A Practical Method for Metal-Free Radical Trifluoromethylation of Styrenes with NaSO₂CF₃

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Abstract: A mild and practical protocol for the metal-free trifluoromethylation of styrenes using NaSO₂CF₃ (Langlois reagent) and TBHP was developed. The approach provides efficient access to α -trifluoromethylated ketones and alcohols in moderate to good yields.

Key words: metal-free, trifluoromethylation, ketones, alcohols, Langlois reagent, styrenes

Organofluorine compounds bearing a CF_3 group are important materials in pharmaceuticals, agrochemicals, and material science.¹ This is because the introduction of fluorine atoms into organic molecules often significantly alters the biological activity, metabolism, solubility, hydrophobicity or bulk properties of such organofluorine compounds.²

During the past several years, a series of methods have been reported that allow transition-metal-mediated/catalyzed or photoredox-catalyzed construction of C–CF₃ bonds.^{3–8} In this context, the synthesis of α -trifluoromethyl ketones has commonly been achieved by the radical and electrophilic CF₃ addition to enolates and silyl enol ethers.⁹ In 2012, Grushin and co-workers developed a nucleophilic trifluoromethylation of α -halogenated ketones by using fluoroform-derived CuCF₃.¹⁰ Very recently, a copper-mediated decarboxylative trifluoromethylation was developed for the preparation of α -trifluoromethyl ketones from propiolic acids.¹¹ However, most of the developed methods suffer from the need to use metal catalysts and/or expensive trifluoromethylating reagents.

In this paper, a mild and practical protocol is described for the metal-free trifluoromethylation of styrenes by using NaSO₂CF₃ (Langlois' reagent) and *tert*-butyl hydroperoxide (TBHP). The approach enables efficient access α -trifluoromethylated ketones and/or alcohols.¹² To the best of our knowledge, only a few examples of the trifluoromethylation of styrenes have been published so far (Scheme 1).¹³ Since the Langlois reagent was first developed in the 1980s as a convenient and inexpensive source of trifluoromethyl radicals, several reports have shown its synthetic usefulness for the construction of C–CF₃ bonds.^{14–16}

Our initial investigation focused on the metal-free reaction of styrene (1a) with NaSO₂CF₃, benzoquinone (BQ), and TBHP at 80 °C in different solvents. The desired trifluoromethylated products **2a** and **3a** (Table 1) were formed in 54% yield by using the mixed solvent MeCN– H₂O (Table 1, entry 6). Other solvent systems such as CH₂Cl₂–H₂O, DMF–H₂O, acetone–H₂O, MeOH–H₂O, or MeCN–CH₂Cl₂–H₂O (Table 1, entries 1–5) afforded the product either in lower yield or not at all. It was found that the use of a mixture of MeCN–H₂O (4:1 v/v) resulted in



Scheme 1 Trifluoromethylation of styrenes; previous work by Zhang et al.^{13a} and Nicewicz et al.,^{13b} and current work

SYNLETT 2014, 25, 1307–1311 Advanced online publication: 27.03.2014 DOI: 10.1055/s-0033-1341057; Art ID: ST-2014-W0053-L © Georg Thieme Verlag Stuttgart · New York an increased yield of **2a** (37%) and **3a** (21%) (Table 1, entries 6–9). The addition of oxidant was very important to increase the yields of the trifluoromethylated products. Without oxidant, only 21% combined yield of the desired products were obtained (Table 1, entry 10). By using other quinoid oxidants such as 2,3-dichloro-5,6-dicyano-1,4benzoquinone (DDQ), 1,4-naphthoquinone, tetrachloro-1,4-benzoquinone, or methyl-*p*-benzoquinone, lower yields were obtained. When CuSO₄ was used as the oxidant (Table 1, entry 15), only trace quantities of the desired products were detected by ¹⁹F NMR analysis. Therefore, BQ was established as the best choice for this trifluoromethylation of styrenes (Table 1, entries 11–14). The addition of 0.5 or 2.0 equivalents BQ afforded the de-

