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Synthesis of highly substituted cyclopentadienes containing quinoline nucleus

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Abstract Synthesis of novel highly substituted cyclopentadienes containing quinoline nucleus is described. The initially prepared Knöevenagel adducts of 2-chloroquinoline-3-carbaldehydes and malononitrile or ethyl cyanoacetate underwent reaction with acetylenecarboxylates and isocyanide in dichloromethane at room temperature within 12 h, affording a variety of the desired products in moderate to good yields. Mild reaction condition, use of simple experimental procedure and prompt isolation of the products are some advantages of this protocol.

Keywords Knöevenagel condensation · Cyclopentadienes containing quinoline nucleus · Isocyanide · Acetylenecarboxylate

Introduction

The so-called multicomponent reactions (MCRs) are one-pot processes in which at least three or more different simple substrates react for the preparation of target materials [1–7]. These reactions, which have gained much attention during the past years, are frequently occurring not through a single-step procedure but rather by several sequential steps [8–13]. Simplicity, greater efficiency, and atom economy with generation of molecular complexity and diversity in the one-pot transformation are some of the advantages of these reactions.

As an important subclass of MCRs, the isocyanide-based multicomponent reactions (IMCRs) are processes in which an isocyanide is used as one of the starting materials to obtain new compounds [14–20]. The pioneering work of Ugi describes the most popular IMCR in which a carboxylic acid, a primary amine, an aldehyde, and an isocyanide react in a one-pot manner to afford an *N*-substituted acyl aminoamide containing four independently varying groups [21–25].

The reaction of isocyanides and acetylene compounds, first described by Winterfeld in 1969, is perhaps the founding basis for a large class of new, accessible scaffolds [26]. This reaction initially affords a zwitterionic adduct, which might undergo cycloaddition to activated alkenes, leading to a variety of novel highly substituted cyclopentadienoid systems [27–36].

On the other hand, quinoline-containing compounds have been extensively used in medicinal chemistry because of various biological activities such as anti-inflammatory [37], antimalarial [38–40], anticancer [41, 42], analgesic [43, 44], and antifungal [45].

The zwitterion derived from isocyanide and dimethyl acetylenedicarboxylate (DMAD) has been shown to be efficiently trapped by dipolarophiles such as aryl aldehydes and *N*-tosylimines leading to a facile synthesis of furan and pyrrole derivatives, respectively [35, 36]. The reported cycloaddition trapping of these species by activated alkenes to highly substituted cyclopentadienoid systems [46, 47], along with the documented properties of quinoline-containing heterocycles prompted us to examine the one-pot three component reaction of 2-((2-chloroquinolin-3-yl)methylene)malononitrile or ethyl 3-(2-chloroquinolin-3-yl)-2-cyanoacrylate with acetylenecarboxylates and isocynanides.

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Experiment

General information

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Bomem B100 series spectrophotometer, in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-300-ADVANCE spectrometer at 300 (^1H) and 75 MHz (^{13}C) using $CDCl_3$ and D2O as solvents and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm), respectively. Mass spectra of the products were obtained with an HP (Agilent Technologies) 5937 Mass Selective Detector. Elemental analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the preparation of 7a–j

To a solution of aldehyde **4** (1 mmol) in EtOH (5 mL) was added malononitrile or ethyl cyanoacetate (1 mmol) and triethylamine (0.101 g, 1 mmol) and the mixture was stirred for 15 min at room temperature. The solid was separated by simple filtration and subsequently added to a solution of acetylenecarboxylate (1.00 mmol) and isocyanide (1.00 mmol) in CH_2Cl_2 (5 mL). After stirring for 12 h at RT and completion as indicated by TLC, the solvent was removed under reduced pressure and the residue was recrystallized, respectively, from methanol and hexane–ethylacetate 3:1 to afford products **7a–j**.

*4-Ethyl 1,2-dimethyl 3-(2-chloroquinolin-3-yl)-4-cyano-5-(cyclohexylamino)cyclopenta-2,5-diene-1,2, 4-tricarboxylate (**7a**)*

