Efficient Method for the Synthesis of Pyranoquinoline, Thiopyranoquinoline, Thienoquinoline, and Naphtho[2,7]naphthyridine Derivatives Catalyzed by Iodine

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A mild and efficient method for the synthesis of pyranoquinoline, thiopyranoquinoline, thienoquinoline, and naphtho[2,7]naphthyridine derivatives via three-component reaction of aromatic aldehyde, naphthalen-2-amine, and heterocycloketones, including tetrahydropyran-4-one, tetrahydrothiopyran-4-one, pyridinone, and thiophenone, is described using iodine as catalyst. The features of this procedure are mild reaction conditions, good to high yields, and operational simplicity.

1. Introduction

Multicomponent reactions (MCRs) can be distinguished from classical, sequential two-component synthetic processes in that they use three or more chemical starting materials for product formation. Up to seven starting components have been used, and MCRs have often been shown to produce higher product yields than classical chemistry.[1] They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds as well as small and druglike heterocycles.[2] Owing to their convergence and productivity, the MCRs have attracted considerable attention from the point of view of combinatorial chemistry.[3]

The heterocyclic system containing a quinoline nucleus has found broad application in drug development for the treatment of MCH (melanin concentrating hormone) receptor related disorders,[4] cell proliferative diseases,[5] transmissible spongiform encephalopathies,[6] malignant tumors such as stomach cancer, brain tumor, and large intestine cancer,[7] and bacterial infections in mammals.[8] It is well-known that 4*H*-pyran fragments have different pharmacological activities, e.g., antifungal activity,[9] antiinflammatory activity,[10] and antimicrobial activity.[11] The 1*H*-benzo[*f*](thio)pyrano[3,4-*c*]quinoline ring system (Figure 1) is a rare condensed heterocycle compared with pyrano[3,2-*h*]quinoline and pyrano[3,2-*c*]quinoline substructures. Moreover, it is envisioned that (thio)pyrano[3,4-*c*]quinoline, which contains both a quinoline ring and (thio)pyran moieties, may afford unique biological activities. Schiemann et al.[12] revealed in 2008 that some pyranoquinoline derivatives could be used for the treatment of proliferative diseases. Many activities such as antibacterial, antiplatelet aggregation, and antihistaminic activity were also reported by other groups to these active compounds in recent years.[13]

In view of the importance of pyranoquinoline and its derivatives, several methods for the synthesis of pyranoquinoline were developed from hydroxyquinoline[14] or by aza-Diels−Alder reactions.[15] In general, hydroxyquinolines are used as reactants to construct the pyran nucleus in order to gain the pyranoquinolines. On the contrary, our interest was focused on the synthesis of pyranoquinoline derivatives using a fragment-containing pyran ring as starting material to form the pyridine moiety. Inspired by this novel idea and as a continuation of our research devoted to the development of new methods for the preparation of heterocycles via multicomponent reactions,[16] we would like to synthesize these potentially active compounds using pyranone, thiopyranone, pyridinone or thiophenone fragments and aromatic aldehyde, and naphthalen-2-amine as reactants to construct four novel series of pyranoquinoline, thiopyranoquinoline, thienoquinoline, and naphtho[2,7] naphthyridine derivatives.

2. Results and Discussion

Treatment of aromatic aldehyde **1**, naphthalen-2-amine **2**, and tetrahydropyran-4-one **3** in THF in the presence of 5 mol % iodine at reflux conditions afforded the corresponding 1*H*-5-arylbenzo[*f*]pyrano[3,4-*c*]quinoline derivatives **4** in high yields (Scheme 1).

In our initial study, the reaction of 4-fluorobenzaldehyde **1a**, naphthalen-2-amine **2**, and tetrahydropyran-4-one **3** was used as a model reaction to optimize the reaction conditions. The reaction was first carried out in THF in the absence of I_2. It was found that no reaction occurred at room temperature or reflux conditions (Table 1, entries 1 and 2). Similar reactions were attempted in the presence of 5, 10, and 20 mol % I_2. The results from Table 1 (entries 5−7) show that 5 mol % I_2 at reflux in THF is sufficient to initiate the

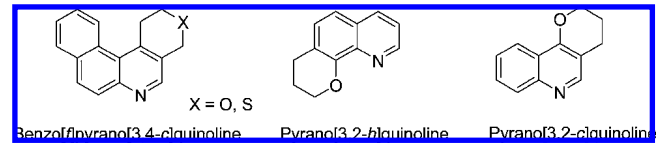

Figure 1. Heterocycles of interest.

