Synthesis of 2-Substituted Furo[2,3-*b*]- and Furo[3,2-*c*]quinolines via Heterogeneous Palladium-catalyzed Heteroannulation

Hee Jung Park,[†] Ok-Kyung Yang,[‡] Young Chul Park,[‡] and Eul Kgun Yum[‡,*]

[†]*Korea Basic Science Institute, Seoul 120-750, Korea*
[‡]*Department of Chemistry, Chungnam National University, Daejon 305-764, Korea.*
**E-mail: ekyum@cnu.ac.kr*
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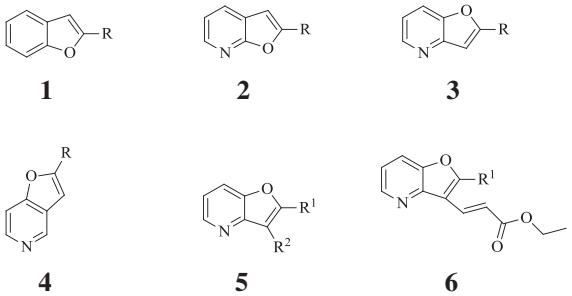
Furoquinoline scaffolds are one of the important heterocycles and their analogues are found not only in nature[1] but also in pharmacological and biological materials, whose properties include anti-inflammatory,[2] TLR8 (Toll-like receptor-8) agonistic,[3] anti-cancerous,[4] a protein inhibitory,[5] and antimicrobial activity.[6] Owing to their diverse biological activities, there have been great efforts to extract[7] or synthesize furoquinolines, *i.e.*, [3 + 2] cyclization reaction for furo[2,3-*b*]quinolines,[8] [4 + 2] cycloaddition of imines with enol ethers,[9] and a three component reaction of 4-hydroxyquinolin-2(*1H*)-one, aromatic aldehyde and isonitrile, and so on.[10] Recently we have paid much attentions to develop green and practical synthetic methods for synthesizing various furoheterocycles **1–6** as shown in Scheme 1.[11]

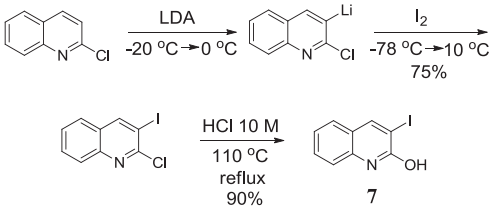
The isomeric 2-substituted furopyridines such as furo[3,2-*b*]-, furo[2,3-*b*]-, and furo[3,2-*c*]pyridine were synthesized starting from *o*-halohydroxypyridines and terminal alkynes catalyzed by commercial Pd/C under copper- and ligand-free conditions. Also we were able to show diversification of our protocol to make 2,3-disubstituted furoquinolines, **5** and **6**, by Suzuki and Heck reactions, respectively.[11a]

As a part of our continuing organometallic studies on diversification of nitrogen-containing biologically active heterocycles, we attempted to synthesize furo[2,3-*b*]- and furo[3,2-*c*]quinolines starting from *o*-halohydroxyquinolines and terminal alkynes with heterogeneous $Pd(OAc)_2$ catalyst, which was supported by nanosized pore carbon ball. The best reaction condition was obtained under CNB–$Pd(OAc)_2$ (5 mol %), LiCl (1 equiv), Cs_2CO_3 (2 equiv), DMF, and 110°C.



Scheme 1. Diversification of furoheterocycles.

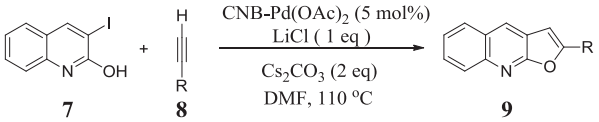
The starting material of 3-iodoquinolin-2-ol (**7**) was prepared as shown in Scheme 2.[12]



