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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(2*H*)-yl)methyl]but-2-enedioate from alkyl isocyanides, dialkyl acetylenedicarboxylates, and 2-hydroxypyridine, in good yields, is described.

Keywords*:* Azadienes; Alkyl isocanides; Activated acetylenes; 2-hydroxypyridine

INTRODUCTION

Isocyanides are known to form zwitterions with activated acetylenic compounds such as dimethyl acetylenedicarboxylate[1]. Reaction between isocyanides, electron-deficient acetylenes and nucleophiles was first documented by Oakes in 1969 and 1973[2, 3]. Such interesting and promising transformation was nearly forgotten until Yavari in 1996 extended its application to dibenzoylmethane as NuH[4]. Later on, more publications on such a reaction were published differing mostly in the nature of NuH used[5-10].

In continuation of our interest in the application of isocyanides in MCRs[11-14], 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 ^{13}C-NMR Spectra: Bruker DRX-400 Avance instrument; in $CDCl_3$ 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 CH_2Cl_2 (5 mL), was slowly added **1** (1 mmol) in CH_2Cl_2 (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). ^{1}H-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). ^{13}C-NMR: 19.2 (2Me); 55.2 (MeO); 55.9 (MeO); 105.2 (CH); 119.5 (CH); 120.4 (CH); 123.8 (CH); 128.1 (CH); 131.6 (2CH); 132.8 (C); 135.3 (2C); 139.9 (CH); 138.5(C); 163.2 (C=O); 168.1 (C=N); 171.1 (C=O); 173.4 (C=O). MS: 368 (17, M+), 309 (21), 274 (75), 169 (100), 105 (42), 94 (71), 59 (25). Anal. calc. for $C_{20}H_{20}N_2O_5$ (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): 1728 (C=O), 1665 (C=O), 1574 (C=N). ^{1}H-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, CH_2O); 4.37 (q, J = 7.2, CH_2O); 6.85 (s, CH); 6.03–7.98 (m, 7 CH). ^{13}C-NMR: 12.9 (Me), 13.1 (Me), 23.5 (2Me), 60.2 (CH_2O), 61.2 (CH_2O), 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); 173.2 (C=O). MS: 396 (15, M+), 323 (20), 302 (77), 197 (100), 105 (40), 94 (68), 73(29). Anal. calc. for $C_{22}H_{24}N_2O_5$ (396.17): C 66.65, H 6.10, N 7.07; found: C 67.09, H 5.59, N 7.15.

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): 1735 (C=O), 1682 (C=O), 1590 (C=N). ^{1}H-NMR: 1.24 (9 H, s, CMe_3); 1.42 (6 H, s, CMe_2); 1.60 (2 H, s, CH_2); 3.71 (s, MeO); 3.79 (s, MeO); 6.73 (s, CH); 6.20–7.40 (m, 4 CH). ^{13}C-NMR: 29.7 (C*Me$_3$*); 30.9 (C*Me$_2$*); 31.5 (*C*Me$_3$); 51.7 (CH_2); 55.2 (*C*Me$_2$); 58.7 (MeO); 61.7 (MeO); 104.6 (CH); 119.4 (CH); 119.8 (CH); 136.4 (CH); 138.2 (C); 139.5 (CH); 163.6 (C=O); 168.5 (C=N); 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 $C_{20}H_{28}N_2O_5$ (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)

