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Title

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Conversion of MT-Sulfone to a Trifluoromethyl group by IF$_5$: the Application of an MT-Sulfone Anion as a Trifluoromethyl Anion Equivalent

Yosuke Imagawa, Syuhei Yoshikawa, Tadahito Fukuhara, and Shoji Hara*

An MT-sulfone group was converted to a trifluoromethyl group by treatment with IF$_5$ 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 use. 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. However, a good yield cannot be expected from a reaction of the trifluoromethyl copper species with aliphatic alkyl halides. Although trifluoromethyltrimethylsilane has been used as a trifluoromethyl anion equivalent, it is rarely used in the $S_N$2 reaction with alkyl halides owing to the low yield of the expected products and the formation of inseparable by-products. On the other hand, MT-sulfone [(methylsulfanyl)methyl tolyl sulfone] is known to afford a stable anion species by treatment with a base under mild conditions, and its subsequent reaction with alkyl halides gives alkylated derivatives. We found that the MT-sulfone group in I can be converted to a trifluoromethyl group by the reaction with IF$_5$. Therefore, the MT-sulfone can be used to introduce the trifluoromethyl group to the substrate (Scheme 1).

The reaction of 1 with IF$_5$ was performed under various conditions, and the best result was obtained by carrying out the reaction in Et$_3$N-5HF using 6 eq of IF$_5$ 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 IF$_5$. 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 IF$_5$ initially occurred to afford 3. 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).
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⁻

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₆H₅COCH₂SO₂Tol</td>
<td>C₆H₅COCH₂CF₃</td>
<td>87</td>
</tr>
<tr>
<td>(E)COOC(CH₂)₂SO₂Tol</td>
<td>(E)COOC(CH₂)₂CF₃</td>
<td>75</td>
</tr>
<tr>
<td>CH₂(C₆H₅)₂SO₂Tol</td>
<td>CH₂(C₆H₅)₂CF₃</td>
<td>81</td>
</tr>
<tr>
<td>TdSO₂</td>
<td>CF₃(CH₂)₂CF₃</td>
<td>71</td>
</tr>
<tr>
<td>BaO(CH₂)₂SO₂Tol</td>
<td>BaO(CH₂)₂CF₃</td>
<td>73</td>
</tr>
<tr>
<td>EtN-C-(CH₂)₂SO₂Tol</td>
<td>EtN-C-(CH₂)₂CF₃</td>
<td>78</td>
</tr>
</tbody>
</table>

*If otherwise not mentioned, the reaction was carried out using 6 eq of IF₅⁻/Et₃N-5HF at 60 °C for 4h. Isolation yield based on substrate used. 8 eq of IF₅⁻/Et₃N-5HF was used.*

10 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 reported. 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 (pKa = 23.412). On the other hand, the organocatalyst-catalyzed asymmetric Michael-addition of bis(phenylsulfonyl)methane (pKa = 12.513) to α,β-unsaturated aldehydes is known. 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 alcohol. After the protection of alcohol with TBDMS, one sulfonyl group was removed by SmI₂ 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 benzyol 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).
Conclusions

We found that the MT-sulfone group can be converted to a trifluoromethyl group by the reaction with IF$_5$. 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 $\beta$-position of crotonaldehyde enantioselectively.

Notes and references

1. IF$_5$ 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$^\text{TM}$ bottle (a glassware cannot be used).


Recently, palladium-catalyzed cross-coupling reaction of trifluoromethyltrimethylsilane with aromatic halides was reproted; B. S. Samant and G. W. Kabalka, Chem. Commun., 2011, 47, 7236.


8. Rozen et al. reported that a trif(methyliodo)methyl group in RCH$_2$C(SMe)$_3$ can be converted to trifluoromethyl group by the reaction with BrF$_3$. However, bromination at $\alpha$-carbon also took place to give RCHBrCF$_3$, see: A. Hagooly, I. Ben-David and S. Rozen, J. Org. Chem., 2002, 67, 8430.


15 The enantiomeric excess of 4 was determined to be 85%ee as reported14.