phenylalanine, ethyl glycinate hydrochloride, and diisopropylethylamine was heated at reflux in 50 ml of tetrahydrofuran for 3 hr. Upon purification, ethyl *N*-benzyloxycarbonyl-L-phenylalanylglycinate was obtained in 85% yield.

Experimental Section

Method I.—The preparation of *N*-*n*-butylacetamide is a typical example of a preparation by method I. A mixture of 13.1 g of triphenylphosphine, 50 ml of CCl_4, and 150 ml of THF was refluxed together for 30 min. The solution was cooled in an ice–water bath to 5° and 2.85 ml of AcOH was added. The mixture was allowed to stand at 5° for 10 min. *n*-Butylamine (9.73 ml) was added, and the mixture was heated at reflux for 45 min. The reaction mixture was cooled to room temperature, and the *n*-butylamine hydrochloride which had precipitated was removed by filtration. The volatile solvents were removed *in vacuo*, and the product was isolated by vacuum distillation, bp 85–87° (0.1 mm), 5.25 g (91%).

Method II.—The preparation of *N*-di-*n*-butylacetamide is a typical example of a preparation by method II. A mixture of 13.1 g of triphenylphosphine, 20.0 g of bromotrichloromethane, 2.85 ml of AcOH, and 16.7 ml of di-*n*-butylamine was refluxed together for 2 hr in 150 ml of THF. The reaction mixture was cooled to room temperature and the di-*n*-butylamine hydrohalide was removed by filtration. The volatile solvents were removed *in vacuo*, and the product was isolated by vacuum distillation, bp 110–112° (11 mm), 7.8 g (92%).

Ethyl *N*-Benzyloxycarbonyl-L-phenylalanylglycinate.—A mixture of 1.31 g (50 mmol) of triphenylphosphine, 1.98 g (100 mmol) of bromotrichloromethane, 1.50 g (50 mmol) of *N*-benzyloxycarbonyl-L-phenylalanine, 0.77 g (55 mmol) of ethyl glycinate hydrochloride, and 1.45 g (112 mmol) of diisopropylethylamine was heated at reflux in 50 ml of THF for 3 hr. The reaction mixture was cooled to room temperature and the diisopropylethylamine hydrohalide was removed by filtration. The volatile solvents were removed *in vacuo*. The peptide was purified by column chromatography upon silicic acid. The product was eluted with ether–methanol (80/20); the yield was 85% after recrystallization from EtOAc–petroleum ether (bp 30–60°), mp 105–106° (lit.[6] mp 106–107°). The optical rotation, $[\alpha]^{25}D$ −16.7° (*c* 2, EtOH), of the product was compared with that of the same peptide prepared by the nitrophenyl ester method,[7] $[\alpha]^{25}D$ −16.8° (*c* 2, EtOH) [lit.[6] $[\alpha]^{20}D$ −16.6° (*c* 2, EtOH)].

Registry No.—**1**, 603-35-0; bromotrichloromethane, 75-62-7; *N*-*n*-butylacetamide, 1119-49-9; *N*-di-*n*-butylacetamide, 1563-90-2; ethyl *N*-benzyloxycarbonyl-L-phenylalanylglycinate, 4526-88-9.

(6) R. W. Young, K. H. Wood, R. T. Joyce, and G. W. Anderson, *J. Amer. Chem. Soc.*, **78**, 2126 (1956).
(7) M. Bodanszky, *Nature*, **175**, 685 (1955).

The Reaction of "Activated" Esters with Amidoximes. A Convenient Synthesis of 1,2,4-Oxadiazoles

JOHN A. DURDEN, JR.,* AND D. L. HEYWOOD

Research and Development Department, Union Carbide Corporation, Chemicals and Plastics, South Charleston, West Virginia 25303

Received September 25, 1970

The preparation of 1,2,4-oxadiazoles by the reaction of amidoximes with acylating agents such as acid chlorides and anhydrides has been described frequently.[1,2]

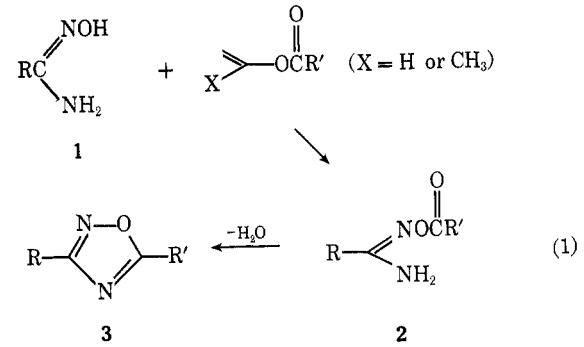
(1) (a) F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962); (b) F. Eloy, *Fortschr. Chem. Forsch.*, **4**, 807 (1965).
(2) J. H. Boyer in "Heterocyclic Chemistry," Vol. 7, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1961, p 508 ff.

