Russian Journal of Organic Chemistry, Vol. 41, No. 5, 2005, pp. 703–706. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 5, 2005, pp. 718–721.

New Opportunities for Duff Reaction

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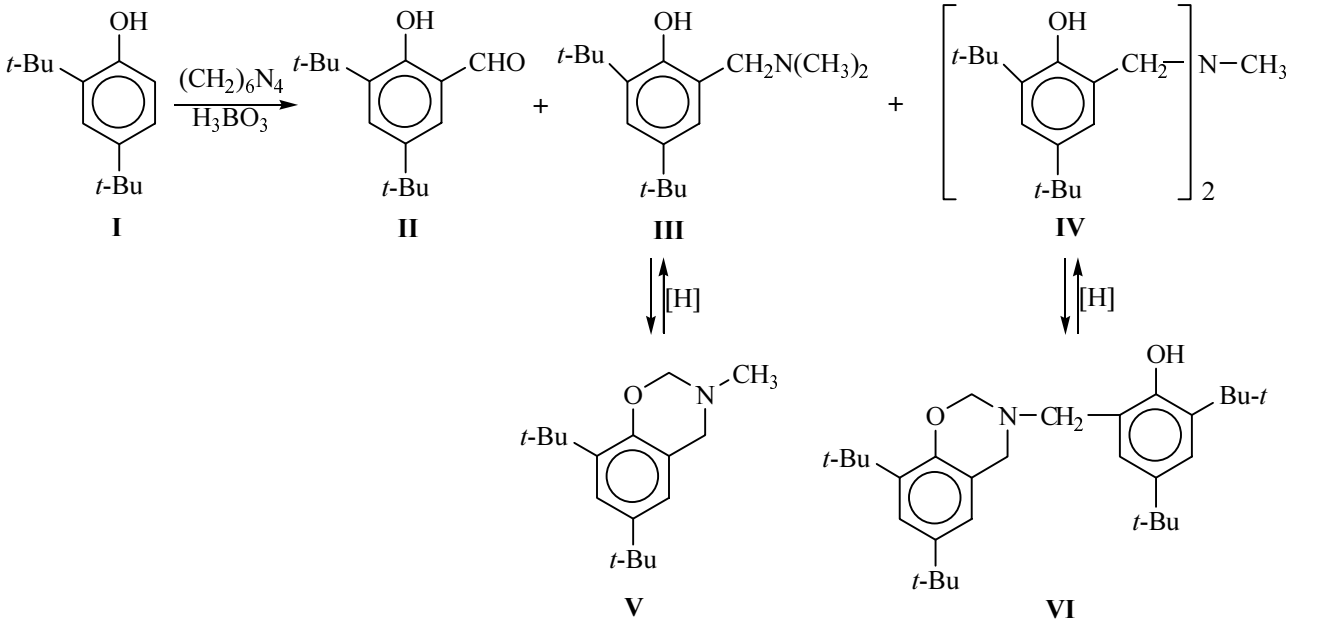
Received June 1, 2004

Abstract—Reaction of 2,4-di-*tert*-butylphenol with urotropin in conditions of Duff reaction takes an abnormal route and instead of the expected di-*tert*-butylsalicylaldehyde provides a mixture of N-substituted 3,5-di-*tert*-butyl-2-hydroxybenzylamines and redox conjugate benzoxazines containing mostly 6,8-di-*tert*-butyl-3-(3,5-di-*tert*-butyl-2-hydroxybenzyl)-2*H*-3,4-dihydrobenz[*e*][1,3]oxazine. A solvolysis of an individual benzoxazine in the system $HO(CH_2)_2OH$–H_2O–HCl affords di(3,5-di-*tert*-butyl-2-hydroxybenzyl)amine, and in AcOH 3,5-di-*tert*-butylsalicilaldehyde. A mechanism of Duff reaction was suggested involving the formation of a benzoxazine intermediate.

Duff reaction consisting in treating phenols with urotropin at elevated temperature in ethylene glycol or glycerol in the presence of H_3BO_3 underlies one of the most convenient preparation methods for *ortho*-hydroxy-substituted aromatic aldehydes [1]. Its mechanism and the reason of the high regioselectivity are poorly understood. Presumably the overall process involves a phenol aminomethylation with iminomethane (CH_2=NH) arising through the thermal decomposition of the urotropin, the oxidation of aminophenol with urotropin to give imine followed by its hydrolysis[2].

