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A new, practical and efficient sulfone-mediated synthesis of trifluoromethyl ketones from alkyl and alkenyl bromides

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Abstract—We report herein a new and efficient method to prepare trifluoromethyl ketones from the corresponding bromides through sulfones in good yields.
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Trifluoromethyl ketones (TFMKs) are an important family of compounds, which have been shown as potent inhibitors of a variety of esterases and proteases.[1] TFMKs act as transition state analogues of the enzyme and the inhibition arises by formation of an adduct of tetrahedral geometry between the serine residue at the active site of the enzyme with the highly electrophilic carbonyl moiety.[2] The inhibition studies carried out with these fluorinated derivatives may be therapeutically significant in different areas, for instance arachidonoyl ethanolamide (anandamide) hydrolysis inhibitors in processes involving analgesia, mood, nausea, memory, etc.,[3] and renin or angiotensin-converting enzyme inhibitors in hypertension phenomena.[4] Therefore, the development of new methodologies for introduction of trifluoromethylated building blocks for the synthesis of fluorinated bioactive molecules is highly desirable.

Synthesis of TFMKs has been accomplished by a number of methods,[5] the most recent approaches involving catalytic aerobic oxidative decarboxylation of α-trifluoromethyl-α-hydroxy acids,[6] conversion of trifluoroethyl amines by NBS/DBU treatment,[7] Pd-catalyzed cross-coupling reaction of aryl trifluoroacetates with organoboron compounds,[8] Ru(II)-catalytic oxidation of trifluoromethyl carbinols,[9] nucleophilic trifluoromethylation of esters with $TMSCF_3$[10] or $Et_3GeNa/C_6H_5SCF_3$,[11] reaction of carboxylic acid chlorides with pyridine and trifluoroacetic anhydride,[12] or by metallation of alkyl iodides followed by reaction with a fluoroacylating agent.[13]

In the context of our project aimed at developing new inhibitors of the antennal esterases of insects,[14] we report herein a practical and efficient procedure to prepare long chain saturated and unsaturated trifluoromethyl ketones through the corresponding sulfones (Scheme 1). Only one example has been found in the literature using a similar approach,[15] but in this report an over reduction of the trifluorinated ketone to the mono- and difluoro analogue was noticed, which makes the approach impractical for preparative purposes.

In our case, a variety of sulfones (**2a**–**l**) were prepared as possible substrates for the trifluoroacylation reaction. The sulfones were easily obtained by reaction of the corresponding bromides[16] with sodium phenyl sulfinate in anhydrous DMF[17] in good to excellent yields (Table 1).

It should be noted that for several unsaturated substrates some isomerization of the double bond was detected, as has been noticed previously in the preparation of similar substrates even under very mild conditions.[18] Isomerization was minimized (up to 5% for sulfone **2d**, entry 4) by running the reaction at room temperature, although longer reaction times (48 h) were generally required except for allylic sulfones (0.5–3 h reaction). In the presence of a phase transfer catalyst (TEBA) in benzene–water–acetone[19] inversion of the stereochemistry of sulfone **2g** was noticed (*Z*/*E* 17/83) (not shown in Table 1), perhaps because the reaction

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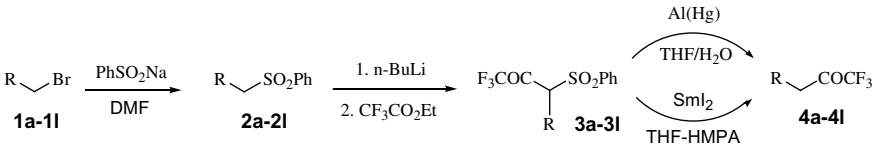

Scheme 1.

