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Direct fluoroalkylthiolation of indoles with iodofluoroethane enabled by Na₂S₂O₄†

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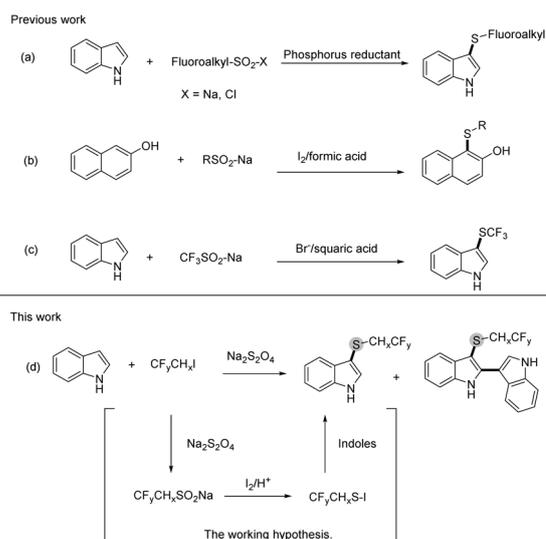
In this paper, we report an efficient approach for the direct fluoroalkylthiolation of indoles with iodofluoroethane in the presence of Na₂S₂O₄. In this work, we employed readily available iodofluoroethane and Na₂S₂O₄ as fluoroalkylthiolation reagents, featuring mild conditions and a wide range of indole substrates. In addition, fluoroalkylthiolated 2,3'-biindole derivatives can also be prepared by this method.

Fluoroalkylthio groups, owing to their unique properties such as high lipophilicity and strong electron-withdrawing effects, have been viewed as vital building blocks, which are widely applied to design and develop pharmaceutical agents and agricultural chemicals.^{1–4} A considerable amount of effort has been expended on the development of fluoroalkylthio group introduction method, particularly for devising novel fluoroalkylthiolation reagents.^{5,6} With regard to electrophilic CF₃S-donors, trifluoromethanesulfinate CF₃SO₂-X (Na, Cl) was often used for trifluoromethylthiolation in the presence of reducing agents.^{7,8} For the reductive reagents, different phosphorus agents (PPh₃,⁹ PCl₃,¹⁰ and PMe₃ (ref. 11)) were evaluated in the deoxygenation of sulfinate (Scheme 1a).^{12,13} Although many methods have been devised to fluoroalkylthiolation, some of these protocols are limited by reaction conditions such as air-sensitive fluoroalkylthiolation reagents and toxic phosphorus reductants. Therefore, the development of a sustainable and effective approach for fluoroalkylthiolation is still of great importance.

In the study of the reduction transformation, we have seen phosphorus reductants as the major player; however, the construction of novel reducing agents to replace phosphorus reductants was seldom described. Previous studies on the fluoroalkylthiolation mechanism have explained that the transformation was governed by the formation of R_F-S-Cl/Br/I intermediates.^{9,14–16} For this reason, halogen was commonly involved in all developed fluoroalkylthiolation systems. The cooperation of halogen and proton was found as the reducing system in the deoxygenation of sulfoxides;^{17,18} by contrast, the halogen-induced deoxygenation of fluoroalkyl-SO₂-X is relatively difficult (Scheme 1b).^{19–21} Jiang and Yi group have reported that fluoroalkylsulfenylation of nucleophiles with R_F-SO₂-X was

promoted by the collaboration of cetyltrimethyl ammonium bromide and squaric acid (Scheme 1c).²² Our previous work has also found that a small amount of trifluoroethylthiolated product was formed by the CH_xF_yCH₂I/Na₂S₂O₄ system without using phosphine reductants.²³ As a deduction, we envisioned that the reactive species CF₃CH₂S-I could also be conceivably produced by the collaboration of CH_xF_yCH₂I and Na₂S₂O₄, *via* the deoxygenation of R-SO₂-X with self-generated I₂/acid (Scheme 1d). In addition, iodofluoroethane and Na₂S₂O₄ are inexpensive and readily available compounds, which are viewed as the idea source of fluoroalkylthio groups.

