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Synthesis of new 2-arylbenzo[*b*]thiophenes using 'Heck-type' technology

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Abstract—Direct 3-substituted benzothiophene arylation using a Heck-type reaction with $Pd(OAc)_2/n\text{-}Bu_4NBr$ as a catalytic system is reported. This reaction was found to perform relatively fast whatever the electron-donating or the electron-withdrawing group at position 3. We also extended this reaction to several aromatic halides, such as benzene, naphthalene and pyridine derivatives, synthesising new 2-arylbenzo[*b*]thiophenes in moderate to good yields. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Over the past few years, 2-arylbenzo[*b*]thiophenes derivatives were found to be promising agents for the treatment of various diseases such as hypolipemia[1] and estrogen dependant diseases.[2] 2-Arylbenzo[*b*]thiophenes are usually synthesised via an intramolecular cyclisation from thiobenzyls.[3] However, most of these methods are not compatible with fragile groups and the cyclisations are often carried out in moderate overall yields after several steps. In this paper, we focussed on a method allowing the direct arylation of benzo[*b*]thiophenes. Contrary to the usual arylation methods,[4] of the Stille,[5] Kumada[6] and Suzuki-type,[7] which all involve a regioselective halogenation of the substrate and the use of an organometallic reagent prior to the coupling, we succeeded in synthesising several 2-arylbenzo[*b*]thiophenes in a one-step reaction. Indeed, Miura[8] and Otha[9] previously managed to arylate benzo[*b*]thiophene selectively in moderate yields by utilising palladium salts, triphenylphosphine and, for the first one, an over stoichiometric amount of copper salt.

We used a catalytic arylation reaction developed in our laboratory on thiophenes,[10] which involved the use of a catalytic amount of palladium diacetate, in the presence of tetra-*n*-butylammonium bromide and an excess of potassium carbonate as an inorganic base. By analogy with the Heck reaction,[11] we assumed that if we could conveniently activate the benzothiophene 2,3-double bond at the 3-position by an electron-withdrawing group, the coupling would thus be facilitated. Hence we first performed the reaction on benzo[*b*]thiophene-3-carbonitrile **1**.[12]

2. Results and discussion

Firstly, we achieved the arylation of the compound **1** at relatively low temperature (90°C, Fig. 1) with aryl iodides such as iodobenzene, 4-iodoanisole, 4-iodobenzotrifluoride and 1-iodonaphthyl (Table 1, entries 1–4).

Even if we observed a low reaction rate, we obtained a good chemical yield but also a moderate selectivity of

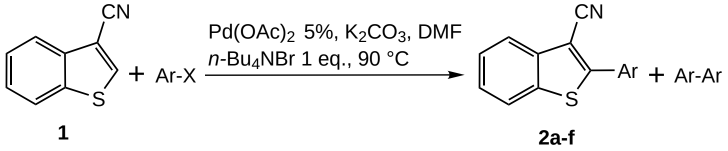

Figure 1. Arylation of benzo[*b*]thiophene-3-carbonitrile.

Keywords: benzo[*b*]thiophene; Heck-type aryl coupling; palladium catalysis.

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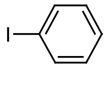
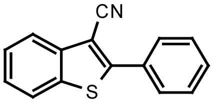
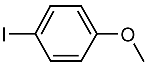
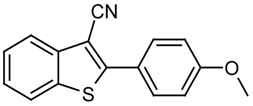
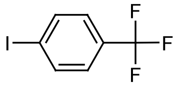
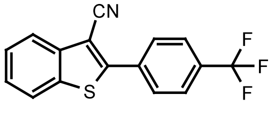
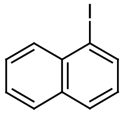
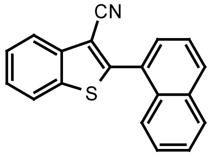
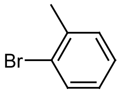
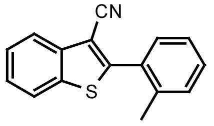
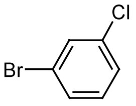
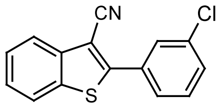
Table 1. Arylation of **1** with aryl iodides

Entry	Ar-X	Products **2**	Time (h)	Chemical yield[(a)] (%)	Selectivity **2**/Ar-Ar[(b)]
1		**2a** 	72	97 (**46**)	1.8
2		**2b** 	48	89 (**51**)	3.5
3		**2c** 	48	91 (**40**)	1.3
4		**2d** 	48	80 (**60**)	> 20
5[(c)]		**2f** 	1.5	85 (**66**)	30
6[(c)]		**2g** 	2.5	99 (**72**)	5

