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Combinatorial Synthesis of Pyrrolo[3,2-*f*]quinoline and Pyrrolo[3,2-*a*]acridine Derivatives via a Three-Component Reaction under Catalyst-Free Conditions

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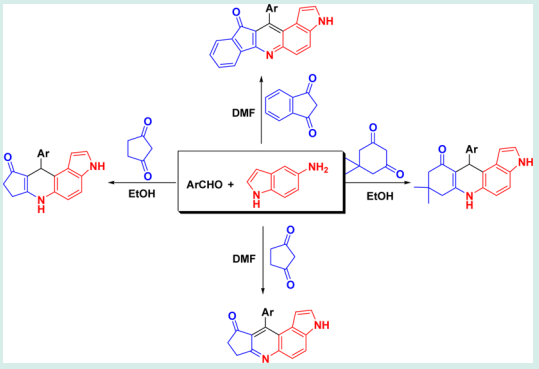
Supporting Information

ABSTRACT: A combinatorial synthesis of pyrrolo[3,2-*f*]quinoline and pyrrolo[3,2-*a*]acridine derivatives is described as a three-component reaction of aromatic aldehyde, 1*H*-indol-5-amine, and 1,3-dicarbonyl compounds under catalyst-free conditions. The 1,3-dicarbonyl compounds include 5,5-dimethylcyclohexane-1,3-dione, cyclopentane-1,3-dione, and 2*H*-indene-1,3-dione. It is interesting that the designed reactions gave aromatized or unaromatized products, which depend on the reaction temperature and reactants of 1,3-dicarbonyl compounds.

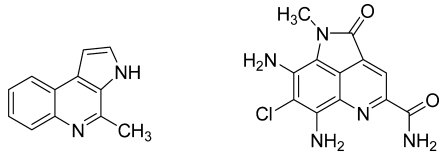


KEYWORDS: *pyrrolo[3,2-f]quinoline, pyrrolo[3,2-a]acridine, 1H-indol-5-amine, catalyst-free, synthesis*

1. INTRODUCTION

Acridine occurs in a large number of natural products and attracts a great deal of attention because of its wide range of biological activities. Its derivatives produce remarkable effects as pharmaceuticals, including antibacterial,[1] anticancer,[2,3] antitumor,[4,5] ribonucleolytic,[6] antiangiogenic,[7] and antifungicidal[8] activities. It is well-known that the three-component reaction of arylamine, aromatic aldehyde, and cyclic 1,3-dicarbonyl compound is an efficient method for synthesizing these potentially active heterocycles.[9] As a member of this family, pyrroloacridine contains both pyrrole and acridine moieties, which may afford unique biological activities for screening. Therefore, a simple, mild, and versatile preparation of pyrroloacridines in a one-pot reaction is still highly desirable.

In addition, pyrroloquinoline is a skeleton of natural alkaloids. For example, Marinoquinoline A (Figure 1, left) is isolated from the gliding bacterium *Ohtaekwangia kribbensis* and shows weak antibacterial and antifungal activities and moderate cytotoxicity against four growing mammalian cell lines.[10]



Marinoquinoline A *Ammosamide* B

Figure 1. Interesting alkaloids containing pyrroloquinoline.

Another important alkaloid containing pyrroloquinoline is Ammosamide B (Figure 1, right), which is well-known for its antitumor activity.[11] Its derivatives also have attracted a great deal of attention recently because of the other remarkable biological and pharmacological activities, such as antioxidative,[12] cytotoxic,[13] anticancer,[14] photochemotherapeutic,[15] and antiviral[16] activity. Therefore, considerable effort has been spent on the synthesis of pyrroloquinoline annulated heterocyclic derivatives because of their wide application.[17−22] As a continuation of our research devoted to the new methods for the preparation of heterocycles via multicomponent reactions,[23] we describe here the synthesis of pyrrolo[3,2-*f*]quinoline and pyrrolo[3,2-*a*]acridine derivatives by a three-component reaction of aromatic aldehyde, 1*H*-indol-5-amine, and 1,3-dicarbonyl compounds under catalyst-free conditions.

2. RESULTS AND DISCUSSION

Treatment of 4-cyanobenzaldehyde **1**{*1*}, 1*H*-indol-5-amine **2**{*1*}, and cyclopentane-1,3-dione **3**{*1*} in refluxing EtOH without catalysts resulted in the corresponding 10-(4-cyanophenyl)-6,7,8,10-tetrahydrocyclopenta[*b*]pyrrolo[3,2-*f*]-quinolin-9(3*H*)-one derivatives **4**{*1,1,1*} in high yields (Scheme 1).

