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One-pot Four-component Reaction between Arylamines, Arylglyoxals, Cyclohexyl Isocyanide, and Acetylene Diesters: An Efficient Synthesis of 2*H*-iminopyran Derivatives

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A facile synthesis of highly functionalized 2*H*-iminopyran derivatives by the multi-component reaction of cyclohexyl isocyanide, dialkyl acetylenedicarboxylates, arylglyoxals and arylamines is provided in this study. The zwitterionic intermediate, produced by addition of cyclohexyl isocyanide to electron-deficient acetylene diesters, is trapped by the electrophilic imine moiety of *α*-iminoketones, derived from arylglyoxals and arylamines, to afford an inner salt intermediate which is converted to 2*H*-iminopyran derivatives by an intramolecular cyclization.

Keywords: *α*-Iminoketones, Isocyanide, Iminopyrans, Four-component reaction, Arylglyoxals

INTRODUCTION

The Michael addition of isocyanides to activated carbon-carbon multiple bonds produces reactive zwitterionic intermediates which may be trapped by carbon or hydrogen electrophiles to afford a wide range of carbocyclic or heterocyclic organic compounds. It has been reported that isocyanide nucleophilic attack to dialkyl acetylenedicarboxylates (DAADs) leads to the zwitterionic species that could be trapped by carbonyl group of aldehydes [1], ketones [2], esters [3], isocyanates [4], acyl chlorides [5] and even carbon dioxide [6] to afford five- to seven-membered oxygen and nitrogen containing heterocyclic compounds. The reaction of isocyanides with DAADs in the presence of immines was also reported to afford functionalized pyrrole or iminolactone derivatives [7,8].

Arylglyoxals, as they contain two vicinal electrophilic centers, have gained much attention for the synthesis of heterocycles by reaction with dinucleophilic compounds. The application of arylglyoxals for preparation of a wide range of three- to six-membered heterocycles has been recently reviewed [9]. α-Iminoketones derived from arylglyoxals have recently attracted much interest for the synthesis of enantiomerically pure aziridines [10], syntrhesis of synthetically interesting β-amino-α-fluoroalkyl alcohols [11,12], and heterocyclic compounds [13].

Iminopyran moiety has recently attracted much attention from chemists for its role in the synthesis of important pyridine, coumarine and other heterocyclic derivatives [14-16]. In continuation of our previous works on isocyanides and arylglyoxal multi-component reactions [17-20], here we wish to report a four-component reaction between cyclohexyl isocyanide, dialkyl acetylenedicarboxylates (DAADs), arylglyoxals and arylamines to afford 2*H*-iminopyrane derivatives in good yields.

MATERIAL AND METHODS

Apparatus and Analysis

All of the utilized arylglyoxals were prepared by SeO_2-

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oxidation of the related aryl methyl ketones on the basis of the reported procedure and used as their monohydrates [21]. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H, and ^{13}C NMR spectra were recorded on Bruker DRX-400 Avance spectrometer at 400 and 100 MH_Z, respectively. The chemicals used in this work were purchased from Merck and used without further purifications.

General Procedure for the Preparation of Compounds 5a-h

A mixture of an arylglyoxal (1 mmol) and an arylamine (1 mmol) in toluene (20 ml) was refluxed in a Din Stark system for 20 min to afford the related α-iminoketone. Cyclohexyl isocyanide (1 mmol) and DAAD 2 (1 mmol) were added respectively and the mixture was refluxed for another 5 h. The solvent was evaporated and the residue was purified by column chromatography using silica gel and hexane-ethyl acetate (5:1 ratio) to afford the pure products 5a-h.

