Journal of Saudi Chemical Society (2016) **20**, 349–356

King Saud University

Journal of Saudi Chemical Society

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ORIGINAL ARTICLE

Brønsted acidic ionic liquid catalyzed synthesis of poly-substituted hydroquinolines through diastereoselective, one-pot and pseudo-eight-component reaction

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Received 2 July 2014; revised 25 October 2014; accepted 6 November 2014
Available online 2 December 2014

KEYWORDS

Pseudo-eight-components reaction;
Meldrum's acid;
Brønsted acidic ionic liquid;
Poly-substituted hydroquinolines;
Aldehydes

Abstract We have developed an efficient diastereoselective synthesis of poly-substituted hydroquinolines from commercially available starting materials, Meldrum's acid, aromatic aldehydes and arylamines, in a simple and one-pot reaction using Brønsted acidic ionic liquid (4-sulfobutyl)-tris(4-sulfophenyl) phosphonium hydrogen sulfate. These three materials react together through pseudo-eight-components reaction to generate complex products with four stereocenters that involves ten new bond formations. This synthetic method can be a combination of Knoevenagel and Michael reactions.

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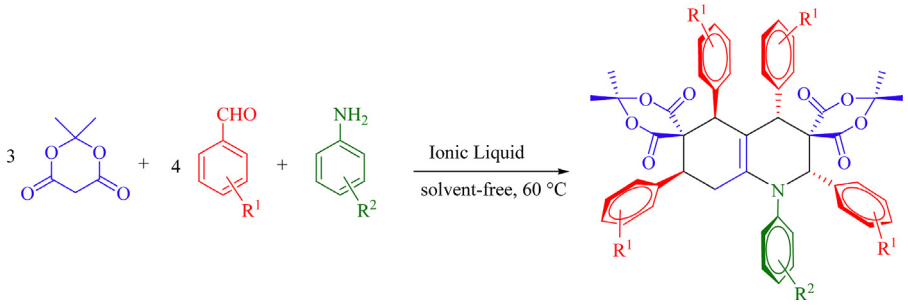
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jscs.2014.11.002



1. Introduction

The nitrogen atom exists in many natural products, biomolecules, pharmaceuticals, and heterocyclic compounds [1]. Hydroquinoline ring system is an important structural unit in many natural occurring alkaloids and therapeutics [2]. They exhibit significant pharmacological activities [3], agonist to serotonin [4], inhibitory activity against acetylcholinesterase [5], D2 receptor antagonists [6] and were used in the treatment of disorders [7]. They have also shown use as pesticides [8], antioxidants [9], and for use in various types of dyes [10].

In recent years, ionic liquids (ILs) have attracted great interest and been applied in a diversity of reactions, both as solvents and catalysts, because of their relatively low vapor pressure, low viscosities, and high chemical and thermic stability [11–13] Brønsted acidic ionic liquids comprise desirable specifications of solid acids and mineral liquid acids and can be replaced with usual mineral acids [14]. Accordingly, we have developed herein the synthesis of poly-substituted hydroquinolines using Brønsted acidic ionic liquid.

2. Experimental

2.1. General

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus (England) and a JASCO FT/IR-460 plus spectrometer (Japan) and Shimadzu IR-460 spectrometer respectively. The ^{1}H and ^{13}C NMR spectra were obtained from a Bruker DRX-400 Avance instrument (Germany) with $CDCl_3$ as a solvent. All reagents were purchased from Merck (Darmastadt, Germany), or Fluka (Buchs, Switzerland), and used without further purification. The X-ray diffraction measurements were made on an Oxford Diffraction Xcalibur Gemini R CCD single crystal diffractometer, using CuKα (λ = 1.54180 Å). Crystallographic calculations were made at the University of Oviedo, on the X-ray group computers, using the following programs: CrysAlisPro [15] for data collection, cell refinement and data reduction; SIR2011 [16] for structure solution; SHELXL-97 [17] for structure refinement and prepare materials for publication; XABS2 for absorption corrections [18]; PARST97 [19] for the geometrical calculations; ORTEP-3 for windows [20] for molecular graphics; and Wingx [21] publication routines to prepare material for publication. The CIF file is deposited at the Cambridge Crystallographic Data Center (CCDC964850) and contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

