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RESEARCH ARTICLE

Synthesis of Ketenimines Derivatives from Reaction between Alkyl Isocyanides and Dialkyl Acetylenedicarboxylates in the Presence of Carboxylic Acid Arylidene-Hydrazides

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Abstract: An improved three-component reaction of cyclohexyl isocyanide is described. The reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of carboxylic acid arylidene-hydrazides to afford highly functionalized ketenimines in good yields. The reaction was characterized by mild conditions, high selectivity and tolerance to various functional groups.

Keywords: Ketenimines, Dialkyl acetylenedicarboxylates, Alkyl isocyanides, NH-acids, Three-component reaction

Introduction

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] 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[6-8], of pivotal importance are the isocyanide-based MCRs[9]. The trapping of the 1:1 intermediate formed between dialkyl acetylenedicarboxylates and isocyanides with OH, NH and CH acids has been widely studied[10-16]. In continuation of our works on the reaction between isocyanides and dialkyl acetylenedicarboxylates in the presence of organic acids[17-19], here we wish to report the results of our studies on the reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates, in the presence of carboxylic acid arylidene-hydrazides.

Experimental

Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Islamic Azad University Yazd Branch. ^{1}H and ^{13}CNMR spectra were recorded on BRUKER DRX-500 AVANCE spectrometer in CDCl3 using TMS as internal standard. The chemicals used in this work were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

Experimental

To a magnetically stirred solution of dialkyl acetylenedicarboxylate (2 mmol) and carboxylic acid arylidene-hydrazide (2 mmol) in acetone (10 mL) was added a solution of alkyl isocyanide (2 mmol) in acetone (5 mL) dropwise at room temperature over 10 minute. The mixture was then allowed to stir for 24 h. The solvent was removed under reduced pressure, and the residue was separated by column chromatography (silica gel, hexane-ethyl acetate, 3:1) to afford the pure titled compounds.

*Dimethyl 2-[N'-benzylidene-N-(3-methyl)hydrazino]-3- (cyclohexyl iminomethylene) succinate (**4a**)*

Yield: 89%; Yellow oil; IR (KBr) (ν_{max}, cm^{-1}): 2078 (N=C=C), 1741, 1666 (C=O). Analyses: Calcd. for $C_{22}H_{27}N_3O_5$: C, 63.91; H, 6.58; N, 10.16%. Found: 63.82; H, 5.71; N, 10.23%. MS (*m/z*, %): 413 (M+, 5). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.20-2.01 (10 H, m, 5 CH_2 of cyclohexyl), 2.33 (3H, s, CH_3), 3.71 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.89 (1 H, m, CH of cyclohexyl), 5.87 (1 H, s, CH), 7.40-7.83 (5 H, m, aromatic), 8.32 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, CDCl3): δ = 24.20, 24.92, 25.47, 30.01 and 33.09 (5CH_2 of cyclohexyl), 33.47 (CH_3), 51.64 (OCH_3), 53.02 (OCH_3), 54.58 (CH of cyclohexyl), 58.31 (N=C=C), 60.37 (CH), 127.75, 128.80, 130.08 and 134.58 (C aromatic), 145.91 (N=CH), 159.27 (N=C=C), 161.23 (CON) ,167.80 (C=O), 170.91 (C=O) ppm.

*Dimethyl2-[N'-4-chloro-benzylidene-N-(4-pyridineoyl)hydrazino]-3-(cyclohexylim inomethylene)succinate (**4b**)*

Yield: 90%; Yellow oil; IR (KBr) (ν_{max}, cm^{-1}): 2105 (N=C=C), 1734, 1667 (C=O). Analyses: Calcd. for $C_{26}H_{27}ClN_4O_5$: C, 61.11; H, 5.33; N, 10.96%. Found: 61.25; H, 5.50; N, 10.81%. MS (*m/z*, %): 510 (M+, 3). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.18-1.98 (10 H, m, 5CH_2 of cyclohexyl), 3.70 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 3.84 (1 H, m, CH of cyclohexyl), 5.61 (1 H, s, CH), 7.28-8.51 (8 H, m ,aromatic), 8.37 (1 H, s, N=CH) ppm. 13C NMR (125.7MHz, $CDCl_3$): δ = 24.21, 25.08, 25.67, 30.18 and 33.36 (5CH_2 of cyclohexyl), 51.65 (OCH_3), 52.90 (OCH_3), 54.47 (CH of cyclohexyl), 59.88 (N=C=C), 62.45 (CH), 122.37, 128.83, 129.24, 133.51, 136.07, 141.75 and 151.40 (C aromatic), 146.11 (N=CH), 164.01 (N=C=C), 167.12 (CON), 168.76 (C=O), 170.4 (C=O) ppm.

