A Simple Procedure for the Synthesis of 4-Aza-podophyllotoxin Derivatives in Water under Microwave Irradiation Conditions

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Abstract: 4-Aza-podophyllotoxin derivatives were synthesized via the three-component reaction of an aldehyde, an aromatic amine, and either tetronic acid or 1,3-indanedione in water under microwave irradiation conditions. This new protocol has the advantages of higher yield, lower cost, reduced environmental impact, and convenient procedure.

Key words: multicomponent reactions, heterocycles, indenoquinoline, 4-aza-podophyllotoxin, microwave irradiation

Multicomponent reactions, in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon–carbon bonds in synthetic chemistry.[1] Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoiding complicated purification operations and allowing savings of both solvents and reagents. Organic reactions accelerated by microwave irradiation have attracted considerable attention over the past number of years for the efficient synthesis of a variety of organic compounds.[2] The use of microwave irradiation for the formation of carbon–heteroatom and carbon–carbon bonds has been successfully demonstrated.[3]

The use of water as a solvent has many advantages in organic synthesis from both economic and environmental points of view.[4] Water has therefore become an attractive medium for many organic reactions, not only as one can avoid to use drying reactants and expensive catalysts and solvents, but also for its unique reactivity and selectivity.[5,6]

Podophyllotoxin **1** (Figure 1) is an anti-tumor lignan that inhibits microtubule assembly. Attempts to use it for the treatment of human neoplasia were mostly unsuccessful and were complicated by side effects. Extensive structural modifications have been performed in order to obtain more potent and less toxic anticancer agents. Among them, 4-aza-podophyllotoxin (**2**, Figure 1) has attracted much attention recently.[7] Takeya and co-workers[7a,b] reported the synthesis of 4-aza-podophyllotoxin derivatives via the sequence condensation, cyclization, and reduction. However, this method was less efficient and the scope was limited. Tratrat et al.[7c] also reported the synthesis of 4-aza-podophyllotoxin derivatives by the one-pot reaction of an aldehyde, tetronic acid, and an aniline in refluxing ethanol with the limitation that the aniline must be substituted in the *meta*-position by an electron-donating group.

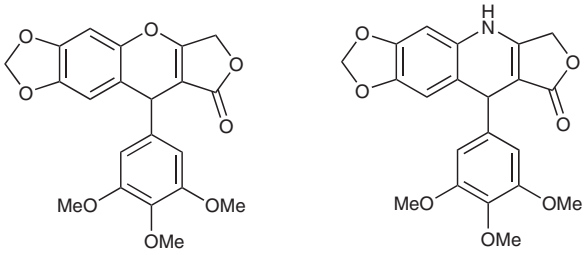
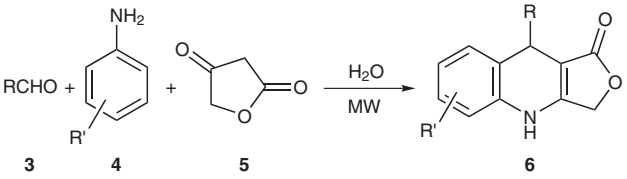


Figure 1 Structures of podophyllotoxin **1** and 4-aza-podophyllotoxin **2**

In continuation of our recent interest in the synthesis of heterocyclic compounds,[8] we herein developed a green multicomponent reaction consisting of aldehyde **3**, aromatic amine **4**, and tetronic acid **5** in water under microwave irradiation conditions without using any catalyst to afford a new series of 4-aza-podophyllotoxin derivatives **6** (Scheme 1).



Scheme 1

Choosing an appropriate solvent is of crucial importance for the successful microwave-assisted synthesis. To search for the optimal solvent, the reaction of 4-bromophenyl aldehyde (**3b**), *p*-toluidine (**4b**), and tetronic acid (**5**) was examined using water, glycol, DMF, glacial acetic acid, and ethanol as solvents, respectively, at 80 °C under microwave irradiation conditions. All the reactions were carried out at the maximum power of 300 W (Table 1).

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As shown in Table 1, the reactions using glycol or water as the solvent resulted in higher yields and shorter reaction times than those using acetic acid, DMF, and ethanol as solvents. Water was used as the solvent for all further microwave-assisted reactions as it is environmentally friendly and the use of toxic organic reagents can be avoided.