2.2. General procedure for the preparation of compounds **4a–m**

A mixture of Meldrum's acid (3.0 mmol), aldehyde (4.0 mmol), aniline (1.0 mmol) and ionic liquid **5** (10 mol%) was stirred at 60 °C for 25 to 35 min. After completion, methanol was added to this mixture and the product was recrystallized, to obtain the pure product. Spectral data of selected and new products are represented below:

2.2.1. 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**)

Yield: 0.641 g (83%); 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}).

2.2.2. 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)] (**4e**)

Yield: 0.531 g (64%); 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}).

2.2.3. 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)] (**4g**)

Yield: 0.556 g (76%); 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}).

*2.2.4. 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)] (**4j**)*

Yield: 0.705 g (82%); 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}).

*2.2.5. 1′-(4-Methoxyphenyl)-2′,4′,5′,7′-tetraphenyl-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydro-quinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] (**4k**)*

Yield: 0.642 g (80%); White solid; mp 219–220 °C; IR (KBr): ν 1765, 1734, 1664, 1617, 1509, 1493, 1455, 1391, 1270, 1242 cm^{-1}; ^{1}H NMR (CDCl3, 400 MHz): δ = 0.36, 0.39, 0.62, 0.63 (4s, 12H, 4Me), 2.55 (dd, 1H, J = 13.2 Hz, J = 4.8 Hz, H′-8′), 2.64–2.72 (m, 1H, H″-8′), 3.72 (s, 3H, OMe), 4.02 (dd, 1H, J = 13.6 Hz, J = 5.6 Hz, H-7′), 4.64, 4.68 (2s, 2H, H-4′, H-5′), 5.22 (s, 1H, H-2′), 6.05 (d, 1H, J = 8.0 Hz, H_{Ar}), 6.09 (d, 1H, J = 8.0 Hz, H_{Ar}), 6.70–7.58 (m, 22H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 27.9, 28.2, 28.4 and 28.5 (4Me), 32.6 (C-8′), 47.6, 50.7, 53.1, (C-4′, C-5′, C-7′), 55.1 (OMe), 61.6 and 61.8 (C-3′, C-6′), 70.15 (C-2′), 101.9 (C-4′a), 105.2, 105.4 (2CMe_2), 127.0, 127.1, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.3, 129.4, 129.5, 130.7, 131.2, 131.5, 135.4, 136.2, 137.2, 137.4, 138.5 and 142.7 (C_{Ar}, C-8′a), 157.6 (C_{Ar}-O), 161.8, 164.1, 168.1 and 169.5 (4C═O).

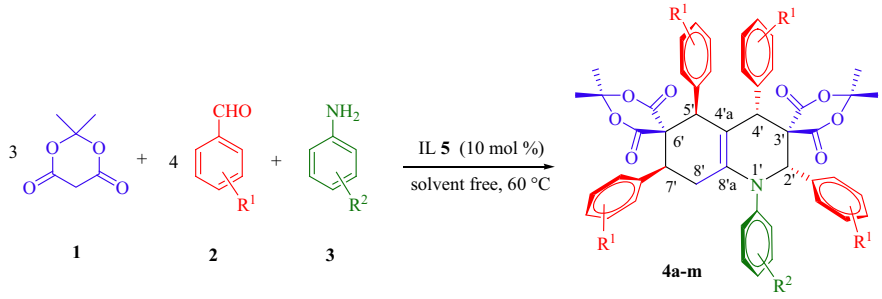
*2.2.6. 1′-(4-fluorophenyl)-2′,4′,5′,7′-tetra(4-Methoxyphenyl)-1′Hdispiro[2′,4′,5′,7′,8′-tetrahydroquinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] (**4l**)*

Yield: 0.693 g (76%); White solid; mp 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).

