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Tetrahedron Letters 46 (2005) 4231–4233
Tetrahedron Letters

An efficient preparation of 1-phenylsulfonylindolyl methyl sulfoxides using KF/*m*-CPBA

Arasambattu K. Mohanakrishnan* and Neelamegam Ramesh

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, Tamil Nadu, India

Received 9 March 2005; revised 7 April 2005; accepted 12 April 2005
Available online 3 May 2005

Abstract—A variety of 1-phenylsulfonylindolylmethyl sulfides are selectively oxidized to the corresponding sulfoxides using a hitherto unexplored KF/*m*-CPBA system. A major advantage is the absence of over-oxidation.

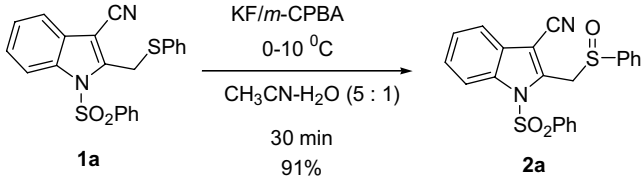
In general, sulfoxides are invariably prepared via the oxidation of the corresponding sulfides and several ways of achieving this transformation have been explored.[1] Despite the plethora of reagents that are available for sulfoxidations, most require careful quantitative control of oxidant to avoid the formation of the over-oxidation product, namely sulfones.

In an ongoing project, we required an array of indolylmethyl sulfoxides for annelation studies.[2] Additionally, the indolylmethyl sulfoxides and sulfones have been explored as potential reverse transcriptase inhibitors.[3] Gray et al. reported a novel synthesis of indolylmethyl sulfoxides involving a tandem sigmatropic rearrangement/Michael addition.[4]

We initiated our oxidation study with sulfide **1a**. All our attempts using one equiv of *m*-CPBA led to the formation of sulfoxide **2a** along with the corresponding sulfone in an appreciable amount (15–20%). Slow addition of *m*-CPBA to a solution of substrate in DCM at 0 °C also led to the formation of the sulfone as a minor product. The oxidation of sulfide was also attempted using Oxone[5] in moist chloroform but without success. The oxidation of **1a** using IBX adopting conditions published by Akamanchi and co-workers[6] led to recovery of starting sulfide **1a**. Thus, under all the conditions tried, incomplete oxidation of sulfide or the formation of sulfone was observed as a side product.

Next, we turned our attention to hypervalent oxidizing reagents. Very recently, oxidation of sulfide to the corresponding sulfoxide using hypervalent iodine has been comprehensively reviewed.[7] Sha and coworkers[8] utilized NaI/*m*-CPBA for iodination of silyl enol ethers. We wondered if the same system could also be used for sulfoxidation, however, the use of NaI/*m*-CPBA led to the selective sulfoxidation of **1a** but only in low yields. The reaction was slow and the product was always contaminated with starting material despite the use of 2 equiv of NaI/*m*-CPBA. We noted a recent report which described an easy conversion of azides into nitro compounds using $HOF{\cdot}CH_3CN$.[9] The oxygen atom of $HOF{\cdot}CH_3CN$ being electrophilic was also used for the oxidation of sulfides into sulfones,[10,11] so we therefore decided to explore a KF/*m*-CPBA system. The interaction of KF and *m*-CPBA in acetonitrile–water followed by the addition of sulfide **1a** led to the isolation of sulfoxide **2a** in 91% yield (Scheme 1).

We tested the KF/*m*-CPBA methodology with various indolylmethyl sulfides (Table 1). In all cases, we obtained the corresponding sulfoxides in good yields



Scheme 1.

