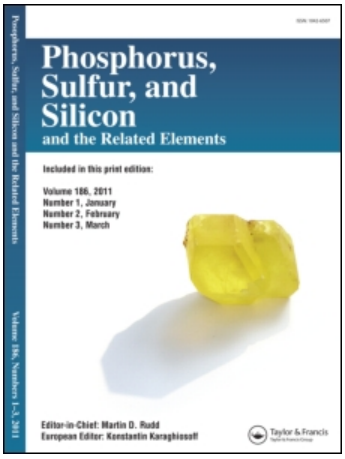

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A Novel Synthesis of Hydrazine Derivatives via a Three-Component Procedure

Mohammad Reza Islami[a]; Nader Gholami[b]; Abolfazl Dehooei[a]; Asghar Amiri[a]
[a] Chemistry Department, Shahid Bahonar University of Kerman, Kerman, Iran [b] Chemistry and Petrochemical Division, Research Institute of Petroleum Industry, Tehran, Iran

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Mohammad Reza Islami
Chemistry Department, Shahid Bahonar University of Kerman, Kerman, Iran

Nader Gholami
Chemistry and Petrochemical Division, Research Institute of Petroleum Industry, Tehran, Iran

Abolfazl Dehooei
Asghar Amiri
Chemistry Department, Shahid Bahonar University of Kerman, Kerman, Iran

A series of hydrazine derivatives containing an ylide moiety is obtained from a reaction of acetylenic esters with N-substituted aryl hydrazine in the presence of triphenylphosphine in ethyl acetate as a solvent in good yields.

Keywords Acetylenic esters; phenylhydrazine; triphenylphosphine

INTRODUCTION

Hydrazine derivatives are of interest as building blocks of heterocyclic compounds containing N—N bonds[1] and azapeptides,[2] due to their pharmaceutical and biological properties.[3] Some hydrazine derivatives such as phthalazin-1-yl-hydrazine were widely used as general antihypertensive and vasodilator agents and are considered at present as a first-line drug in the management of pregnancy-induced hypertension.[4,5] In addition, these compounds are known to decompose easily in the presence of radicals, which are commonly used as rocket fuels; most of the hydrazine derivatives are endothermic compounds.[6,7] Although a wide

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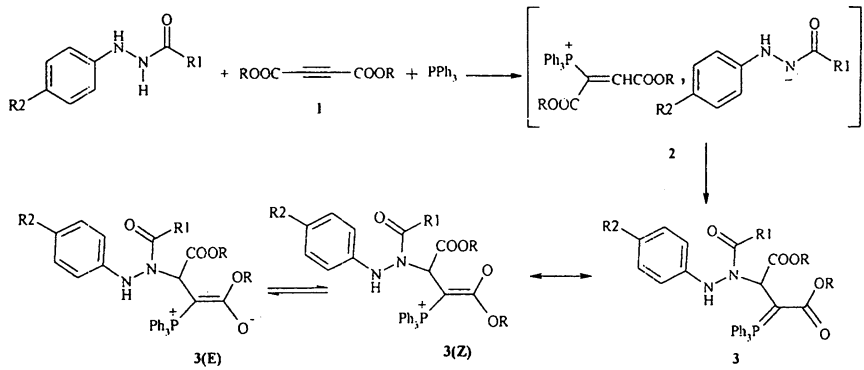
Address correspondence to Mohammad Reza Islami, Shahid Bahonar University of Kerman, Chemistry Department, Kerman 76619, Iran. E-mail: mrislami@mail.uk.ac.ir

range of procedures for the synthesis of hydrazine compounds has been reported,[8–10] however, hydrazine compounds containing a phosphorus atom along with functional groups such as ester groups have received much less attention probably owing to the lack of general methods for their synthesis.[11] Due to the interest of these compounds in medicinal chemistry we wish to report a one-pot synthesis for the preparation of these new hydrazine compounds. The remarkable, simple, and efficient one-pot procedure is one aspect of particular interest in this synthesis in comparison to the other multistep methods that were reported in the literature.[11] On the other hand readily available starting materials, short experimental time, and in addition, a high yield of the final products in the advantage of this method over the previous methods, which have already been reported.

RESULTS AND DISCUSSION

The reaction of aryl hydrazine with acetylenic esters in the presence of triphenlphosphine, which is a good nucleophile,[12–15] gave the products in ethyl acetate as a solvent as shown in Scheme 1. Presumably, initial a Michael attack followed by protonation gave adducts **2**, which readily can form compound **3**.



