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A new synthesis of 3-arylthioindoles as selective COX-2 inhibitors using PIFA

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Abstract—The direct 3-arylthiolation of 2-substituted indoles using phenyliodine(III)bis trifluoroacetate (PIFA) in $(CF_3)_2CHOH$ with a wide variety of benzenethiols has been accomplished. In particular, indoles bearing a 6-$MeSO_2$ and either a 2-methyl or 2-carboxymethyl substituent could be 3-arylthiolated in good to excellent yields to afford the corresponding 3-arylthioindoles as selective COX-2 inhibitors. In a study varying the electronic nature of the 5-substituent of 2-CO_2Et indoles, it was discovered that the yield of the reaction improved as the substituent became more electron withdrawing. This result was consistent with a proposed mechanism involving benzenethiol displacement of an intermediate 3-IPh indole complex.

For an anti-inflammatory program targeting potent and selective cyclooxygenase-2 (COX-2) inhibitors, we required a mild general method for the one-pot 3-arylthiolation of indoles containing a 6-methylsulfonyl moiety. Usually 3-arylthioindoles are prepared from the Fisher indole synthesis,[1] though such methodology proved ineffective for our target molecules. An approach involving direct 3-arylthiolation of a suitably substituted indole would be optimal in terms of the efficiency of analogue generation. Traditional methods for the direct 3-arylthiolation of indoles include alkylation of a disulfide with the C-3 organozinc[2a] or organosodium[2b] salt of an indole, the acid catalyzed alkylation of an indole with either mono-*O*,*S*-acetals[2c,d] or sulfenyl chlorides,[2e,f] and the alkylation of indoles via a sulfenium ion promoted Pummerer rearrangement.[2g] These methods, however, were insufficient to meet our needs either because the 6-methylsulfonyl moiety readily enolized or because the method was impractical for analogue generation.

We thus turned our attention to the use of the hypervalent iodine reagent PIFA,[3] reported for the arylthiolation of anisole.[3a] In the reported mechanism, PIFA reacts with the anisole to form a charge-transfer (CT) complex, which subsequently leads to the formation of a radical cation via single electron transfer (SET). The resulting radical cation would then react with a benzenethiol to form the desired *ortho* or *para* substituted arylthio anisole and iodobenzene. One of the primary driving forces of this reaction is reduction of the iodine moiety of PIFA from I(III) to the I(I) oxidation state. It occurred to us that electron rich heterocycles such as indole may be amenable to a similar thioaryl substitution reaction. Thus, an indole could also form a CT-complex with PIFA. This complex would subsequently lead to a cationic 3-(I–Ph) indole complex, which could undergo a arylthio substitution and reductive elimination sequence to form 3-arylthioindoles such as **2** (Scheme 1).[3d,e] For our COX-2 program, the synthesis of **1A** ($R_1 = Me$) and **1B** ($R_1 = CO_2Me$) would be required in order to effect a transformation to the desired potential COX-2 inhibitors **2**. We have recently described the synthesis of 6-methylsulfonyl indoles **1A** and **1B** using established methodology.[4–6]

We were pleased to find that indoles **1A** and **1B** react with a wide range of benzenethiols containing either electron releasing or electron withdrawing substituents (Table 1) in good to excellent yields. The scope of this reaction is shown by the examples summarized in Table 1. It is of interest to note that the 2-pyridylthio analogue **2e** was prepared in 76% yield. Oxidation of the pyridine moiety was not observed. It is apparent that the electronic nature of the benzenethiol moiety had little effect upon the yield. The presence of a 2-CO_2Me versus a