Selected Spectral Data

Dimethyl-6-(4-chlorophenyl)-2-(cyclohexylimino)-5-(phenylamino)-2*H*-pyran-3,4-dicarboxylate (5a). Pale yellow oil, Yield: 90%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3367 (NH), 1731, 1678, (C=O). Anal. Calcd. for $C_{27}H_{27}ClN_2O_5C$, 65.52; H, 5.50; N, 5.66%. Found: C, 65.3; H, 5.4; N, 5.4%. ^{1}H NMR ($CDCl_3$, 400 MH_Z): δ = 0.83-1.87 (10H, cyclohexyl), 3.50 (1H, m, NCH), 3.70 and 3.84 (6H, 2s, $2OCH_3$), 6.95-8.29 (9H, aromatic), 10.19 (NH). ^{13}C NMR (CD_3Cl, 100 MH_Z): δ = 24.4, 24.9, 32.5, 50.9 (cyclohexyl), 51.4 and52.6 ($2OCH_3$), 119.1, 122.3, 123.5, 125.3, 127.3, 128.7, 128.9, 129.0, 129.3, 132.0, 138.2 (aromatic and olefinic carbons), 159.5 and 160.1 (C=N, and =C-O), 163.1 and 164.9 (2C=O).

Dimethyl-5-(4-chlorophenylamino)-6-(4-chloro-phenyl)-2-(cyclohexylimino)-2*H*-pyran-3,4-dicarboxylate (5b). Pale yellow oil, Yield: 85%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3358 (NH), 1731, 1678 (ester groups). Anal. Calcd. for $C_{27}H_{26}Cl_2N_2O_5C$, 61.25; H, 4.95; N, 5.29%. Found: C, 61.3; H, 5.1; N, 5.4%. ^{1}H NMR ($CDCl_3$, 400 MH_Z): δ = 0.82-1.92 (10H, $5CH_2$ of cyclohexyl), 3.52 (1H, m, NCH), 3.69 and 4.85 (6H, 2s, $2OCH_3$), 6.96-8.30 (8H, aromatic), 10.23 (NH). ^{13}C NMR ($CDCl_3$, 100 MH_Z): δ = 24.4, 24.9, 32.5, 50.9 (cyclohexyl), 51.4 and 52.6 ($2OCH_3$), 114.6, 119.1, 122.3, 123.5, 125.3, 127.3, 128.7, 128.9, 132.0, 137.5, 138.1 (aromatic and olefinic carbons), δ = 159.6 and 160 (C=N, and =C-O)), δ = 163.1 and 164.9 (2C=O).

Dimethyl-6-(4-bromophenyl)-2-(cyclohexylimino)-5-(phenylamino)-2*H*-pyran-3,4-dicarboxylate (5c). Pale yellow oil, Yield: 85%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3350 (NH), 1732, 1678 (ester groups). Anal. Calcd. for $C_{27}H_{27}BrN_2O_5C$, 60.12; H, 5.05; N, 5.19%. Found: C, 60.0; H, 5.1; N, 5.0%. ^{1}H NMR ($CDCl_3$, 400 MH_Z): δ = 0.83-2.09 (10H, $5CH_2$ of cyclohexyl), 3.48 (1H, m, NCH), 3.69 and 3.84 (6H, 2s, $2OCH_3$), 6.98-8.27 (9H, aromatic), 10.19 (NH). ^{13}C NMR ($CDCl_3$, 100 MH_Z): δ = 24.5, 24.9, 32.5, 50.9 (cyclohexyl), 51.4 and 52.6 ($2OCH_3$), 114.7, 117.4, 119.0, 120.5, 123.6, 125.5, 127.6, 128.8, 128.9, 132.0, 138.1 (aromatic and olefinic carbons), 159.5 and 160.1 (C=N and =C-O)), 163.1 and 164.9 (2C=O).

