Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 48 (2007) 6896–6899
Tetrahedron Letters

# Efficient palladium catalyzed synthesis of heteroaromatic sulfoxides

Françoise Colobert,[a,*] Rafael Ballesteros-Garrido,[a] Frédéric R. Leroux,[a] Rafael Ballesteros[b] and Belén Abarca[b,*]

[a]*Laboratoire de Stéréochimie, Université Louis Pasteur (ECPM), CNRS, 25 rue Becquerel, F-67087 Strasbourg Cedex 2, France*
[b]*Departament de Química Orgànica, Facultat de Farmàcia, Universitat de València, Av. Vicente Andrés, s/n, 46100 Burjassot, València, Spain*

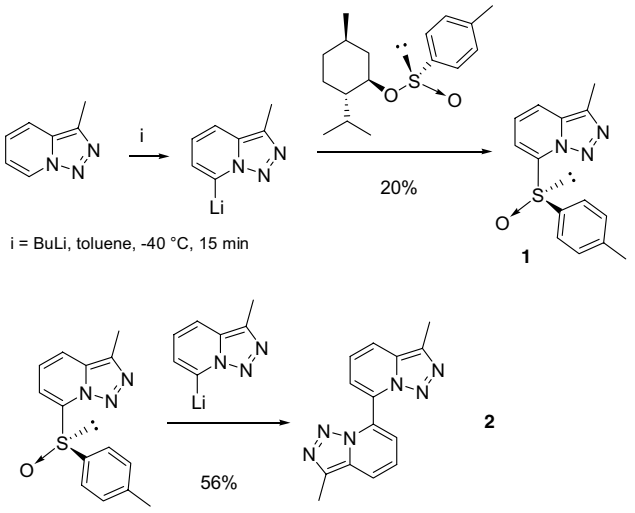
Received 1 July 2007; accepted 25 July 2007
Available online 28 July 2007

**Abstract**—The present Letter describes the efficient synthesis of novel heteroaromatic sulfoxides by means of a palladium catalyzed heteroarylation of sulfenate anions. Triazolopyridine, pyridine and thiophene sulfoxides can be obtained under mild conditions and in high yield from the corresponding heteroaryl bromides.


Aryl sulfoxides are highly important compounds for medicinal and pharmaceutical chemistry.[1] Chiral sulfur-containing species have a great importance and high potential as chiral ligands for asymmetric catalysis, and they also have a promising future for the development of a number of new symmetric heterogeneous or homogeneous reactions.[2] Their preparation relies generally on the stereospecific substitution of optically active sulfinates with Grignard reagents (the Andersen method).[3]

In the framework of our studies dealing with the synthesis of triazolopyridine systems as molecular chemosensors for metal ions, anions, and amino acids as well as fluorescence captors,[4] and as precursors of 2,6-disubstituted pyridines,[5] we were interested in the preparation of sulfoxide bearing [1,2,3]triazolo[1,5-*a*]pyridines **1**. Recently, we showed that this compound is obtained in low yield after metalation of the corresponding triazolopyridine with butyllithium at −40 °C in toluene followed by trapping with (*R*)-(−)-menthyl *p*-toluenesulfinate (Scheme 1).[6]

The major problem is the formation of various side products, mainly the dimerization of the triazolopyridine unit affording the coupling product **2**. Its formation can be explained by means of a nucleophilic substitution of the introduced *p*-toluenesulfoxide substituent by remaining lithiated triazolopyridine. Neither the mode of addition (normal or inverse addition), nor the modification of solvent and temperature improved the situation considerably. Similarly, electron-deficient heteroaromatics like pyridines cannot afford the 2-(*p*-toluenesulfoxide)-substituted analogs by the classical Andersen method. For example, 2-bromopyridine gives after bromine/lithium exchange followed by trapping with (*S*)-(−)-menthyl *p*-toluenesulfinate essentially the dimerization product as shown by Oae and Fukurawa.[7]

