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Conversion of MT-Sulfone to a Trifluoromethyl group by IF₅¹: the Application of an MT-Sulfone Anion as a Trifluoromethyl Anion Equivalent

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An MT-sulfone group was converted to a trifluoromethyl group by treatment with IF₅ after an alkylation reaction. Therefore, an MT-sulfone anion can be used as a trifluoromethyl anion equivalent. The formal asymmetric Michael-addition of a trifluoromethyl anion to crotonaldehyde was also performed.

The introduction of a trifluoromethyl group into a molecule is a challenging area of organic chemistry because both a trifluoromethyl anion and its cation are difficult to generate and use². A carbon-carbon bond forming reaction between a trifluoromethyl anion and alkyl halides is the most fundamental method for introducing a trifluoromethyl group in the molecules, and a trifluoromethyl copper species was most successfully used, especially, for the introduction of a trifluoromethyl group into the aromatic ring or vinylic carbon^{3,4}. However, a good yield cannot be expected from a reaction of the trifluoromethyl copper species with aliphatic alkyl halides⁵. Although trifluoromethyltrimethylsilane has been used as a trifluoromethyl anion equivalent⁶, it is rarely used in the S_N2 reaction with alkyl halides owing to the low yield of the expected products and the formation of inseparable by-products^{5c,7}. On the other hand, MT-sulfone {(methylsulfanyl)methyl tolyl sulfone} is known to afford a stable anion species by treatment with a base under mild conditions, and its subsequent reaction with alkyl halides gives alkylated derivatives **1**⁸. We found that the MT-sulfone group in **1** can be converted to a trifluoromethyl group by the reaction with IF₅⁹. Therefore, the MT-sulfone can be used to introduce the trifluoromethyl group to the substrate (**Scheme 1**).

Scheme 1

The reaction of **1** with IF₅ was performed under various conditions, and the best result was obtained by carrying out the reaction in Et₃N-5HF using 6 eq of IF₅ at 60 °C for 48 h. In this reaction, the presence of a methylsulfanyl group in **1** is critical, and the phenyl alkyl sulfone is inert to IF₅. During the reaction, the formation of tosyl fluoride was observed. From these observations, it can be assumed that the reaction proceeds as follows: the oxidative fluorination of **1** by IF₅ initially occurred to afford **3**¹⁰. In the second step, the tosyl group was eliminated as tosyl fluoride to afford a sulfonium salt **4**, which was converted to difluorosulfide **5** by the attack of a fluoride ion. Finally, the methylsulfanyl group in **5** was substituted by a fluoride ion to afford the trifluoromethylated product **2** (Scheme 2).

Scheme 2

Under these conditions, an alkylated MT-sulfone **1a** was converted to 1,1,1-trifluoroalkane **2a** in good yield. Furthermore, a functional group such as an ester, an amide, and a chloride in **1** is tolerable under these conditions, and the functionalized trifluoromethyl compounds could be obtained as shown in Table 1.

Table 1. The reaction of MT-sulfone derivative with IF₅^a

Substrate	Product	Yield (%) ^b
$\begin{array}{c} \text{SO}_2\text{Tol} \\ \\ \text{C}_{12}\text{H}_{25}-\text{C} \\ \\ \text{SMe} \\ \mathbf{1a} \end{array}$	$\begin{array}{c} \text{C}_{12}\text{H}_{25}-\text{CF}_3 \\ \mathbf{2a} \end{array}$	87
$\begin{array}{c} \text{SO}_2\text{Tol} \\ \\ \text{EtOOC}-(\text{CH}_2)_5-\text{C} \\ \\ \text{SMe} \\ \mathbf{1b} \end{array}$	$\begin{array}{c} \text{EtOOC}-(\text{CH}_2)_5-\text{CF}_3 \\ \mathbf{2b} \end{array}$	75
$\begin{array}{c} \text{SO}_2\text{Tol} \\ \\ \text{Cl}-(\text{CH}_2)_{12}-\text{C} \\ \\ \text{SMe} \\ \mathbf{1c} \end{array}$	$\begin{array}{c} \text{Cl}-(\text{CH}_2)_{12}-\text{CF}_3 \\ \mathbf{2c} \end{array}$	81
$\begin{array}{c} \text{SO}_2\text{Tol} \qquad \text{SO}_2\text{Tol} \\ \qquad \qquad \\ \text{MeS}-\text{C}-(\text{CH}_2)_{10}-\text{C}-\text{SMe} \\ \qquad \qquad \\ \text{MeS} \qquad \qquad \text{SMe} \\ \mathbf{1d} \end{array}$	$\begin{array}{c} \text{CF}_3-(\text{CH}_2)_{10}-\text{CF}_3 \\ \mathbf{2d} \end{array}$	71
$\begin{array}{c} \text{SO}_2\text{Tol} \\ \\ \text{BzO}-(\text{CH}_2)_6-\text{C} \\ \\ \text{SMe} \\ \mathbf{1e} \end{array}$	$\begin{array}{c} \text{BzO}-(\text{CH}_2)_6-\text{CF}_3 \\ \mathbf{2e} \end{array}$	73
$\begin{array}{c} \text{SO}_2\text{Tol} \\ \\ \text{Et}_2\text{N}-\text{C}(=\text{O})-(\text{CH}_2)_5-\text{C} \\ \qquad \qquad \\ \text{O} \qquad \qquad \text{SMe} \\ \mathbf{1f} \end{array}$	$\begin{array}{c} \text{Et}_2\text{N}-\text{C}(=\text{O})-(\text{CH}_2)_5-\text{CF}_3 \\ \mathbf{2f} \end{array}$	78 ^c

