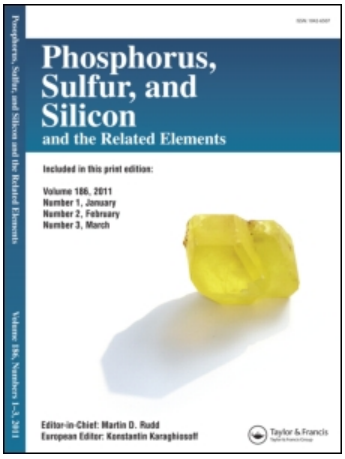

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Addition Reaction Between Trimethyl Phosphite and Dibenzoylacetylene in the Presence of SH- or NH-Acids

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ADDITION REACTION BETWEEN TRIMETHYL PHOSPHITE AND DIBENZOYLACETYLENE IN THE PRESENCE OF SH- OR NH-ACIDS

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The reactive 1:1 intermediate produced in the addition reaction between trimethyl-phosphite and dibenzoylacetylene was trapped by SH- or NH-acids such as 4-nitroimidazole, 4-methyl-5-nitroimidazole, succinimide, or mercaptoacetic acid to produce 2-substituted 1,4-diphenylbutane-1,4-diones.

Keywords: Addition-reduction reaction; dibenzoylacetylene; mercaptoacetic acid; 4-nitroimidazole; succinimide; trimethyl phosphite

Several classes of drugs are based on the imidazole ring system. 2-Nitroimidazole (azomycin) is a naturally occurring antibiotic and some synthetic nitroimidazoles are active against intestinal infections.[1] Metronidazole is used for this purpose and also as a radiosensitizer in x-ray therapy. Other imidazoles are useful antifungal agents: These included bifonazole and clotrimazole. The formation of a carbon-nitrogen bond is of importance for the synthesis of nitrogen-containing natural products and biologically active systems.[2]

The *N*-alkylation of imidazoles with alkyl halides in neutral conditions can lead to further alkylation and formation of quaternary salts. With 4-substituted imidazoles there are two possible products of *N*-alkylation.[3] The nature of the product depends on the choice of alkylation conditions and on the steric and electronic effects of the substituent.[4] We report an efficient synthetic method for *N*-alkylation of electron-deficient imidazole derivatives and other NH acids (see Scheme 1).

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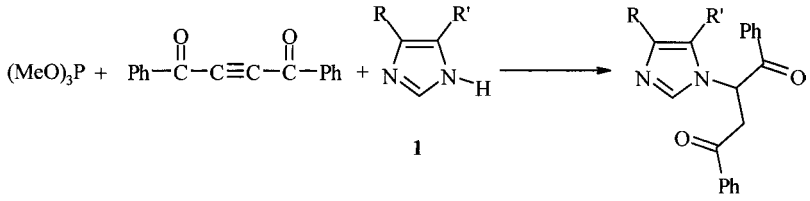


