Tetrahedron Letters 52 (2011) 3726–3728

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 6-bromo-2-arylindoles using 2-iodobenzoic acid as precursor

Ismael Valois-Escamilla [a], Alejandro Alvarez-Hernandez [a,*], Luis Felipe Rangel-Ramos [a], Oscar Rodolfo Suárez-Castillo [a], Francisco Ayala-Mata [b], Gerardo Zepeda-Vallejo [b]

[a] Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Hidalgo, Carr. Pachuca Tulancingo km 4.5 Pachuca, Hidalgo 42184, Mexico
[b] Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Prol. Carpio y Plan de Ayala s/n, 11340 México, D.F., Mexico

ARTICLE INFO

Article history:
Received 14 April 2011
Revised 5 May 2011
Accepted 9 May 2011
Available online 19 May 2011

Keywords:
Curtius rearrangement
Sonogashira coupling
6-Bromoindole
Chemoselective coupling
2-Iodobenzoic acid

ABSTRACT

The synthesis of 6-bromo-2-arylindoles starting from readily available 2-iodobenzoic acid is presented. Regioselective bromination of the latter was followed by Curtius rearrangement and trapping of the isocyanate with benzyl alcohol led to the benzyl carbamate of 2-iodo-5-bromoaniline. Chemoselective Sonogashira coupling of this compound with arylacetylenes followed by TBAF induced *5-endo-dig* cyclization gave the desired bromo indoles. The method allows selective introduction of a bromine atom at the indole C-6 position.

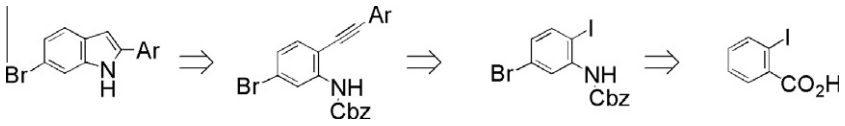
2-Arylindole derivatives have been shown to possess a wide spectrum of pharmacological activities such as hepatitis C virus polymerase- and farnesyl protein transferase inhibitors,[1,2] antibacterial,[3] liver X receptor-, NK1 receptor- and GnRH receptor-antagonists,[4–6] and estrogen receptor ligands.[7] Substituent groups in the six member ring of indole derivatives are associated with an increase of biological activity being the C-5 substitution the most frequently found[5,6] due to the availability of their *para* substituted aniline precursors. Synthetic 6-bromo-2-arylindoles[8] have been much less studied than their C-5 isomers despite 6-bromoindole natural products[9] present in marine organisms exhibit a wide spectrum of biological activity with a promising profile for pharmaceutical development. At least in part, this is a consequence of the issues to selectively introduce the bromine atom at the indole C-6 position; direct bromination of indole at this position is only possible in limited examples that require a blocking C-3 substituent.[10] In consequence, C-6 bromoindoles have to be prepared from suitable functionalized benzene precursors, already containing the bromine atom, that form the azole ring,[11] or alternatively, by bromination of indolines[12] followed by oxidation. Although a number of methods to synthesize 2-arylindoles have been described[13] we became interested in developing a strategy to selectively obtain 6-bromo-2-arylindoles. Consequently, we focused our attention to methods of indole synthesis that rely on transition metal catalyzed transformations of alkynes[14] such as the Sonogashira coupling[15] of an *ortho*-iodoaniline with arylacetylenes followed by intramolecular *5-endo-dig* cyclization of the corresponding *ortho*-alkynylanilines to prepare 2-arylindoles. In this letter we show that commercial 2-iodobenzoic acid can be regioselectively brominated at C-5 and then subjected to Curtius rearrangement to give a carbamate derivative of 2-iodo-5-bromoaniline. This compound can be submitted to a chemoselective Sonogashira coupling at the C–I bond with arylacetylenes and the corresponding products undergo TBAF induced cyclization to afford 6-bromo-2-arylindoles (Scheme 1).

Starting from commercially available 2-iodobenzoic acid **1** regioselective bromination at C-5 was carried out with NBS in H_2SO_4[16] to give 5-bromo 2-iodobenzoic acid **2**.[17] Then, the C–N bond was installed by means of a Curtius rearrangement.[18] Accordingly, acid **2** was treated with thionyl chloride to give the corresponding crude acyl chloride which was mixed with sodium azide in acetone.[19] Solvent evaporation (CAUTION, the acyl azide is potentially explosive, the solution should not be evaporated to dryness) of the crude reaction mixture gave the moisture sensitive acyl azide which was dissolved in dry toluene and heated to afford the corresponding isocyanate which was trapped as the corresponding carbamate **3** by addition of benzyl alcohol and catalytic DMAP. The dihalogenated carbamate **3** was isolated and purified by crystallization. Notably, no chromatography for purification was needed for this five-step sequence (Scheme 2).

