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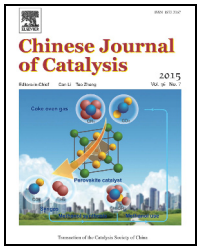

Article

An efficient green synthesis of dispirohydroquinolines via a diastereoselective one-pot eight-component reaction

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ABSTRACT

The one-pot eight-component reaction between Meldrum's acid, an aromatic aldehyde, and an aryl amine was achieved in the presence of citric acid catalyst. The corresponding dispirohydroquinolines were obtained in good yields with excellent diastereoselectivity. This method is a combination of the Knoevenagel and Michael reactions.

1. Introduction

Green chemistry involves intrinsic atom economy, helps to save energy and reduce waste, allows easy work up and avoids hazardous chemicals [1–9]. The development of a simple, eco-friendly reaction protocol for the synthesis of highly functionalized medicinal compound libraries is an attractive area of research [10–12]. In this context, multi-component reactions (MCRs) have become interesting [13–16], where three or more starting materials react in one-pot to form a complex product. The product must contain at least part of the substrate and the starting materials should be commercially available in large quantities or easy to prepare. The MCR is convergent, offers operational simplicity and facile automation, has atom and step economy [17] and generates minimal waste. MCR chemistry can also be used to synthesize heterocycles [18].

As part of our continuing research [19–25], herein we report a green, mild, high yielding one-pot eight-component reaction for the synthesis of a new heterocyclic system from Meldrum's acid **1**, an aromatic aldehyde **2** and an aryl amine **3** in the presence of citric acid (Scheme 1).

2. Experimental

2.1. General methods

Melting points (m.p.) and infrared (IR) spectra were measured on an Electrothermal 9100 instrument and a JASCO FT/IR-460 plus spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer with $CDCl_3$ as the solvent at 400 and 100 MHz, respectively. All reagents were purchased from Merck (Darmastadt, Germany) or Fluka (Buchs, Switzerland), and used without further purification.

2.2. General procedure for the synthesis of

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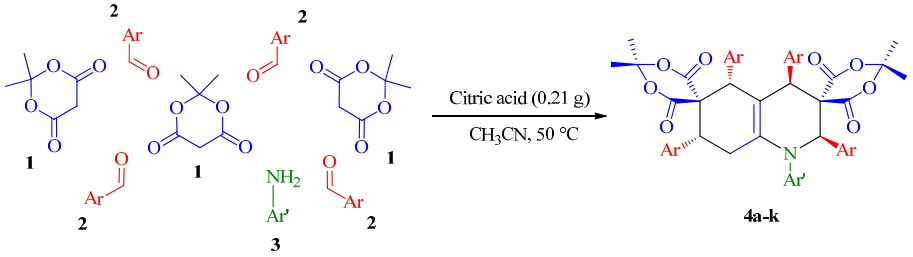

Scheme 1. Synthesis of dispirohydroquinolines via a one-pot eight-component reaction.

dispirohydroquinolines

To a solution of Meldrum's acid (3.0 mmol), aldehyde (4.0 mmol) and aniline (1.0 mmol) in acetonitrile (5 mL), citric acid (0.21 g) was added and magnetically stirred at 50 °C. The reaction progress was monitored by TLC. After 24 h, the resultant precipitates were collected by filtration and washed with acetonitrile (3 × 2 mL).

Spectral data of selected new products are as follows.

1′,2′,4′,5′,7′-Pentaphenyl-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5,3′:6′,5″-bis(2,2-dimethyl [1,3]dioxane-4,6-dione)] (**4a**). White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.36, 0.38, 0.60 and 0.62 (4s, 12H, 4Me), 2.55–2.66 (m, 2H, H′, H″-8′), 4.02 (dd, 1H, J = 11.6 Hz, J = 6.0 Hz, H-7′), 4.65 and 4.67 (2s, 2H, H-4′, H-5′), 5.26 (s, 1H, H-2′), 6.04 (d, 1H, J = 7.6, H_{Ar}), 6.08 (d, 1H, J = 7.6, H_{Ar}), 6.71 (d, 1H, J = 7.6 Hz, H_{Ar}), 6.75 (d, 1H, J = 8.0 Hz, H_{Ar}), 7.00–7.58 (m, 21H, H_{Ar}).

