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A facile method for hydroxytrifluoromethylation of alkenes with Langlois reagent and DMSO

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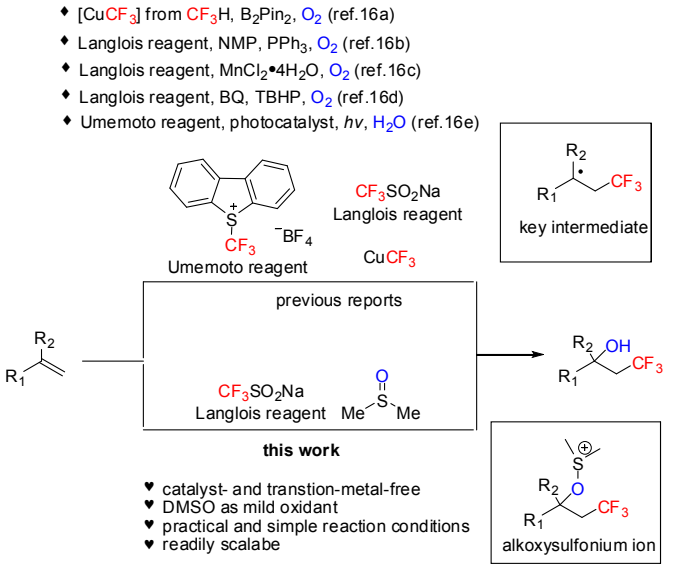
A practical hydroxytrifluoromethylation of alkenes using Langlois reagent as the trifluoromethyl source and DMSO as the oxidant is described. This reaction is mild and operationally simple, without exclusion of either moisture or oxygen, allowing access to a wide range of β-trifluoromethyl alcohols in useful yields. This transformation is environmentally friendly and can be easily scaled up to gram level.

Introduction

Perfluorinated alkyl groups (especially the CF_3 group) can deliver unique biological, chemical and physical properties on organic molecules that are often desirable for pharmaceuticals, agrochemicals and materials.[1,2] Consequently, synthetic organic chemists have a long-standing interest in development of new methodologies for introducing the CF_3 group, which permits the access to trifluoromethylated compounds with structural diversity.[2,3] Notably, a tremendous amount of progress has been made in radical trifluoromethylation by the use of CF_3 radical precursors, such as CF_3I,[4] CF_3SO_2Cl,[5] Togni reagent,[6] Umemoto reagent,[7] Langlois/Baran reagents (CF_3SO_2Na,[8] $(CF_3SO_2)_2Zn$[9]), and Ruppert-Prakash reagent[10] ($TMSCF_3$). Particularly, sodium triflinate (CF_3SO_2Na), developed by Langlois and co-workers in 1991,[11] represents one of the cheapest and most convenient reagents for trifluoromethylation.

In view of that alkenes are a class of easily accessible feedstock, the vicinal difunctionalization of alkenes could serve as one of the most versatile approaches to various functionalized alkanes by the formation of two carbon-carbon and/or carbon-heteroatom bonds.[12] In recent years, the radical addition of a trifluoromethyl group (CF_3) to unfunctionalized olefins has emerged as an important research area.[13-16] Among these reports, the vicinal oxytrifluoromethylation of alkenes provides a useful strategy to simultaneously introduce a CF_3 group and an oxygen atom,[14-16] for example, for the synthesis of α-trifluoromethyl ketones[14] and other diverse molecules containing C–CF_3 and C–O bonds.[15] Although there are a few examples related to hydroxytrifluoromethylation of alkenes which provides a strategy for direct access to useful β-trifluoromethyl alcohols (Scheme 1),[16] these methods usually required transition-metal catalysts, expensive trifluoromethylating reagents, super-stoichiometric amount of strong oxidants, and/or environmentally unfriendly reagents. In most cases, the trapping of the resultant key intermediate β-CF_3-substituted carbon-centered radical by oxygen has been proposed as the key step to form the C–O bond.[16a-d] The nucleophilic attack of H_2O on the β-CF_3-substituted carbocation could also give the corresponding alcohol product.[16e]



Scheme 1 Hydroxytrifluoromethylation of alkenes.

