Tetrahedron Letters 49 (2008) 4260–4264

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A simple approach to highly functionalized benzo[*b*]furans from phenols and aryl iodides via aryl propargyl ethers

V. S. Prasada Rao Lingam [a,b], Ramanatham Vinodkumar [a], Khagga Mukkanti [b,*], Abraham Thomas [a], Balasubramanian Gopalan [a]

[a] Glenmark Research Centre, Medicinal Chemistry Division, MIDC Mahape, Navi Mumbai 400 709, India
[b] Institute of Science and Technology, Jawaharlal Nehru Technological University, Kukatpally, Hyderabad 500 072, India

ARTICLE INFO

Article history:
Received 27 February 2008
Revised 22 April 2008
Accepted 26 April 2008
Available online 1 May 2008

Keywords:
Aryl propargyl ethers
Benzo[*b*]furans
Sonogashira coupling
Claisen rearrangement

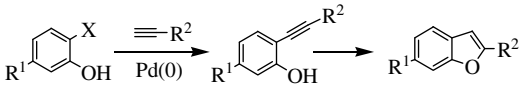
ABSTRACT

A variety of mono- and disubstituted phenols are alkylated with propargyl bromide to give phenyl 2-propynyl ethers, which were further coupled with aryl iodides under Sonogashira reaction conditions to give 3-phenoxy-1-aryl-1-propyne derivatives. The latter compounds underwent an initial Claisen rearrangement followed by ring closure to give functionalized benzo[*b*]furans in moderate to good yields.

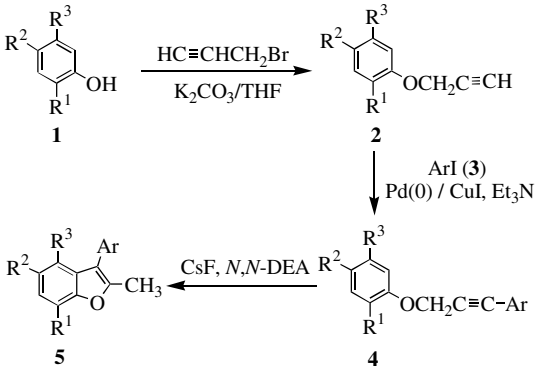
Benzo[*b*]furan structural motifs are present in several pharmaceuticals[1] and natural products.[2] Functionalized benzo[*b*]furans also serve as versatile synthetic intermediates. Several of these intermediates are used for the synthesis of molecules having useful biological properties such as the Tachykinin NK_1 receptor antagonist,[3] Angiotensin-II receptor antagonists,[4] calcium channel blockers[5] and 5-lipoxygenase inhibitors.[6] Traditional methods[7] for the synthesis of benzo[*b*]furans involve reaction of 2-halophenols with a terminal alkyne under palladium catalysis, wherein the intermediate is a 2-alkynylphenol derivative as shown in Scheme 1. Even today, this is one of the most widely used approaches for the synthesis of benzo[*b*]furans.

A major limitation of this approach is the lack of flexibility in terms of substituents on the carbocyclic part of benzofuran nucleus and only 2-substituted benzofurans are generally accessible by this approach. Moreover, limited commercial availability of substituted 2-halophenols further limit the scope of this approach. Other less popular approaches for the synthesis of benzo[*b*]furans include cyclization of vinylic phenols[8] under palladium catalysis, cyclization of 2-acyloxy-1-bromomethylarenes[9] with $Cr(II)Cl_2/BF_3{\cdot}OEt_2$, cyclization of arylketoximes,[10] cyclization of aryloxycarbonyl[11] compounds, intramolecular [2+2] cycloaddition of 2-acyloxyacetic acids,[12] reaction of *p*-benzoquinones with 1-(*N*-methylanilino)-1-methyl-thioester,[13] microwave irradiation of [{2-(aryloxy)propanoyl}-(cyano/ethoxy-carbonyl)-methylene]triphenylphosphoranes[14] and photochemical reaction of phenyliodoniumphenolate with alkynes.[15] However, all the above methods suffer the disadvantage of either lack of commercial availability of the intermediate precursors or require several steps for precursor synthesis.

