SALICYLIC ACID AS AN EFFICIENT CATALYST FOR THE DIASTEREOSELECTIVE SYNTHESIS OF DISPIROHYDROQUINOLINES VIA A ONE-POT DOMINO EIGHT-COMPONENT REACTION

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ABSTRACT

Salicylic acid was used as an efficient catalyst for the diastereoselective synthesis of dispirohydroquinoline-bis (Meldrim's acid) derivatives via a one-pot domino eight-component reaction of arylamines, aromatic aldehydes and Meldrum's acid in CH_3CN at room temperature. The remarkable advantages offered by this method are inexpensive catalyst, good yields, simple and easy work-up procedure. The characterization of products was done by IR, mass, ^1H NMR, ^{13}C NMR spectroscopy, and elemental analyses. The stereoselectivity of compounds was confirmed with crystallography and NMR spectroscopy.

Keywords : Aromatic aldehydes, Aromatic amines, Meldrum's acid, Dispiro compounds.

INTRODUCTION

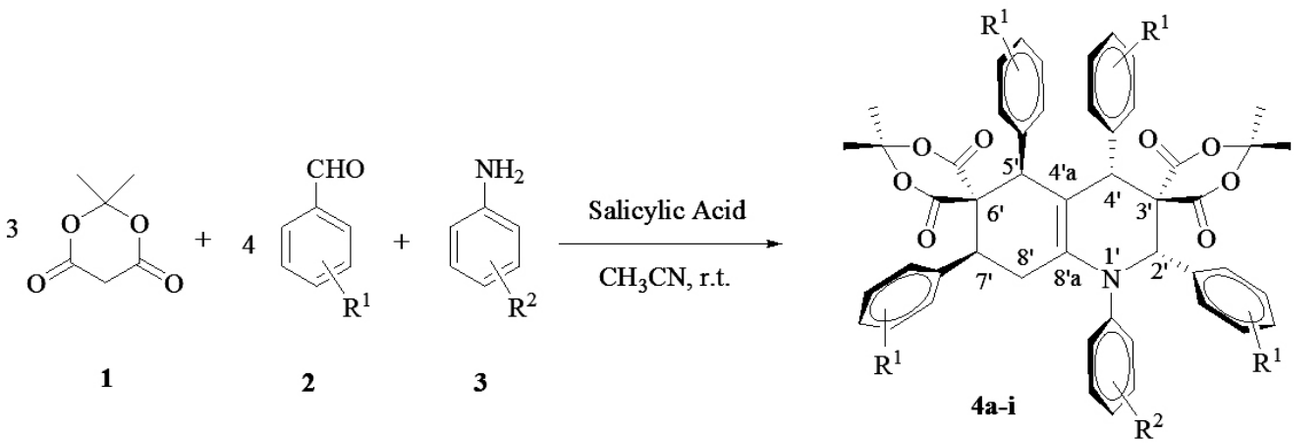
Multicomponent reactions (MCRs) are one-pot processes in which three or more reactants come together in a single reaction vessel to form a product containing substantial elements of all the reactants [1-4]. In the recent years, MCRs have attracted growing interest in the chemical and pharmaceutical industries since this kind of reactions not only have lower production costs due to their high convergence and atom efficiency but also reduce the environmental burden which is the major principle of green chemistry.

Tetrahydroquinoline derivatives are an important subunit of synthetic and natural compounds such as alkaloids and therapeutics which have a considerable potential in biological activities [5, 6] including antimalarial [7], antitumor [8, 9], antioxidant [10, 11] and anti-inflammatory [12]. Therefore, organic chemists have developed many synthetic procedures to prepare these polycyclic quinoline systems as well as spiro compounds [13, 14].

In continuation of our research on synthesis of spiro compounds [15-23], we introduce salicylic acid as an efficient catalyst for the new diastereoselective synthetic method of dispirohydroquinoline-bis(Meldrum's acid) derivatives via a one-pot domino eight-component reaction.