As a low-toxic and inexpensive solvent, dimethyl sulfoxide (DMSO) has been widely used in organic reactions, especially as an oxidant in Swern oxidation,[17] Kornblum oxidation,[18] and formal C–H activation.[19] In most of these reactions, an alkoxysulfonium intermediate could be formed by activation of sulfoxide. However, the transformation of the alkoxysulfonium ions into alcohols is

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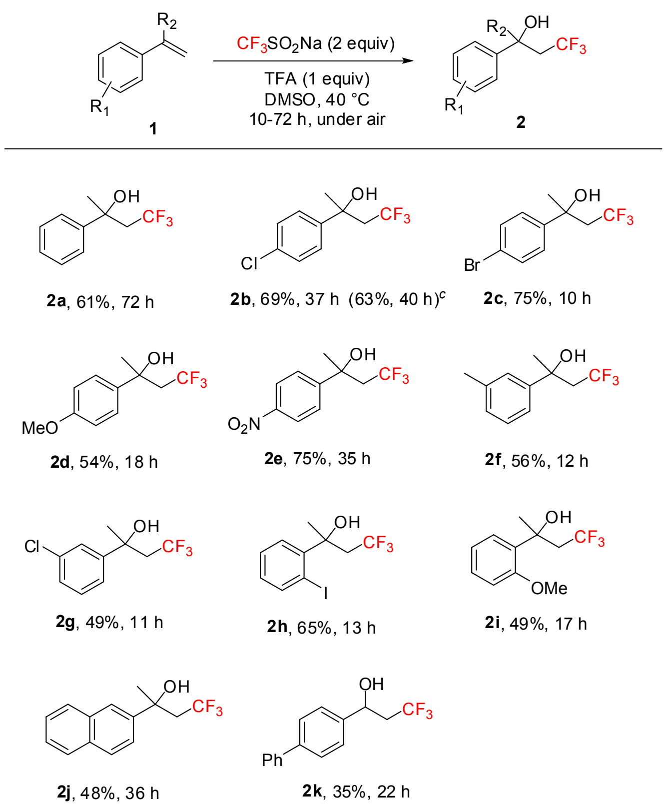
rarely achieved,[19b-c] but giving ketones as the over-oxidative products. In continuation of our research interest in radical trifluoromethylation,[20] we herein report a simple and practical protocol for the synthesis of β-trifluoromethyl alcohols (Scheme 1). In this reaction, the inexpensive and shelf-stable langlois reagent was used as the CF_3 radical source, and the solvent DMSO not only played as an oxidant but also acted as an O-source.

Results and discussion

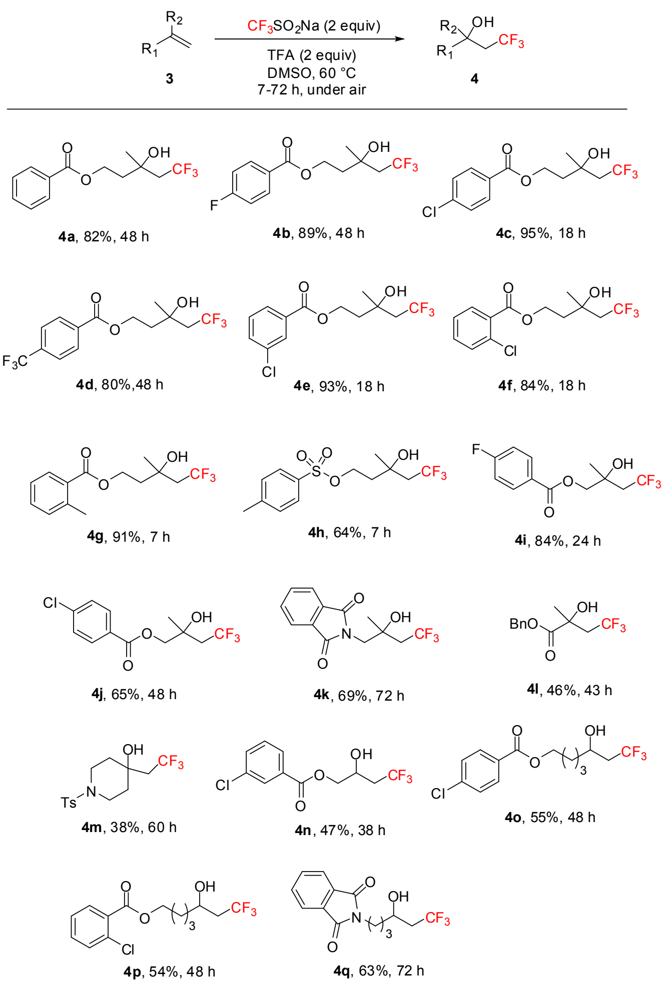
Table 1 Scope of hydroxytrifluoromethylation of styrenes [a,b]