Keywords: Indolylmethyl sulfide; Sulfoxidation; KF/*m*-CPBA; Indolylmethyl sulfoxides.
* Corresponding author. Fax: +91 44 22352494; e-mail: mohan_67@hotmail.com

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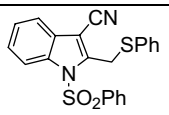
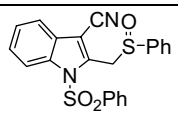
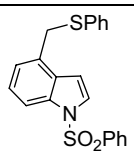
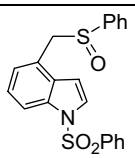
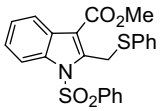
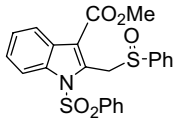
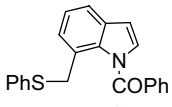
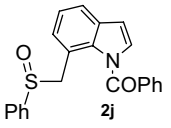
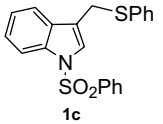
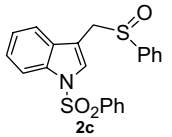
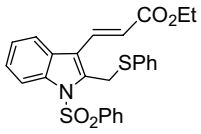
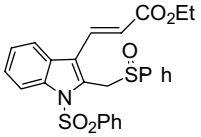
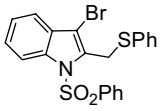
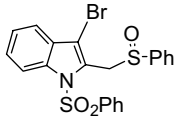
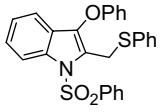
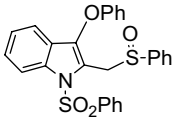
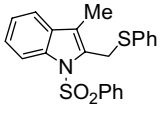
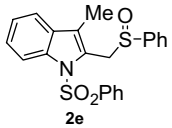
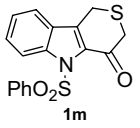
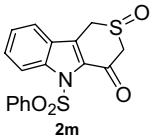
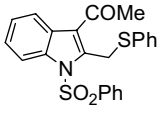
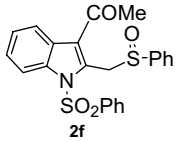
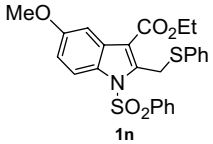
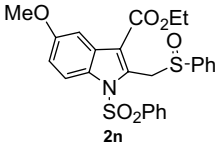
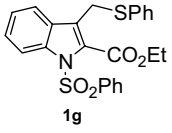
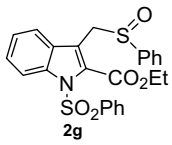
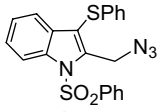
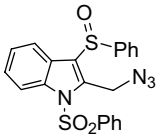
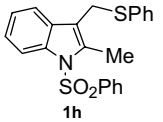
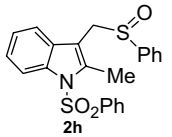
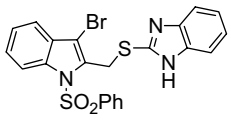
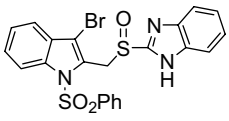
doi:10.1016/j.tetlet.2005.04.067

Table 1. Preparation of indolylmethyl sulfoxides with KF/*m*-CPBA

Entry	Sulfide[13]	Sulfoxide[14]	Yield (%) (mp °C)	Entry	Sulfide[13]	Sulfoxide[14]	Yield (%) (mp °C)
1	 **1a**	 **2a**	91 (142)	9	 **1i**	 **2i**	89 (132)
2	 **1b**	 **2b**	91 (124–126)	10	 **1j**	 **2j**	82 (liquid)
3	 **1c**	 **2c**	84 (136)	11	 **1k**	 **2k**	94 (118)
4	 **1d**	 **2d**	87 (120)	12	 **1l**	 **2l**	87 (145)
5	 **1e**	 **2e**	93 (142)	13	 **1m**	 **2m**	95 (182–184)
6	 **1f**	 **2f**	90 (130)	14	 **1n**	 **2n**	92 (94–96)
7	 **1g**	 **2g**	91 (118)	15	 **1o**	 **2o**	88 (120)
8	 **1h**	 **2h**	88 (182)	16	 **1p**	 **2p**	92 (94)

without any trace of sulfones. Several of these sulfoxides **2a**, **2b**, **2d**, **2f**, **2g** and **2k** are regarded as potential bidentate synthons and they may be useful for the synthesis of biologically important carbazoles. The sulfoxides of relatively unexplored indolyl-4-methyl and indolyl-7-methyl systems were also prepared (entries 9 and 10).