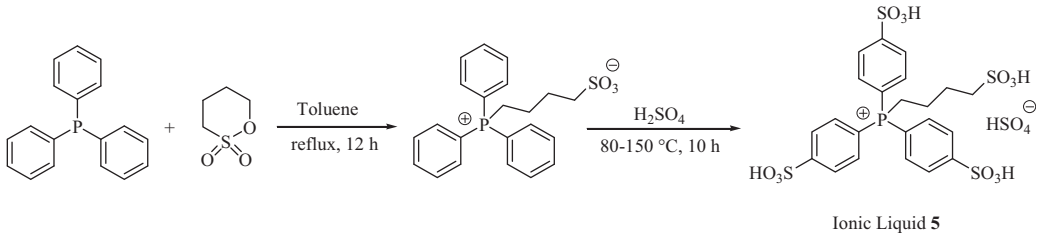
Anal. Calcd for $C_{53}H_{50}FNO_{12}$ C, 69.80; H, 5.53; N, 1.54. Found: C, 70.16: H, 5.61; N, 1.60.

*2.2.7. 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)] (**4m**)*

Yield: 0.562 g (62%); White solid; mp 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,

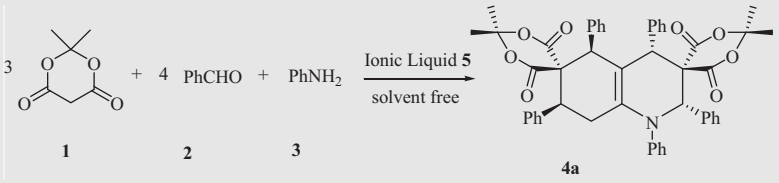


Scheme 1 Synthesis of poly-substituted hydroquinolines through pseudo-eight components reaction.



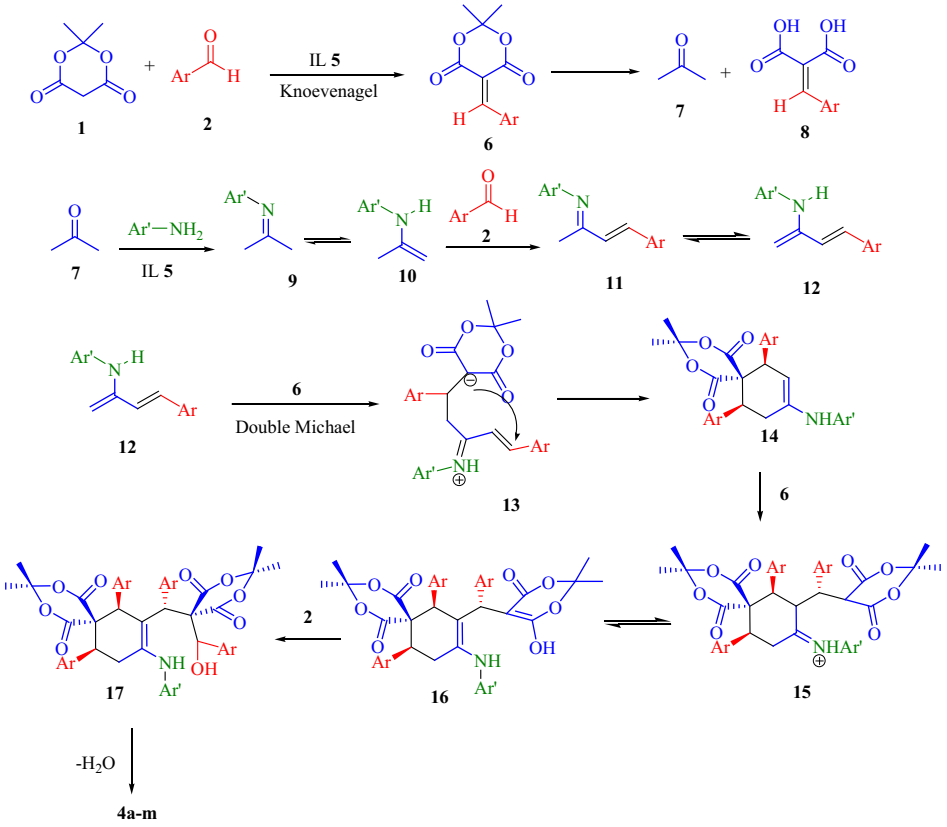
Scheme 2 Synthesis of (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulfate.

