A convenient method for the preparation of N-unsubstituted hydrazones of aromatic ketones and aldehydes

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A general and useful method for the synthesis of *N*-unsubstituted hydrazones of aromatic ketones and aldehydes in good yields was elaborated. The use of a large excess of hydrazine hydrate and catalytic amounts of *p*-toluenesulfonic acid makes it possible to prepare the hydrazones without an admixture of the corresponding azine.

Key words: N-unsubstituted hydrazones of aromatic ketones and aldehydes.

It is difficult to synthesize N-unsubstituted hydrazones in good yields and with high purity, especially in the case of reactive ketones and aldehydes, 1,2 due to the presence of two reactive amino groups in hydrazine, resulting in the formation of azine as a by-product. In addition, hydrazones are highly reactive compounds, which can spontaneously transform into azines or products of resinification under heating as well as by the action of moisture or a catalyst. 1,3,4

Various methods for the synthesis of N-unsubstituted hydrazones were described. One of the main methods is the direct interaction of ketones and aldehydes with hydrazine hydrate in alcohol, water, or acetic acid either in the presence or absence of acidic or basic catalysts.⁵⁻⁷

The reaction of hydrazine hydrate with N-substituted hydrazones^{2,8} is another approach to the synthesis of N-unsubstituted hydrazones. In particular, a method for the synthesis of N-unsubstituted hydrazones from the corresponding N,N-dimethylhydrazones was reported.¹

$$RR'C=0 \xrightarrow{H_2NNH_2 + H_2O} RR'C=N-NMe_2 \xrightarrow{H_2NNH_2 + H_2O} RR'C=N-NH_2$$

All these methods have disadvantages, such as low yields of hydrazones and their contamination with the corresponding azines. In addition, these methods are not general. For example, the synthesis of benzophenone hydrazone by heating of benzophenone in acetic acid with hydrazine hydrate at 85 °C was reported.⁹ However, an attempt to prepare 4-chloroacetophenone

hydrazone under these conditions was unsuccessful, because the corresponding azine is formed in a high yield even at room temperature.

In the present work, we report a convenient general method developed by us for the synthesis of N-unsubstituted hydrazones **1a**—i by the reaction of aromatic ketones and aldehydes with hydrazine hydrate in the presence of p-toluenesulfonic acid.

$$\begin{array}{c} R \\ C = O \end{array} \xrightarrow[EtOH]{} H_2 N N H_2 \cdot H_2 O / T_5 O H \\ \hline R \\ Ar \end{array} \xrightarrow[R]{} C = N - N H_2 \\ \hline Ar \\ 1 \end{array}$$

The yields, melting points, and data of the ¹H NMR spectra of the hydrazones are presented in Table 1.

The reaction was carried out in 96% ethanol in the presence of catalytic quantities of p-toluenesulfonic acid under heating (70-80 °C) for a period varied from 10 min to several hours, depending on the reactivity of the carbonyl compound. The reaction proceeds selectively in a high yield and results in high-purity products. The purity of the hydrazones was checked from the ratio of integral intensities of the signals in the ¹H NMR spectra of the amino group and the residue of the carbonyl compound and by comparison of the measured melting points of the samples synthesized with the published data. According to these data, all hydrazones obtained were individual stereoisomers; however, the determination of their configuration was outside the task of this work. It is noteworthy that even prolonged heating (10 h) of hydrazones under the reaction conditions does not result in the formation of azines, although, according to the available published data,^{4,9} acid catalysis is necessary for the formation of many azines.

We established that the use of a high excess of hydrazine hydrate, acid catalysis by p-toluenesulfonic acid, and the optimum temperature of heating

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Com-	Ar	R	M.p./°C		¹ H NMR,* δ	Yield
pound			Exp.	Ref.		(%)
1a	Ph	Me	25-26	24—25 ⁵	7.68 (d, 2 H, o -H, $J = 8$ Hz); 7.33 (m, 2 H, m -H and p -H); 5.39 (2 H, NH ₂); 2.10 (3 H, Me)	85
16	Ph	Ph	9899	98 4	7.54 (m, 5 H, H arom.); 7.30 (m, 5 H, H arom.); 5.43 (2 H, NH ₂)	95
lc	4-CIC ₆ H ₄	Me	56—57	555	7.57 (2 H, H arom.); 7.30 (2 H, H arom.); 5.40 (2 H, NH ₂); 2.10 (3 H, Me)	95
1d	$4-BrC_6H_4$	Me	85—86	841	7.48 (4 H, H arom.); 5.39 (2 H, NH ₂); 2.11 (3 H, Me)	98
1e	$4-O_2NC_6H_4$	Me	148-150	150	8.19 (2 H, H arom.); 7.80 (2 H, H arom.); 5.68 (2 H, NH ₂); 2.18 (3 H, Me)	98
1ſ	$4-MeOC_6H_4$	Me	134—135	13511	7.60 (2 H, H arom.); 6.90 (2 H, H arom.); 5.28 (2 H, NH ₂); 3.80 (3 H, MeO); 2.10 (3H, Me)	95
1g	4-CIC ₆ H ₄	н	56—57	56—57 ²	7.68 (1 H, CH=N); 7.48 (2 H, H arom.); 7.32 (2 H, H arom.); 5.58 (2 H, NH ₂)	95
lh	4-02NC6H4	н	136—137	13712	8.45 (2 H, H arom.); 7.73 (1 H, CH=N); 7.65 (2 H, H arom.); 5.75 (2 H, NH ₂)	95
1i	$4-Me_2NC_6H_4$	н	69—72	-	7.69 (1 H, CH=N); 7.42 (2H, H arom.); 6.70 (2 H, H arom.); 5.30 (2 H, NH ₂); 2.95 (3 H, Me)	95

