Four-component reaction between aryl aldehydes, ethyl cyanoacetate and dimethyl acetylenedicarboxylate in the presence of cyclohexyl isocyanide

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A four-component reaction between aryl aldehydes, ethyl cyanoacetate and dimethyl acetylenedicarboxylate in the presence of cyclohexyl isocyanide has been developed. The reaction furnishes highly functionalised cyclopentadienes in moderate to good yields in a one-pot process.

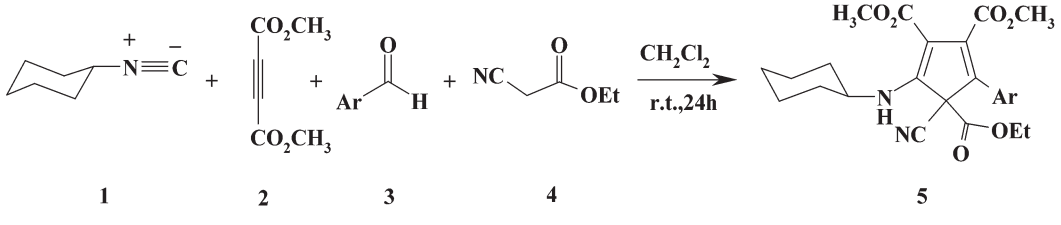
Keywords: cyclohexyl isocyanide, four-component reaction, dimethyl acetylenedicarboxylate, cyclopentadienes

Cyclopentadienes (Cps) or fulvenes are highly useful synthetic intermediates in the field of organic and organometallic chemistry as ligands in coordination chemistry and homogeneous catalysis for olefin polymerisation.[1] They are useful not only as a reactive diene component in the Diels–Alder reaction[2] but also as precursors for the preparation of transition-metal complexes with Cp-type ligands.[3] However, the preparation of well-defined, highly substituted cyclopentadienes is not necessarily easy owing to the absence of general methods[4] and also to the facile migration of the endocyclic double bonds.[5] Among the MCRs, isocyanide based multi-component reactions (IMCRs) have gained the most attention byorganic chemists. Ugi four component reactions (U-4CR)[6–8] and Passerini three component reactions (P-3CR)[9] are among the most important IMCRs. U-4CR and P-3CR describe the reactions of isocyanides with carboxylic acids in the presence of imines or aldehydes, respectively.

Recently, another kind of IMCR has been developed and extensively investigated. Isocyanides react easily with electron-deficient acetylenic diesters such as dimethyl acetylenedicarboxylate (DMAD) to produce a reactive zwitterionic intermediate which can be trapped by an electrophile. Recently, a wide variety of electrophiles have been applied to trap isocyanide-DMAD intermediates, among them are carbon electrophiles such as aldehydes, imines, quinonoids,[10] 1,2-diketones,[11] 1,2,3-tricarbonyl compounds,[12] isocyanates,[13] and hydrogen electrophiles such as pyrrole,[14] amides,[15] hydroxycoumarin,[16] phenols,[17] phthalic anhydride,[18] and isatoic anhydride.[19] Treatment of the isocyanide-DMAD zwitterion with aromatic carboxylic acids has been reported to produce unsaturated amides.[20] Reaction of the isocyanide-DMAD adduct with aromatic-substituted acetic acids has been reported to afford 2,5-diaminofuran derivatives in the presence of two equivalents of an isocyanide.[21] In the context of our previous works on IMCRs,[14–16,22] we now report the results of our investigations on the reaction of cyclohexyl isocyanide **1** with dimethyl acetylenedicarboxylate **2**, aryl aldehydes **3**, and ethyl cyanoacetate **4** to afford aminocyclopentadienes **5**.

Results and discussion

Treatment of the three reactants and cyclohexyl isocyanide in dichloromethane for 24 h at room temperature, after silica gel column chromatography afforded highly functionalised cyclopentadienes **5** in excellent yields (Scheme 1).



5	Ar	%Yield*
a	phenyl	90
b	p-CH_3O-phenyl	92
c	p-Cl-phenyl	90
d	p-NO_2-phenyl	89
e	o-NO_2-phenyl	88
f	m-NO_2-phenyl	85
g	o-Br-phenyl	90

* Isolated yields

Scheme 1 Reaction between aryl aldehydes, ethyl cyanoacetate and dimethyl acetylenedicarboxylate in the presence of cyclohexyl isocyanide.