RESULTS AND DISCUSSION

Selectivity is a key factor in asymmetric synthesis; in particular, chemoselectivity is synthetically useful because of the preferential outcome of one product over a set of other plausible products which obviate the need for separate the products from the reaction mixture. In recent years, domino Knoevenagel/Diels–Alder reactions were reported for the diastereoselective synthesis of highly substituted spirotriones [24-32]. Herein, we have developed a direct diastereoselective synthesis of dispiro[tetrahydroquinoline-bis(Meldrum's acid) derivatives in a diastereoselective manner at room temperature in acetonitrile by using salicylic acid as a catalyst Scheme 1. These compounds are produced through combinations of domino Knoevenagel, aldol and Michael reactions (Figure 1).



Scheme 1: Synthesis of dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] derivatives

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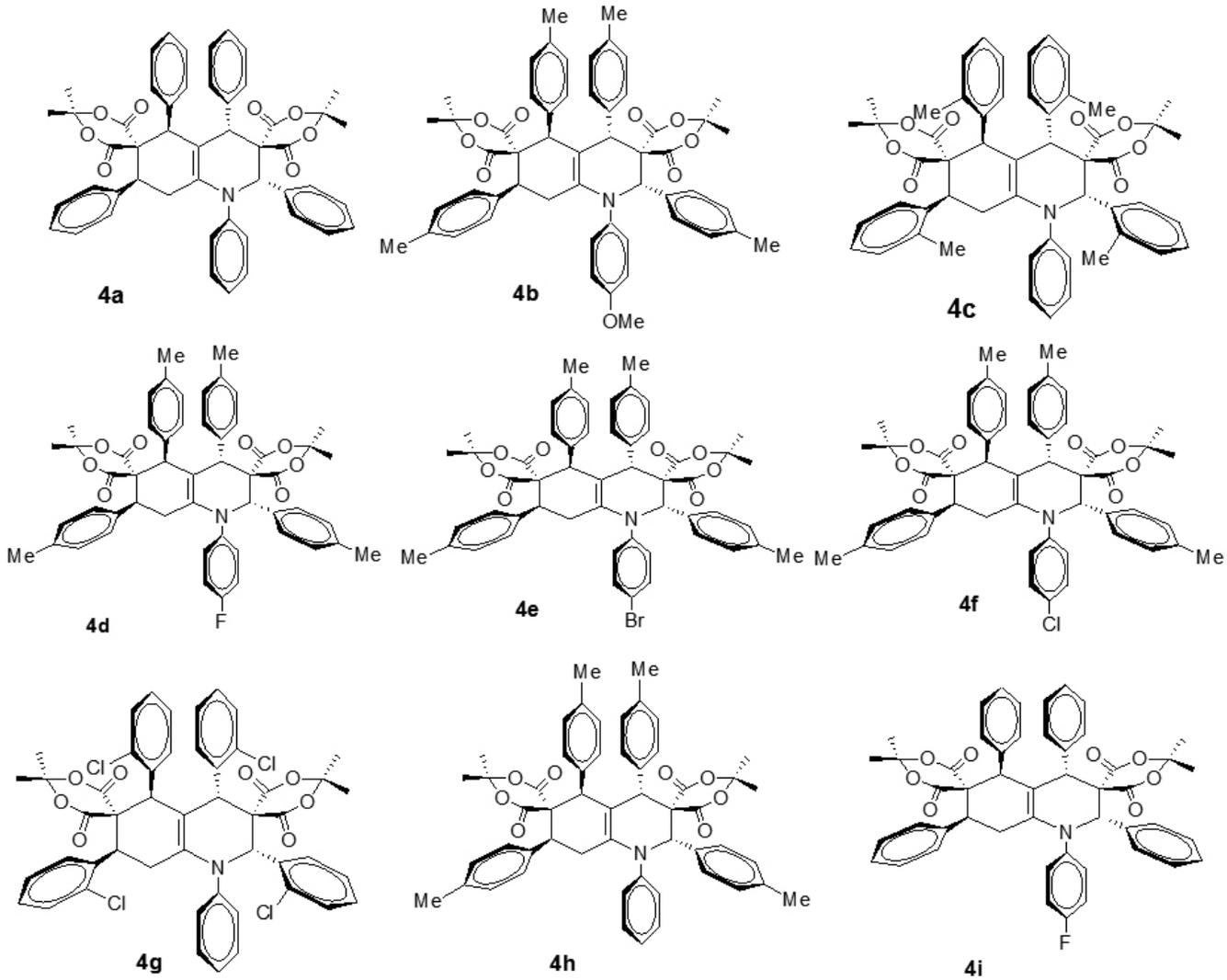


