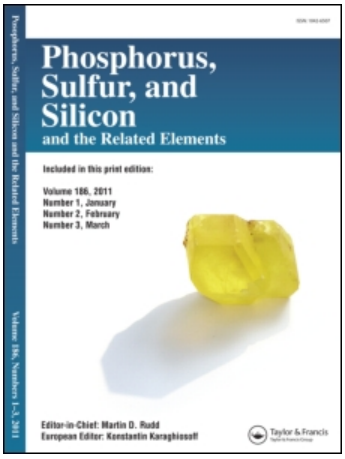

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Abdolali Alizadeh[a]; Mohamad Acedi[a]
[a] Department of Chemistry, Tarbiat Modarres University, Tehran, Iran

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Synthesis of 4,5-Dialkyl 1-Isopropyl 3-Isopropoxy-1*H*-Pyrazole-1,4,5-tricarboxylate by Using Mitsunobu Chemistry

Abdolali Alizadeh
Mohamad Acedi
Department of Chemistry, Tarbiat Modarres University, Tehran, Iran

*4,5-dialkyl 1-isopropyl 3-isopropoxy-1*H*-pyrazole-1,4,5-tricarboxylate was obtained in an excellent yield from the reaction of dialkyl acetylenedicarboxylates and diisopropyl azodicarboxylate in the presence of triphenylphosphine in dry dichloromethane. This reaction provides a useful synthetic route to highly functionalized pyrazoles.*

Keywords Dialkyl acetylenedicarboxylates; diisopropyl azodicarboxylate; Mitsunobu chemistry; pyrazoles; triphenylphosphine

INTRODUCTION

The development of simple synthetic routes for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] The wide range of biological activity of pyrazoles[2–5] has made them popular synthetic targets. These heterocycles can be synthesized both by cyclization and cycloaddition reactions. The most general route to pyrazoles is the reaction of 1,3-dicarbonyl compounds or their equivalents (such as enol esters) with hydrazines.[6,7] This route suffers from the disadvantage that unsymmetrical dicarbonyl compounds or their derivatives sometimes give mixtures of isomeric pyrazoles. Pyrazoles also are made by the cyclization of acetylenic hydrazones by electrocyclization of unsaturated diazo compounds and by 1,3-dipolar addition reactions[8] of diazo compounds and nitrile imides.

Zwitterionic species are known to arise from the addition of nucleophiles such as triphenylphosphine,[9] pyridine,[10] and a wide rang of tertiary amines[11] to activated acetylenes.[12] Of special interest to

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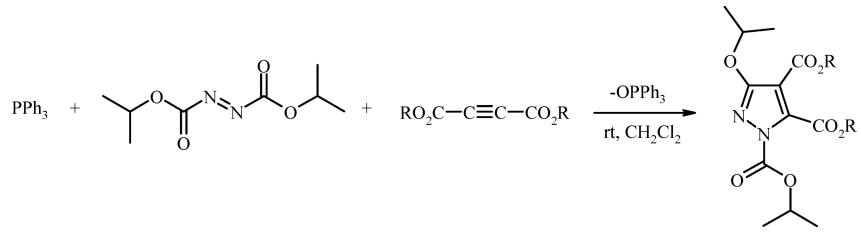
Address correspondence to Abdolali Alizadeh, Tarbiat Modarres University, Department of Chemistry, PO Box 14155-4838, Tehran, Iran. E-mail: Abdolalizad@yahoo.com

us have been zwitterions derived from triphenylphosphine and diisopropyl azodicarboxylate.[13] Earlier attempts to trap this species with dipolarophiles to generate cyclic compounds essentially have been unsuccessful.[14] We were interested in preparing some highly substituted pyrazoles with the purpose to obtain 1,3,4,5-tetrasubstituted pyrazoles. We now report the reaction of dialkyl acetylenedicarboxylate late **1** and diisopropyl azodicarboxylate in the presence of triphenylphosphine (Scheme 1).



1 **2**

1	R
a	Me
b	Et
c	^{i}Pr
d	^{t}Bu

2	R	Yield of
a	Me	7
b	Et	0
c	^{i}Pr	8
d	^{t}Bu	5

SCHEME 1

RESULTS AND DISCUSSION

The reaction of dialkyl acetylenedicarboxylates **1** with diisopropyl azodicarboxylate in the presence of triphenylphosphine proceeded spontaneously at room temperature in dry dichloromethane and was complete within a few hours. ^{1}H and ^{13}C NMR spectra of the crude product clearly indicated the formation of 4,5-dialkyl 1-isopropyl 3-isopropoxy-1*H*-pyrazole-1,4,5-tricarboxylate **2a**.

