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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.

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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 reac-

tion 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 ¹H and ¹³C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer with CDCl₃ as the solvent at 400 and 100 MHz, respectively. All reagents were purchased from Merck (Darmstadt, 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; ^1H 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 Hz, H_{Ar}), 6.08 (d, 1H, J = 7.6 Hz, 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; ^1H 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 Hz, 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'-tetrahydroquinoline-5,3':6',5''-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] (**4c**). White solid; ^1H 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; ^1H 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} ; ^1H 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 (2CMe₂), 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} ; ^1H 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 (2CMe₂), 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; ^1H 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_{vinyl}).

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

Table 1

Optimization of amount of catalyst in the synthesis of dispirohydroquinoline **4a**.

Entry	Catalyst (g)	T (°C)	Time (h)	Isolated yield (%)
1	0.10	30	100	64
2	0.15	30	72	69
3	0.15	50	50	73
4	0.21	30	48	70
5	0.21	40	41	76
6	0.21	50	32	84
7	0.21	75	24	79
8	0.21	100	24	trace
9	0.31	30	23	75
10	0.42	50	20	81
11	200	30	22	82

the conditions in the presence of different quantities of citric acid catalyst at various temperatures. The best yield of corresponding dispirohydroquinoline (84%) was observed when 0.21 g citric acid was used at 50 °C (Table 1, entry 6).

We propose that this transformation involves eight components. Product **4** occurs from the condensation of three moles of Meldrum's acid, four moles of aldehyde and one mole of aniline. The reaction is diastereoselective and generates four new stereogenic centers. Quantum mechanical calculations confirmed this observation [12].

Table 2

Synthesis of structure of dispiro[tetrahydroquinoline-bis(2,2-dimethyl [1,3]dioxane-4,6-dione)] derivatives **4a–k**.

Entry	Ar	Ar'	Product	Isolated yield (%)	Ref. *
1	Ph	Ph	4a	84	[24]
2	4-MeC ₆ H ₄	4-MeOC ₆ H ₄	4b	80	[24]
3	2-MeC ₆ H ₄	Ph	4c	65	[24]
4	4-MeC ₆ H ₄	4-FC ₆ H ₄	4d	74	[24]
5	4-MeC ₆ H ₄	4-ClC ₆ H ₄	4e	77	[24]
6	4-MeC ₆ H ₄	4-BrC ₆ H ₄	4f	81	[24]
7	4-MeOC ₆ H ₄	4-BrC ₆ H ₄	4g	82	[25]
8	2-ClC ₆ H ₄	Ph	4h	72	[23]
9	Ph	4-MeOC ₆ H ₄	4i	79	[23]

* All known products reported previously in the literature were characterized by comparison of m.p., IR and NMR spectra with those of authentic samples.

The chemical structures of all new compounds (Table 2) were confirmed by IR, ¹H and ¹³C NMR spectroscopy and elemental analysis. The relative stereochemistry of these compounds was confirmed by single-crystal X-ray crystallography (Scheme 2) [23–25] and the stereochemistry was determined by comparison of spectroscopic data with those of authentic samples (Table 3).

The suggested mechanism for this eight-component reaction is presented in Scheme 3 and is based on the Knoevenagel and Michael reactions. First, Knoevenagel condensation occurs

Scheme 2. Structures of eight possible diastereomers **4a**.

Table 3 Comparison of ^1H NMR data.

