Visible-Light Promoted Preparation of Trifluoromethylated Tetrahydrofuran and Tetrahydropyran

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Abstract An efficient protocol for facile access to trifluoromethylated tetrahydrofuran and tetrahydropyran has been developed under visible light irradiation conditions via radical 1,2-alkoxyl-trifluoromethylation of unactivated alkene. It features the use of readily commercially available and operatively simple trifluoromethanesulfonyl chloride as a trifluoromethyl radical source, thus making the protocol potentially appealing for practical preparation.

Keywords trifluoromethanesulfonyl chloride; tetrahydrofuran; tetrahydropyran; visible light; alkoxyl-trifluoromethylation

1 Introduction

Tetrahydrofuran and tetrahydropyran are essential motifs of many natural products and bioactive molecules.\textsuperscript{[1]} Thus, their synthesis has attracted many research efforts over the last several decades.\textsuperscript{[2]} On the other hand, the trifluoromethyl group has recently emerged as a greatly useful tool in pharmaceutical\textsuperscript{[3]} and agrochemical\textsuperscript{[4]} sciences due to its unique beneficial effects for enhancing chemical and metabolic stability, bioavailability, and interaction with biologically relevant targets.\textsuperscript{[5]} Therefore, it is highly desirable to develop efficient methods for introducing trifluoromethyl groups\textsuperscript{[6]} into tetrahydrofurans and tetrahydropyrans for potential drug and agrochemical discovery.\textsuperscript{[7]} In this respect, intramolecular 1,2-alkoxyl-trifluoromethylation of unactivated alkene\textsuperscript{[8]} represents a particularly convenient way for accessing various sorts of trifluoromethylated tetrahydrofurans and tetrahydropyrans using different sources of trifluoromethyl radicals, such as Togni’s reagents,\textsuperscript{[9]} Umemoto reagents,\textsuperscript{[10]} and trifluoromethyl halides (Scheme
However, both of the former two types of reagents are relatively expensive and high molecular weights, while the last one is volatile, all of which render these sources uneconomical and impractical for large scale preparations. In contrast, the readily commercially available trifluoromethanesulfonyl chloride (TfCl, CF₃SO₂Cl) is relatively inexpensive, of much lower molecular weight, and is a liquid at ambient temperature, all of which make it an ideal trifluoromethyl radical precursor. As our continuing interest in fluorine chemistry, we herein report an efficient and practical protocol for preparation of a variety of trifluoromethylated tetrahydrofurans and tetrahydropyrans using TfCl-participated 1,2-alkoxyl-trifluoromethylation of unactivated alkene under mild visible-light promoted conditions (Scheme 1).

![Scheme 1 Preparation of tetrahydrofuran and tetrahydropyran via 1,2-alkoxyl-trifluoromethylation of alkene](image)

## Results and discussion

Our investigation began with 1a as a model substrate under our previously employed conditions for generation of trifluoromethyl radical: photosensitizer [Ir(dbtbpy)(ppy)]PF₆ (1 mol%), trifluoromethyl radical source CF₃SO₂Cl (1.5 equiv.), and Na₂HPO₄•12H₂O (2 equiv.) in dichloromethane (DCM) (2 mL) under blue LED irradiation, in which the desired product was obtained in 55% isolated yield on a 0.2 mmol scale (Table 2).

With the optimized conditions in hand, the substrate scope of the current alkoxy-trifluoromethylation reaction was subsequently explored (Table 2). Substrates bearing electron-donating or electron-withdrawing groups on the meta- or para-positions of the alkenyl phenyl rings were tolerated to afford desired trifluoromethylated tetrahydrofurans 2b–2f in 45%–70% isolated yields. The sterically bulky substrates 1g and 1h possessing a 2-methyl substituted phenyl ring and a 1-naphthylene ring also worked well, leading to products 2g and 2h, respectively. A labile benzothiophene ring in substrate 1i survived the reaction conditions to provide product 2i in 40% yield. Noteworthy is that gem-dialkyl-substituted alkene 1j and mono-alkyl-substituted alkenes 1k and 1l were also applicable in the reaction, giving rise to corresponding products in moderate to high yields. In addition, alkenones 1m and 1n bearing only one aryl substituent on the tether also underwent the reaction smoothly, albeit in apparently no diastereoselectivity. Most importantly, substrates 1o–1q with one-carbon-longer tethers were workable under the same conditions to deliver trifluoromethylated tetrahydropyrans 2o–2q in good to excellent yields and low diastereoselectivity. Furthermore, substrate 1r featuring a phenyl-fused tether was also compatible with the reaction conditions to give tetrahydrobenzopyran 2r in moderate yield. The successful formation of trifluoromethylated tetrahydropyran under our conditions is in agreement with literature reports, which indicates that visible-light photoredox catalyzed conditions are more robust and versatile than other conditions in terms of the scope for cyclic ether products.

