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Preparation of 3-arylmethylindoles as selective COX-2 inhibitors

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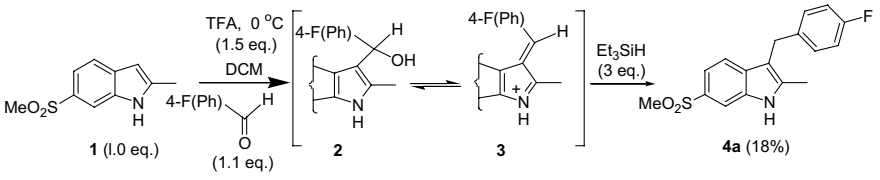
Abstract—The 3-arylmethylation of indoles using TMSOTf/Et_3SiH with a wide variety of substituted benzaldehydes has been accomplished. Under these mild Lewis acid mediated reductive conditions, it was demonstrated that indoles bearing both 6-$MeSO_2$ and 2-methyl substituents could be 3-arylmethylated in good to excellent yields to afford the corresponding 3-arylmethyl indoles, effective as selective COX-2 inhibitors. In addition, the viability of this method for the reductive alkylation of indoles by ketones was demonstrated and shown to be C-3 regioselective. For indoles bearing both a 6-$MeSO_2$ and 2-cyano substituent where this indole reductive alkylation methodology was unsuccessful, an unprecedented Pd(0) mediated arylorganozinc coupling with the requisite substituted 3-methylcarbonatomethylindole proved successful in affording the desired 2-cyano-6-$MeSO_2$-3-arylmethylindoles effective as selective COX-2 inhibitors.

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-arylmethylation of indoles containing a 6-methylsulfonyl moiety. Although 3-substituted indoles can be prepared from the Fisher indole synthesis,[1a–c] such methodology ultimately proved ineffective for our target molecules. It was envisioned that an approach involving direct 3-arylmethylation of a suitably substituted indole would be the most optimal in terms of the efficiency of analogue generation. Traditional methods for the direct 3-arylmethylation of indoles include the base[2a,b] promoted alkylation with benzylic halides, the acid promoted alkylation with benzylic alcohols,[2c] the acid mediated reductive (TFA/Et_3SiH) cleavage of 3-indolecarbinols,[2d] and the one pot reductive alkylation using benzaldehydes and TFA/Et_3SiH.[2e] With the exception of the latter procedure, these methods were unsatisfactory either because of the lack of reactivity with our desired indole substrates, the enolizability of the 6-methylsulfonyl moiety or the impracticality of the method for analogue synthesis.

For our COX-2 inhibitor program, the direct synthesis of potential inhibitors from 6-methylsulfonyl indoles such as **1** using the TFA/Et_3SiH reductive aldehyde coupling method[2e] would be the most expedient approach. We have recently described the synthesis of 6-methylsulfonyl indole **1** from *m*-thioanisidine.[3] We were surprised to find that the TFA/Et_3SiH method carried out under the reported conditions (1.5 equiv TFA/3.0 equiv Et_3SiH using CH_2Cl_2 as solvent)[2e] provided only an 18% yield of the desired indole **4a** from **1** and 4-fluorobenzaldehyde (Scheme 1). The rest of the



Scheme 1. Reductive alkylation of indole **1** with 4-fluorobenzaldehyde and TFA/Et_3SiH.

Keywords: Reductive indole alkylation; 3-Arylmethylindole; 3-Benzylindole; COX-2 inhibitor; TMSOTf; Palladium.
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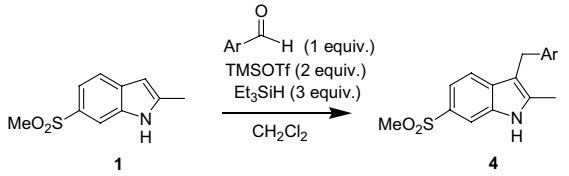
material was either the bisindolylmethane adduct or unidentified baseline material, presumably indole polymers of **1**. In the report, it was noted that the excess of TFA used in the reaction was generally not detrimental, though it was acknowledged that aliphatic aldehydes and ketones can generally self-condense in the presence of TFA. It is noteworthy that using those conditions only 31–36% yields[2e] were reported in the indole reductive alkylation with aliphatic ketones[2f] and there was no improvement in yield even when the ketone reagent was used in excess. It was our belief that TFA may not be the optimal acid catalyst for the reductive alkylation of indoles with either aldehydes or ketones, especially since it is a strong Brønsted acid, which can potentially promote polymerization of the starting substrates. After surveying a number of Lewis acid catalysts ($ZnCl_2$, $TiCl_4$, $MgCl_2$, $BF_3{\cdot}OEt_2$), we discovered the use of TMSOTf to be superior for the Et_3SiH promoted reductive alkylation of indole **1** with aldehydes (Table 1).