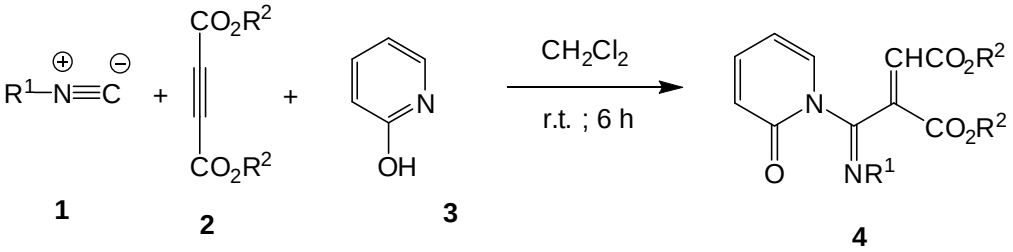
Yield: 0.36 g (89%). Yellow oil. IR (KBr): 1739 (C=O), 1676 (C=O), 1568 (C=N). ^{1}H-NMR: 1.12 (t, J = 7.2, Me); 1.22 (t, J = 7.2, Me); 1.26 (9 H, s, CMe_3); 1.45 (6 H, s, CMe_2); 1.63 (2 H, s, CH_2); 4.07 (q, J = 7.2, CH_2O); 4.18 (q, J = 7.2, CH_2O); 6.80 (s, CH); 6.07–7.54 (m, 4 CH). ^{13}C-NMR: 13.1 (Me); 13.4 (Me); 29.9 (C*Me$_3$*); 30.2 (C*Me$_2$*); 32.5 (*C*Me$_3$); 58.8 (CH_2); 59.9 (*C*Me$_2$); 61.0 (CH_2O); 61.1 (CH_2O); 104.5 (CH); 119.3 (CH); 119.5 (CH); 136.6 (CH); 138.8 (C); 139.8 (CH); 163.4 (C=O); 168.3 (C=N); 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 $C_{22}H_{32}N_2O_5$ (404.51): C 65.32, H 7.97, N 6.93; 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): 1731 (C=O), 1673 (C=O), 1581 (C=N). ^{1}H-NMR: 1.19 (9H, s, CMe_3); 1.27 (t, J = 7.2, Me); 1.39 (t, J = 7.2, Me); 4.15 (q, J = 7.2, CH_2O); 4.35 (q, J = 7.2, CH_2O); 6.75 (s, CH); 6.22–7.45 (m, 4 CH). ^{13}C-NMR: 12.9 (Me), 14.3 (Me), 30.8 (C*Me$_3$*); 57.7 (*C*Me$_3$) 60.6 (CH_2O); 61.7 (CH_2O); 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=N); 171.4 (C=O); 173.6 (C=O). MS: 348 (10, M+), 275 (17), 254 (82), 197 (100), 94 (42), 73 (68), 57 (22). Anal. calc. for $C_{18}H_{24}N_2O_5$ (348.40): C 62.05, H 6.94, N 8.04; found: C 62.19, H 6.86, N 8.01.

RESULTS AND DISCUSSION

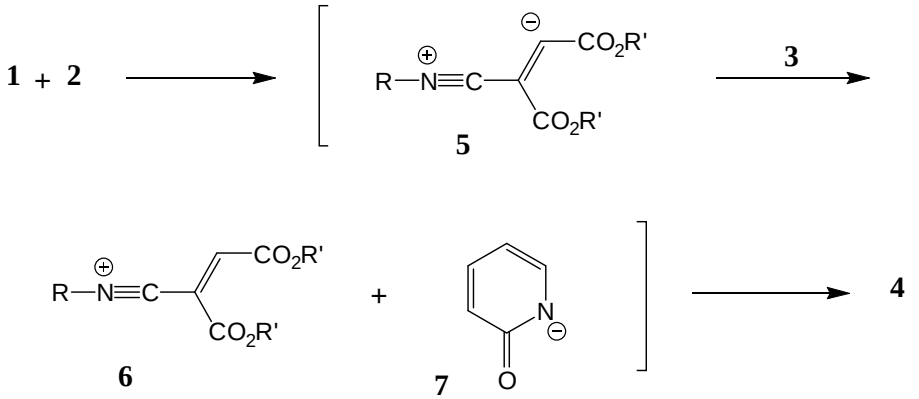
Thus, reaction of isocyanides **1**, acetylenic esters **2**, and 2-hydroxypyridine **3** proceeded spontaneously in CH_2Cl_2, and was completed within a few hours. The ^{1}H- and ^{13}C-NMR spectra of the crude products clearly indicated the formation of dialkyl 2-[(alkylimino)(2-oxopyridin-1(2H)-yl)methyl]but-2-enedioates **4**. The structures of



1 **2** **3** **4**

Entry	R^1	R^2	Product	Yield (%)
1	2,6-dimethylphenyl	Me	4a	95
2	2,6-dimethylphenyl	Et	4b	86
3	1,1,3,3-tetramethylbuty	Me	4c	93
4	1,1,3,3-tetramethylbuty	Et	4d	89
5	*t*-Bu	Et	4e	83

Scheme 1: Synthesis of Compounds 4



Scheme 2: A Plausible Mechanism for the Formation of Products 4.

compounds **4a–4e** were deduced from their IR, ^{1}H-NMR, and ^{13}C-NMR spectra. The ^{1}H-NMR spectrum of **4a** in $CDCl_3$ 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 ä(H) 6.02-7.97. The ^{13}C-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.

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