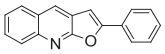
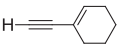
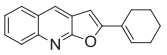
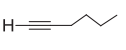
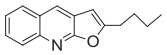
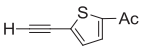
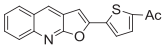
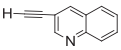
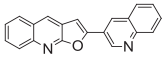
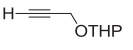
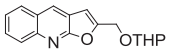
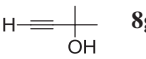
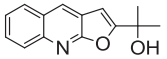
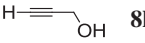
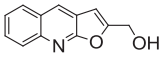
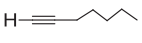
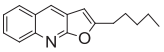
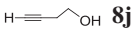
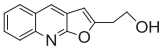
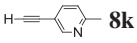
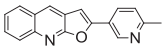
Scheme 2. Preparation of 3-iodoquinolin-2-ol (**7**).

At this step, it turned out that the control of reaction temperature was very important, *i.e.*, maintaining the temperature around −20 to 0°C was critical for good *ortho*-lithiation of chloroquinoline with LDA(LiN*i*-Pr_2). If the temperature was lower or higher than the condition above, the yield of next step (iodination) was low. On the other hand, 7-chloro-3-iodoquinolin-4-ol (**10**), required to synthesize corresponding furo[3,2-*c*]quinolines (**11**), was prepared by modifying a similar procedure.[3] That is, for the electrophilic iodination of 7-chloro-4-hydroxyquinoline, we have used aqueous NaOH (20%) and 2-fold excess of iodine (2 equiv) instead of 2 N NaOH and 20% excess of iodine as was reported for 4-iodoquinolin-3-ol. According to our established reaction conditions, we examined the heterogeneous palladium-catalyzed heteroannulation of *o*-halohydroxyquinolines by terminal alkynes. 2-Substituted furo[2,3-*b*]quinolines **9a–k** were synthesized in moderate to high isolated yields except for **9c,h,k** from the reaction of 3-iodoquinolin-2-ol (**7**) and various alkynes **8a–k** in Table 1. The results showed that the reaction times and yields were quite dependent on terminal alkyne substituents. We also examined the reactions of 7-chloro-3-iodoquinolin-4-ol (**10**) with various alkynes. The isomeric 2-substituted 7-chlorofuro[3,2-*c*]quinolines (**11**) were also obtained in good isolated yields under our established optimization conditions (Table 2).

Table 1. Synthesis of furo[2,3-*b*]quinoline.[a]

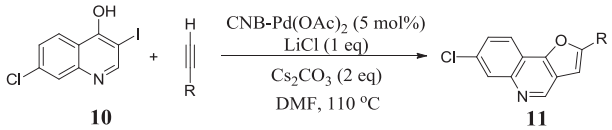


7 **8** **9**

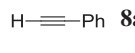
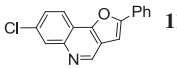
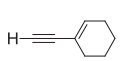
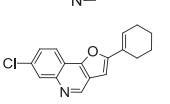
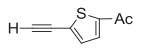
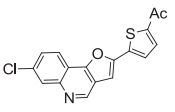
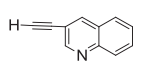
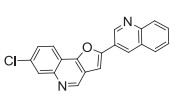
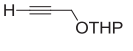
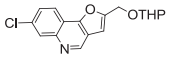
Entry	Alkyne[b]	Reaction times (h)	Product	Isolated yield (%)
1	**8a**	30	 **9a**	80
2	 **8b**	6	 **9b**	60
3	 **8c**	6	 **9c**	30
4	 **8d**	9	 **9d**	70
5	 **8e**	7	 **9e**	69
6	 **8f**	12	 **9f**	55
7	 **8g**	9	 **9g**	73
8	 **8h**	40	 **9h**	25
9	 **8i**	12	 **9i**	73
10	 **8j**	5	 **9j**	70
11	 **8k**	48	 **9k**	35

[a] All reactions were performed on 0.5 mmol scale.
[b] 2 equiv.

Table 2. Synthesis of furo[3,2-*c*]quinoline.[a]



10 **11**

Entry	Alkyne[b]	Reaction times (h)	Product	Isolated yield (%)
1	 **8a**	7	 **11a**	55
2	 **8b**	8	 **11b**	65
3	 **8d**	10	 **11d**	45
4	 **8e**	7	 **11e**	70
5	 **8f**	7	 **11f**	45

[a] All reactions were performed on 0.5 mmol scale.
[b] 2 equiv.