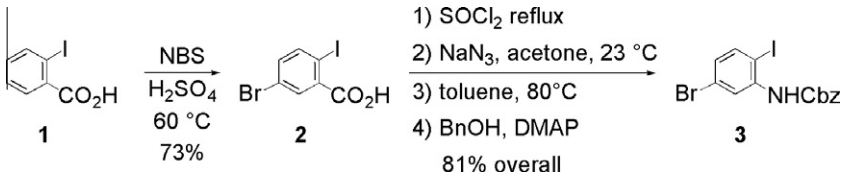
With compound **3** in hand, a Sonogashira reaction with a series of arylacetylenes **4a–o** carrying functional groups at *ortho*, *meta* and *para* positions was conducted to prepare the diarylacetylenes

* Corresponding author. Tel.: +52 771 717 2000x2205; fax: +52 771 717 2000x6502.
E-mail addresses: alalvareher@yahoo.com, alvarez@uaeh.edu.mx (A. Alvarez-Hernandez).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.05.040



Scheme 1. Strategy to prepare 6-bromo-2-arylindoles.



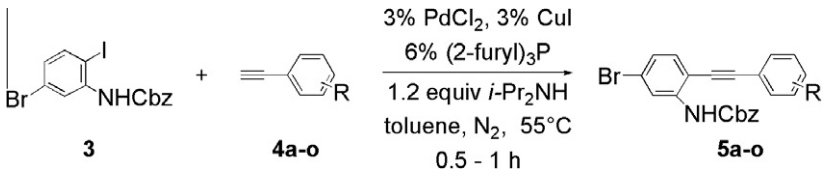
Scheme 2. Synthesis of the dihalogenated carbamate 3 from 2-iodobenzoic acid.

5a–**o** (Table 1). All arylalkynes used bearing either electron-donating or withdrawing groups worked well and coupled exclusively at the C–I bond of **3**. The strength of the C-I compared to that of the C–Br bond (65 vs 85 kcal/mol)[20] makes the oxidative addition of Pd(0) chemoselectively to the weaker C–I bond[21] during the catalytic cycle.

Finally, the *5-endo-dig* cyclization of *ortho*-alkynylaniline derivatives **5a**–**o** with concomitant removal of the carbamate group was carried out by heating with 3 equiv of TBAF in THF[22] leading to the desired 6-bromo-2-arylindoles **6a**–**n** (Table 2). It can be observed that diarylalkynes with electron withdrawing groups cyclize faster than those with electron-donating groups (entries 3 and 12, Table 2) due to activation of the arylalkyne by electron-withdrawing groups toward intramolecular nucleophilic attack. Furthermore, the cyclization tolerates well arylacetylenes with substituent groups at *para* and *meta* positions. However, an *ortho* substituent makes the alkyne less reactive due to steric hindrance. Thus, shorter reaction times are observed for cyclization of *para* and *meta* arylacetylene isomers compared to those of their *ortho* substituted counterparts in the CH_3 and OCH_3 series (entry 9 vs 11 and entry 12 vs 14, Table 2). In these cases, despite different reaction times the yields of the corresponding indole are similar. On the contrary, in the attempted cyclization of the arylacetylene **5f** bearing an *ortho* CHO group no indole product was observed. Likely, the base sensitive aldehyde group induces substrate decomposition in the basic conditions produced by use of TBAF before the slow cyclization to an indole can take place (Table 2, entry 6). In comparison, under the same conditions the *para* CHO isomer **5e** reacts faster and the corresponding indole was obtained in acceptable yield (Table 2, entry 5). Furthermore, in one case, the strong electron-donating group 4-NMe_2 in the arylacetylene **5o** makes the triple bond unreactive and no cyclization occurred at all (Table 2, entry 15); in this case only the corresponding free amine derived from **5o** could be isolated in low yield, this compound decomposed upon standing.

