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Chemoselective Reaction Between 5,5-Diarylhydantoins and Acetylenic Esters in the Presence of Trialkyl Phosphite

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Abstract

The adducts produced in the reaction between trialkyl phosphites and acetylenic esters were trapped by hydantoins to produce highly functionalized dialkyl 2-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl) succinate in good yields.

Keywords: Three-component reaction; Hydantoin; Acetylenic ester; Trialkyl phospha

1. Introduction

The imidazolidine-2,4-dione (hydantoin) are a common 5-membered ring containing a reactive cyclic urea or thiourea core. They are known to exhibit a wide range of biological activities, including anticonvulsant, antiarrhythmic, anti-inflammatory, and antidiabetic properties, as well as herbicidal and fungicidal activity [2]. The formation of a carbon-nitrogen bond is of importance for the synthesis of nitrogen-containing natural products and biologically active systems [3]. In recent years, considerable efforts have been devoted to the development of novel and more efficient methods for the preparation of hydantoin derivatives. Besides conventional multi-step methods, one-pot, solid-phase and microwave-assisted approaches have been published [4]. As part of our current studies on the development of new routes in heterocyclic synthesis [5-9], we now report an efficient one-pot synthesis of dialkyl 2-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl) succinates 4 (Scheme 1).

2. Results and Discussion

Thereactionofdialkylacetylenedicarboxylates with 5,5-diarylhydantoin in the presence of trialkyl phosphite proceeded spontaneously at room temperature in dichloromethane, and was completed within a few hours. 1H and 13C NMR spectra of the crude products clearly indicated the formation of dialkyl 2-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl)succinates 4 (Scheme 1). Any product

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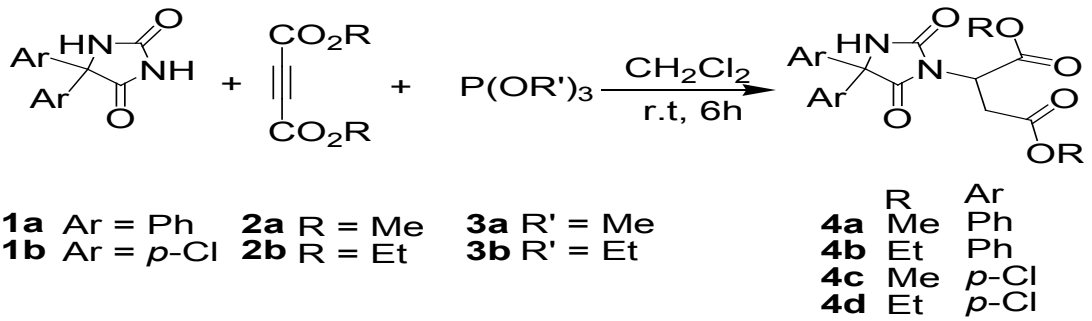
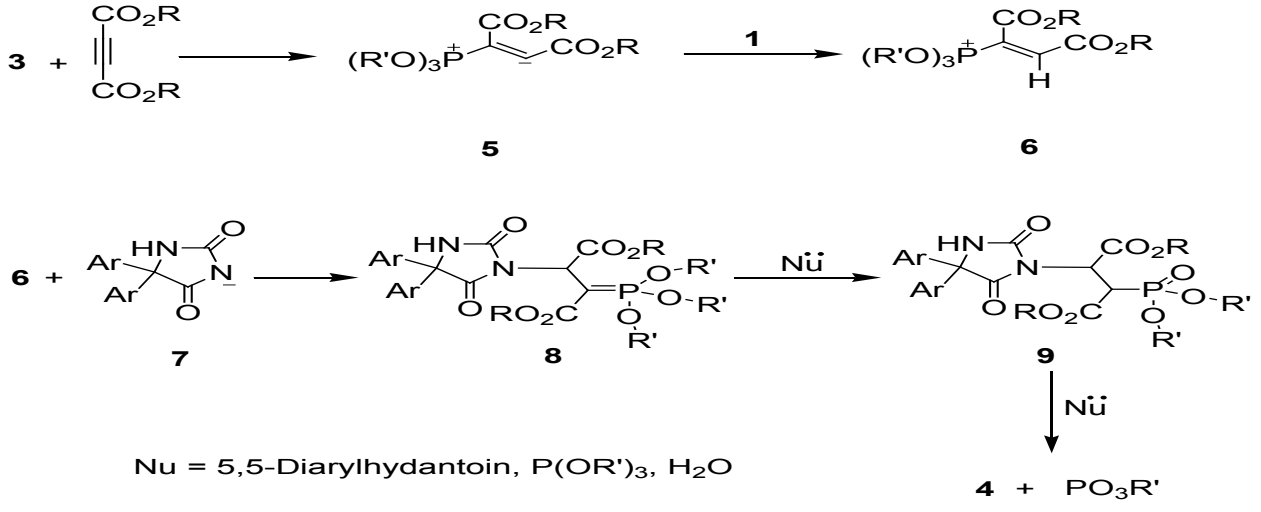


