An unusual tetrazole transacylation by tetrazolylacetic acid chlorides

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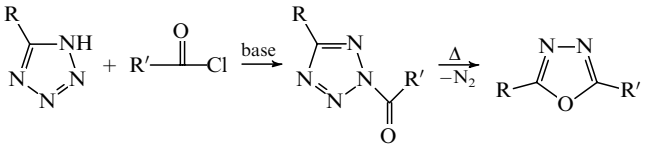
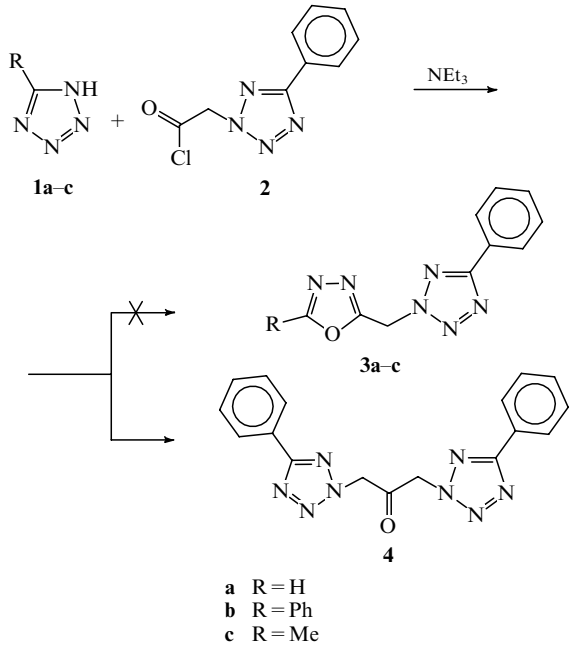
Bis(tetrazolyl)acetones have been obtained instead of the expected 2,5-disubstituted 1,3,4-oxadiazoles from interaction of 5-substituted tetrazoles with chlorides of tetrazolylacetic acids. The mechanism of the reaction is suggested to include *N*-acyl-intermediate heterolysis resulting in acyl-cation formation followed by transacylation of the methylene group in the second molecule of the acyl halide.

It was shown by Huisgen in 1960 that acylation of 5-substituted tetrazoles by acyl halides in pyridine resulted in the formation of the unstable *N*-acyltetrazoles. On heating, these compounds lose a nitrogen molecule and turn into intermediate nitrile imines which cyclize to 2,5-disubstituted 1,3,4-oxadiazoles[1] (Scheme 1). Acylation of 5-substituted tetrazoles by aliphatic and aromatic carboxylic acid halides in the presence of organic bases (such as pyridine or alkylamines) is used widely to obtain 2,5-disubstituted 1,3,4-oxadiazoles.[2–6] However, no information is available on the acylation of 5-substituted tetrazoles by tetrazolylacetic acid halides.



Scheme 1

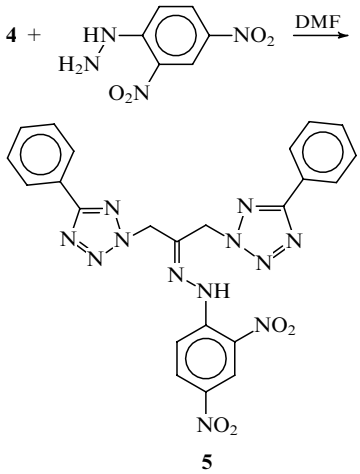
It might be supposed[2–6] that acylation of 5-substituted tetrazoles **1a–c** by 5-phenyl-2-tetrazolylacetic acid halide **2** leads to the corresponding 2,5-disubstituted 1,3,4-oxadiazoles **3a–c** containing a tetrazole ring (Scheme 2). We carried out the reaction between the tetrazoles **1a–c** and the acyl halide **2** using triethylamine as a base.



Scheme 2

A mixture of 55 mmol of tetrazole **1**, 12.2 g (55 mmol) of 5-phenyl-2-tetrazolylacetic acid halide **2** and 5.6 g (55 mmol) of triethylamine was stirred in 20 ml of dry acetone at first for 15 min at 0 °C and then for 1 h at 25 °C. The interaction of tetrazoles with acetone is negligible under such conditions.[7] The precipitated triethylamine hydrochloride was filtered off. On removing solvent from the filtrate, the residue was suspended in 20 ml of boiling water. The resulting solid residue was filtered off, dried and recrystallized from ethanol–dimethylformamide (DMF) (1:1) to give colourless crystals (mp 225–227 °C). Elementary analysis and spectral investigation show that there is only one reaction product (yield 30%), bis(5-phenyltetrazol-2-yl)acetone **4**, regardless of the substrate **1a–c** used.†

The interaction of compound **4** with 2,4-dinitrophenylhydrazine (Scheme 3) resulted in formation of 2,4-dinitrophenylhydrazone **5**.‡

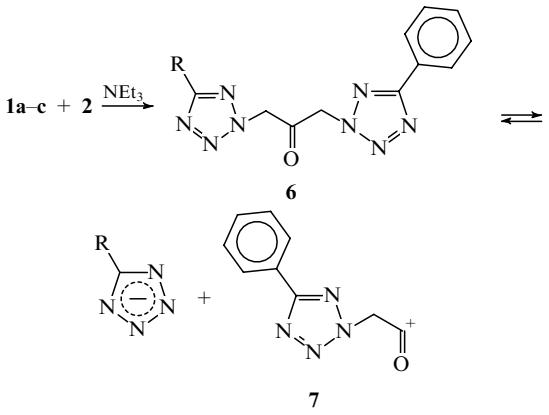


Scheme 3

The formation of bis(5-phenyltetrazol-2-yl)acetone **4** seems to proceed in the following way. In the first stage the respective *N*-acyl derivative **6** is formed. It can decompose to produce the acyl-cation **7**, which is a transacylation active intermediate,[8] Scheme 4.