![Table 1 Preparation of tetrahydrofuran and tetrahydropyran via 1,2-alkoxyl-trifluoromethylation of alkene](image)
Table 1  Optimization of reaction conditions

<table>
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<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive</th>
<th>Solvent</th>
<th>Yield/%</th>
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* Conditions: 1a (0.1 mmol), catalyst (1 mol%), CF3SO2Cl (1.5 equiv.), and additive (2 equiv.) in solvent (1 mL) under blue LED irradiation for 3 h. Yields were based on 19F NMR spectroscopy using α,α,α-trifluorotoluene as an internal standard.

trapping the carbocation with the alkoxyl group followed by facile deprotonation.

3 Summary

In sum, we have prepared a range of trifluoromethylated tetrahydrofurans and tetrahydropyrans using relative inexpensive and atom-economical trifluoromethanesulfonyl chloride as the trifluoromethyl radical source for radical 1,2-alkoxy-trifluoromethylthiation of unactivated alkene under mild visible-light irradiation conditions. This practical protocol may find wide applications in discovering novel drugs and agrochemicals.

4 Experimental section

4.1 General information

All reactions were carried out under argon using Schlenk techniques. Unless otherwise noted, reagents were purchased at the commercial quality and used without further purification. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 GF254 plates. Flash column chromatography was performed using Tsingdao silica gel (60, particle size 0.040~0.063 mm). Visualization on TLC was achieved by use of UV light (254 nm), KMnO4, or iodine stain. NMR spectra were recorded...
on a Bruker DPX 400/500 spectrometers at 400/500 MHz for 1H NMR, 100/125 MHz for 13C NMR, and 376 MHz for 19F NMR in CDCl3 with tetramethylsilane (TMS) as internal standard. 19F NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer (CFCl3 as an external reference). Mass spectrometric data were obtained using a “Bruker Apex IV RTMS”.

4.2 General procedure for visible light promoted alkoxyl-trifluoromethylation of alkene

To a 5-mL single-necked tube equipped with a magnetic stir bar were added compound 1 (0.2 mmol), [Ir(dtbppy)(ppy)]PF6 (1.8 mg, 0.002 mmol) and Na2HPO4•12H2O (143 mg, 0.4 mmol). Then the reaction tube was evacuated with oil pump and back-filled with argon three times. After addition of anhydrous DCM (2 mL) and CF3SO2Cl (32 μL, 0.3 mmol) under argon atmosphere, the reaction tube was sealed. And the mixture was stirred under irradiation with blue LED for appropriate time (1~3 h). Upon completion, the solvent was removed directly under reduced pressure to afford the crude product, which was purified by flash column chromatography to afford the desired product.

3-Phenyl-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (2a). Colourless oil, 55% yield. 1H NMR (400 MHz, CDCl3) δ: 7.47~7.41 (m, 2H), 7.39~7.33 (m, 2H), 7.31~7.25 (m, 1H), 3.83 (d, J=8.3 Hz, 1H), 3.69 (d, J=8.3 Hz, 1H), 2.69 (q, J=10.7 Hz, 2H), 2.43 (d, J=12.8 Hz, 1H), 2.32 (d, J=12.7 Hz, 1H), 1.84~1.73 (m, 1H), 1.71~1.43 (m, 5H), 1.43~1.19 (m, 2H).