3	R	R1	R2	Yield (%)
a	Me	Me	H	79
b	Et	Me	H	86
c	Me	Me	NO_2	74
d	Et	Me	NO_2	83

SCHEME 1

The IR, ^{1}H NMR, ^{13}C NMR, and MS spectrometry data of **3** support the 1:1:1 adduct of the hydrazine derivative, dialkyl acetylenedicarboxylate, and Ph_3P. The ^{1}H and ^{13}CNMR spectral data suggest that

3 exists as a mixture of two rotational isomers caused by resonance between P and the neighboring C=O group.

The ^{1}H NMR spectra of **3a** showed four sharp lines ($\delta = 2.98$, 3.54, 3.62, and 3.72 ppm) arising from methoxy protons along with signals for methyl protons of the acetyl group at $\delta = 2.06$ ppm and methine protons ($\delta = 5.17$, 5.30 ppm), which appear as two doublet peaks, respectively, for the major and minor geometrical isomers and a fairly broad signal at $\delta = 6.63$ ppm for a proton of the NH group. The aromatic protons appear as a multiplet at $\delta = 6.80$–8.48 ppm. The ^{13}C NMR spectrum of **3a** displayed 29 distinct resonances in agreement with the mixture of two rotamer structure. Although the presence of the ^{31}P nucleus complicates both the ^{1}H and ^{13}C NMR spectra of **3a**, it helps in the assignment of signals by long-range spin–spin couplings with ^{1}H and ^{13}C nuclei (see Experimental section).

The ^{1}H and ^{13}C NMR spectra of **3b–d** are similar to those of **3a**, except for the signals from the ester groups, which appear as characteristic resonance lines with the corresponding chemical shifts. The structural assignments made for compounds **3a–d** on the basis of the ^{1}H and ^{13}C NMR spectra were supported by their IR spectra. The carbonyl region of spectra exhibits two distinct IR absorption bands for each compound. Of special interest is the absorption of the ester groups of such compounds at 1751–1640 cm^{-1}. The conjugation of one ester group with a negative charge is a plausible factor in the decrease in the wave number of the corresponding carbonyl absorption bands.

CONCLUSION

We showed that the condensation of phenylhydrazine and its derivatives with acetylenic compounds in the presence of triphenylphosphine efficiently occurred in an organic solvent to provide a convenient and rapid synthesis of hydrazine derivatives.

EXPERIMENTAL

Dialkyl acetylenedicarboxylate, phenylhydrazine, 4-nitrophenylhydrazine, and triphenylphosphine were obtained from Merck Chemical Co. and were used without further purification. Amide derivatives were prepared according to the reported procedure in the literature.[16] Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses for C, H, and N were performed using a Heraeus CHN–O-Rapid analyzer, IR spectra were measured on a Mattson 1000 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were

recorded on a BRUKER DRX-500 AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

Dimethyl 2-(1-acetyl-2-phenylhydrazino)-3-(triphenylphosphoranylidene)succinate 3a

At ambient temperature, dimethyl acetylenedicarboxylate (0.24 mL, 2 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.53 g, 2 mmol) and N-acetyl phenylhydrazine (0.3 g, 2 mmol) in ethyl acet ate (10 mL). After the addition was complete (approximately 15 min) the mixture was stirred for an additional 1 h and subsequently was filtered. The solid collected in the filter was washed thoroughly with ethyl acetate to give a white powder (0.88 g, m.p. 184–185°C, yield 79%); IR (KBr) (ν_{max}, cm^{-1}): 3305 (NH), 1741 and 1641 (C=O). MS, m/z (%): 405 (80), 304 (20), 262 (100), 183 (57), 108 (48), 43 (100), Major isomer, **3a** (Z) (85%), ^{1}H NMR : δ 2.06 (6H, s, 2 CH_3)*, 2.98 and 3.72 (6H, 2s, 2 OCH_3), 5.17 (1H, d, $^3J_{PH}$ 16.8 Hz, P=C–CH), 6.63 (br.s, NH)*, 6.80–8.48 (40H, m, arom)*. ^{13}C NMR: δ 21.34 (2 CH_3)*, 40.24 (d, $^1J_{PC}$ 125.8 Hz, P=C), 49.21 and 52.36 (2 OCH_3), 59.22 (d, $^2J_{PC}$ 18.1 Hz, P=C–CH), 6.63 (br.s, NH)*, 6.80–8.48 (40H, m, arom)*. 112.20 and 119.59 (2CH), 126.12 (d, $^1J_{PC}$ 92.3 Hz, C^{ipso}), 128.59 (d, $^3J_{PC}$ 12.3 Hz, C^{meta}), 129.08 (CH), 131.88 (d, $^4J_{PC}$ 2.4 Hz C^{para})*, 133.44 (d, $^2J_{PC}$ 9.9 Hz, C^{ortho}), 149.72 (C), 171.17 (d, $^2J_{PC}$ 12.7 Hz, C=O), 172.78 (d, $^3J_{PC}$ 10.2 Hz, C=O), 176.13 (C=O). Minor isomer, **3a** (E) (15%), ^{1}H NMR: δ 3.54 and 3.62 (6H, 2s, 2 OCH_3), 5.30 (1H, d, $^3J_{PH}$ 20.8 Hz, P=C–CH). ^{13}C NMR: δ 40.44 (d, $^1J_{PC}$ 127.6 Hz, P=C), 50.23 and 52.26 (2 OCH_3), 58.67 (d, $^2J_{PC}$ 18.6 Hz, P=C–CH), 112.13 and 119.67 (2CH), 125.56 (d, $^1J_{PC}$ 92.6 Hz, C^{ipso}), 128.70 (d, $^3J_{PC}$ 12.3 Hz, C^{meta}), 129.30 (CH), 133.52 (d, $^2J_{PC}$ 9.0 Hz, C^{ortho}), 148.90 (C), 176.25 (C=O).

