Improved synthesis of trifluoromethyl sulfones used as intermediates for the preparation of di- or tri-substituted olefins

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Abstract

Primary and secondary trifluoromethyl sulfones (triflones) are efficiently obtained from easily available sodium trifluoromethanesulfinate (triflinate) and alkyl bromides in *N,N*-dimethylacetamide. This technique is more powerful than the potassium triflinate/acetonitrile system. Ethyl aconitate can be also produced in one step from ethyl bromoacetate and diisopropylethylamine, sodium triflinate being a catalyst.

Introduction

Sulfones are very popular tools in organic synthesis [1] because they increase to a large extent the acidity of hydrogens in α-positions since their conjugated bases are stabilised by a strong inductive effect [1c, 2]. These anions can be further halogenated, nitrated, alkylated or enter Michael, Claisen or Knoevenagel reactions. The sulfonyl moiety is then removed by sodium or aluminium amalgam [1c, 3], in most cases, or, in a few instances, by β-eliminations under strong basic conditions [4].

Replacement of alkyl or aryl sulfonyl moieties by the trifluoromethanesulfonyl ('triflyl') moiety constituted a major progress in this type of chemistry and attractive syntheses from trifluoromethyl sulfones ('triflones') [1c, 1f, 5, 6] and perfluoroalkyl sulfones [7] have been already been reported.

The advantage of the triflyl group lies in its strong electron-withdrawing effect, higher than those of mesyl, benzenesulfonyl and even nitro substituents [8]. Thus, hydrogens in positions α to CF_3SO_2 are very acidic, all the more so since the conjugated anions are also stabilised by conjugative effects [9]. Furthermore, the triflyl moiety can be removed by milder reducers than other sulfonyl groups (for instance with zinc/ethanol or Raney nickel [6]) or, more often, through β-elimination or S_N2 processes [6], since this substituent, although a poorer leaving group than halogens, is a far better leaving group than aryl- or alkyl-sulfonyl [10]. A thermal 1,2-elimination of triflinic acid (CF_3SO_2H) can also be achieved [6], whereas this process is not possible from other sulfones [11].

Triflones can be produced by oxidation of trifluoromethyl thioethers [12], Friedel–Crafts condensations with trifluoromethanesulfonyl chloride [13] and reaction of organometallics upon trifluoromethanesulfonic anhydride [13, 14]. Substitution of alkyl bromides by potassium trifluoromethanesulfinate (potassium 'triflinate') in acetonitrile seems to be the most general method [5, 6] but, because of the low nucleophilicity of the triflinate anion, only primary bromides and not secondary ones are converted into triflones through clean but very slow reactions.

Results and discussion

Recently, a cheap and efficient manufacture of sodium triflinate has been reported from bromotrifluoromethane [15]. Hence, it seemed interesting to examine the reactivity of this easily available reagent in media other than acetonitrile. Of the usual dipolar aprotic solvents known to enhance the reactivity of anions, some suffer from severe drawbacks: hexamethylphosphoric triamide (HMPT) is carcinogenic; the high-boiling sulfolane is very tedious to recover; *N,N*-dimethylformamide (DMF) can formylate anionised triflones [5]; and dimethylsulfoxide (DMSO) is not quite stable upon prolonged heating. *N,N*-Dimethylacetamide (DMAc) is a good candidate, better than acetonitrile since it solvates cations better ($DN_{DMAc} > DN_{CH_3CN}$) and anions lesser ($AN_{DMAc} < AN_{CH_3CN}$) [16] (DN = donor number, AN = acceptor number).

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Formation of triflones in DMAc

Sodium triflinate has been reacted with several primary and secondary carbonylated alkyl bromides in DMAc. A comparison with acetonitrile as solvent has been undertaken for one of the substrates:

$$CF_3SO_2^-Na^+ + Br-R \xrightarrow[\theta\,^\circ C]{\text{solvent}} \underset{\textbf{(1a–f)}}{} \qquad \underset{\textbf{(2a–f)}}{CF_3SO_2-R} + M^+Br^- \quad (1)$$

[R = CH_2CO_2Et (**1a**), $CH(CH_3)CO_2Et$ (**1b**), $(CH_2)_2$-CO_2Et (**1c**), CH_2COPh (**1d**), CH_2–CO–Bu^t (**1e**), $CH(CH_3)COPh$ (**1f**)]

The results obtained are summarised in Table 1.