In summary, 2-substituted furo[2,3-*b*]quinolines and furo [3,2-*c*]quinolines were synthesized from the reaction of 3-iodoquinolin-2-ol and 3-iodoquinolin-4-ol, respectively, with diverse alkynes. The heteroannulation reaction proceeds with Sonogashira coupling followed by 5-*endo-dig* cyclization in good isolated yields under copper and ligand free conditions.

Experimental

General. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL400 Spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using $CDCl_3$ as the solvent and TMS as internal standard. The GC-MS spectra were obtained using a Shimadzu QP 1000 GC-MS. Elemental analyses were carried out by an elemental analyzer (EA-1110). NCB-Pd $(OAc)_2$ catalyst and terminal alkyne were prepared by following a known procedure.[11]

Typical Procedure for the Synthesis of 9 **and** 11**.** In a pressure tube, a suspension of $Pd(OAc)_2$/C (5 mol %), 3-iodoquinolin-2-ol (**7**) (0.5 mmol), LiCl (0.5 mmol), cesium carbonate (1 mmol), and terminal alkyne (1.0 mmol) in DMF (3 mL) was stirred for designated period of time at 110°C. The reaction mixture was filtered and neutralized with saturated NH_4Cl solution, followed by extraction with ethyl acetate. The crude product was purified by column chromatography with the use of hexane and ethyl acetate as eluents. 2-Phenyl-furo[2,3-*b*]quinoline (**9a**) was obtained in 80% yield as yellow solid. mp 180–183°C; ^{1}H NMR ($CDCl_3$) δ 7.10 (s, 1H, ArH), 7.40–7.44 (m, 1H, ArH), 7.47–7.52 (m, 3H, ArH), 7.69 (t, *J* = 8 Hz, 1H, ArH), 7.91 (d, *J* = 8 Hz, 1H, ArH), 7.96 (d, *J* = 8 Hz, 2H, ArH), 8.11 (d, *J* = 8 Hz, 1H, ArH), 8.29 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 99.51, 122.03, 124.77, 125.40, 126.68, 127.70, 128.18, 128.35, 128.63, 128.87, 129.25, 129.71, 144.68, 157.56, 161.50; MS (EI) *m/z* 245 [M^+]; Anal. Calcd for $C_{17}H_{11}NO$: C, 83.25; H, 4.52; N, 5.71; Found : C, 83.27; H, 4.51; N, 5.72.

The following compounds were prepared by following the general procedure.

2-(Cyclohex-1-enyl)furo[2,3-b]quinolone (9b). 60%; pale yellow solid, mp 90–93°C; ^{1}H NMR ($CDCl_3$) δ 1.70–1.83 (m, 4H, CH_2CH_2), 2.31–2.41 (m, 4H, CH_2CH_2), 6.55 (s, 1H, ArH), 6.85 (s, 1H, ArH), 7.47 (t, *J* = 8 Hz, 1H, ArH), 7.65 (t, *J* = 8 Hz, 1H, ArH), 7.87 (d, *J* = 8 Hz, 1H, ArH), 8.06 (d, *J* = 8 Hz, 1H, ArH), 8.18 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 21.99, 22.22, 24.48, 25.74, 98.28, 122.27, 124.52, 126.39, 126.54, 127.43, 127.57, 128.23, 128.26, 129.92, 158.98; MS (EI) *m/z* 249 [M^+]. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62; Found : C, 81.92; H, 6.04; N, 5.61.