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Scheme 1. Reaction of **1**, **2**, and Tetrahydropyran-4-one

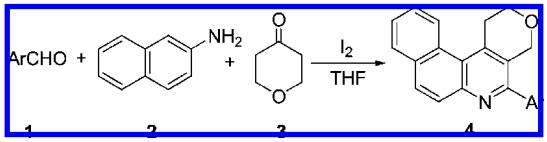


Table 1. Synthesis of **4a** under Different Reaction Conditions[a]

entry	temp (°C)	amount (mol %)	solvent	yields (%)[b]
1	rt	0	THF	0
2	reflux	0	THF	0
3	rt	5	THF	trace
4	50	5	THF	72
5	reflux	5	THF	86
6	reflux	10	THF	83
7	reflux	20	THF	85
8	reflux	5	CH_3CN	77
9	reflux	5	benzene	84
10	80	5	DMF	81
11	reflux	5	$CHCl_3$	76

[a] Reagents and conditions: 4-fluorobenzaldehyde **1a** (0.248 g, 2 mmol), **2** (0.286 g, 2 mmol), **3** tetrahydropyran-4-one (0.200 g, 2 mmol), solvent (10 mL). [b] Isolated yields.

Table 2. Synthesis of **4** Catalyzed by Iodine in THF[a]

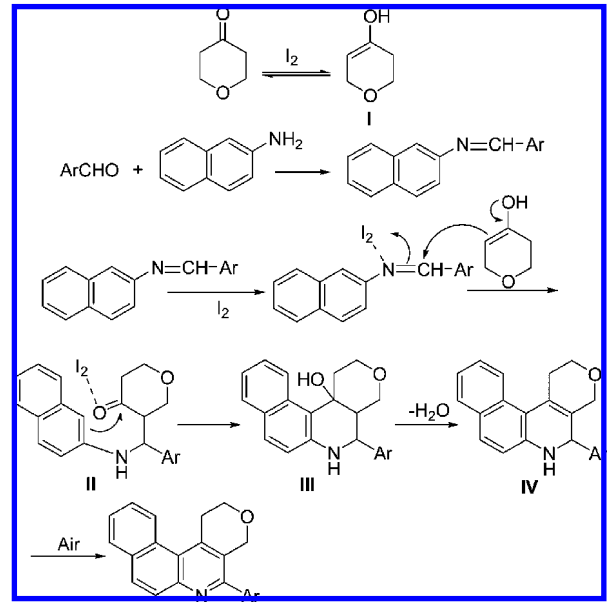
entry	Ar	products	time (h)	yields (%)[b]
1	4-FC_6H_4	**4a**	12	86
2	2-FC_6H_4	**4b**	10	89
3	3-$NO_2C_6H_4$	**4c**	8	90
4	2-$NO_2C_6H_4$	**4d**	8	84
5	4-$NO_2C_6H_4$	**4e**	9	92
6	2-Thienyl	**4f**	14	89
7	C_6H_5	**4g**	15	81
8	4-ClC_6H_4	**4h**	14	88
9	4-BrC_6H_4	**4i**	14	89
10	4-$CH_3C_6H_4$	**4j**	16	80
11	2-$CH_3OC_6H_4$	**4k**	16	83
12	3,4-$Cl_2C_6H_3$	**4l**	12	84
13	2,3-$Cl_2C_6H_3$	**4m**	13	86
14	2,4-$Cl_2C_6H_3$	**4n**	12	90

[a] Reagents and conditions: **1** (2 mmol), **2** (0.286 g, 2 mmol), **3** (0.200 g, 2 mmol), I_2 (0.1 mmol, 0.026 g), THF (10 mL). [b] Isolated yields.

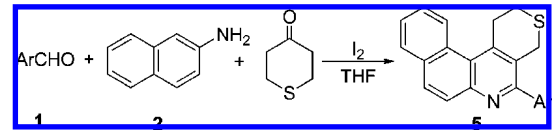
reaction. Higher loading of the catalyst had no significant influence on the reaction yield. To find the optimum reaction temperature, the reaction was carried out with 5 mol % I_2 at room temperature, 50 °C, and reflux temperature, resulting in the isolation of **4a** in a trace amount, 72%, and 86% yields (Table 1, entries 3−5), respectively. Thus, 5 mol % I_2 and a reaction temperature at reflux were optimal conditions. In addition, CH_3CN, benzene, DMF, and $CHCl_3$ (Table 1, entries 8−11) were also tested as solvents. In these cases, product **4a** was formed in slightly lower yields (Table 1, entries 8−11).

