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A synthesis of isoxazoles through the reaction of activated acetylenes and alkyl 2-nitroethanoates in the presence of triphenylphosphine

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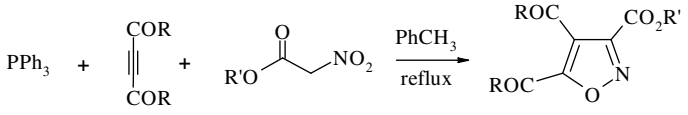
Abstract—The reaction of dialkyl acetylenedicarboxylates or dibenzoylacetylene with alkyl 2-nitroethanoates in the presence of triphenylphosphine leads to functionalized isoxazoles in good yields.

Isoxazoles are an important class of heterocyclic compounds and have served as versatile building blocks in organic synthesis. They can be converted into several important synthetic units such as β-hydroxy-ketones,[1] γ-amino-alcohols,[2] α,β-unsaturated oximes,[3] and β-hydroxy-nitriles.[4] In addition, isoxazoles have long been targeted in synthetic investigations for their known biological activities and pharmacological properties, which includes hypoglycemic,[5] analgesic,[6] anti-inflammatory,[7] and anti-bacterial activities.[8] A powerful method for the construction of isoxazoles is the [3+2] dipolar cycloaddition between alkynes and nitrile oxides.[9] Nitrile oxides, which are formed by dehydration of nitroalkanes[10a] or by oxidation of oximes with hypochlorite,[10b] are useful 1,3-dipoles. As part of our study on the development of new routes to heterocyclic systems,[11] we now report a simple one-pot synthesis of functionalized isoxazoles **3**. Thus, reaction of activated acetylenes **1** with alkyl 2-nitroethanoates **2** in the presence of triphenylphosphine (PPh_3) leads to the corresponding functionalized isoxazoles **3a–e** in good yields[12] (Scheme 1).

The reaction of activated acetylenes **1** with **2** in the presence of PPh_3 under reflux in toluene was complete within a few hours. ^1H and ^{13}C NMR spectra of the crude reaction mixtures clearly indicated the formation of isoxazoles **3**. Products other than **3** could not be detected by NMR spectroscopy. The structures of compounds **3a–e** were deduced from their elemental analyses and their IR, ^1H NMR and ^{13}C NMR



1	R
a	OMe
b	OEt
c	O^{t}Bu
d	Ph

2	R'
a	Me
b	Et

3	R	R'	Yield (%)
a	OMe	Me	90
b	OMe	Et	89
c	OEt	Et	78
d	O^{t}Bu	Et	73
e	Ph	Et	70

Scheme 1.

Keywords: Isoxazole; Activated acetylenes; Triphenylphosphine; CH-Acid; Alkyl 2-nitroethanoates.
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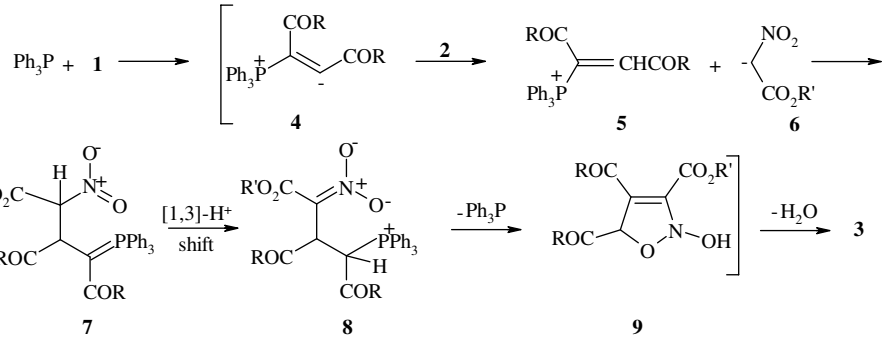

Scheme 2.

spectroscopic data. For example, the ^{1}H NMR spectrum of **3a** exhibited three singlets for the methoxy groups. The ^{1}H decoupled ^{13}C NMR spectrum of **3a** showed nine distinct resonances in agreement with the proposed structure.

A possible mechanism for this transformation is proposed in Scheme 2. It is conceivable that the initial event is the formation of 1,3-dipolar intermediate **4** from Ph_3P and the acetylenic compound, which is subsequently protonated by the alkyl 2-nitroethanoate.[13,14] Nucleophilic attack of the carbon atom of the conjugate base of the CH-acid to the vinylphosphonium cation then produces ylide **7**, which is converted to **8** by a [1,3]-H^+ shift. Next, intermediate **8** is converted to **3** via the *N*-hydroxy compound **9** by elimination of Ph_3P and H_2O (see Scheme 2).

Functionalized isoxazoles **3a**–**e** may be considered as potentially useful synthetic intermediates because they possess atoms with different oxidation states. The presented method features the advantages that the reactions can be performed under neutral conditions and the starting materials and reagents can be mixed without any modifications.