3-(3-Methoxyphenyl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (2b). Colourless oil, 45% yield. 1H NMR (400 MHz, CDCl3) δ: 7.27 (t, J=8.0 Hz, 1H), 7.05 (dd, J=2.6, 1.7 Hz, 1H), 6.98 (ddd, J=7.7, 1.8, 1.0 Hz, 1H), 6.81 (ddd, J=8.2, 2.6, 0.9 Hz, 1H), 3.87~3.80 (m, 4H), 3.70 (d, J=8.3 Hz, 1H), 2.68 (q, J=10.7 Hz, 2H), 2.42 (d, J=12.7 Hz, 1H), 2.31 (d, J=12.8 Hz, 1H), 1.85~1.72 (m, 1H), 1.72~1.44 (m, 5H), 1.43~1.33 (m, 1H), 1.32~1.21 (m, 1H).

3-(m-Tolyl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (2c). Colourless oil, 60% yield. 1H NMR (400 MHz, CDCl3) δ: 7.25~7.15 (m, 3H), 7.08~7.03 (m, 1H), 3.79 (d, J=8.3 Hz, 1H), 3.66 (d, J=8.3 Hz, 1H), 2.65 (q, J=10.7 Hz, 2H), 2.38 (d, J=12.8 Hz, 1H), 2.36 (s, 3H), 2.29 (d, J=12.7 Hz, 1H), 1.84~1.69 (m, 1H), 1.70~1.42 (m, 5H), 1.39~1.29 (m, 1H), 1.29~1.18 (m, 1H).

3-((1,1'-Biphenyl)-3-yl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (2d). Colourless oil, 55% yield. 1H NMR (400 MHz, CDCl3) δ: 7.67~7.65 (m, 1H), 7.60 (d, J=7.4 Hz, 2H), 7.51~7.30 (m, 6H), 3.82 (d, J=8.3 Hz, 1H), 3.69 (d, J=8.4 Hz, 1H), 2.71 (q, J=10.7 Hz, 2H), 2.45 (d, J=12.7 Hz, 1H), 2.34 (d, J=12.8 Hz, 1H), 1.84~1.70 (m, 1H), 1.70~1.40 (m, 5H), 1.41~1.29 (m, 1H), 1.33~1.19 (m, 1H).

3-(2,2,2-Trifluoroethyl)-3-(3-(trifluoromethyl)phenyl)-2-oxaspiro[4.4]nonane (2e). Colourless oil, 53% yield. 1H NMR (400 MHz, CDCl3) δ: 7.72 (s, 1H), 7.62 (d, J=7.8 Hz, 1H), 7.54 (d, J=7.8 Hz, 1H), 7.48 (t, J=7.7 Hz, 1H), 3.84 (d, J=8.4 Hz, 1H), 3.69 (d, J=8.4 Hz, 1H), 2.79~2.62 (m, 2H), 2.43~2.33 (m, 2H), 1.86~1.73 (m, 1H), 1.73~1.43 (m, 5H), 1.40~1.16 (m, 2H).

3-(p-Tolyl)-3-(2,2,2-trifluoroethyl)-2-oxaspiro[4.4]nonane (2f). Colourless oil, 70% yield. 1H NMR (400 MHz, CDCl3) δ: 7.29 (d, J=7.9 Hz, 2H), 7.13 (d, J=7.8 Hz, 1H), 7.05 (dd, J=2.6, 1.7 Hz, 1H), 6.98 (ddd, J=7.7, 1.8, 1.0 Hz, 1H), 6.81 (ddd, J=8.2, 2.6, 0.9 Hz, 1H), 3.87~3.80 (m, 4H), 3.70 (d, J=8.3 Hz, 1H), 2.68 (q, J=10.7 Hz, 2H), 2.42 (d, J=12.7 Hz, 1H), 2.31 (d, J=12.8 Hz, 1H), 1.85~1.72 (m, 1H), 1.72~1.44 (m, 5H), 1.43~1.33 (m, 1H), 1.32~1.21 (m, 1H).
Colourless oil, 90% yield (based on $^{19}$F NMR). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 4.21 ~ 4.07 (m, 1H), 2.74 ~ 2.50 (m, 2H), 2.01 ~ 1.88 (m, 1H), 1.85 ~ 1.68 (m, 2H), 1.59 ~ 1.43 (m, 5H), 0.98 ~ 0.83 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 125.39 (q, $J$= 277.6 Hz), 74.35, 54.96 (q, $J$= 3.2 Hz), 42.59 (q, $J$= 28.4 Hz), 34.50, 32.30, 31.31, 30.86, 7.92, 7.76; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -63.87; HRMS (ESI) calcld for C$_{13}$H$_{15}$F$_3$O$_3$ [M+H]$^+$ = 211.1304, found 211.1326.

