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Three-component reaction of alkyl isocyanides, dialkyl acetylenedicarboxylates and furan-2-carboxylic acid arylidene-hydrazides

Mohammad Hossein. Mosslemin[a]*, Mohammad Reza Nateghi[a], Alireza Hassanabadi[b] and Mohsen Zare[a]

[a]*Department of Chemistry, Islamic Azad University, Yazd Branch, PO Box 89195-155, Yazd, Iran*

[b]*Department of Chemistry, Islamic Azad University, Zahedan Branch, PO Box 98135-978, Zahedan, Iran*

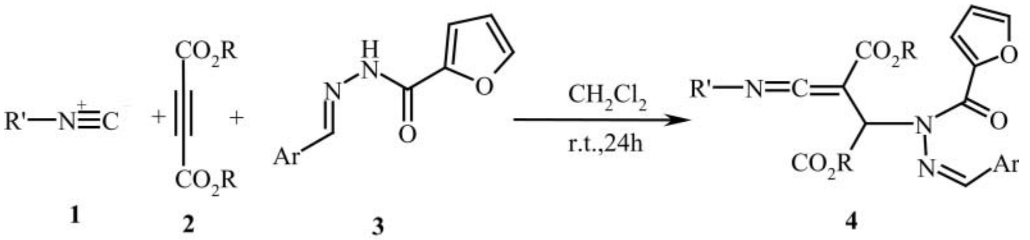
The adduct produced in the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates was trapped by furan-2-carboxylic acid arylidene-hydrazides to afford highly functionalised ketenimines in good yields. The reaction is characterised by mild conditions, high selectivity, and tolerance to various functional groups.

Keywords: ketenimines, acetylenic esters, isocyanides, NH-acids, three-component reaction, furan-2-carboxylic acid arylidene-hydrazide

Ketenimines have been extensively used in organic synthesis as versatile building blocks for the preparation of a large variety of cyclic compounds via inter- or intramolecular cycloaddition reactions.[1,2] There has been intense interest in their addition reactions, such as cycloaddition[3–5] and nucleophilic,[6,7] electrophilic,[8,9] and radical addition.[10–13] In addition, novel synthetic approaches to carbocyclic and N-heterocyclic four-, five-, and six-membered rings using ketenimine transition-metal complexes have been developed.[14,15] A general way to improve synthetic efficiency and also to address other criteria, such as atom-economy, procedural simplicity, and the number of accessible backbones, is through the development of types of multicomponent reactions.[16] Multicomponent reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention in the area of combinatorial chemistry,[17–19] of pivotal importance are the isocyanide-based MCRs.[17–21] The trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with OH, NH, and CH acids has been widely studied.[22–27] In continuation of our work on the reaction between isocyanides and acetylenic esters in the presence of organic acids[28–30], we now report the results of our studies on the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates, in the presence of furan-2-carboxylic acid arylidene-hydrazides. Thus, alkyl isocyanides **1** and dialkyl acetylenedicarboxylates **2** in the presence of furan-2-carboxylic acid arylidene-hydrazides **3** undergo a smooth 1:1:1 addition reaction in dichloromethane at ambient temperature to produce dialkyl 2-[*N′*-arylidene-*N*-(2-furoyl) hydrazino]-3-(alkyliminomethylene)succinate derivatives **4a–f** in excellent yields (Scheme 1).

The structures of compounds **4a–f** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectrum of **4a** displayed the molecular ion peak at *m/z* = 465 which is consistent with the formation of a 1:1:1 adduct of dimethyl acetylenedicarboxylate, cyclohexyl isocyanide, and furan-2-carboxylic acid benzylidene-hydrazide. The IR spectrum of **4a** exhibited the absorption band for the ketenimine moiety at 2060 cm^{-1}and for the ester carbonyl groups at 1748 and 1662 cm^{-1}.