According to the optimized conditions, various aromatic aldehydes **1** were selected to react with naphthalen-2-amine **2** and tetrahydropyran-4-one **3** to give 1*H*-5-aryl-benzo[*f*]-pyrano[3,4-*c*]quinoline derivatives **4** in high yields within a few hours, respectively (Table 2). It can be observed that the process tolerates both electron-donating and electron-withdrawing substituents on the aromatic aldehydes. In all cases, the reactions proceeded efficiently at reflux to afford the corresponding 1*H*-5-arylbenzo[*f*]pyrano[3,4-*c*]quinolines in high yields. However, we failed to get the expected products when other amines were used, such as naphthalen-1-amine or *p*-toluidine. A possible reason is that the activity

Scheme 2. Possible Mechanism for the Formation of Products **4**



Scheme 3. Reaction of **1**, **2**, and Tetrahydrothiopyran-4-one



of *p*-toluidine or naphthalen-1-amine is less than that of naphthalene-2-amine.

According to the literature,[17] we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was proposed as shown in Scheme 2. In the presence of iodine, tetrahydropyran-4-one is in equilibrium with the enol form **I**. The enol immediately attacks iodine-activated Schiff base to form intermediate **II**, followed by an intramolecular Friedel−Crafts cyclization to give **III**. The subsequent dehydration of **III** results in dihydroquinoline **IV**, which is further oxidized by air to afford aromatized 1*H*-5-aryl-benzo[*f*]pyrano[3,4-*c*]quinolines **4**.

As expected, the substrate of tetrahydropyran-4-one could be extended to tetrahydrothiopyran-4-one, which was also chosen to react with the aromatic aldehyde, naphthalen-2-amine (Scheme 3) and were found to generate the corresponding 1*H*-5-aryl-benzo[*f*]thiopyrano[3,4-*c*]quinoline derivatives (**5a**−**n**). The results are summarized in Table 3. The structure of **5k** is confirmed by X-ray diffraction analysis, and its crystal structure is shown in Figure 2.

This sequence is also extended from aliphatic to aromatic pyran-4-one, such as chroman-4-one (Scheme 4). The desired reactions took place successfully to afford 1*H*-benzo[*f*]chromano[3,4-*c*]quinoline derivatives (**6a**−**d**) in moderate yields. The results are summarized in Table 4.

It was noteworthy that the above-mentioned reactions were performed using the same α-hydrogen atoms in the ketone moieties, for example, pyran-4-one, thiopyran-4-one, or chroman-4-one. In our continued study, we selected dihydrothiophen-3(2*H*)-one as a substrate with two different α-hydrogen atoms instead of tetrahydropyran-4-one. To our

Table 3. Synthesis of **5** Catalyzed by Iodine in THF[a]

entry	Ar	products	time (h)	yields (%)[b]
1	4-FC_6H_4	**5a**	10	84
2	2-FC_6H_4	**5b**	8	86
3	3-ClC_6H_4	**5c**	12	78
4	4-ClC_6H_4	**5d**	14	89
5	2-ClC_6H_4	**5e**	10	90
6	C_6H_5	**5f**	14	87
7	3-BrC_6H_4	**5g**	14	82
8	4-BrC_6H_4	**5h**	14	88
9	3-$NO_2C_6H_4$	**5i**	10	90
10	2-Thienyl	**5j**	12	79
11	3,5-$(CH_3O)_2C_6H_3$	**5k**	16	87
12	2,4-$Cl_2C_6H_3$	**5l**	12	82
13	2,3-$Cl_2C_6H_3$	**5m**	10	86
14	3,4-$Cl_2C_6H_3$	**5n**	12	89

[a] Reagents and conditions: **1** (2 mmol), **2** (0.286 g, 2 mmol), thiopyran-4-one (0.232 g, 2 mmol), I_2 (0.1 mmol, 0.026 g), THF (10 mL). [b] Isolated yields.