Table 1. New synthesis of trifluoromethyl ketones from sulfones

Entry	Bromide (%)	Sulfone (%)	Acylated sulfone (%)	TFMK	
				Method[a]	Compound (%)
1	**1a**, Octyl (—)[b]	**2a** (86)	**3a** (80)	A	**4a** (62)
2	**1b**, Dodecyl (—)[b]	**2b** (85)	**3b** (75)	A	**4b** (60)
3	**1c**, 10-Undecenyl (90)	**2c** (72)	**3c** (78)	A	**4c** (75)
4	**1d**, (*Z*)-11-Hexadecenyl (97)[c]	**2d** (78)[c]	**3d** (70)	A	**4d** (68)
5	**1e**, (*Z*)-3-Hexenyl (86)[d]	**2e** (60)[d]	**3e** (72)	A	**4e** (54)
				B	**4e** (58)
6	**1f**, (*E*)-5-Octenyl (77)[e]	**2f** (56)[e]	**3f** (72)	A	**4f** (60)
7	**1g**, (*Z*)-5-Octenyl (84)[f]	**2g** (69)[f]	**3g** (72)	A	**4g** (68)
				B	**4g** (73)
8	**1h**, (*Z*)-4-Nonenyl (—)[b,g]	**2h** (75)[g]	**3h** (70)	A	**4h** (70)
9	**1i**, (*E*,*Z*)-2,6-Nonadienyl (76)[h]	**2i** (90)[h]	—		—
10	**1j**, Cinnamyl (—)[b,i]	**2j** (84)[i]	—		—
11	**1k**, 2-Decynyl (98)	**2k** (96)	—		—
12	**1l**, 3-Phenylpropyl (—)[b]	**2l** (73)	**3l** (77)	A	**4l** (68)

[a] Method A: aluminium amalgam in THF–H_2O 9:1 at reflux. Method B: SmI_2/THF–HMPA at −78 °C.
[b] The absence of yields means that the compounds were either commercially available or had been previously synthesized in our laboratory.
[c] Bromide **1d**: *Z* > 99%. Sulfone **2d**: *Z*/*E* 95/5.
[d] Bromide **1e**: *Z* > 99%. Sulfone **2e**: *Z*/*E* 70/30.
[e] Bromide **1f**: *Z*/*E* 5/95. Sulfone **2f**: *Z*/*E* 20/80.
[f] Bromide **1g**: *Z*/*E* 95/5. Sulfone **2g**: *Z*/*E* 90/10.
[g] Bromide **1h**: *Z* > 99%. Sulfone **2h**: *Z*/*E* 90/10.
[h] Bromide **1i**: *Z*/*E* 90/10. Sulfone **2i**: *Z*/*E* 90/10.
[i] Bromide **1j**: *E* > 99%. Sulfone **2j**: *E* > 99%.

system required heating at 80–85 °C for 24 h for complete conversion.

Assays for the trifluoroacylation of sulfones were carried out using compound **2a** as model. The best conditions implied the use of 1.4 equiv of *n*-BuLi at −78 °C followed by immediate addition of ethyl trifluoroacetate (10 equiv).[20] Lower amounts (5 equiv) of the trifluoroacylating agent led to somewhat lower yields. The reaction mixture was allowed to react for 1 h more at room temperature to furnish **3a** in 80% yield. These conditions provided good yields for long chain saturated (**3a**,**b**,**l**, entries 1, 2, 12) and unsaturated sulfones (**3c**–**h**, entries 3–8), although allylic (**2i**,**j**, entries 9, 10) and propargylic sulfones (**2k**, entry 11) did not react and the starting material was recovered almost quantitatively (Table 1). In this context, other trials to obtain trifluoroacyl sulfones **3i**–**k** under different experimental conditions (higher temperatures, longer reaction times) and different solvents (THF, THF–HMPA 1:1) failed. In addition, replacement of ethyl trifluoroacetate by trifluoroacetic anhydride or (trifluoroacetyl)benzotriazole, a particularly efficient acylating agent for allylic sulfones,[21] resulted also futile in our hands.

Removal of the sulfone group is a key reaction in sulfone-mediated chemical synthesis. Although in general, amalgams with Group IA–IIIA metals in alcoholic solvents have been recommended,[22] in our case, however, sodium amalgam in methanol[23] afforded a mixture of products. By contrast, aluminium amalgam in THF–H_2O 9:1 at reflux[24] (method A) or SmI_2/THF–HMPA[25] at −78 °C (method B) were found reliable desulfonylation reagents to provide the required TFMKs in satisfactory yields. Remarkably, the processes occurred leaving the highly electrophilic trifluoroacyl group intact and in no case phenyl sulfinic acid elimination to eventually produce α,β-unsaturated products was detected. In addition, the stereomeric purity of the unsaturated TFMKs **4d**–**h** was identical to that of the corresponding acyl precursors **3d**–**h**.[26] In contrast to Kobayashi's work, our procedure does not produce any over reduction product perhaps because the portionwise addition of the aluminium amalgam prepared[26] allowed us a better control of the reaction process (4 h reaction time vs 30–45 min in Kobayashi's work). In addition and as cited, the desulfonylation process can alternatively be carried out by SmI_2 treatment with equally good results.[26]

In summary, we have developed an easy, efficient and scalable procedure for the synthesis of trifluoromethyl ketones. In contrast to other methods, the process does not require special fluorination reagents nor any expensive catalyst, and therefore it can advantageously be added to other reported methods for the preparation of this important class of chemicals.

