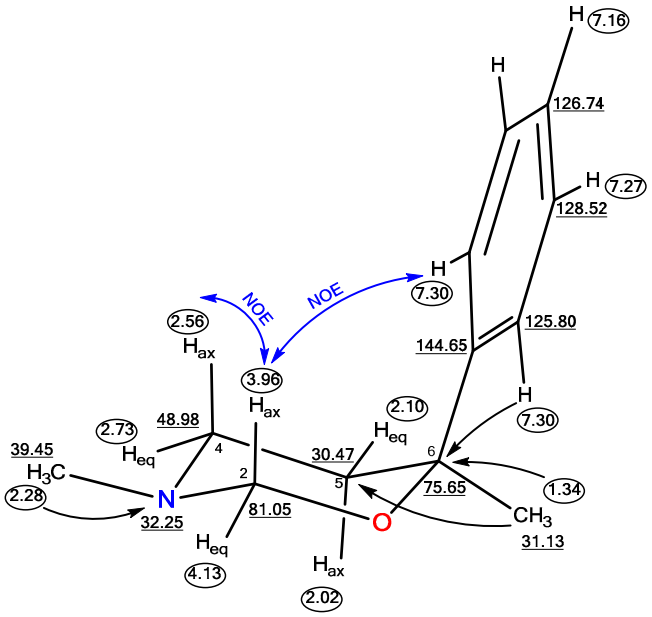


Fig. 1. HMBC and NOE correlations for 3,6-dimethyl-6-phenyl-1,3-oxazinane (**2a**).

was 1 h, we isolated two products, oxazinane **2a** and 4-methyl-4-phenyl-1,3-dioxane (**3**). Intermediate formation of 1,3-dioxane **3** provides an additional support to Scheme 2. Here, 1,3-dioxane **3** is a kinetically controlled product, and oxazinane **2a** is a thermodynamically controlled product, which is confirmed by the calculations of the Gibbs free energies of the reactions (ΔG_r^{368}) by the semiempirical RM1 method [6, 7] in the AM1 approximation [8] which is more accurate. The obtained data showed that the formation of oxazinane **2a** (ΔG_r^{368} = –43.0 kJ/mol) is thermodynamically more favorable than the formation of 1,3-dioxane **3** (ΔG_r^{368} = –18.8 kJ/mol). This is very consistent with published data on the formation of

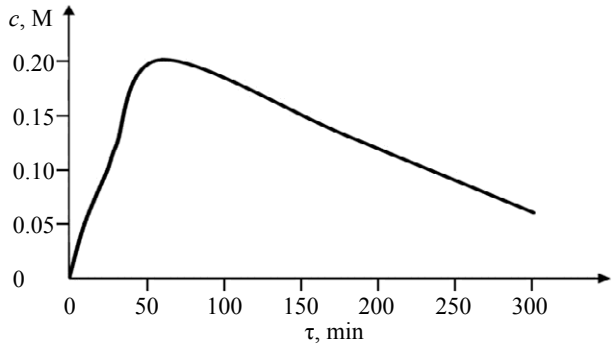


Fig. 2. Kinetic curve for the accumulation of 4-methyl-4-phenyl-1,3-dioxane (**3**) in the reaction of α-methylstyrene with formaldehyde and methylamine hydrochloride (100°C); initial concentrations, M: [**1**] = 3.33, [$MeNH_2 \cdot HCl$] = 3.33, [CH_2O] = 6.66.

1,3-dioxanes in the Prins reaction under kinetic control [9]. Furthermore, the formation of oxazinane **2a** as a result of transformation of intermediate 1,3-dioxane was also confirmed by the extremal character of the kinetic curve for the accumulation of 4-methyl-4-phenyl-1,3-dioxane (**3**) (Fig. 2).

Thus, the reaction of α-methylstyrene with formaldehyde and methylamine yields 3,6-dimethyl-6-phenyl-1,3-oxazinane (**2a**). It has been shown for the first time that compound **2a** is formed as a result of transformation of intermediate 1,3-dioxane which is the product of initial Prins reaction (Scheme 2).

3,6-Dimethyl-6-phenyl-1,3-oxazinane (2a) and 4-methyl-4-phenyl-1,3-dioxane (3). A solution of 3.38 g (0.05 mol) of methylamine hydrochloride and 3.00 g (0.1 mol) of paraformaldehyde in 5.25 mL of water was purged with nitrogen over a period of 5 min, and 6.4 mL (0.05 mol) of α-methylstyrene (**1**) was added. The mixture was refluxed for 1 h with stirring, cooled, treated with a saturated solution of sodium hydrogen carbonate, and extracted with chloroform. The extract was dried over magnesium sulfate, the solvent was removed under reduced pressure, and the yellow oily residue was subjected to chromatographic separation in a column charged with silica gel (eluent hexane– ethyl acetate, 10:1.5).

Compound (**2a**). Yield 5.0 g (52%), colorless oily liquid. ^{1}H NMR spectrum, δ, ppm: 1.34 s (3H, CH_3), 2.02 d.t (1H, 5-H, J = 4.0, 10.5 Hz), 2.10 d.t (1H, 5-H, J = 4.0, 10.3 Hz), 2.28 s (3H, CH_3N), 2.56 m and 2.73 m (1H each, 6-H), 3.96 d and 4.13 d (1H each, 2-H, J = 9.4 Hz), 7.30 m (5H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 30.47 (C^5), 31.13 (CH_3), 39.45 (NCH_3), 48.98 (C^4), 75.65 (C^6), 81.05 (C^2), 125.80 (C^o), 126.74 (C^p), 128.52 (C^m), 144.65 (C^i). ^{15}N NMR spectrum: δ_N 36.25 ppm. Found, %: C 74.92; H 8.87; N 7.15. $C_{12}H_{17}NO$. Calculated, %: C 75.35; H 8.96; N 7.32.

Compound (**3**). Yield 3.2 g (36%). The properties of compound **3** were in agreement with the data of [10].

When the reaction time was 20 h, other conditions being equal, we isolated 7.0 g (80%) of **2a** as the only product.

The NMR spectra were recorded on a Bruker Avance III 500 spectrometer at 500.13 (^{1}H), 125.73 (^{13}C), and 50.68 MHz (^{15}N); 5-mm QNP probe, 298 K; solvent $CDCl_3$, internal standard tetramethylsilane. Gas chromatographic analysis was performed on a Chrom-5 chromatograph equipped with a flame ionization detector; injector and detector temperature 250°C, oven temperature 200°C; 2.0 m×2-mm column

packed with 5% SE-30 on Inerton Super; carrier gas nitrogen, flow rate 10 mL/min; internal standard tetradecane.

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