For typical procedure, see Ref. 15. (a) Values in parentheses are isolated yields. (b) Determined by GC analysis. (c) Temperature = 140°C.

the arylation relative to the major side-reaction: a symmetrical Ullmann-type coupling of the aryl halide.[13] Subsequent purification was complicated by the presence of these by-products, leading to moderate isolated yields of the pure desired compound. Indeed, it is noteworthy to outline that the most selective coupling (entry 4) gave one of the best isolated yields (60%). At higher temperature (140°C), we only noticed a decrease of the selectivity and no better chemical yield. We also performed the arylation on aryl bromides (entries 5 and 6), which are cheaper and more available than their iodide homologues. It appeared that, at a higher temperature (140°C), the reaction was still very selective and did not involve any degradation of the benzo[*b*]thiophene-3-carbonitrile due to lower reaction times. We also observed a good selectivity of the coupling toward the halogen type, as no reaction occurred on the carbon–chlorine bond (entry 6). As these products were prepared in order to evaluate their biological activity towards the diseases mentioned at the beginning of this article, the resulting purification of these compounds was performed very carefully (until +98% purity, determined by microanalysis and ^{1}H NMR) and therefore several flash chromatographs and/or recrystallisations were required.

With an electron-rich benzo[*b*]thiophene, such as 3-methoxybenzo[*b*]thiophene[14] **3** (Fig. 2), isolated yields were slightly higher (Table 2). Within shorter reaction times and at 100°C, 2-aryl-3-methoxybenzo[*b*]thiophenes **4a**–**d** were obtained in quite good isolated yields (from 50 to 77%). This benzothiophene even underwent coupling with 3-bromopyridine in an acceptable reaction time and in a good yield (95% in 25

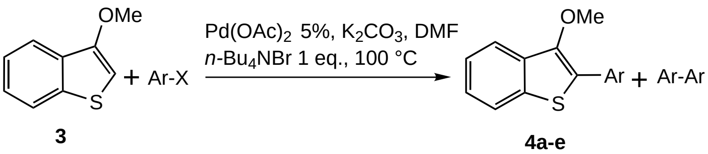
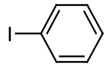
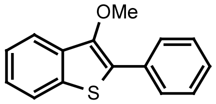
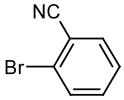
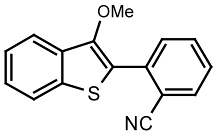
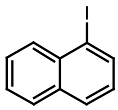
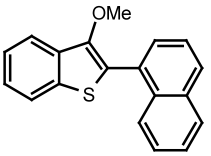
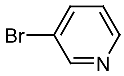
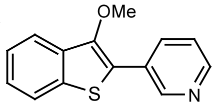


Figure 2. Arylation of 3-methoxybenzo[*b*]thiophene.

Table 2. Arylation of **3** with aryl halides

Entry	Ar-X	Products **4**	Time (h)	Chemical yield[a] (%)	Selectivity **4**/Ar-Ar[b]
1		**4a** 	22	99 (**51**)	8
2		**4b** 	28	92 (**69**)	25
3		**4c** 	24	98 (**77**)	6
4		**4d** 	25	95 (**66**)	> 50

(a) Values in parentheses are isolated yields. (b) Determined by GC analysis.

h, entry 4). Unfortunately, several attempts at higher temperature (140°C) did not give better results. We therefore assumed that the catalytic cycle was different depending on the activating group on position 3. Indeed, only very low conversion was observed by coupling non-substituted benzo[*b*]thiophene with iodobenzene (12% conv. in 2 days) whatever the temperature (100°C or 140°C). In addition, it appeared that 2-substituted benzo[*b*]thiophenes, such as benzo[*b*]thiophene-2-carbonitrile, did not undergo any efficient conversion with aryl halides (less than the amount of catalyst, i.e. 5%). Thus, it is reasonable to suppose that the transition state involves a stabilisation by the sulphur atom.

