An efficient one-pot, three-component synthesis of indeno[1,2-*b*]quinoline-9,11(6*H*,10*H*)-dione, acridine-1,8(2*H*,5*H*)-dione and quinoline-3-carbonitrile derivatives from enaminones†

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Received 30th May 2006, Accepted 3rd August 2006
First published as an Advance Article on the web 17th August 2006
DOI: 10.1039/b607575d

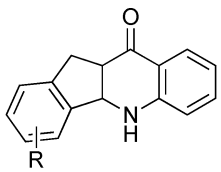
An efficient one-pot, three-component method for the preparation of indeno[1,2-*b*]quinoline-9,11(6*H*,10*H*)-dione, acridine-1,8(2*H*,5*H*)-dione and various multi-substituted quinoline-3-carbonitrile derivatives has been developed through the Michael addition to enaminones, which was achieved by both microwave irradiation and conventional heating.

Introduction

Multi-component reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy and applications in combinatorial chemistry.[1] They have inherent advantages over two-component reactions in several aspects: the simplicity of a one-pot procedure, possible structure variations, complicated synthesis and the large number of accessible compounds.[2] Nevertheless, continued efforts are being made to explore new MCRs for developing popular organic reactions.[3]

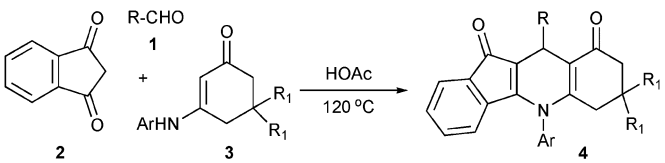
Enaminones and related compounds possessing the structural unit (N–C=C–Z, Z=COR, CO_2R, CN, *etc.*) are versatile synthetic intermediates in organic chemistry that combine the ambient nucleophilicity of enamine and the electrophilicity of enones.[4] They are frequently applied in the preparation of heterocycles.[5]

1,4-Dihydropyridines (1,4-DHPs) are well-known compounds because of their pharmacological profiles as calcium channel modulators.[6] Chemical modifications of the DHP ring such as the introduction of different substituents or heteroatoms[7] have allowed expansion of the research of structure–activity relationships, affording new insights into the molecular interactions at the receptor level. With a 1,4-DHP parent nucleus, indenoquinoline derivatives have showed a diverse range of biological properties such as 5-HT-receptor binding[8] and anti-inflammatory activities.[9] They have also acted as antitumor agents,[10] steroid reductase inhibitors,[11] acetylcholinesterase inhibitors,[12] antimalarials,[13] and new potential topo I/II inhibitors.[14] Because of the biological activities they exhibit, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus the synthesis of these molecules has attracted considerable attention.[15] Recently, the synthesis of indeno[1,2-*b*]quinolin-10-one derivatives (**a**, Fig. 1) was reported by Lee and co-workers.[16] However, the synthesis of new heterocyclic compounds containing the indenoquinoline scaffold and the development of more rapid and efficient entry to these heterocycles are strongly desired. In connection with our previous study modifying the 1,4-DHP scaffold,[17] in this paper we report a rapid and efficient method for synthesizing new heterocyclic compounds containing indenoquinoline unit using enaminones as the precursors (Scheme 1).



a

Fig. 1



Scheme 1

Result and discussion

When treating aldehyde **1** with 1,3-indanedione **2** and enaminone **3** under microwave irradiation, the target compounds **4** were obtained. We first chose 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone **3b** and investigated the optimized conditions for its reaction with 4-bromobenzaldehyde **1q** and 1,3-indanedione **2** affording indeno[1,2-*b*]quinoline-9,11(6*H*,10*H*)-dione derivatives **4q** under microwave irradiation (microwave oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden) (Scheme 2). In this three-component reaction, we found that the temperature and solvent had a significant effect on reaction yields (Scheme 2 and Table 1).

