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Iodine-induced efficient construction of a chromone-linked furo-[3,2-*c*]chromene scaffold by a one-pot 3-component cascade reaction

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ABSTRACT

A novel and efficient method for the construction of 4-(3-chromonyl)furo[3,2-*c*]-1-benzopyran scaffold by molecular iodine-induced cascade reaction between 3-(1-alkynyl)chromone and 1-(2-hydroxyphenyl)-3-*N*,*N*-dimethylaminoprop-2-ene-1-one is described. Two new C–O, one C–C, and one C–I bonds are formed in this one-pot cascade reaction. This tandem process involves Michael addition and double annulation under mild conditions without using transition metal, inert atmosphere, or dry solvent. Deiodination of the product was also accomplished.

Synthetic methodology that induces more than one bond formation and cyclization by a single operation provides an attractive route for the synthesis of polycyclic compounds. 2-(1-Alkynyl)-2-alkene-1-one (**A**) (Fig. 1) is a promising unit for the construction of substituted furans[1] and this motif **A** also acts as a very good synthon for the synthesis of different compounds of pharmaceutical importance.[2]

The ubiquity of the chromone skeleton in the plant kingdom[3] and in many biologically active compounds[4] deserves the synthesis of new chromone-fused or chromone-linked polycyclic heterocycles. 3-(1-Alkynyl)chromone **1** bearing the privileged moiety **A** has drawn the attention of synthetic chemists for the synthesis of biologically relevant and natural product-like frame works.

Literature survey reveals that different activating agents used to activate the alkyne moiety of **A** or of **1** are costly transition metals like $AuCl_3$,[1a] $(Ph_3P)AuOTf$,[5] AuCl/AgOTf,[6] $PtCl_2$,[7] Cu(I) halide,[8] and CuI-$Pd(OAc)_2$[9] mainly in the presence of alcoholic nucleophiles. Nitrogenous nucleophiles in the form of hydroxylamine,[2b] imine,[10] amidine,[11] and carbon nucleophiles developed from active methylene compounds[2a,c,12] have also been employed. Molecular iodine has been utilized to initiate reactions of **A**[13] and **1**[1b] using mainly alcoholic nucleophiles. We envisioned the use of 1-(2-hydroxyphenyl)-3-(*N*,*N*-dimethylamino)propenone **2** as the nucleophilic component considering its dual role: (i) it can act as a nucleophile to facilitate 5-*endo*-*dig* cyclization to form furan **4** and (ii) the proximal hydroxy group to the iminium function in **4** could undergo second annulation to form **5**, which readily forms a chromone-linked furochromone **3** by the elimination of dimethylamine (Scheme 1).

This expected structure **3** contains a furo[3,2-*c*]-1-benzopyran with a pendant chromone moiety. Furo[3,2-*c*]-1-benzopyran skeleton is widely distributed in different biologically active natural products like coumestrol, wedelolactone, medicagol, and plicadin.[14] Again chromones and bichromones are also available in nature and exhibit different pharmaceutical activities.[4,15] It would be of interest to develop processes for the synthesis of molecules having furochromone, chromone, and bichromone motifs in their structural unit for biological screening.

Our studies were initiated by the treatment of equimolar mixture of **1a** and **2a** in the presence of CuBr (10 mol %) in DMF at 80–90 °C for 4 h. But 4*H*-furo[3,2-*c*]chromen-4-one **6**[8b,16] (Fig. 2) was obtained without the involvement of enamine **2** (Table 1, entry 1). Use of CuI or CuCl in the place of CuBr in the above reaction also yielded **6** (entries 2 and 3). On employing $InCl_3$, $BF_3{\cdot}Et_2O$, or $PdCl_2$ as catalyst in the reaction of **1a** and **2a** in CH_3CN or $CHCl_3$, pure compound could not be isolated from the reaction mixture (entries 4–6); whereas 2-(2-hydroxyphenyl)-5-

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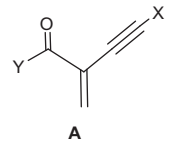


Figure 1. Structure of **A**.