Entry	Product	H shift (found)	H shift [24]
1	4a	4×Me: 0.36, 0.38, 0.60 and 0.62 (4s); H', H''-8': 2.55–2.66 (m); H-7': 4.02 (dd, $J = 11.6$ Hz, $J = 6.0$ Hz); H-4', H-5': 4.65 and 4.67 (2s); H-2': 5.26 (s)	4×Me: 0.37, 0.39, 0.61 and 0.64 (4s); H'-8': 2.59 (dd, $J = 17.2$ Hz, $J = 5.6$ Hz); H''-8': 2.64–2.71 (m); H-7': 4.03 (dd, $J = 11.6$ Hz, $J = 6.0$ Hz); H-4', H-5': 4.66 and 4.69 (2s); H-2': 5.27 (s)
2	4b	4×Me: 0.40, 0.43, 0.65 and 0.66 (4s); 4×ArMe: 2.19, 2.23 and 2.25 (3s); H', H''-8': 2.44–2.67 (m); OMe: 3.71 (s); H-7': 3.95 (dd, $J = 12.0$ Hz, $J = 5.6$ Hz); H-4', H-5': 4.55 and 4.59 (2s); H-2': 5.15 (s)	4×Me: 0.40, 0.43, 0.65 and 0.66 (4s); 4×ArMe: 2.19, 2.22 and 2.24 (3s); H'-8': 2.49 (dd, $J = 17.2$ Hz, $J = 5.6$ Hz); H''-8': 2.58–2.61 (m); OMe: 3.70 (s); H-7': 3.94 (dd, $J = 12.0$ Hz, $J = 5.6$ Hz); H-4', H-5': 4.55 and 4.58 (2s); H-2': 5.15 (s)
3	4c	4×Me: 0.48, 0.50, 1.15 and 1.17 (4s); 4×ArMe: 0.92, 2.32 and 2.51 (3s); H'-8': 2.52 (dd, $J = 14.4$, 5.6 Hz); H''-8': 2.65–2.73 (m); H-7': 4.32 (dd, $J = 12.0$ Hz, $J = 5.2$ Hz); H-4', H-5': 4.76 and 4.82 (2s); H-2': 5.59 (s)	4×Me: 0.48, 0.50, 1.15 and 1.17 (4s); 4×ArMe: 0.92, 2.26 and 2.51 (3s); H'-8': 2.46–2.68 (m); H-7': 4.31 (dd, $J = 12.0$ Hz, $J = 5.2$ Hz); H-4', H-5': 4.76 and 4.82 (2s); H-2': 5.59 (s)
4	4e	4×Me: 0.40, 0.43, 0.66 and 0.67 (4s); 4×ArMe: 2.21, 2.23 and 2.26 (3s); H' and H''-8': 2.47–2.64 (m); H-7': 3.95 (dd, $J = 12.0$ Hz, $J = 5.6$ Hz); H-4', H-5': 4.55 and 4.58 (2s); H-2': 5.14 (s)	4×Me: 0.40, 0.43, 0.66 and 0.67 (4s); 4×ArMe: 2.21, 2.23 and 2.25 (3s); H' and H''-8': 2.47–2.64 (m); H-7': 3.94 (dd, $J = 12.0$ Hz, $J = 5.6$ Hz); H-4', H-5': 4.55 and 4.58 (2s); H-2': 5.13 (s)
5	4j	4×Me: 0.46, 0.49, 0.70 and 0.75 (4s); H'-8': 2.45 (dd, $J = 17.2$ Hz, $J = 5.6$ Hz); H''-8': 2.53–2.60 (m); 4×OMe: 3.70, 3.72 and 3.73 (3s); H-7': 3.92 (dd, $J = 12.0$, $J = 5.6$ Hz); H-4', H-5': 4.51 and 4.53; (2s) H-2': 5.10 (s)	
6	4k	4×Me: 0.40, 0.43, 0.66 and 0.68 (4s); 4×ArMe: 2.22, 2.23 and 2.26 (3s); H', H''-8': 2.47–2.60 (m, 2H); H-7': 3.95 (dd, $J = 11.6$ Hz, $J = 5.6$ Hz); H-4', H-5': 4.55 and 4.58 (2s); H-2': 5.13 (s)	

between benzaldehyde and Meldrum's acid to generate **6** [26]. This intermediate then decomposes to acetone and **8** [27]. Acetone condenses with aniline to give imine **9** and tautomerizes to enamine **10**, which reacts with the aldehyde to produce reactive Barbas dienamine **12** (2-amino-1,3-butadiene) [27–37]. Barbas dienamine undergoes a double Michael addition with the Knoevenagel product to furnish enamine **14** [32]. Then, **14** is added to **6** [36–38] and generates the dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] derivatives. This hypothesis is supported by the mechanistic investigation of proline-catalyzed spirotrione's formation by reaction of an aldehyde and Meldrum's acid with enones reported by Barbas et al. [27,39].

During the preparation of product **4a**, **18** (Knoevenagel

condensation product) and bis-adduct **19** (competing Michael addition of Meldrum's acid with the resulting benzylidene) were isolated from the mixture of reaction as byproducts (Scheme 4) [40].

4. Conclusions

We have reported a one-pot eight-component reaction for the synthesis of dispirohydroquinolines by reacting Meldrum's acid, an aldehyde and aniline. Mild reaction conditions, good isolated yields, short reaction time and use of a green catalyst are the remarkable advantages of this method. The products have four stereocenters and are synthesized in a diastereoselective manner.

Scheme 3. Suggested mechanism for the synthesis of dispirohydroquinolines.

Scheme 4. Generation of byproducts in this reaction.

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Graphical Abstract

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

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

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