Table 1 Optimization of reaction conditions for the synthesis of **4a.**



Entry	Catalyst (mol%)	Temperature (°C)	Time (min)	Yield (%)[a]
1	–	60	60	-
2	5	60	33	69
3	10	50	40	61
4	**10**	**60**	**28**	**83**
5	10	70	25	80
6	15	60	26	80
7	20	60	26	77

Bold values indicates optimized conditions.
[a] Isolated yield.

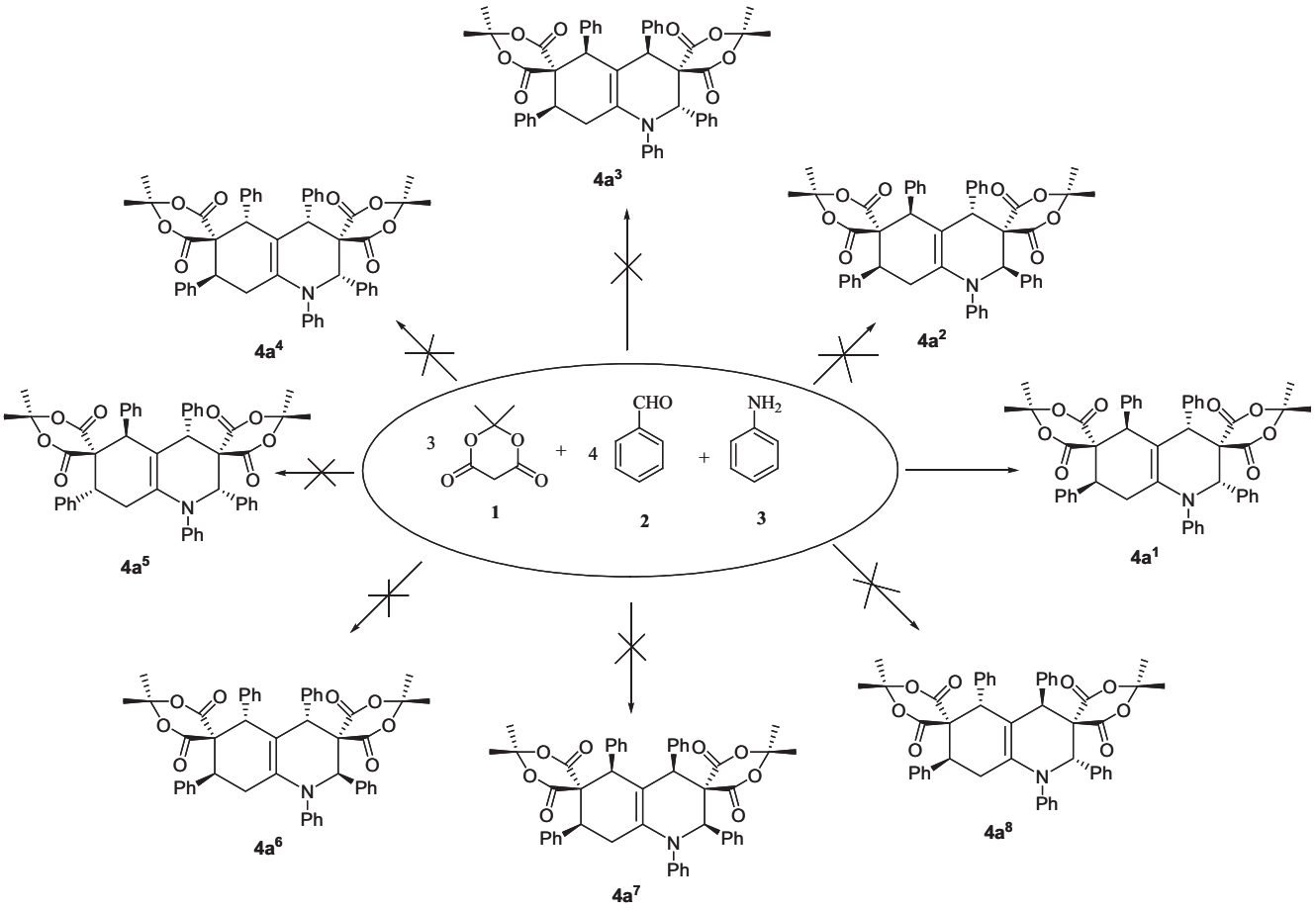


Scheme 3 Suggested mechanism for the pseudo-eight-components reaction.

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); Anal. Calcd for $C_{53}H_{50}BrNO_8$: C, 70.04; H, 5.55; N, 1.54. Found: C, 70.25 H, 5.69 N, 1.59.

*2.3. General procedure for the preparation of compounds **18***

Compound **4a** (2.0 mmol) was heated in acetic acid under reflux condition. After 1.5 h, the reaction mixture was then



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