Table 1 Solvent Optimization for the Synthesis of **6c** under Microwave Irradiation Conditions at 80 °C

Entry	Solvent	Power (W)	Time (min)	Yield (%)
1	glycol	300	12	86
2	H_2O	300	12	85
3	AcOH	300	15	71
4	DMF	300	16	63
5	EtOH	300	18	60

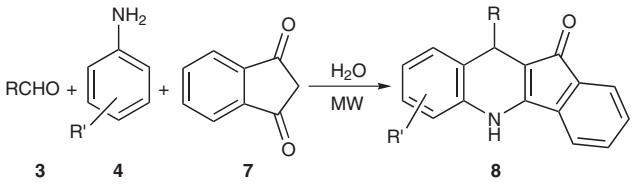
To optimize the reaction temperature, the synthesis of **6c** was performed using water as the solvent at temperatures ranging from 80 to 120 °C, with an increment of 10 °C each time. The yield of product **6c** was increased and the reaction time was shortened when the temperature was increased from 80 °C to 100 °C. The yield levelled off when the temperature was further increased to 110 and 120 °C. Therefore, the most suitable temperature should be 100 °C.

The power of microwave irradiation was optimized by carrying out the same reaction for the synthesis of **6c** at 50, 100, 150, 200, 250, and 300 W respectively, using water as the solvent. At 50 W and 100 W, the time taken for the temperature to reach 100 °C was too long. Microwave irradiation at 150 W generated the highest yield, and the highest temperature reached during the reaction was 103 °C. Therefore, microwave power of 150 W was chosen as the optimal power.

Furthermore, the volume of water was important as well to the yields of the reactions. The synthesis of **6c** was tested in different volumes of water at 100 °C under microwave irradiation conditions. When 2.0 mL of water was used as solvent for the reaction [4-bromophenyl aldehyde (**3b**, 1 mmol), *p*-toluidine (**4b**, 1 mmol), tetronic acid (**5**, 1 mmol)], the yield was the highest.

Under the optimized conditions [water (2.0 mL), 100 °C, 150 W], the 4-aza-podophyllotoxin derivatives **6** were synthesized[9] (Table 2).

In order to expand the scope of the present method, the replacement of tetronic acid (**5**) with 1,3-indanedione **7** was examined. This is particularly attractive because indenoquinoline is one of the most important 'privileged scaffolds'. Compounds with this motif show a wide range of biological activities such as 5-HT-receptor binding[10a] and anti-inflammatory activities,[10b] and also act as anti-tumor agents,[10c,d] inhibitors for steroid reductase,[10e] acetylcholinesterase inhibitors,[10f] and antimalarials.[10g] To our delight, under the above optimized conditions, the reactions proceeded smoothly. The indeno[1,2-*b*]quinoline derivatives **8** were obtained (Scheme 2) in excellent yields (Table 3).[11]



3 4 7 8

Scheme 2

As shown in Table 2 and Table 3 this protocol could be applied not only to aromatic aldehydes with either electron-withdrawing or electron-donating groups, but also to heterocyclic and aliphatic aldehydes. A wide range of aromatic amines including phenylamine, *p*-toluidine, 1-naphthylamine, and 2-naphthylamine were employed successfully in this reaction with excellent results.

Moreover, the synthesis of **6j** was performed under both microwave irradiation and classical heating conditions at 100 °C. The reaction was efficiently promoted by microwave irradiation and the reaction time was strikingly shortened to four minutes, from the six hours required under traditional heating conditions, and the yield was increased to 97% from 72%. Therefore, microwave irradiation exhibited several advantages over conventional heating by significantly reducing the reaction time and dramatically improving the reaction yield.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of 4-aza-podophyllotoxin derivatives **6** could be explained by the reaction sequence presented in Scheme 3. When the reactants were added into the vessel a yellow solid product **9** from the condensation of aldehyde and aromatic amine appeared immediately, which was separated and identified by IR and ^{1}H NMR spectral data. We therefore proposed that the reaction proceeded via a reaction sequence of condensation, addition, cyclization, and dehydration. First, the condensation of aldehyde **3** and aromatic amine **4** gave Schiff base **9**. The addition of Schiff base **9** to tetronic acid **5** then furnished the intermediate product **14**, which upon intermolecular cyclization and dehydration gave rise to **6**.