Dimethyl-2-(cyclohexylimino)-6-(naphthalen-2-yl)-5-(phenylamino)-2*H*-pyran-3,4-dicarboxylate (5d). Pale yellow oil, Yield: 90%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3364 (NH), 1733, 1675 (2C=O). Anal. Calcd. for $C_{31}H_{30}N_2O_5C$, 72.92; H, 5.92; N, 5.49%. Found: C, 73.0; H, 5.8; N, 5.6%.^{1}H NMR ($CDCl_3$, 400 MH_Z): δ = 0.80-1.98 (10H, $5CH_2$ of cyclohexyl), 3.50 (1H, m, NCH), 3.71 and 3.85 (6H, 2s, $2OCH_3$), 6.55-8.18 (12H, aromatic), 8.57 (NH). ^{13}C NMR ($CDCl_3$, 100 MH_Z): δ = 24.5, 25.4, 31.9, 51.2 (cyclohexyl), 51.5 and 52.7 ($2OCH_3$), 114.3, 118.8, 119.9, 122.5, 123.4, 124.5, 125.2, 126.3, 126.6, 127.7, 128.2, 128.4, 129.0, 129.4, 129.7, 132.6, 133.3 (aromatic and olefinic carbons), 159.3 and 161.4 (C=N and =C-O), 162.4 and 164.9(2C=O).

Dimethyl-5-(4-chlorophenylamino)-2-(cyclohexyl-imino)-6-(naphthalen-2-yl)-2*H*-pyran-3,4-dicarboxylate (5e). Pale yellow oil, Yield: 90%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3364 (NH), 1733, 1675 (2C=O). Anal. Calcd. for $C_{31}H_{30}N_2O_5C$, 68.31; H, 5.36; N, 5.14%. Found: C, 63.0; H, 5.5; N, 5.1%. ^{1}H NMR ($CDCl_3$, 400 MH_Z): δ = 0.80-1.98 (10H, $5CH_2$ of cyclohexyl), 3.50 (1H, m, NCH), 3.71 and 3.85 (6H, 2s, $2OCH_3$), 6.55-8.18 (12H, aromatic), 8.57 (NH). ^{13}C NMR ($CDCl_3$, 100 MH_Z): δ = 24.5, 25.4, 31.9, 51.2 (cyclohexyl), 51.5 and 52.7 ($2OCH_3$), 114.3, 118.8, 119.9, 122.5, 123.4, 124.5, 125.2, 126.3, 126.6, 127.7, 128.2, 128.4, 129.0, 129.4, 129.7, 132.6, 133.3 (aromatic

and olefinic carbons), 159.3 and 161.4 (C=N and =C-O), 162.4 and 164.9 (2C=O).

Diethyl-6-(4-chlorophenyl)-2-(cyclohexylimino)-5-(phenylamino)-2*H*-pyran-3,4-dicarboxylate (5f). Pale yellow oil, Yield: 85%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3364 (NH), 1728, 1679 (2C=O). Anal. Calcd. for $C_{29}H_{31}ClN_2O_5C$, 66.60; H, 5.97; N, 5.36%. Found: C, 66.5; H, 5.8; N, 5.6%. ^1H NMR ($CDCl_3$, 400 MH_Z): δ = 0.83-1.92 (10H, $5CH_2$ of cyclohexyl), 1.23 (3H, t, $^3J_{HH}$ = 7H_Z, CH_3), 1.27 (3H, t, $^3J_{HH}$ = 7H_Z, CH_3), 3.51 (1H, m, NCH), 4.16 (2H, q, $^3J_{HH}$ = 7 H_Z, OCH_2), 4.31 (2H, q, $^3J_{HH}$ = 7 H_Z, OCH_2), 6.94-7.53 (9H, aromatic), 10.19 (NH). ^{13}C NMR ($CDCl_3$, 100 MH_Z): δ = 13.8 and 14.2 ($2CH_3$), 24.3, 24.9, 32.5, 51.2 (cyclohexyl), 59.3 and 61.4 ($2OCH_2$), 114.8, 119.0, 122.2, 123.3, 125.2, 127.4, 128.8, 129.0, 129.1, 131.9, 137.8 (aromatic and olefinic carbons), 159.5 and 160.3 (C=N, and =C-O), 162.9 and 164.4 (2C=O)