The reaction of esters with amidoximes might be expected to be influenced by the same factors which govern their basic hydrolysis.[3] In considering these parameters it seemed that two of them, the electrophilicity of the carbonyl and the basicity of the anion being displaced, could be particularly important in influencing the ease of reaction of esters which might lead to the types of substituted oxadiazoles which were the object of this work. Thus, simple esters of trichloro- and dichloroacetic acids, and, particularly, enol esters of aliphatic or aromatic acids, have been found to react with amidoximes in a generally straightforward manner to give 1,2,4-oxadiazoles. With aliphatic esters such as ethyl acetate, however, oxadiazoles were not detected.

The reaction of enol (vinyl or isopropenyl) esters with amidoximes offers a convenient, and apparently general, route to 1,2,4-oxadiazoles. This method is particularly useful for the preparation of the lower boiling dialkyl derivatives, *e.g.*, 3,5-dimethyl-1,2,4-oxadiazole, previously prepared by more indirect routes.[4]

The reaction may be carried out either in excess ester or in an inert solvent such as benzene. The use of an inert solvent does not appear to be advantageous in most cases although in some instances, *e.g.*, vinyl trifluoroacetate, a solvent is needed to moderate the initial reaction of the amidoxime with the ester. In the preparation of 5-methyl compounds, isopropenyl acetate appears to be more effective than the vinyl ester, probably because of its higher boiling point.

That the reaction involved an initial O-acylation of the amidoxime[5] is shown by the isolation of *O*-acetylbenzamidoxime (**2**, R = C_6H_5; R′ = CH_3) as well as 5-methyl-3-phenyl-1,2,4-oxadiazole (**3**, R = C_6H_5; R′ = CH_3) from a reaction in which benzamidoxime (**1**, R = C_6H_5) was heated at reflux in vinyl acetate for 8 hr. No evidence of competing O,N-diacylation was observed (eq 1).[5] The general utility of the enol ester–



(1)

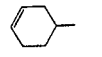
amidoxime reaction is illustrated in Table I and the Experimental Section.

The reaction of benzamidoxime (**1**, R = C_6H_5) with excess methyl trichloroacetate at reflux gave chloroform and methanol in addition to a 38% yield of 3-phenyl-5-trichloromethyl-1,2,4-oxadiazole (**3**, R = C_6H_5; R′ = CCl_3). Use of benzene as solvent increased the yield to 66% and only water and methanol were de-

(3) J. Hine, "Physical Organic Chemistry," 1st ed, McGraw-Hill, New York, N. Y., 1956, p 274.
(4) R. Lenaers, C. Moussebois, and F. Eloy, *Helv. Chim. Acta*, **45**, 441 (1962).
(5) J. A. Durden and D. L. Heywood, *J. Org. Chem.*, **30**, 4359 (1965).

TABLE I

OXADIAZOLES PREPARED *via* VINYL ESTERS

R	R′	Solvent[a]	Yield, %	Bp (mm) or mp, °C
CH_3	CH_3	1	69	118–124[b]
CH_3	C_2H_5	1	62	140.8[c]
C_6H_5	CH_2Cl	2	35	39–40.5[d]
CH_3	CH_2Cl	2	68	80–83 (15)[e]
CH_3	CH_2Cl	1	61	80–83 (15)
C_6H_5	CF_3	4	43	38–39[f]
C_6H_5	H	4	49	73–75 (2)[g]
3-$NO_2C_6H_4$	CH_3[h]	3	21	109–110[i]
	CH_3[h]	3	49	103–109 (10)[j]