The reaction conditions were optimized for the trifluoroethylthiolation of 2-methyl indole with CF₃CH₂I and Na₂S₂O₄ (Table 1). First, the solvent effect was examined, it was found that DMSO gave a better result (Table 1 entries 1–4). Considering the poor solubility Na₂S₂O₄, the mixed solvent

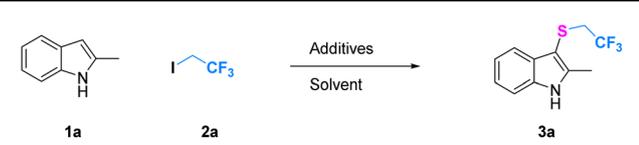


Scheme 1 Represented methods for alkylthiolation.

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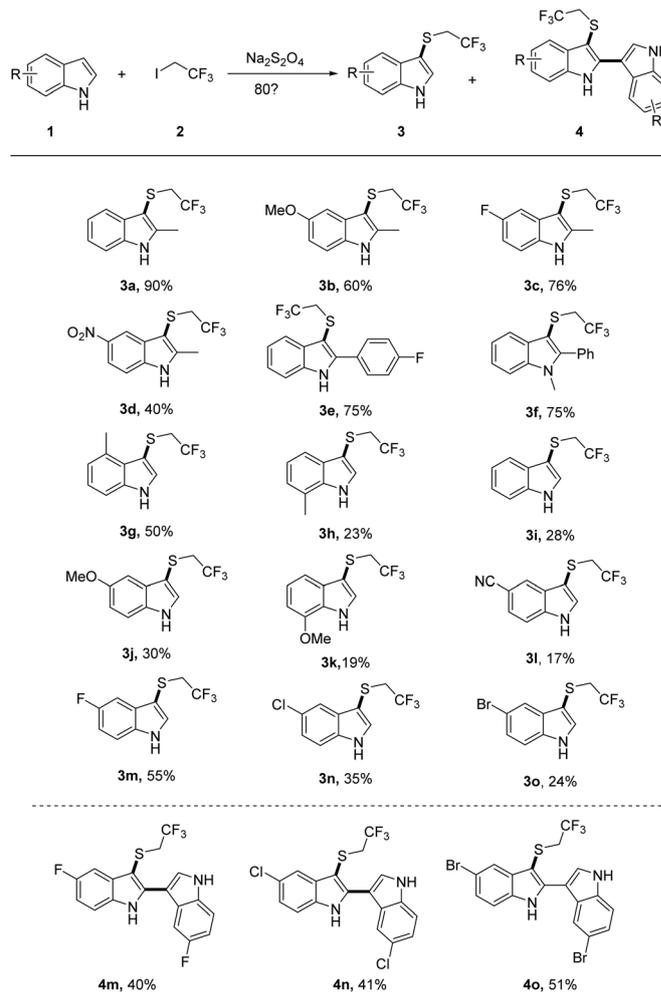
Table 1 Reaction optimization of trifluoroethylthiolation of indoles^a