We were pleased to find that indole **1** (1 equiv), reacts in good yields with a wide range of substituted aromatic aldehydes containing either electron releasing or electron withdrawing substituents using 2 equiv of TMSOTf, and 3 equiv of Et_3SiH (Table 1).[5] It is of interest to note that using these conditions the 4-fluorobenzyl analogue (**4a**) was isolated in a much more respectable 75% yield from **1**. One minor limitation of these conditions was the failure of an aromatic ketone, 4-fluorobenzophenone, to react.

Table 1. 3-Arylmethylation of **1** with substituted benzaldehydes and TMSOTf/Et_3SiH



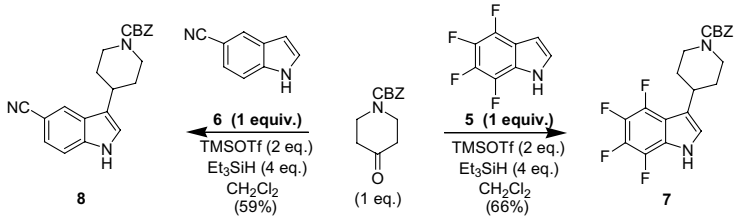
1 **4**

Product-**4**	Ar	R	Yield (%)[a]
4a	4-F(Ph)	H	75
4b	2,4-F(Ph)	H	78[b]
4c	4-Cl(Ph)	H	88
4d	2-Naphthyl	H	69
4e	2-Thiophenyl	H	30
4f	4-F(Ph)	Me	0
4g	4-CF_3(Ph)	H	68
4h	3-F(Ph)	H	81
4i	4-MeO-1-naphthyl	H	67
4j	4-MeO(Ph)	H	67
4k	4-CH_3(Ph)	H	68
4l	4-MeS(Ph)	H	74
4m	4-Br(Ph)	H	72
4n	2-Cl(Ph)	H	64

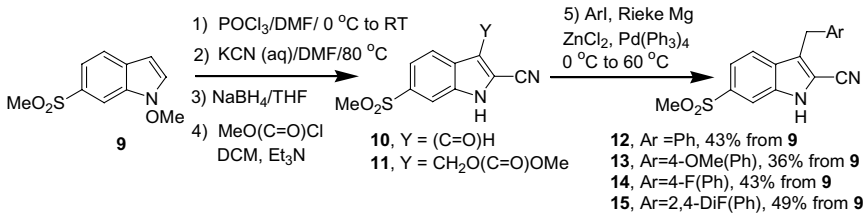
[a] Isolated yield using 1 equiv Ar(C=O)R, 2 equiv TMSOTf, and 3.0 equiv Et_3SiH.
[b] Experimental example provided (see Ref. 5).

Since the TFA/Et_3SiH conditions were reported to work in poor yields for the reductive alkylation of 2-methyl indole with aliphatic ketones,[2e] we decided to attempt the TMSOTf/Et_3SiH conditions (2 and 4 equiv, respectively) with tetrafluoroindole (1 equiv of **5**) and 5-cyanoindole (1 equiv of **6**) using *N*-CBZ 4-piperidone (1 equiv) as the ketone coupling partner (Scheme 2). These indoles were chosen because both lack a 2-substituent and would test the indole alkylation regiochemistry (C-3 vs C-2). In addition, since both indoles are electron deficient, they should be less reactive indole substrates and will suitably test the viability of these conditions for the reductive alkylation of ketones. Fortunately, the self-condensation of *N*-CBZ piperidone did not appear to be a problem using inverse indole addition with either indole **5** or **6** and the corresponding C-3 adducts indoles **7** and **8** were isolated regiochemically pure in yields of 66% and 59%, respectively, on a 10–20 g scale.[4,6]