As shown in Table 1, in the presence of acetic acid, when the temperature was at 80 °C under microwave irradiation, reaction of *p*-bromobenzaldehyde **1q** with 5,5-dimethyl-3-(phenylamino)cyclohex-2-enone **3b** gave 2-(4-bromobenzylidene)-indene-1,3-dione as main product and only trace amount of **4q**

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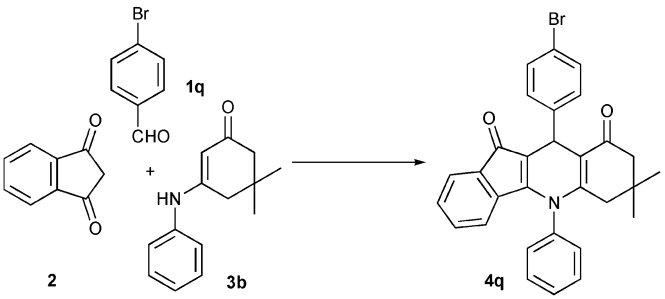
† Electronic supplementary information (ESI) available: Characterization data. See DOI: 10.1039/b607575d

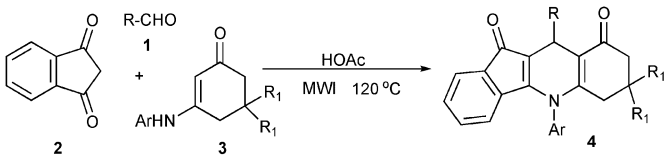


Scheme 2

Table 1 Optimization of reaction conditions for the preparation of compound **4q**

Entry	Solvent	T/°C	Time/min	Yield (%)
1	HOAc	80	10	13
2	HOAc	90	12	63
3	HOAc	100	8	80
4	HOAc	110	6	85
5	HOAc	120	4	91
6	HOAc	130	4	90
7	Glycol	120	8	37
8	DMF	120	10	84
9	Water	120	12	82

was formed. When the temperature was increased from 80 °C to 120 °C, the yield of product **4q** was increased and the reaction time was shortened. However, further increase of the temperature to 130 °C failed to improve the yield of product **4q**. Therefore, 120 °C was chosen as the optimum temperature for all further microwave-assisted reactions. For optimization of the reaction solvent, the same reaction was carried out at 120 °C in various solvents such as glycol, DMF, acetic acid, and water. The reaction using acetic acid gave the best result (Table 1). A series of aldehydes and enaminones were applied under microwave irradiation conditions in this reaction to afford a new type of heterocyclic compounds, the indeno[1,2-*b*]quinoline-9,11(6*H*,10*H*)-dione derivatives **4** (Scheme 3). The initial results are summarized in Table 2.



Scheme 3

As shown in Table 2, the scope of the reaction with regard to the aldehyde is quite large. Not only aromatic aldehydes containing

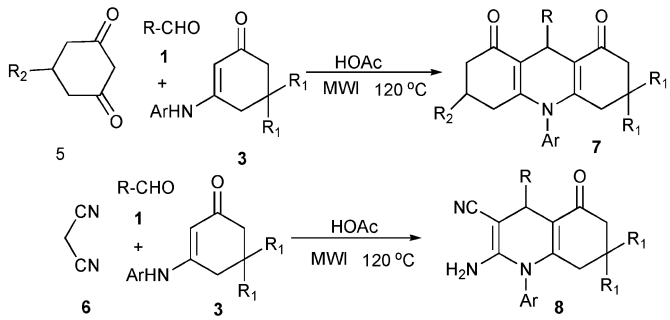
Table 2 Synthesis of compounds **4**, **7**, **8** and **9**