2-Butylfuro[2,3-b]quinoline (9c). 30%; pale yellow solid, mp 78–80°C; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, CH_3), 1.41–1.47 (m, 2H, CH_2), 1.75–1.83 (m, 2H, CH_2), 2.83 (t, 2H, CH_2), 6.45 (s, 1H, ArH), 7.47 (t, 1H, ArH), 7.65 (t, 1H, ArH), 7.87 (d, *J* = 8 Hz, 1H, ArH), 8.07 (d, *J* = 8 Hz, 1H, ArH), 8.16 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.80, 22.26, 28.58, 29.12, 100.57, 121.88, 124.42, 126.38, 127.12, 127.54, 128.11, 128.26, 144.04, 161.63, 162.26; MS (EI) *m/z* 225 [M^+]; Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22; Found: C, 79.92; H, 6.72; N, 6.24.

2-(5-Acetylthiophen-2-yl)furo[2,3-b]quinoline (9d). 70%; pale yellow solid, mp 228–230°C; ^{1}H NMR ($CDCl_3$) δ 2.60 (s, 3H, CH_3), 7.11 (s, 1H, ArH), 7.51–7.55 (m, 1H, ArH), 7. 64–7.74 (m, 3H, ArH), 7.93 (d, *J* = 8 Hz, 1H, ArH), 8.10 (d, *J* = 8 Hz, 1H, ArH), 8.34 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 26.83, 102.04, 121.35, 122.44, 125.15, 126.72, 127.88, 128.43, 129.06, 129.25, 132.95, 139.31, 144.98, 145.12, 151.48, 156.77, 190.32; MS (EI) *m/z* 293 [M^+]; Anal. Calcd for $C_{17}H_{11}NO_2S$: C, 69.61; H, 3.78; N, 4.77; Found: C, 69.58; H, 3.79; N, 4.76.

2-Quinolin-3-yl-furo[2,3-b]quinoline (9e). 69%, pale yellow solid, mp 206–208°C; ^{1}H NMR ($CDCl_3$) δ 7.36 (s, 1H, ArH), 7.49–7.54 (m, 2H, ArH), 7.71–7.79 (m, 2H, ArH), 7.95 (t, *J* = 8 Hz, 2H, ArH), 8.14 (dd, *J* = 4.8, 3.2 Hz, 2H, ArH), 8.40 (s, 1H, ArH), 8.75 (s, 1H, ArH), 9.43 (s, 1H, ArH); ^{13}C NMR (DMSO) δ 102.62, 115.10, 121.33, 121.97, 122.18, 124.96, 126.44, 127.07, 127.55, 127.75, 128.27, 128.77, 129.16, 129.60, 130.57, 131.53, 144.27, 147.36, 154.25, 160.94; MS (EI) *m/z* 296 [M^+]; Anal. Calcd for $C_{20}H_{12}N_2O$: C, 81.07; H, 4.08; N, 9.45; Found: C, 81.05; H, 4.09; N, 9.44.

2-(Tetrahydropyran-2-yloxymethyl)furo[2,3b]quinoline (9f). 55%, pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.54–2.04 (m, 6H, CH_2), 3.56–3.61 (m, 1H, CH), 3.93–3.99 (m, 1H, CH), 4.71 (d, *J* = 16 Hz, 1H, CH), 4.88 (d, *J* = 16 Hz, 2H, CH_2), 6.78 (s, 1H, ArH), 7.51–7.47 (m, 1H, ArH), 7.70–7.66 (m, 1H, ArH), 7.90 (d, *J* = 8 Hz, 1H, ArH), 8.09 (d, *J* = 8 Hz, 1H, ArH), 8.27 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.95, 25.33, 30.28, 61.43, 61.93, 97.94, 103.45, 120.94, 124.62, 126.30, 127.69, 128.30, 128.59, 128.63, 144.57, 157.14, 161.61; MS (EI) *m/z* 283 [M^+]; Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; Found: C, 72.05; H, 6.07; N, 4.84.

2-(2-Hydroxypropan-2-yl)furo[2,3-b]quinoline (9g). 73%, pale yellow solid, mp 142–144°C; ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 6H, CH_3), 3.06 (br, 1H, OH), 6.68 (s, 1H, ArH), 7.49 (t, *J* = 8 Hz, 1H, ArH), 7.67 (t, *J* = 8 Hz, 1H, ArH), 7.88 (d, *J* = 8 Hz, 1H, ArH), 8.08 (d, *J* = 8 Hz, 1H, ArH), 8.22 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 28.56 69.49, 98.82, 121.37, 124.68, 126.42, 127.68, 128.17, 128.62, 128.64, 144.32, 161.39, 165.58; MS (EI) *m/z* 227 [M^+]; Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; Found: C, 73.95; H, 5.79; N, 6.19.