1, 2	R	R'	%Yield of 2
a	NO_2	H	94
b	NO_2	Me	92

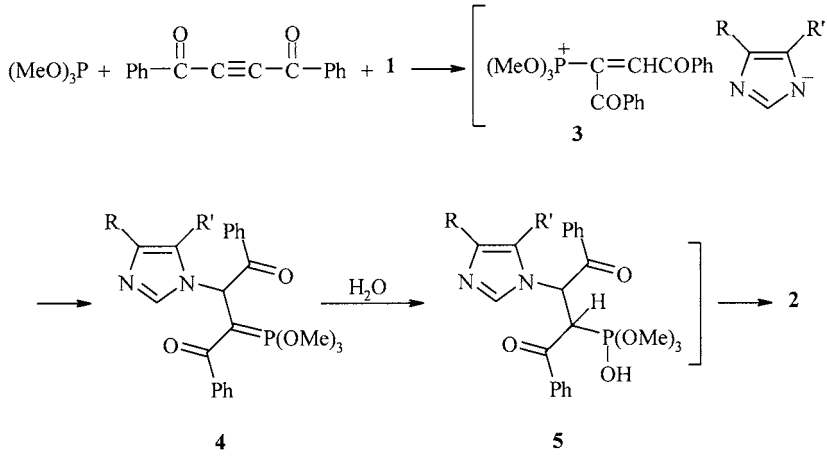
SCHEME 1

RESULTS AND DISCUSSION

The reaction of dibenzoylacetylene with 4-nitroimidazole (**1a**) or 4-methyl-5-nitroimidazole (**1b**) in the presence of trimethyl phosphite proceeded spontaneously at room temperature in dichloromethane, and was completed within a few hours. ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of 2-substituted-1,4-diphenyl-1,4-butandione derivatives **2** (Scheme 1). Any product other than **2** could not be detected by NMR spectroscopy. The structures of compounds **2a** and **2b** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectroscopic data. The mass spectra of these compounds displayed molecular ion peaks at $m/z = 349$ and 363, respectively. The ^{1}H NMR spectrum of **2a** exhibited two single sharp lines readily recognized as arising from CH^5 ($\delta = 7.68$ ppm) and CH^2 ($\delta = 7.98$ ppm) of imidazole; the two protons of the methylene group are diastereotopic and show two characteristic doublet systems at about $\delta = 3.74$ ppm ($J_{AB} = 18.1$ Hz, $J_{AX} = 7.3$ Hz) and 3.98 ppm ($J_{AB} = 18.1$ Hz, $J_{BX} = 5.6$ Hz); the methine group appears at 6.57 ppm ($^3J_{AX} = 7.3$ Hz and $^3J_{BX} = 5.6$ Hz). The phenyl residues gave rise to characteristic signals in the aromatic region of the spectrum. The ^{13}C NMR spectra are in agreement with the *N*-alkylimidazole structure **2**. Partial assignments of these resonances are given in the Experimental section.

Although the mechanism of the reaction between imidazole **1** and dibenzoylacetylene in the presence of trimethyl phosphite has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2.

On the basis of the well established chemistry of trivalent phosphorus nucleophiles[5–12] it is reasonable to assume that **2** results from initial addition of trimethyl phosphite to dibenzoylacetylene and subsequent



SCHEME 2

protonation of the 1:1 adduct by the NH-acid. Then, the positively charged ion **3** might be attacked by the conjugate base of the NH-acid to form phosphorane **4**, which in the presence of water is converted to the betaine **5**, and subsequent loss of trimethyl phosphate leads to compound **2** (see Scheme 2).

Similarly, the reaction of dibenzoylacetylene with succinimide and mercaptoacetic acid in the presence of trimethyl phophite gave the compounds 1-(1-benzoyl-3-oxo-3-phenylpropyl)dihydro-1*H*-pyrrole-2, 5-dione (**6**) and (1-benzoyl-3-oxo-3-phenyl-propylsulfanyl)-acetic acid (**7**) respectively (Scheme 3).

SCHEME 3

The ^{1}H and ^{13}C NMR spectra of **6** and **7** are consistent with the proposed structures. Partial assignment of these resonances is given in the Experimental section.

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; the results agreed favorably with the calculated values. Mass spectra were recorded on a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. These results agreed favorably with calculated values. IR spectra were recorded as KBr discs on a Shimadzu IR-460 spectrometer. ^{1}H and ^{13}C NMR spectra were obtained at 500.1 and 125.7 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with $CDCl_3$ as solvent. Dibenzoylacetylene and **1b** were prepared according to the published procedures.[13,14] The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification.

Preparation of 2-(4-Nitro-1*H*-imidazol-1-yl)-1,4-diphenyl-1,4-butandione (2a)

General Procedure

To a magnetically stirred solution of 0.25 g trimethyl phosphite (2 mmol) and 0.136 g 4-nitroimidazole (2 mmol) in 10 mL of dichloromethane was added dropwise a mixture of 0.47 g of dibenzoylacetylene (2 mmol) in 5 mL of dichloromethane at room temperature over 10 min. After 5 h stirring at room temperature, the solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (Merk 230–400 mesh) using *n*-hexane-ethyl acetate as eluent.