3. Conclusions

We have developed an efficient one step benzo[*b*]thiophene arylation on the 2-position by utilising $Pd(OAc)_2/n\text{-}Bu_4NBr$ as a catalytic system. This reaction proceeds with moderate to good yields with benzo[*b*]thiophenes activated at the 3-position. This method is compatible both with electron-rich and electron-poor aryl halides and may therefore be a good alternative to the synthesis of raloxifene analogues.[2] Additional experiments are now under investigation in order to determine the catalytic mechanism as well as to improve the efficiency of the reaction. Biological studies of the synthesised molecules are currently running.

References

1. Sauter, F. FR 79-2897, 1979.
2. Munster, P. N.; Buzdar, A.; Dhingra, K.; Enas, N.; Ni, L.; Major, M.; Melemed, A.; Seidman, A.; Booser, D.; Theriault, R.; Norton, L.; Hudis, C. *J. Clin. Oncol.* **2001**, *19*, 2002–2009.
3. (a) Jones, C. D.; Jevnikar, M. G.; Pike, A. J.; Peters, M. K.; Black, L. J.; Thompson, A. R.; Falcone, J. F.; Clemens, J. A. *J. Med. Chem.* **1984**, *27*, 1057–1066; (b) Arnoldi, A.; Carughi, M. *Synthesis* **1988**, 155–157; (c) Watanabe, M.; Date, M.; Kawanishi, K.; Akiyoshi, R.; Furukawa, S. *J. Heterocyclic Chem.* **1991**, *28*, 173–176; (d) Capozzi, G.; De Sio, F.; Menichetti, S.; Nativi, C.; Pacini, P. L. *Synthesis* **1994**, 521–525.
4. For a review, see: Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, in press.
5. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508–524.
6. Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669–679.
7. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
8. Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473.
9. Ohta, A.; Akita, Y.; Ohkuwa, T.; Fukunaga, M. C. R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *11*, 1951–1958.
10. Lavenot, L.; Gozzi, C.; Ilg, K.; Orlova, I.; Penalva, V.; Lemaire, M. *J. Organomet. Chem.* **1998**, *567*, 49–55.
11. Heck, R. F. *Org. React.* **1982**, *27*, 345–390.
12. For the synthesis of this molecule, see: Martynoff, M. *C.R. Hebd. Seances Acad. Sci.* **1953**, *236*, 385–387.

13. Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174–2184.
14. For the synthesis of this molecule, see: Acheson, M. R.; Cooper, M. W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1185–1193.

15. **Typical procedure**: A suspension of potassium carbonate (3.75 mmol), tetra-*n*-butylammonium bromide (1.25 mmol), substituted benzothiophene (1.25 mmol) and aryl halide (0.75 mmol) in *N*,*N*-dimethylformamide (1 mL) was stirred under argon at the indicated temperature for 5 min. Palladium diacetate (0.0625 mmol) was then added and the resulting mixture was allowed to stir for the time indicated, adding stepwise aryl halide (0.375 by 0.375 mmol) until no change of the chemical yield (determined by GC). After cooling to room temperature, the mixture was filtered over Celite®, rinsed with dichloromethane (10 mL) and then successively washed with brine (10 mL), a saturated sodium thiosulfate solution (10 mL) and water (10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated to give a brown residue. The latter was then purified by flash column chromatography (silica, cyclohexane/ethyl acetate) and, if necessary, by recrystallisation in pentane, to afford the pure desired compound.

2a isolated yield: 46%, white solid; mp 97–98°C; R_f 0.4 (silica, cyclohexane/AcOEt 95:5); found C, 76.31; H, 3.82; N, 5.99; S, 13.85%, calcd for $C_{15}H_9NS$ C, 76.50; H, 3.82; N, 5.94; S, 13.60%; δ_H (500 MHz, $CDCl_3$) 7.47 (ddd, 1H, H_{benzo}, *J* 1.0, 8.2 and 8.2 Hz), 7.54 (m, 1H, $H_{benzo'}$), 7.56–7.60 (m, 3H, 2 H_{aryl} and H_{benzo}), 7.87 (ddd, 1H, H_{benzo}, *J* 0.8, 1.6 and 8.0 Hz), 7.92 (ddd, 2H, 2 H_{aryl}, *J* 0.9, 1.6 and 7.4 Hz), 8.01 (ddd, 1H, H_{benzo}, *J* 0.8, 1.0 and 8.2 Hz); δ_C (50 MHz, $CDCl_3$) 102.1 (C), 115.2 (CN), 122.4 (CH), 122.6 (CH), 126.2 (2 CH), 128.3 (2 CH), 129.4 (2 CH), 130.5 (CH), 131.5 (C), 137.4 (C), 139.3 (C), 155.1 (C) ppm; *m*/*z* 235 (100).