Figure 1 Structures of dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] derivatives **4a-i**

The reaction was just proceeded in the presence of salicylic acid, no product was detected in the absent of this catalyst. Therefore, in order to determine the appropriate concentration of the used catalyst, we investigated the reaction model at different concentrations of salicylic acid which resulted in different yields. Finally, we determined a solution of 18.2% salicylic acid is sufficient to push the reaction forward and higher amounts of the catalyst did not improve the results to any greater extent. Products have been characterized by IR, MS, ^{1}HNMR, ^{13}CNMR, and elmental analysis (Figure 2).

The suggested mechanism for this transformation is plotted in Scheme 2. In this reaction we proposed that firstly the domino Knoevenagel condensation of Meldrum's acid and aldehyde was done to provide benzylidene Meldrum's acid derivatives **A** [33]. Decomposition of Knoevenagel product releases acetone [24] which then undergoes condensation with amine to give imine **D** followed by enamine **E**. Next, **E** reacts with aldehyde to form reactive Barbas dienamine **G** (2-amino-1,3-butadiene) [24-32]. The latter acts as an activated 1,3-diene and a concerted [4+2] cycloaddition would take place with benzylidene as dienophiles (Diels-Alder), to yield enamine I [29]. Then, **I** adds to the Knoevenagel product (Michael addition) [34-36] and **K** could forms an iminium salt with the aldehyde which finally undergoes intramolecular reaction leading to 4.

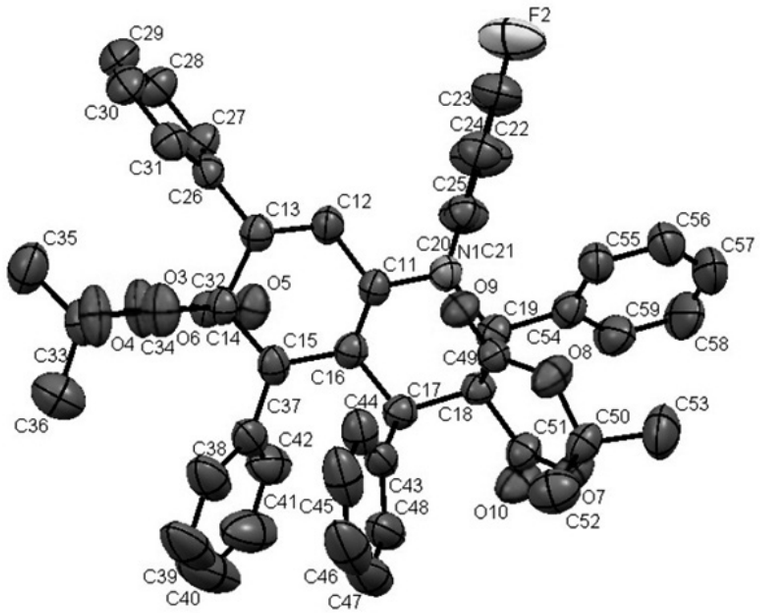
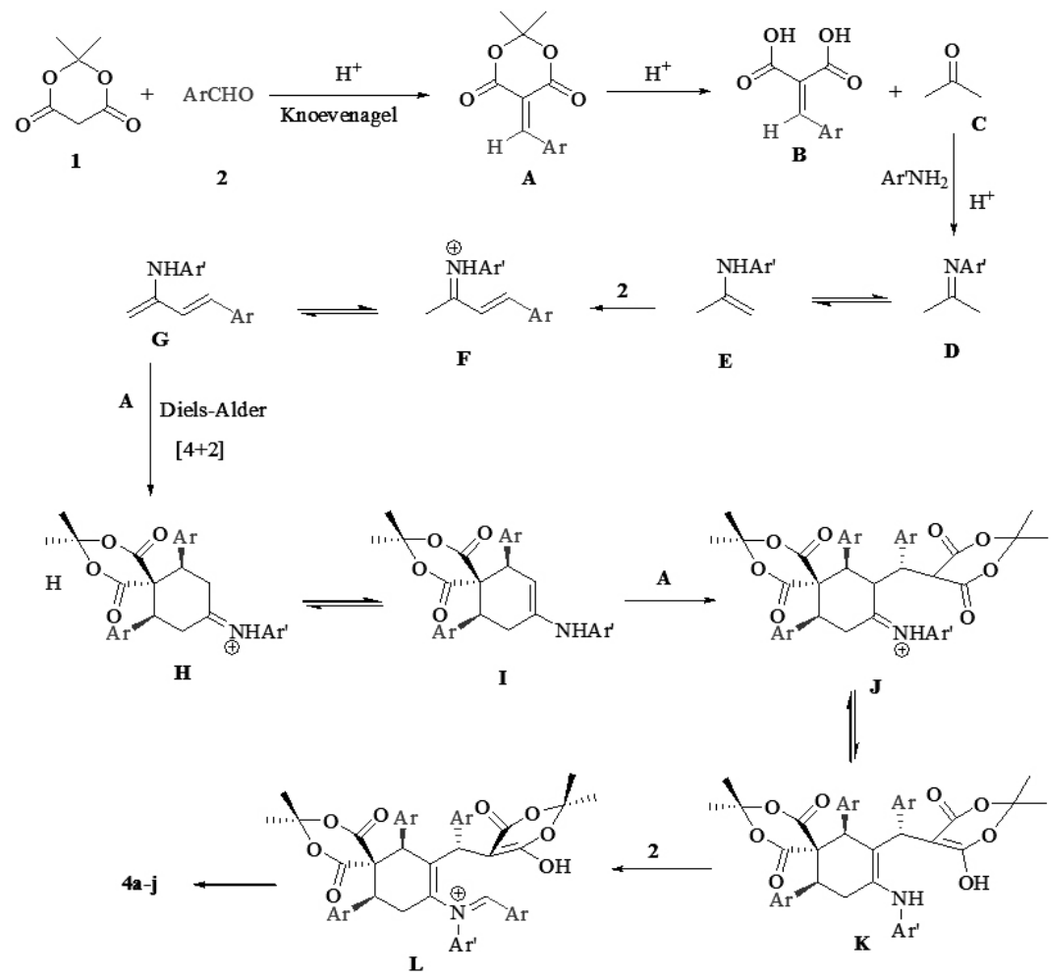