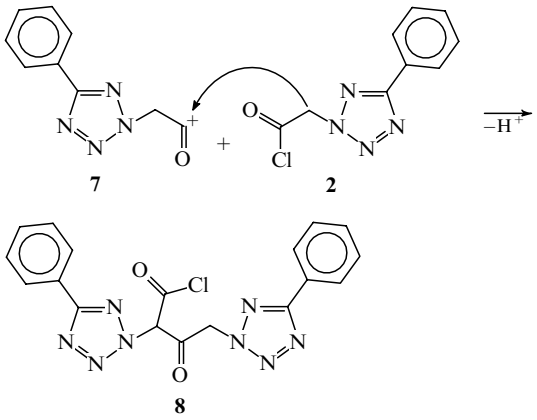
† *Compound* **4**. Calc. for $C_{17}H_{14}N_8O$: C, 58.96; H, 4.05; N, 32.37. Found: C, 58.64; H, 4.34; N, 32.75%. IR (KBr) ν/cm^{-1}: 1750 (C=O), 1020, 1045, 1070, 1290, 1440, 1450, 1525 (tetrazole). ^{1}H NMR ([$^2H_6$]DMSO, TMS, 200 MHz) δ: 6.33 (4H, s, CH_2), 7.57, 8.06 (10H, aromatic). ^{13}C NMR ([$^2H_6$]DMSO, 50 MHz) δ: 59.1 (CH_2), 126.4 (aromatic C), 126.7 (aromatic C), 129.4 (aromatic C), 130.8 (aromatic C), 164.4 (tetrazole C), 194.4 (C=O). After cooling the aqueous filtrate a substance precipitated which turned out to be 5-phenyl-2-tetrazolylacetic acid. In all cases, the expected compounds **3** could not be isolated.

‡ *Compound* **5**, yellow crystals (mp 216.5–218 °C), recrystallized from ethanol–DMF (1:2), yield 70%. Calc. for $C_{23}H_{18}N_{12}O_4$: C, 52.47; H, 3.42; N, 31.94. Found: C, 52.68; H, 3.57; N, 32.26%.



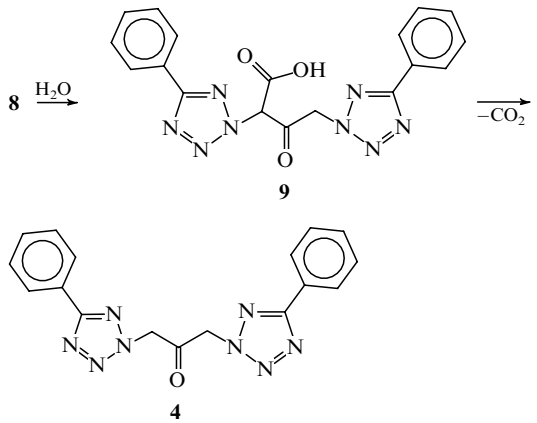
Scheme 4

The acylium ion **7** seems to attack the carbon atom of the methylene group in the second molecule of tetrazolylacetic acid halide **2**, leading to the formation of the acyl halide **8**, Scheme 5.



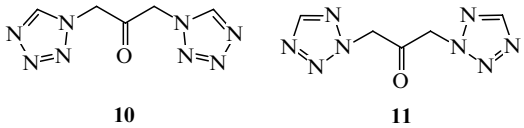
Scheme 5

Hydrolysis of compound **8** and subsequent decarboxylation of carboxylic acid **9** results in the formation of bis(5-phenyltetrazol-2-yl)acetone **4**, Scheme 6.



Scheme 6

We used 1- and 2-tetrazolylacetic acid chlorides in the reaction with tetrazoles **1a–c** to confirm this hypothesis. According to Scheme 2 the respective bis(tetrazolyl)acetones **10** and **11**§ were obtained (yields 12 and 15%, respectively).



The low yields of bis(tetrazolyl)acetones may be due to the competing process of triethylamine acylation.

In conclusion, it should be noted that bis(tetrazolyl)-acetones are not produced when the substrates **1a–c** are absent. These facts are consistent with the transacylation hypothesis. However, more investigations are necessary in order to elucidate the mechanism of the reaction under consideration.

References

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§ *Bis(tetrazol-1-yl)acetone* **10**, colourless crystals (mp 207–208 °C). Calc. for $C_5H_6N_8O$: C, 30.92; H, 3.09; N, 57.73. Found: C, 31.36; H, 2.82; N, 57.28%. IR (KBr) ν/cm^{-1}: 1765 (C=O); 980, 1270, 1410, 1440, 1490 (tetrazole). ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.1 (s, 4H, CH_2), 9.3 (s, 2H, CH).

Bis(tetrazol-2-yl)acetone **11**, colourless crystals (mp 184–185 °C). Calc. for $C_5H_6N_8O$: C, 30.92; H, 3.09; N, 57.73. Found: C, 31.46; H, 3.35; N, 58.32%. IR (KBr) ν/cm^{-1}: 1760 (C=O); 1030, 1050, 1210, 1420 (tetrazole). ^{1}H NMR ([$^2H_6$]DMSO) δ: 6.32 (s, 4H, CH_2), 9.0 (s, 2H, CH).