Synthetic Methods

Copper-Catalyzed Trifluoromethylation of Internal Olefinic C–H Bonds: Efficient Routes to Trifluoromethylated Tetrasubstituted Olefins and N-Heterocycles

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Abstract: The functionalization of internal olefins has been a challenging task in organic synthesis. Efficient Cu II-catalyzed trifluoromethylation of internal olefins, that is, α-oxo-ketene dithioacetals, has been achieved by using Cu(OH) 2 as a catalyst and TMSCF 3 as a trifluoromethylating reagent. The push–pull effect from the polarized olefin substrates facilitates the internal olefinic C–H trifluoromethylation. Cyclic and acyclic dithioalkyl α-oxoketene acetals were used as the substrates and various substituents were tolerated. The internal olefinic C–H bond cleavage was not involved in the rate-determining step, and a mechanism that involves radicals is proposed based on a TEMPO-quenching experiment of the trifluoromethylation reaction. Further derivatization of the resultant CF 3 olefins led to multifunctionalized tetrasubstituted CF 3 olefins and trifluoromethylated N-heterocycles.

Introduction

The incorporation of a trifluoromethyl group into an organic molecule usually brings about remarkable alterations of its physical and biological properties, such as lipophilicity, metabolic stability, and conformational behaviors. Trifluoromethyl functionality is introduced into many pharmaceuticals (for example, panomifene,[1] which exhibits antiestrogenic and tumor-inhibiting activities superior to those of tamoxifen, which is widely used for the clinical treatment of breast cancer), agrochemicals, and advanced materials.[2] Versatile methods have been developed to form C–CF 3 bonds.[3] Addition of trifluoromethylating reagents to C=O[4] and C= N[5] bonds, or olefins,[6] cross-coupling of the CF 3 reagents with prefunctionalized aromatics,[7] and other methods[8] have been applied for this purpose. Owing to the importance of the trifluoromethyl group in drug development, the synthesis of trifluoromethylated olefins has received considerable attention.

Trifluoromethylated olefins are usually prepared by reacting prefunctionalized olefins with trifluoromethylating reagents.[9] Addition of a trifluoromethylating reagent to terminal alkenes,[10] and other indirect routes,[11] can also be found to construct an olefinic C– CF 3 bond. C–H functionalization has recently been employed to realize both transition-metal-catalyzed[12] and metal-free[13] arene and heteroarene C– H trifluoromethylation. On comparison with the trifluoromethylation of (hetero)arenes,[14] the trifluoromethylation of an olefinic C–H bond is very challenging because trifluoromethylating reagents can readily react with terminal olefins to form trifluoromethylated alkanes[15] or allylic products.[16] To date, only a few reports on direct C–H trifluoromethylation of activated olefins, such as quinones[17a, b] and uracil,[17c] and terminal olefins[17d–f] have been documented. Under photocatalytic conditions, terminal olefins can also be trifluoromethylated.[17g, h] Direct C–H/C–X cross-coupling reactions between internal olefins and the usual coupling partners remains to be a challenge because of the low reactivity of the internal olefinic C–H bonds.[18, 19] However, an olefin can be tuned to become highly polarized, exhibiting enhanced reactivity by attaching both an electron-do-

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nating functionality, for example, a dithioalkyl moiety, and an electron-withdrawing moiety, such as a carbonyl group, to the two ends of the C=C bond (Scheme 1a). Under metal-free conditions, some α-oxoketene dithioacetals were trifluoromethylated by \( \text{PhI}^+\text{CF}_3 \) species generated in situ. Intrigued by the push–pull effect of the structural element in such an olefin, we envisioned that α-oxoketene dithioacetals, as internal olefins, may also be utilized as backbones to prepare multi-substituted trifluoromethylated olefins under transition-metal catalysis. Herein, we report Cu\(^{II}\)-catalyzed trifluoromethylation of α-oxoketene dithioacetals and transformation of the resultant CF\(_3\) olefin products (Scheme 1b).