^a If otherwise not mentioned, the reaction was carried out using 6 eq of IF₅/Et₃N-5HF at 60 °C for 48h. ^b Isolation yield based on substrate used. ^c 8 eq of IF₅/Et₃N-5HF was used.

Recently, the asymmetric trifluoromethylation reaction has received much attention and many elegant methods for producing a compound having a trifluoromethyl group at its asymmetric center have been reported¹¹. However, the asymmetric Michael-addition of the trifluoromethyl anion to α,β -unsaturated carbonyl compounds has not yet been reported. Therefore, we applied our method to introduce a trifluoromethyl group at the β -position of the carbonyl group enantioselectively. The asymmetric Michael-addition of MT-sulfone catalyzed by an organocatalyst was unsuccessful owing to the low acidity of MT-sulfone ($pK_a = 23.4$ ¹²). On the other hand, the organocatalyst-catalyzed asymmetric Michael-addition of bis(phenylsulfonyl)methane ($pK_a = 12.5$ ¹³) to α,β -unsaturated aldehydes is known¹⁴. Therefore, the Michael-addition of bis(phenylsulfonyl)methane to crotonaldehyde was performed in the presence of (*S*)-2-(diphenyltrimethylsiloxy)methylpyrrolidine, and the resulting adduct **6** was reduced to an alcohol¹⁵. After the protection of alcohol with TBDMS, one sulfonyl group was removed by SmI₂¹⁶ and a methylsulfanyl group was introduced to afford the (methylsulfanyl)methyl phenyl sulfoxide derivative **8**. Then, the protecting group of **8** was converted to a benzoyl group, and the resulting benzoate **9** was subjected to a reaction with IF₅/Et₃N-5HF. Under the conditions described above, the (methylsulfanyl)methyl phenyl sulfoxide group was converted to the trifluoromethyl group and 3-trifluoromethyl-1-butyl benzoate **10** was obtained in 52% yield with 85% ee. During the reactions, no racemization occurred, and the trifluoromethyl group could be introduced at the β -position of the carbonyl group enantioselectively (Scheme 3).

i, 20 mol% of (S)-2-(diphenyltrimethylsiloxy)methylpyrrole, toluene
 ii, NaBH₄, 78% from bis(phenylsulfonyl)methane, iii TBDMSCl, imidazole, 97%, iv Sml₂, 93% v BuLi, MeSSO₂Me, 79%
 vi TBAF, vii BzCl, Et₃N, 72% from 5

Scheme 3

Conclusions

We found that the MT-sulfone group can be converted to a trifluoromethyl group by the reaction with IF₅. As the MT-sulfone affords a stable anion species by treatment with a base, and its subsequent reaction with alkyl halides gives alkylated derivatives, an MT-sulfone anion can be used as a trifluoromethyl anion equivalent. We also performed the formal asymmetric Michael-addition of a trifluoromethyl anion to crotonaldehyde, where the trifluoromethyl group was introduced to β-position of crotonaldehyde enantioselectively.

Notes and references

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- 1 IF₅ decomposes in air emitting hazardous HF fume, and, therefore, it should be carefully handled in a bench hood with rubber-gloved hands, and the reaction was carried out in a Teflon™ bottle (a glassware cannot be used).
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