In the course of the study of Duff reaction with 2,4-di-*tert*-butylphenol (**I**) under standard conditions we found that the expected 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**II**) was not a single or the main reaction product. Its yield did not exceed 2%. The chromatographic analysis of the reaction products revealed and afforded in a preparative overall yield of around 80% two redox conjugate couples of compounds: 2,4-(di-*tert*-butyl)-6-dimethylaminomethylphenol (**III**), *N*-methyl-bis(3,5-di-*tert*-butyl-2-hydroxybenzyl)amine (**IV**), and the corresponding substituted benzoxazines **V** and **VI**.



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The heating at higher temperature did not increase the yield of aldehyde **II**, and below 100° the interaction of phenol **I** resulted only in a formation of a molecular complex with $(CH_2)_6N_4$ in 1:1 ratio identical to that arising at mixing equimolar amounts of phenol and urotropin in an alcohol solution with subsequent removal of the solvent. The transformations of the complex at heating to 130–140°C furnished the same set of compounds **III– VI**. This fact and also the character of compounds **III– VI** where the nitrogen is linked to three carbon atoms suggest that the urotropin decomposition in the course of Duff reaction is not obligatory. The reaction products arise in the direct reaction between the phenol and the urotropin, and in the first stage of reaction a molecular complex is formed. Theoretically presumable is complexes formation with a stoichiometry from 1:1 to 4:1. An important role in the stabilization of their structure must play the hydrogen bonds between phenol hydroxy groups and the nitrogen atoms of urotropin. The formation of similar complexes from the unsubstituted phenol and urotropin was established by X-ray diffraction study [3]. The complexing makes understandable the regioselectivity of the reaction and facilitates the hydride shifts in the intermediates.

Under standard conditions at a slight urotropin excess (1:1.2) the prevailing product of the Duff reaction was benzoxazine **VI** (yield 55%). On increasing the urotropin excess to the three-fold level we obtained benzoxazine **VI** in a 70% yield with a small amount of initial compound **I** and traces of substances **III–V** as impurities. The experimental results were independent of the presence or absence of boric acid. The traces of **III–V** in the reaction mixture suggest that they could have formed intermediately and then transformed into benzoxazine **VI**.

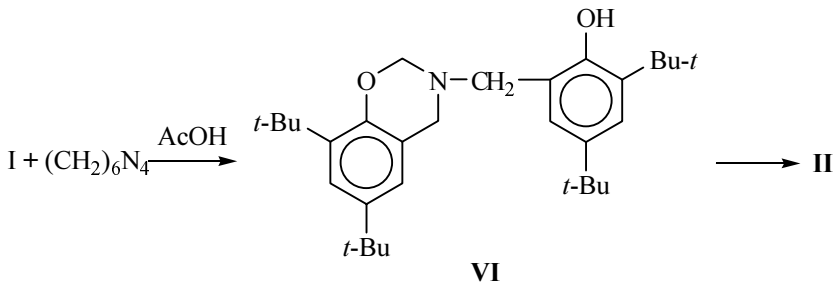
Actually, the authentic amine **III** heated with excess urotropin transformed into benzoxazine **VI**. In the course of reaction the formation of phenol **I** was detected indicating that aminomethylation in the course of Duff reaction was reversible. The retroaminolmethylation is probably one of the reasons of low yield of the salicylaldehyde not exceeding usually 25–30%. The complete conversion of phenol **I** at the use of 3–4-fold urotropin excess is apparently due to the suppression of the retroreaction.

In the "normal" Duff reaction the presumed precursor of the aldehyde is the imine originating from the aminomethylphenol oxidation. In the event of phenol **I** the oxidation products of aminomethylphenols **III** and **IV** are benzoxazines **V** and **VI**. Thus the opportunity to prepare aldehyde from phenol **I** by Duff procedure should depend on the possibility to convert benzoxazines **V** and **VI** into imines.

We previously established investigating the oxidation of amine **III** with inorganic oxidants in various media that benzoxazine **V** and aldehyde **II** formed in a neutral (benzene) and acid (AcOH) media respectively [4]. It was also observed that in AcOH a solvolytic conversion of benzoxazine **V** into aldehyde **II** was possible. We performed a conversion of benzoxazine **VI** into aldehyde **II** by boiling in AcOH in the presence of urotropin. Therewith the conversion occurred in AcOH without urotropin at a considerably smaller rate.