Pantoprazole, which has promising anti-ulcer activity, has a sulfoxide unit bridging pyridine and benzimidazole heterocycles. Large-scale production[12] of this compound via sulfoxidation of the corresponding sulfide always proceeds to give sulfone as a minor impurity. Using our methodology, sulfoxide **2p** (entry 16) containing indole and benzimidazole skeletons was prepared in 75% yield without any trace of the corresponding sulfone. In contrast to the HOF·CH_3CN system,[9] using our system an azide survived (entry 15) and only sulfoxidation occurred. Moreover, oxidation stopped at the sulfoxide stage as opposed to the sulfone obtained with HOF·CH_3CN.[11]

In summary, we have synthesized several indolylmethyl sulfoxides via sulfoxidation using a combination of KF and *m*-CPBA with good selectivity. The unravelling of the synthetic utility of these sulfoxides is currently in progress. Further exploitation of the selective oxidative behaviour of KF/*m*-CPBA will also be explored.

Acknowledgements

A.K.M. thanks the UGC (F.12-140/2001 SR-1), New Delhi, for financial support. Financial support to the Department from DST-FIST is also acknowledged.

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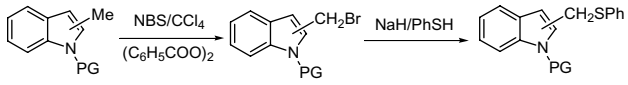
13. All the required sulfides **1a**–**p** were prepared using the two-step procedure as described below:



14. All the sulfoxides **2a**–**p** gave satisfactory spectroscopic and analytical data.Typical experimental procedure for **2a**: To a solution of KF (0.63 g, 10.84 mmol) in acetonitrile–water (40 mL, 8 mL), 70% *m*-CPBA (1.87 g, 10.84 mmol) was added and the mixture stirred at 0 °C for 30 min. To this, 1-phenylsulfonyl-2-phenylthiomethyl-3-cyanoindole **1a** (2.21 g, 5.46 mmol) was added and stirring was continued for an additional 30 min. The reaction mixture was then poured into saturated aq $NaHCO_3$ solution, extracted with ethyl acetate (2×40 mL) and the extracts dried (Na_2SO_4). Removal of solvent followed by crystallization from MeOH afforded **2a** as pale yellow crystals (2.1 g, 91%).
Spectroscopic data for selected sulfoxides: For **2a**: mp 142 °C; IR (KBr) ν_{max}: 2221, 1380, 1181, 1083 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.71 (s, 2 H), 7.26 (d, J = 7.9 Hz, 1H), 7.51 (m, 8H), 7.65 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H). MS(EI) *m/z* (%): 404 (M-16, 9%), 231 (35), 154 (39), 141 (28). Elemental anal. calcd for $C_{22}H_{16}N_2O_3S_2$: C, 62.84; H, 3.84; N, 6.66, S, 15.25%. Found: C, 62.83; H, 3.98; N, 6.51; S, 15.17%.
For **2k**: mp 118 °C; IR (KBr) ν_{max}: 1690, 1360, 1160, 1040 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (t, J = 7.4 Hz, 3H), 4.25 (q, J = 7.4 Hz, 2H), 4.45 (d, J = 14.0 Hz, 1H), 4.65 (d, J = 14.0 Hz, 1H), 6.45 (d, J = 16.0 Hz, 1H-vinylic α-H), 7.75 (m, 15H). MS(EI) *m/z* (%): 477 (M-16, 16%), 361 (38). Elemental anal. calcd for $C_{26}H_{23}NO_5S_2$: C, 63.27; H, 4.70; N, 2.84, S, 12.99%. Found: C, 63.19; H, 4.85; N, 2.73; S, 12.87%.
For **2p**: mp 94 °C; IR (KBr) ν_{max}: 3165, 1370, 1160, 1060 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.15 (d, J = 13.6 Hz, 1H), 5.29 (d, J = 13.6 Hz, 1H), 7.55 (m, 11H), 7.78 (d, J = 7.6 Hz, 2H), 8.07 (d, J = 8.4 Hz, 1H). MS(EI) *m/z* (%): 496 (M-16, 12%), 367 (7), 285 (15), 144 (22). Elemental anal. calcd for $C_{22}H_{16}BrN_3O_3S_2$: C, 51.37; H, 3.14; N, 8.17; S, 12.47%. Found: C, 51.31; H, 3.21; N, 8.06; S, 12.48%.