White solid, mp: 159–161 °C, yield: 0.33 g (62 %). IR (KBr) (ν_{max}, cm^{-1}): 2933, 2207, 1744, 1664; ^1H-NMR (300 MHz, $CDCl_3$): δ_H = 1.26–1.32 (m, 4H, 2C$\underline{H}_2$ of cyclohexyl), 1.37 (t, J = 8.0 Hz, 3H, OCH$_2\underline{Me}$), 1.42–1.75 (m, 6H, 3C$\underline{H}_2$ of cyclohexyl), 3.66 (s, 3H, O$\underline{Me}$), 3.87–3.91 (m, 1H, C$\underline{H}$ of cyclohexyl), 3.96 (s, 3H, O$\underline{Me}$), 4.39–4.42 (m, 2H, OC$\underline{H}_2$Me), 5.48 (d, J = 4.9 Hz, 1H, N$\underline{H}$), 7.57 (t, J = 7.2 Hz, 1H, Ar), 7.73–7.87 (m, 3H, Ar), 8.02 (d, J = 8.3 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.9, 23.7, 23.8, 25.3, 32.2, 32.7, 53.1, 53.4, 54.3, 63.1, 64.6, 113.2, 126.8, 127.8, 127.9, 128.4, 128.6, 131.5, 137.3, 142.7, 146.0, 146.1, 147.4, 150.1, 155.7, 161.9, 163.0, 165.0; EI-MS: *m/z* (%): 538 (61, M^+ [^{35}Cl]), 540 (27, M^+ [^{37}Cl]), 505 (82), 478 (15), 464 (18), 432 (31), 420 (8), 396 (16), 382 (20), 350 (16), 316 (16), 290 (8), 83 (35), 55 (100), 41 (50). Anal. Calcd for $C_{28}H_{28}ClN_3O_6$ (538.17): C 62.51, H 5.25, N 7.81 %. Found: C 62.21, H 5.43, N 7.76 %.

*4-Ethyl 1,2-dimethyl 3-(2-chloroquinolin-3-yl)-4-cyano-5-((2,4,4-trimethylpentan-2-yl)amino)cyclopenta-2, 5-diene-1,2,4-tricarboxylate (**7b**)*

White solid, mp: 121–123 °C, yield: 0.39 g (68 %). IR (KBr) (ν_{max}, cm^{-1}): 2955, 2235, 1725, 1668, 1627; ^1H-NMR (300 MHz, $CDCl_3$): δ_H = 0.93 (s, 9H, C$\underline{Me}_3$), 1.36 (s, 3H, C$\underline{Me}_2$), 1.38 (s, 3H, OCH$_2\underline{Me}$), 142 (s, 3H, C$\underline{Me}_2$), 1.70 (ABq, J = 14.2 Hz, 2H, CC$\underline{H}_2$C), 3.62 (s, 3H, O$\underline{Me}$), 3.92 (s, 3H, O$\underline{Me}$), 4.39 (q, J = 7.1 Hz, 2H, OC$\underline{H}_2$Me), 5.44 (s, 1H, N$\underline{H}$), 7.56 (t, J = 7.4 Hz, 1H, Ar), 7.75 (t, J = 7.4 Hz, 1H, Ar), 7.82 (d, J = 8.1 Hz, 1H, Ar), 7.89 (s, 1H, Ar), 8.01 (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.9, 28.4, 30.0, 31.3 (3C), 31.8, 52.8, 53.0, 54.2, 57.8, 63.2, 64.2, 115.0, 126.8, 127.8, 127.9, 128.4, 128.8, 131.5, 137.4, 140.8, 146.7, 147.4, 148.5, 150.2, 150.5, 162.0, 163.7, 165.7; EI-MS: *m/z* (%): 568 (9, M^+ [^{35}Cl]), 570 (4, M^+ [^{37}Cl]), 496 (14), 455 (30), 420 (13), 396 (20), 382 (15), 249 (61), 212 (13), 144 (91), 107 (48), 91 (100), 57 (94), 41 (33). Anal. calcd for $C_{30}H_{34}ClN_3O_6$ (568.06): C 63.43, H 6.03, N 7.40 %. Found: C 63.59, H 5.83, N 7.31 %.

*Triethyl 3-(2-chloroquinolin-3-yl)-4-cyano-5-((2,4, 4-trimethylpentan-2-yl) amino)cyclopenta-2, 5-diene-1,2,4-tricarboxylate (**7c**)*