1′-(4-Methoxyphenyl)-2′,4′,5′,7′-tetra(4-methylphenyl)-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] (**4b**). White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.40, 0.43, 0.65 and 0.66 (4s, 12H, 4Me), 2.19, 2.23 and 2.25 (3s, 12H, 4ArMe), 2.44–2.67 (m, 2H, H′, H″-8′), 3.71 (s, 3H, OMe), 3.95 (dd, 1H, J = 12.0 Hz, J = 5.6 Hz, H-7′), 4.55 and 4.59 (2s, 2H, H-4′, H-5′), 5.15 (s, 1H, H-2′), 5.94 (d, 1H, J = 8.0 Hz, H_{Ar}), 5.97 (d, 1H, J = 8.0 Hz, H_{Ar}), 6.55 (t, 2H, J = 7.2, H_{Ar}), 6.67–7.48 (m, 16H, H_{Ar}).

1′-(Phenyl)-2′,4′,5′,7′-tetra(2-methylphenyl-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydro-quinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] (**4c**). White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.48, 0.50, 1.15 and 1.17 (4s, 12H, 4Me), 0.92, 2.32 and 2.51 (3s, 12H, 4ArMe), 2.52 (dd, 1H, J = 14.4, 5.6 Hz, H′-8′), 2.65–2.73 (m, 1H, H″-8′), 4.32 (dd, 1H, J = 12.0 Hz, J = 5.2 Hz, H-7′), 4.76 and 4.82 (2s, 2H, H-4′, H-5′), 5.59 (s, 1H, H-2'), 6.71–7.84 (m, 21H, H_{Ar}).

1′-(4-Chlorophenyl)-2′,4′,5′,7′-tetra(4-methylphenyl)-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] (**4e**). White solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.40, 0.43, 0.66 and 0.67 (4s, 12H, 4Me), 2.21, 2.23 and 2.26 (3s, 12H, 4ArMe), 2.47–2.64 (m, 2H, H′,H″-8′), 3.95 (dd, 1H, J = 12.0 Hz, J = 5.6 Hz, H-7′), 4.55 and 4.58 (2s, 2H, H-4′, H-5′), 5.14 (s, 1H, H-2′), 5.96 (t, 2H, J = 8.0 Hz, H_{Ar}), 6.56 (t, 2H, J = 7.2 Hz, H_{Ar}), 6.88–7.42 (m, 16H, H_{Ar}).