From these results, it can be seen that replacement of acetonitrile by DMAc (entries 1–3) dramatically enhanced the reactivity of the triflinate anion since comparable results were obtained from **1a** in DMAc under milder conditions and in a shorter time than in acetonitrile.

The results from Table 1 also show that, under these conditions, activated substrates such as α-bromoketones, even secondary ones (**1f**, entry 8) which are not reactive in acetonitrile [6], formed triflones within a few hours in excellent yield [it should be noted that **1d** needed 48 h at 80 °C to produce **2d** in acetonitrile [6] in contrast to 7 h at 50 °C in DMAc (entry 6)]. Secondary α-bromoesters (e.g. **1b**), which are less reactive in nucleophilic substitution, also provided triflones in medium yield within 0.5 d only at temperatures as low as 65 °C. The advantage was also noticeable with simple primary bromides with no carbonyl group in the α-position (**1c**): they were completely converted in *c.* 2 d at 65 °C in DMAc instead of 7 d at 80 °C in acetonitrile [6].

In contrast, the formation of benzyl triflone from benzyl bromide and alkaline triflinates did not appear to be sensitive to solvent and cation effects: the same yield (91–95%) was obtained, at 80–90 °C for 6 h with 0.1 equiv. potassium iodide as catalyst, from potassium triflinate in acetonitrile [6] or sodium triflinate in DMAc. Such an observation indicates that benzyl triflone probably does not result from an S_N2 process but from an S_N1 substitution which is known to be less affected by the nature of the solvent and cation in aprotic media [17]. This presumption is reinforced by the fact that, contrary to other bromides, benzyl bromide reacted easily with sodium triflinate in a solid–liquid system using toluene as an apolar aprotic solvent and tris(3,6-dioxaheptyl)amine $N[(CH_2CH_2O)_2CH_3]_3$ (TDA-1) as the phase-transfer catalyst:

$$\underset{\textbf{(1g)}}{PhCH_2Br} + CF_3SO_2Na \xrightarrow[\substack{\text{TDA-1 (0.2 equiv.)}\\ \text{PhCH}_3,\ 80\ ^\circ C,\ 10\ h}]{\text{KI (0.1 equiv.)}} \underset{\textbf{(2g)}\ (72\%)}{PhCH_2SO_2CF_3} + NaBr \quad (2)$$

Formation of olefins substituted by carboxy groups from ethyl bromoacetate in the presence of sodium triflinate

During the synthesis of ethyl (trifluoromethanesulfonyl)acetate (**2a**) in DMAc, methyl triflone (**3**) and ethyl fumarate (**4**) were formed as by-products. Their amounts increased with temperature and reaction time (Table 2). This phenomenon did not occur in acetonitrile.

TABLE 1. Synthesis of triflones from bromides in DMAc

$$\underset{(x\text{ equiv.})}{CF_3SO_2Na} + \underset{\textbf{(1)}}{R-Br} \xrightarrow[\theta\,^\circ C]{\text{solvent}} \underset{\textbf{(2)}}{CF_3SO_2-R} + NaBr$$

Entry No.	R		x	Solvent	θ (°C)	Time (h)	Conv. 1[a] (%)	Yield of 2[b] (%)	
								NMR analysis	Isolated
1	EtO_2C-CH_2	(**1a**)	1	CH_3CN	80	40	74	76	68
2	EtO_2C-CH_2	(**1a**)	1	DMAc	60	2.25	66	61	
3	EtO_2C-CH_2	(**1a**)	3	DMAc	60	3.25	76	62	
4	$CH_3O_2C-CH(CH_3)$	(**1b**)	1.5	DMAc	65	13.5	62	58	52
5	$EtO_2C-(CH_2)_2$	(**1c**)	1.2 + 0.4[c]	DMAc	65	52	92[d]	65	57
6	Ph–CO–CH_2	(**1d**)	1	DMAc	50	7	89	87	82
7	Bu^t–CO–CH_2	(**1e**)	1	DMAc	60	1.5	54	100	78
8	Ph–CO–$CH(CH_3)$	(**1f**)	2	DMAc	70	9	76[d]	96	91

[a]From the NMR spectra of the crude product.
[b]Yields versus % converted **1**.
[c]1.2 equiv. at $t = 0$ and 0.4 equiv. at $t = 30$ h.
[d]From isolated products.