White solid, mp: 124–126 °C, yield: 0.42 g (71 %). IR (KBr) (ν_{max}, cm^{-1}): 2957, 2247, 1742, 1716, 1630; ^1H-NMR (300 MHz, $CDCl_3$): δ_H = 0.94 (s, 9H, C$\underline{Me}_3$), 1.04 (t, J = 7.1 Hz, 3H, OCH$_2\underline{Me}$), 1.37 (s, 6H, C$\underline{Me}_2$), 1.38–1.40 (m, 3H, OCH$_2\underline{Me}$), 1.43 (broad s, 3H, OCH$_2\underline{Me}$), 1.72 (ABq, J = 14.2 Hz, 2H, CC$\underline{H}_2$C), 3.99–4.14 (m, 2H, OC$\underline{H}_2$Me), 4.31–4.49 (m, 4H, 2OC$\underline{H}_2$Me), 5.47 (s, 1H, N$\underline{H}$), 7.57 (t, J = 7.5 Hz, 1H, Ar), 7.76 (t, J = 7.5 Hz, 1H, Ar), 7.83 (d, J = 8.0 Hz, 1H, Ar), 7.92 (s, 1H, Ar), 8.03 (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.7, 13.9, 14.1, 28.4, 30.0, 31.3 (3C), 31.9, 54.5, 56.2, 57.8, 62.0, 63.2, 64.2, 115.1, 126.8, 127.7, 127.9, 128.4, 128.9, 131.4, 137.6, 140.9, 142.5, 146.3, 147.4, 150.2, 150.5, 161.5, 163.4, 165.9; EI-MS: *m/z* (%): 597 (19, M^+ [^{35}Cl]), 599 (8, M^+ [^{37}Cl]), 524 (36), 483 (63), 448 (32), 410 (83), 364 (19), 336 (14), 302 (14), 228 (8), 97 (8), 57 (100), 41 (39). Anal. calcd for $C_{32}H_{38}ClN_3O_6$ (597.24): C 64.47, H 6.43, N 7.05 %. Found: C 64.28, H 6.64, N 7.12 %.

*4-Ethyl 1,2-dimethyl 3-(2-chloro-6-methylquinolin-3-yl)-4-cyano-5-(cyclohexylamino)cyclopenta-2, 5-diene-1,2,4-tricarboxylate (**7d**)*

White solid, mp: 143–145 °C, yield: 0.41 g (74 %). IR (KBr) (ν_{max}, cm^{-1}): 2934, 2225, 1741, 1720, 1634; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 1.26–1.35 (m, 4H, 2C$\underline{H}_2$ of cyclohexyl), 1.40 (t, J = 7.1 Hz, 3H, OCH$_2\underline{Me}$), 1.50–1.78 (m, 6H, 3C$\underline{H}_2$ of cyclohexyl), 2.50 (s, 3H, $\underline{Me}$), 3.66 (s, 3H, O$\underline{Me}$), 3.86–3.94 (m, 1H, C$\underline{H}$ of cyclohexyl), 3.97 (s, 3H, O$\underline{Me}$), 4.41 (q, J = 6.7 Hz, 2H, OC$\underline{H}_2$Me), 5.47 (d, J = 4.3 Hz, 1H, N$\underline{H}$), 7.57 (broad s, 1H, Ar), 7.60 (s, 1H, Ar), 7.79 (s, 1H, Ar), 7.92 (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.9, 21.5, 23.7, 23.8, 25.3, 32.2, 32.7, 53.0, 53.4, 54.4, 63.0, 64.5, 113.2, 126.8, 126.9, 128.0, 128.5, 133.7, 136.6, 137.9, 142.8, 146.0, 146.1, 146.9, 149.2, 155.7, 161.9, 163.0, 165.0; EI-MS: *m/z* (%): 551 (80, M^+ [^{35}Cl]), 553 (41, M^+ [^{37}Cl]), 519 (55), 492 (36), 478 (69), 447 (50), 434 (12), 410 (27), 396 (58), 380 (20), 364 (66), 350 (14), 330 (37), 314 (16), 270 (20), 237 (15), 215 (11), 111 (35), 83 (31), 55 (100), 41 (68). Anal. calcd for $C_{29}H_{30}ClN_3O_6$ (551.18): C 63.10, H 5.48, N 7.61 %. Found: C 62.91, H 5.18, N 7.86 %.

*Triethyl 3-(2-chloro-6-methylquinolin-3-yl)-4-cyano-5-(cyclohexylamino)cyclopenta-2,5-diene-1,2, 4-tricarboxylate (**7e**)*

White solid, mp: 142–143 °C, yield: 0.40 g (69 %). IR (KBr) (ν_{max}, cm^{-1}): 2935, 2342, 1744, 1715, 1658; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 1.06 (t, J = 7.1 Hz, 3H, OCH$_2\underline{Me}$), 1.26–1.31 (m, 4H, 2C$\underline{H}_2$ of cyclohexyl), 1.33–1.44 (m, 6H, 2OCH$_2\underline{Me}$), 1.47–1.80 (m, 6H, 3C$\underline{H}_2$ of cyclohexyl), 2.50 (s, 3H, $\underline{Me}$), 3.80–3.86 (m, 1H, C$\underline{H}$ of cyclohexyl), 4.05–4.15 (m, 2H, OC$\underline{H}_2$Me), 4.37–4.47 (m, 4H, 2OC$\underline{H}_2$Me), 5.47 (d, J = 4.8 Hz, 1H, N$\underline{H}$), 7.56–7.60 (m, 2H, Ar), 7.81 (s, 1H, Ar), 7.91 (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.7, 13.9, 14.2, 21.5, 23.6, 23.7, 25.4, 32.2, 32.7, 53.5, 54.3, 62.2, 62.9, 64.5, 113.4, 126.7, 126.8, 128.0, 128.6, 133.6, 136.8, 137.9, 142.9, 145.7, 146.0, 146.2, 149.2, 155.9, 161.4, 162.6, 165.2; EI-MS: *m/z* (%): 579 (42, M^+ [^{35}Cl]), 581 (19, M^+ [^{37}Cl]), 544 (35), 506 (30), 461 (20), 424 (13), 378 (16), 350 (16), 270 (24), 83 (26), 55 (100), 41 (44). Anal. calcd for $C_{31}H_{34}ClN_3O_6$ (579.21): C 64.19, H 5.91, N 7.24 %. Found: C 64.05, H 5.74, N 7.29 %.