An apparent limitation of the method, however, is the lack of reactivity of 6-methylsulfonylindole with ketones when there is an electron withdrawing 2-substituent.[3] To solve this problem, we developed a new method involving a Pd(0) mediated arylorganozinc coupling with the requisite substituted 3-methylcarbonatomethylindole **11** as the key precursor, synthesized in four steps from commercially available *N*-OMe-6-$MeSO_2$-indole **9** (Scheme 3).[7–9] Thus, the Vilsmaeyer reaction of indole **9** using $POCl_3$/DMF (0 °C to rt), followed by heating the resulting 3-formylindole with KCN in DMF at 80 °C, gave the 2-cyano-3-formylindole **10** in 87% overall yield (two steps).[8] The $NaBH_4$ mediated reduction of indole **10** in THF, followed by acylation of the resulting alcohol with methyl chloroformate afforded the requisitely substituted 2-cyano-6-$MeSO_2$-3-methylcarbonatomethylindole **11** in 44% overall yield from **10**. The reaction of indole carbonate **11** with 9 mol% $Pd(Ph_3)_4$, and the corresponding organozinc reagents (5 equiv) derived from iodobenzene, 4-MeO-1-iodobenzene, 4-fluoro-1-iodobenzene, and 2,4-difluoro-1-iodobenzene (0–60 °C in THF), gave indoles **12**, **13**, **14**, and **15** in yields of 43%, 36%, 43%, and 48%,[7,9] respectively. It is noteworthy that this method worked in the presence of a free indole NH, cyano, and 6-$MeSO_2$ moieties.



Scheme 2. Reductive alkylation of indoles **7** and **8** with *N*-CBZ-4-piperidone using TMSOTf/Et_3SiH.



Scheme 3. Preparation of indoles **12**–**15** from indole methylcarbonate **11**.

In summary, two novel methodologies for the preparation of various 2-substituted 3-arylmethylindoles as selective COX-2 inhibitors were presented.[3] The first method utilized a TMSOTF/Et_3SiH reductive coupling of 2-methyl-6-methylsulfonylindole with an aromatic aldehyde to afford the corresponding 3-arylmethylindoles. In addition, the viability of this method for the reductive alkylation of indoles by aliphatic ketones was demonstrated and shown to be C-3 regioselective. For indoles bearing both a 6-$MeSO_2$ and 2-cyano substituent, an unprecedented Pd(0) mediated arylorganozinc coupling with the requisite substituted 3-methylcarbonatomethylindole afforded the desired corresponding 3-arylmethylindoles. The biological data of these compounds and other homologues will be reported elsewhere.

