Reaction of Alkyl Isocyanides, Dialkyl Acetylenedicarboxylates with 4-Hydroxy Quinoline: Synthesis of 1-Azabuta-1,3-Dienes

Bita Mohtat*[,a], Somayeh Rezazadeh[a], Mahnaz Matinfar[a], Vale Arabzadeh[b], Hoorieh Djahaniani[c] and Zinatossadat Hossaini[d]

[a]*Department of Chemistry, Karaj Branch, Islamic Azad University, Karaj, Iran*

[b]*Department of Chemistry, Jooybar Branch, Islamic Azad University, Mazandaran, Iran*

[c]*Department of Chemistry, East Tehran Branch, Islamic Azad University, Tehran, Iran*

[d]*Department of Chemistry, Qaemshahr Branch, Islamic Azad University, Mazandaran, Iran*

Received September 02, 2011: Revised October 14, 2011: Accepted October 25, 2011

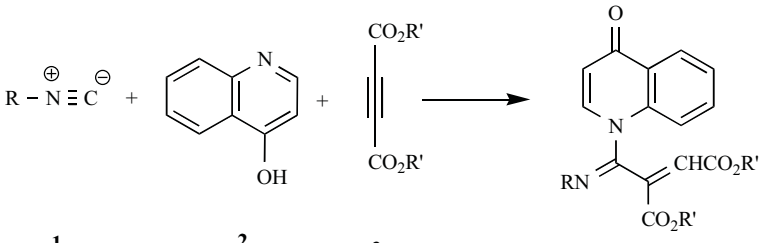
Abstract: The 1:1 reactive intermediates generated by the addition of alkyl isocyanides to dialkyl acetylenedicarboxylates were trapped by 4-hydroxy quinoline to yield highly functionalized 1-azabuta-1,3-dienes.

Keywords: Acetylenic esters, alkyl isocyanides, 1-Azabuta-1,3-dienes, 4-Hydroxy quinoline, multi-component reaction.

INTRODUCTION

Isocyanides are compounds with an extraordinary functional group; their unusual valence structure and reactivity have been discussed for over one and a half century [1]. Isocyanides are the only class of stable organic compounds with a formally divalent carbon. Owing to its reactivity, the isocyanide group differs fundamentally from other functional groups. The fascinating chemistry that stems from the addition of isocyanides to activated acetylenic compounds has evoked considerable interest [2]. Multi-component reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention in the context of combinatorial chemistry. Of pivotal importance in this area are the isocyanide based MCRs such as the versatile Ugi and Passerini reactions [3-10].

The reactions of 1-azadienes with various chiral dienophiles, which lead to substituted pyridines, have been reported [11]. Recently, we have described a convenient method for the preparation of 1-azadienes, by three-component reaction of 2-pyridinol and 1-isoquinolinol with dialkyl acetylenedicarboxylates and alkyl isocyanide [12]. In continuation of our interest in the application of isocyanides in MCRs, [13, 14] we extend this methodology using 4-hydroxyquinoline. Thus, the reaction of alkyl isocyanides **1** and dialkyl acetylenedicarboxylates **3** in the presence of strong NH-acid, such as 4-hydroxy quinoline **2** leads



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

1	R
a	*t*-Butyl
b	*c*-Hexyl
c	*1,1,3,3-tetra metyl* Butyl

3	R'
a	Me
b	Et

4	R	R'	yield %
a	*t*-Butyl	Me	83
b	*c*-Hexyl	Me	78
c	*1,1,3,3-tetra* metyl Butyl	Me	65
d	*t*-Butyl	Et	79
e	*c*-Hexyl	Et	70
f	*1,1,3,3-tetra* metyl Butyl	Et	62

Scheme 1. Typical procedure for compounds **4**.

*Address correspondence to this author at the Karaj Branch, Islamic Azad University, Karaj, Iran; Tel: +989122937695; Fax: +982122921610; E-mail: b.mohtat@jooyan.org

1875-625512 $58.00+.00 © 2012 Bentham Science Publishers

to dimethyl 2-((tert-butylimino)(4-oxoquinolin-1(4H)-yl) methyl)but-2-enedioate **4** in good yields (Scheme **1**).