TABLE 2. Influence of the parameters in the reaction of ethyl bromoacetate and sodium triflinate

$$\underset{\textbf{(1a)}}{BrCH_2CO_2Et} \xrightarrow[DMAc,\ \theta\ °C]{CF_3SO_2Na\ (x\ equiv.)} \underset{\textbf{(2a)}}{CF_3SO_2CH_2CO_2Et} + \underset{\textbf{(3)}}{CF_3SO_2CH_3} + \underset{\textbf{(4)}\ (E\text{-isomer})}{EtO_2C-CH=CH-CO_2Et}$$

Entry No.	x (equiv.)	θ (°C)	Time (h)	Conv. 1a (%)[a]	Product yield (%)		
					2a[a,b]	3[a-c,e]	4[a,b,d]
1	1	60	2.25	66	61	14	0
2	3	60	1.25	60	50	6	0
3	3	60	3.25	76	62	18	0
4	1[f]	100	9	94	7	31	39

[a]From NMR analysis of the crude product.
[b]Yields versus % converted **1a**.
[c]According to the stoichiometry: 1 mol **1a** → 1 mol **3**.
[d]According to the stoichiometry: 2 mol **1a** → 1 mol **4**.
[e]A part of **3** probably lost during work-up.
[f]Conv. $CF_3SO_2Na = 100\%$.

$$\textbf{1a} \xrightarrow[DMAc]{CF_3SO_2Na\ (x\ equiv.)} \underset{\textbf{(2a)}}{CF_3SO_2CH_2CO_2Et} + \underset{\textbf{(3)}}{CF_3SO_2CH_3} + \underset{\textbf{(4)}\ (E\text{-isomer})}{EtO_2C-CH=CH-CO_2Et} \quad (3)$$

As DMAc dissolves and activates bromide anions well, it could be suspected that **3** and **4** resulted from **2a** and Br^-. Thus, pure **2a** was treated with tetrabutylammonium bromide in DMAc: **2a** was almost completely consumed, **3** and **4** appeared as major products and ethyl β-(trifluoromethanesulfonyl)propionate (**5**) as the minor one.

$$\textbf{2a} \xrightarrow[\substack{DMAc/100\ °C,\ 1.5\ h \\ (Conv. = 91\%)}]{Bu_4NBr} \underset{(40\%)}{\textbf{3}} + \underset{(23\%)}{\textbf{4}} + \underset{\textbf{(5)}\ (8\%)}{CF_3SO_2(CH_2)_2CO_2Et} \quad (4)$$

This reaction has been rationalised as indicated in Scheme 1.

$$\underset{\textbf{(2a)}}{Tf-CH_2-CO_2Et} + Br^- \longrightarrow Tf-CH_2-CO_2^- + EtBr \quad (5)$$

$$Tf-CH_2-CO_2^- \longrightarrow \underset{(\mathbf{3}^-)}{Tf-CH_2^-} + CO_2 \quad (6)$$

$$Tf-CH_2^- + Tf-CH_2-E \longrightarrow \underset{\textbf{(3)}}{Tf-CH_3} + \underset{(\mathbf{2a}^-)}{Tf-\bar{C}H-E} \quad (7)$$

$$Tf-\bar{C}H-E + Tf-CH_2-E \longrightarrow \underset{\textbf{(6)}}{Tf-CHE-CH_2-E} + Tf^- \quad (8)$$

$$Tf-\underset{\displaystyle CH_2E}{\underset{|}{CH}}-CO_2Et + Br^- \longrightarrow \underset{(\mathbf{5}^-)}{Tf-\bar{C}H-CH_2-E} + CO_2 + EtBr \quad (9)$$

$$Tf-CHE-CH_2-E \longrightarrow \underset{\textbf{(4)}}{E-CH=CH-E} + CF_3SO_2H \quad (10)$$

$$CF_3SO_2H \longrightarrow CF_3H + SO_2 \quad (11)$$

(Tf = CF_3SO_2; E = CO_2Et)

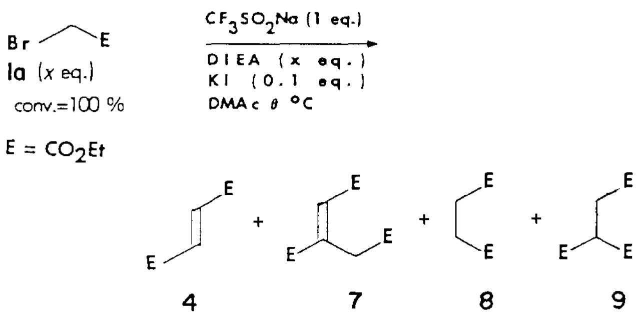
Scheme 1.