To test the mechanism described above, the reaction of intermediate product **9f**[12,13] and tetronic acid **5** was carried out in water at 100 °C under microwave irradiation conditions. The target compound **6f**[14] was obtained, in similar yields by the one-pot reaction. The results supported the proposed mechanism (Scheme 4).

In this study, all the products were characterized by melting point, IR and ^{1}H NMR spectral data, as well as elemental analyses. Furthermore, the structure of **6n** was established by X-ray crystallographic analysis (Figure 2).[15]

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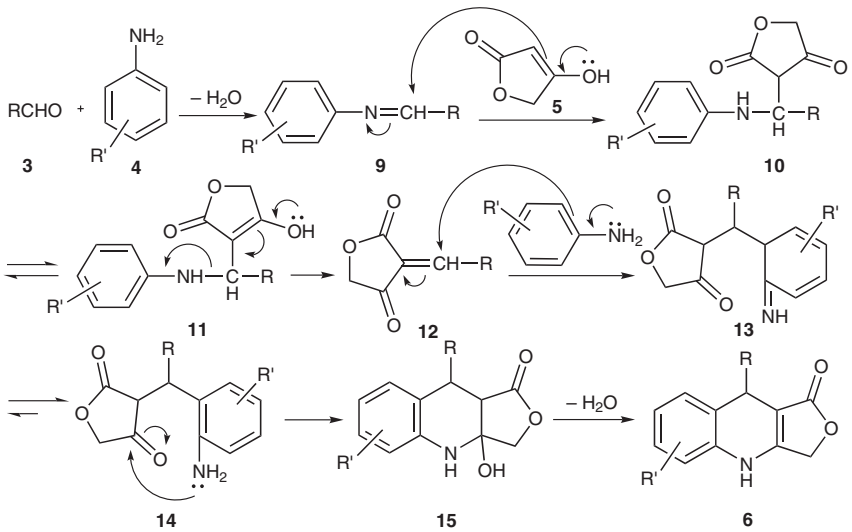
Table 2 Synthesis of **6** in Water under Microwave Irradiation Conditions at 100 °C

Entry	6	3	R	4	Amine	Time (min)	Yield (%)[a]	Mp (°C)
1	**6a**	**3a**	4-FC_6H_4	**4a**	phenylamine	5	96	>300
2	**6b**	**3b**	4-BrC_6H_4	**4a**	phenylamine	5	97	>300
3	**6c**	**3b**	4-BrC_6H_4	**4b**	*p*-toluidine	6	95	>300
4	**6d**	**3c**	4-ClC_6H_4	**4b**	*p*-toluidine	6	95	>300
5	**6e**	**3d**	4-$MeOC_6H_4$	**4b**	*p*-toluidine	3	96	>300
6	**6f**	**3e**	3-$NO_2C_6H_4$	**4b**	*p*-toluidine	7	97	>300
7	**6g**	**3f**	Ph	**4b**	*p*-toluidine	4	98	>300
8	**6h**	**3a**	4-FC_6H_4	**4c**	1-naphthylamine	5	95	>300
9	**6i**	**3b**	4-BrC_6H_4	**4c**	1-naphthylamine	7	96	>300
10	**6j**	**3c**	4-ClC_6H_4	**4c**	1-naphthylamine	4	97	>300
11	**6k**	**3d**	4-$MeOC_6H_4$	**4c**	1-naphthylamine	3	97	>300
12	**6l**	**3g**	thiophen-2-yl	**4c**	1-naphthylamine	6	97	>300
13	**6m**	**3h**	Bu	**4c**	1-naphthylamine	3	94	>300
14	**6n**	**3a**	4-FC_6H_4	**4d**	2-naphthylamine	5	93	>300
15	**6o**	**3b**	4-BrC_6H_4	**4d**	2-naphthylamine	7	98	>300
16	**6p**	**3c**	4-ClC_6H_4	**4d**	2-naphthylamine	5	93	>300
17	**6q**	**3d**	4-$MeOC_6H_4$	**4d**	2-naphthylamine	3	94	>300
18	**6r**	**3e**	3-$NO_2C_6H_4$	**4d**	2-naphthylamine	6	96	>300
19	**6s**	**3i**	3,4-$Cl_2C_6H_3$	**4d**	2-naphthylamine	3	95	>300

[a] Isolated yields.