In our lab, the screening of catalysts was conducted first, for example, KF/Al_2O_3, piperidine, and 1,8-diazabicyclo[5.4.0]-

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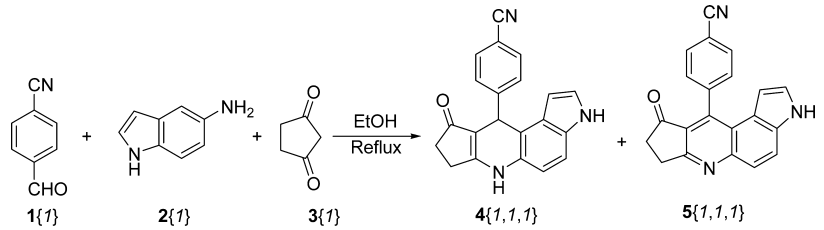
Scheme 1. Reaction of 1{*1*}, 2{*1*}, and 3{*1*}



undec-7-ene (DBU) (Table 1, entries 4–6), taking the reaction of 4-cyanobenzaldehyde **1**{*1*}, **2**{*1*}, and **3**{*1*} as a model. It

Table 1. Synthesis of 4{*1,1,1*} and 5{*1,1,1*} under Different Reaction Conditions[a]

entry	temp	catalyst (mol %)	time (h)	solvent	yield of **4**/**5** (%)[b]
1	room temp	–	10	EtOH	trace/0
2	50 °C	–	16	EtOH	68/0
3	reflux	–	10	EtOH	93/0
4	reflux	KF/Al_2O_3	10	EtOH	90/0
5	reflux	piperidine	10	EtOH	90/0
6	reflux	DBU	10	EtOH	87/0
7	80 °C	–	8	CH_3OH	87/0
8	reflux	–	14	CH_3CN	82/0
9	reflux	–	16	benzene	89/0
10	reflux	–	14	THF	85/0
11	80 °C	–	10	DMF	11/68
12	100 °C	–	10	DMF	0/78
13	reflux	–	6	DMF	0/84

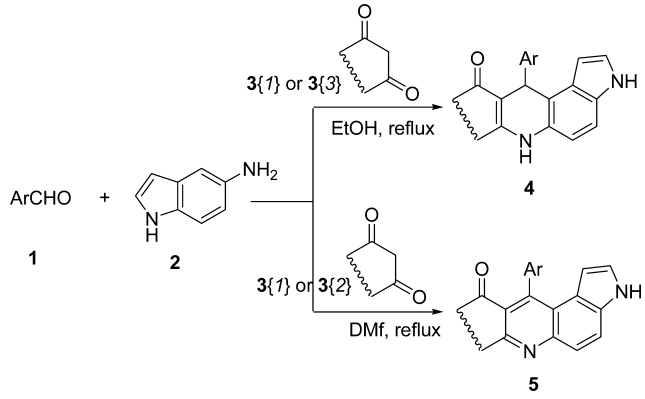
[a]Reagents and conditions: 4-cyanobenzaldehyde **1**{*1*} (0.140 g, 1.0 mmol), **2**{*1*} (0.213 g, 1.0 mmol), **3**{*1*} (0.133 g, 1.0 mmol), and solvent (10 mL). [b]Isolated yields.

was found that without a catalyst, the reaction could take place and give **4**{*1,1,1*} in high yields (93%). Solvents, such as CH_3OH, EtOH, benzene, and tetrahydrofuran (THF) (entries 3 and 7–10), were also tested with this reaction; EtOH gave the best result. Furthermore, the product was collected by filtration without further purification, when the EtOH solution was cooled to room temperature after the completion of the reaction. It was interesting that the same reaction gave the aromatized cyclopenta[*b*]pyrrolo[3,2-*f*]quinolin-9(3*H*)-one derivatives **5**{*1,1,1*} in 68% yield at 80 °C along with an 11% yield of **4**{*1,1,1*} in dimethylformamide (DMF). The yield of **5**{*1,1,1*} also gradually increased with an increase in temperature, and the highest yield of 84% was achieved at reflux in DMF for 6 h (entries 11–13).

The interesting and selective reaction depending on the reaction temperature inspired us to test other 1,3-dicarbonyl compounds in this type of reaction. 2*H*-Indene-1,3-dione **3**{2} was chosen first for its similarity to cyclopentane-1,3-dione. It was found that the products were easily oxidized by air; even if the designed reaction mixtures were treated at slightly lower temperatures in EtOH, they all aromatized to 12-arylindeno-[1,2-*b*]pyrrolo[3,2-*f*]quinolin-11(3*H*)-one derivatives in high yields without catalysts (Scheme 2). Perhaps, the large conjugative system promotes the easy oxidation by air of the center 1,4-dihydropyrdine (1,4-DHP) ring.