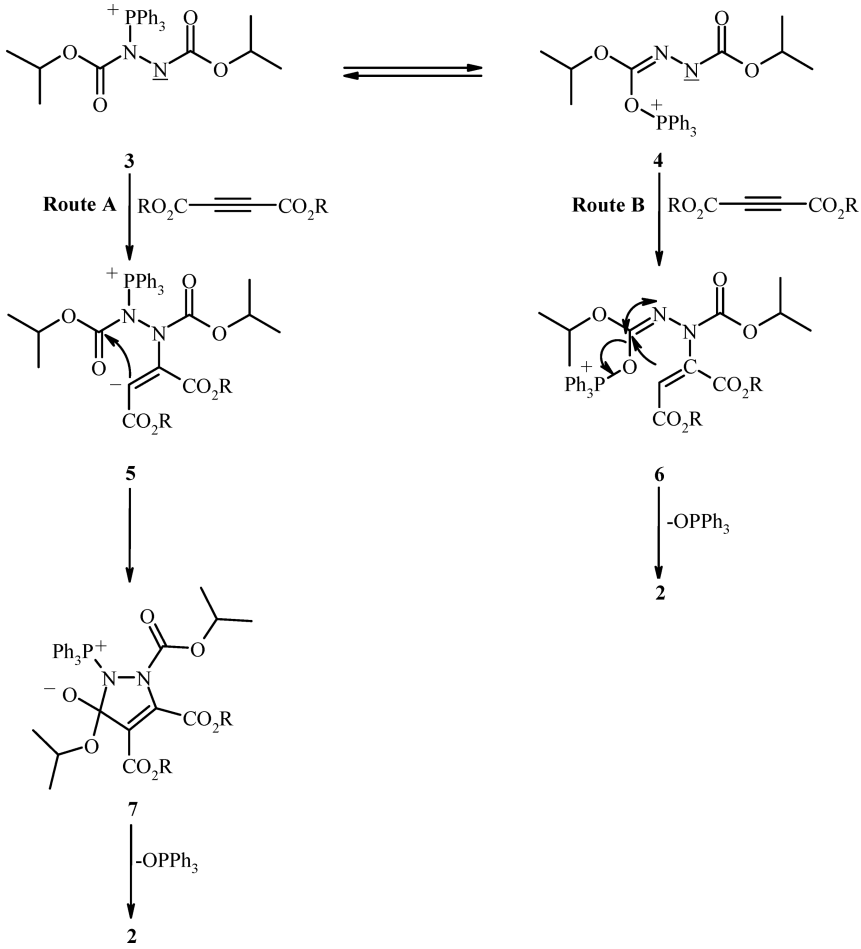
The structure of compounds **2a–d** were deduced from their elemental analyses and their IR, ^{1}H, and ^{13}C NMR spectroscopic data. The mass spectra of these compounds displayed molecular ion peaks at m/z = 328, 356, 384, and 412, respectively.

The ^{1}H NMR spectrum of **2a** exhibited 6 characteristic signals arising from Me_2CH (δ 1.3, $^3J_{HH}$ = 6.1 Hz), $Me_2CHOCON$ (δ 1.31, $^3J_{HH}$ = 6.1 Hz), OCH_3 (δ 3.7), OCH_3 (δ 3.88), $OCHMe_2$ (δ 5.04, $^3J_{HH}$ = 6.1 Hz), and $OCHMe_2$ (δ 5.1, $^3J_{HH}$ = 6.1 Hz).

The ^{13}C NMR spectrum of **2** shows signals for the C-3, C-4, and C-5 atoms of pyrazole at δ 160.57, 104.42, and 140.69, which confirms the

presence of the pyrazole ring in **2**. The ^{13}C NMR spectra are in agreement with the pyrazole structure; partial assignments of these resonances are given in the Experimental Section. The ^{1}H and ^{13}C NMR spectra of **3b–d** are similar to those of **2a** except for the ester groups at C_4 and C_5, which exhibit characteristic signals with appropriate chemical shifts (see Experimental Section).

On the basis of the well-established Mitsunobu chemistry,[15] it is reasonable to assume that the pyazole **2** results from route A or B (Scheme 2).



SCHEME 2

Route A

The initial addition of triphenylphosphine to the diisopropyl azodicarboxylate and the subsequent attack of the resulting zwitterions **3** to the dialkyl acetylenedicarboxylate yields betaine **5**, which apparently cyclizes under the reaction condition that was employed and looses triphenylphosphine oxide to produce the pyrazole **2**.