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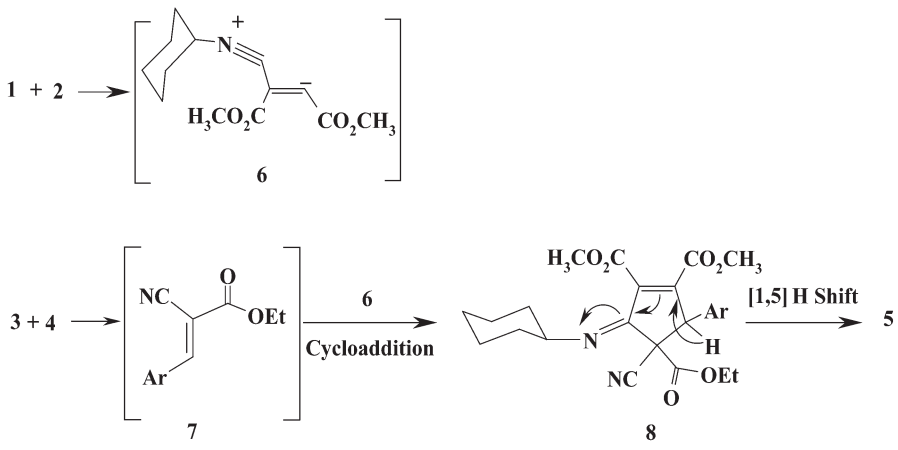

Scheme 2 Suggested mechanism for formation compound **5**.

The structures of compounds **5a–g** were deduced from their elemental analyses and IR, ^{1}H NMR, and ^{13}C NMR spectra. The ^{1}H NMR spectrum of compound **5a** was very simple and exhibited two sharp signals at 3.79 and 3.81 ppm for methoxycarbonyl groups, and one NH group (δ = 8.22 ppm, disappeared with addition of D_2O). Protons of the ethyl group are observed as a triplet at δ = 1.18 ppm ($^3J_{HH}$ = 7 Hz) and a quartet at δ = 4.22 ($^3J_{HH}$ = 7Hz). Cyclohexyl fragment protons resonated as multiplets at δ = 1.23–1.67 and a multiplet at δ = 3.64 ppm and aromatic protons resonated at δ = 7.03–7.68 ppm. The ^{13}C NMR spectrum of compound **5a** showed 23 distinct resonances in agreement with the proposed structure. The IR spectrum showed an absorption bond at 3355 cm^{-1} for the NH group. The carbonyl stretching vibrations observed as strong absorption bands at 1744 and 1675 cm^{-1}. The nitrile stretching vibrations were observed in an absorption band at 2236 cm^{-1}.

On the basis of the well established chemistry of isocyanides[6–8,18] it is reasonable to assume that intermediate **7** is produced by initial Knovenagel condensation of aldehyde **3** with ethyl cyanoacetate **4**. The compound **5** is produced by initial attack of isocyanide-DMAD zwitterion intermediate **6**. The zwitterions can add to the intermediate of **7** resulting in the formation of **8**. The latter then isomerises to the final product **5** via a [1,5]H shift. (Scheme 2)

In conclusion, we report here the four-component reaction between aryl aldehydes, ethyl cyanoacetate and dimethyl acetylenedicarboxylate with cyclohexyl isocyanide as a simple and efficient route for the synthesis of functionalised cyclopentadiene derivatives. The advantages of the reported method are that it is inexpensive with easily available starting materials, it has simple and neutral reaction conditions, gives high yields, is a single-product reaction and is a simple work-up process.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Costech ECS 4010 CHNS-O analyzer at analytical laboratory of Islamic Azad University Yazd branch. 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 were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

General procedure

To a magnetically stirred solution of ethyl cyanoacetate (1 mmol) and aryl aldehydes (1 mmol) in dichloromethane (10 mL) was added a mixture of dimethyl acetylenedicarboxylate (1 mmol) in dichloromethane (2 mL) at room temperature. The reaction mixture was then stirred for 1 min. Cyclohexyl isocyanide (1 mmol) was added and the reaction mixture was stirred for more than 24 h. The solvent was removed and the residue was purified by silica gel column chromatography using hexane-ethyl acetate (3:1) as eluent. The solvent was removed under reduced pressure to give the product.

1,2-Dimethyl 3-ethyl 3-cyano-5-cyclohexylamino-4-(phenyl)-cyclopenta-1,4- diene-1,2,3-tricarboxylate (**5a**): Yellow oil, yield: 90%; IR (KBr) (ν_{max}, cm^{-1}): 3355 (NH), 1744, 1675 (carbonyl groups). Anal. Calcd for $C_{25}H_{28}N_2O_6$: C, 66.36; H, 6.24; N, 6.19. Found: C, 66.45; H,6.16; N, 6.25%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.18 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3), 1.23–1.67 (10 H, m, 5 CH_2 of cyclohexyl), 3.64 (1 H, m, CH of cyclohexyl), 3.79 and 3.81 (6 H, 2s, 2 OCH_3), 4.22 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.03–7.68 (4H, m, aromatic), 8.22 (1 H, d, $^3J_{HH}$ = 11 Hz, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.32 (CH_3), 23.12, 24.75, 25.68, 29.68 and 30.21(5CH_2 of cyclohexyl), 39.05 (CH of cyclohexyl), 51.86 and 52.94 (2 OCH_3), 57.87 (C), 64.40 (OCH_2), 99.68 (CN), 113.92, 120.42, 144.38 and 160.22 (4C olefinic), 127.71, 128.80, 130.13 and 134.48 (aromatic), 163.23, 165.42 and 166.29 (3CO).