In summary, we have developed a new approach to 6-bromo-2-arylindoles starting from readily available *ortho*-iodobenzoic acid. The regioselective bromination and Curtius rearrangement of the latter compound enabled the synthesis of the benzyl carbamate of 5-bromo-2-iodo aniline **3** that could be used in different variants of indole synthesis. In the present work, we illustrate that chemoselective Sonogashira coupling of this compound with arylacetylenes bearing functional groups followed by TBAF promoted cyclization of the corresponding 2-alkynyl carbamates allowed the preparation of a series of 2-arylindoles **6a**–**n** bearing a bromine atom at C-6. *Ortho* substituted acetylenes react slower than *meta*

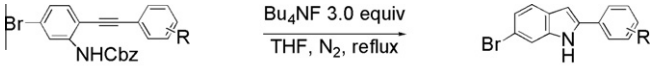
Table 1
Chemoselective Sonogashira coupling of 5-bromo-2-iodophenylbenzyl carbamate **3** with arylacetylenes **4a**–**o** to afford 5-bromo-2-(arylethynyl) phenylbenzyl carbamates **5a**–**o**



Entry	Alkyne	R	Product	Yield[a] (%)
1	**4a**	H	**5a**	90
2	**4b**	4-CN	**5b**	92
3	**4c**	4-NO_2	**5c**	92
4	**4d**	4-$COCH_3$	**5d**	85
5	**4e**	4-CHO	**5e**	88
6	**4f**	2-CHO	**5f**	89
7	**4g**	4-CO_2CH_3	**5g**	81
8	**4h**	4-F	**5h**	88
9	**4i**	4-CH_3	**5i**	86
10	**4j**	3-CH_3	**5j**	93
11	**4k**	2-CH_3	**5k**	90
12	**4l**	4-OCH_3	**5l**	81
13	**4m**	3-OCH_3	**5m**	89
14	**4n**	2-OCH_3	**5n**	88
15	**4o**	4-$N(CH_3)_2$	**5o**	86

[a] Isolated yield after chromatography.

Table 2
TBAF induced cyclization of 5-bromo-2-(arylethynyl) phenylbenzylcarbamates **5a–o** to afford 5-bromo-2-arylindoles **6a–o**



5a-o **6a-o**

Entry	Carbamate	R	Reaction time (h)	Indole	Yield[c] (%)
1	**5a**	H	2.0	**6a**	76
2	**5b**	4-CN	1.0	**6b**	89
3	**5c**	4-NO_2	0.5	**6c**	80
4	**5d**	4-$COCH_3$	1.5	**6d**	85
5	**5e**	4-CHO	1.0	**6e**	75
6	**5f**	2-CHO	1.5[a]	**6f**	0
7	**5g**	4-CO_2CH_3	1.5	**6g**	78
8	**5h**	4-F	1.5	**6h**	67
9	**5i**	4-CH_3	2.5	**6i**	68
10	**5j**	3-CH_3	2.5	**6j**	70
11	**5k**	2-CH_3	8.0	**6k**	63
12	**5l**	4-OCH_3	2.5	**6l**	69
13	**5m**	3-OCH_3	2.5	**6m**	67
14	**5n**	2-OCH_3	8.0	**6n**	73
15	**5o**	4-$N(CH_3)_2$	4.0[b]	**6o**	0

[a] Decomposition of starting carbamate **5f** to a complex mixture was observed.
[b] Only deprotection of carbamate **5o** was observed, the corresponding free aniline was isolated in low yield and decomposed upon standing.
[c] Isolated yield after chromatography.

and *para* isomers. The mild conditions employed in the Sonogashira coupling and the cyclization step, together with its tolerance to a range of functional groups, make this method a useful complement to previous strategies to obtain 6-bromo-2-arylindoles that could be extended to other C-6 functionalized congeners.

Acknowledgment

The authors are grateful for financial support of this work from CONACYT (Grant CB-2006-61247) and predoctoral fellowships for I.V. and L.F.R.

Supplementary data

Supplementary data (experimental procedures and copies of ^1H and ^{13}C NMR spectra for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.040.