It has been reported[24−27] that most 1,4-DHP rings are stable in air, so the results described above raised the interesting question of why the rings were so easily oxidized by air. With

Scheme 2. Reaction of 1, 2, and 3



this question in mind, a single crystal of **4**{*8,1,1*} was grown by slow evaporation at room temperature and assessed by a CCD diffractometer. The crystal structure of **4**{*8,1,1*} is shown in Figure 2. X-ray diffraction analysis indicates that all the atoms

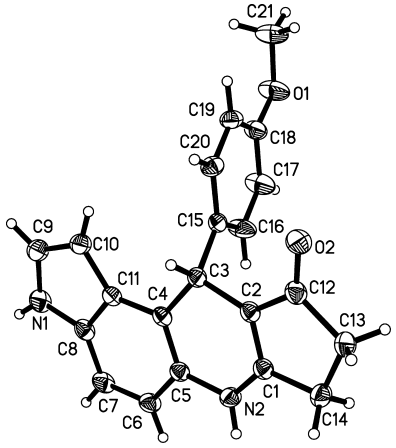


Figure 2. Crystal structure of 4{*8,1,1*} with a molecule of DMF deleted for the sake of clarity.

[C(1)−C(5)/N(2)] on the center 1,4-DHP ring are coplanar, with a mean deviation of 0.0249 Å, which is obviously different from those of similar structures.[28,29] Perhaps the planar 1,4-DHP ring is oxidized more readily than the distorted ones (boat or half-chair conformation). It is also found in the crystal structure of **4**{*8,1,1*} that the adjacent five-membered ring [C(1)/C(2)/C(12)−C(14)] is a planar structure, with a mean deviation of 0.009 Å. Therefore, we think that 1,4-DHP is coplanar just because of the outer five-membered planar ring. Otherwise, 1,4-DHP would undergo a change to a normal distorted conformation, and it would be stable in air.

With this idea in mind, we selected the third 1,3-dicarbonyl compound instead of the five-membered planar ring. 5,5-

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Dimethylcyclohexane-1,3-dione **3**{*3*} (dimedone is not a planar structure) was subjected to reaction with **1** and **2**{*1*} without catalysts. The unaromatized 8,9-dihydro-8,8-dimethyl-11-aryl-3*H*-pyrrolo[3,2-*a*]acridin-10(6*H*,7*H*,11*H*)-one derivatives were obtained as expected, whether the sample was subjected to refluxing EtOH or DMF.

To confirm our assumption, we also grew single crystals of **4**{*19,1,3*}; its crystal structure is shown in Figure 3. X-ray

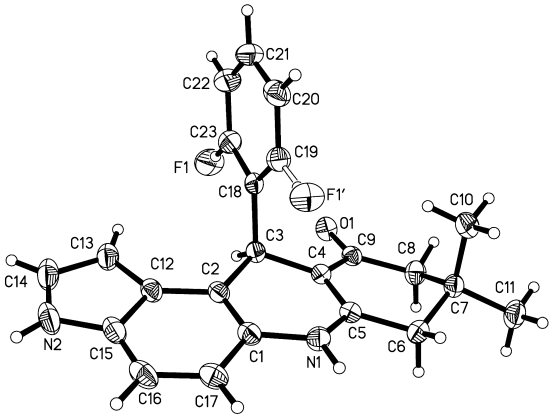

Figure 3. Crystal structure of **4**{*19,1,3*}.

diffraction analysis demonstrates that 1,4-DHP is slightly distorted, adopting a skew boat conformation as expected. Atoms C(1), C(2), C(4), and C(5) are coplanar, with atoms C(3) and N(1) deviating from the defined plane by 0.222(2) and 0.106(2) Å, respectively. The outer six-membered ring adopts a half-chair conformation as expected, and atom C(7) deviates from the plane [C(4)−C(6)/C(8)/C(9)] by 0.640(2) Å.

3. CONCLUSION

In summary, a three-component reaction of aromatic aldehyde, 1*H*-indol-5-amine, and 1,3-dicarbonyl compounds, including 5,5-dimethylcyclohexane-1,3-dione, cyclopentane-1,3-dione, and 2*H*-indene-1,3-dione, was studied under catalyst-free conditions, with pyrrolo[3,2-*f*]quinoline and pyrrolo[3,2-*a*]-acridine derivatives being obtained in high yields. The advantages of this procedure include mild reaction conditions, high yields, one-pot operational simplicity, and catalyst-free conditions.