1,2-Dimethyl 3-ethyl 3-cyano-5-cyclohexylamino-4-(4-methoxyphenyl)- cyclopenta-1,4- diene-1,2,3-tricarboxylate (**5b**): Yellow oil, yield: 92%; IR (KBr) (ν_{max}, cm^{-1}): 1743, 1657 (carbonyl groups). Anal. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.72; H, 6.27; N, 5.81. Found: C, 64.85; H, 6.38; N, 5.74%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.24–1.80 (10 H, m, 5 CH_2 of cyclohexyl), 1.33 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 3.64 and 3.76 (6 H, 2s, 2 OCH_3), 3.71 (1 H, m, CH of cyclohexyl), 3.89 (3 H, s, OCH_3), 4.33 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 6.88 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic), 7.09 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic), 8.24 (1 H, d, $^3J_{HH}$ = 11 Hz, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.34 (CH_3), 23.01, 24.23, 25.84, 29.75 and 30.07 (5 CH_2 of cyclohexyl), 39.16 (CH of cyclohexyl), 53.10 and 53.19 (2 OCH_3), 56.92 (OCH_3), 63.45 (C), 64.60 (OCH_2), 114.50 (CN), 115.00, 127.81, 129.65 and 144.31 (aromatic), 114.27, 129.79, 144.58 and 160.49 (4C olefinic), 162.75, 163.82 and 165.49 (3CO).

1,2-Dimethyl 3-ethyl 3-cyano-5-cyclohexylamino-4-(4-clorophenyl)- cyclopenta-1,4- diene-1,2,3-tricarboxylate (**5c**): Yellow oil, yield: 90%; IR (KBr) (ν_{max}, cm^{-1}): 1746, 1666 (carbonyl groups). Anal. Calcd for $C_{25}H_{27}ClN_2O_6$: C, 61.66; H, 5.59; N, 5.75. Found: C, 61.79; H, 5.43; N, 5.68%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.25–2.02 (10 H, m, 5 CH_2 of cyclohexyl), 1.37 (3 H, t, $^3J_{HH}$ = 7 Hz, CH_3), 3.66 and 3.91 (6 H, 2s, 2 OCH_3), 3.76 (1 H, m, CH of cyclohexyl), 4.35 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.28 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic), 7.38 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic), 8.28 (1 H, d, $^3J_{HH}$ = 11 Hz, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.44 (CH_3), 23.09, 24.82, 25.84, 29.76 and 30.09 (5CH_2 of cyclohexyl), 39.15 (CH of cyclohexyl), 51.73 and 52.83 (2 OCH_3), 58.37 (C), 64.66 (OCH_2), 99.87 (CN), 113.92, 120.42, 129.33 and 160.92 (4C olefinic), 129.44, 130.07, 134.69 and 139.37 (aromatic), 163.35, 165.50 and 166.38 (3CO).

1,2-Dimethyl 3-ethyl 3-cyano-5-cyclohexylamino-4-(4-nitrophenyl)- cyclopenta-1,4- diene-1,2,3-tricarboxylate(**5d**): Yellow oil, yield: 89%; IR (KBr) (ν_{max}, cm^{-1}): 3320 (NH), 1741, 1643 (carbonyl groups). Anal.Calcd for $C_{25}H_{27}N_3O_8$: C, 60.36; H, 5.47; N, 8.45. Found: C, 60.19; H, 5.63; N, 8.33%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.20 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3), 1.25-2.16 (10 H, m, 5 CH_2 of cyclohexyl), 3.74 and 3.76 (6 H, 2s, 2 OCH_3), 3.58 (1 H, m, CH of cyclohexyl), 4.18 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.31 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic), 7.44 (2H, d, $^3J_{HH}$ = 7 Hz, aromatic), 8.29 (1 H, d, $^3J_{HH}$ = 11 Hz, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.02 (CH_3), 23.17,

24.87, 25.79, 29.64 and 30.13 (5CH_2 of cyclohexyl), 39.19 (CH of cyclohexyl), 51.90 and 52.75 (2 OCH_3), 58.46 (C), 64.39 (OCH_2), 99.77 (CN), 114.08, 120.63, 129.42 and 160.87 (4C olefinic), 129.21, 130.19, 133.98 and 139.12 (aromatic), 163.17, 165.43 and 166.52 (3CO).