| Entry | Additives | Solvent | Yield ^a (%) |
|-----------------|---|--|------------------------|
| 1 | Na ₂ S ₂ O ₄ | DMSO | 9 |
| 2 | Na ₂ S ₂ O ₄ | H ₂ O | n.d. |
| 3 | Na ₂ S ₂ O ₄ | CH ₃ CN | n.d. |
| 4 | Na ₂ S ₂ O ₄ | DMF | Trace |
| 5 | Na ₂ S ₂ O ₄ | DMSO/H ₂ O (1/1) | 14 |
| 6 | Na ₂ S ₂ O ₄ | DMSO/CH ₃ CN/H ₂ O (1/1/1) | 45 |
| 7 | Na ₂ S ₂ O ₄ | DMSO/CH ₃ CN/H ₂ O (1/2/1) | 55 |
| 8 | Na ₂ S ₂ O ₄ | DMSO/CH ₃ CN/H ₂ O (1/3/1) | 23 |
| 9 | Na ₂ S ₂ O ₅ | DMSO/CH ₃ CN/H ₂ O (1/2/1) | Trace |
| 10 | Na ₂ S ₂ O ₃ | DMSO/CH ₃ CN/H ₂ O (1/2/1) | Trace |
| 11 | Thiourea dioxide | DMSO/CH ₃ CN/H ₂ O (1/2/1) | 15 |
| 12 ^b | Na ₂ S ₂ O ₄ | DMSO/CH ₃ CN/H ₂ O (1/2/1) | 61 |
| 13 ^c | Na ₂ S ₂ O ₄ | DMSO/CH ₃ CN/H ₂ O (1/2/1) | 83 |
| 14 ^d | Na ₂ S ₂ O ₄ | DMSO/CH ₃ CN/H ₂ O (1/2/1) | 99 (90) ^e |

^a Reaction conditions: 2-methyl-1*H*-indole (0.3 mmol), CF₃CH₂I (0.9 mmol), Na₂S₂O₄ (0.9 mmol), solvent (ratio of volume), 80 °C for 4 h, ¹⁹F-NMR yields using PhCF₃ as an internal standard. ^b Na₂S₂O₄ (5.0 equiv.). ^c Na₂S₂O₄ (7.0 equiv.). ^d Na₂S₂O₄ (9.0 equiv.). ^e Isolated yield.

system was investigated. The yield of desired product will slightly increase by addition of little water, but the reaction will be terminated by large amount of water (ESI-Table S1†). The third mixture solvents were investigated further, and we found that the yield of resulting products varied with the change of solvent component. The solvent consisting of DMSO/CH₃CN/H₂O = 1/2/1 in volume gave the best result in yields of 55% (entry 5, ESI Table S1†). Using this solvent, optimisation of the additives was carried out, a variety of sulfinate additives including Na₂S₂O₅, Na₂S₂O₃, and thiourea dioxide were screened (entries 7 and 9–11, ESI Table S2†). It was identified that Na₂S₂O₄ was the most effective reagent for trifluoroethylthiolation. We next examined the quantity of Na₂S₂O₄ (entries 12–16), and it was unexpected to find that the slightly high loading amounts of Na₂S₂O₄ result in a dramatic influence on the yield. The observation revealed that 9.0 equiv. Na₂S₂O₄ presents the best effect for this reaction with a yield of 99%. Finally, the effects of other additives, temperature and time were also tested (see ESI†). However, no better yield was gained. Gratifyingly, the optimum reaction conditions were obtained as follows: 2-methyl indole (1.0 equiv.) with CF₃CH₂I (3.0 equiv.), Na₂S₂O₄ (9.0 equiv.), DMSO/CH₃CN/H₂O = 1/2/1 (3 ml), 80 °C, and 4 h.

We first investigated the substrate scope of indoles **1** with CF₃CH₂I **2a** (Scheme 2). Diverse functional groups of substituted indoles including methyl, methoxyl, halogen, nitro and nitrile (3 h) functional groups can all be well survived, affording the desired product with moderate to good yields. It was worth mentioning that 2-methyl-5-nitro-1*H*-indole with a strong withdrawing group (–NO₂) gave a moderate yield of 40% of desired product (**3d**). The electron poor aryl group was



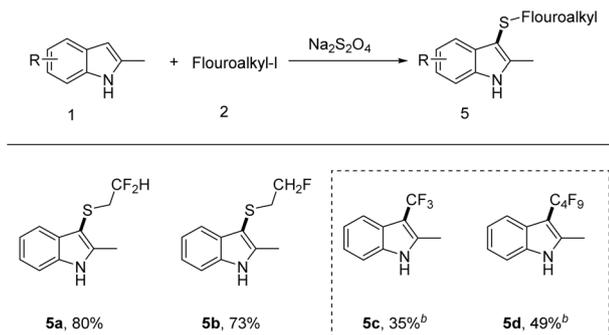
Scheme 2 Scope of trifluoroethylthiolation of substituted indoles. Reaction conditions: indoles (0.3 mmol), CF₃CH₂I (0.9 mmol), Na₂S₂O₄ (2.7 mmol), DMSO/CH₃CN/H₂O (1/2/1) 3 ml, 80 °C for 4 h (8 h for **4**), isolated yield.

