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RECYCLIZATION OF 1,3,4-OXADIAZOLES AND BIS-1,3,4-OXADIAZOLES INTO 1,2,4-TRIAZOLE DERIVATIVES. SYNTHESIS OF 5-UNSUBSTITUTED 1,2,4-TRIAZOLES

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Efficient methods have been developed for obtaining precursors of stable carbenes, viz. 5-unsubstituted 3,4-diaryl-1,2,4-triazoles and 3,3'- or 4,4'-bridge linked bis-1,2,4-triazoles, by the recyclization of 5-unsubstituted 1,3,4-oxadiazoles or p-phenylenebis-1,3,4-oxadiazole with anilines or aromatic diamines in the presence of trifluoroacetic acid or with aniline hydrochlorides in pyridine.

Keywords: 3,4-diaryl-1,2,4-triazoles, precursors of stable carbenes, 1,3,4-oxadiazoles, 3,3'- and 4,4'-bridge linked bis-1,2,4-triazoles, recyclization reaction.

One of the most important methods of obtaining the 1,2,4-triazole system is based on recyclization reactions of 1,3,4-oxadiazoles under the action of amines and hydrazines [1, 2]. These conversions are used for obtaining both monotriazoles and polytriazoles [2]. Recyclization in a series of individual aliphatic derivatives, particularly 2,5-dimethyl-1,3,4-oxadiazole, with amines (taking place at 110°C) has been known for a fairly long time [3]. Recyclization of aromatic derivatives, such as 2,5-diaryl-1,3,4-oxadiazoles, also gives triazoles, but are effected under more forcing conditions (150-200°C) [4]. However the latter process, according to our data, is accompanied by the formation of significant quantities of colored material which hinders the isolation of individual substances. In [5, 6] the recyclization is described of 2,5-dialkyl-1,3,4-oxadiazoles with hydrazines leading to derivatives of 4-amino-1,2,4-triazoles. It proceeds well with unsubstituted hydrazine even at room temperature, with monoalkylhydrazines with significantly more difficulty, on boiling in an excess of reactant, and leads to a low yield of 4-alkylamino-1,2,4-triazoles.

Among the numerous variants of recyclization, the reaction of 5-unsubstituted oxadiazoles has not been studied, and might give 5-unsubstituted 1,2,4-triazoles, important precursors in the synthesis of stable carbenes of the 1,2,4-triazole series (their salts act as precursors). The reaction was not used for the synthesis of bistriazole systems, including those unsubstituted in positions 3 or 5.

In connection with the development of the chemistry of stable carbenes it seemed of interest to synthesize 3-unsubstituted triazoles and the triazolium system. A method of obtaining triazolium salts is known, which consists of the conversion of amides with phosphorus oxychloride into the corresponding imidoyl chlorides, reaction of the latter with 1-substituted formhydrazides and cyclization of the condensation products

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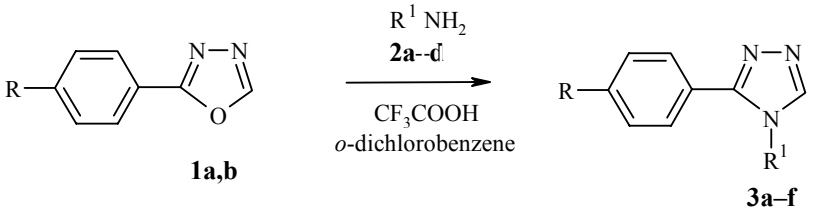
with acetic anhydride [7]. But in this synthesis good yields (58-84%) of the desired salts were achieved in only three cases, in the others, particularly in the synthesis of bisazolium systems, extremely moderate or low yields of salts (11-41%) were obtained. Data are not presented in this paper on the possibility of synthesizing neutral triazoles and conjugated bistriazole systems.

Our problem is the development of a means of recyclizing 1,3,4-oxadiazoles which should be useful for obtaining triazole precursors of stable carbenes, 5-unsubstituted 1,2,4-triazoles, particularly conjugated 1,2,4-triazoles, and would not lead to the formation of colored material.

To solve this problem initially the effect of acid additives on the yield of triazoles was studied in the example of the reaction of model compound 2-phenyl-1,3,4-oxadiazole (**1a**) with aniline **2a**.