Table 2 Synthesis of poly-substituted hydroquinolines **4a–m.**

Entry	R^1	R^2	Products	Yield (%)[a]	Refs.
1	H	H	**4a**	83	[27]
2	4-Cl	H	**4b**	79	[27]
3	4-Cl	4-Br	**4c**	74	[27]
4	4-Cl	4-Cl	**4d**	70	[27]
5	2-Me	H	**4e**	64	[27]
6	4-Me	4-F	**4f**	71	[27]
7	4-Me	4-Cl	**4g**	76	[27]
8	4-Me	4-Br	**4h**	80	[27]
9	4-NO_2	4-MeO	**4i**	79	[27]
10	4-Me	4-MeO	**4j**	82	[27]
11	H	4-MeO	**4k**	80	[29]
12	4-MeO	4-F	**4l**	76	[b]
13	2-Me	4-Br	**4m**	62	[b]

[a] Isolated yield.

[b] The new compounds synthesized in this work. All known products reported previously in the literature were characterized by comparison of m.p., IR and NMR spectra with those of authentic samples.

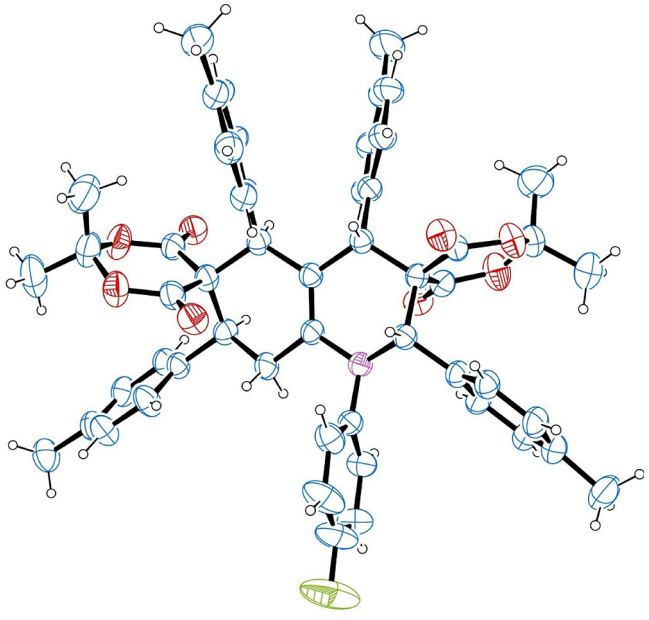


Figure 1 ORTEP view of the molecular geometry of compound **4f**. Ellipsoids have been drawn at the 50% probability level.