2b isolated yield: 66%, white solid; mp 118–120°C; R_f 0.4 (silica, cyclohexane/AcOEt 95:5); found C, 72.60; H, 4.24; N, 5.33; O, 6.28; S, 12.03; calcd for $C_{16}H_{11}NOS$ C, 72.38; H, 4.15; N, 5.27; O, 6.03; S, 12.06%; δ_H (300 MHz, $CDCl_3$) 3.80 (s, 3H, OCH_3), 6.94 (d, 2H, 2 H_{aryl}, *J* 8.9 Hz), 7.34 (ddd, 1H, H_{benzo}, *J* 1.3, 7.8 and 7.8 Hz), 7.43 (ddd, 1H, H_{benzo}, *J* 1.3, 7.8 and 7.8 Hz), 7.75 (dd, 1H, H_{benzo}, *J* 1.3 and 7.8 Hz), 7.77 (d, 2H, 2 H_{aryl}, *J* 8.9 Hz), 7.85 (dd, 1H, H_{benzo}, *J* 1.3 and 7.8 Hz); δ_C (75 MHz, $CDCl_3$) 55.9 (OCH_3), 101.0 (C), 115.1 (2 CH), 115.9 (CN), 122.6 (CH), 122.7 (CH), 124.4 (C), 126.2 (CH), 126.4 (CH), 130.0 (2 CH), 137.3 (C), 139.7 (C), 155.5 (C), 161.8 (C) ppm; *m*/*z* 265 (100), 250 (80), 222 (80).

2c isolated yield: 58%; white solid; mp 74–76°C; R_f 0.45 (silica, cyclohexane/AcOEt 95:5); found C, 63.30; H, 2.80; N, 4.65; F, 18.48; S, 10.85%, calcd for $C_{16}H_8NF_3S$ C 63.32; H, 2.61; N, 4.61; F, 18.80; S, 10.55%; δ_H (300 MHz, $CDCl_3$) 7.49 (ddd, 1H, H_{benzo}, *J* 1.3, 7.5 and 7.9 Hz), 7.58 (ddd, 1H, H_{benzo}, *J* 1.3, 7.5 and 7.9 Hz), 7.80 (bd, 2H, 2 H_{aryl}, *J* 8.3 Hz), 7.92 (ddd, 1H, H_{benzo}, *J* 0.6, 1.5 and 7.5 Hz), 8.01 (m, 3H, 1 H_{benzo} and 2 H_{aryl}); δ_C (75 MHz, $CDCl_3$) 101.3 (C), 112.6 (CN), 120.4 (CH), 120.8 (CH), 124.3 (2 CH), 124.4 (CH), 124.7 (CH), 126.5 (2 CH), 129.8 (q, CF_3), 132.7 (C), 132.8 (C), 135.6 (C), 136.9 (C), 159.5 (C) ppm; *m*/*z* 303 (100), 284 (20), 233 (25).

2d isolated yield: 60%; white solid, mp 125–131°C; R_f 0.4 (silica, cyclohexane/AcOEt 95:5); found C, 79.61; H, 3.98; N, 4.82; S, 11.00%, calcd for $C_{19}H_{11}NS$ C, 79.96; H, 3.89; N, 4.91; S, 11.24%; δ_H (300 MHz, $CDCl_3$) 7.38–7.42 (m, 5H), 7.58 (dd, 1H, H_{aryl}, *J* 1.3 and 7.2 Hz), 7.80 (ddd, 1H, H_{benzo}, *J* 0.8, 1.2 and 7.9 Hz), 7.84–7.92 (m, 3H), 7.96 (ddd, 1H, H_{benzo}, *J* 0.8, 1.3 and 7.9 Hz); δ_C (75 MHz, $CDCl_3$) 107.4 (C), 115.0 (CN), 123.1 (CH), 123.4 (CH), 125.8 (CH), 125.9 (CH), 126.9 (CH), 127.0 (CH), 127.4 (CH), 128.0 (CH), 129.3 (CH), 129.4 (CH), 129.9 (CH), 131.6 (C), 132.1 (C), 134.5 (C), 138.9 (C), 139.4 (C), 154.6 (C) ppm; *m*/*z* 286 (55), 285 (100), 258 (60), 129 (55).