[a]Reaction conditions: **1a** (0.8 mmol), CF_3SO_2Na (1.6 mmol), TFA (0.8 mmol), DMSO (4 mL), 40 °C, under air, 10- 72 h. [b]Isolated yield. [c]**1b** (1.0 g, 6.6 mmol)

We speculated that CF_3 radical could be generated by oxidation of the Langlois reagent with DMSO. To verify the hypothesis, we set out to investigate the reaction using α-methylstyrene **1a** as the acceptor to capture the CF_3 radical. As shown in Table 1, the desired β-trifluoromethyl alcohol **2a** was obtained in 61% yield. Encouraged by this result, a series of styrene derivatives were tested under air to determine the generality. As shown in Table 1, α-methylstyrenes bearing either electron-donating or -withdrawing substituents on the aryl ring could be employed as CF_3 radical acceptors to yield the corresponding products **2b-j** in moderate to good yields. A range of functional groups, such as halogen, methoxy, and nitro substituents were well tolerated in this reaction. Notably, the efficiency of this transformation was not impeded by the steric effect of *ortho* substituents on the phenyl ring (**2h–i**). In the examples of **2c** and **2h**, the reserved bromine and iodine atoms could provide the options for further cross-coupling. The mono-substituted ethylene derivative was also suitable for this protocol (**2k**) though an over-oxidative α-trifluoromethyl ketone byproduct was found. To demonstrate the synthetic utility of this protocol, a gram-scale (1 g of **1b**) reaction was conducted, providing the desired product **2b** in 63% yield.

Table 2 Scope of hydroxytrifluoromethylation of unactivated alkenes [a]

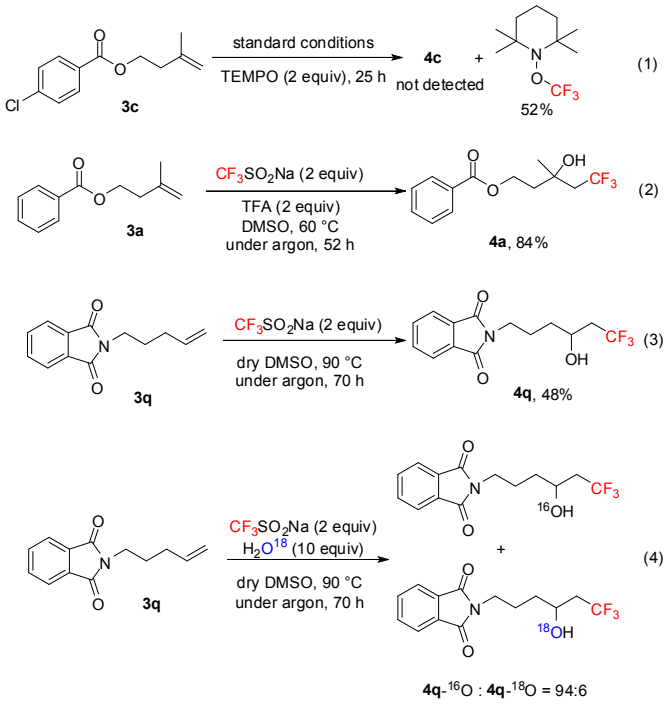


[a]Reaction conditions: **1a** (0.2 mmol), CF_3SO_2Na (0.4 mmol), TFA (0.4 mmol), DMSO (1 mL), 60°C, under air, 7- 72 h. [b]Isolated yield.