*4-Ethyl 1,2-dimethyl 3-(2-chloro-6-methylquinolin-3-yl)-4-cyano-5-((2,4,4-trimethylpentan-2-yl)amino) cyclopenta-2,5-diene-1,2,4-tricarboxylate (**7f**)*

White solid, mp: 135–137 °C, yield: 0.46 g (79 %). IR (KBr) (ν_{max}, cm^{-1}): 2952, 2282, 1742, 1667, 1632; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 0.94 (s, 9H, C$\underline{Me}_3$), 1.38 (s, 3H, C$\underline{Me}_2$), 1.40 (t, J = 7.8 Hz, 3H, OCH$_2\underline{Me}$), 1.43 (s, 3H, C$\underline{Me}_2$), 1.71 (ABq, J = 14.2 Hz, 2H, CC$\underline{H}_2$C), 2.52 (s, 3H, $\underline{Me}$), 3.64 (s, 3H, O$\underline{Me}$), 3.94 (s, 3H, O$\underline{Me}$), 4.40 (q, J = 7.1 Hz, 2H, OC$\underline{H}_2$Me), 5.44 (s, 1H, N$\underline{H}$), 7.58 (broad s, 1H, Ar), 7.61 (s, 1H, Ar), 7.81 (s, 1H, Ar), 7.92 (d, J = 8.5 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.9, 21.6, 28.4, 29.9, 31.3 (3C), 31.9, 52.7, 53.0, 54.3, 57.9, 63.2, 64.2, 115.0, 126.8, 126.9, 128.1, 128.6, 133.7, 136.8, 137.9, 142.1, 146.1, 146.4, 149.3, 150.5, 155.0, 162.1, 163.8, 165.8; EI-MS: *m/z* (%): 581 (54, M^+ [^{35}Cl]), 583 (27, M^+ [^{37}Cl]), 511 (42), 471 (62), 434 (48), 410 (43), 396 (38), 378 (14), 365 (14), 330 (18), 301 (8), 215 (5), 57 (100), 41 (24). Anal. calcd for $C_{31}H_{36}ClN_3O_6$ (581.23): C 63.96, H 6.23, N 7.22 %. Found: C 63.89, H 6.28, N 7.09 %.

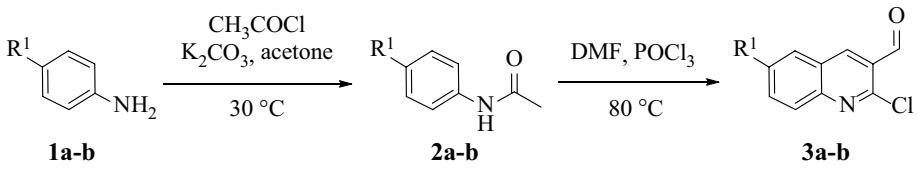
*Triethyl 3-(2-chloro-6-methylquinolin-3-yl)-4-cyano-5-((2,4,4-trimethylpentan-2-yl)amino)cyclopenta-2, 5-diene-1,2,4-tricarboxylate (**7 g**)*