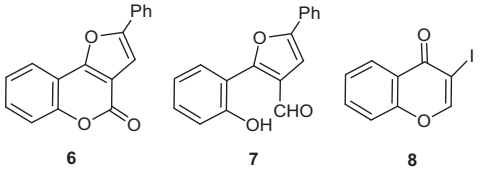
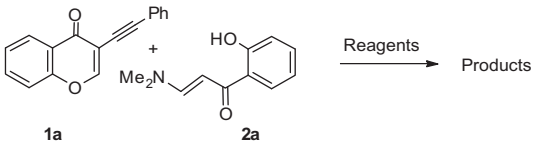


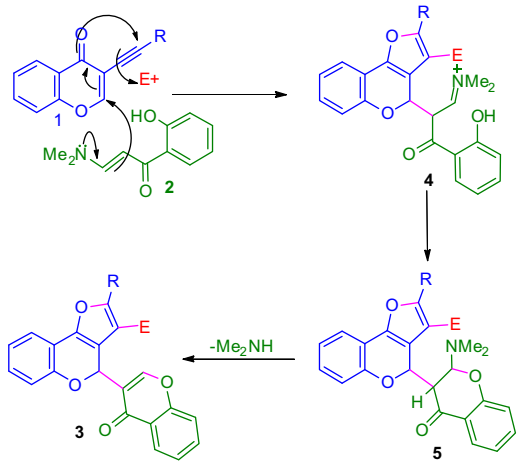
Figure 2. Structures of **6–8**.

Table 1
Reaction of **1a** with **2a** in the presence of different reagents



Entry	Reagents (equiv)	Reaction conditions	Product	Yield[d] (%)
1	CuBr (0.1)	DMF/80–90 °C/4 h	**6**	70
2	CuI (0.1)	DMF/80–90 °C/4 h	**6**	65
3	CuCl (0.1)	DMF/80–90 °C/4 h	**6**	65
4	$InCl_3$ (0.2)	CH_3CN/Reflux/4 h	—[a]	—
5	$BF_3{\cdot}Et_2O$ (0.2)	$CHCl_3$/RT/12 h	—[a]	—
6	$PdCl_2$ (0.1)	$CHCl_3$/RT/12 h	—[a]	—
7	$Pd(OAc)_2$ (0.1)	$CHCl_3$/RT/12 h	**7**	30
8	$AgNO_3$ (0.2)	$CHCl_3$/RT/ 12 h	**7**	42
9	$Ag(OCOCF_3)$ (0.1)	$CHCl_3$/RT/12 h	**7**	52
10	$Yb(OTf)_3$ (0.1)	$CHCl_3$/RT/24 h	NR[b]	—
11	$PdCl_2(PPh_3)_2$ (0.1)	$CHCl_3$/RT/24 h	NR[b]	—
12	I_2 (1.0)	CH_2Cl_2/RT/24 h	**3a**	43
			8	20
13	I_2 (1.1)[c]	CH_2Cl_2/RT/15 h	**3a**	67
14	I_2 (1.1)/K_3PO_4 (1.5)	CH_2Cl_2/RT/15 h	**3a**	10
15	ICl (1.2)	CH_2Cl_2/RT/15 h	**3a**	50
16	I_2 (1.1)[c]	$CHCl_3$/RT/15 h	**3a**	70

[a] Pure compound could not be isolated.
[b] No reaction.
[c] Stirred a mixture of **1a** (0.2 mmol) and I_2 (0.22 mmol) in solvent (5 mL) for 1 h and then a solution of **2a** (1.25 equiv) in solvent (5 mL) was added and stirred.
[d] Yield of isolated product based on **1a**. 'RT' stands for room temperature.



Scheme 1. Our envisioned one-pot synthesis of 4-(3-chromonyl)furo[3,2-*c*]-1-benzopyran (**3**).