2e isolated yield: 66%, beige solid; mp 113–114°C; R_f 0.25 (silica, cyclohexane/AcOEt 95:5); found C, 76.87; H, 4.40; N, 5.53; S, 13.23%, calcd for $C_{16}H_{11}NS$ C, 77.07; H, 4.45; N, 5.62; S, 12.86%; δ_H (300 MHz, $CDCl_3$) 2.46 (s, 3H, CH_3), 7.32–7.48 (m, 4H), 7.50 (ddd, 1H, H_{benzo}, *J* 1.3, 7.4 and 7.7 Hz), 7.58 (ddd, 1H, H_{benzo}, *J* 1.3, 7.4 and 7.9 Hz), 7.90 (ddd, 1H, H_{benzo}, *J* 0.8, 1.3 and 7.8 Hz), 8.03 (ddd, 1H, H_{benzo}, *J* 0.8, 1.3 and 7.7 Hz); δ_C (75 MHz, $CDCl_3$) 20.7 (CH_3), 106.4 (C), 114.8 (CN), 122.8 (CH), 122.9 (CH), 126.5 (2 CH), 126.6 (CH), 130.7 (CH), 131.0 (CH), 131.4 (CH), 137.5 (2 C), 138.5 (C), 138.8 (C), 155.8 (C) ppm; *m*/*z* 249 (100), 222 (30), 221 (50), 110 (40).

2f isolated yield: 72%; pale yellow solid; mp 145–146°C; R_f 0.20 (silica, cyclohexane/AcOEt 95:5); found C, 66.90; H, 3.02; N, 5.10; S, 12.08%, calcd for $C_{15}H_8ClNS$ C, 66.79; H, 2.99; N, 5.19; S, 11.89%; δ_H (500 MHz, $CDCl_3$) 7.45–7.47 (m, 2H_{aryl}), 7.48 (ddd, 1H, H_{benzo}, *J* 1.3, 7.3 and 8.2 Hz), 7.54 (ddd, 1H, H_{benzo}, *J* 1.0, 7.3 and 8.2 Hz), 7.78–7.82 (m, 2H_{aryl}), 7.85 (ddd, 1H, H_{benzo}, *J* 0.6, 1.0 and 8.2 Hz), 7.97 (ddd, 1H, H_{benzo}, *J* 0.6, 1.3 and 8.2 Hz); δ_C (75 MHz, $CDCl_3$) 103.3 (C), 115.1 (CN), 122.8 (CH), 123.2 (CH), 126.7 (2 CH), 126.9 (CH), 128.6 (CH), 131.8 (CH), 131.0 (CH), 133.5 (C), 135.7 (C), 137.8 (C), 139.4 (C), 153.3 (C) ppm; *m*/*z* 271 (30), 269 (100), 233 (30), 190 (30), 117 (20).

4a isolated yield: 51%; colourless oil; R_f 0.45 (silica, cyclohexane/AcOEt 95:5); found C, 74.77; H, 5.27; O, 6.35; S, 13.61%, calcd for $C_{15}H_{12}OS$ C, 74.97; H, 5.03; O, 6.66; S, 13.34%; δ_H (300 MHz, $CDCl_3$) 3.91 (s, 3H, CH_3), 7.34–7.44 (m, 3H), 7.44–7.52 (m, 2H), 7.81 (dd, 2H, H_{aryl}, *J* 1.3 and 7.4 Hz), 7.88–7.94 (m, 2H); δ_C (75 MHz, $CDCl_3$) 61.3 (CH_3), 121.4 (CH), 123.2 (CH), 124.7 (CH), 125.4 (CH), 127.2 (C), 128.2 (CH), 128.3 (2 CH), 129.2 (2 CH), 133.4 (C), 135.2 (C), 136.2 (C), 147.8 (C) ppm; *m*/*z* 240 (90), 225 (100), 197 (90), 77 (30).