4. EXPERIMENTAL PROCEDURES

Melting points were determined in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Tensor 27 spectrometer in a KBr pellet. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded from a solution in dimethyl sulfoxide-d_6 (DMSO-d_6) with Me_4Si as an internal standard using a Bruker-400 spectrometer. HRMS analyses were conducted using a Bruker micro-TOF-Q-MS analyzer.

General Procedure for the Syntheses of 4. A dry 50 mL flask was charged with aromatic aldehyde **1** (1.0 mmol), 1*H*-indol-5-amine **2** (0.132 g, 1.0 mmol), 1,3-dicarbonyl compounds **3** (1.0 mmol), and EtOH (10 mL). The reaction mixture was stirred at reflux for 5−10 h. After the completion of the reaction, as indicated by TLC, products **4** were obtained as a pale yellow powder or crystals, when the mixture was allowed to cool to room temperature.

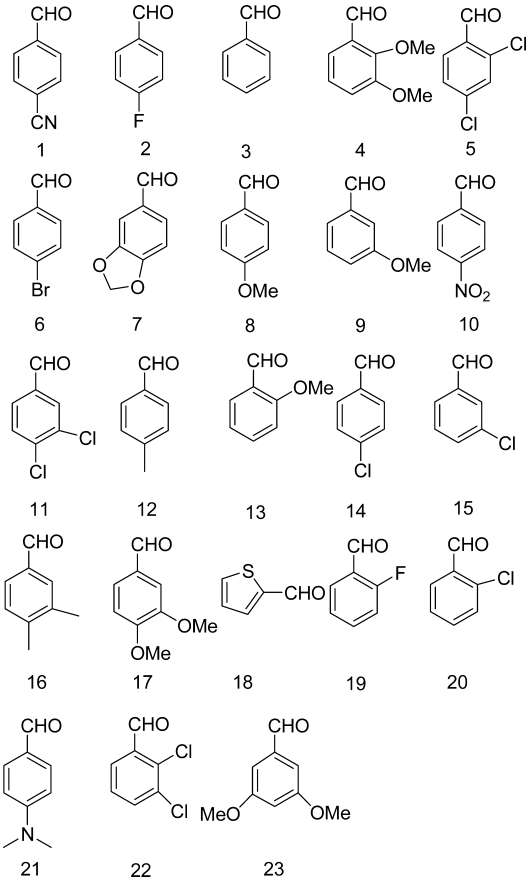

Figure 4. Diversity of aldehydes **1**{*1*−*23*}.

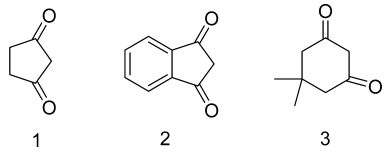

Figure 5. Diversity of 1,3-dicarbonyl compounds **3**{*1*−*3*}.

10-(4-Methoxyphenyl)-6,7,8,10-tetrahydrocyclopenta[*b*]-pyrrolo[3,2-*f*]quinolin-9(3*H*)-one **4**{*8,1,1*}: mp 289−291 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.18−2.28 (m, 2H, CH_2), 2.62−2.67 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 5.18 (s, 1H, CH), 6.19 (s, 1H, ArH), 6.70 (d, J = 8.0 Hz, 2H, ArH), 6.84 (d, J = 8.4 Hz, 1H, ArH), 7.08 (d, J = 8.0 Hz, 2H, ArH), 7.16 (s, 1H, ArH), 7.24 (d, J = 8.0 Hz, 1H, ArH), 9.92 (s, 1H, NH), 10.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 23.9, 33.2, 37.9, 54.8, 99.8, 110.6, 111.2, 111.6, 113.1, 114.8, 125.3, 126.9, 128.6, 129.1, 132.7, 139.5, 157.0, 164.9, 199.4; IR (KBr) 3247, 3076, 3036, 2922, 2837, 2805, 2717, 2576, 1689, 1613, 1561, 1510, 1453, 1436, 1354, 1341, 1293, 1253, 1191, 1175, 1161, 1125, 1033, 989, 892, 836, 749, 725, 697 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{21}H_{19}N_2O_2$ $[M + H]^+$ 331.1447, found 331.1442.