*Dimethyl 2-[N'-4-chloro-benzylidene-N-(3-methyl)hydrazino]-3-(cyclohexylimino methylene)succinate (**4c**)*

Yield: 87%; Yellow oil; IR (KBr) (ν_{max}, cm^{-1}): 2065 (N=C=C), 1740, 1686 (C=O). Analyses: Calcd. for $C_{22}H_{26}ClN_3O_5$: C, 58.99; H, 5.85; N, 9.38%. Found: 58.80; H, 5.69; N, 9.48%. MS (*m/z*, %): 447 (M+, 9). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.21-2.13 (10 H, m, 5 CH_2 of cyclohexyl), 2.37 (3H, s, CH_3), 3.69 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.80 (1 H, m, CH of cyclohexyl), 5.62 (1 H, s, CH), 7.33 (2H, d, 3JHH = 7 HZ, aromatic), 7.61 (2H, d, 3JHH = 7 HZ, aromatic), 8.00 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 24.24, 24.99, 25.52, 30.07 and 33.42 (5 CH_2 of cyclohexyl), 33.03(CH_3), 48.79 (CH of cyclohexyl), 52.08 (OCH_3), 52.65 (OCH_3), 57.25 (N=C=C), 60.28 (CH), 128.89, 129.32, 133.55 and 136.01 (C aromatic), 140.09 (N=CH), 164.56 (N=C=C), 168.41 (CON), 169.68 (C=O), 171.23 (C=O) ppm.

*Diethyl 2-[N'-4-chloro-benzylidene-N-(4-pyridineoyl)hydrazino]-3-(cyclohexylim inomethylene)succinate (**4d**)*

Yield: 93%; Yellow oil; IR (KBr) (ν_{max}, cm^{-1}): 2070 (N=C=C), 1743, 1669 (C=O). Analyses: Calcd. for $C_{28}H_{31}ClN_4O_5$: C, 62.39; H, 5.80; N, 10.39%. Found: C, 62.20; H, 5.93; N, 10.58%. MS (*m/z*, %): 538 (M+, 3). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.22-2.01 (10 H, m, 5 CH_2 of cyclohexyl), δ =1.14- 1.30 (6H, m, $2CH_3$), 3.88 (1 H, m, CH of cyclohexyl), 4.11- 4.36 (4H, m, $2OCH_2$), 5.83 (1 H, s, CH), 7.33-8.56 (8 H, m ,aromatic), 8.39 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = δ =14.55 and 14.82 ($2CH_3$), 24.28, 25.03, 25.63, 30.27 and 33.18 ($5CH_2$ of cyclohexyl), 54.59 (CH of cyclohexyl), 58.32 (N=C=C), 60.44 (OCH_2), 62.58 (OCH_2), 63.08 (CH), 122.41, 128.81, 129.20, 133.45, 136.05, 141.77 and 151.35 (C aromatic), 145.69 (N=CH), 164.07 (N=C=C), 167.10 (CON), 168.74 (C=O), 170.6 (C=O) ppm.

*Di-t-butyl2-[N'-4-chloro-benzylidene-N-(3-methyl)hydrazino]-3-(cyclohexylimino methylene)succinate (**4e**)*

Yield: 94%; White powder; m.p. 162-164 ˚C. IR (KBr) (ν_{max}, cm^{-1}): 2060 (N=C=C), 1730, 1688 (C=O). Analyses: Calcd. for $C_{27}H_{38}ClN_3O_5$: C, 62.36; H, 7.36; N, 8.08%. Found: C, 62.50; H, 7.22; N, 8.24%. MS (*m/z*, %): 519 (M+, 10). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.42-1.99 (10 H, m, 5 CH_2 of cyclohexyl), 1.42 (s, 9 H, $3CH_3$ of t-Bu), 1.45 (s, 9 H, $3CH_3$ of t-Bu), 2.39 (3H, s, CH_3), 3.80 (1 H, m, CH of cyclohexyl), 5.60 (1 H, s, CH), 7.36 (2 H, d, 3J = 7 Hz, aromatic), 7.62 (2 H, d, 3J = 7 Hz, aromatic), 7.96 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ = 22.45, 24.72, 25.74, 30.55 and 33.71 (5 CH_2 of cyclohexyl), 28.29 and 28.86 (6 CH_3 of 2 t-Bu), 33.51(CH_3), 54.18 (CH of cyclohexyl), 58.27 (N=C=C), 60.81 (CH), 80.72 and 82.59 ($2O\text{-}C(CH_3)_3$), 128.76, 129.33, 133.91 and 135.80 (C aromatic), 146.17 (N=CH), 159.10 (N=C=C), 165.01 (CON) ,166.07 (C=O), 169.75 (C=O) ppm.

