An efficient synthesis of symmetrical 2,5-diaryl-1,3,4-oxadiazoles

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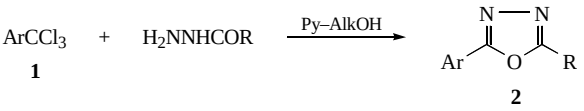
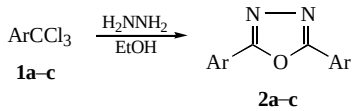
The interaction of trichloromethylarenes with excess hydrazine hydrate in alcohols leads to symmetrical 2,5-diaryl-1,3,4-oxadiazoles in 68–98% yields.

In previous papers[1,2] some factors governing the direction of the reaction of trichloromethylarenes (TCMA) with acylhydrazines and thioacylhydrazines were studied. In alcohols as solvents benzotrichloride **1a** and its substituted derivatives give predominantly alkyl arenecarboxylates formed as the result of alcoholysis while target 1,3,4-oxadiazoles (thiadiazoles) are minor products. In pyridine solutions the products of reductive condensation, *viz.* the respective N-substituted aromatic aldohydrazones are formed preferentially or exclusively. For heterocyclization leading to 1,3,4-oxadiazole **2** or thiadiazole derivatives carrying out the reaction in a mixture of pyridine with methanol or ethanol appeared to be optimal conditions.



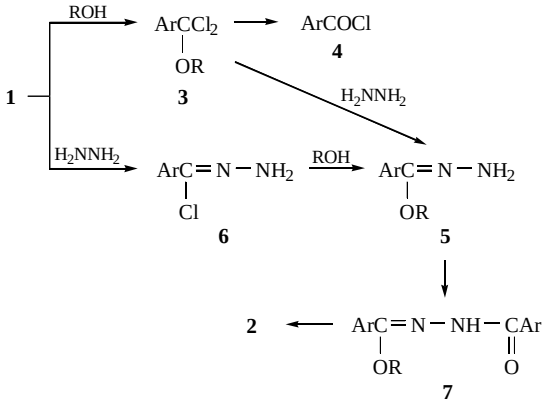
At the same time, in reactions of TCMA with an equimolar amount of hydrazine hydrate in a pyridine–methanol mixture, symmetrically-substituted 2,5-diaryl-1,3,4-oxadiazoles were obtained in low yields (20%) and, additionally, methyl esters and hydrazides of the corresponding arenecarboxylic acids were isolated.[2] In the present work we found unexpectedly that the yield of 2,5-diphenyl-1,3,4-oxadiazole **2a** became near to quantitative when pyridine was excluded and the reaction was carried out by refluxing for 40 min in ethanol and using excess hydrazine as an HCl acceptor.



a Ar = Ph **b** Ar = 4-ClC_6H_4 **c** Ar = 3-BrC_6H_4

4-Chlorobenzotrichloride **1b** and 3-bromobenzotrichloride **1c** reacted with hydrazine in a similar fashion to benzotrichloride; yields of compounds **2b**,**c** were 81% and 68%, respectively.† 2-Chlorobenzotrichloride and 2,4-dimethylbenzotrichloride, as well as mesitotrichloride, which gives only products of reductive condensation in alcohol–pyridine mixtures, failed to undergo heterocyclisation since they almost completely transform to the alcoholysis products, the corresponding aromatic carboxylates. Our attempts to prepare diphenyl-1,3,4-oxadiazole **2a** from benzotrichloride and benzohydrazide using an excess of the latter as an HCl acceptor gave the target product in only ~15% yield. It is possible that benzotrichloride interacts with benzohydrazide slower than with hydrazine hydrate and the process of heterocycle formation cannot compete with the undesirable reaction of benzotrichloride alcoholysis.

TCMA reactions with O-nucleophiles, and hydrolysis and alcoholysis in particular, probably proceed according to an S_N1 mechanism, the reaction rate being independent of alkali or acid additives. The limiting stage involves elimination of a Cl^- anion with the formation of an ArC^+Cl_2 cation and further transformations which proceed faster.[3–5] One can suppose that on benzotrichloride alcoholysis the intermediate **3** forms, which can transform either to aroyl chloride **4** by RCl elimination (*cf.* ref. 6) or to hydrazonoate **5** by reaction with the hydrazine present. It is possible, as we proposed,[2] that TCMA reacts first with hydrazine and then the hydrazonoyl chloride **6** formed converts to the ester **5**. The latter on interaction with trichloride **1**, aroyl chloride **4** or dichloroacetal **3** gives *N*-acylhydrazonoate **7** that transforms readily to 2,5-diaryl-1,3,4-ozadiazole **2**.



It should be noted that esters such as **7** were isolated in 30–50% yields in reactions of benzotrichloride with acylhydrazines[7] as well as with *N*-phenylsemicarbazide,[8] and on heating esters **7** converted almost quantitatively to heterocyclisation products, oxadiazoles of the type **2**. One can suppose that sterically hindered *O*-chlorobenzotrichloride, 2,4-dimethylbenzotrichloride and mesitochloride mainly react not with alcohol or hydrazine molecules but with water molecules to give aroyl chlorides that transform on further interaction with alcohol to esters, which, as we have shown, cannot undergo reaction with hydrazine under the conditions employed here.

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† 2,5-*Diphenyl*-1,3,4-*oxadiazole* **2a** was obtained from benzotrichloride (2.7 ml, 19.2 mmol) and hydrazine hydrate (3.82 g, 76.4 mmol) in 10 ml of ethanol (reflux, 40 min). The resulting crystals were filtered off, washed with aqueous ethanol, recrystallised from ethanol and dried in a vacuum dessicator. Yield 2.04 g (96%), mp 139.5–141 °C (*cf.* refs. 1,2).

2,5-*Bis*(4-*chlorophenyl*)-1,3,4-*oxadiazole* **2b** was obtained according the same procedure from 4-chlorobenzotrichloride in 81% yield, mp 243–245 °C (from DMF, *cf.* ref. 9). ^{1}H NMR (Bruker AC-200, 200 MHz, [$^2H_6$]DMSO) δ: 7.23 (s, 8H).

2,5-*Bis*(3-*bromophenyl*)-1,3,4-oxadiazole **2c** was prepared in a similar way from 3-bromobenzotrichloride in 68% yield, mp 178–180 °C (from DMF, *cf.* ref. 10). ^{1}H NMR (Bruker AC-200, 200 MHz, [$^2H_6$]DMSO) δ: 7.75 (d, 2H, *p*-H, *J* 8 Hz), 7.54 (br., 2H, *m*-H), 7.35 (t, 4H, *o*-H, *J* 8 Hz).

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