Diethyl 2-(1-acetyl-2-phenylhydrazino)-3-(triphenylphosphoranylidene) succinate 3b

(1.0 g, m.p. 142–144°C, yield 86%); IR (KBr); (ν_{max} cm^{-1}): 3310 (NH), 1741 and 1641 (C=O). MS, m/z(%): 434 (50), 262 (52), 185 (18), 108 (32), 43 (100). Major isomer, **3b** (Z) (87%), ^{1}H NMR: δ 0.34 (3H, t, $^3J_{HH}$ 7.0 Hz, CH_3), 1.24 (3H, t, $^3J_{HH}$ 7.1 Hz, CH_3), 2.05 (6H, s, 2 CH_3)*, 3.48–4.26 (8H, m, 4 OCH_2)*, 5.17 (1H, d, $^3J_{PH}$ 18.8 Hz, P=C–CH), 6.60 (br.s, NH)*, 6.66–7.46 (40H, m, arom)* ^{13}C NMR: δ 13.94 and 14.20 (2 CH_3), 21.35 (2 CH_3)*, 39.98 (d, $^1J_{PC}$ 125.7 Hz, P=C), 57.82 and 61.71 (2 OCH_2), 59.39 (d, $^2J_{PC}$ 18.1 Hz, P=C–CH)*, 112.25 and 119.53 (2CH),

126.31 (d, $^{1}J_{PC}$ 92.2 Hz, C^{ipso}), 128.50 (d, $^{3}J_{PC}$ 12.3 Hz, C^{meta})*, 129.07 (CH), 131.82 (C^{para})*, 133.51 (d, $^{2}J_{PC}$ 9.8 Hz, C^{ortho}), 149.77 (C), 170.70 (d, $^{2}J_{PC}$ 12.9 Hz, C=O), 172.18 (d, $^{3}J_{PC}$ 10.4 Hz, C=O), 176.23 (C=O). Minor isomer, **3b** (E) (13%), ^{1}H NMR: δ 1.21 (3H, t, $^{3}J_{HH}$ 7.2 Hz, CH_3), 1.28 (3H, t, $^{3}J_{HH}$ 6.8 Hz, CH_3), 5.27 (1H, d, $^{3}J_{PH}$ 20.4 Hz, P=C–CH). ^{13}C NMR: δ 14.45 and 15.04 (2 CH_3), 39.88 (d, $^{1}J_{PC}$ 136.0 Hz, P=C), 58.60 and 58.69 (2 OCH_2), 111.99 and 119.64 (2CH), 125.82 (d, $^{1}J_{PC}$ 92.1 Hz, C^{ipso}), 129.26 (CH), 148.95 (C), 176.17 (C=O).

Dimethyl 2-[1-acetyl-2-[4-nitrophenylhydrazino)]-3-(triphenylphosphoranylidene) Succinate 3c