White powder, m.p. 152–154°C, yield 0.32 g, 94%. IR (KBr): (ν_{max}, cm^{-1}): 1669 (C=O), 1495 and 1337 (NO_2). Analysis: calcd for $C_{19}H_{15}N_3O_4$ (349.34): C, 65.32; H, 4.32; N, 12.02%. Found: C, 65.5; H, 4.4; N, 11.9%. MS (*m/z*, %): 349 (M^+, 10), 321 (5), 264 (13), 208 (30), 192 (22), 163 (31), 154 (45), 127 (24), 105 (66), 82 (72), 69 (34), 54 (100), 52 (35). ^{1}H NMR (500.1 MHz, δ, $CDCl_3$): 3.74 (1H, dd, $J_{AB} = 18.1$ Hz, $J_{AX} = 7.3$ Hz, CH_2), 3.98 (1H, dd, $J_{AB} = 18.1$ Hz, $J_{BX} = 5.6$ Hz, CH_2), 6.57 (1H, t, $^{3}J_{HH} = 6.3$ Hz, CH), 7.46 (2H, t, $^{3}J_{HH} = 7.6$ Hz, $2CH_{meta}$ of C_6H_5), 7.52 (2H, t, $^{3}J_{HH} = 7.6$ Hz, $2CH_{meta}$ of C_6H_5), 7.6 (1H, t, $^{3}J_{HH} = 7.3$ Hz, CH_{para} of C_6H_5), 7.65 (1H, t, $^{3}J_{HH} = 7.5$ Hz, CH_{para} of C_6H_5), 7.68 (1H, s, CH of imidazole), 7.91 (2H, d, $^{3}J_{HH} = 7.79$ Hz,

$2CH_{ortho}$ of C_6H_5), 7.98 (1H, s, CH of imidazole), 8.00 (2H, d, $^3J_{HH} = 7.8$ Hz, $2CH_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, δ, $CDCl_3$): 42.15 (CH_2), 56.64 (CH), 118.93 (CH of imidazole), 128.22, 128.78, 128.97, 129.43, 133.36, 134.43, 134.96, and 135.15 (2 C_6H_5), 136.12 (CH of imidazole), 148.28 (C_4 of imidazole), 192.72 and 194.53 (2C=O).

2-(5-Methyl-4-nitro-1*H*-imidazole-1-yl)-1,4-diphenyl-1,4-butanedione (2b)

With powder, m.p. 156–160°C, yield 0.33 g, 92%, IR (KBr): (ν_{max}, cm^{-1}): 1683 and 1667 (C=O), 1558 and 1339 (NO_2). Analysis: calcd for $C_{20}H_{17}N_3O_4$ (363.37): C, 66.11; H, 4.70; N, 11.56%. Found: C, 65.8; H, 4.9; N, 11.4%. MS (*m/z*, %): 363 (M^+, 2), 236 (25), 208 (13), 131 (10), 105 (100), 77 (83), 51 (27). ^1H NMR (500.1 MHz, δ, $CDCl_3$): 2.76 (3H, s, CH_3), 3.71 (1H, dd, $J_{AB} = 18.0$ Hz, $J_{AX} = 6.93$ Hz, CH_2), 4.04 (1H, dd, $J_{AB} = 18.1$ Hz, $J_{BX} = 6.1$ Hz, CH_2), 6.44 (1H, t, $^3J_{HH} = 6.48$ Hz, CH), 7.46 (2H, t, $^3J_{HH} = 7.7$ Hz, $2CH_{meta}$ of C_6H_5), 7.51 (2H, t, $^3J_{HH} = 7.7$ Hz, $2CH_{meta}$ of C_6H_5), 7.57 (1H, s, CH of imidazole), 7.60 (1H, t, $^3J_{HH} = 7.5$ Hz, CH_{para} of C_6H_5), 7.64 (1H, t, $^3J_{HH} = 7.33$ Hz, CH_{para} of C_6H_5), 7.91 (2H, d, $^3J_{HH} = 7.3$ Hz, $2CH_{ortho}$ of C_6H_5), 7.93 (2H, d, $^3J_{HH} = 7.35$ Hz, $2CH_{ortho}$ of C_6H_5). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 10.45 (CH_3), 40.37 (CH_2), 56.00 (CH), 128.23, 128.74, 128.81, 129.11, 133.78, 133.85, 134.27, 135.50, (2 C_6H_5), 131.67 (C_5 of imidazole), 135.65 and 143.82 (imidazole), 194.24 and 195.58 (2C=O).