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12. Typical procedure for the synthesis of **3**: To a stirred solution of Ph_3P (0.57 g, 2.2 mmol) and methyl 2-nitroethanoate (0.27 g, 2 mmol) in toluene (10 mL), a solution of dimethyl acetylenedicarboxylate (0.31 g, 2.2 mmol) in toluene (2 mL) was added dropwise and then the reaction mixture was refluxed for 24 h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (Merck 230–400 mesh) using *n*-hexane–EtOAc (4:1) as eluent to afford **3a**: yellow powder; yield: 0.22 g (90%), mp 99–101 °C. IR (KBr) (ν_{max}/cm^{-1}): 1737 (C=O), 1734 (C=O), 1730 (C=O), 1437, 1233, 1087, 1017. ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 3.97$ (3H, s, OMe), 4.01 (3H, s, OMe), 4.03 (3H, s, OMe) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 53.4$ (OMe), 53.5 (OMe), 53.6 (OMe), 117.8 (C), 154.1 (C=N), 155.5 (C–O), 158.4 (C=O), 159.0 (C=O), 160.1 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 243 (M^+, 24), 212 (100), 168 (18), 140 (100), 96 (56), 59 (100). Anal. Calcd for $C_9H_9NO_7$ (243.1): C, 44.45; H, 3.73; N, 5.76. Found: C, 44.36; H, 3.70; N, 5.74.
Compound **3b**: Yellow oil; yield: 0.23 g (89%), IR (KBr) (ν_{max}/cm^{-1}): 1735 (C=O), 1731 (C=O), 1727 (C=O), 1438, 1222, 1086, 1019. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.42$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 3.97 (3H, s, OMe), 4.01 (3H, s, OMe), 4.47 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.1$ (CH_3), 53.5 (OMe), 53.6 (OMe), 63.1 (OCH_2), 117.8 (C), 154.4 (C=N), 155.6 (C–O), 157.9 (C=O), 159.0 (C=O), 160.2 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 257 (M^+, 2), 212

(4), 226 (6), 154 (8), 126 (84), 82 (18), 59 (100). Anal. Calcd for $C_{10}H_{11}NO_7$ (257.2): C, 46.70; H, 4.31; N, 5.45. Found: C, 46.76; H, 4.23; N, 5.44.

Compound **3c**: Yellow oil, yield: 0.22 g (78%). IR (KBr) (ν_{max}/cm^{-1}): 1740 (C=O), 1736 (C=O), 1731 (C=O), 1458, 1221, 1084, 1021. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.40$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.42 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.43 (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 4.42 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 4.47 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 4.48 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.8$ (CH_3), 13.9 (CH_3), 14.0 (CH_3), 62.7 (OCH_2), 63.0 (OCH_2), 63.2 (OCH_2), 117.9 (C), 154.4 (C=N), 155.1 (C–O), 158.0 (C=O), 159.1 (C=O), 159.8 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 285 (M^+, 1), 240 (5), 212 (7), 168 (10), 140 (38), 112 (38), 68 (100), 57 (22). Anal. Calcd for $C_{12}H_{15}NO_7$ (285.2): C, 50.53; H, 5.30; N, 4.91. Found: C, 50.46; H, 5.40; N, 4.84.

Compound **3d**: Dark yellow oil, yield: 0.25 g (73%). IR (KBr) (ν_{max}/cm^{-1}): 1725 (C=O), 1722 (C=O), 1720 (C=O), 1454, 1246, 1089, 1018. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.34$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 1.52 (9H, s, C*Me*$_3$), 1.53 (9H, s, C*Me*$_3$), 4.39 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 14.0$ (CH_3), 27.8 (C*Me*$_3$), 27.9 (C*Me*$_3$), 62.7 (OCH_2), 84.0 (*C*Me$_3$), 85.4 (*C*Me$_3$), 118.1 (C), 154.3 (C=N), 154.4 (C–O), 158.2 (C=O), 158.6 (C=O), 160.0 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 341 (M^+, 1), 230 (8), 212 (4), 168 (2), 140 (4), 94 (2), 57 (100). Anal. Calcd for $C_{16}H_{23}NO_7$ (341.3): C, 56.30; H, 6.79; N, 4.10. Found: C, 56.36; H, 6.72; N, 4.14.

Compound **3e**: Pale yellow powder, yield: 0.24 g (70%), mp 96–98 °C. IR (KBr) (ν_{max}/cm^{-1}): 1735 (C=O), 1731(C=O), 1728 (C=O) 1667, 1229, 884. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.28$ (3H, t, $^3J_{HH} = 7.2$ Hz, CH_3), 4.41 (2H, q, $^3J_{HH} = 7.2$ Hz, OCH_2), 7.57 (2H, t, $^3J_{HH} = 7.2$ Hz, CH), 7.64 (2H, t, $^3J_{HH} = 7.7$ Hz, CH), 7.71 (1H, t, $^3J_{HH} = 7.4$ Hz, CH), 7.78 (1H, t, $^3J_{HH} = 7.3$ Hz, CH), 7.93 (2H, d, $^3J_{HH} = 7.7$ Hz, CH), 8.23 (2H, d, $^3J_{HH} = 7.9$ Hz, CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 63.0 (OCH_2), 124.6 (C), 128.9 (CH), 129.0 (CH), 129.2 (CH), 130.2 (CH), 134.2 (CH), 134.4 (C), 134.9 (CH), 136.4 (C), 155.0 (C=N), 158.0 (C), 166.0 (C=O), 180.0 (C=O), 186.6 (C=O) ppm. MS (EI, 70 eV): m/z (%) = 349 (M^+, 5), 256 (10), 105 (10), 85 (45), 77 (100), 57 (100). Anal. Calcd for $C_{20}H_{15}NO_5$ (349.3): C, 68.76; H, 4.33; N, 4.01. Found: C, 68.66; H, 4.30; N, 4.14.

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