Scheme 1

other than 4 could not be detected by NMR spectroscopy. The structures of compounds 4a were deduced from their elemental analyses and their IR, 1H NMR, and 13C NMR spectroscopic data. The 1H NMR spectrum of 4a exhibited a single broad line readily recognized as arising from NH (δ = 8.82 ppm) of hydantoin; the two protons of the methylene group are diastereotopic and show two characteristic doublet systems at about δ = 3.11 ppm (JAX = 7.9, JAB = 15.9 Hz) and 3.25 ppm (JBX = 6.7, JAB = 15.9 Hz); the methine group appears at 5.80 ppm (JAX = 7.9, JBX = 6.7 Hz). The phenyl residues gave rise to characteristic signals in the aromatic region of the spectrum. Further evidence was obtained from the 13C NMR spectra, which displayed CH-CH2 carbon resonances at about 30-55 ppm. Partial assignments of these resonances are given in the Experimental section.

Although we have not yet established the mechanism of the reaction between trialkyl phosphite and acetylenic esters in the presence of 5,5-diarylhydantoin in an experimental manner, a possible explanation is proposed in Scheme 2. Compounds 4 apparently result from the initial addition of the phosphite to the acetylenic ester and the subsequent protonation of the 1:1 adduct by 5,5-diarylhydantoin (Scheme 2).

On the basis of the well established chemistry of trivalent phosphorus nucleophiles [10, 11] it is reasonable to assume that 8 results from initial addition of trialkyl phosphite to dialkyl acetylenedicarboxylates and subsequent protonation of the 1:1 adduct by the NH-acid. Then, the positively charged ion 6 might be attacked by the conjugate base of the NH-acid to form phosphorane 8. Intermediate 8 with loss of trialkyl phosphate either leads to 4 (Scheme 2). The structures of the stable



Scheme 2

crystalline solids 4 and 5 were deduced from their elemental analyses and their IR, 1H and 13CNMR spectra. The mass spectra of these compounds display molecular ion peaks. Any initial fragmentation involved the complete loss of the ester moieties and scission of the heterocyclic ring system.

In conclusion, we found that the reaction of 5,5-diarylhydantoin with dialkyl acetylenedicarboxylates in the presence of trialkyl phosphite leads to facile chemoselective synthesis of dialkyl 2-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl)succinates 4. The present method has the advantage that not only is the reaction performed under neutral conditions, but the starting materials can be mixed without any activation or modification. The one-pot nature of the present procedure makes it an interesting alternative to multistep approaches [12].

3. Experimental

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHNO-Rapid analyzer. IR spectra were measured on a Shimadzu IR-460 spectrometer.1H and 13C NMR spectra were measured with a Bruker DRX-300 Avance instrument with CDCl3 as solvent at 300.1 and 75.1 MHz. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Isocyanides and dialkyl acetylenedicarboxylates were obtained from Fluka and were used without further purification. 5,5-arylimidazolidine-2,4-diones 1 were prepared by known methods [4].

Dimethyl 2-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl) succinate (4a)

White powder; mp: 157-159°C; yield: 0.39 g (47%); 1H NMR (300 MHz, CDCl3): δ = 3.11 (1 H, dd, (AB)X system, JAX = 7.9, JAB = 15.9 Hz, CH), 3.25 (1 H, dd, (AB)X system, JBX = 6.7, JAB = 15.9 Hz, CH), 3.55 (3 H, s, MeO), 3.68 (3 H, s, MeO), 5.80 (1 H, dd, JAX = 7.9, JBX = 6.7 Hz, CH), 7.32-7.49 (10 H, m, CH), 8.82 (1 H, s, NH). 13C NMR (75 MHz, CDCl3): δ = 33.9 (CH2), 51.7 (MeO), 51.8 (CH), 52.8 (MeO), 78.5 (C), 127.5 (2 CH), 127.9 (2 CH), 128.0 (2 CH), 128.2 (2 CH), 128.5 (CH), 128.6 (CH), 140.9 (C), 141.0 (C), 161.2 (OC=O), 168.4 (OC=O), 170.2 (NC=O), 178.6 (C=O); IR (KBr): = 3708 (NH), 1743 (C=O), 1440 (C=C) cm 1.