White solid, mp: 136–138 °C, yield: 0.44 g (73 %). IR (KBr) (ν_{max}, cm^{-1}): 2945, 2341, 1742, 1719, 1664; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 0.95 (s, 9H, C$\underline{Me}_3$), 1.04 (t, J = 7.1 Hz, 3H, OCH$_2\underline{Me}$), 1.38–1.43 (m, 12H, C$\underline{Me}_2$, 2OCH$_2\underline{Me}$), 1.72 (ABq, J = 14.2 Hz, 2H, CC$\underline{H}_2$C), 2.51 (s, 3H, $\underline{Me}$), 4.01–4.12 (m, 2H, OC$\underline{H}_2$Me), 4.31–4.49 (m, 4H, 2OC$\underline{H}_2$Me), 5.45 (s, 1H, N$\underline{H}$), 7.57 (broad s, 1H, Ar), 7.60 (s, 1H, Ar), 7.84 (s, 1H, Ar), 7.92 (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.7, 13.9, 14.1, 21.5, 28.4, 29.9, 31.3 (3C), 31.9, 54.5, 56.3, 57.9, 62.0, 63.2, 64.1, 115.1, 126.8, 126.9, 128.0, 128.8, 133.7, 136.9, 137.8, 142.2, 146.0, 146.4, 149.3, 150.6, 155.1, 161.5, 163.4, 165.9; EI-MS: *m/z* (%): 610 (9, M^+ [^{35}Cl]), 612 (4, M^+ [^{37}Cl]), 538 (24), 497 (46), 462 (35), 424 (71), 378 (13), 350 (9), 316 (11), 57 (100), 41 (35). Anal. calcd for $C_{33}H_{40}ClN_3O_6$ (610.14): C 64.96, H 6.61, N 6.89 %. Found: C 64.83, H 6.87, N 6.71 %.

*Dimethyl 3-(2-chloro-6-methylquinolin-3-yl)-4,4-dicyano-5-((2,4,4-trimethylpentan-2-yl)amino)cyclopenta-2, 5-diene-1,2-dicarboxylate (**7 h**)*

White solid, mp: 153–155 °C, yield: 0.34 g (63 %). IR (KBr) (ν_{max}, cm^{-1}): 2953, 2332, 1748, 1726; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 0.96 (s, 9H, C$\underline{Me}_3$), 1.52 (s, 3H, C$\underline{Me}_2$), 1.65 (s, 3H, C$\underline{Me}_2$), 1.77 (ABq, J = 14.2 Hz, 2H, CC$\underline{H}_2$C), 2.51 (s, 3H, $\underline{Me}$), 3.69 (s, 3H, O$\underline{Me}$), 3.96 (s, 3H, O$\underline{Me}$), 5.71 (s, 1H, N$\underline{H}$), 7.60 (s, 1H, Ar), 7.63 (broad s, 1H, Ar), 7.72 (s, 1H, Ar), 7.94 (d, J = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 21.6, 29.5, 30.2, 31.3 (3C), 31.8, 53.1, 53.4, 55.0, 57.9, 64.5, 111.6, 113.4, 126.6, 126.8, 127.2, 128.2, 134.2, 136.3, 138.3, 140.6, 144.7,

Scheme 1 Synthesis of 2-chloroquinoline-3-carbaldehydes **3a–b**



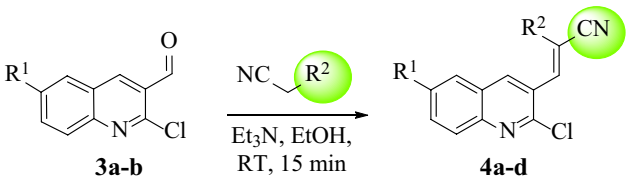
146.2, 149.2, 150.5, 155.1, 161.4, 162.9; EI-MS: *m/z* (%): 535 (24, M^+ [^{35}Cl]), 537 (8, M^+ [^{37}Cl]), 463 (6), 422 (57), 387 (55), 368 (25), 328 (13), 112 (12), 97 (19), 57 (100), 41 (55). Anal. calcd for $C_{29}H_{31}ClN_4O_4$ (535.03): C 65.10, H 5.84, N 10.47 %. Found: C 65.04, H 5.96, N 10.31 %.

*Diethyl 3-(2-chloro-6-methylquinolin-3-yl)-4,4-dicyano-5-((2,4,4-trimethylpentan-2-yl)amino)cyclopenta-2,5-diene-1,2-dicarboxylate (**7i**)*

White solid, mp: 150–152 °C, yield: 0.38 g (66 %). IR (KBr) (ν_{max}, cm^{-1}): 2957, 2219, 1721, 1638; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 0.96 (s, 9H, C<u>Me</u>$_3$), 1.38–1.43 (m, 12H, C<u>Me</u>$_2$, 2OCH$_2$<u>Me</u>), 1.72 (ABq, *J* = 14.2 Hz, 2H, CC<u>H</u>$_2$C), 2.52 (s, 3H, <u>Me</u>), 4.07–4.13 (m, 4H, 2OC<u>H</u>$_2$Me), 5.47 (s, 1H, N<u>H</u>), 7.57 (broad s, 1H, Ar), 7.60 (s, 1H, Ar), 7.79 (s, 1H, Ar), 7.93 (d, *J* = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.7, 13.9, 21.5, 28.4, 30.0, 31.3 (3C), 31.9, 54.3, 57.9, 62.0, 62.9, 64.2, 114.1, 115.2, 126.4, 126.7, 128.0, 128.4, 133.5, 136.6, 137.6, 142.6, 146.1, 146.2, 149.2, 150.3, 155.3, 161.6, 163.4; EI-MS: *m/z* (%): 562 (53, M^+ [^{35}Cl]), 564 (23, M^+ [^{37}Cl]), 492 (13), 450 (60), 415 (57), 377 (52), 341 (12), 314 (9), 269 (7), 57 (100), 41 (19). Anal. calcd for $C_{31}H_{35}ClN_4O_4$ (562.23): C 66.12, H 6.27, N 9.95 %. Found: C 65.98, H 6.35, N 9.83 %.