Entry	Product	R	**3**	Ar	R_1	R_2	Time	Yield (%)[c]	Mp/°C
1	**4a**	4-OH-3-$NO_2C_6H_3$	**3a**	4-$CH_3C_6H_4$	CH_3	—	4[a], 2.5[b]	90[a], 88[b]	265–266
2	**4b**	4-$CH_3C_6H_4$	**3a**	4-$CH_3C_6H_4$	CH_3	—	6[a], 3.5[b]	87[a], 87[b]	283–285
3	**4c**	4-$NO_2C_6H_4$	**3a**	4-$CH_3C_6H_4$	CH_3	—	4[a], 2.0[b]	92[a], 91[b]	290–291
4	**4d**	4-FC_6H_4	**3a**	4-$CH_3C_6H_4$	CH_3	—	4[a], 2.5[b]	88[a], 85[b]	225–227
5	**4e**	3,4-$OCH_2OC_6H_3$	**3a**	4-$CH_3C_6H_4$	CH_3	—	7[a], 4.0[b]	85[a], 82[b]	258–260
6	**4f**	4-BrC_6H_4	**3a**	4-$CH_3C_6H_4$	CH_3	—	4[a], 3.0[b]	91[a], 90[b]	255–256
7	**4g**	3,4,5-$(CH_3O)_3C_6H_2$	**3a**	4-$CH_3C_6H_4$	CH_3	—	5[a], 4.5[b]	87[a], 88[b]	168–170
8	**4h**	2,4-$Cl_2C_6H_3$	**3a**	4-$CH_3C_6H_4$	CH_3	—	4[a], 2.0[b]	93[a], 92[b]	291–293
9	**4i**	4-(Benzo[*d*]oxazol-2-yl)C_6H_4	**3a**	4-$CH_3C_6H_4$	CH_3	—	5[a], 2.5[b]	92[a], 89[b]	277–278
10	**4j**	$CH_3(CH_2)_2CH_2$	**3a**	4-$CH_3C_6H_4$	CH_3	—	10[a], 4.5[b]	85[a], 86[b]	260–261
11	**4k**	$CH_3(CH_2)_{10}CH_2$	**3a**	4-$CH_3C_6H_4$	CH_3	—	9[a], 5.0[b]	88[a], 85[b]	167–169
12	**4l**	3-$NO_2C_6H_4$	**3b**	C_6H_5	CH_3	—	4[a], 2.5[b]	92[a], 90[b]	242–244
13	**4m**	4-$CH_3OC_6H_4$	**3b**	C_6H_5	CH_3	—	6[a], 3.0[b]	86[a], 87[b]	250–251
14	**4n**	4-OH-3-$CH_3OC_6H_3$	**3b**	C_6H_5	CH_3	—	6[a], 4.0[b]	88[a], 82[b]	272–274
15	**4o**	C_6H_5	**3b**	C_6H_5	CH_3	—	5[a], 2.5[b]	90[a], 85[b]	257–258
16	**4p**	2-Thienyl	**3b**	C_6H_5	CH_3	—	8[a], 3.5[b]	85[a], 87[b]	230–232
17	**4q**	4-BrC_6H_4	**3b**	C_6H_5	CH_3	—	4[a], 3.0[b]	91[a], 90[b]	283–284
18	**4r**	4-ClC_6H_5	**3b**	C_6H_5	H	—	4[a], 3.5[b]	91[a], 89[b]	236–237
19	**4s**	3,4-$(CH_3O)_2C_6H_3$	**3a**	4-$CH_3C_6H_4$	H	—	6[a], 4.5[b]	90[a], 86[b]	257–259
20	**7a**	4-BrC_6H_4	**3a**	4-$CH_3C_6H_4$	CH_3	CH_3	2[a],1.5[b]	93[a], 90[b]	229–230
21	**7b**	3,4-$OCH_2OC_6H_3$	**3a**	4-$CH_3C_6H_4$	CH_3	CH_3	4[a], 2.0[b]	92[a], 91[b]	168–169
22	**7c**	4-OH-3-$NO_2C_6H_3$	**3b**	C_6H_5	CH_3	CH_3	2[a], 1.0[b]	94[a], 92[b]	216–218
23	**7d**	2,4-$Cl_2C_6H_3$	**3b**	C_6H_5	CH_3	C_6H_5	2[a], 1.0[b]	95[a], 93[b]	>300
24	**7e**	4-(Benzo[*d*]oxazol-2-yl)C_6H_4	**3b**	C_6H_5	CH_3	C_6H_5	3[a], 2.0[b]	89[a], 92[b]	291–292
25	**7f**	2-Thienyl	**3a**	4-$CH_3C_6H_4$	CH_3	C_6H_5	3[a], 1.5[b]	90[a], 91[b]	297–299
26	**8a**	2,4-$Cl_2C_6H_3$	**3b**	C_6H_5	CH_3	—	7[a], 4.0[b]	87[a], 88[b]	256–258
27	**8b**	3,4-$OCH_2OC_6H_3$	**3a**	4-$CH_3C_6H_4$	CH_3	—	8[a], 3.0[b]	86[a], 85[b]	277–279
28	**8c**	4-$NO_2C_6H_4$	**3b**	C_6H_5	CH_3	—	6[a], 3.5[b]	90[a], 87[b]	294–295
29	**8d**	4-ClC_6H_5	**3a**	4-$CH_3C_6H_4$	H	—	8[a], 3.0[b]	85[a], 83[b]	262–264
30	**8e**	3-$NO_2C_6H_4$	**3a**	4-$CH_3C_6H_4$	H	—	5[a], 3.5[b]	91[a], 89[b]	235–236
31	**8f**	3-$NO_2C_6H_4$	**3b**	C_6H_5	H	—	7[a], 3.5[b]	92[a], 89[b]	260–262
32	**9a**	1,4-$CHOC_6H_4$	**3a**	4-$CH_3C_6H_4$	CH_3	—	5[a], 4.0[b]	90[a], 91[b]	289–290
33	**9b**	1,3-$CHOC_6H_4$	**3b**	C_6H_5	CH_3	—	6[a], 3.5[b]	91[a], 89[b]	296–297
34	**9c**	1,4-$CHOC_6H_4$	**3b**	C_6H_5	CH_3	—	5[a], 4.5[b]	89[a], 90[b]	>300