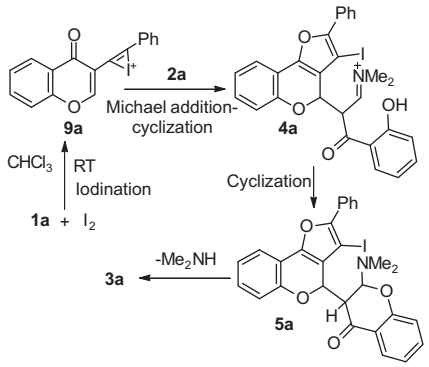
phenylfuran-3-carbaldehyde (**7**)[5] (Fig. 2) was isolated in varying amounts when $Pd(OAc)_2$ or $AgNO_3$ or $AgOCOCF_3$ were used as catalysts in $CHCl_3$ medium (entries 7–9). Use of $Yb(OTf)_3$ or $PdCl_2(PPh_3)_2$ as catalyst caused no change in **1a** (entries 10 and 11). Surprisingly, when an equimolar mixture of **1a**, **2a,** and iodine in CH_2Cl_2 was stirred for 24 h at room temperature, the reaction mixture produced **3a** in 43% yield along with 3-iodochromone **8** (Fig. 2) in 20% yield (entry 12). Formation of **8** from **2a** is a well-established reaction.[17] To avoid the formation of this side product **8**, the mode of addition was changed. At first a mixture of **1a** (1 equiv) and I_2 (1.1 equiv) was stirred in CH_2Cl_2 at room temperature for 1 h and then **2a** (1.25 equiv) was added to the reaction mixture and stirred for 14 h under similar reaction conditions. To our delight, the reaction mixture afforded **3a** in 67% yield (entry 13). To check the role of additional base, K_3PO_4 was added to the reaction mixture, but addition of K_3PO_4 showed a detrimental effect (entry 14).

Formation of **3a** may be rationalized by considering the initial activation of the alkyne by iodine to form iodonium ion **9a**, which undergoes Michael addition of enamine **2a** followed by cyclization to form furan **4a** (Scheme 2). The suitably placed hydroxy group in **4a** attacks the iminium ion and causes second annulation to form **5a**, which eliminates dimethylamine to produce **3a**.

Encouraged by the role of iodine, iodine monochloride was also tested as a substitute of iodine in the above reaction. However, on stirring a mixture of **1a** (1 equiv) and ICl (1.2 equiv) in CH_2Cl_2 for 1 h followed by addition of **2a** (1.25 equiv) and stirring for 14 h produced **3a** but in decreased yield compared to the use of iodine (entries 13 and 15). Effect of solvent in this iodine-initiated reaction was studied using **1a** and **2a** as substrates in different solvents. Using solvents like DMF, Et_2O, and CH_3CN, no reaction was observed. $CHCl_3$ was found to be a better choice over CH_2Cl_2 (entries 13 and 16). Stirring a mixture of **1a** (1 equiv) and I_2 (1.1 equiv) in $CHCl_3$ for 1 h at room temperature followed by the addition of **2a** (1.25 equiv) and further stirring for 14 h at room temperature is the optimized reaction condition for the synthesis of **3a** (entry 16).

To study the scope and limitation of this methodology, various 3-(1-alkynyl)chromones **1** were used under the optimized reaction conditions. It has been observed that electron donating groups on the phenyl ring of chromone moiety in **1** increases the yield of **3** (**3c**, **3g,** and **3h**) (77–83%) (Table 2), whereas having an electron withdrawing group in **1**, **3e** was obtained in only 45% yield, which is much lesser than corresponding unsubstituted derivative **3b** (60%).

Different substitutions on the alkyne part of **1** showed that aryl substituents generally work well than the alkyl group (**3l**) or trimethylsilyl group (**3m**). It needs to mention that the reaction conditions in the present methodology are mild enough to survive trimethylsilyl group in the product **3m** contrary to the earlier reports.[1b,10,13a] Effect of substituent on the aryl part attached to the alkyne moiety in **1** (R^3 = Aryl) was also studied. Presence of electron donating group was found to facilitate the reaction (**3j**, **3k** in comparison to **3n**). To consider the substituent effect on **2**, a series of enaminoketones **2** were synthesized and employed in the iodine-mediated reaction with **1**. Presence of an electron-donating group on **2** facilitates the reaction (**3f**, 71%) whereas the presence of weak electron-withdrawing groups decrease the yield (**3d**, 53% and **3i**, 57%) and strong electron-withdrawing NO_2 group decreases markedly the yield of **3o** (28%) (Table 2).