As bromide is known to remove alkoxycarbonyl groups from esters [18], the first step is assumed to be a decarbethoxylation which delivers the stabilised anion $\mathbf{3}^-$, the conjugated base of **3**. The pK_a value of **3** has been reported as *c.* 18 [9]. As Cameo simulation led us to estimate the pK_a value of **2a** to be *c.* 6–8, we propose that an acid/base reaction occurs between **2a** and $\mathbf{3}^-$ and delivers $\mathbf{2a}^-$, the conjugated base of **2a**, which is sufficiently nucleophilic to substitute the triflyl group of **2a** and leads to the secondary triflone **6**. Triflone **6** can eliminate trifluoromethanesulfinic acid ('triflinic acid') to deliver ethyl fumarate (**4**). The triflinic acid then decomposes thermally into fluoroform and sulfur dioxide. This assumption is in accordance with the observation that sodium triflinate was completely converted when ethyl fumarate became an important product (Table 2, entry 4). Ethyl β-(trifluoromethanesulfonyl)propionate (**5**) can also be formed, in a side process, through decarbethoxylation of **6**.

As the above-described formation of ethyl fumarate could be a good model for the preparation of olefins

bearing electron-withdrawing substituents from the corresponding alkyl bromides and triflinate, this reaction has been investigated more thoroughly.

In the proposed Scheme 1, 1 mol alkyl bromide and 1 mol triflinate are consumed to produce 1 mol of the non-valuable methyl triflone (3). In addition, another mol of triflinate is destroyed through reaction (11). In order to circumvent these drawbacks, ethyl bromoacetate was reacted with sodium triflinate in DMAc in the presence of a strong non-nucleophilic base. Diisopropylethylamine (DIEA, $pK_a \approx 11$ [19]) was chosen for this purpose:

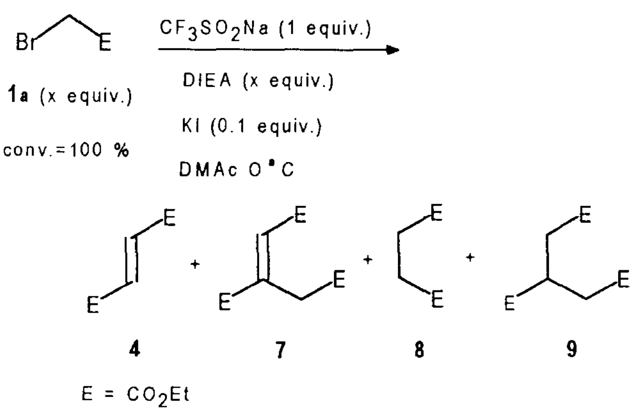


(12)

The results obtained are reported in Table 3.

In fact, when ethyl bromoacetate (**1a**) and sodium triflinate were reacted in DMAc at 100 °C in the presence of diisopropylethylamine, no methyl triflone (**3**) was obtained. Ethyl fumarate (**4**) was formed in only small amounts and ethyl aconitate (**7**) was the major product. This latter compound **7** became the only significant one at a lower temperature (80 °C) (Table 3, entry 3). Such a quasi-selective reaction, in which the triflinate anion acts as a catalyst (conv. $CF_3SO_2Na = 28\%$) could be a good model for the preparation of trisubstituted olefins from α-bromocarbonylated substrates.

TABLE 3. Synthesis of ethyl aconitate from ethyl bromoacetate diisopropylethylamine and sodium triflinate



Entry No.	θ (°C)	Time (h)	x (equiv.)	Conv. Tf^- (%)[a]	Product yield (%) 4^b	7^b	8^b	9^b
1	100	9	2	39	19	77	<1	<1
2	100	14.5	3	48	0	47	6	24
3	80	14.5	3	28	9	67	<1	<1

[a] $Tf^- = CF_3SO_2^-$.
[b] From the ^1H NMR spectra.