**Results and Discussion**

Cu\(^{II}\)-catalyzed, Ag\(^{I}\)-mediated trifluoromethylation of α-oxoketene dithioacetals (1) with TMSCF\(_3\) (2)

Although metal-free organic transformations of ketene dithioacetals have been well explored, only a few transition-metal-catalyzed reactions of these substrates are established, owing to the ease with which the dithioalkyl moiety can poison a transition-metal catalyst. Thus, suitable metal catalysts and compatible reaction conditions need to be applied for the transformation of dithioacetal substrates. In our initial study, the reaction of internal olefin 1a with Ruppert’s reagent (TMSCF\(_3\), 2) was conducted to screen the reaction conditions. In the presence of Cu (10 mol%), 1,10-phenanthroline (1,10-phen, 10 mol%) as the ligand, Ag\(_2\)CO\(_3\) (two equivalents) as the oxidant, and KF (three equivalents) as the base, in 1,2-dichloroethane (DCE) at 60 °C, the reaction afforded target product 3a in 27% yield within 24 h (Table 1, entry 1). Elevating the temperature to 80 °C dramatically improved the reaction efficiency (Table 1, entry 2). Among the screened Cu and Cu\(^{II}\) sources, Cu(OH)\(_2\) was found to provide 3a in 96% yield (Table 1, entry 5). Without a copper catalyst, the reaction proceeded slowly (Table 1, entry 6). The bidentate ligand 1,10-phenanthroline (1,10-phen) was crucial for the reaction (Table 1, entry 2 and 6). Ag\(_2\)CO\(_3\) behaved as the most efficient oxidant; in the absence of an oxidant the reaction did not proceed well (Table 1, entries 12–15). Increasing the temperature to 100 °C drove the reaction to completion, forming 3a in 92% yield (Table 1, entry 16). It was noted that an air atmosphere slightly decreased the yield, and AgF and Cu(OH)\(_2\) could not be solely used as the base/oxidant or catalyst/oxidant (Table 1, entries 17–19), respectively.

Under the optimized conditions, the protocol generality was explored by using various cyclic α-oxoketene dithioacetals 1 (Table 2). With benzoyl ketene dithioacetals as substrates, the target trifluoromethylation products 3b–m were obtained in 70–91% yields. Substituents, such as methyl, methoxy, chloro, bromo, and fluoro groups were tolerated. A larger aryl group, that is, 2-naphthyl, inhibited formation of the target product 3n (61%) owing to the increased steric hindrance. The furyl analogue of 1a also reacted with 2, forming product 3o (75%). Unexpectedly, the 2-thienoyl substrate underwent both mono- and di-trifluoromethylation to afford target product 3p (62%) and the di-trifluoromethylation product, 3p' (10%). With 3p as the reactant, on a 1.5 mmol scale, 3p' was prepared in 67% yield (Eq. [1]). The reactions of cinnamoyl ketene dithioacetals gave products 3q–t in 47–59% yields, revealing an obvious electronic effect from the cinnamoyl functionality. By extending the dithioalkyl moiety to -S(CH\(_3\))\(_2\)-S, the corresponding ketene dithioacetals also exhibited good reactivity to form the target products 3u–w (61–88%). The molecular structures of 3

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**Table 1. Screening of reaction conditions.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Cu] Base Oxidant Temperature [°C] Yield [%]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Cu KF Ag(_2)CO(_3) 60 27</td>
</tr>
<tr>
<td>2</td>
<td>Cu KF Ag(_2)CO(_3) 80 84</td>
</tr>
<tr>
<td>3</td>
<td>CuOAc KF Ag(_2)CO(_3) 80 83</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)(_2) KF Ag(_2)CO(_3) 80 66</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OH)(_2) KF Ag(_2)CO(_3) 80 96</td>
</tr>
<tr>
<td>6-</td>
<td>KF KF Ag(_2)CO(_3) 80 29</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OH)(_2) KF Ag(_2)CO(_3) 80 6(^{[c]})</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OH)(_2) CsF Ag(_2)CO(_3) 80 3</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OH)(_2) K(_2)CO(_3) Ag(_2)CO(_3) 80 54</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OH)(_2) NaOAc Ag(_2)CO(_3) 80 36</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OH)(_2) KOrBu Ag(_2)CO(_3) 80 0</td>
</tr>
<tr>
<td>12</td>
<td>Cu(OH)(_2) KF Ag(_2)CO(_3) 80 4</td>
</tr>
<tr>
<td>13</td>
<td>Cu(OH)(_2) KF PhI(OAc)(_2) 80 34</td>
</tr>
<tr>
<td>14</td>
<td>Cu(OH)(_2) KF Cu(OAc)(_2) 80 3</td>
</tr>
<tr>
<td>15</td>
<td>Cu(OH)(_2) KF AgOAc 80 68</td>
</tr>
<tr>
<td>16</td>
<td>Cu(OH)(_2) KF Ag(_2)CO(_3) 100 &gt;99 (92)(^{[e]})</td>
</tr>
<tr>
<td>17</td>
<td>Cu(OH)(_2) KF Ag(_2)CO(_3) 100 94(^{[e]})</td>
</tr>
<tr>
<td>18</td>
<td>Cu(OH)(_2) KF – AgF 100 21</td>
</tr>
<tr>
<td>19</td>
<td>Cu(OH)(_2) KF – 100 0</td>
</tr>
</tbody>
</table>