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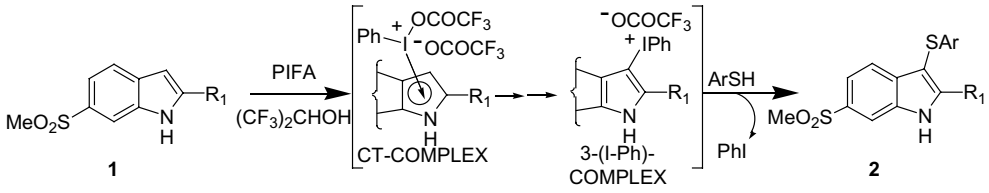
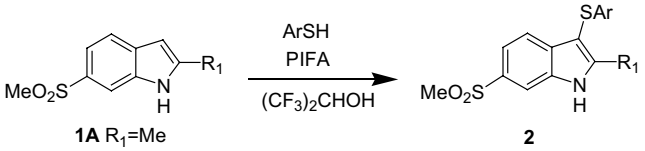


Scheme 1. Proposed mechanism of formation of **2** from **1** using PIFA and ArSH.

2-Me moiety on the indole, however, appeared to improve the yield of the reaction. To explore the potential mechanistic implications of this result, a study was conducted varying the electronic nature of the 5-substituent of 2-carboalkoxy indole. It was discovered that the yield of the reaction improved as the substituent became more electron withdrawing (Table 2, products **4a**–**f**). This would apparently rule out a mechanism involving nucleophilic attack of the indole on a PIFA derived thioaryl electrophile. Replacement of the indole N–H of 5-nitro-2-carboalkoxyindole with an N–Me showed no improvement in yield (compare **4a** to **4e**), but demonstrated that protection of the indole NH was not required.

In summary, the direct 3-thioarylation of indoles using phenyliodine(III)bis trifluoroacetate (PIFA) in $(CF_3)_2$CHOH with a wide variety of benzenethiols has been accomplished. Under these mild conditions, it was demonstrated that indoles bearing a 6-$MeSO_2$ and either a 2-methyl or 2-carboxymethyl substituent could be 3-thioarylated in good to excellent yields to afford the corresponding 3-arylthioindoles as selective COX-2 inhibitors.[6] The biological data for these compounds and other homologues will be reported elsewhere. In a study varying the electronic nature of the 5-substituent of 2-carboalkoxyindole, it was discovered that the yield of the reaction improved as the substituent became more electron withdrawing. This result was consistent with a proposed mechanism involving benzenethiol displacement of an intermediate 3-IPh indole complex.

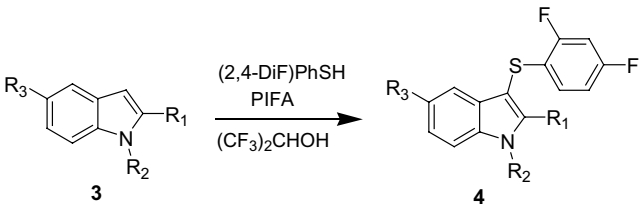
Table 1. 3-Arylthioindole syntheses



Product-**2**	R_1	Ar	Yield (%)
2a	Me	4-F(Ph)	76[a]
2b	Me	2,4-DiF(Ph)	67[a]
2c	Me	2-Cl(Ph)	64[a]
2d	Me	2-Cl,4-F(Ph)	52[a]
2e	Me	2-Pyridyl	76[a]
2f	Me	2-F(Ph)	62[a]
2g	CO_2Me	4-F(Ph)	83[b]
2h	CO_2Me	2,4-DiF(Ph)	88[b,c]
2i	CO_2Me	2-Cl(Ph)	74[b]
2j	CO_2Me	4-Me(Ph)	84[b]
2k	CO_2Me	4-EtO(Ph)	74[b]
2l	CO_2Me	4-MeO(Ph)	74[b]

[a] Isolated yield using 2 equiv ArSH and 1.5 equiv PIFA.
[b] Isolated yield using 2.7 equiv ArSH and 2.0 equiv PIFA.
[c] Experimental example provided (see Ref. 7).