Table 3 Crystallographic and structure-refinement data for compound **4f.**

Formula	$C_{53}H_{50}FNO_8$
Formula weight	847.94
Temperature (K)	293(2)
Wavelength (Å)	1.54180
Crystal system	Monoclinic, $C_{2/c}$
Crystal size/mm^3	$0.35 \times 0.32 \times 0.12$
Unit cell dimensions	a = 21.7494 (17)
	b = 14.6285 (13)
	c = 29.400 (2)
β	97.821 (7)
Volume Å^3	9266.9 (13)
Z	8
Density(calculated) g cm^{-3}	1.216
Theta ranges for data collection	3.6240–63.6410
$F(000)$	3584
Absorption coefficient	0.682
Index ranges	$-26 \leqslant h \leqslant 25$
	$0 \leqslant k \leqslant 17$
	$0 \leqslant l \leqslant 35$
Data collected	8625
Unique data (R_{int})	[R_{int} = 0.092]
Parameters/restraints	0/568
Final R_1, wR_2^a (Obs. data)	0.0708, 0.1485
Final R_1, wR_2^a (all data)	0.1538, 0.1919
Absolute structure parameter	293(2)
Goodness of fit on F^2 (S)	1.604
CCDC	**964850**

cooled to room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 1:3) to give the product **18**.

*2.3.1. 3,3-Dimethyl-7,11-diphenyl-2,4-dioxaspiro[5.5]-undecane-1,5,9-trione (**18**)*

Yield: 0.317 g (84%); White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.57 (s, 6H, 2Me); 2.67 (dd, J_{HH} = 15.2 Hz, J_{HH} = 4.4 Hz, 2H), 3.75 (t, J = 14.8 Hz, 2H), 4.03 (dd, J_{HH} = 14.4 Hz, J_{HH} = 4.0 Hz, 2H), 7.25–7.37 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 28.3, 42.8, 50.1, 60.5, 106.4, 128.4, 128.7, 129.2, 137.1, 165.2, 168.2, 207.7.

3. Results and discussion

In continuation of our research on multicomponent reactions [22–29], herein we report a simple, efficient and eco-friendly procedure for the synthesis of poly-substituted hydroquinolines through pseudo-eight-components reaction between Meldrum's acid **1**, aromatic aldehydes **2** and arylamines **3** using (4-sulfobutyl)tris(4-sulfophenyl)phosphonium hydrogen sulfate (Scheme 1). Ionic liquid **5** can be easily synthesized from the readily available starting materials (Scheme 2) [30].

At the outset of the experiment, the one-pot, pseudo-eight-component reaction between Meldrum's acid, benzaldehyde and aniline was chosen as a pattern to optimize the reaction conditions in the presence of different amounts of the ionic liquid 5 at 50, 60, and 70 °C. In the absence of the ionic liquid, no product was formed indicating the catalyst is necessary for this transformation (Table 1, entry 1). Herein, the reaction occurred efficiently affording the corresponding poly-substituted hydroquinolines in 83% yield when 10 mol% ionic liquid **5** was used at 60 °C under solvent-free conditions (Table 1, entry 4).

The suggested mechanism for this pseudo-eight-components reaction is presented in Scheme 3. Mechanism of the reaction can be a combination of Knoevenagel and Michael reactions. First, Knoevenagel condensation was carried out between aldehyde and Meldrum's acid to generate the benzylidene of Meldrum's acid [31]. This intermediate decomposed to acetone and **8** [32]. Acetone undergoes condensation with aniline to give imine **9** and tautomerized to enamine **10**. **10** reacts with the aldehyde to afford the reactive Barbas dienamine **12** (2-amino-1,3-butadiene) [32-40]. The Barbas dienamine undergoes a double Michael addition with the Knoevenagel product to furnish enamine **14** [37]. Then, **14** adds to the Knoevenagel product **6** [41-43] followed by an attack on the aldehyde to afford dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)]. This hypothesis is supported by the mechanistic investigation of proline-catalyzed spirotrione's formation through the reaction of aldehyde and Meldrum's acid with enones reported by Barbas III et al. [32,44].