[a] The time (min) and the yield of the product under microwave irradiation at 120 °C. [b] The time (h) and the yield of the product by using the traditional heating mode at 120 °C. [c] Isolated yields.

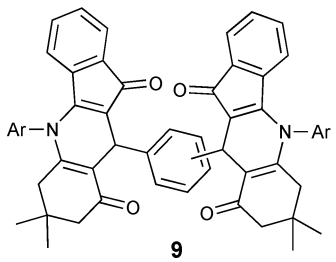
either electron-withdrawing groups or electron-donating groups can be used, dialdehydes, aliphatic and heterocyclic aldehydes gave also excellent results. A range of indeno[1,2-*b*]quinoline-9,11(6*H*,10*H*)-diones **4** have been conveniently synthesized in high yields.

In order to examine the applicability of this new three-component cyclocondensation reaction to other active methylene compounds, we employed 5-substituted-cyclohexane-1,3-dione **5** or malononitrile **6** instead of 1,3-indanedione **2** in the reaction with aldehydes **1** and enaminones **3** (Scheme 4). The results (Table 2) show that a wide range of aldehydes including aromatic aldehydes with either electron-withdrawing or electron-donating groups and heterocyclic aldehydes can likewise take part in this reaction, leading to the preparation of a series of acridine-1,8(2*H*,5*H*)-diones **7** or multi-substituted quinolines **8.**



Scheme 4

Furthermore, we have synthesized bifunctional compounds containing two indenoquinoline units (**9**) using *o*-phthalaldehyde and *p*-phthalaldehyde as precursors (Scheme 5).



Scheme 5

Additionally, all the reactions were performed at 120 °C under classical heating conditions in acetic acid. A comparison of the results for the 34 compounds listed in Table 2 indicated that the reactions are efficiently promoted by microwave irradiation, and when almost quantitative yields were obtained, the reaction time was strikingly shortened from 1.0–4.5 h in traditional heating conditions to 2–10 min under microwave irradiation.

All the products were characterized by IR, ^{1}H NMR and elemental analyses. The structure of **4g** was established by an X-ray crystallographic analysis (Fig. 2).[18] The IR spectrum of compound **4g** shows C=O stretchings at 1686 cm^{-1} and 1634 cm^{-1}. It is particularly noteworthy that in the ^{1}H NMR spectra of compounds (**4a–s** and **9a–c**), two absorption peaks appeared at 4.91 ppm and 5.35 ppm, which belonged to the aromatic