In this Letter, we report a convenient and very general procedure for the synthesis of highly functionalized benzo[*b*]furans from



Scheme 1. Literature method for the synthesis of benzo[*b*]furans.[7]

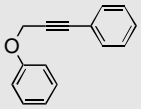
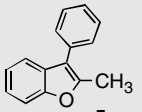
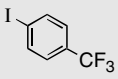
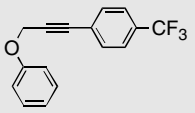
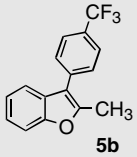
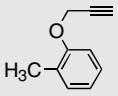
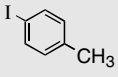
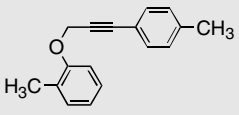
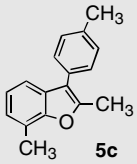
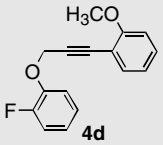
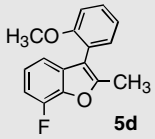
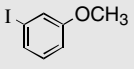
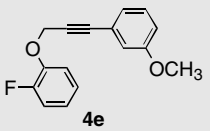
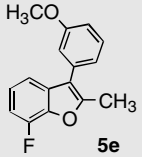
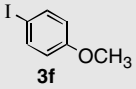
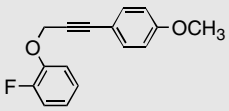
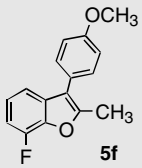
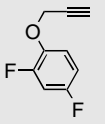
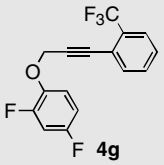
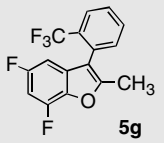
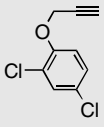
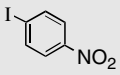
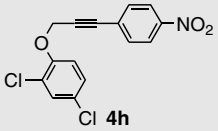
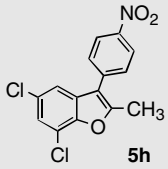
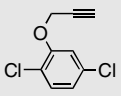
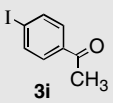
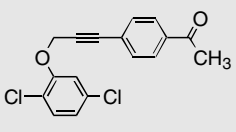
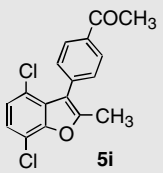
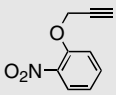
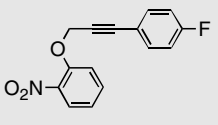
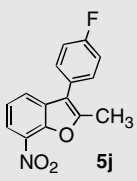


Scheme 2. General method for the synthesis of benzo[*b*]furan.

* Corresponding author. Tel.: +91 9963909007; fax: +91 40 23155413.
E-mail address: kmukkanti@gmail.com (K. Mukkanti).

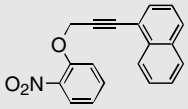
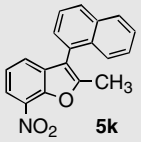
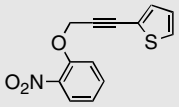
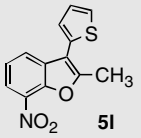
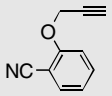
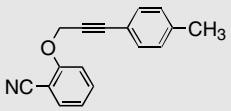
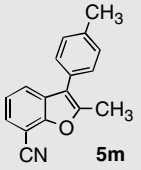
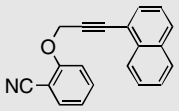
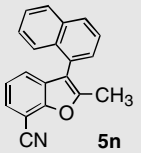
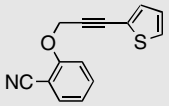
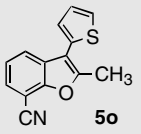
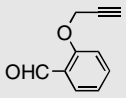
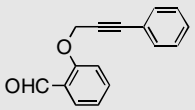
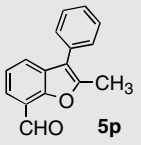
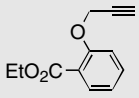
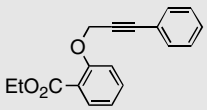
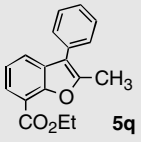
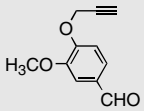
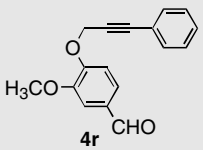
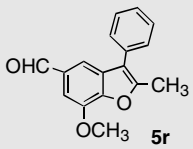
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.04.150