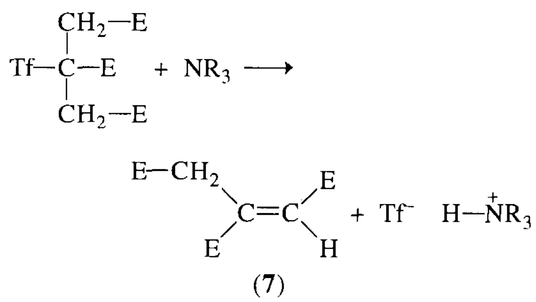
In the presence of DIEA, the mechanism proposed in Scheme 1 must be modified as indicated in Scheme 2.

$$\underset{(\mathbf{2a})}{Tf{-}CH_2{-}E} + NR_3 \longrightarrow \underset{(\mathbf{2a}^-)}{Tf{-}\bar{C}H{-}E} + H{-}\overset{+}{N}R_3 \quad (13)$$

$$Tf{-}\bar{C}H{-}E + \underset{(\mathbf{1a})}{Br{-}CH_2{-}E} \longrightarrow \underset{(\mathbf{6})}{Tf{-}CHE{-}CH_2{-}E} + Br^- \quad (8)$$

$$Tf{-}CHE{-}CH_2{-}E + NR_3 \longrightarrow \underset{(\mathbf{6}^-)}{Tf{-}\bar{C}E{-}CH_2{-}E} + H\overset{+}{N}R_3 \quad (14)$$

$$Tf{-}\bar{C}E{-}CH_2{-}E + Br{-}CH_2{-}E \longrightarrow \underset{(\mathbf{10})}{Tf{-}CE(CH_2{-}E)_2} + Br^- \quad (15)$$



(16)

($Tf = CF_3SO_2$; $E = CO_2Et$)

Scheme 2.

In the first step, an acid–base reaction between **2a** and DIEA matches the decarbethoxylation of **2a** so that $\mathbf{2a}^-$, the conjugated base of **2a**, is obtained without the occurrence of **3**. As $\mathbf{2a}^-$ is formed as soon as **2a** is produced, $\mathbf{2a}^-$ can co-exist with ethyl bromoacetate (**1a**) which is more sensitive to nucleophilic displacement than **2a** [10]. Thus, **6** is readily formed and deprotonated by DIEA to $\mathbf{6}^-$, the conjugated base of **6**. Then, $\mathbf{6}^-$ can substitute ethyl bromoacetate to deliver the tertiary triflone **10** which, in the presence of DIEA, leads to ethyl aconitate and the triflinate anion (which is thus recovered).

In order to reinforce the proposed hypotheses and to detect intermediates, the reaction has been performed under milder conditions:

$$\underset{\substack{\textbf{(1a)}\ (1\ \text{equiv.})\\(\text{Conv.}=100\%)}}{BrCH_2CO_2Et} + \underset{\substack{(1\ \text{equiv.})\\(\text{Conv.}=70\%)}}{CF_3SO_2Na} \xrightarrow[\text{DMAc/60 °C, 4h}]{\text{DIEA (2 equiv.)}} \underset{(48\%)}{\textbf{7}} + \underset{(14\%)}{\textbf{6}} + \underset{(7\%)}{\textbf{10}} \quad (17)$$

The occurrence of **6** and **7** has thus been confirmed.

The two first entries of Table 3 show that, under high temperature and long reaction time, ethyl succinate (**8**) and ethyl tricarballylate (**9**) arose as by-products alongside **4** and **7**. Their amounts also increased when potassium iodide was omitted as the catalyst:

$$\underset{(1\ \text{equiv.})}{CF_3SO_2Na} + \underset{\substack{(2\ \text{equiv.})\\(\text{Conv.}=100\%)}}{BrCH_2CO_2Et} \quad (18)$$

$$\xrightarrow[\substack{\text{DMAc}\\100\ °C,\ 9\ h}]{\text{DIEA (2 equiv.)}} \textbf{4} + \textbf{7} + \textbf{8} + \textbf{9}$$

(Conv. = 39%)	KI: 0.1 equiv.	10%	60%	<1%	<1%
(Conv. = 63%)	KI: 0 equiv.	8%	40%	30%	19%
			(isolated yields)		

Thus, the system CF_3SO_2Na/DIEA/KI in DMAc at 80 °C seems to provide the best conditions for obtaining ethyl aconitate directly from ethyl bromoacetate.