 Table 1
 Optimization of the Trifluoromethylation of Styrene 1a^a

sired products in only 34 and 54% combined yields, respectively (Table 1, entries 16 and 17). The reaction temperature was also changed to 60 or 80 °C, however, neither the yields nor the ratios of the products changed significantly (Table 1, entries 18 and 19). In an attempt to make the trifluoromethylation more efficient, the amounts of NaSO₂CF₃ and TBHP were reduced, however, under these conditions the product was obtained in lower yield (41%; Table 1, entry 20). It is notable that none of the desired product was obtained when this reaction was carried out under an N₂ atmosphere (Table 1, entry 21).

With these results in hand, we then investigated the substrate scope of this metal-free trifluoromethylation with



| (1.0 equiv) | | | | |
|-----------------|------------------------------------|--|-----------|----------------------------|
| Entry | Oxidant (equiv) | Solvent (v/v) | Temp (°C) | Yield $(2a + 3a) (\%)^{b}$ |
| 1 | BQ (1.0) | CH ₂ Cl ₂ –H ₂ O (2.5:1) | 80 | trace |
| 2 | BQ (1.0) | DMF-H ₂ O (2.5:1) | 80 | 0 |
| 3 | BQ (1.0) | acetone– $H_2O(2.5:1)$ | 80 | 29 (20 + 9) |
| 4 | BQ (1.0) | MeOH-H ₂ O (2.5:1) | 80 | 15 (4 + 11) |
| 5 | BQ (1.0) | MeCN-CH ₂ Cl ₂ -H ₂ O (2.5:0.5:1) | 80 | 53 (31 + 22) |
| 6 | BQ (1.0) | MeCN-H ₂ O (2.5:1) | 80 | 54 (30 + 24) |
| 7 | BQ (1.0) | MeCN-H ₂ O (1:1) | 80 | 52 (8 + 44) |
| 8 | BQ (1.0) | MeCN-H ₂ O (7:1) | 80 | 55 (36 + 19) |
| 9 | BQ (1.0) | MeCN-H ₂ O (4:1) | 80 | 58 (37 + 21) |
| 10 | none | MeCN-H ₂ O (4:1) | 80 | 21 (10 + 11) |
| 11 | DDQ (1.0) | MeCN-H ₂ O (4:1) | 80 | trace |
| 12 | 1,4-naphthoquinone (1.0) | MeCN-H ₂ O (4:1) | 80 | 11 (7 + 4) |
| 13 | tetrachloro-1,4-benzoquinone (1.0) | MeCN-H ₂ O (4:1) | 80 | 27 (16 + 11) |
| 14 | methyl-p-benzoquinone | MeCN-H ₂ O (4:1) | 80 | 49 (36 + 13) |
| 15 | CuSO ₄ (1.0) | MeCN-H ₂ O (4:1) | 80 | trace |
| 16 | BQ (0.5) | MeCN-H ₂ O (4:1) | 80 | 34 (21 + 13) |
| 17 | BQ (2.0) | MeCN-H ₂ O (4:1) | 80 | 54 (35 + 19) |
| 18 | BQ (1.0) | MeCN-H ₂ O (4:1) | 60 | 47 (31 + 16) |
| 19 | BQ (1.0) | MeCN-H ₂ O (4:1) | 100 | 53 (26 + 27) |
| 20 ^c | BQ (1.0) | MeCN-H ₂ O (4:1) | 80 | 41 (28 + 13) |
| 21 ^d | BQ (1.0) | MeCN-H ₂ O (4:1) | 80 | 0 |

^a Reaction conditions: styrene 1a (0.3 mmol), NaSO₂CF₃ (1.8 mmol), TBHP (70% aqueous), solvent (4 mL), sealed tube under 1 atm O₂.

^b Yield was determined by ¹⁹F NMR spectroscopic analysis using benzotrifluoride as internal standard.

