SYNTHESIS OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES FROM TRICHLOROMETHYLARENES AND ACYLHYDRAZINES

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A preparative synthesis of 2,5-disubstituted 1,3,4-oxadiazoles by the reaction of trichloromethylarenes with hydrazides of carboxylic acids of the aliphatic, aromatic and heteroaromatic series in methanol or ethanol in the presence of pyridine was developed.

In the study of the reactions of benzotrichloride with hydroxylamine and hydrazines in pyridine [1-4] in addition to the reductive condensation products — benzaldoxime, benzonitrile, benzaldazine and N-substituted benzalhydrazones — the heterocyclization products — 3,5-diphenyl-1,2,4-oxadiazole and 2,5-diphenyl-1,3,4-oxadiazole — have also been isolated in low yields. Similar results were also obtained by us in the reaction of trichloromethylarenes with semicarbazide and thiosemicarbazide [5, 6]: in addition to the corresponding semicarbazones and thiosemicarbazones, 2-amino-5-aryl-1,3,4-oxadiazoles and 2-amino-5-aryl-1,3,4-thiadiazoles were isolated in up to 30% yields. Furthermore, the ratio of the two competing processes is substantially dependent on the structure of trichloromethylarene and is probably determined by the relative ease of reduction of the latter — for benzotrichloride the yields of oxo- and thiadiazoles were higher than those of the reductive condensation products, in the case of 2,4-dimethylbenzotrichloride, the products of the two reactions were obtained in close to 1:1 ratios, while 2,4,6-trimethylbenzotrichloride gave only the corresponding semicarbazone and thiosemicarbazone.

The aim of the present work was to find such conditions for the reaction of trichloromethylarenes (I) with acylhydrazines (II), which would be optimal for the heterocyclization (Scheme 1, path "a"), leading to 2,5-disubstituted 1,3,4-oxadiazoles (III-V), and which would enable the suppression of the reductive condensation (path "b") leading to hydrazones (VI).

In order to find the dependence of the yield of the desired reaction end products on the structure of the starting compounds, we used six trichloromethylarenes (Ia-f) differing in the presence and character of the substituents and 11 hydrazides — derivatives of aliphatic (Ia), aromatic (IIb-g) and heteroaromatic (IIh-k) carboxylic acids.

The simplest method of optimization of the heterocyclization conditions could be by avoiding the use of pyridine as a solvent, since the latter, as we have shown previously [3], itself participates in the reduction process, converting into N-[[N'-α-chlorobenzyl-4-pyridyl]pyridinium salt (VII), which gives further reductive condensation products with hydrazines. We made several attempts to exclude pyridine from the reaction studied, which, however, were unsuccessful. In particular, the restricted character was clarified of the range of applicability of the known synthesis of disubstituted 1,3,4-oxadiazoles from benzotrichloride and benzhydrazide or its 4-substituted derivatives in an alcoholic solution in the presence of sodium carbonate [7]: on using methanol (method A) or ethanol (method B) as solvents, with transition from benzotrichloride to its alkyl-substituted derivatives Ib and Ic, the alcoholysis of trichloromethylarenes is sharply accelerated, so that esters of the corresponding substituted benzoic acids became the main products, while the yields of oxadiazoles did not exceed 25% (see Table 1). In the case of mesitotrichloride Id, the esters of 2,4,6-trimethylbenzoic acids were found to be the only reaction products, and the yields reached 80-85%.

The use of triethylamine as solvent and base (method C), although excluding the possibility of alcoholysis, does not lead to increase in the yield of oxadiazoles. In the absence of a base the alcoholysis preferentially takes place in methanol or ethanol.
Better results are obtained by boiling the reagents in a methanol—pyridine (method D) or ethanol-pyridine (method E) solution (ratio of alcohol—pyridine 2:1–5:1) for 6–16 h. Addition of sodium carbonate to the methanol—pyridine mixture (method F) only leads to a decrease in the yield because of a more effective alcoholysis. The yields of oxadiazoles (III–V), the reaction conditions and the characteristics of the compounds obtained are listed in Table 1.

Considering the influence of the structure of the starting compounds on the ease of formation of oxadiazoles III–V, it should be emphasized that the effect of the structure of the hydrazide is manifested fairly weakly. Thus, in the reaction of trichloromethylarenes Ia–c with nitrobenzhydrazides IId–f some decrease in the yields of oxadiazoles IV is observed on transition from meta- and para-nitrobenzhydrazides to the ortho-isomer, which can be explained by steric hindrances to the heterocyclization produced by the ortho-nitro group. At the same time, the OH group at the ortho-position — a less bulky substituent, having in addition an opposite polar character, cannot possibly exhibit any substantial influence on the yield of the oxadiazoles. For the reactions of trichloromethylarenes with hydrazides of the heteroaromatic series some decrease is observed in the yields of the desired end products V in comparison with the yields of oxadiazoles IV in reactions with the hydrazides of aromatic acids, which decrease is especially evident for hydrazides IIh, i — derivatives of 4,5-dibromo-2-furancarboxylic and 2-thiophencarboxylic acids.

On transition from unsubstituted benzotrichloride Ia to alkyl-substituted Ib, c, e, the yields of oxadiazoles decrease, which is attributable to the acceleration in the same sequence of the parallel proceeding alcoholysis. In the case of 2,4,6-trimethylbenzotrichloride Id, even under the optimal conditions for of heterocyclization, i.e., on heating of the trichloromethylarene and hydrazide in an alcohol-pyridine solution (methods D and E), the desired oxadiazoles cannot be obtained: only the reductive condensation products are formed — the substituted hydrazones of 2,4,6-trimethylbenzaldehyde VI and esters of 2,4,6-trimethylbenzoic acid, formed as the result of the alcoholysis of trichloride Id. This result may be con-