[a] Conditions: 1a (0.5 mmol), 2 (1.5 mmol), [Cu] (0.05 mmol), 1,10-phenanthroline (1,10-phen) (0.05 mmol), base (1.5 mmol), oxidant (1.0 mmol), 1,2-dichloroethane (DCE) (5 mL), 0.1 MPa Ar, 24 h. [b] Determined by GC analysis with PhCF\(_3\) as an internal standard. [c] Without 1,10-phen. [d] Yield of isolated product given in parentheses. [e] In air. [f] Cu(OH)\(_2\) (three equivalents).
were further confirmed by the single-crystal X-ray structure determination of 3h (Figure 1).

Next, the substrate scope was further extended to acyclic α-oxoketene dithioacetals 1\(^a\) (Table 3). The acyclic dimethylthio analogue of 1\(^a\) reacted with 2 to afford target product 4a in 80% yield, whereas the corresponding acyclic benzoyl substrates exhibited a lower reactivity. Thus, 4b had to be prepared by using 20 mol% Cu(OH)\(_2\) to reach 83% yield. Under similar conditions, over a period of 24–48 h, the target products 4c–j were obtained in 62–83% yields. The acyclic diethylthio substrates also exhibited good reactivity, undergoing the Cu\(^{II}\)-catalyzed trifluoromethylation reaction to give products 4k (82%) and 4l (74%). Moreover, the ester ketene dithioacetal substrate underwent the reaction to afford 4m in good yield (70%). On comparison with the recently documented metal-free electrophilic trifluoromethylation of α-oxoketene dithioacetals by PhI\(^+\)CF\(_3\) generated in situ,\(^{[20]}\) the present Cu\(^{II}\)-catalyzed protocol has demonstrated a much wider substrate scope and better efficiency. The molecular structure of 4j was structurally characterized by single-crystal X-ray analysis (see the Supporting Information).

\(\text{Cu}^{\text{II}}\)-catalyzed, Ag\(^1\)-mediated versatile trifluoromethylation of internal olefins with TMSCF\(_3\) (2)

To our delight, readily available ketene monomethylthio acetals 5\(^{[21]}\) underwent the same reaction to form products of type 6, for example, 6a (70%) and 6b (65%), which were then conveniently transformed into tetrasubstituted CF\(_3\) alkenes 8 by Liebeskind–Srogl cross-coupling reactions,\(^{[19, 22]}\) in good yields (74–81%; Scheme 2). This transformation suggests the potential application of the present trifluoromethylation methodology in the synthesis of multisubstituted CF\(_3\) olefins.\(^{[1]}\) Starting from internal olefin 9,\(^{[21]}\) the corresponding trifluoromethylation product 10 was also obtained in 68% yield (Eq. (2)).
Reactions of Compound 4

Condensation of 4 with guanidine (11) and hydrazine (13) was carried out to synthesize fully substituted trifluoromethylated pyrimidines 12 (68–75%) and multifunctionalized 1H-pyrazoles 14 (74–81%), respectively (Scheme 3). Considering easy transformation of the SMe moiety in 12 and 14 into other functionalities,\[19\] the present trifluoromethylation method provides a potentially useful route to highly functionalized five- and six-membered N-heterocycles. The molecular structure of 12c was determined by X-ray crystallographic analysis (Figure 2).

Mechanism studies

To explore the reaction mechanism, kinetic isotope effect (KIE) experiments were performed by using deuterated benzoyl ketene dithioacetal, 1b[D], under the optimized conditions. No KIE (kH/kD = 1.0) was observed (Scheme 4), suggesting that cleavage of the internal olefinic C–H bond was not involved in the rate-determining step of the overall catalytic cycle.