References and notes

1. Harper, S.; Pacini, B.; Avolio, S.; Di Filippo, M.; Migliaccio, G.; Laufer, R.; De Francesco, R.; Rowley, M.; Narjes, F. *J. Med. Chem.* **2005**, *48*, 1314–1317.
2. Trotter, B. W.; Quigley, A. G.; Lumma, W. C.; Sisko, J. T.; Walsh, E. S.; Hamann, C. S.; Robinson, R. G.; Bhimnathwala, H.; Kolodin, D. G.; Zheng, W.; Buser, C. A.; Huber, H. E.; Lobell, R. B.; Kohl, N. E.; Williams, T. M.; Graham, S. L.; Dinsmore, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 865–869.
3. Ambrus, J. I.; Kelso, M. J.; Bremner, J. B.; Ball, A. R.; Casadei, G.; Lewis, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4294–4297.
4. Kher, S.; Lake, K.; Sircar, I.; Pannala, M.; Bakir, F.; Zapf, J.; Xu, K.; Zhang, S. H.; Liu, J.; Morera, L.; Sakurai, N.; Jack, R.; Cheng, J. F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4442–4446.
5. Cooper, L. C.; Chicchi, G. G.; Dinnell, K.; Elliott, J. M.; Hollingworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K. L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1233–1236.
6. Chu, L.; Lo, J. L.; Yang, Y. T.; Cheng, K.; Smith, R. G.; Fisher, M. H.; Wyvratt, M. J.; Goulet, M. T. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 515–517.
7. Dykstra, K. D.; Guo, L.; Birzin, E. T.; Chan, W.; Yang, Y. T.; Hayes, E. C.; DaSilva, C. A.; Pai, L. Y.; Mosley, R. T.; Kraker, B.; Fitzgerald, P. M. D.; DiNinno, F.; Rohrer, S. P.; Schaeffer, J. M.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2322–2328.
8. (a) Dann, O.; Ruff, J.; Wolff, H. P.; Griessmeier, H. *Liebigs Ann. Chem.* **1984**, 409–425; (b) Scribner, A.; Moore, J. A.; Ouvry, G.; Fisher, M.; Wyvratt, M.; Leavitt, P.; Liberator, P.; Gurnett, A.; Brown, C.; Mathew, J.; Thompson, D.; Schmatz, D.; Biftu, T. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1517–1521; (c) Izumi, T.; Yokota, T. *J. Heterocycl. Chem.* **1992**, *29*, 1085–1090; (d) Du, Y.; Chang, J.; Reiner, J.; Zhao, K. *J. Heterocycl. Chem.* **2008**, *73*, 2007–2010; (e) Clark, C. I.; White, J. M.; Kelly, D. P.; Martin, R. F.; Lobachevsky, P. *Aust. J. Chem.* **1998**, *51*, 243–248.
9. (a) Pauletti, P. M.; Cintra, L. S.; Braguine, C. G.; Filho, A. A. S.; Silva, M. L. A.; Cunha, W. R.; Januário, A. H. *Mar. Drugs* **2010**, *8*, 1526–1549; (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497; (c) Gupta, L.; Talwar, A.; Chauhan, P. M. S. *Curr. Med. Chem.* **2007**, *14*, 1789–1803.
10. (a) Miki, Y.; Umemoto, M.; Nakamura, M.; Hibino, H.; Ohkita, N.; Kato, A.; Aoki, Y. *Heterocycles* **2006**, *68*, 1893–1899; (b) Murray, M. M.; Kaszynski, P.; Kaisaki, D. A.; Chang, W.; Dougherty, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 8152–8161; (c) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Org. Lett.* **2000**, *2*, 2121–2123.
11. (a) Moyer, M. P.; Shiurba, J. F.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 5106–5110; (b) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823–1828; (c) Carrera, G. M.; Sheppard, G. S. *Synlett* **1994**, 93–94; (d) Schumachert, R. W.; Davidson, B. S. *Tetrahedron* **1999**, *55*, 935–942; (e) Konda-Yamada, Y.; Okada, C.; Yoshida, K.; Umeda, Y.; Arima, S.; Sato, N.; Kai, T.; Takayanagi, H.; Harigaya, Y. *Tetrahedron* **2002**, *58*, 7851–7861; (f) Siu, J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 160–167.
12. Miyake, Y.; Kikugawa, Y. *J. Heterocycl. Chem.* **1983**, *20*, 349–352.
13. For selected examples see: (a) Bellina, F.; Calandri, C.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 1970–1980; (b) Joucla, L.; Batail, N.; Djakovitch, L. *Adv. Synth. Catal.* **2010**, *352*, 2929–2936; (c) Joucla, L.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 673–714; (d) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174; (e) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676–14681; (f) Kobayashi, K.; Iitsuka, D.; Fukamachi, S.; Konishi, H. *Tetrahedron* **2009**, *65*, 7523–7526; (g) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073; (h) Gallou, F.; Yee, N.; Qiu, F. H.; Senanayake, C.; Linz, G.; Schnaubelt, J.; Soyka, R. *Synlett* **2004**, 883–885; (i) Liang, Z.; Yao, B.; Zhang, Y. *Org. Lett.* **2010**, *12*, 3185–3187; (j) Liu, F.; Ma, D. *J. Org. Chem.* **2007**, *72*, 4844–4850; (k) Kraus, G. A.; Guo, H. *Org. Lett.* **2008**, *10*, 3061–3063.