Table 1
Syntheses of benzo[*b*]furans **5** from phenyl propargyl ethers **2** and aryl iodides **3** via 3-phenoxy-1-aryl-1-propyne intermediates **4**

Entry	Ether (**2**)	Iodide (**3**)	Propyne ether (**4**)	Yield (%)	Benzo[*b*]furan (**5**)	Time (h)	Yield (%)
1	 **2a**	 **3a**	 **4a**	90	 **5a**	10	65
2	**2a**	 **3b**	 **4b**	91	 **5b**	10	64
3	 **2b**	 **3c**	 **4c**	96	 **5c**	16	71
4	 **2c**	 **3d**	 **4d**	95	 **5d**	9	68
5	**2c**	 **3e**	 **4e**	94	 **5e**	8	70
6	**2c**	 **3f**	 **4f**	95	 **5f**	8	70
7	 **2d**	 **3g**	 **4g**	96	 **5g**	4	73
8	 **2e**	 **3h**	 **4h**	90	 **5h**	2	75
9	 **2f**	 **3i**	 **4i**	91	 **5i**	3	70
10	 **2g**	 **3j**	 **4j**	85	 **5j**	0.5	58

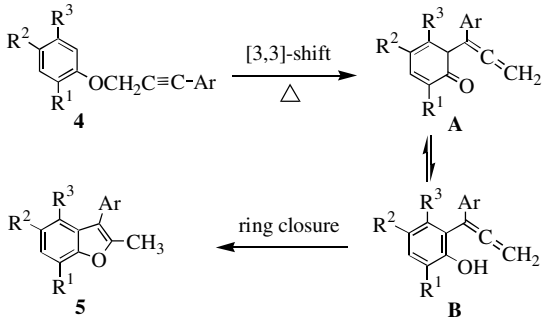
(*continued on next page*)

Table 1 (*continued*)

Entry	Ether (**2**)	Iodide (**3**)	Propyne ether (**4**)	Yield (%)	Benzo[*b*]furan (**5**)	Time (h)	Yield (%)
11	**2g**	 **3k**	 **4k**	80	 **5k**	0.5	55
12	**2g**	 **3l**	 **4l**	83	 **5l**	0.5	50
13	 **2h**	**3c**	 **4m**	88	 **5m**	1	65
14	**2h**	**3k**	 **4n**	90	 **5n**	1	60
15	**2h**	**3l**	 **4o**	83	 **5o**	1	67
16	 **2i**	**3a**	 **4p**	87	 **5p**	2	62
17	 **2j**	**3a**	 **4q**	89	 **5q**	2	75
18	 **2k**	**3a**	 **4r**	95	 **5r**	2	77

inexpensive and readily available substituted phenols and aryl iodides. As outlined in Scheme 2, the phenols **1** underwent smooth alkylation[16] with propargyl bromide in the presence of potassium carbonate in tetrahydrofuran to give phenyl propargyl ethers **2a–k** in quantitative yields. The alkynes **2a–k** were arylated with various aryl iodides **3a–l** under Sonogashira-reaction conditions[17] to give aryl propargyl ethers **4a–r** in 80–96% isolated yields as shown in Table 1. The coupling reactions for entries 1–9 were carried out using catalytic amounts of Pd $(PPh_3)_2Cl_2$ (0.01 equiv) and copper (I) iodide (0.03 equiv) using triethylamine[18] serving as a base and solvent. In the case of entries 10–18, dimethyl sulfoxide (DMSO) was used as the solvent with 1.5 equiv of triethylamine as a base, a catalytic amount of $Pd(PPh_3)_4$ (0.01 equiv) and copper (I) iodide (0.03 equiv) to improve the homogeneity of the reaction mixture and thereby the yield of the reaction. Where electron-withdrawing groups such as nitro, cyano, ester, aldehyde or keto were present on the substrates, the use of excess triethylamine reduced the yield in the Sonogashira[19]-coupling reaction. The best yields were obtained when 1.5 equiv of triethylamine in DMSO were employed (entries 10–18).

