Insulation was packed around the sides of the dish and the sample was then irradiated for 20 hr with the Hanovia arc (Pyrex filter) placed 4 in. above the top of the dish. The crude product was dissolved in 20 ml of hot benzene and filtered to remove insoluble tar. Cyclohexane (80 ml) was added, and the solution was heated to boiling, treated with Darco, and again filtered. The filtrate was cooled to room temperature and then overnight at 10° to yield 250 mg (14.6%) of pale yellow crystals. Recrystallization from benzene–cyclohexane gave crystals: mp 185.5–186.5°; nmr ($CDCl_3$) δ 2.57 (m, CH_2CH_2), 4.2 (2 H, m, CHAr), and 7.1 and 7.95 (8 H, 2 d, J = 8.5 Hz, 4-nitrophenyls); mass spectrum (50 eV, direct inlet) m/e (relative intensity) 298 (2.2), 270 (0.5), 150 (9.7) 149 (100), 133 (5.3), 120 (4.5), 119 (43.4), 115 (4.0), 103 (31.9), 102 (9.7), 91 (27.5), 78 (6.0), 77 (52.5), 76 (4.5), 65 (7.5), 63 (3.5), 51 (11.2), 39 (10.2), 30 (6.0).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39; mol wt, 298.3. Found: C, 64.48; H, 4.85; N, 9.39; mol wt, 303 ($CHCl_3$).

Isomerization of *cis*-1,2-Di(4-nitrophenyl)cyclobutane (6).—A solution of 439 mg of photodimer 6 in 20 ml of piperidine was heated at 85° for 24 hr. After removal of the piperidine *in vacuo*, the residue was taken up in ether. This solution was washed with dilute HCl and water, dried ($MgSO_4$), and evaporated. The residue was recrystallized from benzene–cyclohexane to give 80 mg (18.2%) of pale yellow crystals: mp 86–88°; nmr ($CDCl_3$) δ 2.38 (m, CH_2CH_2), 3.72 (2 H, m, CHAr groups), and 7.40 and 8.15 (8 H, 2 d, J = 9 Hz, 4-nitrophenyls); mass spectrum (50 eV, direct inlet) m/e (relative intensity) 298 (2.2), 270 (0.9), 150 (10.5), 149 (100), 133 (4.5), 119 (23.5), 115 (3.4), 103 (22.1), 102 (5.6), 91 (15.4), 77 (26.5), 74.5 (metastable, 298 → 149^+ + 149), 51 (3.9).

Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39; mol wt, 298.3. Found: C, 64.45; H, 4.72; N, 9.33; mol wt, 301 ($CHCl_3$).

Registry No.—**1b,** 28131-17-1; **1d,** 28042-27-5; **1e,** 28042-28-6; **1e** photodimer, 28042-29-7; **1f,** 28042-30-0; **2a,** 28131-18-2; **2b,** 28042-31-1; **4,** 28042-32-2; **5,** 28042-33-3; **6,** 28042-34-4; **7,** 28042-35-5; 4-nitrostyrene, 100-13-0.

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A Simple Method for the Synthesis of Amides[1]

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It has been known for some time that treatment of alcohols with the adduct of triphenylphosphine and bromine (or chlorine) leads to the formation of the corresponding halides in high yield.[2] In this early report,[2] Horner and coworkers also showed that organic acids could be converted to acid chlorides by this method. More recently, Lee[3] and Bestmann and Mott[4] have extended these early observations and shown that treatment of acids or acid anhydrides with the adduct of triphenylphosphine and either bromine[4] or carbon tetrachloride[3] afforded the acid bromide (or chloride). This communication outlines an extension of these methods to a simple, high-yield method for the formation of amide bonds.