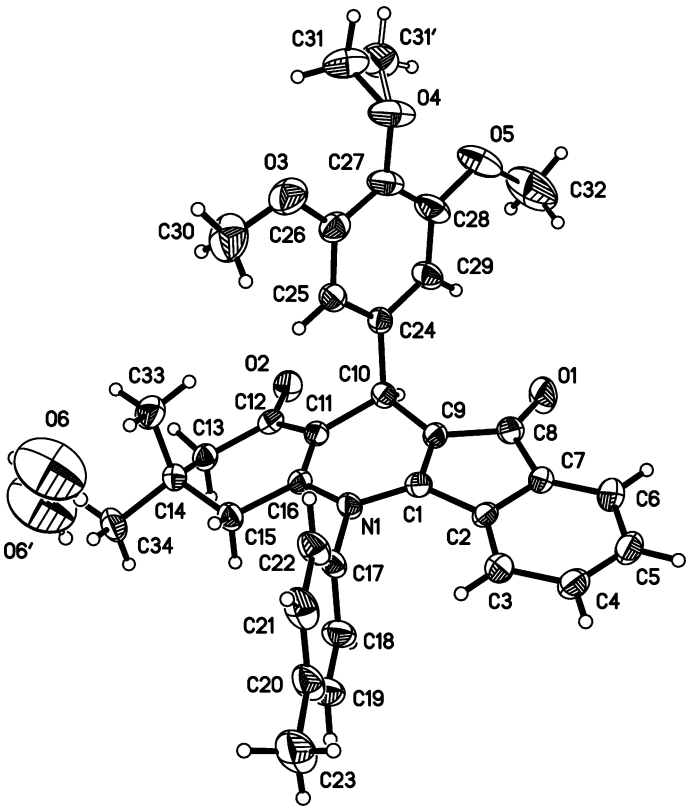


Fig. 2 Crystal structure of **4g**.

protons (see ^{1}H NMR data). This could be explained by the X-ray structure of **4g**. In the crystal structure of **4g** (Fig. 2), the distance between the protons at C_3 and the phenyl ring (C_{17} to C_{22}) is 2.46 Å, indicating that the proton at C_3 is shielded by the benzene ring (C_{17} to C_{22}), which caused its ^{1}H NMR absorption to be shifted to upfield and it appeared as a doublet at 5.19 ppm.

Conclusion

In summary, we have demonstrated a rapid and direct method that offered a simple and efficient route for one-pot, three-component synthesis of highly functionalized indeno[1,2-*b*]quinoline-9,11(6*H*,9*H*)-dione, acridine-1,8(2*H*,5*H*)-dione and poly-substituted quinoline-3-carbonitrile derivatives in excellent yields. Particularly valuable features of this method, which was achieved by both microwave irradiation and conventional heating, include high yields, broad substrate scope and convenient operation. This series of indeno[1,2-*b*]quinoline, and acridine-1,8(2*H*,5*H*)-dione, poly-substituted quinoline-3-carbonitrile derivatives may prove to be of biological interest and provide new classes of compounds for biomedical screening.

Experimental

General

Microwave irradiation was carried out with microwave oven Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are

uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR spectra were measured on a Bruker DPX 400 MHz spectrometer in DMSO-d_6 with chemical shifts (δ) given in ppm relative to TMS as internal standard. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General procedure for the synthesis of enaminones 3 with microwave irradiation in a monomodal Emrys™ Creator microwave

The reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 20 mL Emrys™ reaction vial, aromatic amine (11 mmol), dimedone (10 mmol) or cyclohexane-1,3-dione (10 mmol) and water (3 mL) were mixed and then capped. The mixture was irradiated for 6 min with 200 W power at 100 °C. The reaction mixture was cooled to room temperature and then poured into cold water. The solid product was filtered, washed with water and EtOH (95%), and recrystallized from acetone to give the pure product.

General procedure for the synthesis of compounds 4, 7, 8 and 9 with microwave irradiation in a monomodal Emrys™ Creator microwave

All the reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10 mL Emrys™ reaction vial, aldehyde (**1**, 1 mmol), 1,3-indanedione (**2**, 1 mmol) (or 5-substituted-cyclohexane-1,3-dione (**5**, 1 mmol) or malononitrile (**6**, 1 mmol)), enaminone (**3**, 1 mmol) and acetic acid (1.0 mL) were mixed and then capped. The mixture was irradiated for a certain time (Table 2) at a power of 200 W at 120 °C. Upon completion of the reaction as indicated by TLC monitoring, the reaction mixture was cooled to room temperature and then poured into cold water. The solid product was filtered, washed with water and EtOH (95%), and subsequently dried and recrystallized from EtOH (95%) to give the pure product.

General procedure for the synthesis of compounds 4, 7, 8 and 9 with conventional heating

A mixture containing aldehyde (**1**, 1 mmol), 1,3-indanedione (**2**, 1 mmol) (or 5-substituted-cyclohexane-1,3-dione (**5**, 1 mmol) or malononitrile (**6**, 1 mmol)), enaminone (**3**, 1 mmol) and acetic acid (1.0 mL) was introduced into a 10 mL Emrys™ reaction vial, the vial was capped and the mixture was then stirred at 120 °C (oil bath temperature) for the designated time. When the reaction was completed (TLC monitoring), work-up as mentioned above gave the product.