Diethyl-5-(4-chlorophenylamino)-6-(4-chlorophenyl)-2-(cyclohexylimino)-2*H*-pyran-3,4-dicarboxylate (5g). Pale yellow oil, Yield: 90%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3358 (NH), 1730 and 1683 (2C=O). Anal. Calcd. for $C_{29}H_{30}Cl_2N_2O_5C$, 62.48; H, 5.42; N, 5.03%. Found: C, 62.3; H, 5.6; N, 5.0%. ^1H NMR ($CDCl_3$, 400 MH_Z): δ = 0.83-1.93 (10H, $5CH_2$ of cyclohexyl), 1.22 (3H, t, $^3J_{HH}$ = 7H_Z, CH_3), 1.27 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 3.50 (1H, m, NCH), 4.15 (2H, q, $^3J_{HH}$ = 7 H_Z, CH_2), 4.31 (2H, q, $^3J_{HH}$ = 7H_Z, OCH_2), 6.95-8.29 (8H, aromatic), 10.33 (NH). ^{13}C NMR ($CDCl_3$, 100 MH_Z): δ = 13.7 and 14.2 ($2CH_3$), 24.3, 24.9, 32.5, 51.2 (cyclohexyl), 59.3 and 61.5 ($2OCH_2$), 114.8, 115.1, 118.8, 120.6, 125.2, 127.3, 128.7, 129.1, 131.9, 137.1, 137.8 (aromatic and olefinic carbons), 159.7 and 160.2 (C=N, and =C-O), 162.9 and 164.4 (2C=O).

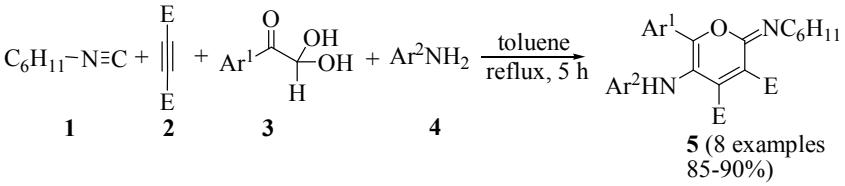
Diethyl-5-(4-chlorophenylamino)-2-(cyclohexyl-imino)-6-(naphthalen-2-yl)-2*H*-pyran-3,4-dicarboxylate (5h). Pale yellow oil, Yield: 90%. IR (KBr) ($\bar{\upsilon}_{max}$, cm^{-1}): 3350 (NH), 1732, 1682 (2C=O). Anal. Calcd. for $C_{33}H_{33}ClN_2O_5C$, 69.16; H, 5.80; N, 4.89%. Found: C, 69.0; H, 5.8; N, 4.6%. ^1H NMR ($CDCl_3$, 400 MH_Z): δ = 0.80-1.97 (10H, $5CH_2$ of cyclohexyl), 1.18 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 1.31 (3H, t, $^3J_{HH}$ = 7 H_Z, CH_3), 3.50 (1H, m, NCH), 4.17 (2H, q, $^3J_{HH}$ = 7 H_Z, OCH_2), 4.18 (2H, q, $^3J_{HH}$ = 7 H_Z, OCH_2), 6.30-8.24 (11H, aromatic), 8.56 (NH). ^{13}C NMR ($CDCl_3$, 100 MH_Z): δ = 14.1and 14.4 ($2CH_3$), 24.5, 25.4, 31.9, 51.4 (cyclohexyl), 59.7 and 61.7 ($2OCH_2$), 114.20, 120.1, 121.1, 122.5, 123.2, 126.1, 126.6, 127.5, 128.1, 128.3, 128.6, 129.0, 129.8, 129.9, 132.5, 133.3, 139.3 (aromatic and olefinic carbons), 159.1 and 161.4 (C=N and =C-O), 162.0, 165.7 (2C=O).