(0.89 g, m.p. 169–171°C, yield 74%); IR (KBr) (ν_{max}, cm^{-1}): 3308 (NH), 1750 and 1646 (C=O). MS, *m/z* (%): 262 (25), 183 (67), 107 (30), 43 (100). Major isomer, **3c** (Z) (84%), ^{1}H NMR: δ 2.02 (6H, s, 2 CH_3)*, 3.00 and 3.72 (6H, 2s, 2 OCH_3), 5.08 (1H, d, $^{3}J_{PH}$ 18.2 Hz, P=C–CH), 6.47–7.85 (38H, m, arom)*, 8.15 (br.s, NH)*. ^{13}C NMR: δ 21.28 (2 CH_3)*, 40.63 (d, $^{1}J_{PC}$ 125.1 Hz, P=C), 49.39 and 52.59 (2 OCH_3), 59.97 (d, $^{2}J_{PC}$ 17.9 Hz, P=C–CH), 126.04 (d, $^{1}J_{PC}$ 92.2 Hz, C^{ipso}), 128.67 (d, $^{3}J_{PC}$ 12.3 Hz, C^{meta}), 128.76 and 128.81 (2CH), 132.33 (d, $^{4}J_{PC}$ 2.6 Hz C^{para}), 133.24 (d, $^{2}J_{PC}$ 9.8 Hz, C^{ortho}), 140.37 and 155.29 (4C)*, 170.04 (d, $^{2}J_{PC}$ 12.8 Hz, C=O), 172.37 (d, $^{3}J_{PC}$ 10.6 Hz, C=O), 175.54 (C=O)*. Minor isomer, **3c** (E) (16%), ^{1}H NMR: δ 3.51 and 3.67 (6H, 2s, 2 OCH_3), 5.20 (1H, d, $^{3}J_{PH}$ 19.6 Hz, P=C–CH). ^{13}C NMR: δ 40.30 (d, $^{1}J_{PC}$ 129.1 Hz, P=C), 50.30 and 52.56 (2 OCH_3), 59.45 (d, $^{2}J_{PC}$ 17.0 Hz, P=C–CH), 125.71 (d, $^{1}J_{PC}$ 97.2 Hz, C^{ipso}), 128.41 (d, $^{3}J_{PC}$ 11.7 Hz, C^{meta}), 131.85 and 131.95 (2CH), 131.86 (d, $^{4}J_{PC}$ 2.0 Hz C^{para}), 133.36 (d, $^{2}J_{PC}$ 9.7 Hz, C^{ortho}).

Diethyl 2-[1-acetyl-2-[4-nitrophenylhydrazino)]-3-(triphenylphosphoranylidene) Succinate 3d

(1.0 g, m.p. 167–168°C, yield 83%); IR (KBr) (ν_{max}, cm^{-1}): 3307 (NH), 1751 and 1642 (C=O). MS, *m/z* (%): 433 (27), 278 (24), 262 (85), 183 (77), 108 (68), 43 (100). Anal. calcd. for $C_{34}H_{34}N_3O_7P$ (627.64): C, 65.07; H, 5.46; N, 6.69%. Found: C, 64.87; H, 5.45; N, 7.13%. Major isomer, **3d** (Z) (88%), ^{1}H NMR: δ 0.35 (3H, t, $^{3}J_{HH}$ 6.9 Hz, CH_3), 1.25 (3H, t, $^{3}J_{HH}$ 7.1 Hz, CH_3), 2.02 (6H, s, 2 CH_3)*, 3.52–4.27 (8H, m, 4 OCH_2)*, 5.07 (1H, d, $^{3}J_{PH}$ 18.3 Hz, P=C–CH), 6.50–7.81 (38H, m, arom)*, 8.10 (br.s, NH)*. ^{13}C NMR: δ 13.92 and 14.18 (2 CH_3), 21.28 (2 CH_3)*, 40.47 (d, $^{1}J_{PC}$ 124.9 Hz, P=C), 58.09 and 61.50 (2 OCH_2), 60.12 (d, $^{2}J_{PC}$ 17.8 Hz, P=C–CH)*, 125.99 (d, $^{1}J_{PC}$ 92.3 Hz, C^{ipso}), 128.56 (d, $^{3}J_{PC}$ 12.3 Hz, C^{meta}), 128.67 and 132.02 (2CH), 133.52 (d, $^{4}J_{PC}$ 2.4 Hz C^{para}), 133.31

(d, $^{2}J_{PC}$ 9.9 Hz, C^{ortho}), 140.31 and 155.36 (2C), 170.59 (d, $^{2}J_{PC}$ 12.7 Hz, C=O), 171.80 (d, $^{3}J_{PC}$ 10.6 Hz, C=O), 175.68 (C=O). Minor isomer, **3d** (E) (12%), ^{1}H NMR: δ 1.17 (3H, t, $^{3}J_{HH}$ 7.0 Hz, CH_3), 1.29 (3H, t, $^{3}J_{HH}$ 7.1 Hz, CH_3), 5.17 (1H, d, $^{3}J_{PH}$ 19.9 Hz, P=C–CH). ^{13}C NMR: δ 14.00 and 14.10 (2 CH_3), 40.25 (d, $^{1}J_{PC}$ 136.0 Hz, P=C), 58.81 and 61.22 (2 OCH_2), 125.63 (d, $^{1}J_{PC}$ 93.3 Hz, C^{ipso}), 128.41 (d, $^{3}J_{PC}$ 12.5 Hz, C^{meta}), 131.86 (d, $^{4}J_{PC}$ 1.4 Hz C^{para}), 131.94 and 133.52 (2CH), 133.46 (d, $^{2}J_{PC}$ 8.8 Hz, C^{ortho}), 140.31 and 154.38 (2C), 175.49 (C=O).

*For two rotamers

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