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Direct fluoroalkylthiolation of indoles with iodofluoroethane enabled by $Na_2S_2O_4$†

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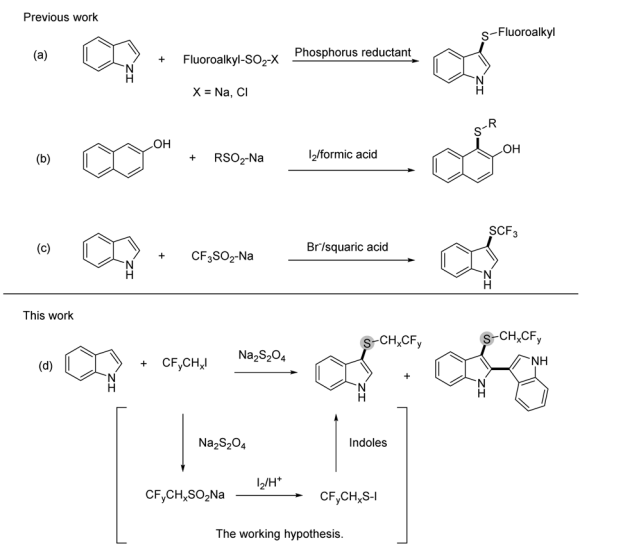
In this paper, we report an efficient approach for the direct fluoroalkylthiolation of indoles with iodofluoroethane in the presence of $Na_2S_2O_4$. In this work, we employed readily available iodofluoroethane and $Na_2S_2O_4$ as fluoroalkylthiolation reagents, featuring mild conditions and a wide range 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 CF_3S-donors, trifluoromethanesulfinate CF_3SO_2–X(Na, Cl) was often used for trifluoromethylthiolation in the presence of reducing agents.[7,8] For the reductive reagents, different phosphorus agents (PPh_3,[9] PCl_3,[10] and PMe_3 (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-SO_2–X is relatively difficult (Scheme 1b).[19–21] Jiang and Yi group have reported that fluoroalkylsulfenylation of nucleophiles with R_f-SO_2–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 $CH_xF_yCH_2I/Na_2S_2O_4$ system without using phosphine reductants.[23] As a deduction, we envisioned that the reactive species CF_3CH_2S–I could also be conceivably produced by the collaboration of $CH_xF_yCH_2I$ and $Na_2S_2O_4$, *via* the deoxygenation of R–SO_2–X with self-generated I_2/acid (Scheme 1d). In addition, iodofluoroethane and $Na_2S_2O_4$ 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 CF_3CH_2I and $Na_2S_2O_4$ (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 $Na_2S_2O_4$, the mixed solvent



Scheme 1 Represented methods for alkylthiolation.

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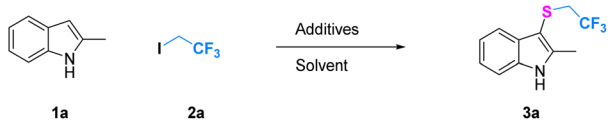
Table 1 Reaction optimization of trifluoroethylthiolation of indoles[a]