1,2-Dimethyl 3-ethyl 3-cyano-5-cyclohexylamino-4-(2-nitrophenyl)- cyclopenta-1,4- diene-1,2,3-tricarboxylate (**5e**): Yellow oil, yield: 88%; IR (KBr) (ν_{max}, cm^{-1}): 3380 (NH), 1734, 1671 (carbonyl groups). Anal.Calcd for $C_{25}H_{27}N_3O_8$: C, 60.36; H, 5.47; N, 8.45. Found: C, 60.19; H, 5.63; N, 8.33%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.21 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3), 1.25–2.19 (10 H, m, 5 CH_2 of cyclohexyl), 3.32 (1 H, m, CH of cyclohexyl), 3.57 and 3.71 (6 H, 2s, 2 OCH_3), 4.24 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.53–7.99 (4H, m, aromatic), 8.44 (1 H, d, $^3J_{HH}$ = 11 Hz, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.14 (CH_3), 24.10, 24.77, 25.44, 32.76 and 34.23 (5CH_2 of cyclohexyl), 39.15 (CH of cyclohexyl), 51.60 and 53.36 (2 OCH_3), 55.52 (C), 65.11 (OCH_2), 98.57 (CN), 114.05, 125.18, 140.87 and 160.95 (4C olefinic), 126.29, 129.69, 130.52, 133.34, 134.67 and 149.08 (aromatic), 163.49, 164.85 and 165.62 (3CO).

1,2-Dimethyl 3-ethyl 3-cyano-5-cyclohexylamino-4-(3-nitrophenyl)- cyclopenta-1,4- diene-1,2,3-tricarboxylate (**5f**): Yellow oil, yield: 85%; IR (KBr) (ν_{max}, cm^{-1}): 3330 (NH), 1744, 1670 (carbonyl groups). Anal.Calcd for $C_{25}H_{27}N_3O_8$: C, 60.36; H, 5.47; N, 8.45. Found: C, 60.19; H, 5.63; N, 8.33%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.18 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3), 1.23–1.78 (10 H, m, 5 CH_2 of cyclohexyl), 3.63 (1 H, m, CH of cyclohexyl), 3.76 and 3.83 (6 H, 2s, 2 OCH_3), 4.25 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.50–8.26 (4H, m, aromatic), 8.39 (1 H, d, $^3J_{HH}$ = 11 Hz, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.51 (CH_3), 23.09, 25.35, 29.76, 33.05 and 34.61 (5CH_2 of cyclohexyl), 39.22 (CH of cyclohexyl), 51.90 and 53.15 (2 OCH_3), 55.89 (C), 65.10 (OCH_2), 99.96 (CN), 113.63, 125.61, 135.68 and 161.35 (4C olefinic), 118.37, 122.57, 130.28, 133.32, 141.44 and 148.86 (aromatic), 163.20, 165.41 and 165.13 (3CO).

1,2-Dimethyl 3-ethyl 3-cyano-5-cyclohexylamino-4-(2-bromophenyl)- cyclopenta-1,4- diene-1,2,3-tricarboxylate (**5g**): Yellow oil, yield: 90%; IR (KBr) (ν_{max}, cm^{-1}): 3320 (NH), 1743, 1667 (carbonyl groups). Anal.Calcd for $C_{25}H_{27}BrN_2O_6$: C, 56.51; H, 5.12; N, 5.27. Found: C, 56.65; H, 5.03; N, 5.35%. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 1.12 (3H, t, $^3J_{HH}$ = 7 Hz, CH_3), 1.18–1.77 (10 H, m, 5 CH_2 of cyclohexyl), 3.60 (1 H, m, CH of cyclohexyl), 3.74 and 3.76 (6 H, 2s, 2 OCH_3), 4.18 (2 H, q, $^3J_{HH}$ = 7 Hz, OCH_2), 7.32–7.70 (4H, m, aromatic), 8.33 (1 H, d, $^3J_{HH}$ = 11 Hz, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 14.42 (CH_3), 23.15, 25.40, 29.85, 34.83 and 35.25 (5CH_2 of cyclohexyl), 39.19 (CH of cyclohexyl), 51.65 and 52.73 (2 OCH_3), 55.62 (C), 64.59 (OCH_2), 99.92 (CN), 113.88, 122.90, 139.41 and 160.98 (4C olefinic), 120.43, 128.50, 129.18, 129.65, 132.26 and 149.45 (aromatic), 163.34, 165.48 and 166.34 (3CO).

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