RESULT AND DISCUSSION

The reaction proceeded spontaneously in CH_2Cl_2, and was completed within a few hours. The structures of compounds **4a–4f** were deduced from their IR, ^{1}H-NMR, and ^{13}C-NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values, the ^{1}H-NMR spectrum of **4a** exhibited four sharp lines for tert-butyl (δ = 1.32 ppm), methoxy (δ = 3.67 and 3.69 ppm), and vinyl (δ = 6.66 ppm) protons. The quinolinol moiety appeared at δ = 6.31–8.29 ppm. The ^{13}C-NMR spectrum of **4a** showed 18 distinct resonances in agreement with the dimethyl 2-((tert-butylimino)(4-oxoquinolin-1(4H)-yl) methyl)but-2-enedioate. Structure partial assignments of these resonances are given in the experimental section. The ^{1}H-NMR spectra of **4b–4f** are similar to that of **4a**, except for the signals of the alkyl, and alkoxy moieties. The structural assignments of compounds **4a–4f** made on the basis of their NMR spectra were supported by their IR spectra. Of special interest are the imine absorption bands at about 1620 cm^{-1} in all compounds.

A plausible mechanism for the formation of polyfunctionalized 1-azadienes **4a–4f** is shown in Scheme **2**. The reaction proceeds by addition of the isocyanide to the activated acetylene to produce the zwitterionic intermediate **5**, which is protonated by the NH acid **3** [15]. Then, the positively charged ion is attacked by the carbon atom of the bidentate anion of the NH acid, direct addition leads to 1-azadiene **4** (Scheme **2**). The absence of the strong ketenimine absorption bands at about 2060 cm^{-1} in all compounds excludes the conjugate addition of the anion **7** to the intermediate **6**.

CONCLUSION

In conclusion, the reaction of alkyl isocyanide with electron-deficient acetylenic esters in the presence of some NH acid provides a simple one-pot entry into the synthesis of polyfunctionalized 1-azadienes of potential synthetic interest. The present procedure carries the advantage that not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification.

EXPERIMENTAL

General

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. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance instrument with $CDCl_3$ at (300.1 and 75.5 MHz, respectively). Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. Alkyl isocyanides, dialkyl acetylenedicarboxylates, and compounds **2** were obtained from (Fluka) and were used without further purification.

General Procedure for the Preparation of Compounds 4

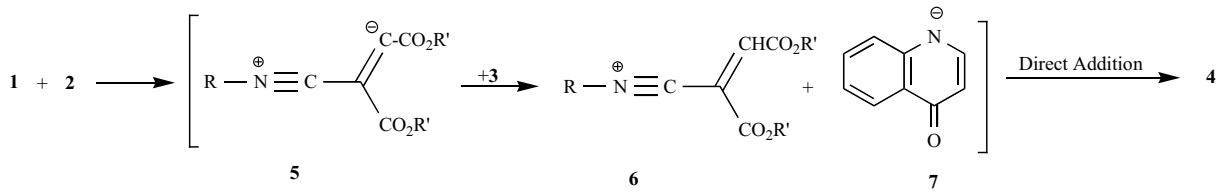
To a stirred solution of 4-quinolinol (2 mmol) and tert-butyl isocyanide (2 mmol) in 10 mL of CH_2Cl_2, dimethyl acetylenedicarboxylate (DMAD) (2 mmol) was added dropwise at -10 ºC over 10 min. The reaction mixture was then allowed to warm to room temperature and stand for 24 h. The solvent was removed under reduced pressure, and the residual was purified by preparative TLC on silica gel (Merck silica gel DC-Fertigplatten 60/Kieselgur F254) 20×20 cm plates using n-hexane-EtOAc (1:1) as an eluent.

Dimethyl 2-((tert-butylimino)(4-oxoquinolin-1(4H)-yl) methyl)but-2-enedioate (4a)

Yellow oil, yield 0.66 g (83%), IR (neat) (ν_{max}/cm^{-1}): 1735, 1666 (C=O), 1632 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.32 (s, 9H, 3CH_3), 3.67 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 6.31 (t, 1H, *J* = 7.4 Hz, CH), 6.66 (s, 1H, CH), 7.37 (m, 1H, CH), 7.67 (m, 2H, 2CH), 8.03 (d, 1H, *J* = 7.4 Hz, CH), 8.29 (d, 1H, *J* = 8.8 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 28.6 (3 CH_3), 52.3 (OCH_3), 52.5 (OCH_3), 56.2 (C-N), 109.5 (CH=), 119.1 (CH=), 124.3 (CH=), 126.0 (CH=), 126.5 (C=), 128.6 (C=), 129.3 (CH=), 132.7 (CH=), 140.6 (CH), 141.1 (C=), 141.7 (C=), 165.1 (C=O), 169.4 (C=O), 178.7 (C=O). MS (EI, 70 eV): *m/z* (%) = 398 (M+, 7), 262 (73), 146 (100), 71 (65), 58 (62). Anal. calcd. for $C_{20}H_{22}N_2O_5$ (370.41): C, 64.85, H, 5.99, N, 7.56, found: C, 64.89, H, 5.94, N, 7.60.