*1-(1-Benzoyl-3-oxo-3-phenylpropyl)dihydro-1*H*-pyrrole-2,5-dione (6)*

With powder; m.p. 141–145°C, yield 0.30 g, 90%. IR (KBr): (ν_{max}, cm^{-1}): 1763, 1696, 1680 (C=O), 1570 and 1361 (NO_2). Analysis: calcd for $C_{20}H_{17}NO_4$ (335.36): C, 71.63; H, 5.10; N, 4.17%. Found: C, 71.5; H, 4.8; N, 4.7%. MS (*m/z*, %): 335 (M^++1, 12), 318 (12), 230 (12), 213 (2), 185 (2), 159 (2), 131 (3), 105 (100), 77 (85), 51 (31). ^1H NMR (500.1 MHz, δ, $CDCl_3$): 2.58 (4H, s, $2CH_2$ of pyrrole), 3.56 (1H, dd, $J_{AB} = 17.7$ Hz, $J_{AX} = 7.0$ Hz, CH_2), 4.00 (1H, dd, $J_{AB} = 17.7$ Hz, $J_{BX} = 6.1$ Hz, CH_2), 6.17 (1H, t, $^3J_{HH} = 6.6$ Hz, CH), 7.39 (2H, t, $^3J_{HH} = 7.5$ Hz, $2CH_{meta}$ of C_6H_5), 7.42 (2H, t, $^3J_{HH} = 7.68$ Hz, $2CH_{meta}$ of C_6H_5), 7.51 (1H, t, $^3J_{HH} = 7.47$ Hz, CH_{para} of C_6H_5), 7.53 (1H, t, $^3J_{HH} = 7.17$ Hz, CH_{para} of C_6H_5), 7.77 (2H, d, $^3J_{HH} = 7.59$ Hz, $2CH_{ortho}$ of C_6H_5), 7.93 (2H, d, $^3J_{HH} = 7.93$ Hz, $2CH_{ortho}$ of C_6H_5). ^{13}C NMR (500.1 MHz, δ, $CDCl_3$): 28.02 ($2CH_2$), 36.41 (CH_2), 52.00 (CH), 128.00, 128.20, 128.67, 128.79, 133.39, 133.53, 134.64, and 136.21 (2 C_6H_5), 176.37 (2C=O), 197.54 and 196.15 (C=O).

(1-Benzoyl-3-oxo-3-phenyl-propylsulfanyl)-acetic Acid (7)

Pale yellow crystals; m.p. 170–174°C, yield 0.31 g, 95%. IR (KBr): (ν_{max}, cm^{-1}): 3030 (OH), 1700 (C=O), 1652 (COOH), 1578 (Ph), 1433 (Ph), 1203 (C–O). Analysis: calcd for $C_{18}H_{16}SO_4$ (328.38): C, 65.83; H, 4.91; N, 4.26%. Found: C, 65.5; H, 4.4; N, 4.1%. MS (*m/z*, %): 328 (M^+, 2), 236 (5), 208 (4), 159 (1), 131 (4), 105 (100), 77 (60), 51 (27). ^1H NMR (500.1 MHz, δ, acetone-d_6): 3.43 (2H, AB system, $J_{AB} = 15.5$ Hz, SCH_2), 3.68 (1H, dd, $^1J_{HH} = 18.0$ Hz, $^3J_{HH} = 3.1$ Hz, CH_2), 4.16 (1H, dd $^1J_{HH} = 18.1$ Hz, $^3J_{HH} = 10.7$ Hz, CH_2), 5.14 (1H, dd, $^3J_{HH} = 10.7$ Hz, $^3J_{HH} = 3.1$ Hz, CH), 7.54–7.56 (4H, 4CH of $2C_6H_5$), 7.63 (2H, q, $^3J_{HH} = 6.8$ Hz, $2CH_{meta}$ of C_6H_5), 8.03 (2H, d, $^3J_{HH} = 7.5$ Hz, $2CH_{ortho}$ of C_6H_5), 8.15 (2H, d, $^3J_{HH} = 7.4$ Hz, $2CH_{ortho}$ of C_6H_5), (OH, br). ^{13}C NMR (125.7 MHz, acetone-d_6): δ_C 31.33 (CH_2COOH), 41.26 (CH_2), 41.56 (CH), 127.96, 128.55, 128.66, and 128.70 (2 C_6H_5), 133.01 (CH_{para} of C_6H_5), 133.34 (CH_{para} of C_6H_5), 136.09 (C_{ipso} of C_6H_5), 136.34 (CH_{ipso} of C_6H_5), 170.33 (COOH), 194.56 and 197.29 (2C=O).

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