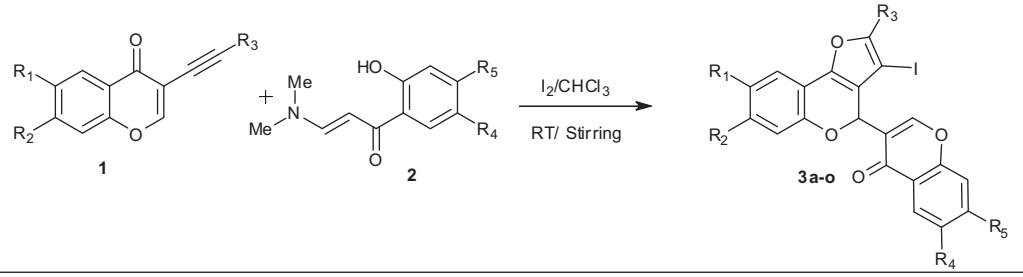


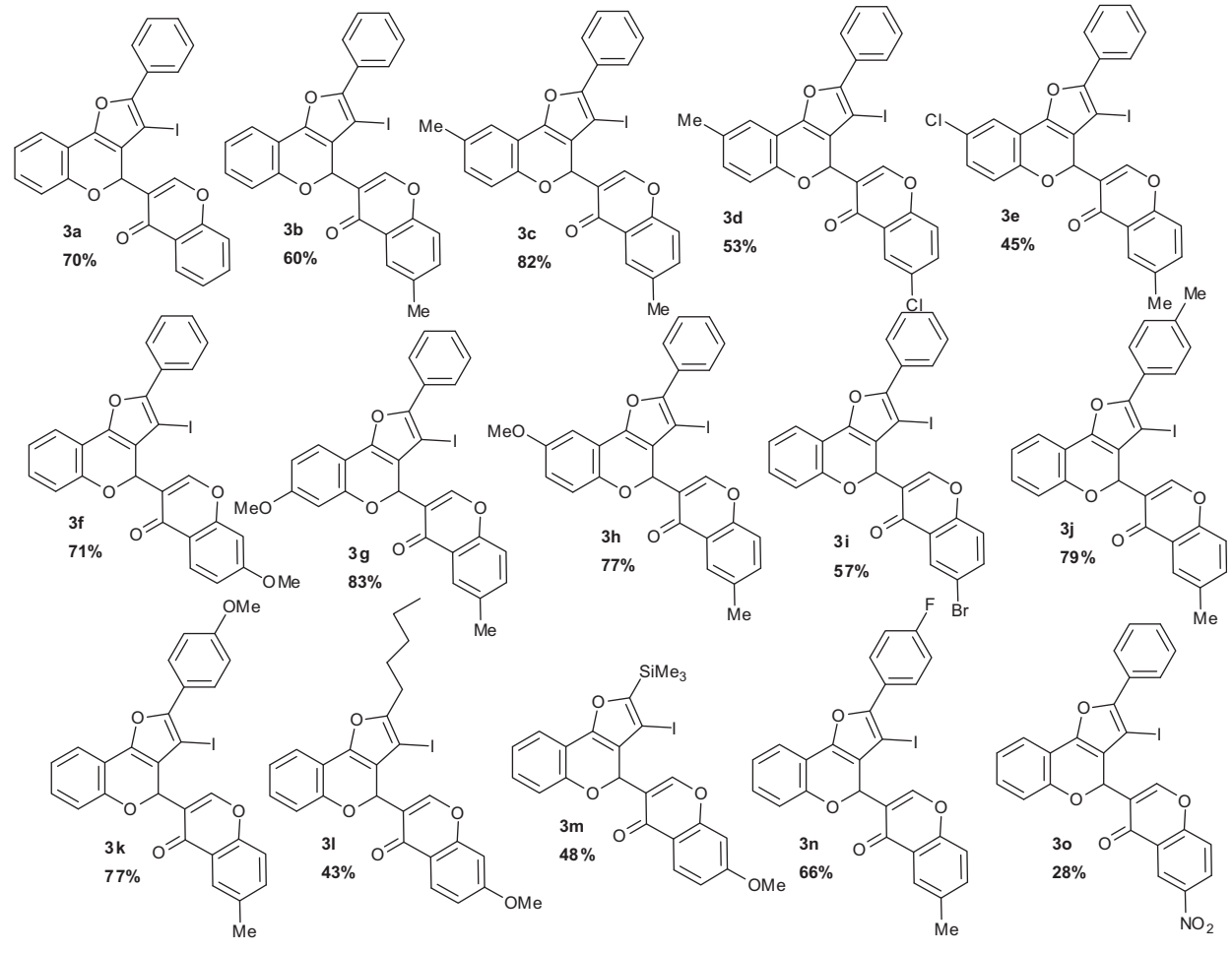
Scheme 2. Probable mechanism for the formation of **3a**.