Table 1. Characteristics of N-unsubstituted hydrazones of aromatic ketones and aldehydes

* The signals of CH and Me groups are singlets, those of NH_2 groups are broadened singlets, and in the case of hydrazone Ii, a broad signal; the signals of aromatic protons of hydrazones 1c,e-i have the shape of two doublets with J = 8 Hz, and that of 1d is a multiplet.

 $(70-80 \ ^{\circ}C)$ are the most important conditions for the selective path of the reaction. It can be assumed that due to a lower basicity of hydrazones of aromatic aldehydes and ketones, as compared to that of hydrazine (see review¹³), an excess of the latter almost completely binds the catalyst and thus excludes the possibility of activation of hydrazone, which is necessary for the preparation of azine. It should be mentioned that in all cases studied, base catalysis results in the formation of either a mixture of azine and hydrazone or azine only.

The method is rather versatile and makes it possible to prepare N-unsubstituted hydrazones in the case of both less reactive carbonyl compounds and unstable hydrazones. For example, benzophenone and acetophenone hydrazones were obtained in high yields. p-Dimethylaminobenzaldehyde hydrazone is the only exception: it contained a ~5% admixture of the corresponding azine (¹H NMR data) and on storage was transformed into products whose structure requires a special study.

Experimental

Melting points were determined on a Kofler hot stage. ¹H NMR spectra were recorded on a Bruker WM-250 instrument in CDCl₃. TLC was carried out on Silufol UV-254 plates in the hexane—EtOAc (7 : 1, v/v) system.

Preparation of N-unsubstituted hydrazones (general procedure). The corresponding ketone or aldehyde (10 mmol) was added to a solution of hydrazine hydrate (60 mmol) and *p*-toluenesulfonic acid (0.4 mmol) in 96% ethanol (5 mL). The mixture was heated at 70-80 °C until the starting carbonyl compound was completely consumed (the reaction course was monitored by TLC). Then the reaction mixture was cooled to 5-10 °C, and ice-cold water was added to it dropwise until the mass became completely thickened. The latter was filtered, and the residue on the filter was washed with cold water (3×10 mL) and dried in air. Recrystallization of hydrazones can result in their partial transformation into azines, which was observed in the case of hydrazones 1c and 1f. In the case of low-melting acetophenone hydrazone (1a), the reaction mixture was cooled to 5-10 °C, poured into cold water, and extracted with ether. The extract was washed with water and dried above CaCl₂. The ether was evaporated to give hydrazone 1a.

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Mass spectra of the negative ions of some dioxanes

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It was established by mass spectrometry of negative ions that fragmentation of some 1,3- and 1,4-dioxanes proceeds through intermediate $[M - H]^-$ ions. The fragmentation pathway depends on the site of negative charge localization in these ions.

Key words: substituted dioxanes, resonance capture of electrons, negative ions, mass spectra, fragmentation, $[M - H]^-$ ions.

Earlier,¹ we studied the formation of negative ions (NIs) from molecules of 1,3-dithianes and 1,3-dithiolanes using mass spectrometry of NIs in the regime of resonance capture of electrons. The present paper reports the results of a study of the formation of NIs from molecules of 1,4-dioxane (1), 1,3-dioxane (2), 2-methyl-1,3-dioxane (3), 2-phenyl-1,3-dioxane (4), 4-phenyl-1,3-dioxane (5), 2-vinyl-1,3-dioxane (6), and 2-nitrophenyl-1,3-dioxane (7).

Compounds 1-6 form NIs by capturing electrons with energies -8-9 and 6-7 eV, the latter providing lower yields (Table 1). These resonances are difficult to interpret because the photoelectronic spectra contain little information. Even in the case of compounds 1 and 2, *i.e.*, the simplest dioxanes, we could determine (because of broad ionization bands) only the ionization energies corresponding to removal of an electron from combinations of lone electron pairs on oxygen atoms, n_0^- and n_0^+ .² Nevertheless, one can state that compounds 1-6 form NIs in the region of electron-excited molecular states.

The fragmentation of compounds 2, 4, and 5 mainly proceeds through $[M - 31]^-$ ions presumably formed upon loss of a formaldehyde molecule from $[M - H]^-$ ions.

An analysis of the mass spectra of compounds 2-6 shows that the fragmentation can be represented by a scheme of decomposition of $[M - H]^-$ ions with charge localization on the C(5) atom (this scheme requires minimum structural changes).



Another pathway of the fragmentation of 1,3-dioxane, which leads to NIs with m/z 45 (C₂H₅O)⁻, is less distinct and implies removal of a hydrogen atom from the C(2) atom:



When $R^{\dagger} = Ph$, this pathway becomes more pronounced, probably, because of a greater stability of both the resulting ion and NI $[M - H]^{-}$ with charge localiza-

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