2-Phenyl-5-(2,2,2-trifluoroethyl)tetrahydrofur an (2m): Colourless oil, 87% yield, $dr$ 1:0:1 (based on quantitative $^{13}$C NMR). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40 ~ 7.26 (m, 5H+5H), 4.80 ~ 4.64 (m, 1H+1H), 4.22 ~ 4.07 (m, 1H+1H), 2.69 ~ 2.43 (m, 2H+2H), 2.11 ~ 1.95 (m, 2H+2H), 1.95 ~ 1.81 (m, 2H+1H), 1.79 ~ 1.67 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$: 144.24, 144.17, 128.79, 128.76, 128.66 ~ 122.01 (m, 1C+1C), 128.04, 127.98, 125.88, 125.82, 74.18, 73.59, 54.37 (q, $J$= 3.3 Hz), 53.97 (q, $J$= 3.2 Hz), 42.93 ~ 42.19 (m, 1C+1C), 34.36, 35.15, 34.71, 34.26; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -63.83; HRMS (ESI) calcld for C$_{13}$H$_{15}$F$_3$O$_3$ [M+H]$^+$ = 231.0991, found 231.0993.

2-(4-Methoxyphenyl)-5-(2,2,2-trifluoroethyl)tetrahydrofur an (2n): Colourless oil, 71% yield, $dr$ 1:0:1 (based on quantitative $^{13}$C NMR). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.30 ~ 7.21 (m, 2H+2H), 6.93 ~ 6.84 (m, 2H+2H), 4.70 ~ 4.59 (m, 1H+1H), 4.23 ~ 4.06 (m, 1H+1H), 3.80 (s, 3H+3H), 2.69 ~ 2.41 (m, 2H+2H), 2.14 ~ 1.77 (m, 3H+1H), 1.76 ~ 1.62 (m, 1H+1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 159.37, 159.33, 136.37, 136.29, 128.67 ~ 122.01 (m, 1C+1C), 127.17, 127.10, 114.11, 114.09, 73.77, 73.23, 54.37 (q, $J$ = 3.3 Hz), 53.99 (q, $J$ = 3.2 Hz), 42.93 ~ 42.18 (m, 1C+1C), 35.36, 35.08, 34.79, 34.38; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -63.83; HRMS (ESI) calcld for C$_{13}$H$_{15}$F$_3$O$_3$ [M+H]$^+$ = 261.1097, found 261.1088.

2-Phenyl-6-(2,2,2-trifluoroethyl)tetrahydro-2H-pyran (2o): Colourless oil, 90% yield, $dr$ 1:0:1 (based on quantitative $^{13}$C NMR). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.47 ~ 7.27 (m, 5H+5H), 4.76 ~ 4.65 (m, 1H+1H), 4.19 ~ 4.05 (m, 1H+1H), 2.74 ~ 2.44 (m, 2H+2H), 1.98 ~ 1.53 (m, 5H+6H), 1.54 ~ 1.38 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 144.58 (1.1C), 144.56 (1C), 128.67 (2.2C+2C), 127.85 (1.1C), 127.83 (1C), 125.94 (2.2C), 125.90 (2C), 125.36 (d, $J$ = 277.5 Hz, 1C+1C), 74.47 (1C), 74.38 (1C), 54.14 ~ 54.06 (m, 1C+1C, 42.83 ~ 42.13 (m, 1C+1C), 38.20 (1C), 38.18 (1C), 37.99 (1C), 37.95 (1C), 22.52 (1C), 22.49 (1C); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -63.78; HRMS (ESI) calcld for C$_{13}$H$_{15}$F$_3$O$_3$ [M+H]$^+$ = 245.1148, found 245.1139.