also well-tolerated, with the formation of the desired indoles **3e** in 75% yields. The reactivity of halogen substituted indoles showed a slightly decreasing tendency with the following order, F (**3m**) > Cl (**3n**) > Br (**3o**). Notably, the 2-position-substituted indoles have a higher yield than one unsubstituted.

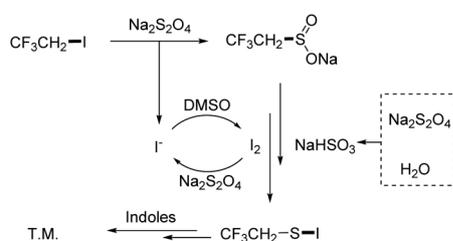
To gain more insights into trifluoroethylthiolation of 2-position unsubstituted indoles, we carefully examined the reaction of halogen (F, Cl, and Br)-substituted indoles and CF₃CH₂I (Scheme 2). Interestingly, we found that the additional product of 3-trifluoroethylthiolated 2,3'-biindoles (**4m**, **4n**, **4o**) were formed with a moderate yield, probably because halogen(i) was created in the course of sulfination, thereby leading to the formation of 2,3'-biindoles.^{24,25} From further evaluation of the reaction, we found that it has less effects to improve the yield of **4** if one increases the loading of indoles.

Next, we turned our attention to investigate the scope of iodoalkane **2** (Scheme 3). The monofluoro/difluoro-iodoethane can readily undergo transformation, delivering the corresponding products in yields of 80 and 73%, respectively.





Scheme 3 Scope of iodofluoroalkane on fluoroalkylthiolation of substituted indoles^a. ^aReaction conditions: 2-methyl-1*H*-indole (0.3 mmol), CF₃CH₂I (0.9 mmol), Na₂S₂O₄ (2.7 mmol), DMSO/CH₃CN/H₂O (1/2/1) 3 ml, 80 °C for 4 h, isolated yield. ^b70 °C.



Scheme 4 Proposed mechanism for the trifluoroethylthiolation of indoles.

Unfortunately, the reaction failed with perfluoroalkyl iodide, which only led to perfluoroalkylation products (**5c** and **5d**).

According to the experiment results (ESI Fig. S1†) and the previous report,^{19–21} a possible reaction pathway was depicted in Scheme 4. The sulfination of CF₃CH₂I yielded CF₃CH₂SO₂Na with Na₂S₂O₄, accompanied by the formation of I[−] ions. Meanwhile, the rest of Na₂S₂O₄ heated with water decomposed to NaHSO₃. Then, CF₃CH₂SO₂Na was deoxygenated in the presence of NaHSO₃/I₂, which could subsequently be converted into CF₃CH₂S-I. Finally, the desired product was formed by the reaction of CF₃CH₂S-I of indoles.

Conclusions

In summary, the novel fluoroethylthiolation protocol has been demonstrated establishing iodofluoroethane/Na₂S₂O₄ as the powerful tool for fluoroethylthiolation of indoles and construction of 2,3'-biindoles. Various indole derivatives underwent smoothly by this mild and simple system. We proposed a possible mechanism of fluoroethylthiolation. The protocol paves an alternative route for the incorporation of fluoroethylthiol groups along the way toward the development of metal- and phosphorus-free systems.

Author contributions

N. Yu and J. Huang prepared and characterized the fluoroalkylthiolated indoles. F. Leng conceived the idea of

fluoroalkylthiolation synthesis, analysed the results and coordinated the work.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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