A one-pot Synthesis of Functionalized Azadienes from 2-hydroxypyridine, Activated Acetylenes and Alkyl Isocyanides

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ABSTRACT

A one-pot synthesis of dialkyl 2-[(alkylimino)(2-oxopyridin-1(2H)-yl)methyl]but-2-enedioate from alkyl isocyanides, dialkyl acetylenedicarboxylates, and 2-hydroxypyridine, in good yields, is described.

Keywords: Azadienes; Alkyl isocyanides; Activated acetylenes; 2-hydroxypyridine

INTRODUCTION

Isocyanides are known to form zwitterions with activated acetylenic compounds such as dimethyl acetylenedicarboxylate1. Reaction between isocyanides, electron-deficient acetylenes and nucleophiles was first documented by Oakes in 1969 and 19732, 3. Such interesting and promising transformation was nearly forgotten until Yavari in 1996 extended its application to dibenzoylmethane as NuH4. Later on, more publications on such a reaction were published differing mostly in the nature of NuH used5-10.

In continuation of our interest in the application of isocyanides in MCRs11-14, we report an efficient synthesis of functionalized azadienes using isocyanides 1, dialkyl acetylenedicarboxylates 2, and 2-hydroxypyridine 3. This three-component reaction produces highly functionalized azadienes 4 in good yields (Scheme 1).

EXPERIMENTAL

All chemicals were obtained commercially and used without further purification. IR Spectra: Shimadzu-IR-460 spectrometer; bond positions in cm⁻¹. ^1H- and ^13C-NMR Spectra: Bruker DRX-400 Avance instrument; in CDCl₃ at 400 and 100 MHz, resp.; δ in ppm, J in Hz. MS: Finnigan-MAT-8430EI-MS mass spectrometer; at 70 eV; in m/z (rel. %). Elemental analyses: Vario EL III CHNOS elemental analyzer.
General procedure for the preparation of compounds 4

To a stirred mixture of 3 (1 mmol) and acetylenic ester 2 (1 mmol) in CH₂Cl₂ (5 mL), was slowly added 1 (1 mmol) in CH₂Cl₂ (3 mL) at room temperature. After completion of the reaction [about 6 h; TLC (AcOEt/hexane 1:3) monitoring], the solvent was evaporated and the residue was purified by column chromatography [silica gel (230–240 mesh; Merck), hexane/AcOEt 2:1] to give product.

Dimethyl 2-[[2,6-dimethylphenylimino](2-oxopyridin-1(2H)-yl)methyl]but-2-enedioate (4a)

Yield: 0.35 g (95%). Yellow oil. IR (KBr): 1725 (C=O), 1660 (C=O), 1590 (C=N). ¹H-NMR: 2.24 (6H, s, 2Me); 3.65 (s, MeO), 3.83 (s, MeO), 6.79 (s, CH), 6.02–7.97 (m, 7 CH). ¹³C-NMR: 19.2 (2Me); 55.2 (MeO); 55.9 (MeO); 105.2 (CH); 119.5 (CH); 120.4 (CH); 123.8 (CH); 131.6 (2CH); 132.8 (C); 135.3 (2C); 139.9 (CH); 138.5 (C); 163.2 (C=O); 168.1 (C=N); 171.6 (C=O); MS: 368 (17, M⁺), 309 (21), 274 (75), 169 (100), 105 (42), 94 (71), 59 (25). Anal. calc. for C₂₀H₂₀N₂O₅ (368.39): C 65.21, H 5.47, N 7.60; found: C 65.42, H 5.40, N 7.68.

Diethyl 2-[[2,6-dimethylphenylimino](2-oxopyridin-1(2H)-yl)methyl]but-2-enedioate (4b)

Yield: 0.34 g (86%). Yellow oil. IR (KBr): 1725 (C=O), 1660 (C=O), 1590 (C=N). ¹H-NMR: 1.26 (t, J = 7.2, Me); 1.45 (t, J = 7.2, Me); 2.15 (6H, s, 2Me); 4.24 (q, J = 7.2, CH₂O); 4.37 (q, J = 7.2, CH₂O); 6.79 (s, CH), 6.02–7.97 (m, 7 CH). ¹³C-NMR: 12.9 (Me), 13.4 (Me), 23.5 (2Me), 60.2 (CH₂O), 61.2 (CH₂O), 104.9 (CH); 120.1 (CH); 121.4 (CH); 124.3 (CH); 128.9 (CH); 132.6 (2CH); 134.8 (C); 136.3 (2C); 139.7 (CH); 138.7(C); 163.1 (C=O); 168.3 (C=N); 171.5 (C=O); MS: 368 (17, M⁺), 309 (21), 274 (75), 169 (100), 105 (42), 94 (71), 59 (25). Anal. calc. for C₂₀H₂₀N₂O₅ (368.39): C 65.21, H 5.47, N 7.60; found: C 65.42, H 5.40, N 7.68.