Diethyl 2-(2,5-dioxo-4,4-diphenylimidazolidin-1-yl)succinate (4b)

White powder; mp: 150-152°C; yield: 0.40 g (45%); 1H NMR (300 MHz, CDCl3): δ = 1.11 (3 H, t, 3JHH = 7.1, Me), 10.15 (3 H, t, 3JHH = 7.1, Me), 3.15 (1 H, dd, (AB)X system, JAX = 8.4, JAB = 16.5 Hz, CH), 3.37 (1 H, dd, (AB) X system, JBX = 6.3, JAB = 16.5 Hz, CH), 4.02–4.29 (4 H, complex (AB)X3 system, 2 CH2O), 5.79 (1 H, dd, JAX = 8.4, JBX = 6.3 Hz, CH), 7.28-7.52 (10 H, m, CH), 8.80 (1 H, s, NH). 13C NMR (75 MHz, CDCl3): δ = 14.1 (Me), 14.4 (Me), 34.6 (CH2), 52.0 (CH), 61.6 (CH2O), 62.8 (CH2O), 78.8 (C), 127.6 (2 CH), 127.8 (2 CH), 128.1 (2 CH), 128.2 (2 CH), 128.7 (CH), 129.2 (CH), 140.4 (C), 140.5 (C), 161.1 (OC=O), 168.1 (OC=O), 170.3 (NC=O), 178.5 (C=O); IR (KBr): = 3711 (NH), 1740 (C=O), 1449 (C=C) cm 1.

Dimethyl 2-(4,4-bis(4-chlorophenyl)-2,5-dioxoimidazolidin-1-yl)succinate (4c)

White powder; mp: 170-172°C; yield: 0.43 g (45%); 1H NMR (300 MHz, CDCl3): 3.09 (1 H, dd, (AB)X system, JAX = 8.4, JAB = 16.8 Hz, CH), 3.30 (1 H, dd, (AB)X system, JBX = 6.0, JAB = 16.8 Hz, CH), 3.62 (3 H, s, MeO), 3.72 (3 H, s, MeO), 5.77 (1 H, dd, JAX = 8.4, JBX = 6.0 Hz, CH), 7.25-7.45 (10 H, m,

CH), 8.82 (1 H, s, NH). 13C NMR (75 MHz, CDCl3): δ = 33.9 (CH2), 51.7 (MeO), 51.8 (CH), 52.8 (MeO), 78.1 (C), 129.3 (2CH), 129.5 (2CH), 129.8 (2CH), 129.9 (2CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 161.0 (OC=O), 168.1 (OC=O), 170.2 (NC=O), 178.6 (C=O); IR (KBr): = 3710 (NH), 1740 (C=O), 1450 (C=C) cm 1.

Diethyl 2-(4,4-bis(4-chlorophenyl)-2,5-dioxoimidazolidin-1-yl)succinate (4d)

White powder; mp: 165-167°C; yield: 0.43 g (42%); 1H NMR (300 MHz, CDCl3): δ = 1.12 (3 H, t, 3JHH = 7.1, Me), 1.16 (3 H, t, 3JHH = 7.1, Me), 3.08 (1 H, dd, (AB)X system, JAX = 8.5, JAB = 16.5 Hz, CH), 3.30 (1 H, dd, (AB) X system, JBX = 6.0, JAB = 16.5 Hz, CH), 4.02–4.34 (4 H, complex (AB)X3 system, 2 CH2O), 5.80 (1 H, dd, JAX = 8.5, JBX = 6.0 Hz, CH), 7.29-7.46 (10 H, m, CH), 8.81 (1 H, s, NH). 13C NMR (75 MHz, CDCl3): δ = 13.8 (Me), 14.4 (Me), 34.6 (CH2), 52.0 (CH), 61.6 (CH2O), 62.8 (CH2O), 77.4 (C), 129.3 (2CH), 129.5 (2CH), 129.8 (2CH), 129.9 (2CH), 131.5 (C), 131.6 (C), 138.4 (C), 138.5 (C), 161.0 (OC=O), 168.1 (OC=O), 170.2 (NC=O), 178.5 (C=O); IR (KBr): = 3708 (NH), 1742 (C=O), 1444 (C=C) cm 1.

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