[a] 1 is excess ester, 2 is benzene, 3 is xylene, and 4 is toluene. [b] Reference 4 reports bp 124.5°. [c] Reference 10 reports bp 139°. [d] Reference 1b reports mp 38–39°. [e] The infrared spectrum is identical with that of known material (ref 9). [f] Melting point. Calcd for $C_9H_5F_3N_2O$: C, 50.47; H, 2.34. Found: C, 50.77; H, 2.03. [g] Reference 4 reports bp 71–72° (1 mm). [h] Used isopropenyl acetate. [i] From heptane, ref 1b reports mp 109°. [j] Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37. Found: C, 65.88; H, 7.37.

tected as by-products. In similar reactions acetamidoxime gave only minor amounts of 3-methyl-5-trichloromethyl-1,2,4-oxadiazole (**3**, R = CH_3; R′ = CCl_3) together with by-products such as methanol, chloroform, 3,5-dimethyl-1,2,4-oxadiazole, and dimethyl carbonate. The occurrence of 3,5-dimethyloxadiazole may indicate some thermolysis of the acetamidoxime under the reaction conditions.[1a]

Benzamidoxime with excess methyl dichloroacetate gave 52% of 3-phenyl-5-dichloromethyl-1,2,4-oxadiazole (**3**, R = C_6H_5; R′ = $CHCl_2$) while with a stoichiometric amount of ester in benzene a yield of 61% was obtained. Acetamidoxime under similar conditions gave 3-methyl-5-dichloromethyl-1,2,4-oxadiazole (**3**, R = CH_3; R′ = $CHCl_2$) in yields of 33% (slightly impure) and 28%, respectively.

Experimental Section[6]

General Procedure for Reactions Involving Methyl Di- and Trichloroacetate.—A mixture of almost equivalent amounts of ester and amidoxime in 100 ml of solvent (where no solvent was used an excess of ester was employed) was heated at reflux under azeotroping conditions (where excess ester was the solvent, the reaction was carried out under a distillation head at high reflux ratio). When no more volatile materials (methanol, water, chloroform) could be detected by glc in the distillate, the reaction mixture was cooled, filtered to remove any solid, and distilled. In most cases unreacted ester, solvent, and oxadiazole were collected as discrete fractions, whereas by-products such as dimethyl carbonate and dimethyl oxadiazole were detected as components of fractions by combinations of infrared, glc, and mass spectral studies.

Using this procedure a mixture of 27.2 g (0.2 mol) of benzamidoxime and 60 g (0.33 mol) of methyl trichloroacetate was slowly heated to 104° over a period of 7 hr to give 19.5 g (37%) of **3-phenyl-5-trichloromethyl-1,2,4-oxadiazole**, bp 97–104° (0.05–0.15 mm) [lit.[7] mp 26°, bp[8] 95–96° (0.01 mm)]. The infrared spectrum of this product was identical with that of a known material prepared by the method of Sousa, *et al.*[8]

A reaction involving benzamidoxime (13.6 g, 0.1 mol) and methyl dichloroacetate (22 g, 0.15 mol) in 100 ml of benzene carried out according to the general procedure with a reflux period of 20 hr gave 14 g (61%) of **3-phenyl-5-dichloromethyl-1,2,4-oxadiazole**, mp 39–40° (ethanol–water) (lit.[9] 46°). The infrared spectrum of this product was identical with that of a sample prepared by the reaction of benzamidoxime and dichloroacetyl chloride.[8]

Anal. Calcd for $C_9H_6Cl_2N_2O$: N, 12.23. Found: N, 12.19.

The Reaction of Amidoximes with Enol Esters.—The following examples illustrate the general procedure used to prepare the compounds in Table I.

3,5-Dimethyl-1,2,4-oxadiazole (3, R = R′ = CH_3).—A suspension of 37 g (0.5 mol) of acetamidoxime in 107 ml (0.5 mol + 50 ml) of isopropenyl acetate was heated at reflux under a distilling head for 5–6 hr during which time acetone was slowly removed at a head temperature of 65°. When acetone removal was essentially complete, the reaction mixture was distilled through an 18-in. Nester-Faust spinning-band column (stainless steel band) to give 39.5 g (81%) of product, bp 118–123° (lit.[5] 124.5°). The infrared spectrum shows a band at 6.34 μ, together with others, characteristic of 3,5-disubstituted 1,2,4-oxadiazoles[10] but showed no bands indicative of a carbonyl-containing impurity. No impurities could be detected by glc.