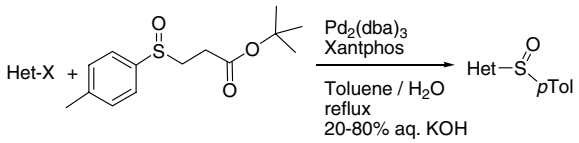



**Scheme 1.**

* Corresponding authors. Tel.: +33 3 90 24 27 44; fax: +33 3 90 24 27 42 (F.C.); e-mail: fcolober@chimie.u-strasbg.fr

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.165

Recently, Poli et al. reported on the palladium catalyzed synthesis of arylic sulfoxides. These authors could show that in situ generated sulfenate anions[8] from β-sulfinyl esters can provide under biphasic conditions several aryl sulfoxides. The sulfoxides were obtained in good yields from the corresponding aryl iodides. However, the use of arylbromides was unsuccessful.[9]



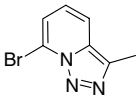
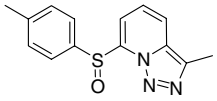
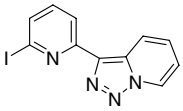
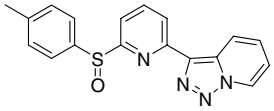
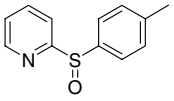
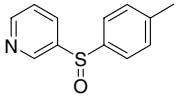
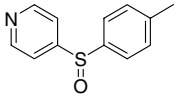
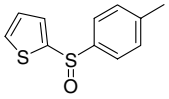
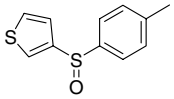
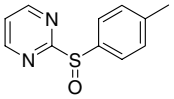
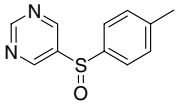
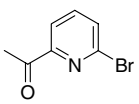
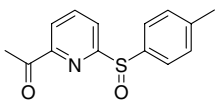

**Scheme 2.**

Encouraged by these results, we decided to apply this new methodology for the preparation of [1,2,3]triazolo[1,5-*a*]pyridine sulfoxides starting from the corresponding halides. The C–S coupling reaction was performed under biphasic conditions in a toluene/water mixture at 85 °C (Scheme 2).[10]

The brominated triazolopyridine[11] afforded compound **1** in an yield of 82% without any trace of dimerization (entry 1).[12] 3-(6′-Iodopyridin-2′-yl)-[1,2,3]triazolo[1,5-*a*]-pyridine (entry 2)[13] gave compound **3**[14] in 95% yield and again without traces of the corresponding dimer.

In order to determine the scope and limitations of this methodology we applied it to various heteroaromatic compounds (triazolopyridines, pyridines, thiophenes and pyrimidines). Due to their lower cost and commercial availability we decided to use heteroaryl bromides as substrates. The corresponding sulfoxides were obtained in good yields as depicted in Table 1. 2-Bromopyridine,

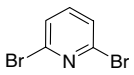
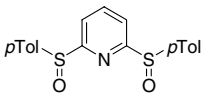
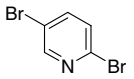
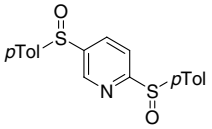
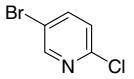
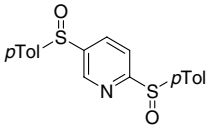
**Table 1.** C–S coupling of various heteroaryl bromides via Scheme 2[a]

| Entry | Heteroaryl halide | Product | | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  | **1** | 82 |
| 2 |  |  | **3** | 95 |
| 3 |  |  | **4** | 63 |
| 4 |  |  | **5** | 82 |
| 5 |  |  | **6** | 75 |
| 6 |  |  | **7** | 69 |
| 7 |  |  | **8** | 50 |
| 8 |  |  | **9** | 41 |
| 9 |  |  | **10** | 31 |
| 10 |  |  | **11** | 52 |

[a] Reagents and conditions: aryl halide (1.0 equiv), β-sulfinylester (1.3 equiv), $Pd_2dba_3$ (5 mol %), xantphos (10 mol %), KOH (50% aqueous solution) in 1:1 toluene/$H_2O$ at 85 °C.

[b] Yields are given for isolated products.