Route B

Although the Morrison-Brunn-Huisgen betaine **3** is the proven intermediate in the first step of this reaction, the P—O bonded tetracoordinate species of type **4** also was proposed as another possible intermediate in the earlier literature.[16] In the light of route B, pyrazole **2** results from the addition of zwitterions **4** to the dialkyl acetylenedicarboxylate to yield betaine **6**, which cyclizes, under the reaction condition that was employed, to produce the pyrazole **2**.

In conclusion, the present method carries the advantage that not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.

EXPERIMENTAL

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C spectra were recorded at 500.1 and 125.7 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with $CDCl_3$ as solvent. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification.

General Procedure for the Preparation of Compounds 2a–d, Exemplified on 2a

To a magnetically stirred solution of 0.14 g of dimethyl acetylenedicarboxylate (1 mmol) and 0.202 g of diisopropyl azodicarboxylate (1 mmol) in 5 mL of dry dichloromethane was added dropwise a solution of 0.26 g of triphenylphosphine (1 mmol) in 3 mL of dry dichloromethane at room

temperature over 10 min. The reaction mixture then was allowed to stir for 5 h. The solvent was removed under reduced pressure and the residue was separated by silica gel (Merck 230–240 mesh) column chromatography using hexane-ethyl acetate as eluent.

1-Isopropyl 4,5-Dimethyl 3-Isopropoxy-1*H*-pyrazole-1,4,5-tricarboxylate (2a)

Yellow oil, yield, 0.23 g, 70%. IR (KBr) (ν_{max}, cm^{-1}): 1762 (CO_2Me), 1741 ($NCO_2^i pr$), 1716 (CO_2Me), 1573 (C=N), 1372, 1321, 1272, and 1185 (C—O of esters and ether). ^1H NMR (500.1 MHz, $CDCl_3$): δ_H = 1.30 (6H, d, $^3J_{HH}$ = 6.1 Hz, Me_2CH), 1.31 (6H, d, $^3J_{HH}$ = 6.1 Hz, Me_2CH), 3.71 (OCH_3), 3.88 (OCH_3), 5.04 (1H, hept, $^3J_{HH}$ = 6.1 Hz, $OCHMe_2$), 5.10 (1H, hept, $^3J_{HH}$ = 6.1 Hz, $OCHMe_2$). ^{13}C NMR (125.75 MHz, $CDCl_3$): δ_C = 21.19 (*Me*$_2$CH), 21.44 (*Me*$_2$CH), 51.58 (O*C*H_3), 53.03 (O*C*H_3), 73.19 (O*C*HMe_2), 73.97 (O*C*HMe_2), 104.42 (C_4 of pyrazole), 140.69 (C_5 of pyrazole), 147.17 ($NCO_2^i pr$), 160.57 (*C*=N), 160.62 (*C*O_2Me), 160.66 (*C*O_2Me). MS (*m/z*, %): 329 ($M^+ + 1$, 1), 328 (M^+, 1), 200 (18), 168 (42), 149 (42), 101 (25), 57 (49), 43 (100), 41 (100). Anal. Calcd. for $C_{14}H_{20}N_2O_7$ (328.31): C, 51.32; H, 6.14; N, 8.53%. Found: C, 51.3; H, 6.1; N, 8.6%.

1-Isopropyl 4,5-Diethyl 3-Isopropoxy-1*H*-pyrazole-1,4,5-tricarboxylate (2b)

Yellow oil, yield, 0.30 g, 85%. Anal. Calcd. for $C_{16}H_{24}N_2O_7$ (356.37): C, 53.92; H, 6.78; N, 7.86%. Found: C, 54.0; H, 6.8; N, 7.9%.

Triisopropyl 3-Isopropoxy-1*H*-pyrazole-1,4,5-tricarboxylate (2c)

Colorless solid, m.p.: 65–67°C, yield, 0.32 g, 83%. Anal. Calcd. for $C_{18}H_{28}N_2O_7$ (384.42): C, 56.24; H, 7.34; N, 7.29%. Found: C, 56.2; H, 7.3; N, 7.3%.

4,5-Di(*tert*-butyl) 1-isopropyl 3-isopropoxy-1*H*-pyrazole-1,4,5-tricarboxylate (2d)

Colorless solid, m.p.: 67–69°C, yield, 0.38 g, 90%. Anal. Calcd. for $C_{20}H_{32}N_2O_7$ (412.48): C, 58.24; H, 7.82; N, 6.79%. Found: C, 58.1; H, 7.8; N, 6.7%.

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