*Diethyl 3-(2-chloro-6-methylquinolin-3-yl)-4,4-dicyano-5-(cyclohexylamino)cyclopenta-2,5-diene-1,2-dicarboxylate (**7j**)*

White solid, mp: 163–165 °C, yield: 0.32 g (61 %). IR (KBr) (ν_{max}, cm^{-1}): 2937, 2131, 1735, 1708; ^{1}H-NMR (300 MHz, $CDCl_3$): δ_H = 1.17–1.29 (m, 4H, 2C<u>H</u>$_2$ of cyclohexyl), 1.30–1.38 (m, 6H, 2OCH$_2$<u>Me</u>), 1.50–1.96 (m, 6H, 3C<u>H</u>$_2$ of cyclohexyl), 2.51 (s, 3H, <u>Me</u>), 3.99 (broad s, 1H, C<u>H</u> of cyclohexyl), 4.02–4.39 (m, 4H, 2OC<u>H</u>$_2$Me), 5.65 (d, *J* = 5.1 Hz, 1H, N<u>H</u>), 7.56–7.60 (m, 2H, Ar), 7.81 (s, 1H, Ar), 7.91 (d, *J* = 8.4 Hz, 1H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$): δ_c = 13.5, 13.9, 21.0, 23.2, 24.3, 24.7, 31.6, 32.5, 53.0, 61.3, 61.9, 63.4, 110.5, 112.0, 125.9, 126.4, 127.2, 127.3, 134.2, 136.6, 138.0, 142.6, 145.3, 145.6, 148.3, 149.0, 152.5, 161.5, 162.4; EI-MS: *m/z* (%) 532 (12, M^+ [^{35}Cl]), 534 (5, M^+ [^{37}Cl]), 486 (9), 422 (9), 404 (10), 377 (100), 363 (16), 349 (13), 314 (16), 254 (20), 177 (16), 83 (57), 55 (88), 41 (35). Anal. calcd for



Scheme 2 Synthesis of Knöevenagel adducts **4a–d**

$C_{29}H_{29}ClN_4O_4$ (532.19): C 65.35, H 5.48, N 10.51 %. Found: C 65.21, H 5.62, N 10.46 %.

Results and discussion

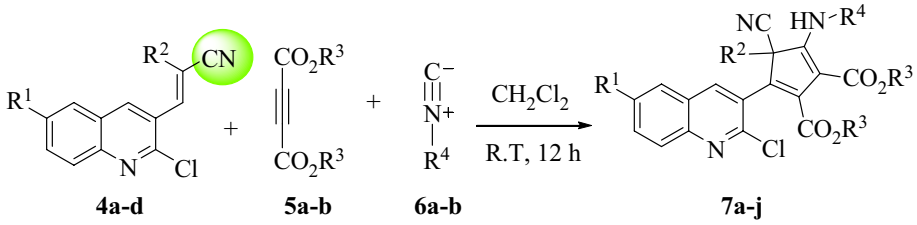
Initially, 2-chloroquinoline-3-carbaldehydes **3a–b** were prepared using the traditional Vilsmeier–Haack cyclization of acetanilides **2a–c** (Scheme 1) [48, 49].

In the next step, reaction of **3a–b** with malononitrile or ethylcyanoacetate in the presence of triethylamine in EtOH within 15 min afforded the Knöevenagel adducts **4a–d** (Scheme 2).