Furo[2,3-b]quinolin-2-yl-methanol (9h). 25%, brown oil; ^{1}H NMR ($CDCl_3$) δ 3.43 (br, 1H, OH), 4.85 (s, 2H, CH_2), 6.73 (s, 1H, ArH), 7.49 (t, *J* = 8 Hz, 1H, ArH), 7.68 (t, *J* = 8 Hz, 1H, ArH), 7.87 (d, *J* = 8 Hz, 1H, ArH), 8.06 (d, *J* = 8 Hz, 1H, ArH), 8.23 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 65.25, 102.14, 120.95, 121.20, 124.81, 126.30, 127.80, 128.91, 129.12, 130.58, 144.10, 159.45; MS (EI) *m/z* 199 ([M^+]; Anal. Calcd for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03; Found: C, 72.37; H, 4.53; N, 7.01.

2-Pentylfuro[2,3-b]quinoline (9i). 73%, pale yellow solid, mp 84–86°C; ^{1}H NMR ($CDCl_3$) δ 0.89–0.93 (t, J = 8 Hz, 3H, CH_3), 1.39–1.42 (m, 4H, CH_2), 1.77–1.83 (m, 2H, CH_2), 2.83 (t, J = 8 Hz, 2H, CH_2), 6.46 (s, 1H, ArH), 7.46–7.49 (m, 1H, ArH), 7.63–7.68 (m, 1H, ArH),7.88 (d, J = 8 Hz, 1H, ArH), 8.07 (d, J = 8 Hz, 1H, ArH), 9.17 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 14.04, 22.42, 26.78, 28.90, 31.34, 100.59, 121.92, 124.45, 126.41, 127.15, 127.55, 128.14, 128.30, 144.07, 161.67, 162.32; MS (EI) *m/z* 239 [M^+]; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85; Found: C, 80.34; H, 7.12; N, 5.84.

2-(Ethanol-2-yl)furo[2,3-b]quinoline (9j). 70%, pale yellow solid, mp 106–108°C; ^{1}H NMR ($CDCl_3$) δ 3.09 (t, J = 8 Hz, 2H, CH_2), 4.19 (t, J = 8 Hz, 2H, CH_2), 4.21 (br, 1H, OH), 6.41 (s, 1H, ArH), 7.45 (t, J = 7.2 Hz, 1H, ArH), 7.62-7.73 (m, 3H, ArH), 7.96 (d, J = 8 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 32.97, 59.69, 102.72, 124.36, 124.48, 126.05, 127.40, 127.47, 127.69, 128.35, 143.42, 158.93, 160.91; MS (EI) *m/z* 213 [M^+]; Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57; Found: C, 73.20; H, 5.22; N, 6.52.

2-(2-Methylpyridin-5-yl)furo[2,3-b]quinoline (9k). 35%, pale yellow solid, mp 214–215°C; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 1H, CH_3), 7.49–7.53 (m, 2H, ArH), 7.64–7.72 (m, 2H, ArH), 7.95 (t, J = 8 Hz, 2H, ArH), 8.11 (d, J = 8.4 Hz, 1H, ArH), 8.39 (s, 1H, ArH), 8.53 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 30.97, 102.07, 116.08, 120.13, 124.83, 126.68, 127.84, 128.32, 128.85, 129.23, 133.86, 137.31, 144.93, 145.51, 149.61, 150.50, 156.81; MS (EI) *m/z* 260 [M^+]; Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76; Found: C, 78.34; H, 5.27; N, 6.53.