The mechanistic details of this trifluoromethylation reaction remain unclear at the present stage, but the possibility of a radical pathway was explored. By using TMSCF₃, Ag₂CO₃, and KF base, CF₃ radicals from in situ generated AgCF₃ were found to be involved in the ortho-trifluoromethylation of aromatic triazenes.[7c] In our case, addition of two equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO), a well-known radical scavenger, or BHT (2,6-di-tert-butyl-4-methylphenol), to the reaction mixture of 1a and 2 completely inhibited formation of the target product 3a, revealing the involvement of radical species during the reaction (Scheme 5). However, the radical-trapped adduct, TEMPO-CF₃,[6d, 15b] was not detected by [19F NMR analysis of the reaction mixture. Such a phenomenon was also observed by Qing et al.[23] Under the same conditions, addition of one or two equivalents of nitrobenzene, a known electron scavenger used to inhibit the single-electron-transfer (SET) reaction of perfluoroalkyl radicals,[24] had no effect on the reaction (see the Supporting Information). This finding is in agreement with the observation reported by Sanford et al. that...
Caged and/or Ag-associated radicals may be involved in the AgOTf/KF-promoted reaction of benzene with TMSCF₃.[12f] These results suggest the absence of free CF₃ intermediates during the reaction of 1a with 2. Thus, it is plausible to propose that the present trifluoromethylation reaction between 1 and 2 proceeds through a SET pathway[23, 25] involving Ag-associated CF₃ radicals (Scheme 6).

Conclusion

In conclusion, Cu²⁺-catalyzed trifluoromethylation of the internal olefinic C–H bond in α-oxoketene dithioacetals has been efficiently achieved by using TMSCF₃, Ag₂CO₃, and KF, exhibiting a wide substrate scope and substituent tolerance. Easy transformations of the monothioalkyl functionality in the resultant CF₃ olefins render the present synthetic methodology a potentially useful tool for the preparation of multifunctionalized tetrassubstituted CF₃olefins and trifluoromethylated N-heterocycles.

Experimental Section

General considerations

All the manipulations of air- and/or moisture-sensitive compounds were carried out under a nitrogen atmosphere by using the standard Schlenk techniques. Reaction solvents were dried and distilled prior to use by literature methods.¹H and ¹³C{¹H} NMR spectra were recorded on a Bruker DRX-400 spectrometer and all chemical shift values refer to δ_TMS = 0.00 ppm or CDCl₃ (δ_H, 7.26 ppm; δ_C, 77.16 ppm). The HRMS analysis was achieved on a Waters GC-TOF CA156 mass spectrometer. All melting points are uncorrected. Analytical TLC plates, Sigma–Aldrich silica gel 60F₂₅₄, were viewed by UV light (254 nm). Chromatographic purifications were performed on SDZF silica gel 160. FeCl₃·6H₂O was purchased from Alfa Aesar Co. Known products were identified by comparison of their NMR features with the reported data of the authentic samples.

Typical procedure for the trifluoromethylation of α-oxoketene dithioacetals (1) with TMSCF₃ (2)

Synthesis of 3-(1,3-dithiolan-2-ylidene)-4,4,4-trifluorobutan-2-one (3a): Under an argon atmosphere, a mixture of α-oxoketene dithioacetal 1a (160 mg, 1.0 mmol), TMSCF₃ (2) (426 mg, 3.0 mmol), Cu(OH)$_2$ (97.9 mg, 0.1 mmol), 1,10-phen (180 mg, 0.1 mmol), Ag₂CO₃ (547.6 mg, 2.0 mmol), and KF (174.0 mg, 3.0 mmol) in DCE (8 mL) was stirred at 100 °C for 24 h. After cooling to ambient temperature, the resulting mixture was filtered through a short pad of Celite and rinsed with CH₂Cl₂ (20 mL). The combined organic filtrate was evaporated under reduced pressure. The resultant residue was purified by silica-gel column chromato-
Typical procedure for the direct trifluoromethylation of 1' with TMSF₃ (2)

Synthesis of 4,4-bis(methylthio)-3-(trifluoromethyl)but-3-en-2-one (6a): Under an argon atmosphere, a mixture of α-oxoketene dithiaoacetald 1' (162 mg, 1.0 mmol), TMSF₃ (2) (426 mg, 3.0 mmol), Cu(OH)₂ (19.4 mg, 0.2 mmol), phen (36.0 mg, 0.2 mmol), KF (174.0 mg, 3.0 mmol), and Ag₂CO₃ (547.6 mg, 2.0 mmol) in DCE (8 mL) was stirred at 100 °C for 24 h. After cooling to ambient temperature, the resulting mixture was filtered through a short pad of Celite and rinsed with CH₂Cl₂ (20 mL). The combined organic filtrate was evaporated under reduced pressure. The resultant residue was purified by silica-gel column chromatography (eluens: petroleum ether (60–90 °C)/CH₂Cl₂ = 10:1) to afford 6a as a yellow oil (182.0 mg, 70%).