1a,b **3a–f**

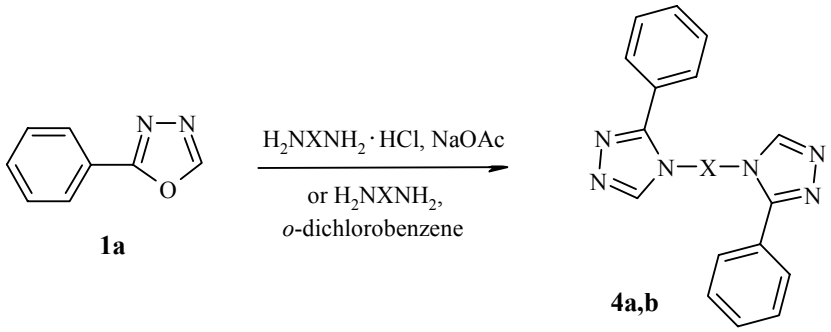
1 a R = H, **b** R = Br; **3 a-d** R =H; **e,f** R = Br; **2**, **3 a** R^1 = Ph, **b** $R^1 = C_6H_4Br$-*p*, **c** $R^1 = C_6H_4Me$-*p;* **d** $R^1 = \alpha$-$C_{10}H_7$; **3 e** R^1 = Ph, **f** $R^1 = C_6H_4Br$-*p*

On carrying out the reaction of oxadiazole **1a** with some aniline salts **2a** (hydrochloride, hydrobromide) without solvent the process is accompanied by sublimation of the aniline salt, which does not enable a yield of triazole **3a** greater than 30-40% to be achieved. The application of high-boiling aromatic solvents such as 1,2,4-triethylbenzene, without acid components makes an increase in the yield of triazole **3a** to 50% possible, but as in the melt colored material was obtained. Under the same conditions sublimation was also observed with aniline hydrochloride, as also on carrying out the process in the more polar *o*-dichlorobenzene (μ 2.50 D). We note that the use of high boiling aprotic solvents (DMF, N-methylpyrrolidone) leads to the formation of a significant amount of unidentified byproducts.

In order to prevent sublimation of the reactant in the process of recyclizing compound **1a** in aromatic solvents, in place of aniline hydrohalides we used aniline trifluoroacetate, which was prepared *in situ* from aniline and trifluoroacetic acid. Heating the mixture at 190°C in *o*-dichlorobenzene gives a high yield (95%) of 3,4-diphenyl-1,2,4-triazole (**3a**). In this reaction the favorable action on the yield and purity of triazole **3a** proves to be both the acid catalyst and the use of *o*-dichloro-benzene, as a result of probably, the adequate polarity of the solvent and the azeotropic mode of removing water during the process.

This procedure was used for the synthesis of other derivatives of 3,4-diaryl-1,2,4-triazole **3b-f** and also gave mainly good results (Table 1, 52-77% yields). In the majority of cases significant formation of colored contaminants did not occur. However in the case of the synthesis of naphthyltriazole **3d** the formation of colored material was observed, probably with the participation of the naphthyl group which is very inclined to combination reactions, and leads to a reduction in the yield of triazole to 36%.

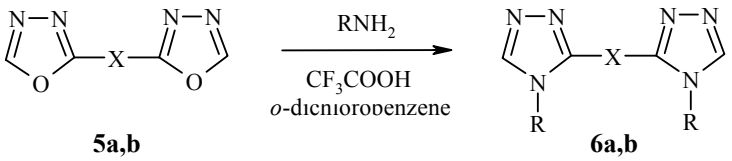
It was interesting to extend the method to the preparation of 3,3'- and 4,4'-bridge linked bistriazoles, precursors of triazole biscarbenes. On interacting oxadiazole **1a** with *p*-phenylenediamine hydrochloride in the presence of 2 equiv. sodium acetate in *o*-dichlorobenzene 4,4'-*p*-phenylenebis-1,2,4-triazole **4a** was obtained in 56% yield. The analogous procedure with *m*-phenylenediamine dihydrochloride gave only 24% bistriazole **4b**. Carrying out the same recyclization process with **1a** and *m*-phenylenediamine base in the presence of an equivalent amount of trifluoroacetic acid in dichlorobenzene increased the yield of bistriazole **4b** to 54%.