Products **4a–d** without characterization were then treated with dimethyl acetylenecarboxylate and isocyanide in CH_2Cl_2 at RT. The highly substituted cyclopentadienes containing quinoline nucleus **7a–j** were obtained in moderate to good yields (Scheme 3; Table 1). The structure of **7a–j** was deduced by their analytical and spectral data. The mass spectra of **7a** displayed the molecular ion peak at 538 for M^+ ([^{35}Cl]) and 540 for M^+ ([^{37}Cl]) consistent with the molecular structure. The ^{1}H-NMR spectrum of **7a** exhibited characteristic singlets at δ 3.66 and 3.96 and two triplet and multiplet at δ 1.37 and 4.39–4.42 for OCH$_2$<u>Me</u> and OC<u>H</u>$_2$Me, respectively, along with a doublet at 5.48 due to NH. The ester carbonyl groups displayed ^{13}C resonance signals at δ 161.9, 163.0 and 165.0 supporting the IR absorption at 1744 cm^{-1}. The IR absorption at 2207 cm^{-1} and the ^{13}C resonance signal at δ 113.2 were attributed to the cyano group.

Although the precise mechanism is not known, a mechanistic postulate as shown in Scheme 3 may be invoked to rationalize the formation of **7a**. It is conceivable that the zwitterionic intermediate **I**, formed by the 1:1 interaction between the acetylenedicarboxylate **5a** and isocyanide **6a,** attacks **4a** leading to a 1,5-dipolar intermediate **II**. The subsequently generated **III** upon ring closure is finally transformed into **7a** via a [1, 5] H shift.

Scheme 3 Synthesis of cyclopentadienes containing quinolones **7a–j**



4a-d **5a-b** **6a-b** **7a-j**

Table 1 Structures of products **7a–j**

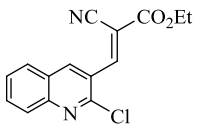
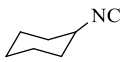
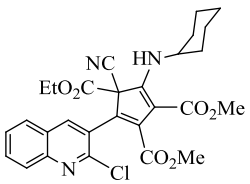
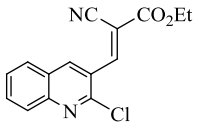
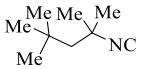
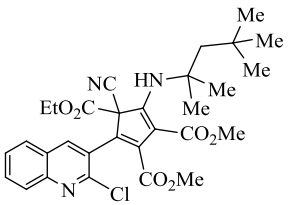
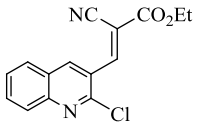
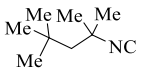
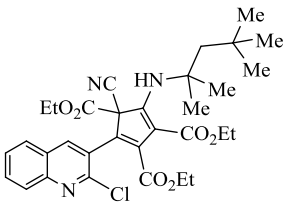
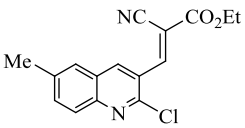
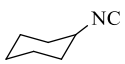
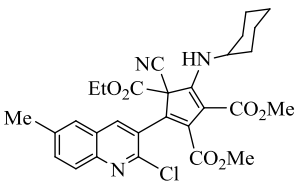
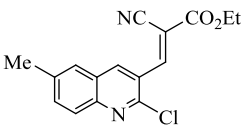
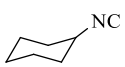
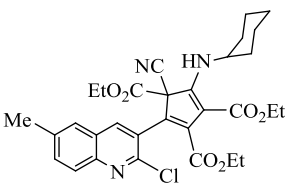
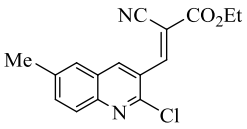
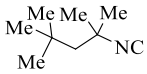
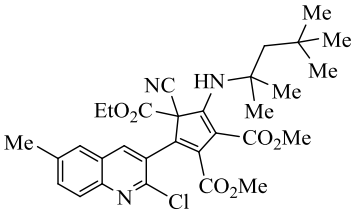
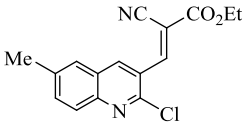
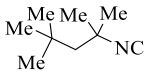
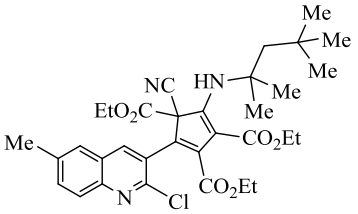
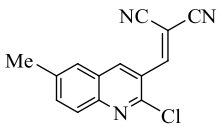
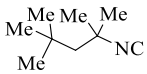
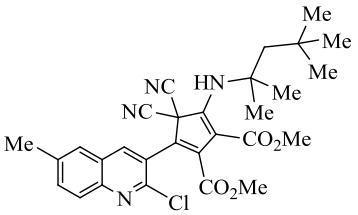
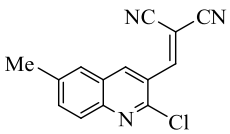
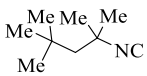
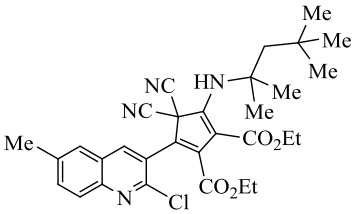
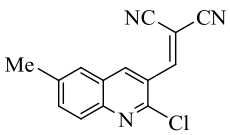
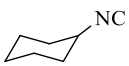
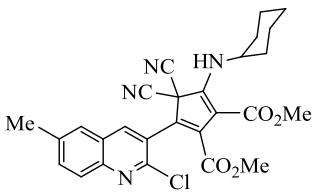
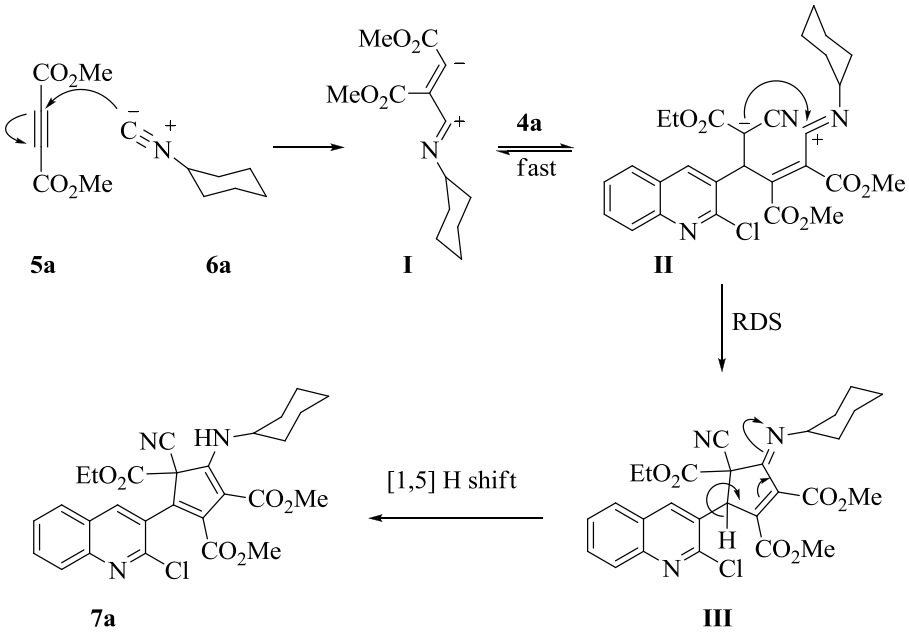
Entry	Alkene	Isocyanide	DMAD/DEAD	Product	Yield (%)
1			DMAD	 **7a**	62
2			DMAD	 **7b**	68
3			DEAD	 **7c**	71
4			DMAD	 **7d**	74
5			DEAD	 **7e**	69