References and notes

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3. Broka, C. A.; Campbell, J. A. (F. Hoffmann-La Roche Ag, Switz). PCT Int. Appl. CODEN: PIXXD2 WO 0329212 A1 20030410, 2003, 46 pp.
4. These examples show the potential of this method for the syntheses of CNS-related targets.
5. Representative indole–aldehyde coupling procedure. Preparation of **4b** (Table 1): A solution of indole **1** (136 mg, 0.65 mmol)[3] and commercially available 2,4-difluorobenzaldehyde (93 mg, 0.65 mmol) in dry CH_2Cl_2 (7 mL), was added slowly over 5 min to a stirred solution of TMSOTf (0.236 mL, 1.30 mmol) in dry CH_2Cl_2 (2 mL) cooled to 0 °C under Ar. This mixture was stirred for 15 min and Et_3SiH (0.31 mL, 2.60 mmol) added in one portion. The solution was stirred for 30 min, warmed to room temperature, and the reaction quenched by the slow addition of saturated aqueous $NaHCO_3$ (2 mL). The resulting biphasic mixture was partitioned with CH_2Cl_2 (200 mL) and brine (20 mL). The CH_2Cl_2 layer was dried ($MgSO_4$), concentrated, and the residue purified over a 20×40 cm 1000υ Analtech PTLC plate (eluted with 70% EtOAc/hexanes) to afford 170 mg (78%) of 3-(2,4-difluorobenzyl)-6-methanesulfonyl-2-methyl-*1H*-indole **4b**: ^1H NMR δ 2.44 (s, 3H), 3.18 (s, 3H), 4.04 (s, 2H), 6.75–7.00 (m, 3H), 7.47 (d, 1H, $J = 6.0$ Hz), 7.60 (d, 1H, $J = 6.0$ Hz), 8.00 (s, 1H), 8.76 (s, 1H). MS m/e 335 (M^+).
6. Representative indole–ketone coupling procedure. Preparation of **7** (Scheme 2): To a stirred solution of *N*-CBZ 4-piperidone (6.7 g, 30.2 mmol) in dry CH_2Cl_2 (200 mL) cooled to 0 °C under Ar, was added neat TMSOTf (11.7 mL, 60.4 mmol) dropwise over 5–10 min. To this mixture was added tetrafluoroindole (5.71 g, 30.2 mmol of **5**) in 103 mL of CH_2Cl_2 slowly dropwise over 2.5 h, followed by Et_3SiH (19.3 mL, 120.8 mmol) in one portion. After stirring 1.5 h, the solution was warmed to room temperature for 30 min, and the reaction was quenched by the slow addition of saturated aqueous $NaHCO_3$ (50 mL). The resulting biphasic mixture was partitioned with CH_2Cl_2 (200 mL), the CH_2Cl_2 layer dried ($MgSO_4$), and concentrated. The residue was partitioned between 50% hexane and CH_3CN (1400 mL) and the CH_3CN layer washed with an additional 700 mL portions of hexane, followed by backwashing the combined hexane layers with 70 mL of CH_3CN. The combined CH_3CN layers were dried ($MgSO_4$), concentrated, and the resulting solid recrystallized from the minimum amount of EtOH (~30 mL) to afford 7.88 g (66%) of pure indole **7** in three crops as a solid. Mp 167–168 °C; ^1H NMR ($CDCl_3$) δ 1.50–1.67 (m, 2H), 2.00–2.10 (m, 2H), 2.77–3.15 (m, 3H), 4.25–4.46 (m, 2H), 5.17 (s, 3H), 6.92 (d, 1H, $J = 2.4$ Hz), 7.25–7.42 (m, 5H), 8.79 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 33.0 (t), 33.9 (d), 44.5 (t), 67.2 (t), 112.3 (m), 121.1 (m), 121.3 (m), 121.7 (d), 127.8 (d), 128.0 (d), 128.5 (d), 134.3 (m), 135.0 (m), 136.5 (m), 136.8 (s), 140.1 (m), 155.5 (s); MS m/e 407 (M^+).
7. Representative organozinc–$Pd(Ph_3)_4$ coupling with indole carbonate **11** to prepare **14** (Scheme 3): To a suspension of Rieke Mg in THF (12.6 mL; 12.6 mmol of a suspension of 5 g Rieke Mg/200 mL of THF) was added dropwise a solution of 1-fluoro-4-iodobenzene (2.15 g, 12.57 mmol) in 8 mL of THF. The mixture was then heated to reflux for 3 h, cooled to 0 °C, solid $ZnCl_2$ (2.20 g, 16.18 mmol) added, and the resulting arylorganozinc solution stirred for 1 h. To a solution of indole **11** (93 mg, 0.302 mmol) in 5 mL of THF was added dropwise 1.5 mL (1.5 mmol) of ~1 M 4-fluorophenylzinc chloride solution over 1–2 min, followed by 27 mg (9 mol%) of $Pd(PPh_3)_4$ catalyst added in one portion. The mixture was then quickly warmed to room temperature and heated to 60 °C overnight. The reaction mixture was cooled to room temperature, and diluted with CH_2Cl_2 (250 mL). The mixture was partitioned with saturated aqueous NH_4Cl solution (50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. The resulting residue was purified over a 20×40 cm 1000υ Analtech Preparative TLC plate (eluted with 50% EtOAc/hexanes) to afford 79 mg (43%) of 3-(4-fluorobenzyl)-6-methanesulfonyl-*1H*-indole-2-carbonitrile **14**: ^1H NMR (DMSO-d_6, 300 MHz) δ 12.83

(s, 1H), 7.98 (d, 1H, $J = 1.4$ Hz), 7.90 (d, 1H, $J = 8.6$ Hz), 7.61 (dd, 1H, $J = 8.6$, 1.4 Hz), 7.31 (dd, 2H, $J = 8.7$, 5.6 Hz), 7.12 (t, 2H, $J = 8.8$ Hz), 4.28 (s, 2H), 3.22 (s, 2H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 161.2 (d, $J_{C-F} = 242$ Hz), 138.1, 135.9, 130.4 (d, $J_{C-H} = 8.1$ Hz), 128.4, 126.8, 122.0, 118.5, 115.5 (d, $J_{C-H} = 21.2$ Hz), 113.7, 112.8, 108.7, 44.2, 29.5; MS (ESI): $(M-H)^-$ 327.

8. For related addition–elimination reactions of a 2-formyl *N*-OMe indole as well as the methodology for preparation, see: Yamada, F.; Fukui, Y.; Shinmyo, D.; Somei, M. *Heterocycles* **1993**, *35*(1), 99.
9. The purity of all intermediates and products provided in this communication was determined either by HPLC and/or ^{1}H NMR.