Taking into account the data obtained it is presumable that compounds like benzoxazines **V** and **VI** are common intermedistes of the Duff reactuin, and the character of the trial products is governed by the solvolytic stability of the benzoxazine ring depending on the nature of the medium. The "abnormal" Duff reaction found for phenol **I** is apparently due to the stability of benzoxazine **VI** in the neutral ethylene glycol. In reaction carried out in AcOH the benzoxazine ring is able to open, and the "normal" Duff reaction occurs furnishing aldehyde **II**, and the intermediate formation of benzoxazine **VI** is detected in the course of hte process by chromotography.

Noteworthy that formation of aldehyde **II** in AcOH was inhibited by the presence of water: in 80% AcOH



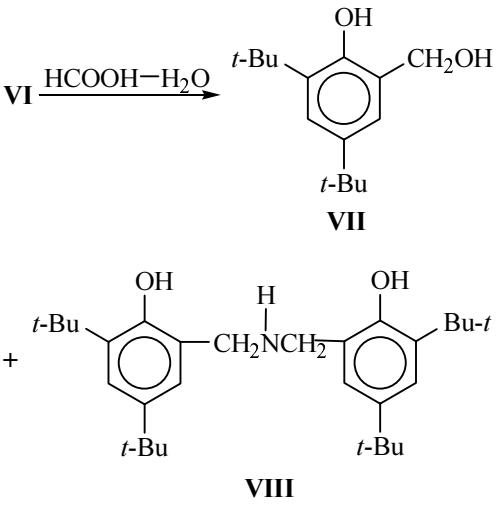
VI

the aldehyde yield decreased to 10%, and in 70% AcOH the reaction was virtually stopped at the stage of benzoxazine **VI** formation. Analogously in 85% HCOOH the maximum (≈5%) yield of benzoxazine **VI** was obtained, and at higher water content alongside benzoxazine **VI** also benzyl alcohol (**VII**) and traces of dibenzylamine (**VIII**) were detected. Compounds **VII** and **VIII** are solvolysis products of benzoxazine **VI**. This fact was proved by heating a benzoxazine **VI** sample in aqueous HCOOH or in ethylene glycol in the presence of aqueous HCl (Scheme 1).

Dibenzylamines similar to compoumd **VIII** as a rule accompany the aldehyde formation in the Duff reaction [5].

The solvent effect observed by an example of Duff reaction with phenol **I** is apparently of general character and is due to the possibility of alternative solvolytic transformations of the benzoxazine intermediate. The key point of these transformations is the opening of the benzoxazine ring catalyzed by a proton affording aminomethyl cation **IX** that may cleave with a loss of a methylene unit (in the medium HCOOH–H_2O) or may undergo isomerization resulting from 1,3-hydride shift giving iminium ion **X** (in AcOH), the direct precursor of imine **XI** and aldehyde **II** (Scheme 2). Therefore the urotropin role becomes understandable: it increases the lifetime of ion **IX** and the possibility of its isomerization. Ion **X** may be responsible for the appearance of side products of Duff reaction methylated in the aromatic ring [5]. We succeeded to observe imine **XI** by ^{1}H NMR method when performing the reaction in AcOH, and also to isolate it preparatively in reaction of equimolar mixture phenol–urotropin in the presence of catalytic quantity of AcOH under heating in a microwave oven.

Scheme 1.