Typical procedure for the direct trifluoromethylation of 5 with TMSF₃ (2)

Synthesis of 4-(methylthio)-4-phenyl-3-(trifluoromethyl)but-3-en-2-one (5a): Under a nitrogen atmosphere, a mixture of 5 (192.0 mg, 1.0 mmol), TMSF₃ (2) (426 mg, 3.0 mmol), Cu(OH)₂ (19.4 mg, 0.2 mmol), phen (36.0 mg, 0.2 mmol), KF (174.0 mg, 3.0 mmol), and Ag₂CO₃ (547.6 mg, 2.0 mmol) in DCE (8 mL) was stirred at 100 °C for 24 h. After cooling to ambient temperature, the resulting mixture was filtered through a short pad of Celite and rinsed with CH₂Cl₂ (20 mL). The combined organic filtrate was evaporated under reduced pressure. The resultant residue was purified by silica-gel column chromatography (eluens: petroleum ether (60–90 °C)/CH₂Cl₂ = 10:1) to afford 5a as a white crystalline solid (209.8 mg, 92%).

Typical procedure for the arylation of 6 with phenylboronic acid (7)

Synthesis of 4,4-diphenyl-3-(trifluoromethyl)but-3-en-2-one (8a): A mixture of 6 (260 mg, 1.0 mmol), phenylboronic acid (7) (183 mg, 1.5 mmol), Pd(PPh₃)₄ (86 mg, 0.075 mmol), 1,2-bis(diphenylphosphino)ethane (dppe, 30 mg, 0.075 mmol), 1,2-bis(diphenylphosphino)ethane (dppe, 30 mg, 0.075 mmol), and K₂CO₃ (276 mg, 2.0 mmol) in THF (10 mL) was stirred at 50 °C for 13 h. After cooling to ambient temperature, the resulting mixture was filtered through a short pad of Celite and rinsed with CH₂Cl₂ (20 mL). The combined organic filtrate was evaporated under reduced pressure. The resultant residue was purified by silica-gel column chromatography (eluens: petroleum ether (60–90 °C)/CH₂Cl₂ = 10:1) to afford 8a as a yellow oil (235 mg, 81%).

Trifluoromethylation of 9 with TMSF₃ (2)

Synthesis of 4,4-dip-tolyl-3-(trifluoromethyl)but-3-en-2-one (10): Under an argon atmosphere, a mixture of 9 (250.0 mg, 1.0 mmol), TMSF₃ (2) (426 mg, 3.0 mmol), Cu(OH)₂ (19.4 mg, 0.2 mmol), phen (36.0 mg, 0.2 mmol), KF (174.0 mg, 3.0 mmol), and Ag₂CO₃ (547.6 mg, 2.0 mmol) in DCE (8 mL) was stirred at 100 °C for 24 h. After cooling to ambient temperature, the resulting mixture was filtered through a short pad of Celite and rinsed with CH₂Cl₂ (20 mL). The combined organic filtrate was evaporated under reduced pressure. The resultant residue was purified by silica-gel column chromatography (eluens: petroleum ether (60–90 °C)/CH₂Cl₂ = 10:1) to afford 10 as a yellow oil (216.3 mg, 68%).

Kinetic isotope effect (KIE) experiments

The trifluoromethylation reactions of 1b and its deuterated form, 1b[CD₂], were carried out in a parallel manner under the optimized conditions. The GC yields from the reactions were carefully checked by the signal integration of the target product 3b with n-dodecane as the internal standard. The kᵣ/kᵢ (0.41/0.42 = 1.0) value was calculated according to the yields of 3b from the reactions at 2 h.

TEMO- or BHT-trapping radical experiment

Under an argon atmosphere, a mixture of α-oxoketene dithiaoacetald 1a (160 mg, 1.0 mmol), TMSF₃ (2) (426 mg, 3.0 mmol), Cu(OH)₂ (97.9 mg, 0.1 mmol), phen (18.0 mg, 0.1 mmol), KF (174.0 mg, 3.0 mmol), TEMPO or BHT (2.0 mmol), and Ag₂CO₃ (547.6 mg, 2.0 mmol) in DCE (8 mL) was stirred at 100 °C for 24 h. The resultant mixture was cooled to room temperature and subject to GC analysis by using PhCF₃ as the internal standard. No target product 3a was found in the reaction mixture.
Inhibition of SET reaction experiment

In a fashion similar to the radical trapping experiment, one or two equivalents of nitrobenzene, instead of TEMPO or BHT, was added to the reaction mixture. At the end of the reaction, GC analysis of the reaction mixture revealed formation of the target product 3a in >99% yield, suggesting that inhibition of the SET reaction in the overall catalytic cycle did not occur during the trifluoromethylation reaction.

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