Attempted Claisen rearrangement[20] (Table 1, entry 1) by pyrolysis of 3-phenoxy-1-phenyl-1-propyne **4a** at 180 °C in the absence



Scheme 3. Proposed mechanism for the formation of benzo[*b*]furans.

of solvent resulted in a tarry material and no identifiable product was formed in the mixture. Reaction of **4a** in polyethylene glycol[21] (PEG) up to 220 °C resulted in recovery of the starting material. Reactions using Hg $(OCOCF_3)_2$ in chloroform did not proceed at all and the starting material remained intact even after 12 h of reflux.[22] Reactions under Lewis acid $(AgBF_4)$[23] catalysis resulted in a complex mixture. The caesium chloride (CsCl)[24] catalyzed reaction in *N*,*N*-diethylaniline (*N*,*N*-DEA) resulted in an unidentifiable less polar product along with the unreacted alkyne ether **4a**. The reaction catalyzed by caesium fluoride (CsF) in *N*,*N*-DEA[25] resulted in the formation of the desired benzo[*b*]furan **5a** in a 65% isolated yield.

The generality of this approach was studied using selectively substituted phenols **1** and aryl iodides **3** as shown in Table 1. To our delight, we found that the present method tolerated a wide range of substituents on both of the aryl rings. In addition to this, it was also observed that electron deficient phenols showed excellent reactivity and formed products in shorter reaction times (entries 10–18), whilst prolonged reaction times were required for electron rich phenols (entries 1–9). Even sterically demanding, *ortho*-substituted aryl iodides (entries 4 and 7) delivered good yields of benzo[*b*]furans **5** under these conditions.

The general transition states involved in the thermolytic Claisen rearrangement and cyclization of aryl prop-2-ynyl ether **4** are shown in Scheme 3.[23,24] Intermediate **4** on [3,3]-sigmatropic rearrangement gives the allenyl dienone **A**, which on enolization gives thermodynamically more stable phenol **B**. The phenoxide anion formed in the presence of caesium fluoride would cyclize to benzo[*b*]furan **5**. No trace of dihydro-2*H*-1-benzopyran was detected in all the cases studied.[21]

In conclusion, we have developed a novel three-step procedure for the synthesis of highly functionalized 2-methyl-3-arylbenzo[*b*]furans from commercially available, suitably functionalized phenols and substituted aryl iodides. The present method can be utilized to synthesize various functionalized analogues of Isoparvifuran,[2b,c] a known anti-fungal agent. The present method has several advantages: simple reaction conditions and experimental simplicity combined high functional group tolerance. We believe that this methodology will be a valuable addition to the existing methods in the field of benzo[*b*]furan synthesis which allows the preparation of annelated benzofuran analogues for biological screening. Further work is in progress towards generating synthetic routes for the recently isolated and naturally occurring benzo[*b*]furan compounds from Dalbergia Cochinchinensis Pierre (Leguminosae)[2c,26] and the details will be published elsewhere.

Acknowledgement

The authors thank Glenmark Pharmaceuticals Limited for granting permission to carry out the present research work.