1a **4a,b**

4 a X = *p*-C_6H_4; **b** X = *m*-C_6H_4

To obtain 3,3'-bridge linked bis-1,2,4-triazoles recyclization was carried out of *p*-phenylenebis-1,3,4-oxadiazole **5a** and tetramethylenebis-1,3,4-oxadiazole **5b** with aniline and *p*-bromoaniline respectively. Reaction of oxadiazole **5a** proceeds extremely smoothly and gives bistriazole **6a** in high yield (95%). The yield of bistriazole **6b** was significantly less (27%) from the reaction of the aliphatic derivative **5b**. The reason for the reduction may be side reactions linked with the kinetic lability of alkyl-substituted azoles compared with the phenyl analogs [8].



5a,b **6a,b**

6 a R = Ph, **b** R = *p*-BrC_6H_4; **5, 6 a** X = *p*-C_6H_4, **b** X = $(CH_2)_4$

In spite of the fact that the method using trifluoroacetic acid is fairly convenient, it is not the only route to optimization of the conditions for this recyclization. The use of amine hydrochlorides and pyridine, which is taken in stoichiometric amount or in excess to the amine, also makes possible carrying out this process efficiently. On boiling a mixture of oxadiazole **1a** and aniline hydrochloride **2a** in a 3-4-fold excess of pyridine for 30 min the yield of triazole **3a** reaches 57%. Carrying out the reaction in *o*-dichlorobenzene in the presence of a stoichiometric amount of pyridine enables the yield of triazole **3a** to rise to almost 100 %. This result is probably caused by the efficient removal under the reaction conditions of water, the presence of which in the reaction mixture causes hydrolysis of the 2-unsubstituted oxadiazole.

Carrying out the recyclization of oxadiazoles under the action of amines on heating (180-190°C) in high boiling solvents, in *o*-dichlorobenzene in particular, under conditions of catalysis with trifluoroacetic acid or the analogous recyclization with amine salts in the presence of pyridine gives the best yields of 3-unsubstituted 1,2,4-triazoles.

In the ^{1}H NMR spectra of all the compounds investigated (Table 2) signals were detected for the aromatic CHN protons at 8.3-9.0 and for the benzene ring protons at 7.1-8.4 ppm. It is interesting that the signals of the CHN protons for bistriazoles **4a,b** and **6a** were displaced substantially towards low field in relation to the analogous monotriazole signal in the spectra of compounds **3a-f** (by 0.4-0.6 ppm), which probably indicates the presence of conjugation of the thiazole and phenylene nuclei in the bistriazole molecules, even for the *m*-substituted bistriazole **4b** (8.83 against 8.93 ppm for the *para* analog **4a**). Almost the same as in the 4,4'-linked bistriazoles **4a,b**, but seemingly more marked, conjugation is observed in the 3,3'-linked compound **6a** (8.97 ppm). Confirmation of this conclusion may also be the fact that the effect of the unconjugated triazole nuclei on the chemical shift of the signals of the CHN group proton in the spectrum of compound **6b** is insignificant and the signal is observed at 8.17 ppm. The latter is even somewhat displaced