Experimental

All NMR analyses were undertaken with deuterochloroform as solvent. ^1H NMR spectra were recorded at 60 MHz on a Varian EM 360 spectrometer; chemical shifts (δ) are given in ppm with TMS as internal reference. ^{19}F NMR spectra were recorded either at 56.4 MHz on a Varian EM 360 spectrometer or at 75.2 MHz on a Bruker WP 80 one or at 188.2 MHz on a Bruker AC 200 apparatus; chemical shifts are given in ppm with $CFCl_3$ as reference (δ positive upfield). ^{13}C NMR spectra were recorded at 15.1 MHz with TMS as internal reference. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet). Coupling constants (J) are given in Hz. Quantitative NMR analyses of the organic phases were obtained with benzotrifluoride as internal standard. Unreacted sodium triflinate was estimated, after work-up, by ^{19}F NMR ($\delta = -87.8$ ppm) spectroscopic analysis of the aqueous phase with sodium trifluoroacetate as internal standard.

Reactions were monitored by gas-phase chromatography on a Varian 3300 apparatus fitted with a thermal conductivity detector and a 15-m length semicapillary column (internal diameter, 0.25 mm); the stationary phase was either DB1 or DBwax. Helium was the carrier gas.

In some cases, IR spectra, coupled with GPC, were recorded on a Bruker IFS 85 apparatus. IR frequencies are given in cm^{-1}. Mass spectrometry has been performed on a VG 305 spectrometer.

Flash chromatographic separations were performed on Merck 60H silica. The products were eluted with petroleum ether (abbr.: PE), pure or mixed with diethyl ether (abbr.: E) or methylene chloride.

Pure commercially available acetonitrile (SDS-Chromasol) was stored over 3 Å molecular sieves. *N,N*-Dimethylacetamide (DMAc) (Aldrich-GC) was distilled at atmospheric pressure prior to use and dried over 4 Å molecular sieves for 24 h. Sodium trifluoromethanesulfinate was generously provided by Rhône-Poulenc Co. and other commercially available substrates (Aldrich or Janssen) were used as received.

Reaction of sodium trifluoromethanesulfinate with ethyl bromoacetate

In a 50 ml flask, fitted with a reflux condenser, a thermometer and a magnetic stirrer, were placed consecutively, under nitrogen, the required quantities of sodium triflinate, solvent and ethyl bromoacetate. The stirred reaction mixture was then heated under nitrogen at the desired temperature and maintained at this temperature for the requisite time. After reaction, 30 ml of water were added. The resulting mixture was extracted with 3×20 ml of diethyl ether. The etheral phase was then washed twice with 15 ml of water, dried over magnesium sulfate, filtered and concentrated at room temperature under reduced pressure. The crude organic residue was either analysed by ^1H and ^{19}F NMR spectroscopy with benzotrifluoride as the internal standard or purified by flash chromatography. The gathered aqueous phases were analysed by ^{19}F NMR spectroscopy using sodium trifluoroacetate as the internal standard. Details for each experiment are given in Table 4.

From 5.93 g of the crude product resulting for the experiment reported in Table 4 (entry 1) were obtained, by flash chromatography, 0.68 g $BrCH_2CO_2Et$ (**1a**) (PE/E = 94:6) and 3.00 g $CF_3SO_2CH_2CO_2Et$ (**2a**) (PE/E = 90:10). Spectroscopic data for **2a**: ^1H NMR δ: 1.30 (t, 3H, CH_3, $^3J = 8$ Hz); 4.30 (q, 2H, OCH_2, $^3J = 8$ Hz); 4.35 (s, 2H, CH_2CO) (lit. value [6]: 4.35) ppm. ^{19}F NMR (56.4 MHz) δ: −77.7 (s) ppm. IR (cm^{-1}): 2991; 1769; 1400; 1277; 1223; 1130; 1030; 717; 621.