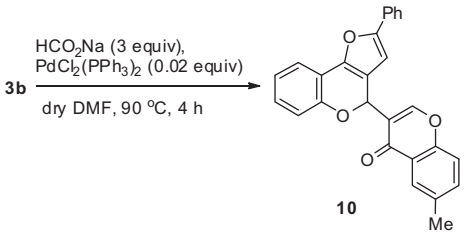
After developing the process for the synthesis of **3**, an attempt was made to deiodinate **3** by the reductive cleavage of the C–I bond. As a test case **3b** was converted into **10** by treating **3b** (1 equiv) with sodium formate (3 equiv) in dry DMF in the presence of $PdCl_2(PPh_3)_2$ (0.02 equiv) as catalyst to produce **10** in 79% yield (Scheme 3). This two-step process will be a very good method for the synthesis of furo[3,2-*c*]chromene scaffold avoiding the use of costly gold or silver catalysts.

In conclusion, we have synthesized hitherto unreported 3-iodo-4-(3-chromonyl)furo[3,2-*c*]chromene **3** by a one-pot molecular iodine-induced cascade reaction between 3-(1-alkynyl)chromone **1** and 1-(2-hydroxyphenyl)-3-*N*,*N*-dimethylaminopropenone **2** under mild reaction conditions without using any transition metal or dry solvent. This reaction involves Michael addition and double annulation. Finally, reductive cleavage of C–I bond in **3** was accomplished and the overall attempt developed a method for the

Table 2
Synthesis of 4-(3-chromonyl)-3-iodofuro[3,2-*c*]-1-benzopyrans **3**







Scheme 3. Reductive cleavage of C–I bond in **3b**.

synthesis of 4-(3-chromonyl)furo[3,2-*c*]chromene **10** without using any costly catalyst.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.046.