**Table 2.** C–S coupling of heteroaryl dibromides via Scheme 2[a]

| Entry | Heteroaryl halide | Product | | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  | **12** | 74 |
| 2 |  |  | **13** | 84 |
| 3 |  |  | **13** | 30 |

[a] Reagents and conditions: aryl halide (1.0 equiv), β-sulfinylester (1.3 equiv), $Pd_2dba_3$ (5 mol %), xantphos (10 mol %), KOH (50% aqueous solution) in 1:1 toluene/$H_2O$ at 85 °C.
[b] Yields are given for isolated products.

for example, afforded 63% of sulfoxide **4** (entry 3) contaminated with 35% of 2,2′-bipyridyl. In contrast to the triazolopyridine substrates, the dimerization could not be completely avoided on 2-bromopyridine. We realized, that the dimerization occurred on the 2-bromopyridine and not on the final sulfoxide **4**, as with the Andersen method. Actually, when 2-bromopyridine was submitted to the coupling reaction without sulfoxide-source, 2,2′-bipyridine was obtained in an yield of 33%. In contrary, 3- and 4-bromopyridines afforded the corresponding sulfoxides **5** and **6** in a yield of 82% and 75%, respectively (entries 4 and 5). Sulfoxide substituted thiophenes were obtained, using 2- or 3-bromothiophene, in an yield of 69% and 50%, respectively (entries 6 and 7). 2-Bromopyrimidine as well as 5-bromopyrimidine underwent the coupling reaction more reluctantly affording the sulfoxide in 41% and 31% yields (entries 8 and 9). When 2-acetyl-6-bromopyridine was used as starting material, sulfoxide **11** was obtained in an yield of 52%.[15] This compound reflects the utility of the C–S coupling method, as it cannot be obtained by the classical Andersen method involving a halogen/metal exchange.

Due to our interest in chiral fluorescence captors we next decided to develop new target molecules bearing two sulfoxide groups. When 2,6-dibromopyridine was submitted to the C–S coupling using 1.3 equiv of sulfoxide-source, only the corresponding bis-sulfoxides **12** was obtained in an yield of 74% (Table 2, entry 1).[16]

No traces of mono-sulfoxide were detected. The yield decreased to 48% when 2 equiv of β-sulfinylester was used. Thus, the best coupling conditions for mono- and bis-sulfoxides are those described in Scheme 2. Analogously, 2,5-dibromopyridine afforded bis-sulfoxide **13** (entry 2) in an yield of 84%.[17] The sulfoxides were obtained as mixtures of the possible enantiomeric diastereomers (dl and meso). In their Letter, Poli et al.[9] reported on the C–S coupling of 1,2-diiodobenzene. The authors obtained the bis-sulfoxide in a 45% yield and a ratio dl/meso of 90:10. In our case we obtained a ratio dl/meso of 66:33 (measured by $^1H$ NMR) for **12** and a diastereomeric ratio of 55:44 for **13**. Thus, we can deduce that there is no chiral induction due to the first introduced sulfoxide group.

In order to check the selectivity of bromine versus chlorine, we replaced 2,5-dibromopyridine by 2-chloro-5-bromopyridine. Bis-sulfoxide **13** was obtained in an yield of 30%. However, 3-chloropyridine revealed to be unreactive towards the C–S coupling when we screened different reaction conditions and ligands. In fact, the first introduction of the sulfoxide group on 2-chloro-5-bromopyridine occurs on the position of the bromine atom, which renders the pyridine ring more electron-deficient, facilitating the second introduction of a sulfoxide, now on the position of the chlorine atom (Table 2, entry 3).

In conclusion, we could show that hetaryl bromides and β-sulfinyl esters undergo very efficiently the palladium catalyzed C–S coupling under biphasic conditions affording the pharmaceutically important class of heteroaromatic sulfoxides and bis-sulfoxides. Applying this methodology, hetaryl sulfoxides become accessible, which cannot be obtained by means of the classical Andersen method. We could extend this approach on electron-deficient hetaryl chlorides.

