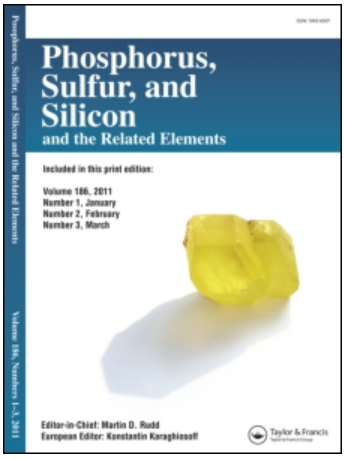

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Synthesis of Dialkyl 8-Oxo-2,8-dihydroisoxazolo[3,2-*a*]isoindole-2,3-dicarboxylates from Dialkyl Acetylenedicarboxylates, *N*-Hydroxy Phthalimide and Tributylphosphine

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Protonation of the highly reactive 1:1 intermediates, produced in the reaction between tributylphosphine and dialkyl acetylenedicarboxylates by N-hydroxy phthalimide leads to vinyltributylphosphonium salts, which undergo electrophilic substitution reaction with conjugate base to produce corresponding stabilized phosphorus ylides. Microwave was found to catalyze conversion of the stabilized phosphorus ylides to dialkyl 8-oxo-2,8-dihydroisoxazolo[3,2-a]isoindole-2,3-dicarboxylates in the presence of solid catalysts in solvent-free conditions.

Keywords Intermolecular Wittig reaction; *N*-hydroxy phthalimide; microwave irradiation; solvent-free conditions; Tributylphosphine

INTRODUCTION

A well known method for achieving alkenylation is the Wittig reaction.[1] β -Additions of nucleophiles to the vinyl group of vinylic phosphonium salts leading to the formation of new alkylidenephosphoranes has attracted much attention as a very convenient and synthetically useful method in organic synthesis.[1,2] Organophosphorus compounds have been extensively used in organic synthesis.[1,2]

Isoindoles and their derivatives are very useful as starting materials to produce pharmaceutically and industrially important

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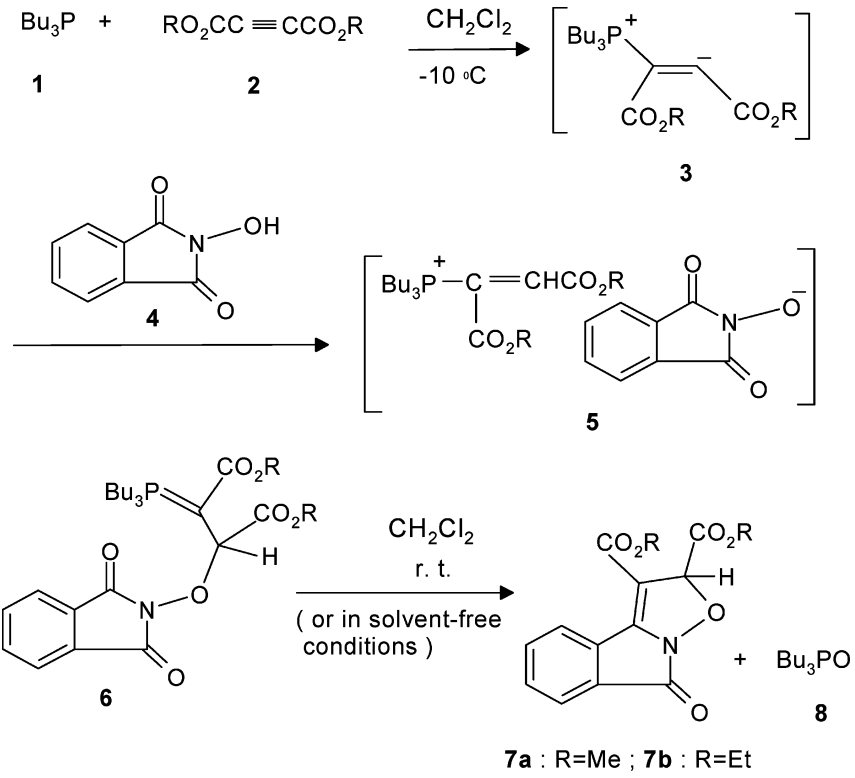
compounds.[3,4]Some of these compounds are selective monoamine oxidase inhibitors and, therefore, are useful for treating or preventing diseases mediated by monoamine oxidase.[3] In addition to being used in the pharmaceutical industry,[3] isoindoles also find a wide application in the dye and polymer industry.[5] Owing to these characteristics and our interest in the synthesis of heterocycles,[6,7] we were prompted to synthesize dialkyl 8-oxo-2,8-dihydroisoxazolo[3,2-*a*]isoindole-2,3-dicarboxylates (**7**) from tributylphosphine (**1**), dialkyl acetylenedicarboxylates (**2**),*and N*-hydroxy phthalimide (**3**) in the presence of solid catalysts in solvent-free conditions (Scheme 1).