General Procedure for the Syntheses of 5. A dry 50 mL flask was charged with aldehyde **1** (1.0 mmol), 1*H*-indol-5-amine **2** (0.132 g, 1.0 mmol), 1,3-dicarbonyl compounds **3** (1.0 mmol), and DMF (10 mL). The reaction mixture was stirred at reflux for 7−18 h. After the completion of the reaction, as indicated by TLC, a small amount of water was added to the mixture at reflux. Products **5** were obtained as a pale yellow

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Table 2. Reaction Times and Yields of Products 4[a]

entry	Ar	time (h)	products	isolated yield (%)
1	4-CNC$_6$H$_4$	6	4{*1,1,1*}	87
2	4-FC$_6$H$_4$	6	4{*2,1,1*}	90
3	C$_6$H$_5$	7	4{*3,1,1*}	92
4	2,3-(MeO)$_2$C$_6$H$_3$	8	4{*4,1,1*}	86
5	2,4-Cl$_2$C$_6$H$_3$	5	4{*5,1,1*}	90
6	4-BrC$_6$H$_4$	6	4{*6,1,1*}	84
7	piperonyl	8	4{*7,1,1*}	88
8	4-MeOC$_6$H$_4$	9	4{*8,1,1*}	90
9	3-MeOC$_6$H$_4$	6	4{*9,1,1*}	94
10	4-NO$_2$C$_6$H$_4$	5	4{*10,1,1*}	92
11	4-BrC$_6$H$_4$	6	4{*6,1,3*}	92
12	piperonyl	10	4{*7,1,3*}	95
13	3-MeOC$_6$H$_4$	8	4{*9,1,3*}	90
14	3,4-Cl$_2$C$_6$H$_3$	6	4{*11,1,3*}	90
15	4-MeC$_6$H$_4$	6	4{*12,1,3*}	91
16	2-MeOC$_6$H$_4$	8	4{*13,1,3*}	89
17	4-ClC$_6$H$_4$	5	4{*14,1,3*}	90
18	3-ClC$_6$H$_4$	6	4{*15,1,3*}	95
19	3,4-(CH$_3$)$_2$C$_6$H$_3$	10	4{*16,1,3*}	96
20	3,4-(MeO)$_2$C$_6$H$_3$	10	4{*17,1,3*}	96
21	2-thienyl	6	4{*18,1,3*}	95
22	2-FC$_6$H$_4$	8	4{*19,1,3*}	87

[a]Reaction condition: EtOH (10 mL), **1** (1.0 mmol), **2**{*1*} (0.132 g, 1.0 mmol), and **3** (1.0 mmol), reflux.

Table 3. Reaction Times and Yields of Products 5[a]

entry	Ar	time (h)	products	isolated yield (%)
1	4-CNC$_6$H$_4$	10	5{*1,1,1*}	84
2	C$_6$H$_5$	16	5{*3,1,1*}	84
3	2,4-Cl$_2$C$_6$H$_3$	12	5{*5,1,1*}	92
4	3,4-Cl$_2$C$_6$H$_3$	15	5{*11,1,1*}	87
5	4-MeC$_6$H$_4$	16	5{*12,1,1*}	90
6	2-MeOC$_6$H$_4$	18	5{*13,1,1*}	83
7	3-ClC$_6$H$_4$	10	5{*15,1,1*}	88
8	2-ClC$_6$H$_4$	10	5{*20,1,1*}	90
9	4-Me$_2$NC$_6$H$_4$	12	5{*21,1,1*}	90
10	2,3-Cl$_2$C$_6$H$_3$	12	5{*22,1,1*}	89
11	3,5-(MeO)$_2$C$_6$H$_3$	18	5{*23,1,1*}	92
12	2,4-Cl$_2$C$_6$H$_3$	10	5{*5,1,2*}	87
13	4-BrC$_6$H$_4$	10	5{*6,1,2*}	90
14	piperonyl	10	5{*7,1,2*}	90
15	3-MeOC$_6$H$_4$	10	5{*9,1,2*}	95
16	3,4-Cl$_2$C$_6$H$_3$	10	5{*11,1,2*}	88
17	4-MeC$_6$H$_4$	9	5{*12,1,2*}	87
18	2-MeOC$_6$H$_4$	8	5{*13,1,2*}	96
19	4-ClC$_6$H$_4$	7	5{*14,1,2*}	92
20	3-ClC$_6$H$_4$	7	5{*15,1,2*}	90
21	3,4-(CH$_3$)$_2$C$_6$H$_3$	12	5{*16,1,2*}	85
22	2-ClC$_6$H$_4$	8	5{*20,1,2*}	94
23	3,5-(MeO)$_2$C$_6$H$_3$	12	5{*23,1,2*}	92

[a]Reaction condition: DMF (10 mL), **1** (1.0 mmol), **2**{*1*} (0.132 g, 1.0 mmol), and **3** (1.0 mmol), reflux.

powder or crystals, when the mixture was allowed to cool to room temperature.