References and notes

1. (a) Assens, J.-L.; Bernhart, C.; Cabanel-Haudricourt, F.; Gautier, P. N.; Dino. WO 2002, 016339; *Chem. Abstr.* **2002**, *136*, 216637.; (b) Carlsson, B.; Singh, B. N.; Temciue, M.; Nilsson, S.; Li, Y.-L.; Mellin, C.; Malm, J. *J. Med. Chem.* **2002**, *45*, 623–630; (c) Norinder, U.; Bajorath, J.; Stearns, J. WO 1992, 20 331; *Chem. Abstr.* **1993**, *118*, 212874t; (d) Scherrer; R.A. US Patent 3920828, 1975; *Chem Abstr.* **1976**, *84*, 889985e.
2. (a) Schneiders, G. E.; Stevenson, R. *J. Org. Chem.* **1979**, *44*, 4710–4711; (b) Huang, K.-S.; Lin, M.; Cheng, G.-F. *Phytochemistry* **2001**, *58*, 357–362; (c) Shirota, O.; Pathak, V.; Sekita, S.; Stake, M.; Nagashima, Y.; Hirayama, Y.; Hakamata, Y.; Haysahi, T. *J. Nat. Prod.* **2003**, *66*, 1128–1131; (d) Okamoto, Y.; Ojika, M.; Sakagami, Y. *Tetrahedron Lett.* **1999**, *40*, 507–510; Okamoto, Y.; Ojika, M.; Suzuki, S.; Murakami, M.; Sakagami, Y. *Bioorg. Med. Chem.* **2001**, *9*, 179–183; (e) Donnelly, D. M. X.; O'Cridain, T.; O'Sullivan, M. *J. Chem. Soc., Chem. Commun.* **1981**, 1254–1255.
3. Boyle, S.; Guard, S.; Higginbottom, M.; Horwell, D. C.; Howson, W.; McKnight, A. T.; Martin, K.; Pritchard, M. C.; O'Toole, J.; Raphy, J.; Rees, D. C.; Roberts, E.; Watling, K. J.; Woodruff, G. N.; Hughes, J. *Bioorg. Med. Chem.* **1994**, *2*, 357–370.
4. (a) Kiyama, R.; Homna, T.; Hayashi, K.; Ogawa, M.; Hara, M.; Fujimoto, M.; Fujishita, T. *J. Med. Chem.* **1995**, *38*, 2728–2741; (b) Yoo, S.; Kim, S.-H.; Lee, S.-H.; Kim, N.-J.; Lee, D.-W. *Bioorg. Med. Chem.* **2000**, *8*, 2311–2316.
5. (a) Gubun, J.; de Vogelaer, H.; Inion, H.; Houben, C.; Lucchetti, J.; Mahaux, J.; Rosseels, G.; Peiren, M.; Clinat, M.; Polster, P.; Chatelain, P. *J. Med. Chem.* **1993**, *36*, 1425–1433; (b) Kozikowsky, A. E. WO 2006, 010008; *Chem. Abstr.* **2006**, *144*, 164278.
6. Ohemeng, K. A.; Apollina, M. A.; Nguyen, V. N.; Schwender, C. F.; Singer, M.; Steber, M.; Araseli, J.; Argentieri, D.; Hageman, W. *J. Med. Chem.* **1994**, *37*, 3663–3667.
7. (a) Stephens, R. D.; Castro, C. E. *Synthesis* **1963**, 3313–3315; (b) Castro, C. E.; Gaughan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071–4078; (c) Barton, T. J.; Groh, B. L. *J. Org. Chem.* **1985**, *50*, 158–166; (d) Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255–1261; (e) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905–1909; (f) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271; (g) Bernini, R.; Caccha, S.; Salve, I. D.; Fabriza, G. *Synthesis* **2007**, *6*, 873–882.
8. (a) Hosokawa, T.; Maeda, K.; Koga, K.; Moritani, I. *Tetrahedron Lett.* **1973**, *14*, 739–740; (b) Casiraghi, G.; Casnati, G.; Pugli, G.; Sartori, G.; Terenghi, C. *Synthesis* **1977**, 122–123; (c) Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonodo, A. *J. Chem. Soc., Chem. Commun.* **1978**, 687–688.