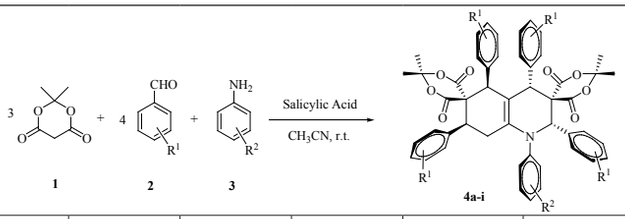
Figure 2 ORTEP representation of the x-ray structure of **4i.**



Scheme 2 Suggested mechanism for the synthesis of dispiro[tetrahydroquinoline-bis(2,2-dimethyl[1,3] dioxane-4,6-dione)] derivatives.

To examine the efficiency of this method, different aldehydes and arylamines were tested. The reactants were converted into the corresponding products with good yields. The results are summarized in Table 1.

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



Entry	R^1	R^2	Product	Yield (%)[a]	Ref.
1	H	H	**4a**	84	21
2	4-Me	4-OMe	**4b**	76	21
3	2-Me	H	**4c**	69	21
4	4-Me	4-F	**4d**	74	21
5	4-Me	4-Br	**4e**	79	21
6	4-Me	4-Cl	**4f**	76	21
8	2-Cl	H	**4g**	70	22
7	4-Me	H	**4h**	80	b
9	H	4-F	**4i**	75	b

[a] Isolated yield.
[b] The new compounds are synthesized in this work.

To compare the efficiency and applicability of salicylic acid with the reported catalysts in the literature for the synthesis of dispirohydroquinolines, we have tabulated the results of these catalysts in Table 2.

Table 2 Crystal data and structure refinement for $C_{49}H_{42}FNO_8$ (**4i**).