4g. IR (KBr, ν, cm^{-1}): 2956, 2833, 1687, 1644, 1457, 1491, 1365, 1126, 888; ^1H NMR (DMSO-d_6) (δ, ppm): 7.54–7.48 (m, 4H, ArH), 7.27 (d, 1H, ArH, $J = 6.8$ Hz), 7.18 (t, 1H, ArH, $J = 7.4$ Hz), 7.01 (t, 1H, ArH, $J = 7.6$ Hz), 6.59 (s, 2H, ArH), 5.19 (d, 1H, ArH, $J = 7.6$ Hz), 4.82 (s, 1H, CH), 3.76 (s, 6H, CH_3), 3.61 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 2.48 (d, 1H, CH_2, $J = 16.4$ Hz), 2.31 (d, 1H, CH_2, $J = 17.6$ Hz), 2.10 (d, 1H, CH_2, $J = 16.4$ Hz), 2.03 (d, 1H, CH_2, $J = 17.6$ Hz), 0.97 (s, 3H, CH_3), 0.93 (s, 3H, CH_3). Anal calcd. for $C_{34}H_{33}NO_5$, C, 76.24; H, 6.21; N, 2.61; found C, 76.35; H, 6.25; N, 2.55%.

7a. IR (KBr, ν, cm^{-1}): 3033, 2956, 2929, 2870, 1634, 1575, 1484, 1363, 1223, 1009, 840, 763; ^1H NMR (DMSO-d_6) (δ, ppm): 7.44–7.40 (m, 5H, ArH), 7.25 (d, 3H, ArH, $J = 8.0$ Hz), 4.99 (s, 1H, CH), 2.42 (s, 3H, CH_3), 2.33–2.00 (m, 5H, CH_2), 1.98–1.84 (m, 4H, CH_2), 0.88 (s, 3H, CH_3), 0.78 (d, 3H, CH_3, $J = 6.4$ Hz), 0.66 (s, 3H, CH_3); Anal calcd. for $C_{29}H_{30}BrNO_2$, C, 69.05; H, 5.99; N, 2.78; found C, 69.17; H, 5.91; N, 2.84%.

8a. IR (KBr, ν, cm^{-1}): 3459, 3321, 3214, 2959, 2870, 2179, 1651, 1592, 1564, 1374, 1258, 1042, 871, 832, 743; ^1H NMR (DMSO-d_6) (δ, ppm): 7.62–7.53 (m, 4H, ArH), 7.47–7.40 (m, 4H, ArH), 5.34 (s, 2H, NH_2), 4.99 (s, 1H, CH), 2.42 (d, 1H, CH_2, $J = 17.6$ Hz), 2.18 (d, 1H, CH_2 $J = 16.4$ Hz), 1.97 (d, 1H, CH_2, $J = 16.4$ Hz), 1.75 (d, 1H, CH_2, $J = 17.6$ Hz), 0.89 (s, 3H, CH_3), 0.80 (s, 3H, CH_3); Anal calcd. For $C_{24}H_{21}Cl_2N_3O$, C, 65.76; H, 4.83; N, 9.59; found C, 65.81; H, 4.79; N, 9.56%.

Acknowledgements

We are grateful for financial support from the National Science Foundation of China (No. 20372057) and Natural Science Foundation of the Jiangsu Province (No. BK2006033).

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18 The single-crystal growth was carried out in ethanol at room temperature. X-Ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer. Crystal data for **4g**:$C_{34}H_{33}NO\cdot\frac{1}{2}H_2O$, red, crystal dimension 0.50 × 0.46 × 0.26 mm, monoclinic, space group $C2/c$, a = 25.094(6) Å, b = 12.755(3) Å, c = 19.891(5) Å, $\alpha = \gamma = 90°$, β = 103.926(4)°, V = 6179(3) Å^3, M_r = 544.62, Z = 8, D_c = 1.171 Mg m^{-3}, λ (Mo-Kα) = 0.71073 Å, μ = 0.079 mm^{-1}, $F(000)$ = 2312, 2.62° < θ < 25.01°, R = 0.0741, wR_2 = 0.1786. S = 0.999, Largest diff. Peak and hole: 0.700 and −0.248 e Å^{-3}. CCDC reference number 602003. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b607575d.