Scheme 3

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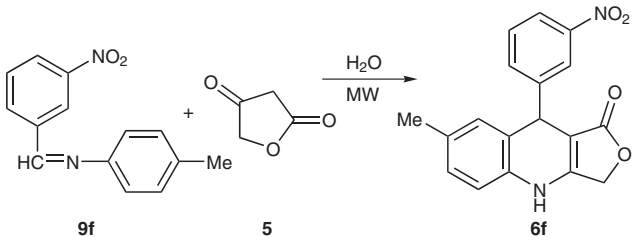
Table 3 Synthesis of **8** in Water under Microwave Irradiation Conditions at 100 °C

Entry	8	3	R	4	Amine	Time (min)	Yield (%)[a]	Mp (°C)
1	**8a**	**3a**	4-FC_6H_4	**4b**	*p*-toluidine	7	96	>300
2	**8b**	**3b**	4-BrC_6H_4	**4b**	*p*-toluidine	6	93	>300
3	**8c**	**3c**	4-ClC_6H_4	**4b**	*p*-toluidine	5	94	>300
4	**8d**	**3d**	4-$MeOC_6H_4$	**4b**	*p*-toluidine	4	97	>300
5	**8e**	**3j**	4-$NO_2C_6H_4$	**4b**	*p*-toluidine	7	95	>300
6	**8f**	**3a**	4-FC_6H_4	**4c**	1-naphthylamine	5	97	>300
7	**8g**	**3b**	4-BrC_6H_4	**4c**	1-naphthylamine	4	96	>300
8	**8h**	**3c**	4-ClC_6H_4	**4c**	1-naphthylamine	3	93	>300
9	**8i**	**3e**	3-$NO_2C_6H_4$	**4c**	1-naphthylamine	5	94	>300
10	**8j**	**3f**	Ph	**4c**	1-naphthylamine	6	95	>300
11	**8k**	**3g**	thiophen-2-yl	**4c**	1-naphthylamine	6	98	>300
12	**8l**	**3a**	4-FC_6H_4	**4d**	2-naphthylamine	7	96	>300
13	**8m**	**3b**	4-BrC_6H_4	**4d**	2-naphthylamine	6	93	>300
14	**8n**	**3c**	4-ClC_6H_4	**4d**	2-naphthylamine	6	93	>300
15	**8o**	**3d**	4-$MeOC_6H_4$	**4d**	2-naphthylamine	4	95	>300
16	**8p**	**3e**	3-$NO_2C_6H_4$	**4d**	2-naphthylamine	5	97	>300
17	**8q**	**3f**	Ph	**4d**	2-naphthylamine	3	97	>300

[a] Isolated yields.



Scheme 4

In conclusion, we have developed a three-component reaction of an aldehyde, an aromatic amine, and either tetronic acid or 1,3-indanedione for the synthesis of 4-azapodophyllotoxin derivatives in water under microwave irradiation conditions. Particularly valuable features of this method include excellent yields of the products, shorter reaction time, reduced environmental impact, and straightforward procedure.