7-Chloro-2-phenylfuro[3,2-c]quinoline (11a). 55%, pale brown solid, mp 142–144°C; ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 1H, ArH), 7.39 (t, J = 8 Hz, 1H, ArH), 7.47 (t, J = 8 Hz, 2H, ArH), 7.56 (dd, J = 8, 2 Hz, 1H, ArH) 7.87 (d, J = 8 Hz, 2H, ArH), 8.16 (s, 1H, ArH), 8.22 (d, J = 8 Hz, 1H, ArH), 9.12 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 100.24, 115.29, 121.13, 122.01, 124.83 127.66, 128.82, 128.87, 129.05, 129.37, 133.75, 145.91, 146.20, 154.70, 156.62; MS (EI) *m/z* 279 [M^+]; Anal. Calcd for $C_{17}H_{10}ClNO$: C, 73.00; H, 3.60; N, 5.01; Found: C, 73.10; H, 3.55; N, 5.03.

7-Chloro-2-(cyclohexen-1-yl)furo[3,2-c]quinoline (11b). 65%, pale brown solid, mp 128–130°C; ^{1}H NMR ($CDCl_3$) δ 1.72–1.82 (m, 4H, CH_2CH_2) 2.30–2.40 (m, 4H, CH_2CH_2), 6.61 (s, 1H, ArH), 6.71 (s, 1H, ArH), 7.52 (d, J = 8 Hz, 1H, ArH), 8.14 (d, J = 8 Hz, 2H, ArH), 9.04 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 22.01, 22.24, 24.94, 25.47, 98.83, 115.22, 121.14, 121.94, 126.49, 127.31, 127.42, 128.66, 133.44, 145.74, 146.01, 154.26, 158.20; MS (EI) *m/z* 283 [M^+]; Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94; Found: C, 71.86; H, 4.94; N, 4.99.

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References

1. A. B. Nouga, J. C. Ndom, E. M. Mpondo, J. C. N. Nyobe, A. Njoya, L. M. Meva'a, P. B. Cranwell, J. A. S. Howell, L. M. Harwood, J. D. Wansi, *Nat. Prod. Res.* **2016**, *30*, 305.
2. N. Pramod, M. Sreenivasulu, G. M. Basha, S. C. Basha, Y. Pradeep, B. H. M. Swamy, *Asian J. Pharm. Anal. Med. Chem.* **2013**, *1*, 118.
3. H. P. Kokatla, D. Sil, S. S. Malladi, R. Balakrishna, A. R. Hermanson, L. M. Fox, X. Wang, A. Dixit, S. A. David, *J. Med. Chem.* **2013**, *56*, 6871.
4. C. C. Tzeng, Y. L. Chen, Y. W. Chen, P. J. Lu, From Taiwan TW I419894 B 20131221, **2013**.
5. T. Trieselmann, D. Hamprecht, H. Wagner, PCT Int. Appl. WO Patent 2013024130, **2013**.
6. M. Banerjee, S. Kumar, R. Paira, S. Ghosh, S. Karmakar, N. B. Mondal, *Lett. Drug Des. Discovery* **2014**, *11*, 104.
7. A. Samad, M. Adeel, D. Khan, S. Dilfaraz, S. Badshah, Z. Muhammad, S. Khan, J. H. Han, *Asian J. Chem.* **2015**, *27*, 2468.
8. L.-Z. Yu, X.-B. Hu, Q. Xu, M. Shi, *Chem. Commun.* **2016**, *52*, 2701.
9. F. K. Behbahani, P. Ziaei, *Synth. React. Inorg., Met.-Org., Nano-Met. Chem.* **2015**, *45*, 839.
10. M. Kumar, T. Kaur, V. K. Gupta, A. Sharma, *RSC Adv.* **2015**, *5*, 17087.
11. (a) H. J. Park, J.-E. Kim, E. K. Yum, Y. H. Kim, C.-W. Han, *Bull. Korean Chem. Soc.* **2015**, *36*, 211; (b) E. K. Yum, O.-K. Yang, J.-E. Kim, H. J. Park, *Bull. Korean Chem. Soc.* **2013**, *34*, 2645.
12. F. Marsais, A. Gogard, G. Queguiner, *J. Heterocycl. Chem.* **1989**, *26*, 1589.