Entry	Catalyst	Yield	Ref.
1	(4-SB)T(4-SPh)$PHSO_4$	83	19
2	Citric Acid	84	20
3	Acetic acid	80	21
4	Benzoic Acid	82	22
5	Trichloroacetic acid	75	23
6	Salicylic acid	84	This Work

EXPERIMENTAL

Materials and Methods

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 1H- and 13C-NMR spectra were obtained from a Bruker DRX-400 Avance instrument (Germany) with CDCl3 as a solvent. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer (Germany). The mass spectra were recorded on an Agilent Technology (HP) mass spectrometer, operating at an ionization potential of 70 eV (Japan). All reagents were purchased from Merck (Darmastadt, Germany), or Fluka (Buchs, Switzerland), and used without further purification.

General procedure for Synthesis of Dispirohydroquinoline-bis(Meldrum's acid) 4a-i:

Meldrum's acid (3.0 mmol), aldehyde (4.0 mmol) and aniline (1.0 mmol) were added to solution of 18.2 % Salicylic acid in acetonitrile. After 24 h stirred at room temperature, the precipitate was collected by filtration and washed with acetonitrile (3 × 2 mL) to obtain the pure product. Spectral data of new products are represented below:

*1′-(Phenyl)-2′,4′,5′,7′-tetra(2-Chlorophenyl-1′H-dispiro[2′,4′,5′,7′,8′-tetrahydro-quinoline-5,3′:6′,5″-bis(2,2-dimethyl[1,3]dioxane-4,6-dione)] (**4g**)*

White powder; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.63 and 0.98 (2s, 12H, 4Me), 2.57-2.64 (m, 2H, H′,H″-8′), 4.74 (dd, 1H, J=11.2 Hz, J=6.4 Hz, H-7′), 4.99 and 5.06 (2s, 2H, H-4′, H-5′), 6.05 (s, 1H, H-2′), 6.97-7.88 (m, 21H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 28.1, 28.6 and 29.3 (4Me), 33.9 (C-8′), 42.6, 44.9 and 45.9 (C-4′, C-5′, C-7′), 57.9 and 58.3 (C-3′, C-6′), 64.9 (C-2′), 102.1 (C-4′a), 105.3 and 105.5 ($2CMe_2$), 126.1, 126.8, 126.9, 127.1, 127.9, 128.0, 128.4, 128.5, 128.8, 129.2, 129.3, 129.4, 129.6, 129.8, 130.1, 130.6, 131.4, 132.4, 132.3, 132.8, 133.4, 133.5, 133.8, 135.1, 136.0, 136.5, 136.9, 142.8 and 144.6 (C_{Ar}, C-8′a), 162.4, 164.8, 165.7 and 167.17 (4C=O);

*1′-Phenyl-2′,4′,5′,7′-tetra(4-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)] (**4h**)*

White powder; mp 241-244 °C; IR (KBr): ν 1768, 1736, 1662, 1594, 1511, 1490, 1284, 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.40, 0.43, 0.64 and 0.67 (4s, 12H, 4Me), 2.18, 2.23 and 2.24 (3s, 12H, 4ArMe), 2.46-2.65 (m, 2H, H′, H″-8′), 3.97 (dd, 1H, *J*=11.6 Hz, *J*=6.0 Hz, H-7′), 4.57 and 4.59 (2s, 2H, H-4′, H-5′), 5.20 (s, 1H, H-2′), 5.95 (d, 1H, *J*=8.0 Hz, H_{Ar}), 5.98 (dd, 1H, *J*=8.0 Hz, *J*=1.6 Hz, H_{Ar}), 6.55 (t, 2H, *J*=7.2, H_{Ar}), 6.90-7.45 (m, 17H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 20.9, 21.0 and 21.1 (4ArMe), 27.9, 28.3, 28.5 and 28,6 (4Me), 32.8 (C-8′), 47.3, 50.3 and 52.6 (C-4′, C-5′, C-7′), 61.8 and 61.9 (C-3′, C-6′), 69.9 (C-2′), 102.6 (C-4′a), 105.1 and 105.3 ($2CMe_2$), 126.3, 127.0, 128.3, 128.4, 128.6, 128.7, 128.8, 129.1, 129.2, 129.2, 129.3, 130.7, 131.2, 131.5, 132.2, 133.2, 134.2, 135.65, 136.6, 136.7, 137.5, 137.9, 142.0 and 144.7 (C_{Ar}, C-8′a), 162.0, 164.2, 168.4 and 169.7 (4C=O); MS (EI, 70 eV) m/z (%): 829 (M+, 1); Anal. Calcd for $C_{53}H_{51}NO_8$: C, 76.70; H, 6.19; N, 1.69. Found: C, 76.91; H, 6.28; N, 1.66.