## Acknowledgements

We are grateful to the CNRS and Ministerio de Educación y Ciencia (Spain) for its financial support (project CTQ2006-15672-C05-03). R.B.G. is much grateful to the Ministère de la Recherche for an MRT grant.

## References and notes

1. For reviews, see: (a) Legros, J.; Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 19; (b) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609; (c) Fernández, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651.

2. (a) Pellissier, H. *Tetrahedron* **2007**, *63*, 1297; (b) Hanquet, G.; Colobert, C.; Lanners, S.; Solladié, G. *Arkivoc* **2003**, *vii*, 328.
3. (a) Andersen, K. K. *Tetrahedron Lett.* **1962**, *3*, 93; (b) Andersen, K. K.; Gaffield, W.; Papanikolau, N. P.; Foley, J. W.; Perkins, R. I. *J. Am. Chem. Soc.* **1964**, *86*, 5637.
4. Chadlaoui, M.; Abarca, B.; Ballesteros, R.; de Arellano, C. R.; Aguilar, J.; Aucejo, R.; Garcia-España, E. *J. Org. Chem.* **2006**, *71*, 9030.
5. Jones, G.; Mouat, D. J.; Tonkinson, D. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2719.
6. Ballesteros-Garrido, R.; Abarca, B.; Ballesteros, R.; Leroux, F. R.; Colobert, F., in preparation.
7. (a) Oae, S. *Tetrahedron Lett.* **1984**, *25*, 2549; (b) Furukawa, N.; Ogawa, S.; Matsumura, K.; Furihara, Y. H. *J. Org. Chem.* **1991**, *56*, 6341; (c) Vinishi, J.; Tanaka, T.; Wakabayashi, S.; Oae, S. *Tetrahedron Lett.* **1990**, *31*, 4625.
8. Caupène, C.; Boudou, C.; Perrio, S.; Metzner, P. *J. Org. Chem.* **2005**, *70*, 2812.
9. Maitro, G.; Vogel, S.; Prestat, G.; Madec, D.; Poli, G. *Org. Lett.* **2006**, *8*, 5951.
10. General procedure for palladium-catalyzed arylation of sulfenate anions under biphasic conditions: To a solution of $Pd_2(dba)_3$ (5 mol %) in toluene (0.500 mL) was added xantphos (10 mol %). The solution was stirred at room temperature for 5 min. Then, a solution of hetaryl bromide (0.5 mmol in 1.5 mL of toluene), β-sulfinylester (0.7 mmol in 1.5 mL of toluene), distilled water (3.5 mL) and 50% aq KOH solution (10 mmol) were successively added. The resulting biphasic system was stirred and heated to reflux. The reaction was monitored by TLC. Upon completion of the reaction (2–4 h) and cooling to room temperature, the aqueous phase was extracted with dichloromethane ($3 \times 50$ mL). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography.
11. Abarca, B.; Ballesteros, R.; Jones, G.; Fatemeh, M. *Tetrahedron Lett.* **1986**, *27*, 3543.
12. *3-Methyl-7-(toluene-4-sulfinyl)-[1,2,3]triazolo[1,5-a]pyridine* (**1a**): mp 145–147 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 7.89$ (d, $J = 8.2$ Hz, 2H), 7.71 (dd, $J = 6.9$, 1.0 Hz, 1H), 7.65 (dd, $J = 8.9$, 1.0 Hz, 1H), 7.38 (dd, $J = 8.9$, 6.9 Hz, 1H), 7.22 (d, $J = 8.2$ Hz, 2H), 2.58 (s, 3H), 2.30 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta = 143.04$ (C), 141.29 (C), 137.84 (C), 135.19 (C), 132.08 (CH), 129.92 (C), 126.28 (CH), 123.88 (CH), 118.88 (CH), 111.68 (CH), 21.47 ($CH_3$) 10.35 ($CH_3$). MS (E.I): $m/z$ (%) = 273 (3), 271 (40), 243 (63), 226 (35), 195 (30), 139 (100), 120 (36), 104 (60), 91 (42), 77 (67). HRMS for $C_{14}H_{13}N_3OS$: calcd, 271.0779; found, 271.0778.
