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PREPARATION OF 5-SUBSTITUTED 2-METHYL-1,3,4-OXADIAZOLES FROM 5-SUBSTITUTED TETRAZOLES AND ACETIC ANHYDRIDE

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Abstract: Readily available tetrazoles can be transformed into the corresponding 2-methyl-1,3,4-oxazodiazoles by heating their acetic anhydride solution. The procedure is simple, short, gives high yields, and is applicable to large scale syntheses.

1,3,4-Oxadiazoles as biologically active compounds have a wide variety of applications in medicine[1] and agriculture.[2] Several 2-alkyl-5-aryl-1,3,4-oxadiazoles have been reported, although less frequently in recent years, as photographic color formers.[3] So there is considerable need for simple a method for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles.

1,3,4-Oxadiazoles are mainly obtained from acyclic precursors. The most widely used procedure is thermal or catalyzed cyclization of 1,2-diacylhydrazines. The method may also be used for mono-

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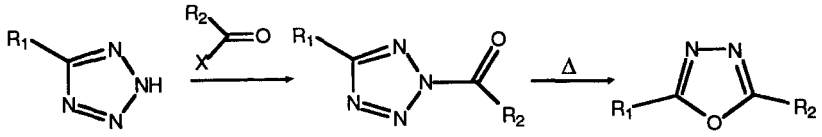


Scheme 1

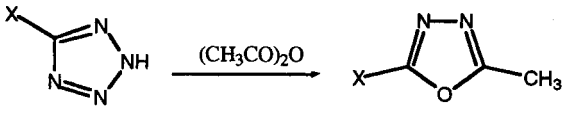
substituted oxadiazoles and oxadiazoles with ester groups.[4] Asymmetric 2,5-diaryl-1,3,4-oxadiazoles can be obtained in good yield by heating 5-substituted tetrazoles with carboxylic acid chlorides in pyridine.[5]

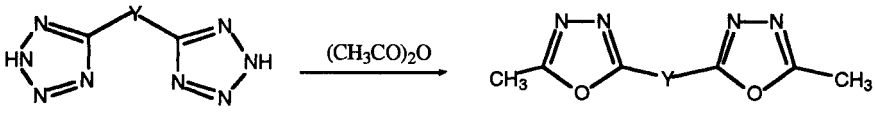
Recently, we have shown that N-acyltetrazoles are highly reactive intermediates in the preparation of acid derivatives.[6] The reaction is temperature sensitive, and substantial amounts of the 2,5-substituted-1,3,4-oxadiazoles as byproduct at elevated temperature were formed.

The method which will be described is extremely simple, gives a high yield of pure compound, and the starting materials can be obtained from readily available organic cyanides.[7] Our best synthetic procedure for the preparation of 2,5-disubstituted 1,3,4-oxadiazoles from tetrazoles and acids is demonstrated by the example of the reaction of 5-phenyltetrazole with racemic 2-phenylbutanoic acid. Because the tetrazoles have pKa values comparable to carboxylic acid, it is not surprising that the N-acyltetrazoles behave like acid anhydrides. One of our approaches in the preparation of the oxadiazoles was to use tetrazole as an acid catalyst which will protonate the ester and eliminate the alcohol part producing N-acyltetrazole as the reaction intermediate (Scheme 1).

Mixing ethyl 2-phenylbutanoate with 5-phenyltetrazole in dioxane or diglyme after heating for three days at 100 °C gives only starting material. Pyrolyses at 180 °C for 10 min results in only negligible amounts of product (~5%) and thermal degradation of the tetrazole. To activate the acid and allow for a reaction temperature <100 °C, 1,3-dicyclohexylcarbodiimide (DCC) was used. Equivalent amounts of the tetrazole, the acid, and DCC (10 mmol) in THF (20 mL) were stirred at room temperature for 0.5 h and refluxed overnight. Conversion was more than 90% (NMR). The purification was performed on silica gel in chloroform-petroleum ether (4:1) to obtain product in 63% yield. The method has two drawbacks, namely the low overall yield, and cumbersome purification of the product from dicyclohexylurea. 1,1'-Carbonyldiimidazole was studied next as acid activating compound. In this case the separation of the imidazole from the product was mere extraction of the chloroform solution with base, but the yield of the reaction was again low (57%). Eventually, the oxadiazole can be obtained in 75% yield by heating (90 °C) a mixture of the tetrazole and the acid chloride in pyridine for several hours.[5] An anhydride prepared by heating an acetic anhydride solution of 2-phenylbutanoic acid,[8] after removal of the excess solvent and formed acetic acid by distillation, was also used as a source for the acyl group. The such anhydride (2.1 equivalents) was heated in pyridine with the tetrazole. After work-up 2-(1-phenyl-1-propyl)-5-phenyl-1,3,4-oxadiazole (1) was obtained in 92% yield. Although the acid can be recovered from the reaction mixture by a base extraction and crystallization, the method seems not to be suited when an expensive starting acid is used as starting material.

Table 1. The yields of 2-methyl-1,3,4-oxadiazoles prepared from the corresponding tetrazole and acetic anhydride.





	X	Y	Yield (%)
2	C_6H_5		96[a]
3	3-$CH_3C_6H_4$		93
4	4-$CH_3C_6H_4$		91
5	3-$O_2NC_6H_4$		94
6	4-$O_2NC_6H_4$		98
7		1,4-C_6H_4	93
8		1,3-C_6H_4	94
9		$(CH_2)_4$	82
10		$(CH_2)_5$	85

[a]Obtained on a 0.1 mol scale whereas the others are obtained on a 5 mmol scale.