Dimethyl 2-((cyclohexylimino)(4-oxoquinolin-1(4H)-yl) methyl)but-2-enedioate (4b)

Yellow oil, yield 0.62 g (78%), IR (neat) (ν_{max}/cm^{-1}): 1732, 1660 (C=O), 1622 (C=N). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.28-2.08 (m, 10H, 5CH_2), 3.62 (s, 3H, OCH_3), 3.65(s, 3H, OCH_3), 3.79 (m, 1H, CH), 6.25 (t, 1H, *J* = 7.8 Hz, CH), 6.62 (s, 1H, CH), 7.21 (m, 1H, CH), 7.42 (m, 2H, 2CH), 7.76 (d, 1H, *J* = 7.5 Hz, CH), 8.30 (d, 1H, *J* = 8.1 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 22.8 (CH_2), 24.0 (CH_2), 25.7 (CH_2), 32.0 (CH_2), 32.2 (CH_2), 51.9 (CH-N), 52.8 (OCH_3), 54.0 (OCH_3), 108.3 (CH=), 119.0 (CH=), 124.7 (CH=), 126.3 (CH=), 126.9 (C=), 127.1 (C=), 130.8 (CH=), 132.1 (CH=), 140.2 (CH), 141.2 (C=), 141.4 (C=), 163.3 (C=O), 164.9 (C=O), 178.4 (C=O). MS (EI, 70 eV): *m/z* (%)



Scheme 2. A possible mechanism for the preparation of compound **4**.

=_396 (M^+, 10), 288 (100), 146 (49), 71 (85), 43 (77)._Anal. Calcd. For $C_{22}H_{24}N_2O_5$: C, 66.65, H, 6.10, N, 7.07, found: C, 66.70, H, 6.07, N, 7.05.

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

Yellow oil, yield 0.55 g (65%), IR (neat) (ν_{max}/cm^{-1}): 1731, 1670 (C=O), 1633 (C=N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.02 (s, 9H,3 CH_3), 1.42 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 1.85 (m, 2H, 2CH), 3.73 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 6.29 (d, 1H, *J* = 7.4 Hz, CH), 6.72 (s, 1H, CH), 7.39 (m, 1H, CH), 7.67 (m, 2H, CH), 8.03 (d, 1H, *J* = 7.3 Hz, CH), 8.30 (d, 1H, *J* = 8.1 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.4 (3 CH_3), 31.6 (CH_3), 31.7 (CH_3), 31.8 (C), 34.0 (CH_2), 52.2 (OCH_3), 52.5 (OCH_3), 56.2 (C-N), 109.6 (CH=), 119.2 (CH=), 124.3 (CH=), 126.0 (CH=), 126.7 (C=), 128.6 (C=), 130.3 (CH=), 132.7 (CH=), 140.9 (CH), 141.2 (C=), 141.6 (C=), 165.2 (C=O), 169.4 (C=O), 178.6 (C=O). MS (EI, 70 eV): *m/z* (%) = 426 (M^+, 8), 388 (54), 318 (100), 146 (100), 71 (48), 58 (81). Anal. calcd for $C_{24}H_{30}N_2O_5$: C, 67.59, H, 7.09, N, 6.57%, Found: C, 67.64, H, 6.92, N, 6.54.

Diethyl 2-((tert-butylimino)(4-oxoquinolin-1(4H)-yl) methyl)but-2-enedioate (4d)