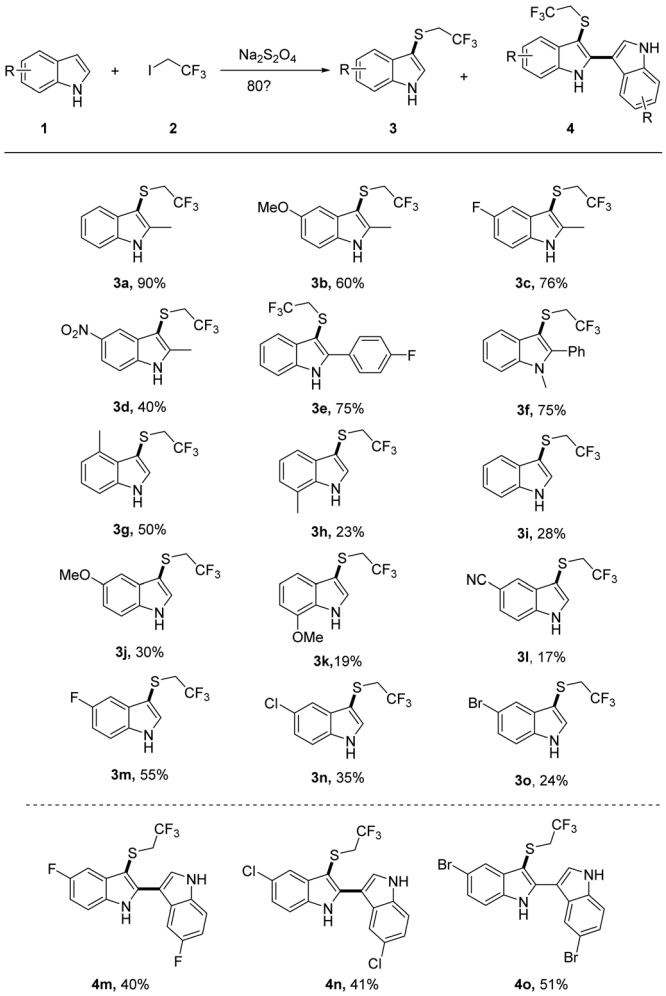


Entry	Additives	Solvent	Yield[a] (%)
1	$Na_2S_2O_4$	DMSO	9
2	$Na_2S_2O_4$	H_2O	n.d.
3	$Na_2S_2O_4$	CH_3CN	n.d.
4	$Na_2S_2O_4$	DMF	Trace
5	$Na_2S_2O_4$	DMSO/H_2O (1/1)	14
6	$Na_2S_2O_4$	DMSO/CH_3CN/H_2O (1/1/1)	45
7	$Na_2S_2O_4$	DMSO/CH_3CN/H_2O (1/2/1)	55
8	$Na_2S_2O_4$	DMSO/CH_3CN/H_2O (1/3/1)	23
9	$Na_2S_2O_5$	DMSO/CH_3CN/H_2O (1/2/1)	Trace
10	$Na_2S_2O_3$	DMSO/CH_3CN/H_2O (1/2/1)	Trace
11	Thiourea dioxide	DMSO/CH_3CN/H_2O (1/2/1)	15
12[b]	$Na_2S_2O_4$	DMSO/CH_3CN/H_2O (1/2/1)	61
13[c]	$Na_2S_2O_4$	DMSO/CH_3CN/H_2O (1/2/1)	83
14[d]	$Na_2S_2O_4$	DMSO/CH_3CN/H_2O (1/2/1)	99 (90)[e]

[a] Reaction conditions: 2-methyl-1*H*-indole (0.3 mmol), CF_3CH_2I (0.9 mmol), $Na_2S_2O_4$ (0.9 mmol), solvent (ratio of volume), 80 °C for 4 h, ^{19}F-NMR yields using $PhCF_3$ as an internal standard. [b] $Na_2S_2O_4$ (5.0 equiv.). [c] $Na_2S_2O_4$ (7.0 equiv.). [d] $Na_2S_2O_4$ (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/CH_3CN/H_2O = 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 $Na_2S_2O_5$, $Na_2S_2O_3$, and thiourea dioxide were screened (entries 7 and 9–11, ESI Table S2†). It was identified that $Na_2S_2O_4$ was the most effective reagent for trifluoroethylthiolation. We next examined the quantity of $Na_2S_2O_4$ (entries 12–16), and it was unexpected to find that the slightly high loading amounts of $Na_2S_2O_4$ result in a dramatic influence on the yield. The observation revealed that 9.0 equiv. $Na_2S_2O_4$ 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 CF_3CH_2I (3.0 equiv.), $Na_2S_2O_4$ (9.0 equiv.), DMSO/CH_3CN/H_2O = 1/2/1 (3 ml), 80 °C, and 4 h.

We first investigated the substrate scope of indoles **1** with CF_3CH_2I **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 (–NO_2) gave a moderate yield of 40% of desired product (**3d**). The electron poor aryl group was

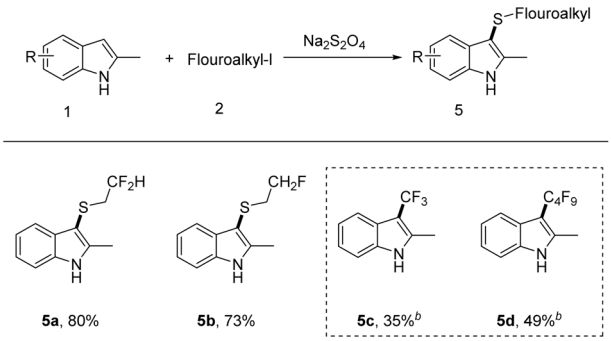


Scheme 2 Scope of trifluoroethylthiolation of substituted indoles. Reaction conditions: indoles (0.3 mmol), CF_3CH_2I (0.9 mmol), $Na_2S_2O_4$ (2.7 mmol), DMSO/CH_3CN/H_2O (1/2/1) 3 ml, 80 °C for 4 h (8 h for **4**), isolated yield.

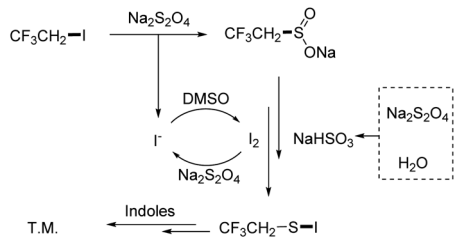
also well-tolerated, with the formation of the desired indoles **3e** in 75% yields. The reactivity of halogen substituted indoles showed a slightly decreasing tendency with the following order, F (**3m**) > Cl (**3n**) > Br (**3o**). Notably, the 2-position-substituted indoles have a higher yield than 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 CF_3CH_2I (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 iodofluoroalkane 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]. [a]Reaction conditions: 2-methyl-1*H*-indole (0.3 mmol), CF_3CH_2I (0.9 mmol), $Na_2S_2O_4$ (2.7 mmol), DMSO/CH_3CN/H_2O (1/2/1) 3 ml, 80 °C for 4 h, isolated yield. [b]70 °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 CF_3CH_2I yielded $CF_3CH_2SO_2Na$ with $Na_2S_2O_4$, accompanied by the formation of I^- ions. Meanwhile, the rest of $Na_2S_2O_4$ heated with water decomposed to $NaHSO_3$. Then, $CF_3CH_2SO_2Na$ was deoxygenated in the presence of $NaHSO_3/I_2$, which could subsequently be converted into CF_3CH_2S–I. Finally, the desired product was formed by the reaction of CF_3CH_2S–I of indoles.

Conclusions

In summary, the novel fluoroethylthiolation protocol has been demonstrated establishing iodofluoroethane/$Na_2S_2O_4$ 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.

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