*Diethyl2-[N'-4-chloro–benzylidene-N-(3-methyl)hydrazino]-3-(tert-butylimino methylene)succinate (**4f**)*

Yield: 88%; Yellow oil; IR (KBr) (ν_{max}, cm^{-1}):2065 (N=C=C), 1739, 1680 (C=O). Anal. Calcd for $C_{22}H_{28}ClN_3O_5$: C, 58.73; H, 6.27; N, 9.34. %. Found: C, 58.91; H, 6.34; N, 9.23 %. MS (*m/z*, %): 449 (M+, 6). ^{1}H NMR (500 MHz, $CDCl_3$): δ =1.23- 1.31 (6H, m, $2CH_3$), 1.43 (9 H, s, 3 CH_3 of t-Bu), 2.39 (3H, s, CH_3), 4.15- 4.30 (4H, m , $2OCH_2$), 5.59 (1 H, s, CH), 7.34 (2 H, d, 3J = 7 Hz, aromatic), 7.62 (2 H, d, 3J = 7 Hz, aromatic), 7.98 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.53 and 14.75 ($2CH_3$), 22.09 (CH_3), 30.77 ($3CH_3$ of t-Bu), 53.35 (C), 60.81 and 62.38 ($2OCH_2$), 62.78 (N=C=C), 63.39 (CH), 128.86, 129.32, 133.64 and 135.96 (C aromatic), 139.83 (N=CH), 164.43 (N=C=C), 167.80 (CON), 170.62 (C=O), 172.91 (C=O) ppm.

*Diethyl 2-[N'-4-chloro-benzylidene-N-(3-methyl)hydrazino]-3-(cyclohexylimino methylene)succinate (**4g**)*

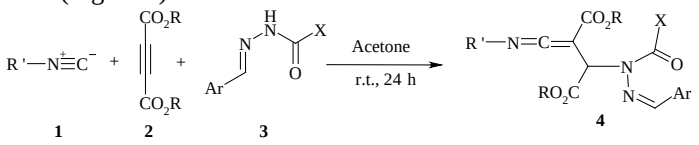
Yield: 90%; Yellow oil; IR (KBr) (ν_{max}, cm^{-1}): 2084 (N=C=C), 1745, 1668 (C=O). Analyses: Calcd. for $C_{24}H_{30}ClN_3O_5$: C, 60.56; H, 6.35; N, 8.83%. Found: 60.75; H, 6.20; N, 8.99%. MS (*m/z*, %): 475 (M+, 3). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ =1.17- 1.33 (6H, m, $2CH_3$), 1.25-1.99 (10 H, m, 5 CH_2 of cyclohexyl), 2.38 (3H, s, CH_3), 3.86 (1 H, m, CH of cyclohexyl), 4.10 - 4.28 (4H, m, $2OCH_2$), 5.62 (1H, s, CH), 7.34 (2H, d, 3JHH = 7 HZ, aromatic), 7.62 (2H, d, 3JHH = 7 HZ, aromatic), 8.03 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ =14.55 and 14.82 ($2CH_3$), 22.16 (CH_3), 24.13, 25.59, 25.68, 30.10 and 33.39 ($5CH_2$ of cyclohexyl), 53.52 (CH of cyclohexyl), 59.28 (N=C=C), 60.80 and 62.42 ($2OCH_2$), 61.66 (CH), 128.87, 129.32, 133.66 and 135.95 (C aromatic), 140.01 (N=CH), 167.88 (N=C=C), 169.34 (CON) ,170.68 (C=O), 173.03 (C=O) ppm.