TABLE 1. Characteristics of Compounds **3-6**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent for recrystallization)	R_f	Yield, %
		C	H	Br	N			
3a	$C_{14}H_{11}N_3$	76.3 / 76.0	5.0 / 5.0	—	12.1 / 12.0	155-157 (2-propanol)	0.75	95
3b	$C_{14}H_{10}BrN_3$	56.2 / 56.0	3.2 / 3.4	26.7 / 26.6	14.2 / 14.0	214-216 (DMF)	0.70	60
3c	$C_{15}H_{13}N_3$	76.4 / 76.6	5.8 / 5.6	—	17.9 / 17.9	151 (DMF)	0.68	57
3d	$C_{18}H_{13}N_3$	79.9 / 79.7	4.6 / 4.8	—	15.8 / 15.5	160-163 (benzene–hexane, 1:1)	0.62	36
3e	$C_{14}H_{10}BrN_3$	56.1 / 56.0	3.4 / 3.4	26.8 / 26.6	14.1 / 14.0	160-161 (DMF)	0.75	52
3f	$C_{14}H_9Br_2N_3$	44.3 / 44.4	2.4 / 2.4	42.0 / 42.2	11.2 / 11.1	225-226 (DMF)	0.58	77
4a	$C_{22}H_{16}N_6$	72.8 / 72.5	4.4 / 4.4	—	23.2 / 23.1	332-334 (methanol)	0.41	56
4b	$C_{22}H_{16}N_6$	72.4 / 72.5	4.5 / 4.4	—	23.4 / 23.1	221-223 (methanol)	0.56	54
5a	$C_{10}H_6N_4O_2$	56.0 / 56.1	2.8 / 2.8	—	26.0 / 26.2	240-241 (*o*-dichlorobenzene)	0.85	95
6a	$C_{22}H_{16}N_6$	72.6 / 72.5	4.6 / 4.4	—	23.0 / 23.1	>300 (DMF)	0.65	95
6b	$C_{20}H_{18}Br_2N_6$	47.7 / 47.8	3.5 / 3.6	32.1 / 31.8	16.7 / 16.7	325-326 (DMF)	0.65	27

towards high field in relation to the CHN signal of diaryl-substituted monotriazoles **3a-f** (8.3-8.4 ppm), probably due to the electron-donating action of the alkylene chain in the absence of conjugation of the triazole nuclei with one another. In the spectrum of bisoxadiazole **5** the signal of the CHN group proton is at substantially lower field (9.40) than in bistriazoles **4a,f** and **6a** (8.83-8.97 ppm) which is caused by the higher acceptor action of the oxygen atoms in the **5a** molecule than of the nitrogen atoms in structures **4** and **6**.

TABLE 2. ^{1}H NMR Spectra of the Synthesized Compounds **3-6**

Compound	Chemical shifts, δ, ppm. (*J*, Hz)
3a	7.28 (5H, m, Ar); 7.47 (5H, m, Ar); 8.34 (1H, s, CHN)
3b	7.16 (2H, d, ^3J = 8.6, Ar); 7.43 (5H, m, Ar); 7.63 (2H, d, ^3J = 8.6, Ar); 8.35 (1H, s, CHN)
3c	2.43 (1H, s, CH_3C); 7.11 (2H, d, ^3J = 8.6, Ar); 7.30 (5H, m, Ar); 7.47 (2H, d, ^3J = 8.6, Ar); 8.31 (1H, s, CHN)
3d	7.20 (3H, m, Ar); 7.43 (4H, m, Ar); 7.55 (3H, m, Ar); 8.02 (2H, m, Ar); 8.36 (1H, s, CHN)
3e	7.28 (4H, m, Ar); 7.48 (5H, m, Ar); 8.32 (1H, s, CHN)
3f	7.13 (2H, d, ^3J = 8.6, Ar); 7.31 (2H, d, ^3J = 8.6, Ar); 7.49 (2H, d, ^3J = 8.6, Ar); 7.63 (2H, d, ^3J = 8.6, Ar); 8.31 (1H, s, CHN)
4a	7.41-7.55 (14H, m, Ar); 8.93 (1H, s, CHN)
4b	7.44 (14H, m, Ar); 8.83 (1H, s, CHN)
5a	8.23 (4H, m, CH arom.); 9.40 (2H, s, CHO)
5b	2.44 (4H, m, β-CH_2), 2.88 (4H, m, α-CH_2), 8.80 (c, CHO)
6a	7.50 (14H, m, CH arom.); 8.97 (2H, s, CHN)
6b	1.77 (4H, m, CH_2C); 2.69 (4H, m, CH_2C); 7.18 (4H, d, *J* = 8.4, CHN); 7.68 (4H, d, *J* = 8.4, CHN); 8.17 (2H, s, CHN)

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer (200 MHz), internal standard was TMS. The purity of substances was assessed by TLC on Silufol silica gel, eluent was chloroform–methanol, 10:1.