From 1.04 g of the crude product resulting from the experiment reported in Table 4 (entry 5) were obtained, by flash chromatography, 0.050 g $BrCH_2CO_2Et$ (**1a**) (PE/E = 93:7) and 0.210 g ethyl fumarate (**4**) (PE/

TABLE 4. Experimental data for the reaction of CF_3SO_2Na and ethyl bromoacetate (**1a**)

Entry No.	CF_3SO_2Na [g (mmol)]	**1a** [g (mmol)]	Solvent (ml)	θ (°C)	Time (h)	Crude product (g)	NMR analysis [g (%)][a]		
1	4.22 (27.1)	4.52 (27.1)	MeCN (30)	80	40	5.93	**1a**	1.20	(26)
							2a	3.33	(76)
2	5.54 (35.5)	1.94 (11.6)	DMAc (15)	60	1.25	2.00	**1a**	0.77	(40)
							2a	0.77	(50)
							3	0.06	(6)
3	1.84 (11.8)	1.99 (11.9)	DMAc (15)	60	2.25	2.07	**1a**	0.68	(34)
							2a	1.03	(61)
							3	0.16	(14)
4	5.50 (35.2)	1.94 (11.6)	DMAc (15)	60	3.25	2.10	**1a**	0.46	(24)
							2a	1.20	(62)
							3	0.24	(18)
5	2.12 (13.6)	2.26 (13.5)	DMAc (20)	100	9	2.01	**1a**	0.14	(6)
							2a	0.19	(7)
							3	0.58	(31)
							4	0.43	(39)

[a]Versus introduced **1a** for remaining **1a**; versus converted **1a** for other compounds.

E=93:7). Spectroscopic data for **4**: ^{1}H NMR δ: in accordance with the literature [20]. IR (cm^{-1}): 2988; 2947; 1744; 1647; 1472; 1394; 1321; 1298; 1259; 1155; 1098; 1043; 902; 862; 662.

Because of its rather high volatility, methyl trifluoromethyl sulfone (**3**) (Eb_{760}=128 °C [21]) could not be isolated in this way. However, its occurrence has been demonstrated in the above crude product via the following spectroscopic characteristics. ^{1}H NMR δ: 3.11 (s) (lit. value [5m, 21]: 3.11) ppm. ^{19}F NMR (56.4 MHz) δ: −81 (s) (lit. value [21]: 3.6 (versus CF_3CO_2H)) ppm. IR (cm^{-1}): 1389; 1329; 1232; 1202; 1136; 957; 771; 735.

Synthesis of triflones 2b–f

The procedure was the same as above, except that the bromo compounds **1b–f** were used as substrates instead of ethyl bromoacetate. *N,N*-Dimethylacetamide only was used as solvent. The experimental data are given in Table 5.

Methyl 2-(trifluoromethanesulfonyl)propionate (2b)

From the total crude product resulting from **1b** (Table 5, entry 1), flash chromatography delivered 1.76 g $BrCH(CH_3)CO_2CH_3$ (**1b**) (PE/E=93:7) and 2.00 g $CF_3SO_2CH(CH_3)CO_2CH_3$ (**2b**) (PE/E=80:20). NMR characteristics for **2b**: ^{1}H NMR δ: 1.77 (d, 3H, $CH-CH_3$, ^3J=7 Hz); 3.87 (s, 3H, CO_2CH_3); 4.30 (q, 1H, $CH-CH_3$, ^3J=7 Hz) ppm. ^{19}F NMR (188.2 MHz) δ: −75.12 (s) ppm.

Ethyl 3-(trifluoromethanesulfonyl)propionate (2c)

From 4.00 g of the crude product resulting from **1c** (Table 5, entry 2), flash chromatography delivered 0.33 g $BrCH_2CH_2CO_2Et$ (**1c**) (PE/E=94:6) and 2.80 g $CF_3SO_2CH_2CH_2CO_2Et$ (**2c**) (PE/E=90:10).

As the conversion rate of **1c** could not be determined from the ^{1}H NMR spectrum of the crude product, it has been estimated from the amount of **1c** recovered by chromatography: conv. **1c**=92%; yield **2c**=65% (crude), 57% (isolated) both versus converted **1c**. NMR characteristics for **2c**: ^{1}H NMR δ: 1.27 (t, 3H, $CO_2CH_2CH_3$, ^3J=7 Hz); 2.87 (t, 2H, CH_2CO_2Et, ^2J=8 Hz); 3.57 (t, 2H, $CF_3SO_2CH_2$, ^3J=8 Hz); 4.17 (q, 2H, $CO_2CH_2CH_3$, ^3J=7 Hz) ppm. ^{19}F NMR (56.4 MHz) δ: −79.0 (s) ppm.