Table 2. 3-Arylthioindole mechanism study



Product-**4**	R_1	R_2	R_3	Yield (%)[a]
4a	CO_2Et	H	NO_2	89
4b	CO_2Et	H	Cl	50
4c	CO_2Et	H	H	29
4d	CO_2Et	H	OCH_3	8
4e	CO_2Me	Me	NO_2	83
4f	CO_2Me	Me	Cl	58

[a] Isolated yield using 2.7 equiv (2,4-DiF)PhSH and 2.0 equiv PIFA.

References and notes

1. Hamel, P.; Girard, Y. *Chem. Ber.* **1963**, *96*, 260.
2. (a) Browder, C. C.; Mitchell, M. O.; Smith, R. L.; Sulayman, G.-E. *Tetrahedron Lett.* **1993**, *34*, 6245; (b) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synth. Commun.* **1988**, *6*, 480; (c) Matsugi, M.; Murata, K.; Nambu, H.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 1077; (d) Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 2434; (e) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567; (f) Raban, M.; Chern, L. J. *J. Org. Chem.* **1980**, *45*, 1688; (g) Jain, S.; Shukla, A.; Mukhopadhyay, A.; Suryawanshi, S. N.; Bhakuni, D. S. *Synth. Commun.* **1990**, *20*, 1315.
3. (a) Kita, Y.; Takada, T.; Tohma, H. *Pure Appl. Chem.* **1996**, *68*, 627; (b) Pohnert, G. *J. fuer. Praktishe Chemie.* **2000**, *342*, 731; (c) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179; (d) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431; (e) Moriarty, R. M.; Ku, Y. Y.; Sultana, M.; Tuncay, A. *Tetrahedron Lett.* **1987**, *28*, 431.
4. Allais, A. *Eur. J. Med. Chem. Chim. Ther.* **1975**, *10*, 187.
5. (a) Adams, R. E.; Press, J. P.; Deegan, E. G. *Synth. Commun.* **1991**, *12*, 675; (b) Semerth, S. *J. Heterocycl. Chem.* **1981**, *18*, 1373.
6. Broka, C. A.; Campbell, J. A. (F. Hoffmann-La Roche Ag, Switz.). PCT Int. Appl. WO 0329212, 2003; p 46.
7. General PIFA promoted indole 3-thioarylation procedure: Preparation of **2h**, 3-(2,4-difluorophenyl-sulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid methyl ester.

To a stirred solution of 2-carbomethoxy-6-methylsulfonylindole (750 mg, 2.8 mmol) in dry $(CF_3)_2CHOH$ (10 mL) under Ar was added 2,4-difluorothiophenol (1.0 g, 7.56 mmol), followed by PIFA (2.40 g, 5.60 mmol) at room temperature. After stirring overnight, the dark solution was partitioned between CH_2Cl_2 (100 mL) and NH_4OH (10 mL). The CH_2Cl_2 layer was washed with more NH_4OH (3×10 mL), water (30 mL), dried ($MgSO_4$) and concentrated to ~20 mL volume. To this mixture was then added 30 mL of hexane, which precipitated the 977 mg (88%) of the product, 3-(2,4-difluorophenylsulfanyl)-6-methanesulfonyl-1*H*-indole-2-carboxylic acid methyl ester, **2h**, as a white solid: mp 202.5–203 °C; ^{1}H NMR ($CDCl_3$): δ 3.09 (s, 3H), 3.97 (s, 3H), 6.72–7.04 (m, 3H), 7.63 (d, 1H, $J = 8.5$ Hz), 7.78 (d, 1H, $J = 8.5$ Hz), 8.21 (s, 1H), 11.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 49.9, 57.5, 108.9, 109.3, 109.6, 117.1, 117.2, 119.1, 123.9, 127.0, 136.6, 136.7, 138.0, 138.2, 140.4, 142.2, 166.0; MS m/e 397 (M^+); Anal. Calcd for $C_{17}H_{13}F_2NO_4S_2.0.60$ H_2O: C, 50.02; H, 3.51; N, 3.43. Found: C, 50.01; H, 3.21; N, 3.49.