Next, we examined the scope of the unactivated alkenes. As revealed in Table 2, a broad range of trifluoromethylated products with various functional groups were readily furnished in moderate to excellent yields (**4a-q**). For this reaction, higher reaction temperature was required compared to the reaction of the styrene substrates in Table 1. It is of note that the electron-deficient alkene **3l** and geminally disubstituted alkene **3m** were both employed well in the reaction, affording the desired products in reasonable yields (**4l-m**). With respect to mono-substituted alkenes, we found that the reaction also proceeded smoothly (**4n-q**)

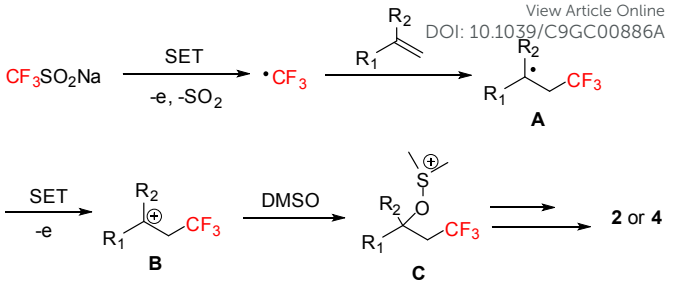
though it led to lower chemical yields compared to that of the 1,1-disubstituted alkenes. However, when extending this protocol to internal alkene, the reaction gave an inseparable product mixture.

Control experiments were performed to gain more mechanistic insights into the reaction (Scheme 2). With TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxyl) as radical scavenger, the reaction led to no desired product **4c** formation but gave TEMPO-CF_3 as the product (Scheme 2, eq 1). It was found that the absence of oxygen (from air) could also provide the desired product **4a** in 84% yield (eq 2). In addition, the use of dry DMSO under TFA-free conditions yielded the desired product **4q** as well though much higher reaction temperature was required for the reaction (eq 3). In order to confirm the fact that the introduced oxygen atom of the products was from DMSO, an isotopic labelling experiment using H_2O^{18} was conducted (eq 4). As might be expected, the result indicated that the formation of an alkoxysulfonium intermediate could be the dominated pathway.



Scheme 2 Control experiments.

On the basis of the experimental results, a plausible reaction mechanism is simply depicted in Scheme 3. The Langlois reagent is single-electron oxidized to give a trifluoromethyl radical (•CF_3), followed by the addition of •CF_3 to an alkene to form a carbon-centred radical **A** which undergoes further single-electron oxidation to afford a *β*-CF_3-substituted carbocation **B**. Subsequently, the nucleophilic attack of DMSO on the carbocation intermediate produces an alkoxysulfonium **C**. Finally, the *β*-trifluoromethyl alcohol product **2** or **4** is furnished.[19b-c]



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, we have developed a mild and practical method for the hydroxytrifluoromethylation of alkenes using the langlois reagent as the CF_3 radical source and DMSO as the oxidant, oxygen source, and solvent. This redox reaction demonstrates a broad substrate scope and good functional group tolerance, affording various *β*-trifluoromethyl alcohols. Further studies on the synthetic applications of this protocol in medicinal and agrochemical fields are underway in this group.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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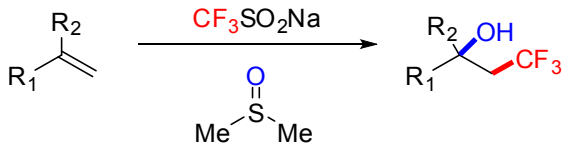

- catalyst- and transtion-metal-free
- DMSO as mild oxidant
- practical and simple reaction conditions
- readily scalabe

A simple and mild protocol is developed for the synthesis of *β*-trifluoromethyl alcohols from alkenes.