The ^{1}H NMR spectrum of compound **4a** exhibited three sharp singlet signals readily recognised as arising from methoxy (δ = 3.74 and 3.76), and CH (δ = 5.82) protons. The N*CH* proton was appeared as a multiplet at 3.91 ppm and the



4	Ar	R	R'	%Yield
a	phenyl	Me	Cy	88
b	phenyl	Me	t-Bu	89
c	p-Cl-phenyl	Me	Cy	87
d	p-Cl-phenyl	Et	Cy	90
e	p-Cl-phenyl	t-Bu	Cy	93
f	p-Cl-phenyl	Me	t-Bu	94

*isolated yields

Scheme 1

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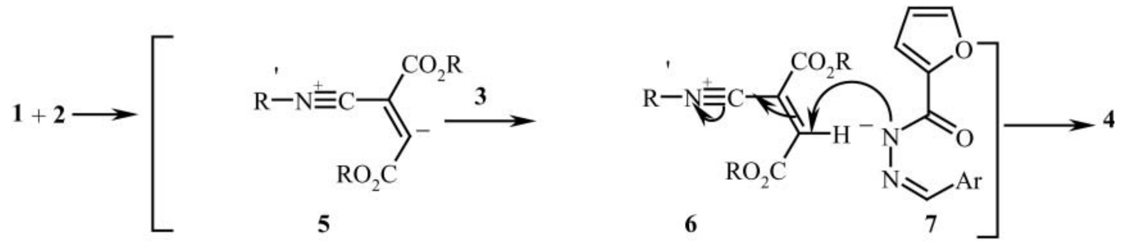
* Correspondent. E-mail: mhmosslemin@yahoo.com



Scheme 2

signals related to methylene groups of cyclohexyl moiety were observed as multiplets at 1.26–2.05 ppm.

The protons of the aryl and furyl groups exhibited characteristic signals in the aromatic region of the spectrum. A single signal was observed at 8.35 ppm which arises from N=CH proton. The ^{13}C NMR spectrum of compound **4a** showed 21 distinct resonances in agreement with the proposed structure. The sp^2- hybridised carbon atom of the ketenimine residue appears at δ = 58.24 ppm, as a result of strong electron delocalisation. Partial assignments of these resonances are given in the experimental section.

Although we have not established the mechanism of the reaction between an isocyanide and an acetylenic ester in the presence of furan-2-carboxylic acid arylidene-hydrazides **3** experimentally a possible explanation is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides,[1,2,6,7] it is reasonable to assume that the functionalised ketenimine **4** results from the initial addition of the isocyanide to the acetylenic ester and subsequent protonation of the 1:1 adduct **5** by furan-2-carboxylic acid arylidene-hydrazides. Then, the positively charged ion **6** is attacked by anion **7** to give the product **4** (Scheme 2).

In summary, the simple one-pot reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of furan-2-carboxylic acid arylidene-hydrazides provides access to stable ketenimine derivatives of potential synthetic interest. The presented method has the advantage of being performed under neutral conditions and requires no activation or modification of the reagents.

Experimental

Melting points were determined with an electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyser. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionisation potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-500 Avance spectrometer at solution in $CDCl_3$ using TMS as internal standard. The chemicals used in this work purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

To a magnetically stirred solution of dialkyl acetylenedicarboxylate (2 mmol) and furan-2-carboxylic acid arylidene-hydrazide (2 mmol) in dichloromethane (10 mL) was added a solution of alkyl isocyanide (2 mmol) in dichloromethane (5 mL) dropwise at r.t. over 10 min. The mixture was then stirred for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel, hexane–EtOAc, 3:1) to afford the pure title compounds.

Dimethyl 2-[N'-benzylidene–N-(2-furanoyl)hydrazino]-3-(cyclohexyliminomethylene)succinate (**4a**): White powder; m.p. 131–133 °C. IR (KBr) (ν_{max}, cm^{-1}): 2060 (N=C=C), 1748, 1662 (C=O). Anal. Calcd for $C_{25}H_{27}N_3O_6$: C, 64.50; H, 5.85; N, 9.03. Found: 64.6; H, 5.7; N, 9.1%. MS (*m/z*, %): 465 (M$^+$, 3). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.26–2.05 (10 H, m, 5 CH_2 of cyclohexyl), 3.74 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 3.91 (1 H, m, CH of cyclohexyl), 5.82 (1 H, s, CH), 6.58(1H, m, CH furan), 7.46 (1H, s, CH furan), 7.65 (1H, d, $^3J_{HH}$ = 2 H_Z, CH furan),7.42–7.76 (5 H, m, aromatic), 8.35 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 23.94, 25.21, and 33.03 (5 CH_2 of cyclohexyl), 51.68 (OCH_3), 53.06 (OCH_3), 54.51 (CH of cyclohexyl), 58.24 (N=C=*C*), 60.44 (CH), 111.75, 120.69, 143.58 and 145.72(C Furan),127.79, 128.86, 130.06 and 134.52 (C aromatic), 145.97 (N=CH), 159.19 (N=*C*=C), 161.15 (*C*ON), 167.82 (*C*O$_2$Me), 170.81 (*C*O$_2$Me) ppm.