RESULTS AND DISCUSSION

Cyclohexyl isocyanide 1 and DAAD 2 in the presence of α-iminoketones were prepared by the reaction of arylamines 4 with arylglyoxals 3, undergo a smooth 1:1:1 addition reaction in boiling toluene to produce dialkyl 2-alkylimino-6-aryl-5-arylamino-2*H*-pyrane-3,4-dicarboxylate derivatives 5a-h in good yields (Scheme 1). To investigate the scope of the reaction, different arylamines and arylglyoxals were reacted with cyclohexyl isocyanide and dimethyl acetylenedicarboxylate (DMAD) or diethyl acetylenedicarboxylate (DEAD) and the related 2*H*-pyrane derivatives 5a-h were obtained in good yields (Table 1). The structures of compounds 5a-h were deduced from their elemental analyses and their IR, ^1H NMR, ^{13}C NMR spectra. For example the ^1H NMR spectrum of compound 5a exhibited two single signals at 3.70 and 3.84 ppm for methoxy protons. The cyclohexyl protons were observed as multiplets at 0.83-1.87 ppm (5 CH_2) and a multiple signal at 3.50 ppm (NCH). The aromatic protons were resonated at 6.95-8.29 ppm. A broad signal was observed at 10.19 ppm for NH proton. The ^{13}C NMR spectrum of 5a showed twenty-one distinct signals in agreement with the proposed structure. The structure of compound 5a was also confirmed by its IR spectrum that exhibited absorption bands at 3367, 1731 and 1678 cm^{-1} for NH and carbonyl groups, respectively.

Although the mechanism of this reaction has not been established experimentally, a plausible rationalization can be advanced to explain product formation (Scheme 2). It is reasonable to assume that cyclohexyl isocyanide attacks to dialkyl acetylenedicarboxylate to produce zwitterionic intermediate 7. Addition of zwittwrion 7 to imine group of iminoketone 6, derived from arylglyoxal 3 and arylamine 4, produces inner salt 8 which is cyclized to afford the iminopyran 5.

The 1,3-dipolar cycloaddition of intermediate 7 with iminoketone 6 may afford the pyrrole derivative 10 *via* the intermediate 9, however the absence of the signal of the



Scheme 1. Synthesis of dialkyl 2-alkylimino-6-aryl-5-arylamino-2*H*-pyrane-3,4-dicarboxylate derivatives 5 by the reaction of cyclohexyl isocyanide (1), dialkyl acetylenedicarboxylates (2), arylglyoxals (3), and arylamines (4)

Table 1. Synthesis of Dialkyl-2-alkylimino-6-aryl-5-arylamino-2*H*-pyrane-3,4-dicarboxylate Derivatives 5 by the Reaction between Cyclohexyl Isocyanide (1), Dialkyl Acetylenedicarboxylates (2), Arylglyoxals (3), and Arylamines (4)

Iminolactone 5	Ar^1	Ar^2	E	Yield (%)[a]
5a	ClC_6H_4	C_6H_5	CO_2Me	90
5b	ClC_6H_4	ClC_6H_4	CO_2Me	85
5c	BrC_6H_4	C_6H_5	CO_2Me	85
5d	2-Naphthyl	C_6H_5	CO_2Me	90
5e	2-Naphthyl	ClC_6H_4	CO_2Me	87
5f	ClC_6H_4	C_6H_5	CO_2Et	85
5h	ClC_6H_4	ClC_6H_4	CO_2Et	90
5i	2-Naphthyl	ClC_6H_4	CO_2Et	90

[a]Isolated yields.

ketone carbonyl group in the ^{13}C NMR spectra of products at about 190 ppm shows that pyrrole derivative 10 is not the through structure for the product.

CONCLUSIONS

We have developed a simple and efficient method for preparation of functionalized 2*H*-pyrans by a one pot, four component reaction between arylamines, arylglyoxals, cyclohexyl isocyanide and acetylene diesters. Through this advantageous method, not only the reactions are performed under neutral conditions, but also the substances can be mixed without any purification or activation.