13. Abarca, B.; Alkorta, I.; Ballesteros, R.; Blanco, F.; Chadlaoui, M.; Elguero, J.; Mojarrad, F. *Org. Biomol. Chem.* **2005**, *3*, 3905.
14. *3-[6′-(Toluene-4-sulfinyl)-pyridin-2′-yl]-[1,2,3]triazolo [1,5-a]pyridine* (**1b**): mp 167–170 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 8.69$ (d, $J = 7.0$ Hz, 1H), 8.37 (d, $J = 8.9$ Hz, 1H), 8.27 (dd, $J = 7.2$, 1.8 Hz, 1H), 7.91 (dd, $J = 7.1$, 7.8 Hz, 1H) 7.88 (dd, $J = 7.8$, 1.8 Hz, 1H), 7.65 (d, $J = 8.1$ Hz, 2H) 7.33 (dd, $J = 7.0$, 8.9 Hz, 1H), 7.2 (d, $J = 8.1$ Hz, 2H), 7.0 (dd, $J = 7.0$, 6.9 Hz, 1H), 2.30 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta = 165.00$ (C), 152.40 (C), 141.90 (C), 141.26 (C), 138.67 (CH), 136.16 (C), 132.19 (C), 129.93 (CH), 126.96 (CH), 125.42 (CH), 125.35 (CH), 121.19 (CH), 120.84 (CH), 116.74 (CH), 116.05 (CH), 21.82 ($CH_3$). MS (E.I): $m/z$ (%) = 336 (3), 334 (40), 306 (75), 258 (65), 215 (10), 199 (5), 183 (86), 167 (100), 139 (80), 113 (20), 91 (44), 78 (47). HRMS for $C_{18}H_{14}N_4OS$: calcd, 334.0888; found: 334.0904.
15. *1-(6-(p-Tolylsulfinyl)pyridin-2-yl)ethanone* (**10**): mp 140–144 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 8.12$ (dd, $J = 6.3$, 2.7 Hz, 1H), 7.90 (m, 2H), 7.60 (d, $J = 8.1$ Hz, 2H), 7.17 (d, $J = 8.1$ Hz, 2H), 2.55 (s, 3H), 2.26 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta = 198.5$, 165.8, 153.1, 141.8, 140.5, 138.9, 129.8, 124.6, 122.1, 121.5, 25.5, 21.3. HRMS for $C_{14}H_{13}NO_2S$: calcd, 259.0667; found: 259.0669.
16. *2,6-Bis(p-tolylsulfinyl)pyridine* (**11**): oil. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 8.03$ (m, 3H), 7.63/7.43 (d, $J = 8.1$ Hz, 2H), 7.28/7.10 (d, $J = 8.0$ Hz, 2H), 2.39/2.36 (s, 6H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta = 166.8$ (C), 141.9/141.4 (C), 140.4/140.2 (C), 140.0 (CH), 130.0/129.7 (CH), 124.8/124.7 (CH), 119.3/118.9 (CH), 21.4/21.3 ($CH_3$). HRMS for $C_{19}H_{17}NO_2S_2$: calcd, 355.0701; found, 355.0700.
17. *2,5-Bis(p-tolylsulfinyl)pyridine* (**12**): mp 89–92 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 8.68/8.66$ (m, 1H), 8.12 (m, 2H), 7.63/7.52 (d, $J = 8.1$ Hz, 2H), 7.29/7.23 (d, $J = 8.1$ Hz, 2H), 2.38/2.37 (s, 3H). $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta = 168.8/168.7$ (C), 146.3, (CH) 144.0/143.8 (C), 142.8/142.7 (C), 142.1/142.0 (C), 140.8/149.7 (C), 140.2/140.1 (C), 134.5/134.4 (CH), 130.5/130.0 (CH), 125.5 (CH), 125.0/124.9 (CH), 119.0/118.9 (CH), 21.5 ($CH_3$), 21.4 ($CH_3$). HRMS for $C_{19}H_{17}NO_2S_2$: calcd, 355.0701; found, 355.0703.