RESULTS AND DISCUSSION

The stabilized phosphorus ylide (**6**) may result from initial addition of tributylphosphine **1** to the acetylenic ester **2** and concomitant protonation of the 1:1 adduct, followed by the electrophilic attack of the



SCHEME 1

TABLE I Synthesis of Electron-Poor Isoindoles 7 in the Presence of Silica Gel and Manganese Dioxide in Solvent-Free Conditions

Product	Catalyst	Thermal conditions	Microwave conditions	Yields (%)
7a	MnO_2	25°C, 60 min	0.1 KW, 3 min	65
7b	MnO_2	25°C, 60 min	0.1 KW, 3 min	61
7a	SiO_2	90°C, 60 min	0.5 KW, 3 min	65
7b	SiO_2	90°C, 60 min	0.5 KW, 3 min	61

vinyltributylphosphonium cation to the conjugate base (Scheme 1). TLC indicated formation of ylides **6** in CH_2Cl_2. Solid catalysts (manganese dioxide and silica gel) were found to catalyze conversion of the stabilized phosphorus ylides (**6**) to dialkyl 8-oxo-2,8-dihydroisoxazolo[3,2-*a*]isoindole-2,3-dicarboxylates (**7**) in solvent-free conditions under microwave irradiation (0.1–0.5 KW during 3 min) or under thermal conditions (25–90° C, 60 min) (Table I).The reaction proceeded smoothly and cleanly under solvent-free conditions; no side reactions were observed. In the absence of the catalysts, this reaction did not afford the corresponding compounds **7** and decomposition of the ylides **6** was observed. We also used ZnO, MgO, CuO, $MgSO_4$, K_2HPO_4, and KH_2PO_4 in this reaction under thermal and microwave conditions; but in all cases, the conversions were fairly low, and in all cases decomposition of the ylides **6** were observed. The structures **7** were deduced from their IR, ^{1}H NMR and ^{13}C NMR spectra. The ^{1}H NMR spectrum of **7a** consisted of two singlets for the methyl groups (OCH_3, $\delta = 3.72$ and 3.85 ppm), one singlet for the isoxazole ring, $\delta = 5.20$ ppm, and a multiplet for the aromatic ring ($\delta = 7.48$–7.93 ppm). The ^{1}H decoupled ^{13}C NMR spectrum of **7a** showed 14 distinct resonances, partial assignment of these resonances is given in the experimental section.[1,4,6,7]

CONCLUSION

In summary, we have developed a convenient, one-pot method for the preparation of dialkyl 8-oxo-2,8-dihydroisoxazolo[3,2-*a*]isoindole-2,3-dicarboxylates (**7**) from the reaction between tributylphosphine, dialkyl acetylenedicarboxylates, and *N*-hydroxy phthalimide in fairly good yields (Scheme 1). Other aspects of this process are under investigation.

EXPERIMENTAL

Commercial oven Butane M245 was used for microwave irradiation. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^{1}H and

^{13}C NMR spectra were measured with a BRUKER DRX-250 AVANCE spectrometer at 250 and 62.5 MHz, respectively.

General Procedure for the Preparation of Isoindoles (7a–b)

To a magnetically stirred solution of tributylphosphine **1** (0.202 g, 1 mmol) and *N*-hydroxy phthalimide **4** (1 mmol) in CH_2Cl_2(5 ml), a mixture of **2** (1 mmol) in CH_2Cl_2 (3 ml) was added dropwise at $-10^{\circ}C$ over 15 min. The mixture was allowed to warm up to room temperature. Solid catalyst (manganese dioxide or silica gel) (1 g) was added and the solvent was evaporated. Dry catalyst powder and the residue were irradiated in the microwave oven at microwave power 0.1-0.4 KW for 3 min. (or heated under thermal conditions at 25–90°C for 60 min) and then placed over a column of silica gel (10 g) (Table I). The column chromatography was washed using ethyl acetate-light petroleum ether (1:9) as eluent. The solvent was removed under reduced pressure and products were obtained as light yellow oils (**7a** (65%) and **7b** (61%)) (See **Scheme 1**). The characterization data of the compounds (**7a–b**) are summarized in the following sections.

Dimethyl 8-Oxo-2,8-dihydroisoxazolo[3,2-a]isoindole-2,-3-dicarboxylate (7a)

Viscose yellow oil, Yield: 65.0%. δ_H (250 MHz, $CDCl_3$): 3.72 and 3.85 (6 H, s, 2 OCH_3); 5.20 (1 H, s, HC—O); 7.48–7.93 (4H, m, arom.). δ_C (250 MHz, $CDCl_3$): 51.91 and 53.21 (2 OCH_3); 97.41 (CH—O); 111.98 (=*C*(CO)OMe); 124.43, 126.42, 128.39, 130.10, 135.21, and 146.53 (6 CH); 157.96 (C=O, amide); 156.71 (=C—N); 161.35, 163.35 (2 C=O, ester). IR (KBr) (ν_{max}, cm^{-1}): 1751 (C=O, ester); 1265 (C—N); 1650 (C=C); 2962 (CH, aliph.); 1149 (C—O).

Diethyl 8-Oxo-2,8-dihydroisoxazolo[3,2-a]isoindole-2,3-dicarboxylate (7b)

Viscose yellow oil; Yield: 61.0%; δ_H(250 MHz, $CDCl_3$): 1.26 and 1.29 (6 H, t, $^3J_{HH}$ = 7.2 Hz, 2 CH_3); 4.08 and 4.32 (4 H, q, $^3J_{HH}$ = 7.2 Hz, 2 OCH_3); 4.18 (1 H, s, HC—O); 7.46-8.02 (4 H, m, arom.). δ_C (250 MHz, $CDCl_3$): 13.59 and 13.54 (2 CH_3); 62.98 and 59.37 (2 OCH_2); 97.31(CH—O); 111.06 (=*C*(CO)OEt); 124.54, 126.52, 128.37, 130.26, and 135.26 and 146.30 (6 C, arom.); 167.59 and 173.97 (2 C=O, ester); 160.91 (C=O, amid); 157.63 (=C—N). IR (KBr) (ν_{max}, cm^{-1}): 1751 (C=O, ester); 1265 (C—N); 1650 (C=C); 2962 (CH, aliph.); 1149 (C—O).

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