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20. *Acylation of sulfone* **2c**: *Representative procedure*. To a stirred solution of sulfone **2c** (3.93 mmol) dissolved in 5 mL of anhydrous THF was added, under Ar at −78 °C, 3.9 mL of a 1.4 M solution of *n*-butyllithium in hexane (5.50 mmol). Then ethyl trifluoroacetate (39.30 mmol) was added and the mixture was allowed to react at rt for an additional hour. The solvent was evaporated off and the residue extracted with ether. The combined organic phases were washed with brine, dried, and the residue chromatographed on silica gel eluting with hexane–ether (95:5) to give the acylated sulfone **3c** (78% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (dm, J = 8.7 Hz, 2H), 7.74 (tt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 7.60 (tm, J = 7.2 Hz, 2H); 5.79 (ddt, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.6 Hz, 1H), 5.01–4.90 (m, 2H), 4.60 (dd, J_1 = 10.8 Hz, J_2 = 4.2 Hz, 1H), 1.97 (m, 4H), 1.21 (m, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 185.47 (q, J = 38.3 Hz, COCF$_3$), 139.03, 136.22, 134.93, 129.56, 129.37, 114.62 (q, J = 291.9 Hz, COCF$_3$), 114.18, 69.90, 33.69, 29.09, 28.93, 28.88, 28.86, 28.75, 28.54, 26.53 ppm. ^{19}F NMR (282 MHz): δ −79.06 (s) ppm. IR (film) υ 1758 cm^{-1}.
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26. *Desulfonylation of sulfone* **3c**. *Representative procedure* (*method A*). Freshly prepared aluminium amalgam was obtained by immersing Al foil (200 mg, 8.6 g matoms/mmol of sulfone, 99.8% Aldrich), cut into small pieces, into a 2% aq $HgCl_2$ solution for 2 min (Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345–1353). Then the amalgam was added in four portions (50 mg/h) into a solution of sulfone **3c** (0.86 mmol) in a mixture THF/H_2O (9:1) (18 mL). The reaction mixture was heated to reflux for 4 h, cooled, filtered and the solid was washed with THF. After evaporation of the solvent, the residue was taken up in ether, washed with brine and dried. The solvent was removed and the crude purified by column chromatography on silica gel to give the TFMK **4c**[6] (75% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.80 (ddt, J_1 = 17.1 Hz, J_2 = 10.2 Hz, J_3 = 6.6 Hz, 1H), 5.02–4.90 (m, 2H), 2.70 (t, J = 7.8 Hz, 2H), 2.03 (m, 2H), 1.65 (m, 2H), 1.28 (m, 12H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.58 (q, J = 34.7 Hz, COCF$_3$), 139.12, 115.56 (q, J = 290.4 Hz, COCF$_3$), 114.09, 36.32, 33.76, 29.33, 29.26, 29.13, 29.04, 28.87, 28.69, 22.33 ppm. ^{19}F NMR (282 MHz): δ −79.88 (s) ppm. IR (film) υ 1765 cm^{-1}. MS (EI), *m*/*z* (%): 250 (M$^+$, 0.96).
Desulfonylation of sulfone **3g**. *Representative procedure* (*method B*). Under Ar 0.16 g (0.46 mmol) of acylated sulfone **3g** was dissolved in 23 mL of a 0.1 M solution of SmI_2 in THF (2.3 mmol). The solution was cooled to −20 °C and then anhydrous HMPA (1.8 mL) was slowly added. The mixture was stirred for 1 h, left to warm to rt and the reaction poured into NH_4Cl satd solution. The solvent was removed and the residue extracted with ether. Conventional work up led to a residue, which was chromatographed on silica gel to afford pure **4g** (70 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.33 (m, 2H), 2.70 (t, J = 7.5 Hz, 2H), 2.02 (m, 4H), 1.68 (m, 2H), 1.39 (m, 2H), 0.95 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.50 (q, J = 34.6 Hz, COCF$_3$), 132.45, 128.00, 115.56 (q, J = 290.7 Hz, COCF$_3$), 36.23, 28.73, 26.57, 21.94, 20.51, 14.28. ^{19}F NMR (282 MHz, $CDCl_3$): δ −79.89 (s). IR (film) υ 1765 cm^{-1}. Exact mass: calculated for $C_{10}H_{15}F_3O$: 208.107500. Found: 208.106787.