2-(4-Methoxyphenyl)-6-(2,2,2-trifluoroethyl)tetrahydro-2H-pyran (2p): Colourless oil, 75% yield, $dr$ 1:0:1 (based on quantitative $^{13}$C NMR). $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.28 (d, $J$ = 8.5 Hz, 2H+2H), 6.91 (d, $J$ = 8.7 Hz, 2H+2H), 4.68 ~ 4.57 (m, 1H+1H), 4.17 ~ 4.04 (m, 2H+1H), 3.83 (s, 3H+3H), 2.72 ~ 2.43 (m, 2H+2H), 1.94 ~ 1.51 (m, 5H+6H), 1.51 ~ 1.36 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 159.24 (1.1C), 159.23 (1C), 136.73 (1C),
136.70 (1.1C), 127.21 (2.2C), 127.17 (2C), 125.37 (d, J = 277.4 Hz, 1.1C + 1C), 114.02 (2.2C + 2C), 74.07 (1C), 74.00 (1.1C), 55.39 (1.1C + 1C), 54.16 ~ 54.07 (m, 1.1C + 1C), 42.84 ~ 42.13 (m, 1.1C + 1C), 38.11 (1C), 38.09 (1.1C), 37.97 (1C), 22.58 (1C), 22.55 (1.1C); 19F NMR (376 MHz, CDCl3) δ: −63.81; HRMS (ESI) calec for C17H18F3O [M + H]+ 275.1253, found 245.1244.

(2-Naphthalen-2-yl)-6-(2,2,2-trifluoroethyl)tetrahydro-2H-pyran (2q): Colourless oil, 76% yield, d = 1.0 (based on quantitative 13C NMR). 1H NMR (400 MHz, CDCl3) δ: 7.90 ~ 7.83 (m, 3H + 3H), 7.80 (s, 2H), 7.57 ~ 7.50 (m, 2H + 3H), 7.48 (t, J = 2.0 Hz, 1H), 4.91 ~ 4.82 (m, 1H + 1H), 4.18 ~ 4.05 (m, 1H + 1H), 2.72 ~ 2.43 (m, 2H + 2H); 2.01 ~ 1.58 (m, 5H + 5H), 1.56 ~ 1.42 (m, 1H), 13C NMR (126 MHz, CDCl3) δ: 141.90, 141.87, 133.35 (1C + 1C), 133.14, 133.13, 128.56, 128.54, 128.03 (1C + 1C), 128.82 (1C + 1C), 126.38 (1C + 1C), 126.06 (1C + 1C), 125.36 (q, J = 277.5 Hz, 1C + 1C), 124.74, 124.68, 123.99 (1C + 1C), 74.59, 74.49, 54.14 ~ 54.05 (m, 1C + 1C), 42.82 ~ 42.12 (m, 1C + 1C), 38.06 (1C + 1C), 37.99, 37.96, 22.54, 22.49; 19F NMR (376 MHz, CDCl3) δ: −63.76; HRMS (ESI) calec for C17H18F3O [M + H]+ 295.1304, found 295.1300.

3-(2,2,2-Trifluoroethyl)isochromene (2r): Colourless oil, 58% yield. 1H NMR (400 MHz, CDCl3) δ: 7.44 ~ 7.39 (m, 1H), 7.38 ~ 7.30 (m, 2H), 7.30 ~ 7.26 (m, 1H), 4.81 ~ 4.69 (m, 2H), 4.53 ~ 4.42 (m, 1H), 3.29 (dd, J = 14.5, 6.0 Hz, 1H), 3.21 (dd, J = 14.5, 8.6 Hz, 1H), 2.77 ~ 2.61 (m, 2H); 13C NMR (125 MHz, CDCl3) δ: 138.94, 135.54, 130.81, 129.50, 128.52, 128.75, 125.44 (q, J = 277.6 Hz), 63.61, 54.51 (q, J = 3.1 Hz), 42.05 (q, J = 28.6 Hz), 41.10; 19F NMR (376 MHz, CDCl3) δ: −63.51; HRMS (ESI) calec for C17H18F3O [M + H]+ 217.0835, found 217.0834.

Supporting Information 1H NMR and 13C NMR spectra of the products. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn.

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