Dimethyl 2-[N'-benzylidene-N-(2-furanoyl)hydrazino]–3–(ter-butyliminomethylene)succinate (**4b**): White powder; m.p. 150–152 °C. IR (KBr) (ν_{max}, cm^{-1}): 2090 (N=C=C), 1751, 1669 (C=O). Anal. Calcd for $C_{23}H_{25}N_3O_6$: C, 62.86; H, 5.73; N, 9.56. Found: 62.7; H, 5.8; N, 9.7%. MS (*m/z*, %): 439 (M$^+$, 5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.45 (9 H, s, 3 CH_3), 3.73 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 5.78 (1 H, s, CH), 6.57(1H, m, CH furan), 7.44 (1H, s, CH furan), 7.63 (1H, d, $^3J_{HH}$ = 2 H_Z, CH furan), 7.42–7.74 (5 H, m, aromatic), 8.29 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 30.01 (3 CH_3), 51.71 (OCH_3), 52.93 (OCH_3), 54.24 (C), 59.75 (N=C=*C*), 62.50 (CH), 111.73, 120.68, 143.28 and 145.74(C Furan),127.70, 128.83, 130.04 and 134.43 (C aromatic), 145.85 (N=CH), 159.06 (N=*C*=C), 162.23 (*C*ON), 167.85 (*C*O$_2$Me), 170.79 (*C*O$_2$Me) ppm.

Dimethyl 2-[N'-4-chlorobenzylidene-N-(2-furanoyl)hydrazino]-3–(cyclohexyliminomethylene)succinate (**4c**): White powder; m.p. 168–170 °C. IR (KBr) (ν_{max}, cm^{-1}): 2080 (N=C=C), 1742, 1662 (C=O). Anal. Calcd for $C_{25}H_{26}ClN_3O_6$: C, 60.06; H, 5.24; N, 8.40. Found: 60.2; H, 5.1; N, 8.5%. MS (*m/z*, %): 499 (M$^+$, 7). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.26–2.02 (10 H, m, 5 CH_2 of cyclohexyl), 3.40 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.80 (1 H, m, CH of cyclohexyl), 5.78 (1 H, s, CH), 6.58(1H, m, CH furan), 7.45 (1H, s, CH furan), 7.64 (1H, d, $^3J_{HH}$ = 2 H_Z, CH furan),7.39 (2H, d, $^3J_{HH}$ = 7 H_Z, aromatic), 7.68 (2H, d, $^3J_{HH}$ = 7 H_Z, aromatic), 8.32 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 23.82, 25.13, and 32.93 (5 CH_2 of cyclohexyl), 51.60 (OCH_3), 53.37 (OCH_3), 54.55 (CH of cyclohexyl), 58.03 (N=C=*C*), 60.43 (CH), 111.71, 120.64, 139.94 and 142.83 (C Furan), 128.80, 129.13, 133.05 and 135.86 (C aromatic),145.87 (N=CH), 159.14 (N=*C*=C), 167.62 (*C*ON), 170.63 (*C*O$_2$Me), 170.82 (*C*O$_2$Me) ppm.