9. (a) Ledoussal, B.; Gorgues, A.; Le Coq, A. *J. Chem. Soc., Chem. Commun.* **1986**, 171–172; (b) Ledoussal, B.; Gorgues, A.; Le Coq, A. *Tetrahedron* **1987**, *43*, 5841–5852.
10. (a) Sheradsky, T. *J. Heterocycl. Chem.* **1967**, *4*, 413–414; (b) Kaminsky, D.; Shavel, J. J.; Meltzer, R. I. *Tetrahedron Lett.* **1967**, *8*, 859–861; (c) Mooradian, A.; Dupoint, P. E. *Tetrahedron Lett.* **1967**, *8*, 2867–2870; (d) Bender, D. R.; Hearst, J. E.; Rapoport, H. *J. Org. Chem.* **1979**, *44*, 2176–2180; (e) Alemagna, A.; Baldoli, C.; Buttero, P. D.; Licandro, E.; Maiorana, S. *J. Chem. Soc., Chem. Commun.* **1985**, 417–418.
11. (a) Tarbell, D. S.; Carman, R. M.; Chapman, D. D.; Cremer, S. E.; Cross, A. D.; Huffman, K. R.; Kunstmann, M.; McCorkindale, N. J.; McNally, J. G.; Rosowsky, A.; Varino, F. H. L.; West, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 3096–3113; (b) Macleod, J. K.; Worth, B. R. *Tetrahedron Lett.* **1972**, *13*, 237–240.
12. (a) Horaguchi, T.; Matsuda, S.; Tanemura, K.; Suzuki, T. *J. Heterocycl. Chem.* **1987**, *24*, 965–969; (b) Brady, W. T.; Gu, Y.-Q. *J. Heterocycl. Chem.* **1988**, *25*, 969–971.
13. Takahata, T.; Anazawa, A.; Moriyama, K.; Yamazaki, Y. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1501–1504.
14. Rama Rao, V. V. N. S.; Reddy, G. V.; Yadla, R.; Narsaiah, B.; Rao, P. S. *Arkivoc* **2005**, *iii*, 211–220.
15. Spyroudis, S. P. *J. Org. Chem.* **1986**, *51*, 3453–3456.
16. Ishii, H.; Ishikawa, T.; Takeda, S.; Ueki, S.; Suzuki, M. *Chem. Pharm. Bull.* **1992**, *40*, 1148–1153.
17. (a) Sonagashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470; (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922. and references cited therein.
18. *Typical procedure for the Sonogashira coupling*: *Method A for compounds* **4a–i**: To a solution of **2f** (1.0 g, 4.974 mmol) and 4-iodoacetophenone **3i** (1.23 g, 4.999 mmol) and $Pd(PPh_3)_2Cl_2$ (35 mg, 0.049 mmol) in triethylamine (5.0 mL) was added CuI (28.5 mg, 0.149 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with EtOAc (50 mL), washed with water (3 × 50 mL) and dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography using 20% EtOAc in petroleum ether to give 1.45 g (91%) of **4i** as an off-white solid; mp 80–83 °C; IR (KBr) 3069, 2288, 1678, 1585, 1482, 1381, 1265, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3H), 4.99 (s, 2H), 6.92 (dd, J = 1.8, 6.3 Hz, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.48 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 57.7, 85.6, 87.3, 114.7, 121.6, 122.2, 126.4 (2C), 128.0, 130.8, 131.8 (2C), 132.7, 136.5, 153.3, 196.9; MS *m*/*z* (+ cAPCI): 319.16 $(M)^+$; Anal. Calcd for $C_{17}H_{12}Cl_2O_2$: C, 63.97; H, 3.79. Found: C, 63.94; H 3.83.
19. *Method B*: For entries 10–18, to a solution of compounds **2g–k** (5 mmol) in dry DMSO (20 mL) was added iodide (**3**) (5 mmol), $(PPh_3)_4Pd$ (0.05 mmol) and CuI (0.15 mmol) followed by triethylamine (7.5 mmol). The reaction mixture was