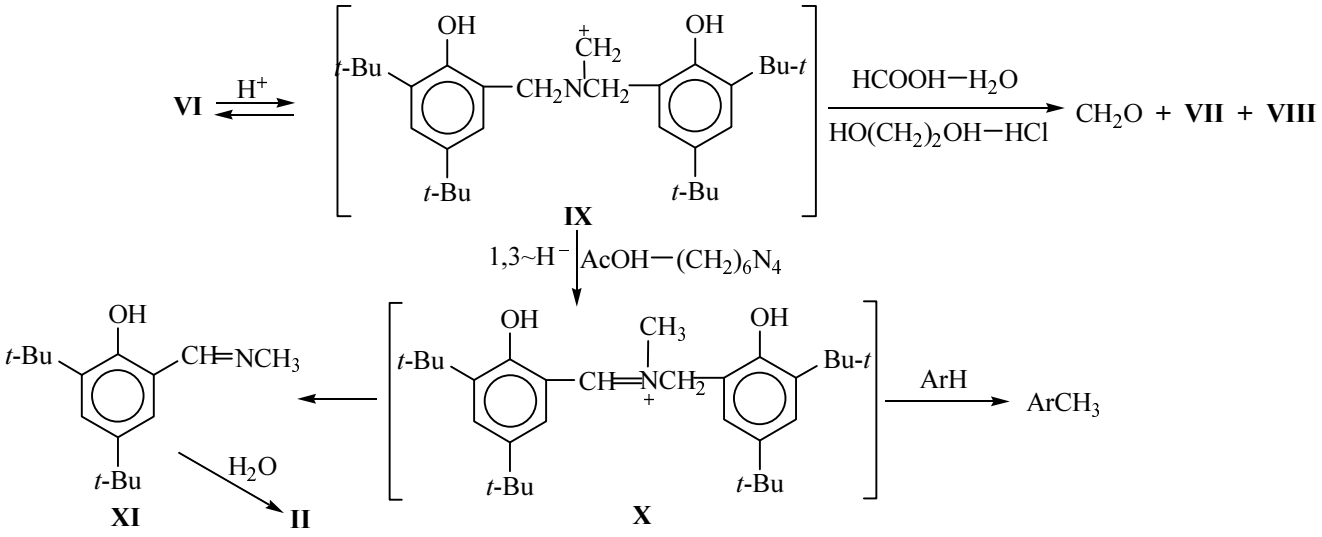


Therefore the study of the "abnormal" Duff reaction with phenol **I** provided a possibility to reveal details of the reaction mechanism, and the stepwise performance of the reaction with replacement of solvent extended its synthetic opportunities. Therewith we succeeded to increase the yield of the "normal" reaction product, aldehyde **II** virtually to a quantitative value.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker WH-250.

Scheme 2.



Molecular complex of phenol I with urotropin. In 20 ml of EtOH 0.41 g (2 mmol) of phenol **I** and 0.28 g (2 mmol) of urotropin was heated for 1 h. On evaporating the solvent the precipitated crystals were recrystallized from hexane, mp 82–83°C. ^{1}H NMR spectrum $CDCl_3$), δ, ppm (*J*, Hz): 1.29 s (9H, *t*-Bu), 1.41 s (9H, *t*-Bu), 4.73 s (12H, CH_2), 6.56 d (1H, Ph, *J* 8.4), 7.07 d.d (1H, Ph, 8.4, *J* 2.6), 7.29 d (1H, Ph, *J* 2.6).

Benzoxazine (VI) from 2,4-di-*tert*-butyl-6-dimethylaminomethylphenol (III). A mixture of 0.9 g (3.5 mmol) of amine **III** and 1 g (7 mmol) of urotropin was heated in 50 ml of ethylene glycol for 45 min at 140–150°C. On cooling the reaction mixture was poured in water, the reaction products were extracted into ether, the extract was dried over $MgSO_4$. On evaporating the solvent to the oily residue methanol was added, and crystals precipitated [6]. We obtained 0.6 g of benzoxazine **VI**, yield 87%.

Reaction of phenol I with urotropin. *a*. In a glacial and in diluted acetic acid. A mixture 0.4 g (2 mmol) of phenol **I** and 0.5 g (4 mmol) of urotropin was heated for 1 h in 50 ml of glacial ACOH. After treating the reaction mixture with water, extraction of products with ether, and evaporating the extract we obtained 0.33 g (67%) of aldehyde **II** [7]. The heating of the mixture with the same composition in 70% ACOH afforded 0.48 g (94%) of benzoxazine **VI**.

b. In formic acid. A mixture 0.4 g (2 mmol) of phenol **I** and 0.5 g (4 mmol) of urotropin was heated for 1 h in 50 ml of 85% formic acid. The precipitated crystals were filtered off to obtain 0.44 g (95%) of benzoxazine **VI**.

Di(3,5-di-*tert*-butyl-2-hydroxybenzyl)-amine (VIII). In ethylene glycol with 5 ml of hydrochloric acid added 0.46 g (1 mmol) of benzoxazine **VI** was heated for 30 min at 130°C. On cooling the reaction mixture the separated crystals of hydrochloride were filtered off, washed with water, and dried; mp of amine **VIII** hydrochloride 231–232°C. To the hydrochloride obtained was added dropwise at intermittent shaking under a layer of ether a water solution of KOH. On evaporation of ether we obtained 0.36 g (81%) of amine **VIII**, mp 153–154°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.29 s (18H, *t*-Bu), 1.43 s (18H, *t*-Bu), 3.92 s (4H, CH_2), 6.95 d (2H, Ph, *J* 2.5), 7.25 d (2H, Ph, *J* 2.5). Found, %: C 79.00; H 9.96. $C_{30}H_{47}NO_2$. Calculated %: C 79.35; H 10.40.

The study was carried out under the financial support of the Russian Foundation for Basic Research (grant no. 02-04-49452).

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