4b isolated yield: 69%; pink crystals; mp 120–121°C; R_f 0.3 (silica, cyclohexane/AcOEt 95:5); found C, 72.32; H, 4.15; N, 5.28; O, 6.06; S, 12.19%, calcd for $C_{16}H_{11}NOS$ C, 72.43; H, 4.18; N, 5.28; O, 6.03; S, 12.09%; δ_H (500 MHz, $CDCl_3$) 3.82 (s, 3H, CH_3), 7.40 (ddd, 1H, H_{benzo}, *J* 1.7; 7.1 and 7.1 Hz), 7.43 (ddd, 1H, H_{benzo}, *J* 1.7, 7.1 and 7.2 Hz), 7.49 (ddd, 1H, H_{aryl}, *J* 1.4, 7.3 and 7.8 Hz), 7.66 (ddd, 1H, H_{aryl}, *J* 1.5, 7.3 and 7.9 Hz), 7.69 (ddd, 1H, H_{aryl}, *J* 0.7, 1.5 and 7.8 Hz), 7.78 (ddd, 1H, H_{benzo}, *J* 0.8, 1.7 and 7.2 Hz), 7.80 (ddd, 1H, H_{aryl}, *J* 0.7, 1.4 and 7.9 Hz), 7.86 (ddd, 1H, H_{benzo}, *J* 0.8, 1.7 and 7.1 Hz); δ_C (125 MHz, $CDCl_3$) 61.6 (CH_3), 113.8 (C), 118.4 (C), 120.1 (CN), 122.1 (CH), 123.0 (CH), 124.8 (CH), 126.0 (CH), 128.8 (CH), 132.1 (CH), 132.8 (CH), 133.6 (C), 133.8 (C), 136.7 (C), 137.3 (C), 149.3 (C) ppm; *m*/*z* 265 (90), 250 (100), 222 (60), 146 (40).

4c isolated yield: 77%; pink crystals; mp 130–132°C; R_f 0.3 (silica, cyclohexane/AcOEt 95:5); found C, 78.25; H, 4.89; O, 5.75; S, 11.46%, calcd for $C_{19}H_{14}OS$ C, 78.59; H, 4.86; O, 5.51; S, 11.04%; δ_H (500 MHz, $CDCl_3$) 3.56 (s, 3H, CH_3), 7.41 (ddd, 1H, H_{benzo}, J 1.3, 7.3 and 7.9 Hz), 7.46 (ddd, 1H, H_{benzo}, J 1.1, 7.3 and 7.9 Hz), 7.50–7.55 (m, 2H), 7.55 (dd, 1H, H_{aryl}, J 7.0 and 8.2 Hz), 7.70 (dd, 1H, H_{aryl}, J 1.1 and 7.0 Hz), 7.80 (ddd, 1H, H_{benzo}, J 0.8, 1.3 and 7.9 Hz), 7.88 (ddd, 1H, H_{benzo}, J 0.8, 1.1 and 7.9 Hz), 7.91–7.96 (m, 2H), 8.02 (dd, 1H, H_{aryl}, J 1.8 and 7.1 Hz); δ_C (75 MHz, $CDCl_3$) 60.9 (CH_3), 120.7 (C), 121.7 (CH), 122.8 (CH), 124.7 (CH), 125.5 (CH), 125.6 (CH), 126.7 (CH), 126.8 (CH), 127.1 (CH), 128.7 (CH), 129.5 (CH), 129.9 (CH), 131.0 (C), 133.2 (C), 134.0 (C), 134.5 (C), 137.4 (C), 148.2 (C) ppm; m/z 290 (90), 275 (100), 247 (90), 127 (40).

4b isolated yield: 66%; orange-red oil; R_f 0.15 (silica, cyclohexane/AcOEt 95:5); found C, 69.85; H, 4.69; N, 5.74; O, 6.51; S, 13.21%, calcd for $C_{14}H_{11}NOS$ C, 69.68; H, 4.59; N, 5.80; O, 6.63; S, 13.29%; δ_H (300 MHz, $CDCl_3$) 3.88 (s, 3H, CH_3), 7.33 (ddd, 1H, H_{aryl}, J 0.7, 4.9 and 8.0 Hz), 7.34–7.41 (m, 2H), 7.73–7.80 (m, 2H), 8.10 (ddd, 1H, H_{aryl}, J 1.7, 2.3 and 8.0 Hz), 8.54 (dd, 1H, H_{aryl}, J 1.7 and 4.9 Hz), 9.10 (bd, 1H, H_{aryl}, J 2.3 Hz); δ_C (75 MHz, $CDCl_3$) 61.5 (CH_3), 121.6 (CH), 123.3 (CH), 123.4 (C), 124.0 (CH), 125.0 (CH), 125.9 (CH), 129.6 (C), 134.6 (C), 135.1 (CH), 136.5 (C), 149.0 (CH), 149.1 (C), 149.4 (CH) ppm; m/z 241 (70), 226 (100), 198 (40).