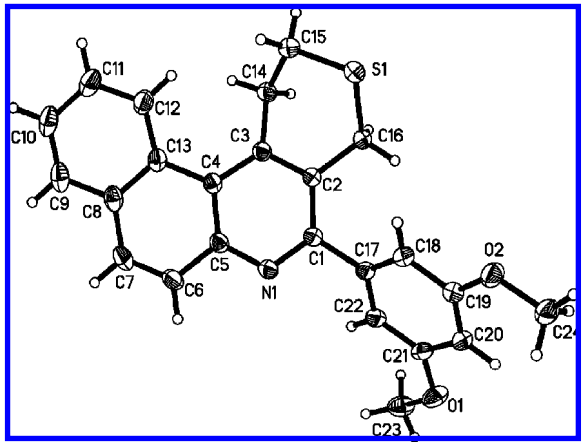


Figure 2. Crystal structure of product **5k**.

Scheme 4. Reaction of **1**, **2**, and Chroman-4-one

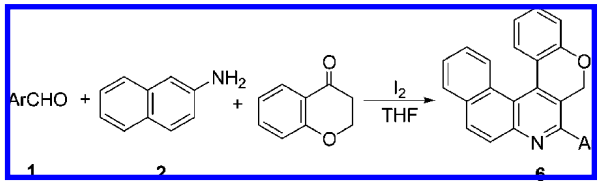


Table 4. Synthesis of **6** Catalyzed by Iodine in THF[a]

entry	Ar	products	time (h)	yields (%)[b]
1	C_6H_5	**6a**	16	72
2	4-ClC_6H_4	**6b**	15	76
3	2,3-$Cl_2C_6H_3$	**6c**	14	68
4	2,4-$Cl_2C_6H_3$	**6d**	14	71

[a] Reagents and conditions: **1** (1 mmol), **2** (0.143 g, 1 mmol), chroman-4-one (0.148 g, 1 mmol), I_2 (0.05 mmol, 0.013 g), THF (10 mL). [b] Isolated yields.

delight, the reaction of aromatic aldehyde **1**, naphthalen-2-amine **2**, and dihydrothiophen-3(2*H*)-one in THF in the presence of 5 mol % iodine at reflux selectively afforded the corresponding benzo[*f*]thieno[2,3-*c*]quinoline **7** in good to high yields (Scheme 5, Table 5). The structure of **7b** is confirmed by X-ray diffraction analysis, and its crystal structure is shown in Figure 3.

The naphtho[2,1-*c*][2,7]naphthyridine ring system is also a rare heterocycle compared with the [1,8]naphthyridine and [1,5]naphthyridine substructures. Naphthyridines, which encompass two pyridine rings, are known to display a wide

Scheme 5. Reaction of **1**, **2**, and Dihydrothiophen-3(2*H*)-one

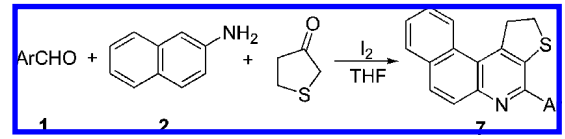


Table 5. Synthesis of **7** Catalyzed by Iodine in THF[a]

entry	Ar	products	time (h)	yields (%)[b]
1	2,4-$Cl_2C_6H_3$	**7a**	8	85
2	2-$CH_3OC_6H_4$	**7b**	6	82
3	C_6H_5	**7c**	9	81
4	3,5-$(CH_3O)_2C_6H_3$	**7d**	8	86
5	3-BrC_6H_4	**7e**	8	78
6	2,3-$Cl_2C_6H_3$	**7f**	6	76
7	2-$NO_2C_6H_4$	**7g**	6	82
8	2-BrC_6H_4	**7h**	8	80
9	4-ClC_6H_4	**7i**	8	79

[a] Reagents and conditions: **1** (2 mmol), **2** (0.286 g, 2 mmol), dihydrothiophen-3(2*H*)-one (0.204 g, 2 mmol), I_2 (0.1 mmol, 0.026 g), THF (10 mL). [b] Isolated yields.