*1′-(4-Flourophenyl)-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)] (**4i**)*

White powder; mp 242-244 °C; IR (KBr): ν 1765, 1730, 1654, 1600, 1509, 1287, 1223 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 0.37, 0.39, 0.62, 0.64 (4s, 12H, 4Me), 2.54 (dd, 1H, *J*=17.2 and *J*=5.6 Hz, H′-8′), 2.62-2.69 (m, 1H, H″-8′), 4.02 (dd, 1H, *J*=12.0 and *J*=5.2 Hz, H-7′), 4.64, 4.68 (2s, 2H, H-4′, H-5′), 5.20 (s, 1H, H-2′), 6.05 (d, 1H, *J*=7.6 Hz, H_{Ar}), 6.08 (d, 1H, *J*=8.0 Hz, H_{Ar}), 6.71-7.55 (m, 22H, H_{Ar}); ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 27.98, 28.21, 28.46, 28.52 (4Me), 32.80 (C-8′), 47.57, 50.78, 53.09 (C-4′, C-5′, C-7′), 61.45, 61.69 (C-3′, C-6′), 70.19 (C-2′), 102.78 (C-4′a), 105.37, 105.60 ($2CMe_2$), 127.14, 127.28, 128.04, 128.07, 128.09, 128.15, 128.54, 128.59, 128.78, 128.80, 129.21, 129.35, 129.44, 130.88, 131.30, 131.60, 135.05, 136.10, 137.09, 138.35 (C_{Ar}), 140.67 (d, J_{CF}=3.0 Hz, C_{Ar}), 142.13 (C-8′a), 160.81 (d, J_{CF}=246.0 Hz C_{Ar}-F), 161.93, 164.18, 168.06, 169.44 (4C=O); Anal. Calcd for $C_{49}H_{42}FNO_8$: C, 74.32; H, 5.35; N, 1.77. Found: C, 74.45; H, 5.13; N, 1.5. CCDC **971840**.

Crystal structure analysis

The X-ray diffraction measurements were made on a Xcalibur, Ruby, Gemini diffractometer with graphite-monochromated CuKα radiation (λ = 1.54180Å). A Colorless Prismatic crystal of the title compound, of dimensions 0.35× 0.30 × 0.10 mm3, was mounted on a glass fiber and used for data collection. The crystal structure was solved by direct methods. The intensities were measured using the ω scan method. A refined absorption correction was applied. Structure was refined using full-matrix least squares on F2. All non-H atoms were anisotropically refined. All H atoms were geometrically placed and H-atoms parameters were refined with constrained geometries. Crystallographic calculations were made at the University of Oviedo, on the X-ray group computers, using the following programs: CrysAlisPro [37] for data collection, cell refinement and data reduction; SIR2011 [38] for structure solution; SHELXL-97 [39] for the geometrical calculations; ORTEP-3 for windows [40] for molecular graphics; and Wingx [41] publication routines to prepare material for publication. Crystallographic data and the refinement procedures are given in Table 3, and selected bond lengths, bond angles, and torsion angles of 4i are listed in Table 4. An ORTEP view of the molecule is reported in Figure 2.

Table 3 Selected Bond Lengths (Å), Bond Angles (°) and Torsion Angles for compound **4i.**