As can be seen in the structure of the product, this reaction leads to creation of four stereogenic centers, and among the eight possible diastereomers, one diastereomer is produced in good yields (Scheme 4).

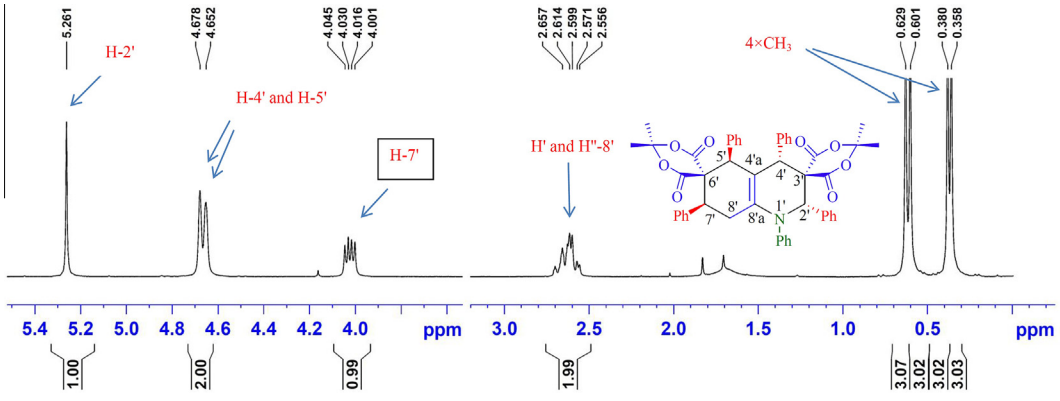
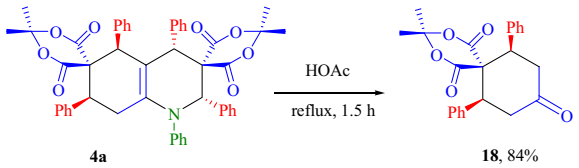


Figure 2 ^{1}H NMR spectrum of **4a.**



Scheme 5 Hydrolysis of poly-substituted hydroquinoline.

The chemical structures of all compounds (Table 2) were confirmed by FT-IR, ^{1}H and ^{13}C NMR spectroscopies, mass spectrometry. Also stereochemistry of compounds was assigned by the single crystal X-ray diffraction method. Fig. 1 shows that stereochemistry of products were stabilized through crystalized processes. Crystallographic data and the refinement procedures are given in Table 3.

A part of the ^{1}H NMR spectrum of **4a** is shown in Fig. 2. In this figure, four methyl of Meldrum's acid, H′ and H″-8′, H-7′, H-4′, H-5′ and H-2′ were characterized and assigned.

To examine the efficiency and the applicability of this new domino multi-component reaction, different aldehydes and arylamines were tested. Aromatic aldehydes bearing either electron-withdrawing functional groups, such as nitro and halo substituents, or electron-donating ones, such as methyl were converted into the corresponding products in good yields. Also we applied arylamines with either electron-donating groups such as methoxy or electron-withdrawing groups such as halo substituents (Scheme 1). Results are summarized in Table 2.

In addition, hydrolysis of compound **4a** in acidic media resulted in substituted spiro[5,5]undecane-1,5,9-trione **18** in good yield (Scheme 5) [32].

4. Conclusions

In conclusion, synthesis of poly-substituted hydroquinolines from commercially available starting materials as a single synthetic operation through pseudo-eight-components reaction was accomplished. During this research work, it is distinguished that the products have four stereocenters and ten new bonds are formed. This transformation takes place with Meldrum's acid, aromatic aldehydes and arylamines with excellent diastereoselectivity.

Acknowledgments

We gratefully acknowledge the funding support received for this project from the Research Council of the University of Sistan and Baluchestan. This work was partially supported by FEDER funding, the Spanish Ministerio de Economía y Competitividad MAT2006-01997, MAT2010-15094 and the Factoría de Cristalización (Consolider Ingenio 2010).

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