1′-(4-Fluorophenyl)-2′,4′,5′,7′-tetra(4-methoxyphenyl)-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] (**4j**). White solid; m.p. 247–248 °C; IR (KBr): ν 1767, 1730, 1652, 1610, 1509, 1462, 1381, 1302, 1245, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.46, 0.49, 0.70 and 0.75 (4s, 12H, 4Me), 2.45 (dd, 1H, J = 17.2 Hz , J = 5.6 Hz, H'-8′), 2.53–2.60 (m, 1H, H″-8′), 3.70, 3.72 and 3.73 (3s, 12H, 4 MeO), 3.92 (dd, 1H, J = 12.0, J = 5.6 Hz, H-7′), 4.51, 4.53 (2s, 2H, H-4′, H-5′), 5.10 (s, 1H, H-2′), 5.99–6.04 (m, 2H, H_{Ar}), 6.31–6.35 (m, 1H, H_{Ar}), 6.63 (dd, 1H, J = 8.8 Hz, J = 2.8 Hz, H_{Ar}), 6.71 (dd, 1H, J = 8.8 Hz, J = 2.8 Hz, H_{Ar}), 6.75–7.01 (m, 9H, H_{Ar}), 6.71 (dd, 1H, J = 7.2 Hz, J = 2.4 Hz, H_{Ar}), 7.37 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz, H_{Ar}), 7.44 (dd, 1H, J = 8.4 Hz, J = 2.0 Hz, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.1, 28.3, 28.6, 28.7 (4Me), 32.0 (C-8′), 46.8, 49.8 and 52.2 (C-4′, C-5′, C-7′), 55.1, 55.2 and 55.3 (4OMe), 61.7 and 61.9 (C-3′, C-6′), 69.7 (C-2′), 103.3 (C-4′a), 105.2 and 105.5 ($2CMe_2$), 112.77, 113.4, 113.6, 113.7, 113.8, 114.0, 114.3, 127.7, 128.2, 129.3, 129.7, 130.2, 130.3, 130.4, 130.5, 132.0, 132.2, 132.6, 140.6 (d, J_{CF} = 2.9 Hz), 141.9 (C_{Ar}, C-8′a), 158.7, 158.8, 159.2 and 159.4 ($4C_{Ar}$–O), 160.7 (d, J_{CF} = 245.7 Hz, C_{Ar}–F), 162.1, 164.3, 168.4 and 169.8 (4C=O).

1′-(4-Bromophenyl)-2′,4′,5′,7′-tetra(2-methylphenyl)-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] (**4k**). White solid; m.p. 230–232 °C; IR (KBr): ν 1768, 1736, 1664, 1513, 1486, 1392, 1290, 1069 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.40, 0.43, 0.66 and 0.68 (4s, 12H, 4Me), 2.22, 2.23 and 2.26 (3s, 12H, 4 ArMe), 2.47–2.60 (m, 2H, H′, H″-8′), 3.95 (dd, 1H, J = 11.6 Hz, J = 5.6 Hz, H-7′), 4.55 and 4.58 (2s, 2H, H-4′, H-5′), 5.13 (s, 1H, H-2′), 5.95 (t, 2H, J = 8.0 Hz, H_{Ar}), 6.55 (t, 2H, J = 6.8 Hz, H_{Ar}), 6.88–7.41 (m, 16H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.9, 20.9, 21.0 and 21.1 (4ArMe), 27.9, 28.2, 28.4 and 28.5 (4Me), 32.9 (C-8′), 47.2, 50.2 and 52.6 (C-4′, C-5′, C-7′), 61.6 and 61.7 (C-3′, C-6′), 69.7 (C-2′), 103.2 (C-4′a), 105.2 and 105.4 ($2CMe_2$), 120.0, 128.3, 128.4, 128.6, 128.8, 129.0, 129.1, 129.1, 129.2, 129.3, 130.8, 131.2, 131.5, 131.6, 131.8, 132.9, 133.9, 135.4, 136.6, 136.8, 137.7, 138.3, 141.5, 143.9 (C_{Ar}, C-8′a), 162.0, 164.2, 168.2 and 169.6 (4C=O).

Benzylidene Meldrum's acid (**18**). White solid; m.p. 120–122 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.84 (s, 6H, 2Me), 7.51 (t, 2H, J = 8.0 Hz, H_{Ph}), 7.59 (t, 1H, J = 8.0 Hz, H_{Ph}), 8.08 (d, 2H, J = 8.0 Hz, H_{Ph}), 8.46 (s, 1H, $H_{vinylic}$).

Bis-adduct (**19**). White solid; m.p. 180–182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.71 and 1.84 (2s, 6H, 2Me), 4.64–4.70 (m, 3H, $CH_{benzylic}$, $2CH_{Meldrum's\ acid}$), 7.30–7.59 (m, 5H, H_{Ph}).

3. Results and discussion

The one-pot eight-component reaction of Meldrum's acid, benzaldehyde and aniline was chosen as a model to optimize