^c Reactions were performed with styrene **1a** (0.3 mmol), NaSO₂CF₃ (3.0 equiv), TBHP (5.0 equiv).

^d Reaction performed under a nitrogen atmosphere

Synlett 2014, 25, 1307-1311

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NaSO₂CF₃, TBHP, and a range of styrenes. As shown in Table 2, styrenes with either electron-withdrawing or electron-donating groups on the phenyl ring could be transformed into the corresponding oxidative-trifluoromethylation products in moderate to good yields (Table 2, entries 1–12), except in the case of 2,4,6-trimethylstyrene (Table 2, entry 13), which was deactivated due to its high steric bulk. The position of the substituent had some influence on the reaction. On replacement of ortho-chlorostywith para-chloro analogue, rene the the trifluoromethylated products in the latter case were obtained in higher yields (Table 2, entries 4 vs. 5). The reaction was also tested with other alkenes such as indene (Table 2, entry 14), an internal olefin (Table 2, entry 15), and an aliphatic olefin (Table 2, entry 16), but they were not suitable substrates for this reaction.

To obtain the single trifluoromethylated product ketone or alcohol, after the metal-free radical trifluoromethylation, either an oxidative or a reductive reaction was conducted by applying two-step successive reactions. To our delight, both the trifluoromethylated ketone and alcohol could be independently obtained in moderate yields by these methods (Scheme 2).



Scheme 2 Synthesis of α -trifluoromethyl ketone or alcohol

| Table 2 S | Substrate Scope of Metal-Free | Trifluoromethylation of Styrenes ^a |
|-----------|-------------------------------|---|
|-----------|-------------------------------|---|

| R + CF ₃ SO ₂ Na 1 (6.0 equiv) (1.0 equiv) | $\begin{array}{c ccccc} t\text{-BuOOH (8.0 equiv)} & & & & O \\ \hline BQ(1.0 equiv) & & & & & OH \\ \hline MeCN-H_2O (4:1) & & & & & R \\ & & & & & CF_3 & + & & \\ & & & & & & R \\ \hline & & & & & & & & \\ & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & & \\ & & & & & & & & \\ & & & & & & & & \\ & & & & & & & & \\ & & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & & & \\ & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & & \\ & & & & & $ | | | |
|---|--|------------------------------|------------------------|------------------|
| Entry | Styrene | Products 2 + 3 | Yield (%) ^b | Ratio 2/3 |
| 1 | | 2a + 3a | 57 | 63:37 |
| 2 | MeO | 2b + 3b | 59 | 31:69 |
| 3 | Me | 2c + 3c | 53 | 61:39 |
| 4 | CI | 2d + 3d | 57 | 44:56 |
| 5 | CI | 2e + 3e | 67 | 55:45 |
| 6 | Br | 2f + 3f | 58 | 61:39 |
| 7 | F | 2g + 3g | 58 | 60:40 |
| 8 | F ₃ C | 2h + 3h | 45 | 65:35 |

| Table 2 | Substrate Scope of Metal-Free | e Trifluoromethylation of Styrenes ^a | (continued) |
|---------|-------------------------------|---|-------------|
|---------|-------------------------------|---|-------------|

| R → CF3SO2Na | <i>t-</i> BuOOH (8.0 equiv) BQ(1.0 equiv) | \rightarrow \downarrow | | | |
|-------------------------------------|--|---|------------------------|---------------------------|--|
| 1 (6.0 equiv) (1.0 equiv) | MeCN–H ₂ O (4:1) 80 °C, 16 h | $\mathbf{R}^{r} \sim \mathbf{R}^{r} \sim \mathbf{R}^{r} \sim \mathbf{S}^{r}$ 2 3 | | | |
| Entry | Styrene | Products 2 + 3 | Yield (%) ^b | Ratio 2 / 3 | |
| 9 | O ₂ N | 2i + 3i | 58 | 62:38 | |
| 10 | NC | 2j + 3j | 70 | 54:46 | |
| 11 | | $2\mathbf{k} + 3\mathbf{k}$ | 56 | 56:44 | |
| 12 | Ph | 2l + 3l | 53 | 66:34 | |
| 13 | Me Me Me | 2m + 3m | 18° | 31:69° | |
| 14 | | 2n + 3n | 0 | _ | |
| 15 | OMe | 20 + 30 | 0 | - | |
| 16 | | 2 p + 3 p | 0 | - | |