10-(2,3-Dichlorophenyl)-7,8-dihydrocyclopenta[*b*]pyrrolo-[3,2-*f*]quinolin-9(3*H*)-one **5**{*22,1,1*}: mp >300 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 2.73−2.79 (m, 2H, CH$_2$), 3.31−3.36 (m, 2H, CH$_2$), 5.15 (s, 1H, ArH), 7.32−7.35 (m, 2H, ArH), 7.55−7.59 (m, 1H, ArH), 7.82 (d, J = 9.2 Hz, 1H, ArH), 7.89 (d, J = 8.0 Hz, 1H, ArH), 8.05 (d, J = 8.8 Hz, 1H, ArH), 11.92 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 27.7, 36.2, 103.3, 119.7, 120.7, 121.3, 122.5, 123.0, 125.1, 128.6, 129.0, 129.9, 130.6, 132.0, 132.5, 138.4, 140.9, 149.5, 167.9, 203.6; IR (KBr) 3449, 3034, 2927, 1704, 1570, 1538, 1488, 1456, 1429, 1414, 1368, 1341, 1311, 1275, 1185, 1166, 1149, 1099, 1044, 892, 797, 742 cm^{-1}; HRMS (ESI, m/z) calcd for $C_{20}H_{13}N_2OCl_2$ [M + H]$^+$ 367.0405, found 367.0391.

■ ASSOCIATED CONTENT

Supporting Information

NMR, IR, and HRMS spectra of **4** and **5** and crystallographic information files (CIF) of **4**{*8,1,1*} and **4**{*19,1,3*}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Bonnet, A.; Werth, M.; Sebire, P.; Flat, J.-J.; Pradel, J.-L. Fluoropolymer with antibacterial activity. PCT Int. Appl. WO 2008009865 A1, 2008.

(2) Belmont, P.; Bosson, J.; Godet, T.; Tiano, M. Acridine and acridone derivatives, anticancer properties and synthetic methods: Where are we now? *Anti-Cancer Agents Med. Chem.* **2007**, *7*, 139−169.

(3) Han, G. P.; Kim, E.; Ju, L.; Jeong, O.; Sim, Y. G.; Wang, J. J. Method for preparation of acridine derivatives having anticancer activity. Korean Kongkae Taeho Kongbo KR 2002028391 A 20020417, 2002.

(4) Antonini, I. Intriguing classes of acridine derivatives as DNA-binding antitumour agents: From pyrimido[5,6,1-*de*]acridine to bis(acridine-4-carboxamides). *Med. Chem. Rev.—Online* **2004**, *1*, 267−290.

(5) Kolodziejczyk, A. M.; Dzierzbicka, K.; Kolodziejczyk, A. S. A new class of antitumor agents: Conjugates of MDP and acridine/acridone derivatives. *Pol. J. Chem.* **1994**, *68*, 1023−1029.

(6) Tung, C. H.; Ebright, Y.; Shen, X.; Stein, S. A peptide-acridine conjugate with ribonucleolytic activity. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 303−306.

(7) Chen, H.-H.; You, L.-L.; Li, S.-B. Artesunate reduces chicken chorioallantoic membrane neovascularisation and exhibits antiangiogenic and apoptotic activity on human microvascular dermal endothelial cell. *Cancer Lett.* **2004**, *211*, 163−173.

(8) Srivastava, A. Synthesis and fungicidal activity of some acridine derivatives. *Indian J. Heterocycl. Chem.* **2004**, *13*, 261−264.

(9) (a) Nadaraj, V.; Selvi, S. T.; Mohan, S. Microwave-induced synthesis and antimicrobial activities of 7,10,11,12-tetrahydrobenzo-[*c*]acridin-8(9*H*)-one derivatives. *Eur. J. Med. Chem.* **2009**, *44*, 976−980. (b) Ghorbani-Vaghei, R.; Malaekehpoor, S. M. One-pot facile synthesis of acridine derivatives under solvent-free condition. *J. Iran. Chem. Soc.* **2010**, *7*, 957−964. (c) Shi, F.; Zhou, D.; Li, C.; Shao, Q.; Cao, L.; Tu, S. An efficient and facile microwave-assisted synthesis of benzo[*b*][4,7]phenanthroline derivatives in water. *J. Heterocycl. Chem.* **2008**, *45*, 405−410. (d) Kozlov, N. G.; Tereshko, A. B.; Gusak, K. N.