References and notes

1. (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164–11165; (b) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679–7685; (c) Xiao, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1903–1906; (d) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505–5508; (e) Gao, H.; Wu, X.; Zhang, J. *Chem. Eur. J.* **2011**, *17*, 2838–2841; (f) Rauniar, V.; Wang, Z. J.; Burks, H. E.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 8486–8489; (g) Zhou, L.; Zhang, M.; Li, W.; Zhang, J. *Angew. Chem.* **2014**, *126*, 6660–6663; (h) Reddy, B. V. S.; Reddy, V. V.; Karthik, G.; Jagadeesh, B. *Tetrahedron* **2015**, *71*, 2572–2578.
2. (a) Xiao, Y.; Zhang, J. *Chem. Commun.* **2009**, 3594–3596; (b) Yu, X.; Du, B.; Wang, K.; Zhang, J. *Org. Lett.* **2010**, *12*, 1876–1879; (c) Hu, J.; Liu, L.; Yang, S.; Liang, Y.-M. *Org. Biomol. Chem.* **2011**, *9*, 3375–3379.
3. (a) Ellis, G. P. In *Heterocyclic Compounds*; Weissberger, A., Ed.; Inter-science: New York, 1977; Vol. 31, pp 903–1083. Chapters XVIII–XXI; (b) Staunton, J. In *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon press: Oxford, 1979; Vol. 4, pp 659–692. Chapter 18.3.
4. (a)*Comprehensive Medicinal Chemistry*; Hansch, C., Sammes, P. G., Taylor, J. B., Eds.; Pergamon Press: New York, 1990; Vol. 6, (b) Korkina, G. L.; Afanas'ev, I. B. In *Advances in Pharmacology*; Sies, H., Ed.; Academic Press: San Diego, 1997; Vol. 38, p 151; (c) Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. *Chem. Rev.* **2014**, *114*, 4960–4992.
5. Hu, F.; Chen, T.; Yan, J.; Cheng, M.; Huang, L.; Hu, Y. *RSC Adv.* **2012**, *2*, 11238–11241.
6. Gao, H.; Wu, X.; Zhang, J. *Chem. Commun.* **2010**, 8764–8766.
7. Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307–5310.
8. (a) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531–4534; (b) Cheng, G.; Hu, Y. *J. Org. Chem.* **2008**, *73*, 4732–4735.
9. Li, W.; Zhang, J. *Chem. Commun.* **2010**, 8839–8841.
10. Yan, J.; Cheng, M.; Hu, F.; Hu, Y. *Org. Lett.* **2012**, *14*, 3206–3209.
11. (a) Li, D.; Duan, S.; Hu, Y. *J. Comb. Chem.* **2010**, *12*, 895–899; (b) Iaroshenko, V. O.; Dudkin, S.; Sosnovskikh, V. Y.; Villinger, A.; Langer, P. *Eur. J. Chem.* **2013**, 3166–3173.
12. (a) Zhao, L.; Xie, F.; Cheng, G.; Hu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 6520–6523; (b) Liu, Y.; Huang, L.; Xie, F.; Hu, Y. *J. Org. Chem.* **2010**, *75*, 6304–6307; (c) Liu, Y.; Huang, L.; Xie, F.; Hu, Y.; Chen, X.; Hu, Y. *Org. Biomol. Chem.* **2011**, *9*, 2680–2684.
13. (a) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609–4611; (b) Cho, C.-H.; Larock, R. C. *Tetrahedron Lett.* **2010**, *51*, 3417–3421.
14. (a) Schuster, N.; Christiansen, C.; Jakupovic, J.; Mungai, M. *Phytochemistry* **1993**, *34*, 1179–1181; (b) Boland, G. M.; Donnelly, D. M. X. *Nat. Prod. Rep.* **1998**, *15*, 241–260; (c) Wang, X.; Bastow, K. F.; Sun, C.-M.; Lin, Y.-L.; Yu, H.-J.; Don, M.-J.; Wu, T.-S.; Nakamura, S.; Lee, K.-H. *J. Med. Chem.* **2004**, *47*, 5816–5819; (d) Zhao, L.; Brinton, R. D. *J. Med. Chem.* **2005**, *48*, 3463–3466; (e) Wang, W.; Zhao, Y.-Y.; Liang, H.; Jia, Q.; Chen, H.-B. *J. Nat. Prod.* **2006**, *69*, 876–880.
15. (a) Drewes, S. E.; Hudson, N. A.; Bates, R. B.; Linz, G. S. *J. Chem. Soc., Perkin Trans 1* **1987**, 2809–2813; (b) Jiang, Z.-H.; Tanaka, T.; Sakamoto, T.; Kouno, I.; Duan, J. A.; Zhou, R. H. *Chem. Pharm. Bull.* **2002**, *50*, 137–139; (c) Sangrera, G.; Seoane, G. *Synthesis* **2010**, 2776–2786.
16. Cheng, G.; Hu, Y. *Chem. Commun.* **2007**, 3285–3287.
17. Gammill, R. B. *Synthesis* **1979**, 901–903.