^a Reaction conditions: styrene **1a** (0.3 mmol), NaSO₂CF₃ (1.8 mmol), TBHP (70% aqueous), MeCN-H₂O (4:1; 4 mL), sealed tube under 1 atm O₂ atmosphere.

^b Isolated combined yield.

^c Yields and ratio of **2m** and **3m** were determined by ¹⁹F NMR spectroscopic analysis using benzotrifluoride as internal standard.

A plausible mechanism is proposed as shown in Scheme 3. From the control reaction (Table 1, entry 20), it is clear that O_2 is necessary to form intermediate I, however, the role of BQ in this reaction is not clear. A detailed study of the mechanism of this reaction is in progress.

In conclusion, we have demonstrated a mild, metal-free trifluoromethylation reaction of various styrenes with the stable solid NaSO₂CF₃.¹⁷ Based on these results, a convenient method for the synthesis of α -trifluoromethylated ketones and alcohols has been developed.

Acknowledgment

The authors are grateful for financial support by NSF of Jiangxi Provincial Education Department (GJJ12570, KJLD13081), we also thank the research fund of the China Scholarship Council.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.



Scheme 3 Proposed mechanism

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 (b) Lu, Q.; Liu, C.; Peng, P.; Liu, Z.; Fu, L.; Huang, J.; Lei, A. Asian J. Org. Chem. 2014, 3, 273.
- (17) **Typical Procedure:** To a septum-capped 25 mL sealed tube with a magnetic stirring bar were added CF₃SO₂Na (1.8 mmol) and BQ (0.3 mmol) in MeCN–H₂O (4:1; 4 mL) under O₂, followed by the addition of styrene **1a** (0.3 mmol) and *t*BuOOH (2.4 mmol). The sealed tube was screw capped and heated at 80 °C for 16–24 h (oil bath). Upon completion, the mixture was cooled to room temperature and diluted with H₂O (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residue was purified by silica gel chromatography (hexane) to provide pure products **2a** and **3a** in 57% combined yield. Purification by flash column chromatography on silica gel (hexanes–EtOAc, 20:1 v/v) gave the pure products.

Compound 2a: Yield: 36%; white solid. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.87$ (d, J = 7.4 Hz, 2 H), 7.57 (t, J = 7.4 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 3.73 (q, J = 10.0 Hz, 2 H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 189.7$ (q, J = 2.8 Hz), 135.7, 134.1, 128.9, 128.3, 124.0 (q, J = 276.7 Hz), 41.9 (q, J = 28.3 Hz). ¹⁹F NMR (376 MHz, CDCl₃): $\delta = -62.1$ (t, J = 10.0 Hz, 3F).

Compound 3a: Yield: 21%; colorless oil. ¹H NMR (400 MHz, CDCl₃): δ = 7.32–7.41 (m, 5 H), 7.08 (dd, *J* = 9.0, 3.6 Hz, 1 H), 2.56–2.70 (m, 1 H), 2.39–2.52 (m, 1 H), 2.25 (s, 1 H). ¹³C NMR (100 MHz, CDCl₃): δ = 142, 128.9, 128.4, 125.9 (q, *J* = 275.7 Hz), 125.7, 68.8 (d, *J* = 3.3 Hz), 42.9 (q, *J* = 26.9 Hz). ¹⁹F NMR (376 MHz, CDCl₃): δ = –63.7 (t, *J* = 10.5 Hz, 3F). HRMS (EI): *m/z* [M + H]⁺ calcd. for C₉H₁₀F₃O: 191.0684; found: 191.0688.

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