14. (a) Larock, R. C. *Top. Organomet. Chem.* **2005**, *14*, 147–182; (b) Krüger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153–2167; (c) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2304–2307; (d) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475; (e) Okamoto, N.; Miwa, Y.; Minami, H.; Takeda, K.; Yanada, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9693–9696; (f) Ackermann, L.; Sandmann, R.; Villar, A.; Kaspar, L. T. *Tetrahedron* **2008**, *64*, 769–777; (g) Denmark, S. E.; Baird, J. D. *Tetrahedron* **2009**, *65*, 3120–3129; (h) Nakamura, I.; Sato, Y.; Konta, S.; Terada, M. *Tetrahedron Lett.* **2009**, *50*, 2075–2077; (i) Boyer, A.; Isono, N.; Lackner, S.; Lautens, M. *Tetrahedron* **2010**, *66*, 6468–6482; (j) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Perboni, A.; Sferrazza, A.; Stabile, P. *Org. Lett.* **2010**, *12*, 3279–3281; (k) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572–4576; (l) Takaya, J.; Udagawa, S.; Kusama, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4906–4909; (m) Lamar, A. A.; Nicholas, K. M. *Tetrahedron* **2009**, *65*, 3829–3833; (n) Carpita, A.; Ribecai, A. *Tetrahedron Lett.* **2009**, *50*, 6877–6881; (o) Nakamura, I.; Mizushima, Y.; Yamagishi, U.; Yamamoto, Y. *Tetrahedron* **2007**, *63*, 8670–8676; (p) Lu, B. Z.; Zhao, W.; Wei, H. X.; Dufour, M.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2006**, *8*, 3271–3274; (q) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129–4132; (r) Oh, C. H.; Karmakar, S.; Park, H. S.; Ahn, Y. C.; Kim, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 1792–1793; (s) Li, G.; Huang, X.; Zhang, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 346–349.
15. (a) Heravi, M. M.; Sadjadi, S. *Tetrahedron* **2009**, *65*, 7761–7775; (b) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566–1568; (c) Plenio, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 6954–6956; (d) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922; (e) Doucet, H.; Hierso, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871; (f) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, *10*, 3793–3796.
16. Rajesh, K.; Somasundaram, M.; Saiganesh, R.; Balasubramanian, K. K. *J. Org. Chem.* **2007**, *72*, 5867–5869.
17. (a) Zhou, N.; Wang, L.; Thompson, D. W.; Zhao, Y. *Org. Lett.* **2008**, *10*, 3001–3004; (b) Frahn, J.; Schlüter, A. D. *Synthesis* **1997**, 1301–1304.
18. For recent synthesis of indoles based on rearrangement reactions of 2-iodobenzoic acid see: (a) Leogane, O.; Lebel, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 350–352; (b) Okamoto, N.; Miwa, Y.; Minami, H.; Takeda, K.; Yanada, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9693–9696.
19. Kim, J. G.; Jang, D. O. *Synlett* **2008**, 2072–2074.
20. Mphahlele, M. J.; Lesenyeho, L. G.; Makelane, H. R. *Tetrahedron* **2010**, *66*, 6040–6046. and references cited therein.
21. For recent examples of chemoselective Sonogashira coupling see: (a) Layek, M.; Gajare, V.; Kalita, D.; Islam, A.; Mukkanti, K.; Pal, M. *Tetrahedron* **2009**, *65*, 4814–4819; (b) Layek, M.; Rao, A. V. D.; Gajare, V.; Kalita, D.; Barange, D. K.; Islam, A.; Mukkanti, K.; Pal, M. *Tetrahedron Lett.* **2009**, *50*, 4878–4881.
22. (a) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529–534; (b) Suzuki, N.; Yasaki, S.; Yasuhara, A.; Sakamoto, T. *Chem. Pharm. Bull.* **2003**, *51*, 1170–1173.