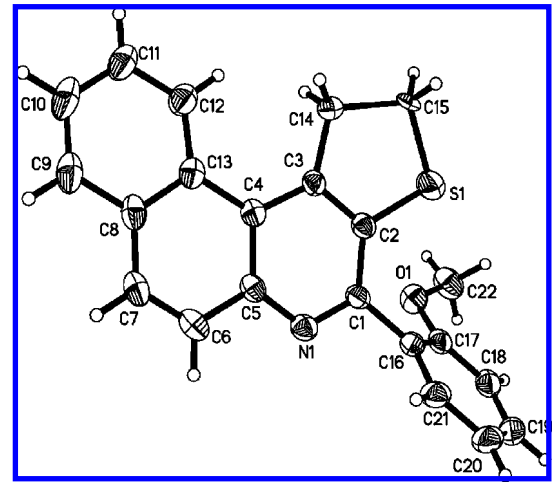
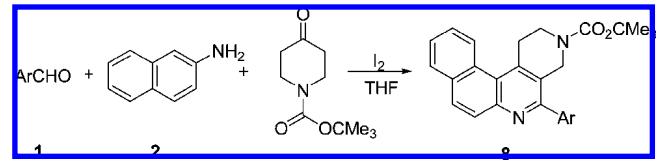


Figure 3. Crystal structure of product **7b**.

Scheme 6. Reaction of **1**, **2**, and BOC 4-Piperidinone



range of biological activities, including antibacterial activity,[18] antimalarial activity,[19] antimicrobial activity,[20] anticancer activity,[21] and antiinflammatory activity.[22]Barta-szalai et al.[23] revealed in 2003 that spiro[naphto[2,1-*c*][2,7]naphtiridine-5,4′-piperidine] derivatives were potent inhibitors of lipid peroxidation. In our initial study, we utilized piperidin-4-one in this reaction in order to obtain the potentially active naphtha[2,1-*c*][2,7]naphthyridines. However, to our surprise, we failed to get the expected products when 4-piperidinone, *N*-methyl-4-piperidinone, and *N*-benzyl-4-piperidinone were used as reactants. Perhaps the stabilities of these above-mentioned 4-piperidinones inhibited their reactions. Subsequently, we selected BOC 4-piperidinone to react with aromatic aldehyde, naphthalen-2-amine, under the same reaction conditions (Scheme 6), with naphtho[2,1-*c*][2,7]naphthyridine derivatives being obtained successfully in high yields. The structure

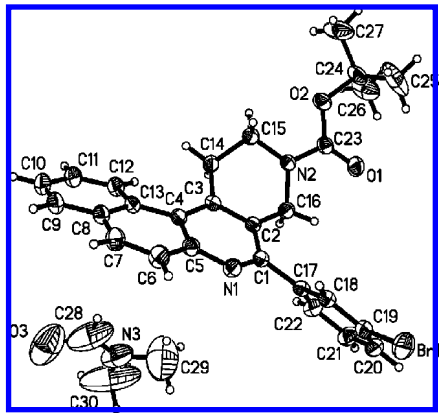


Figure 4. Crystal structure of product **8d** with DMF solvate.

Table 6. Synthesis of **8** Catalyzed by Iodine in THF[a]

entry	Ar	products	time (h)	yields (%)[b]
1	4-ClC_6H_4	**8a**	12	83
2	3-ClC_6H_4	**8b**	14	87
3	4-FC_6H_4	**8c**	10	79
4	3-BrC_6H_4	**8d**	17	82
5	3-$NO_2C_6H_4$	**8e**	10	89
6	3,4-$Cl_2C_6H_3$	**8f**	10	88

[a] Reagents and conditions: **1** (2 mmol), **2** (0.286 g, 2 mmol), BOC 4-piperidinone (0.398 g, 2 mmol), I_2 (0.1 mmol, 0.026 g), THF (10 mL). [b] Isolated yields.

of **8d** is confirmed by X-ray diffraction analysis, and its crystal structure is shown in Figure 4.

3. Conclusion

In conclusion, we found a mild and efficient method for the synthesis of pyranoquinoline, thiopyranoquinoline, thienoquinoline, and naphtho[2,7]naphthyridine derivatives via three-component reaction of aromatic aldehyde, naphthalen-2-amine, and heterocycloketones, including tetrahydropyran-4-one, tetrahydrothiopyran-4-one, pyridinone, and thiophenone using iodine as catalyst. The features of this procedure are mild reaction conditions, good to high yields and operational simplicity.

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Supporting Information Available. Representative experimental procedures, spectral data of compounds **4a**−**n**, **5a**−**n**, **6a**−**d**, **7a**−**i**, and **8a**−**f**, and crystallographic information files (CIF) of **4k**, **7b**, and **8d**. This material is available free charge via the Internet at http://pubs.acs.org.

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