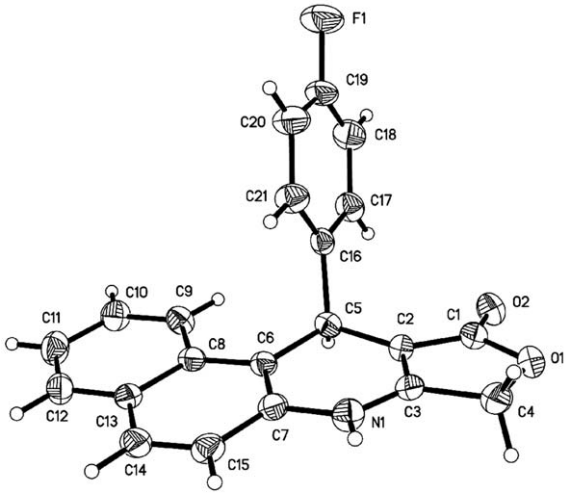


Figure 2 ORTEP diagram of **6n**

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Acknowledgment

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(9) **Compounds 6; General Procedure**: All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. In a 10-mL Emrys™ reaction vial, aldehyde **3** (1 mmol), aromatic amine **4** (1 mmol), tetronic acid **5** (1 mmol), and H_2O (2 mL) were mixed and then capped. The mixture was irradiated at 150 W and 100 °C for a given time. The reaction mixture was cooled to r.t. and filtered to give the crude product, which was further purified by recrystallization (DMF–EtOH) to give pure 4-aza-podophyllotoxin derivatives **6**.
Compound **6c**: Yellow solid; mp > 300 °C. IR (KBr): 3233, 3181, 3119, 3075, 2985, 2931, 1712, 1640, 1545, 810, 756, 689 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 10.01 (1 H, s, NH), 7.46 (2 H, d, *J* = 8.4 Hz, ArH), 7.16 (2 H, d, *J* = 8.0 Hz, ArH), 6.96 (1 H, d, *J* = 7.6 Hz, ArH), 6.85–6.82 (2 H, m, ArH), 5.00 (1 H, s, CH), 4.97–4.85 (2 H, m, CH_2), 2.13 (3 H, s, CH_3). Anal. Calcd for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96; N, 3.93. Found: C, 60.75; H, 3.90; N, 3.89. Compound **6h**: Yellow solid; mp >300 °C. IR (KBr): 3276, 3059, 2927, 2858, 1727, 1645, 1538, 1509, 1488, 803, 782, 758, 733, 723 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 10.28 (1 H, s, NH), 8.22 (1 H, d, *J* = 8.4 Hz, ArH), 7.86 (1 H, d, *J* = 8.0 Hz, ArH), 7.65–7.49 (3 H, m, ArH), 7.30–7.27 (2 H, m, ArH), 7.19–7.07 (3 H, m, ArH), 5.24 (1 H, s, CH), 5.11–4.97 (2 H, m, CH_2). Anal. Calcd for $C_{21}H_{14}FNO_2$: C, 76.12; H, 4.26; N, 4.23. Found: C, 76.23; H, 4.20; N, 4.16. Compound **6q**: Yellow solid; mp >300 °C. IR (KBr): 3231, 3108, 3057, 2958, 2934, 1722, 1650, 1600, 1584, 1532, 814, 777, 742 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 10.27 (1 H, s, NH), 7.86–7.79 (3 H, m, ArH), 7.39–7.27 (3 H, m, ArH), 7.11 (2 H, d, *J* = 8.8 Hz, ArH), 6.75 (2 H, d, *J* = 8.4 Hz, ArH), 5.61 (1 H, s, CH), 4.98–4.87 (2 H, m, CH_2), 3.64 (3 H, s, OCH_3). Anal. Calcd for $C_{22}H_{17}NO_3$: C, 76.95; H, 4.99; N, 4.08. Found: C, 77.01; H, 4.95; N, 4.02.

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(11) Compounds **8**; General Procedure: In a 10-mL Emrys™ reaction vial aldehyde **3** (1 mmol), aromatic amine **4** (1 mmol), 1:3-indanedione **7** (1 mmol), and H_2O (2 mL) were mixed and then capped. The mixture was irradiated at 150 W and 100 °C for a given time. The reaction mixture was cooled to r.t. and filtered to give the crude product which was further purified by recrystallization (DMF–EtOH) to give pure indeno[1,2-*b*]quinoline derivatives **8**. Compound **8m**: Yellow solid; mp >300 °C. IR (KBr): 3220, 3065, 2855, 1710, 1662, 1574, 1533, 1485, 858, 738, 645 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 10.99 (1 H, s, NH), 7.94 (1 H, d, *J* = 8.8 Hz, ArH), 7.87 (2 H, t, *J* = 8.0 Hz, ArH), 7.63 (1 H, d, *J* = 7.2 Hz, ArH), 7.53 (1 H, d, *J* = 8.8 Hz, ArH), 7.49–7.34 (6 H, m, ArH), 7.27 (1 H, d, *J* = 8.0 Hz, ArH), 7.20 (2 H, d, *J* = 8.4 Hz, ArH), 5.80 (1 H, s, CH). Anal. Calcd for $C_{26}H_{16}BrNO$: C, 71.25; H, 3.68; N, 3.20. Found: C, 71.34; H, 3.62; N, 3.10.