Formula	$C_{49}H_{42}FNO_8$
Formula weight	791.84
Temperature(K)	293(2)
Wavelenght (Å)	1.54180
Crystal system	Orthorhombic
Space group	P_{bca}
Crystal size/mm^3	0.35 × 0.30 × 0.10
Unit cell dimentions	a=22.4162(7)
	b=16.2028(6)
	c=22.6814(6)
Volume	8238.0(5)
Z	8
Density(calculated) g cm^{-3}	1.277
Theta ranges for data collection	3.8750-59.3200
F(000)	3328.0
Absorption coefficient	0.732
Index ranges	-26≤h≤27
	-19≤k≤19
	-27≤l≤27
Data collected	38853
Unique data (R_{int})	[R(int) = 0.0804]
parameters / restraints	0 / 532
Final R_1, wR_2[a] (Obs. data)	0.0660, 0.1508
Final R_1, wR_2[a] (all data)	0.1354, 0.1884
bsolute structure parameter Goodness of fit on F2 (S)	1.043
CCDC	971840
[a]R1 = Σ||Fo|-|Fc||/Σ|F_o|, wR2 = [Σ[w(F_o^2-F_c^2)^2]/Σ[w(F_o^2)^2]]	

Table 4 Selected Bond Lengths (Å), Bond Angles (°) and Torsion Angles for compound **4i.**

Bond Lengths	*(Å)*	*Bond Angles*	*(°)*	*Torsion Angles*	*(°)*
N1 -C11	1.414(4)	C11 -N1 -C19	118.0(2)	N1 -C11 -C16 -C15	179.6(3)
N1 -C19	1.461(4)	N1-C19 -C18	110.3(3)	N1 -C11 -C16 -C17	2.3(5)
C11 -C16	1.340(4)	C17 -C18 -C19	109.2(2)	C12 -C11 -C16 -C15	2.8(5)
C18 -C19	1.573(4)	C16 -C17 -C18	112.1(3)	N1 -C11 -C12 -C13	-162.1(3)
C17 -C18	1.565(4)	C15 -C16 -C17	115.1(3)	C11 -C12 -C13 -C14	-45.8(4)
C16 -C17	1.523(4)	C14 -C15 -C16	114.6(3)	C12 -C13 -C14 -C15	57.8(3)
C15 -C16	1.529(4)	C13 -C14 -C15	108.5(2)	C13 -C14 -C15 -C16	-40.5(4)
C14 -C15	1.563(4)	C12 -C13 -C14	111.5(3)	C14 -C15 -C16 -C11	11.5(4)
C13 -C14	1.573(5)	C11 -C12 -C13	114.5(3)	C19 -N1 -C11 -C16	13.5(5)
C12 -C13	1.518(5)	N1 -C11 -C12	113.8(3)	C11 -N1 -C19 -C18	-43.3(4)
C11 -C12	1.494(4)	H12A -C12 -H12B	108.00	N1 -C11 -C16 -C17	2.3(5)
		C26 -C13 -H13	106.00	C16 -C17 -C18 -C19	-42.3(3)
		C54 -C19 -H19	107.00	C11 -C16 -C17 -C18	14.2(4)
		C43 -C17 -H17	106.00	C12 -C11 -C16 -C17	-174.5(3)
		C37 -C15 -H15	105.00	C20 -N1 -C11 -C12	-22.0(4)
		C26 -C13 -H13	106.00	C20 -N1 -C19 -C18	168.3(2)
		C11 -N1 -C20	118.3(2)	C20 -N1 -C19 -C54	42.7(4)
		C19 -N1 -C20	115.7(3)	C11 -C12 -C13 -C26	-173.8(3)
				C26 -C13 -C14 -C15	-174.3(3)
				C13 -C14 -C15 -C37	-170.8(3)
				C37 -C15 -C16 -C17	-41.3(4)
				C15 -C16 -C17 -C43	-35.6(4)
				C11 -C16 -C17 -C43	141.9(3)
				C37 -C15 -C16 -C11	141.2(3)
				C43 -C17 -C18 -C19	-172.7(3)

CONCLUSION

In conclusion, we reported a mild and efficient method for the synthesis of dispirohydroquinoline-bis(Meldrum's acid) derivatives via a one-pot domino eight-component reaction using salicylic acid as a catalyst for the first time. The easy work-up procedure, inexpensive catalyst and very good yields make this method a valid contribution to the existing methodologies. The claimed product was confirmed by IR, mass, ^{1}H NMR, ^{13}CNMR spectroscopy, and elemental analyses. The stereoselectivity of product was demonstrated by X-ray crystallography and NMR spectroscopy.

ACKNOWLEDGMENT

We gratefully acknowledgement financial support for this project from the Research Council of 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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