Condensation of quinolin-5-amine with aromatic aldehydes and cyclohexane-1,3-dione. *Russ. J. Org. Chem.* **2007**, *43*, 1371−1378. (e) Zang, H.; Zang, H.; Zhang, Y.; Mo, Y.; Cheng, B. Ultrasound-promoted one-pot synthesis of 7-aryl-7,10,11,12-tetrahydrobenzo[*c*]-acridin-8(9*H*)-one derivatives. *Synth. Commun.* **2011**, *41*, 3207−3214. (f) Kidwai, M.; Rastogi, S. Solvent-free neat synthetic route to tetrahydroacridinones. *Heteroat. Chem.* **2005**, *16*, 138−141. (g) Heravi, M. M.; Alinejhad, H.; Derikvand, F.; Oskooie, H. A.; Baghernejad, B.; Bamoharram, F. F. NH_2SO_3H and $H_6P_2W_{18}O_{62}{\cdot}18H_2O$ Catalyzed, Three-Component, One-Pot Synthesis of Benzo[*c*]acridine Derivatives. *Synth. Commun.* **2012**, *42*, 2033−2039. (h) Jin, J.; Zhang, J.; Liu, F.; Shang, W.; Xin, Y.; Zhu, S. One-pot preparation of fluorinated polyhydrobenzoacridine-1-one derivatives under microwave irradiation and solvent-free conditions. *Chin. J. Chem.* **2010**, *28*, 1217−1222.

(10) Okanya, P. W.; Mohr, K. I.; Gerth, K.; Jansen, R.; Mueller, R. Marinoquinolines A-F, pyrroloquinolines from *Ohtaekwangia kribbensis* (Bacteroidetes). *J. Nat. Prod.* **2011**, *74*, 603−608.

(11) Reddy, P. V. N.; Banerjee, B.; Cushman, M. Efficient Total Synthesis of Ammosamide B. *Org. Lett.* **2010**, *12*, 3112−3114.

(12) Qiu, X.; Liu, C.; Xu, L.; Zhao, J.; Wu, S. Effect of pyrroloquinoline quinone on anti-oxidative competence of AGS cell radiated by γ-ray. *Jiangsu Daxue Xuebao, Yixueban* **2009**, *19*, 293−295.

(13) Dalla Via, L.; Gia, O.; Chiarelotto, G.; Ferlin, M. G. DNA-targeting pyrroloquinoline-linked butenone and chalcones: Synthesis and biological evaluation. *Eur. J. Med. Chem.* **2009**, *44*, 2854−2861.

(14) Shankar, B. S.; Pandey, R.; Amin, P.; Misra, H. S.; Sainis, K. B. Role of glutathione in augmenting the anticancer activity of pyrroloquinoline quinone (PQQ). *Redox Rep.* **2010**, *15*, 146−154.

(15) Barraja, P.; Caracausi, L.; Diana, P.; Carbone, A.; Montalbano, A.; Cirrincione, G.; Brun, P.; Palu, G.; Castagliuolo, I.; Dall'Acqua, F. Synthesis of pyrrolo[3,2-*h*]quinolinones with good photochemotherapeutic activity and no DNA damage. *Bioorg. Med. Chem.* **2010**, *18*, 4830−4843.

(16) Nieman, J. A.; Nair, S. K.; Heasley, S. E.; Schultz, B. L.; Zerth, H. M.; Nugent, R. A.; Chen, K.; Stephanski, K. J.; Hopkins, T. A.; Knechtel, M. L. Modifications of C-2 on the pyrroloquinoline template aimed at the development of potent herpes virus antivirals with improved aqueous solubility. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3039−3042.

(17) Saito, T.; Furukawa, N.; Otani, T. A facile synthesis of pyrrolo[2,3-*b*]quinolines via a Rh(I)-catalyzed carbodiimide-Pauson-Khand-type reaction. *Org. Biomol. Chem.* **2010**, *8*, 1126−1132.

(18) Almeida, A. I. S.; Silva, A. M. S.; Cavaleiro, J. A. S. 4-Chloro-3-iodoquinoline as a synthon in the development of new syntheses of 1,2-disubstituted 1*H*-pyrrolo[3,2-*c*]quinolines. *Synlett* **2011**, 2955−2958.

(19) Zahra, J. A.; Al-Jaber, H. I.; El-Abadelah, M. M.; Abadleh, M. M. Heterocycles H.-fused to 4-oxoquinoline-3-carboxylic acid. Part IX. Synthesis of 2,6-dioxotetrahydro-1*H*-pyrrolo [3,2-*h*]quinoline-7-carboxylic acid. *Heterocycles* **2011**, *83*, 2165−2175.

