Irreversible cysteine-selective labelling of a protein using modular electrophilic fluoroalkylation reagents

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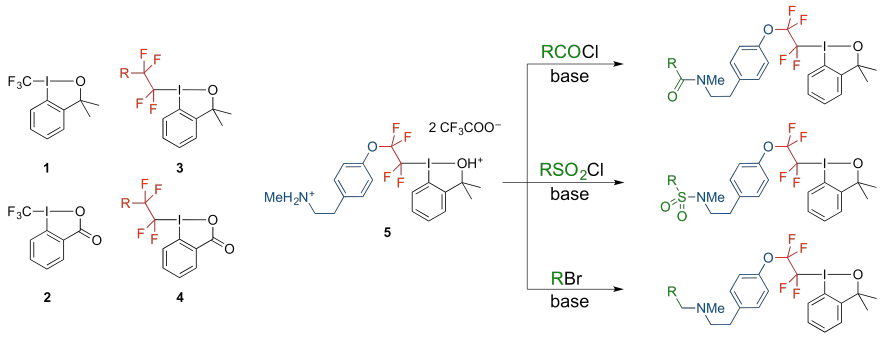
Hypervalent iodine-based compounds **1** and **2** have become popular reagents for formally electrophilic trifluoromethylation owing to their ease of use and reactivity with a broad variety of nucleophilic substrates [1]. In 2016, we extended the reagents bearing the terminal trifluoromethyl group by synthesizing a series of λ^3-iodanes **3** and **4** containing a CF_2CF_2R motif (where R = SAr, OAr, *N*-heterocycle) [2]. As the reactivity of the resulting reagents was comparable with that of the original ones (**1**, **2**) and the tetrafluoroethylene moiety can serve as a linker, giving the possibility of functional applications, we explored the potential of this concept further.

Reagents **3** and **4** were limited to rather basic structures as most functional groups would not tolerate the synthetic pathway. Hence, a reagent containing a secondary amine was prepared (**5**) and investigated in late-stage derivatization *via* mild formation of amides, sulfonamides and tertiary amines. Eventually, we arrived at 22 modular reagents containing manifold functional units (*e.g.*, tetraethylene glycol, biotin, and several fluorophores) [3].

All the reagents (**1**–**5**) display high reactivity toward thiols. Therefore, we envisaged that the modular λ^3-iodanes derived from **5** could be useful as reagents for cysteine-selective tagging of biomolecules. Indeed, when tested with artificial retro-aldolase RA95.5–8 S25C K210M, the exposed cysteine site was labelled selectively [3]. In contrast, the enzyme's active site containing a reactive lysine was left intact, which was not the case with conventional reagents based on maleimide and iodoacetamide. Therefore, the reagents' applicability goes beyond pure organic synthesis – they have the potential to constitute the basis of a new approach to protein labelling.



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