Diethyl 2-[N'-4-chlorobenzylidene-N-(2-furanoyl)hydrazino]-3-(cyclohexyliminomethylene)succinate (**4d**): White powder; m.p. 134–136 °C. IR (KBr) (ν_{max}, cm^{-1}): 2075 (N=C=C), 1744, 1680 (C=O). Anal. Calcd for $C_{27}H_{30}ClN_3O_6$: C, 61.42; H, 5.73; N, 7.96. Found: C, 61.5; H, 5.6; N, 7.8%. MS (*m/z*, %): 527 (M$^+$, 5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.24–2.05 (10 H, m, 5 CH_2 of Cy),1.22 (6H, m, 2C*H*$_3$), 3.92–3.95 (1 H, m, CHN), 4.17–4.30 (4H, m, 2OC*H*$_2$), 5.79 (1 H, s, CH), 6.58 (1H, m, CH furan), 7.44 (1H, s, CH furan), 7.64 (1H, d, $^3J_{HH}$ = 2 H_Z, CH furan), 7.42 (2 H, d, ^3J = 7 Hz, aromatic), 7.68 (2 H, d, ^3J = 7 Hz, aromatic), 8.34 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 14.42 (*C*H$_3$),14.83 (*C*H$_3$), 24.13, 25.67, and 33.35 (5 CH_2 of cyclohexyl), 55.16 (CH of cyclohexyl), 58.87 (N=C=*C*), 60.79 (O*C*H$_2$), 62.68 (O*C*H$_2$), 63.39 (CH), 112.09, 120.80, 139.87 and 142.51 (C Furan), 129.26, 129.53, 133.61 and 136.24 (C aromatic),146.13 (N=CH), 146.43 (N=*C*=C), 159.56 (*C*ON), 167.55 (*C*O$_2$Et), 170.87 (*C*O$_2$Et) ppm .

Di-tert-butyl 2-[N'-4-chlorobenzylidene-N-(2-furanoyl)hydrazino]-3-(cyclohexyliminomethylene)succinate (**4e**): White powder; m.p. 162–164 °C. IR (KBr) (ν_{max}, cm^{-1}): 2075 (N=C=C), 1730, 1661 (C=O). Anal. Calcd for $C_{31}H_{38}ClN_3O_6$: C, 63.74; H, 6.56; N, 7.19. Found: 63.8; H, 6.7; N, 7.3%. MS (*m/z*, %): 583 (M$^+$, 3). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.27–2.02 (10 H, m, 5 CH_2 of cyclohexyl), 1.43 (s, 9 H), 1.45 (s, 9 H), 3.88 (1 H, m, CH of cyclohexyl), 5.70 (1 H, s, CH), 6.56 (1H, m, CH furan), 7.41 (1H, s, CH furan), 7.63 (1H, d, $^3J_{HH}$ = 2 H_Z, CH furan), 7.39 (2 H, d, ^3J = 7 Hz, aromatic), 7.66 (2 H, d, ^3J = 7 Hz, aromatic), 8.25 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 23.84, 25.32, and 33.06 (5 CH_2 of cyclohexyl), 27.90

and 28.45 (6 CH_3 of 2 t-Bu), 51.74 (OCH_3), 53.07 (OCH_3), 55.35 (CH of cyclohexyl), 60.27 (N=C=*C*), 60.37 (CH), 80.33 and 82.42 (2 O-$C(CH_3)_3$), 111.64, 120.13, 141.82 and 145.53 (C Furan), 128.73, 129.14, 133.41 and 135.63 (C aromatic), 146.22 (N=CH), 159.12 (N=*C*=C), 165.02 (*C*ON), 166.05 (*C*=O), 169.67 (*C*=O) ppm.

Dimethyl 2-[N'-4-chloro–benzylidene-N-(2-furanoyl)]-3-(tert-butyl iminomethylene)succinate (**4f**): White powder; m.p. 158–160 °C. IR (KBr) (ν_{max}, cm^{-1}):2070 (N=C=C), 1747, 1665 (C=O). Anal. Calcd for $C_{23}H_{24}ClN_3O_6$: C, 58.29; H, 5.10; N, 8.87. %. Found: C, 58.4; H, 5.2; N, 8.9 %. MS (*m/z*, %): 473 (M^+, 5). ^1H NMR (500 MHz, $CDCl_3$): δ =1.46 (9 H, s, 3 CH_3), 3.74 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 6.24 (1 H, s, CH), 6.85 (1H, m, CH furan), 7.55 (1H, s, CH furan), 8.12 (1H, d, $^3J_{HH} = 2$ H_Z, CH furan), 7.69 (2 H, d, $^3J = 7$ Hz, aromatic), 7.85 (2 H, d, $^3J = 7$ Hz, aromatic), 8.55 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 29.02$ (3 CH_3), 51.10 (OCH_3), 52.17 (OCH_3), 52.64 (C), 59.95 (N=C=*C*), 61.59 (CH), 111.72, 120.14, 141.92 and 144.53 (C Furan), 128.51, 128.74, 132.47 and 134.23 (C aromatic), 146.33 (N=CH), 157.51 (N=*C*=C), 163.46 (*C*ON), 166.84 (*C*O_2Me), 168.93 (*C*O_2Me) ppm.

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