(20) Zhou, F.; Liu, J.; Ding, K.; Liu, J.; Cai, Q. Copper-catalyzed tandem reaction of isocyanides with *N*-(2-haloaryl)propiolamides for the synthesis of pyrrolo[3,2-*c*]quinolin-4-ones. *J. Org. Chem.* **2011**, *76*, 5346−5353.

(21) Li, X.; Li, C.; Zhang, W.; Lu, X.; Han, S.; Hong, R. Highly Stereoselective 7-Endo-Trig/Ring Contraction Cascade to Construct Pyrrolo[1,2-*a*]quinoline Derivatives. *Org. Lett.* **2010**, *12*, 1696−1699.

(22) Mphahlele, M. J.; Lesenyeho, L. G.; Makelane, H. R. Synthesis of 1*H*-pyrrolo[3,2-*c*]quinoline derivatives via palladium-catalyzed heteroannulation of 2-aryl-3-iodo-4-(phenylamino)quinolines and 4-(*N*,*N*-allylphenylamino)-2-aryl-3-iodoquinolines. *Tetrahedron* **2010**, *66*, 6040−6046.

(23) (a) Wang, X. S.; Li, Q.; Wu, J. R.; Tu, S. J. Efficient Method for the Synthesis of Pyranoquinoline, Thiopyranoquinoline, Thienoquinoline, and Naphtho[2,7]naphthyridine Derivatives Catalyzed by Iodine. *ACS Comb. Sci.* **2009**, *11*, 433−437. (b) Wang, X. S.; Li, Q.; Yao, C. S.; Tu, S. J. An Efficient Method for the Synthesis of Benzo[*f*]quinoline and Benzo[*a*]phenanthridine Derivatives Catalyzed by Iodine by a Three-Component Reaction of Arenecarbaldehyde, Naphthalen-2-amine, and Cyclic Ketone. *Eur. J. Org. Chem.* **2008**, 3513−3518. (c) Wang, X. S.; Zhang, M. M.; Li, Q.; Yao, C. S.; Tu, S. J. An improved and clean procedure for the synthesis of one-donor poly-acceptors systems containing 2,6-dicyanoamine moiety in aqueous media catalyzed by TEBAC in the presence and absence of K_2CO_3. *Tetrahedron* **2007**, *63*, 5265−5273. (d) Wang, X. S.; Wu, J. R.; Zhang, J.; Tu, S. J. Green Method for the Synthesis of Highly Substituted Cyclohexa-1,3-diene, Polyhydroindene, Polyhydronaphthalene, Isochromene, Isothiochromene, and Isoquinoline Derivatives in Ionic Liquids. *ACS Comb. Sci.* **2009**, *11*, 1011−1022.

(24) Quiroga, J.; Mejía, D.; Insuasty, B.; Abonía, R.; Nogueras, M.; Sánchez, A.; Cobo, J.; Low, J. N. Regioselective synthesis of 4,7,8,9-tetrahydro-2*H*-pyrazolo[3,4-*b*]quinolin-5(6*H*)-ones. Mechanism and structural analysis. *Tetrahedron* **2001**, *57*, 6947−6953.

(25) Wang, X. S.; Zhang, M. M.; Jiang, H.; Yao, C. S.; Tu, S. J. Three-component green synthesis of N-arylquinoline derivatives in ionic liquid $[Bmim^+][BF_4^-]$: Reactions of arylaldehyde, 3-arylamino-5,5-dimethylcyclohex-2-enone, and active methylene compounds. *Tetrahedron* **2007**, *63*, 4439−4449.

(26) Khurana, J. M.; Chaudhary, A.; Nand, B.; Lumb, A. Aqua mediated indium(III) chloride catalyzed synthesis of fused pyrimidines and pyrazoles. *Tetrahedron Lett.* **2012**, *53*, 3018−3022.

(27) Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. J.; Wei, X. Y.; Zong, Z. M. A simple and clean procedure for the synthesis of polyhydroacridine and quinoline derivatives: Reaction of Schiff base with 1,3-dicarbonyl compounds in aqueous medium. *Tetrahedron Lett.* **2005**, *46*, 7169−7173.

(28) Wang, X. S.; Li, Q.; Wu, J. R.; Yao, C. S. Synthesis and Crystal Structure of 4-(2-Bromophenyl)-3,4,7,8-tetrahydro-7,7-dimethyl-1-*p*-tolylquinoline-2,5(1*H*,6*H*)-dione. *Chin. J. Struct. Chem.* **2009**, *28*, 813−818.

(29) Wang, X. S.; Shi, D. Q.; Tu, S. J. Synthesis and crystal structure of 7,7-dimethyl-2,4-diphenyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline. *J. Chem. Crystallogr.* **2002**, *32*, 381−384.