Yellow oil, yield 0.63 g (79%), IR (neat) (ν_{max}/cm^{-1}): 1733, 1665 (C=O), 1628 (C=N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.16 (t, 3H, *J* = 7.1 Hz, CH3), 1.25 (t, 3H, *J* = 7.1 Hz, CH3), 1.40 (s, 9H, $3CH_3$), 4.00-4.35 (m, 4H, $2OCH_2$), 6.16 (d, 1H, *J* = 7.5 Hz, CH), 6.67 (s, 1H, CH), 7.34 (m, 1H, CH), 7.64 (m, 2H, 2CH), 7.65 (d, 1H, *J* = 7.5 Hz, CH), 7.94 (d, 1H, *J* = 8.0 Hz, CH) . ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 14.3 (CH_3), 28.5 (3 CH_3), 51.9 (C-N), 61.6 (OCH_2), 62.4 (OCH_2), 109.9 (CH=), 119.0 (CH=), 123.9 (CH=), 126.2 (CH=), 127.1 (C=), 129.3 (C=), 129.6 (CH=), 132.5 (CH=), 139.9 (CH), 141.3 (C=), 141.9 (C=), 164.6 (C=O), 164.7 (C=O), 178.5 (C=O). MS (EI, 70 eV): *m/z* (%) = 398 (M^+, 2), 310 (24), 254 (23), 198 (35), 145 (82), 57 (100), 41 (30). Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 68.71, H, 7.56, N, 6.14, found: C, 68.73, H, 7.50, N, 6.12.

Diethyl 2-((cyclohexylimino)(4-oxoquinolin-1(4H)-yl) methyl)but-2-enedioate (4e)

Yellow oil, yield 0.59 g (70%), IR (neat) (ν_{max}/cm^{-1}): 1729 (C=O), 1657 (C=O), 1626 (C=N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, 3H, *J* = 7.1 Hz, CH3), 1.27 (t, 3H, *J* = 7.1 Hz, CH3), 1.28-1.94 (m, 10H, $5CH_2$), 3.83 (m, 1H, CH), 4.13-4.35 (m, 4H, 2 OCH_2), 6.13 (d, 1H, *J* = 7.5 Hz, CH), 6.73 (s, 1H, CH), 7.35 (m, 1H, CH), 7.63 (m, 2H, 2 CH), 7.90 (d, 1H, *J* = 7.5 Hz, CH), 8.24 (t, 1 H, *J* = 7.3 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 14.3 (CH_3), 23.5 (CH_2), 25.1 (CH_2), 25.5 (CH_2), 32.4 (CH_2), 32.6 (CH_2), 49.6 (CHN), 62.2 (OCH_2), 63.6 (OCH_2), 109.9 (CH=), 118.9 (CH=), 123.9 (CH=), 126.3 (CH=), 127.2 (C=), 129.0 (C=), 130.4 (CH=), 132.5 (CH=), 139.7 (CH), 140.8 (C=), 141.5 (C=), 162.9 (C=O), 163.0 (C=O), 178.4 (C=O). MS (EI, 70 eV): *m/z* (%) = 424 (M^+, 7), 280 (31), 253 (56), 227 (100), 171 (48), 83 (41), 29 (35). Anal. calcd. for $C_{24}H_{28}N_2O_5$ (424.49): C, 67.91, H, 6.65, N, 6.60, found: C, 67.88, H, 6.68, N, 6.63.

Diethyl 2-((2,4,4-trimethylpentan-2-ylimino)(4-oxoquinolin-1(4H)-yl)methyl)but-2-enedioate (4f)

Yellow oil, yield 0.56 g (62%), IR (neat) (ν_{max}/cm^{-1}): 1735, 1665 (C=O), 1624 (C=N). ^1H NMR (300 MHz, $CDCl_3$): δ 1.04 (s, 9 H, $3CH_3$), 1.22 (t, 3H, *J* = 7.1 Hz, CH_3), 1.34 (t, 3H, *J* = 7.1 Hz, CH_3), 1.43 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 1.82 (m, 2H, 2CH), 4.04-4.23 (m, 4H, 2 OCH_2), 6.23 (d, 1H, *J* = 7.4 Hz, CH), 6.74 (s, 1H, CH), 7.34 (m, 1H, CH), 7.65 (m, 2H, 2CH), 7.98 (d, 1H, *J* = 7.4 Hz, CH), 8.26 (d, 1H, *J* = 7.9 Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.3 (CH_3), 14.4 (CH_3), 30.6 (3 CH_3), 31.6 (2 CH_3), 31.7 (C), 34.0 (CH_2), 56.2 (C-N), 61.4 (OCH_2), 62.5 (OCH_2), 109.7 (CH=), 119.1 (CH=), 124.1 (CH=), 126.2 (CH=), 126.9 (C=), 129.3 (C=), 131.0 (CH=), 132.6 (CH=), 140.0 (CH), 141.2 (C=), 141.9 (C=), 164.4 (C=O), 164.7 (C=O), 178.4 (C=O). MS (EI, 70 eV): *m/z* (%) = 454, (M^+, 6), 310 (37), 198 (29), 145 (100), 57 (63), 29 (72). Anal. calcd for $C_{26}H_{34}N_2O_5$: C, 68.70, H, 7.54, N, 6.16%, Found: C, 68.73, H, 7.50, N, 6.18.