Two reaction schemes were used for the preparation of amides. In the first method, triphenylphosphine (**1**) and carbon tetrachloride are refluxed together for 30 min in tetrahydrofuran to form the adduct.[5] The solution is cooled to 5° in an ice–water bath, the carboxylic acid is added, and the mixture is allowed to stand for 10 min to form the triphenylacyloxyphosphonium chloride.[3] The amine (2 equiv) is added and the mixture is heated under reflux for about 45 min. The amine hydrochloride that forms is separated, and the solvent is removed *in vacuo*. The amide is isolated by distillation, or by sublimation, or by extraction of the amide with ethyl ether followed by recrystallization. Some typical yields of amides obtained by this method (method I) are presented in Table I.

TABLE I

PREPARATION OF AMIDES BY METHOD I

Acid	Amine	Yield, %	Method of purification[a]
Acetic	*n*-Butyl	91	A
Acetic	*tert*-Butyl	97	B
Acetic	Benzyl	87	A
Acetic	Diphenyl	85	C
Acetic	Di-*n*-butyl	81	A
Benzoic	*n*-Butyl	85	A
Benzoic	*tert*-Butyl	87	C
Benzoic	Benzyl	83	A
Benzoic	Di-*n*-butyl	95	A
Benzoic	Diphenyl	61	C

[a] A, distillation; B, sublimation; C, extraction with ether and recrystallization.

In the alternative procedure (method II), triphenylphosphine (**1**), bromotrichloromethane, the carboxylic acid, and the amine are refluxed together for 2 hr in tetrahydrofuran. The product **2** is then isolated as in the first method. Presumably this reaction proceeds through the same intermediates formed when the reagents are added stepwise. A few examples of preparations by this method (method II) are presented in Table II.

$$(C_6H_5)_3P\ (\mathbf{1}) + BrCCl_3 + RCO_2H + 2R''R'NH \longrightarrow RC(=O)NR'R''\ (\mathbf{2}) + (C_6H_5)_3PO + HCCl_3 + R''R'\overset{+}{N}H_2Br^- \downarrow$$

TABLE II

PREPARATION OF AMIDES BY METHOD II

Acid	Amine	Yield, %	Method of purification[a]
Acetic	Di-*n*-butyl	92	A
Acetic	Benzyl	89	A
Acetic	*tert*-Butyl	93	B
Acetic	*n*-Butyl	88	A

[a] A, distillation; B, sublimation.

The application of our method to peptide synthesis was also tested. A mixture of triphenylphosphine (**1**), bromotrichloromethane, *N*-benzyloxycarbonyl-L-

(1) Supported by Grant AM-13411 from the U. S. Public Health Service and Grant GB-11781 from the National Science Foundation.

(2) L. Horner, H. Oediger, and H. Hoffmann, *Justus Liebigs Ann. Chem.*, **626**, 26 (1959).

(3) J. B. Lee, *J. Amer. Chem. Soc.*, **88**, 3440 (1966).

(4) H. J. Bestmann and L. Mott, *Justus Liebigs Ann. Chem.*, **693**, 132 (1966).

(5) P. C. Crofts and I. M. Downie, *J. Chem. Soc.*, 2559 (1963); I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Commun.*, 1350 (1968).

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

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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]

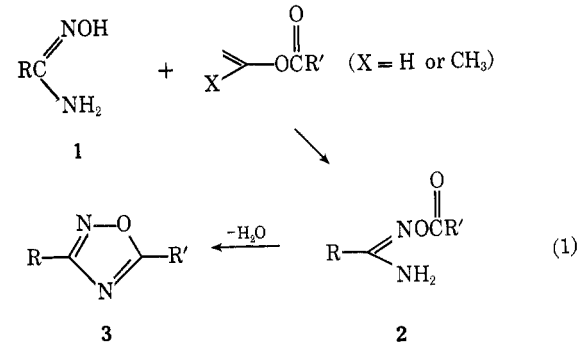
(1) (a) F. Eloy and R. Lenaers, *Chem. Rev.*, **62**, 155 (1962); (b) F. Eloy, *Fortschr. Chem. Forsch.*, **4**, 807 (1965).
(2) J. H. Boyer in "Heterocyclic Chemistry," Vol. 7, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1961, p 508 ff.

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).