3,4-Diaryl-1,2,4-triazoles 3a-f (General Method Using Trifluoroacetic Acid). A. Trifluoroacetic acid (10 mmol) and *o*-dichlorobenzene (1-2 ml) were added to a mixture of 2-aryl-1,3,4-oxadiazole (10 mmol) and aromatic amine (10 mmol), and the mixture was heated at 190°C for 10 h. The resulting solution was washed with hexane (20 ml) and the resinous or crystalline substance was treated with a 20% solution of sodium carbonate (1.59 g, 15 mmol). The solid was filtered off, washed with water, and recrystallized from the appropriate solvent (Table 1).

3,4-Diphenyl-1,2,4-triazole (3a) (Method Using Aniline Hydrochloride and Pyridine). B. A mixture of compound **1** (1.46 g, 10 mmol), aniline hydrochloride (1.29 g, 10 mmol), and pyridine (4 ml) was refluxed for 6 h. The excess of pyridine was distilled off, and the residue rubbed with 20% sodium carbonate solution (10 ml). The solid was filtered off and dried. Yield of crude triazole **3a** 2.2 g (100%). There was no depression of melting point with a sample of compound **3a** obtained by method A.

1,4-Bis(3-phenyl-1,2,4-triazol-4-yl)benzene (4a). A mixture of oxadiazole **1a** (2.92 g, 20 mmol), *p*-phenylenediamine dihydrochloride (1.81 g, 10 mmol), sodium acetate (1.64 g, 20 mmol), and *o*-dichlorobenzene (1.5 ml) was refluxed for 3 h 30 min. The reaction mixture was cooled, the solid rubbed with hexane (20 ml), the solid filtered off, and washed with hexane. A solution of sodium hydroxide (0.8 g, 20 mmol) in methanol (10 ml) was added to the residue, which was rubbed, the solid filtered off, washed with water to neutral reaction, and dried. Yield 2.03 g (56%).

1,3-Bis(3-phenyl-1,2,4-triazol-4-yl)benzene (4b). A mixture of oxadiazole **1a** (3.47 g, 23.8 mmol), *m*-phenylenediamine (1.28 g, 11.9 mmol), trifluoroacetic acid (1.82 ml, 23.8 mmol), and *o*-dichlorobenzene (2.5 ml) was refluxed for 4 h 30 min. The reaction mixture was cooled, the solid was rubbed with petroleum ether (40 ml), then filtered off, washed with petroleum ether, dried, and rubbed with methanol (15 ml) cooled to -10°C. The solid was filtered off, washed with methanol, and dried. Yield 2.32 g (54%).

Compounds 5a,b were obtained by the general approach described in [9], starting from the appropriate dihydrazides of dicarboxylic acids and an excess of ethyl orthoformate. Compound **5a**, in the pure state, and **5b,** as the crude product with a content of the main product of 60-70% (according to data of ^{1}H NMR spectra, Table 2), were used to obtain bistriazole **6b** without further purification.

1,4-Bis(4-phenyl-1,2,4-triazol-3-yl)benzene (6a). A mixture of compound **5a** (5 g, 23.4 mmol), aniline (4.25 ml, 46.7 mmol), trifluoroacetic acid (3.47 ml, 93.5 mmol), and *o*-dichlorobenzene (5 ml) was heated at 190°C for 14 h. The reaction mixture was washed with petroleum ether (20 ml), the solvent decanted, and the crystalline residue rubbed with an aqueous solution of sodium carbonate (5.3 g, 50 mmol). The crystalline powder of **6a** was washed with water to neutral reaction, filtered off, washed with petroleum ether, and dried. Yield 8.1 g (95%).

1,4-Bis(4-bromophenyl-1,2,4-triazol-3-yl)butane (6b) was obtained analogously to bistriazole **6a**, starting from 70% crude compound **5b** (2.86 g, 10.3 mmol) (synthesized by the general method for obtaining oxadiazoles [9]), 4-bromoaniline (3.55 g, 20.6 mmol), trifluoroacetic acid (1.58 ml, 20.6 mmol), and *o*-dichlorobenzene (3 ml). The mixture was heated for 10 h, then rubbed with petroleum ether (2 × 10 ml). The ether was decanted, toluene (10 ml) and 20% aqueous sodium carbonate solution (10 ml) were added, and the mixture stirred for 15 min. The solid was filtered off, and washed with petroleum ether. Yield of compound **6b** 1.4 g (27%).

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