The 2-methyloxadiazoles synthesized by this method are presented in Table 1.

The preparation of 2-methyl substituted 1,3,4-oxadiazoles, on the other hand, can be achieved in high yield from very inexpensive starting materials, and in a short time. The starting tetrazole was mixed with the acid anhydride as solvent and refluxed for 0.5 h. The solvent was evaporated, and the residue crystallized. The whole procedure can be completed in 1-2 h and oxadiazoles isolated in greater than 90% yield. The procedure is applicable to large scale[9] oxadia-

zole synthesis and in the case of 5-phenyltetrazole (**2**) the yield is greater than 95%.

Conclusion

In conclusion, we have demonstrated that the simple transformation of readily available 5-substituted tetrazoles into commercially precious 2-methyl-5-substituted 1,3,4-oxadiazoles can be achieved by brief heating of the tetrazole in acid anhydride. The method is applicable to scale up and can be used for preparation of 2-alkyl or aryl oxadiazoles if the acid component is inexpensive or can be recovered in the process.

Experimental

Mass spectra were recorded on a 70 eV GC-MS Hewlett Packard 5890 Series, II, ^{13}C (75 MHz) and ^{1}H NMR (300 MHz) spectra were recorded on a Varian Gemini NMR spectrometer, with tetramethylsilane as reference and in $CDCl_3$ as solvent. IR spectra were recorded on a Nicolet 550 FT-IR at 2 cm^{-1} resolution as KBr plates. Thin layer chromatography (TLC) was performed on 0.2 mm silica gel 60 F_{254} plates from E. Merck. The chromatograms were developed in a chloroform-petroleum ether mixture (4:1, if not indicated otherwise). Melting points (uncorrected) were determined on an Electrothermal IA 9000 Digital Melting Point Apparatus. All chemicals were obtained from Aldrich and used as such.

Preparation of (*R,S*)-2-(1-phenyl-1-propyl)-5-phenyl-1,3,4-oxadiazole (1)

The mixture of 2-phenybutanoic acid (345 mg; 2.1 mmol) in acetic anhydride (10 mL) was refluxed for three hours. The solvent was evaporated and a pyridine (10 mL) solution of 5-phenyltetrazole (146 mg; 1 mmol) was added to the oily residue. The reaction mixture was heated at 90 °C for five hours. The solvent was evaporated at reduced pressure. The residue was dissolved in chloroform (20 mL) and washed with water (3x20 mL), 10% sodium hydroxide (3x10 mL) and again with water (3x20 mL). The organic layer was dried over anhydrous magnesium sulfate and flash evaporated. The oily residue was crystallized from chloroform-petroleum ether. The yield was 92% (240 mg); >99% pure (GC); IR (KBr) 3450, 3258, 1722, 1714, 1667, 1280, 1170, 741, and 699 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.68 (d of d, J=8 Hz, 2H, ortho 5-phenyl hydrogen), 7.17 and 705 (m, 3H +5H aromatic protons), 3.85 (t, J=8 Hz, 1H, hydrogen atom), 2.02 (octet, J=7, diastereotopic hydrogen atom), 1.85 (octet, J=7 Hz, diastereotopic hydrogen atom), 0.68 (t, J=7 Hz, CH_3).; ^{13}H NMR ($CDCl_3$) δ 167.3, 163.4 (oxadiazole carbon atoms), 138.1, 130.8, 128.1, 128.0, 127.1, 126.7, 126.0, 122.9 (eight aromatic carbon atoms), 44.3 (chiral carbon atom), 26.7 (CH_2), 11.4 (CH_3). MS e/m 51, 63, 77, 91 106, 132, 179, 236, 249, 264 (M^+), 265 ($M+1^+$), 266 ($M+2^+$).

Preparation of 2-methyl-5-phenyl-1,3,4-oxadiazole (2)

Acetic anhydride (100 mL) and 5-phenyltetrazole (14.6 g; 0.1 mol) was refluxed for 30 minutes. The solvent (acetic anhydride and

acid) was evaporated, and the oily residue was crystallized from petroleum ether. The yield was 96% (15.4 g); >99% pure (GC); m. p. 66.5-66.8 °C; IR (KBr) 3440, 3335, 3245, 3178, 3131, 1640, 1630, 1500, 1422, 1300, 1037, 779, and 585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.69 (d of d, 2H, J=6.5 Hz, ortho aromatic protons), 7.19 (t, 2H, J=6.5Hz, meta aromatic protons), 7.16 (t, 1H, J=6.5Hz, para aromatic proton), 2.20 (s, 3H, methyl); ^{13}C NMR δ 163.2, 162,3 (oxadiazole carbon protons), 130,1 127.7, 125.2, 122.7 (four phenyl carbon atoms), 9.7 (methyl carbon atoms).; MS m/e 47, 50, 51, 63, 77, 78, 89, 90 103,104, 105, 118, 160 (M^+), 161 ($M+1^+$), and 162 ($M+2^+$).

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7. For an excellent selection of tetrazoles syntheses from organic nitriles see: Kadaba, P. K. *Synthesis* **1973**, 71.
8. See experimental part.
9. The reaction between 5-phenyltetrazole and acid anhydride was carried out with 300 g of the tetrazole. The time necessary to obtain the pure product in 98% yield was less than two hours.

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