*Diethyl 2-[N'-benzylidene-N-(3-methyl)hydrazino]-3-(cyclohexyliminomethylene) succinate (**4h**)*

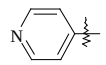
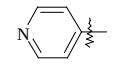
Yield: 92%; Yellow oil; IR (KBr) (ν_{max}, cm^{-1}): 2060 (N=C=C), 1737, 1687 (C=O). Analyses: Calcd. for $C_{24}H_{31}N_3O_5$: C, 65.29; H, 7.08; N, 9.52%. Found: 62.40; H, 7.23; N, 9.41%. MS (*m/z*, %): 441 (M+, 7). ^{1}H NMR (500.1 MHz, $CDCl_3$): δ =1.14 - 1.29 (6H, m, $2CH_3$), 1.47-1.92 (10 H, m, 5 CH_2 of cyclohexyl), 2.04 (3H, s, CH_3), 3.87 (1 H, m, CH of cyclohexyl), 4.04 - 4.24 (4H, m , $2OCH_2$), 5.46 (1 H, s, CH), 7.08-7.64 (5 H, m ,aromatic), 7.96 (1 H, s, N=CH) ppm. ^{13}C NMR (125.7MHz, $CDCl_3$): δ =14.57 and 14.71 ($2CH_3$), 22.05 (CH_3), 24.19, 25.53, 25.81, 29.97 and 33.37 (5 CH_2 of cyclohexyl), 54.20 (CH of cyclohexyl), 59.93 (N=C=C), 61.70 and 62.80 ($2OCH_2$), 62.38 (CH), 128.92, 129.47, 131.23 and 134.45(C aromatic), 146.81 (N=CH), 159.31 (N=C=C), 161.90 (CON) ,168.03 (C=O), 170.91 (C=O) ppm.

Results and Discussion

Thus, alkyl isocyanides **1** and dialkyl acetylenedicarboxylates (**2**) in the presence of carboxylic acid arylidene-hydrazides (**3**) undergo a smooth 1:1:1 addition reaction in acetone at ambient temperature to produce highly functionalized ketenimines (**4a-h)** in excellent yields (Figure 1).



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

4	Ar	X	R	R '	*%Yield
a	phenyl	Me	Me	Cy	89
b	p-Cl-phenyl		Me	Cy	90
c	p-Cl-phenyl	Me	Me	Cy	87
d	p-Cl-phenyl		Et	Cy	93
e	p-Cl-phenyl	Me	t-Bu	Cy	94
f	p-Cl-phenyl	Me	Et	t-Bu	88
g	p-Cl-phenyl	Me	Et	Cy	90
h	phenyl	Me	Et	Cy	92

*isolated yields

Figure 1. Three-component reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of carboxylic acid arylidene-hydrazides

The structures of compounds **4a-h** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The IR spectrum of **4e** exhibited the absorption band for the ketenimine moiety at 2060 $cm^{-1}$and for the ester carbonyl groups at 1730 and 1688 cm^{-1}.

The ^{1}H NMR spectrum of compound 4e exhibited three sharp singlet signals readily recognized as arising from methyl groups of the t-Bu (δ = 1.42 and 1.45) and the protons of

the methyl was appeared at 2.39 ppm. The proton CH was appeared at δ = 5.60 ppm. The NCH proton was appeared as a multiplet at 3.80 ppm and the signals related to methylene groups of cyclohexyl moiety were observed as multiplets at 1.42-1.99 ppm. A single signal was observed at 7.96 ppm which arises from N=CH proton. The ^{13}C NMR spectrum of compound **4e** showed **22** distinct resonances in agreement with the proposed structure. The sp^2- hybridized carbon atom of the ketenimine residue appears at δ = 58.27 ppm, as a result of strong electron delocalization. Partial assignments of these resonances are given in the experimental section.

A plausible mechanism for the formation of ketenimine **4a-h** is shown in Figure 2. On the basis of the well-established chemistry of isocyanides, **1,2,6,7** it is reasonable to assume that the functionalized ketenimine **4** results from the initial addition of the isocyanide to the dialkyl acetylenedicarboxylate and subsequent protonation of the 1:1 adduct **5** by carboxylic acid arylidene-hydrazide. Then, the positively charged ion 6 is attacked by anion **7** to give the product **4** (Figure 2).

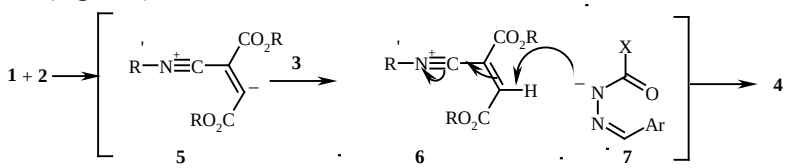


Figure 2. Suggested mechanism for formation compound **4**

The present method carries the advantage that, not only is the reaction performed under neutral conditions, but the educts can be mixed without any activation or modification.

Conclusion

In summary, the simple one-pot reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of carboxylic acid arylidene-hydrazides provides access to stable ketenimine derivatives of potential synthetic interest in high yields.

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