Dimethyl 2-[[2,4,4-trimethylpentan-2-ylimino](2-oxopyridin-1(2H)-yl)methyl]but-2-enedioate (4c)

Yield: 0.35 g (93%). Yellow oil. IR (KBr): 1725 (C=O), 1660 (C=O), 1590 (C=N). ¹H-NMR: 1.25 (9 H, s, CMe₃); 1.42 (6 H, s, CMe₂); 1.60 (2 H, s, CH₂); 3.71 (s, MeO); 3.79 (s, MeO); 6.73 (s, CH); 7.00–7.40 (m, 4 CH). ¹³C-NMR: 29.7 (CMe₂); 30.9 (CMe₂); 31.5 (CMe₂); 51.7 (CH₂); 55.2 (CMe₂); 58.7 (MeO); 61.7 (MeO); 106.4 (CH); 119.4 (CH); 119.8 (CH); 136.4 (CH); 138.2 (C); 139.5 (CH); 163.6 (C=O); 168.5 (C=O); 171.3 (C=O); 173.7 (C=O); MS: 376 (15, M⁺), 317 (19), 282 (80), 169 (100), 113 (69), 94 (45), 59 (19). Anal. calc. for C₂₀H₂₅N₂O₅ (376.45): C 63.81, H 7.50, N 7.44; found: C 64.11, H 7.56, N 7.48.

Diethyl 2-[[2,4,4-trimethylpentan-2-ylimino](2-oxopyridin-1(2H)-yl)methyl]but-2-enedioate (4d)

Yield: 0.36 g (89%). Yellow oil. IR (KBr): 1725 (C=O), 1660 (C=O), 1590 (C=N). ¹H-NMR: 1.12 (t, J = 7.2, Me); 1.22 (t, J = 7.2, Me); 1.26 (9 H, s, CMe₃); 1.45 (6 H, s, CMe₂); 1.63 (2 H, s, CH₂); 4.07 (q, J = 7.2, CH₂O); 4.18 (q, J = 7.2, CH₂O); 6.80 (s, CH); 6.02–7.54 (m, 4 CH). ¹³C-NMR: 29.9 (CMe₂); 30.2 (CMe₂); 32.5 (CMe₂); 58.8 (CH₂); 59.0 (CMe₂); 61.0 (CH₂O); 61.1 (CH₂O); 104.5 (CH); 119.3 (CH); 119.5 (CH); 136.6 (CH); 138.3 (C); 139.8 (CH); 163.4 (C=O); 168.3 (C=O); 171.2 (C=O); 173.5 (C=O); MS: 404 (12, M⁺), 331 (17), 310 (80), 197 (100), 113 (72), 94 (40), 73 (22). Anal. calc. for C₂₂H₃₂N₂O₅ (404.51): C 65.21, H 7.97, N 6.94; found: C 65.63, H 8.03, N 6.94.

Diethyl 2-[[tert-butylimino](2-oxopyridin-1(2H)-yl)methyl]but-2-enedioate (4e)

Yield: 0.29 g (83%). Yellow oil. IR (KBr): 1725 (C=O), 1660 (C=O), 1590 (C=N). ¹H-NMR: 1.19 (9 H, s, CMe₃); 1.27 (t, J = 7.2, Me); 1.39 (t, J = 7.2, Me); 4.15 (q, J = 7.2, CH₂O); 4.35 (q, J = 7.2, CH₂O); 6.75 (s, CH); 6.22–7.45 (m, 4 CH). ¹³C-NMR: 12.9 (Me), 14.3 (Me), 30.8 (CMe₂); 57.7 (CMe₂); 60.6 (CH₂O); 61.7 (CH₂O); 109.5 (CH); 121.3 (CH); 126.5 (CH); 136.9 (CH); 137.8 (C); 139.2 (CH); 163.5 (C=O); 168.2 (C=O); 171.4 (C=O); 173.6 (C=O). MS: 348 (10, M⁺), 275 (17), 254 (82), 197 (100), 134 (72), 94 (42), 73 (68), 57 (22). Anal. calc. for C₁₈H₂₄N₂O₅ (348.40): C 62.05, H 6.94, N 8.04; found: C 62.19, H 6.86, N 8.01.

RESULTS AND DISCUSSION

Thus, reaction of isocyanides 1, acetylenic esters 2, and 2-hydroxypyridine 3 proceeded spontaneously in CH₂Cl₂, and was completed within a few hours. The 'H- and ¹³C-NMR spectra of the crude products clearly indicated the formation of dialkyl 2-[(alkylimino)(2-oxopyridin-1(2H)-yl)methyl]but-2-enedioates 4. The structures of 4...
Compounds 4a–4e were deduced from their IR, 1H-NMR, and 13C-NMR spectra. The 1H-NMR spectrum of 4a in CDCl3 showed a singlet for the two methyl of 2,6-dimethylphenyl (δ(H) 2.24), along with three singlets for methoxy (δ(H) 3.65 and 3.83) and methine (δ(H) 5.79) H-atoms. Characteristic multiplets for the Ph H-atoms were observed at δ(H) 6.02-7.97. The 13C-NMR spectrum of 4a exhibited 17 resonances in agreement with the proposed structure. The mass spectrum of 4a displayed the molecular ion peak at m/z 368. The NMR spectra of 4b-4e were similar to those of 4a except for the substituents.

A possible mechanism for these transformations is proposed in Scheme 2. It is conceivable that the reaction involves the initial formation of the 1:1 zwitterionic intermediate 5 between the isocyanide 1 and acetylenic ester 2 (Scheme 1). Protonation of 5 by the acidic compound 3 leads to intermediate 6. Subsequent attack of the resulting nucleophile 7 on the positively charged ion 6 affords azadiene derivatives 4.

In conclusion, the three-component reaction of alkyl isocyanides, dialkyl acetylene dicarboxylates, and 2-hydroxypyridine provides a simple one-pot synthesis of stable functionalized azadienes. This procedure has the advantages of high yields and mild reaction conditions.
REFERENCES