3-Methyl-5-phenyl-1,2,4-oxadiazole (3, R = CH_3; R′ = C_6H_5).—A suspension of 7.4 g (0.1 mol) of acetamidoxime in 22 g (0.15 mol) of vinyl benzoate was heated at a gentle boil under distillation conditions, and acetaldehyde was slowly removed while the suspended solid dissolved. When acetaldehyde evolution was complete, water evolution began (indicative of ring closure); heating was continued for 3 hr to complete cyclization. The reaction mixture was evaporated *in vacuo*, the residue was washed with 10% sodium hydroxide solution, and the insoluble material was taken up in a petroleum ether–hexane mixture with a trace of ethanol added. After drying over sodium sulfate, this solution, upon chilling, gave 8 g (60%) of product, mp 57–58.5° (lit.[1a] 57°), ir 6.34 (μ) (characteristic of 1,2,4-oxadiazoles).

Reaction of Benzamidoxime with Vinyl Acetate. A. In Excess Ester. Preparation of *O*-Acetylbenzamidoxime (2, R = C_6H_5; R′ = CH_3) and 5-Methyl-3-phenyl-1,2,4-oxadiazole (3, R = C_6H_5; R′ = CH_3).—A mixture of 13.6 g (0.1 mol) of benzamidoxime and 30 ml of vinyl acetate was stirred and heated under gentle distillation for 8 hr while acetaldehyde was slowly removed. The cooled reaction mixture was diluted with 200 ml of petroleum ether (bp 30–60°); an oil separated which crystallized upon chilling. When collected and dried this amounted to 11 g (59.5%) of **2** (R = C_6H_5; R′ = CH_3), mp 93–94.5° (lit.[11] mp 96°). The infrared spectrum was completely analogous to that *O*-benzoylbenzamidoxime.[5] The petroleum ether filtrate, upon concentration and charcoal treatment, gave 4 g (24%) of **3** (R = C_6H_5; R′ = CH_3), mp 38–39° (lit.[12] 41°).

B. In Benzene. 5-Methyl-3-phenyl-1,2,4-oxadiazole (3, R = C_6H_5; R′ = CH_3).—A mixture of 13.6 g (0.1 mol) of benzamidoxime and 9.8 g (0.1 mol) of vinyl aceate in 60 ml of benzene was heated at reflux under a Dean-Stark trap until 1.6 ml of water was collected (12 hr). The reaction mixture was washed with water, evaporated to 20 ml *in vacuo*, and then diluted with petroleum ether. Chilling produced a solid which was collected and recrystallized from ethanol–water to give the product, 5 g (30%), mp 39° (lit.[11] 41°).

Reaction of Benzamidoxime with Isopropenyl Acetate. 5-Methyl-3-phenyl-1,2,4-oxadiazole (3, R = C_6H_5; R′ = CH_3).—A mixture of 6.8 g (0.05 mol) of benzamidoxime and 40 ml of isopropenyl acetate was heated at reflux for 24 hr. The mixture was then evaporated *in vacuo* and the residue was recrystallized from ethanol–water to give 6 g (75%) of product, mp 35–36° (lit.[11] 41°).

Registry No.—**3** (R = C_6H_5; R′ = CF_3), 1736-55-6; **3** (R = cyclohexen-4-yl; R′ = CH_3), 27925-50-4.

(6) The melting points are uncorrected. The infrared spectra were obtained using a Perkin-Elmer 21 infrared spectrophotometer. The glc analyses were carried out on A-90 instrument using a 5-ft 10% silicone on Fluoropak column at 127° and 12.5 psig helium flow. Vinyl and isopropenyl acetate are products of Union Carbide Corp.; the other vinyl esters are also commercially available. Acetamidoxime[4] and benzamidoxime[1a] were prepared from the corresponding nitriles and hydroxylamine.

(7) R. Lenaers and F. Eloy, *Helv. Chim. Acta*, **46**, 1067 (1963).

(8) A. A. Sousa, H. C. Chitwood, and J. A. Durden, U. S. Patent 3,192,103 (1965).

(9) R. Buyle, F. Eloy, and R. Lenaers, Union Carbide European Research Associated, unpublished results.

(10) J. Barrans, *C. R. Acad. Sci.*, **249**, 1096 (1959).

(11) F. Eloy and R. Lenaers, *Bull. Soc., Chim. Belges*, **72**, 91 (1963).

(12) F. Tiemann and P. Kruger, *Ber.*, **17**, 1685 (1884).