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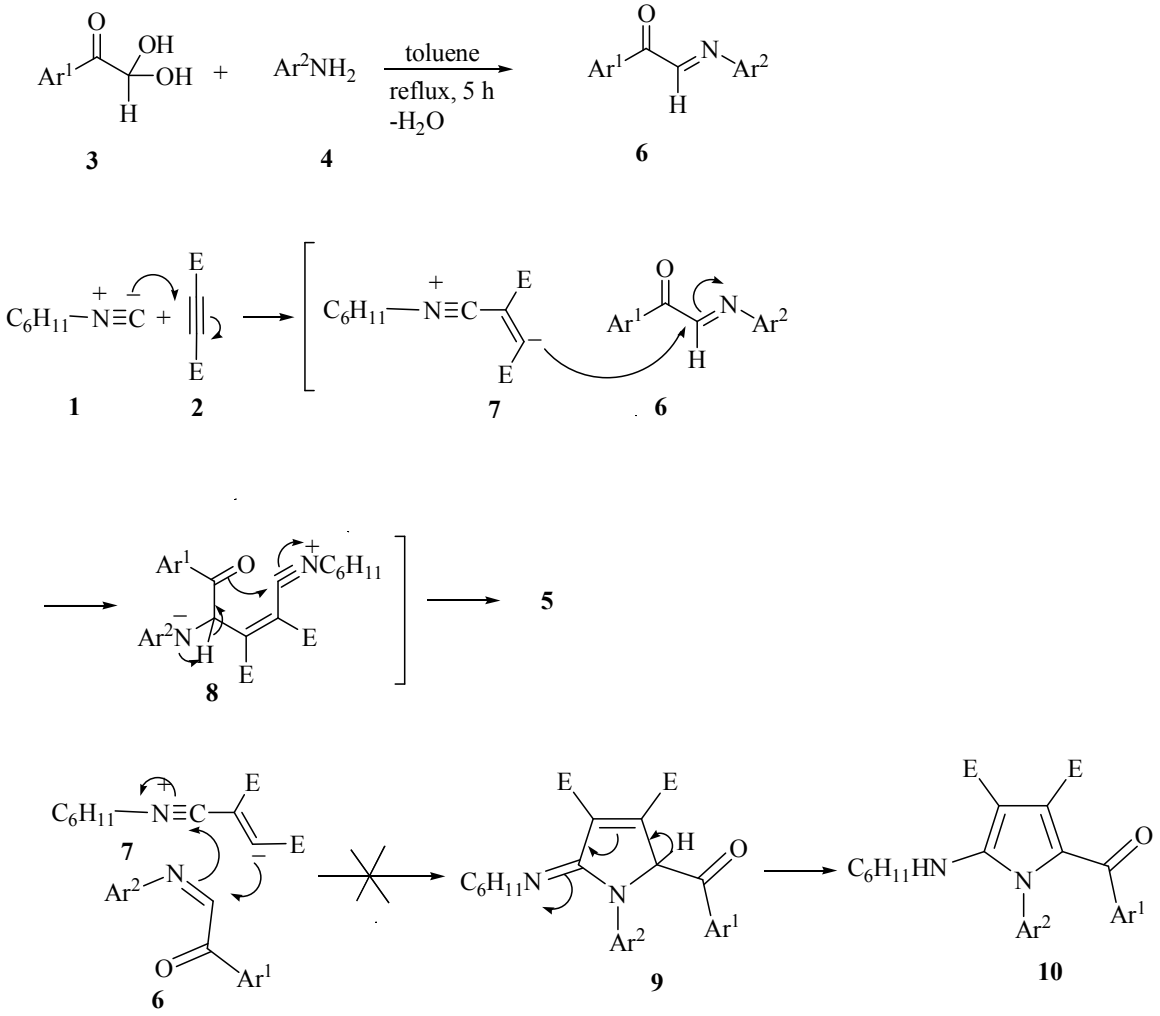

Scheme 2. Suggested mechanism for the formation of iminopyrans 5 from the reaction between cyclohexyl isocyanide (1), dialkyl acetylenedicarboxylates (2), arylglyoxals (3) and arylamines (4)

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