stirred at room temperature for 6–8 h under a nitrogen atmosphere. The reaction mixture was diluted with EtOAc (50 mL) and washed with water (3 × 50 mL) followed by brine (20 mL) and then dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography using 20% EtOAc in petroleum ether to give pure products **4j**–**r**.

20. (a) Sarcevic, N.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 1457–1476; (b) Bruhn, J.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1978**, *61*, 2542–2559.
21. Gopalsamy, A.; Balasubramanian, K. K. *J. Chem. Soc., Chem. Commun.* **1988**, 28–29.
22. Balasubramanian, T.; Balasubramanian, K. K. *Tetrahedron Lett.* **1991**, *32*, 6641–6644; Bates, D. K.; Jones, M. C. *J. Org. Chem.* **1978**, *40*, 3775–3777.
23. Koch-Pomeranz, U.; Hansen, H. -J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2981–3004.
24. Ghosh, S. C.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3705–3708.
25. *Typical procedure for the Claisen rearrangement and ring closure*: A mixture of **4i** (600 mg, 1.879 mmol) and CsF (514 mg, 3.383 mmol) in *N*,*N*-diethylaniline (10 mL) was refluxed for 3 h under a nitrogen atmosphere. The mixture was cooled to room temperature, diluted with EtOAc (50 mL) and washed with 5 N HCl (3 × 50 mL) and water (2 × 50 mL) and then dried over anhydrous Na_2SO_4. The residue obtained after evaporation of the solvent was purified by silica gel column chromatography using 5% EtOAc in petroleum ether as eluent to give 421 mg (70%) of **5i** as a white solid; mp 99–101 °C; IR (KBr) 2917, 1680, 1604, 1463, 1398, 1258, 1155, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.66 (s, 3H), 7.07 (d, J = 8.4 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 7.8 Hz, 2H), 8.00 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.56, 26.70, 115.04, 117.03, 123.86, 124.03, 124.50, 126.74, 127.65 (2C), 131.09 (2C), 136.04, 136.29, 149.95, 154.27, 197.49; MS m/z (− cAPCI): 319.23 $(M)^-$; Anal. Calcd for $C_{17}H_{12}Cl_2O_2$: C, 63.97; H, 3.79. Found C, 64.01; H, 3.83.Spectral data for **5c**: white solid; mp 77–79 °C; IR(KBr) 2914, 1513, 1421, 1254, 1180, 1113, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.53 (s, 6H), 7.04–7.14 (m, 2H), 7.29 (d, J = 7.8Hz, 2H), 7.38–7.41 (m, 3H); MS m/z (+ cAPCI): 237.47 $(M+H)^+$; Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found C, 86.43; H, 6.76.
Spectral data for **5f**: white solid; mp 69–72 °C; IR (KBr) 2951, 1605, 1514, 1441, 1247, 1175, 1035, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 3.91 (s, 3H), 6.99–7.02 (m, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.12–7.19 (m, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H); MS m/z (+ cAPCI): 257.43 $(M+H)^+$; Anal. Calcd for $C_{16}H_{13}FO_2$: C, 74.99; H, 5.11. Found C, 75.05; H 5.07.
Spectral data for **5g**: viscous oil; IR (neat) 2927, 1605, 1484, 1316, 1172, 1129, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3H), 6.55 (d, J = 8.1 Hz, 1H), 6.75 (t, J = 8.2 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 7.51–7.63 (m, 2H), 7.80 (d, J = 7.8 Hz, 1H); MS m/z (− cAPCI): 311.09 $(M-H)^-$; Anal. Calcd for $C_{16}H_9F_5O$: C, 61.55; H, 2.91. Found C, 61.61; H, 2.94.
Spectral data for **5h**: yellow solid; mp 190–193 °C; IR (KBr) 2922, 1597, 1515, 1352, 1166, 957, 857 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.60 (s, 3H), 7.29 (s, 1H), 7.38 (s, 1H), 7.60 (d, J = 8.1 Hz, 2H), 8.34 (d, J = 7.8 Hz, 2H); MS m/z (− cAPCI): 321.14 $(M-H)^-$; Anal. Calcd for $C_{15}H_9C_{l2}NO_3$: C, 55.93; H, 2.82; N, 4.35. Found C, 56.00; H, 2.85; N, 4.30.
Spectral data for **5l**: Yellow solid; mp 135–137 °C; IR (KBr) 3083, 1523, 1433, 1356, 1220, 1180, 1122, 1069, 920 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (s, 3H), 7.17–7.20 (m, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.43 (d, J = 5.1 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H); MS m/z (+ cAPCI): 260.24 $(M+H)^+$; Anal. Calcd for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40; S, 12.37. Found C, 60.17; H, 3.56; N, 5.43; S, 12.43.
Spectral data for **5m**: off-white solid; mp 136–138 °C; IR (KBr) 2921, 2230, 1607, 1514, 1429,1247, 1184, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 2.57 (s, 3H), 7.23–7.35 (m, 5H), 7.51 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H); MS m/z (+ cAPCI): 248.30 $(M+H)^+$; Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found C, 82.60; H, 5.26; N, 5.71.
Spectral data for **5q**: viscous oil, IR (neat) 2981, 1714, 1608, 1425, 1291, 1174, 1038, 950 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (t, J = 7.2 Hz, 3H), 2.60 (s, 3H), 4.47 (q, J = 7.5 Hz, 2H), 7.23–7.27 (m, 1H), 7.33–7.36 (m, 1H), 7.42–7.46 (m, 4H), 7.72 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H); MS m/z (+ cAPCI): 281.03 $(M+H)^+$; Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found C, 77.15; H, 5.80.
Spectral data for **5r**: Off-white solid; mp 140–142 °C; IR (KBr) 2842, 1698, 1613, 1429, 1265, 1184, 1009 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.58 (s, 3H), 4.08 (s, 3H), 7.35 (s, 1H), 7.37–7.40 (m, 1H), 7.46–7.49 (m, 4H), 7.68 (s, 1H), 9.94 (s, 1H); MS m/z (+ cAPCI):267.19 $(M+H)^+$; Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found C, 76.71; H, 5.34.
26. Nigel, C. V. *Nat. Prod. Rep.* **2007**, *24*, 417–464.