DISCLOSURE

Some part of information included in this article has been previously published in "Synthetic Communications Volume 41, Issue 6, 2011".

ACKNOWLEDGEMENT

Declared none.

CONFLICT OF INTEREST

Declared none.

REFERENCES

[1] Weber, L.; The application of multi-component reactions in drug discovery. *Curr. Med. Chem.* **2002**, *9*, 2085-2093.

[2] Dillinger, H.J.; Fengler, G.; Schumann, D.; Winterfeldt, E. Additionen an die Dreifachbindung, XXI: Das kinetisch kontrollierte addukt aus tert-butylisonitril und acetylendicarbonester. *Tetrahedron* **1974**, *30*, 2553-2559.

[3] Junjappa, H.; Saxena, M.K.; Ramaiah. D.; Loharay, B.B.; Rath, N.P.; George, M.V. Structure and thermal isomerization of the adducts formed in the reaction of cyclohexyl isocyanide with dimethyl acetylenedicarboxylate. *J. Org. Chem.* **1998**, *63*, 9801-9805.

[4] Nair, V.; Vinod, A.U. The reaction of cyclohexyl isocyanide and dimethyl acetylene dicarboxylate with aldehydes: A novel synthesis of aminofuran derivatives. *Chem. Commun.* **2000**, 1019-1020.

[5] Ugi, I. From isocyanides *via* four-component condensations to antibiotic syntheses. *Angew. Chem., Int. Ed.* **1982**, *21*, 810-812.

[6] Ugi, I.; Lohberger, S.; Karl, R. In: *Comprehensive Organic Synthesis*; B. M. Trost, I. Fleming Ed.; Pergamon Oxford, **1991** Vol. 2, pp. 1033.

[7] Domling, A.; Ugi, I. Multicomponent reactions with isocyanides. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169-3210.

[8] Yavari, I.; Karimi, E. A. Synthesis of functionalized 1-azadienes by reaction of 2,6-dimethylphenyl isocyanide and acetylenic esters in the presence of CH acids. *Synth. Commun.* **2007**, *37*, 1189–1194.

[9] Baharfar, R.; Hossein nia, R.; Baghbanian, S. M. A Novel Approach to the Synthesis of Highly Functionalized Thiophenes

Using Isocyanides Catalyzed Reaction of Acetylenic Esters with 3-Mercapto-2-Butanone. *Lett. Org. Chem.* **2008**, *2*, 128-132.

[10] Yavari, I.; Nasiri, F.; Djahaniani, H. Synthesis and dynamic NMR study of ketenimines derived from tert-butyl isocyanide, alkyl 2-arylamino-2-oxo-acetates, and dialkyl acetylenedicarboxylates. *Mol. Divers.* **2004**, *8*, 431-435.

[11] Beaudegnies, R.; Ghosez, L. Asymmetric Diels–Alder reactions with chiral 1-azadienes. *Tetrahedron: Asymmetry* **1994**, *5*, 557-560.

[12] Mohtat, B.; Djahaniani, H.; Khorrami, R.; Mashayekhi, S.; Yavari, I. Three-component synthesis of functionalized 1-azabuta-1,3-dienes from alkyl isocyanides, activated acetylenes, and pyridin-2(1H)-one or isoquinolin-1(2H)-one. *Synth. Commun.* **2011**, *41*, 784-791.

[13] Yavari, I.; Zare, H.; Mohtat, B. Three-component synthesis of dialkyl 2-(alkylimino-methylene)-3-(2,2,5-trimethyl-4,6-dioxo-1,3-dioxan-5-yl)-succinates. *Mol. Divers.* **2006**, *10*, 247-250.

[14] Mohtat, B.; Djahaniani, H.; Yavari, I.; Dehbalaei, M.G.; Jam, S.A. Synthesis of 4H-chromene derivatives by reaction between alkyl isocyanides and dialkyl acetylenedicarboxylate in the presence of 6-hydroxyquinoline. *Chin. Chem. Lett.* **2011**, *22*, 771-773.

[15] Walborsky, H.M.; Persiasamy, M.P. In: *The Chemistry of Functional Groups,* Patai, S.; Rappoport, Z. Ed.; Wiley, New York, **1983**; pp. 835.