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(13) Compound **9f**: In a 10-mL Emrys™ reaction vial 3-nitrobenzaldehyde (**3e**, 2 mmol), *p*-toluidine (**4b**, 2 mmol), and H_2O (3 mL) were mixed and then capped. The mixture was irradiated at 150 W and 100 °C for 2 min. The reaction mixture was cooled to r.t. and filtered to give the crude product which was further purified by recrystallization (EtOH) to give pure *N*-(3-nitrobenzylidene)-4-methylbenzenamine (**9f**). Yellow solid; mp 87–88 °C. IR (KBr): 3092, 3026, 2879, 1622, 1572, 1440, 1268, 1044, 860, 765 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 8.76 (1 H, s, CH), 8.58 (1 H, s, ArH), 8.33 (1 H, d, *J* = 8.0 Hz, ArH), 8.27 (1 H, d, *J* = 7.6 Hz, ArH), 7.68 (1 H, d, *J* = 8.0 Hz, ArH), 7.29–7.20 (4 H, m, ArH), 2.41 (3 H, s, CH_3). Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.09; H, 4.95; N, 11.60.

(14) Reaction of Schiff Base **9f** and Tetronic Acid (**5**): In a 10-mL Emrys™ reaction vial, *N*-(3-nitrobenzylidene)-4-methylbenzenamine (**9f**, 1 mmol), tetronic acid (**5**, 1 mmol), H_2O (2 mL) were mixed and then capped. The mixture was irradiated at 150 W and 100 °C for 7 min. The reaction mixture was cooled to r.t. and filtered to give the crude product, which was further purified by recrystallization (DMF–EtOH) to give pure 7-methyl-9-(3-nitrophenyl)-4,9-dihydrofuro[3,4-*b*]quinolin-1 (3*H*)-one(**6f**). Yellow solid; mp >300 °C. IR (KBr): 3237, 3183, 3121, 3077, 2932, 1714, 1640, 1544, 1348, 1205, 1109, 934, 861 cm^{-1}. ^1H NMR (DMSO-d_6, 400 MHz): δ = 10.11 (1 H, s, NH), 8.05 (2 H, d, *J* = 7.2 Hz, ArH), 7.69 (1 H, d, *J* = 7.6 Hz, ArH), 7.60 (1 H, t, *J* = 8.0 Hz, ArH), 7.00 (1 H, d, *J* = 8.4 Hz, ArH), 6.89 (2 H, t, *J* = 8.0 Hz, ArH), 5.26 (1 H, s, CH), 5.02–4.88 (2 H, m, CH_2), 2.13 (3 H, s, CH_3). Anal. Calcd for $C_{18}H_{14}N_2O_4$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.15; H, 4.29; N, 8.54.

(15) The single crystal growth was carried out in EtOH–DMF at r.t. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Semens P4 diffractometer (graphite monochromator, Mo Kα radiation λ = 0.71073 Å). Crystal data for **6n**: Empirical formula $C_{21}H_{14}FNO_2$, yellow, crystal dimension 0.23 × 0.18 × 0.16 mm, monoclinic, space group *C*2/*c*, a = 21.010 (7) Å, b = 11.388 (4) Å, c = 15.123 (5) Å, α = 90°, β = 121.380 (5)°, γ = 90°, *V* = 3089.3 (16) $Å^3$, *Mr* = 331.33, Z = 8, Dc = 1.425 Mg/m^3, λ = 0.71073 Å, μ (Mo-K_α) = 0.100 mm^{-1}, *F*(000) = 1376, *S* = 0.991, *R*1 = 0.049, *wR*2 = 0.136. Crystallographic data for the structures of **6n** reported in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC-608399.

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