Table 1 continued

Entry	Alkene	Isocyanide	DMAD/DEAD	Product	Yield (%)
6			DMAD	 **7f**	79
7			DEAD	 **7g**	73
8			DMAD	 **7h**	63
9			DEAD	 **7i**	66
10			DMAD	 **7j**	61

As is evident in Table 1, the isocyanide component of the MCR was variable. Compared to cyclohexyl isocyanide, utilization of tetramethylbutyl isocyanide afforded the desired products in higher yields (entries 1 and 4 versus 2 and 6 or 5 versus 7, Table 1). Tetramethylbutyl isocyanide as an electron-rich nucleophile seems to be responsible for affording the corresponding products in higher yields [31]. The alkene component of the MCR was also variable. When malononitrile was used in the reaction instead of ethylcyanoacetate, lower yields of the products were obtained (entries 4 and 6 versus 10 and 8, Table 1). Whereas the pK_a of the former is smaller (11.25) than that of the latter (11.70) [50], the formation of the products with ethyl cyanoacetate in higher yields is anticipated if the

Scheme 4 Mechanistic rationalization for the formation of compound **7a**



transformation of **II** to **III** becomes rate determining step (RDS) (see Scheme 4). This proposal finds support, since the products resulted from alkene component containing electro-donating quinolines were generated in higher yields (entries 1 and 2 versus 4 and 6, Table 1). Such behavior is expected if **II** is generated in a rapid equilibrium step (see Scheme 4).

Conclusion

In conclusion, a number of highly substituted cyclopentadienes containing quinoline nucleus were synthesized in moderate to high yields. These new structures broaden the scaffolds that are accessible through multicomponent cyclization of Knöevenagel adducts of 2-chloroquinoline-3-carbaldehydes and malononitrile or ethyl cyanoacetate with acetylenecarboxylates and isocyanides. In contrast to many other multicomponent reactions in which heterocycle scaffolds are generally produced, these reactions delivered quinoline-based cyclopentadiene carbocycles that some of them may represent interesting pharmacophores.

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