α-(Trifluoromethanesulfonyl)acetophenone (2d)

From the total crude product resulting from **1d** (Table 5, entry 3), flash chromatography offered 0.30 g $C_6H_5-CO-CH_2Br$ (**1d**) (PE/CH_2Cl_2=80:20) and 3.72 g $C_6H_5-CO-CH_2SO_2CF_3$ (**2d**) (PE/CH_2Cl_2=65:35). NMR characteristics for **2d**: ^{1}H NMR δ: 4.9 (s, 2H, CH_2) (lit. value [6]: 5.0); 7.3–7.9 (m, 5H, C_6H_5) ppm.

1-Trifluoromethanesulfonyl-3,3-dimethyl-2-butanone (2e)

From the total crude product resulting from **1e** (Table 5, entry 4), flash chromatography delivered 0.35 g $Bu^t-CO-CH_2-Br$ (**1e**) (PE/CH_2Cl_2=80:20) and 0.62 g $Bu^t-CO-CH_2SO_2CF_3$ (**2e**) (PE/CH_2Cl_2=70:30). NMR characteristics for **2e**: ^{1}H NMR δ: 1.23 (s, 9H,

TABLE 5. Experimental data for the synthesis of triflones **2b–f**

Entry No.	CF_3SO_2Na [g (mmol)]		RBr (**1**) [g (mmol)]			DMAc (ml)	θ (°C)	Time (h)	Crude product (g)	NMR analysis [g (%)][a]		
1	6.72	(43.1)	**1b**	4.69	(28.1)	70	65	13.5	5.41	CF_3SO_2Na	2.91	(43)
										1b	1.76	(38)
										2b	2.26	(58)
2	4.23	(27.2)	**1c**	4.11	(22.7)	38	65	52	4.45	CF_3SO_2Na	0	
	+1.50	(9.6)[b]								**1c**[c]		
										2c	3.19	(60)[d]
3	3.80	(24.3)	**1d**	4.02	(20.2)	35	50	7	5.36	CF_3SO_2Na	0	
										1d	0.44	(11)
										2d	3.94	(87)
4	1.09	(7.0)	**1e**	1.13	(6.3)	10	60	1.5	1.58	CF_3SO_2Na	0	
										1e	0.53	(47)
										2e	0.79	(100)
5	6.47	(41.5)	**1f**	4.39	(20.6)	60	70	9	4.85	CF_3SO_2Na	0	
										1f[c]		
										2f	4.0	(73)[d]

[a]Versus introduced reagents for CF_3SO_2Na and **1b–f**; versus converted **1b–f** for other compounds.
[b]1.50 g CF_3SO_2Na added after 30 h.
[c]^1H NMR spectra of **1** and **2** too close to estimate **1** in the crude product.
[d]Versus introduced **1**.

$C(CH_3)_3$); 4.5 (s, 2H, $COCH_2$) ppm. ^{19}F NMR (75.2 MHz) δ: −78.2 (s) ppm.

α-(Trifluoromethanesulfonyl)propiophenone (2f)

From the total crude product resulting from **1f** (Table 5, entry 5), flash chromatography delivered 1.05 g $BrCH(CH_3)COC_6H_5$ (**1f**) (PE/CH_2Cl_2 = 80:20) and 3.8 g $CF_3SO_2CH(CH_3)COC_6H_5$ (**2f**) (PE/CH_2Cl_2 = 60:40).

As the conversion of **1f** could not be estimated from the ^1H NMR spectrum of the crude product, it has been calculated from the quantity of **1f** recovered by chromatography: conv. **1f** = 76%; yield **2f** = 96% (crude), 91% (isolated) both versus converted **1f**. NMR characteristics for **2f**: ^1H NMR δ: 1.73 (d, 3H, CH_3, ^3J = 7 Hz); 5.19 (q, 1H, $CH-CH_3$, ^3J = 7 Hz); 7.40–8.15 (m, 5H, C_6H_5) ppm. ^{19}F NMR (56.4 MHz) δ: −75.7 (s) ppm.

Synthesis of benzyltriflone (2g)

In a homogeneous phase (DMAc)

In a 100 ml flask, fitted with a reflux condenser, a thermometer and a mechanical stirrer, were placed, consecutively, under nitrogen, 7.49 g (48 mmol) of sodium triflinate, 0.63 g (3.8 mmol) of potassium iodide, 40 ml of DMAc and, finally, 6.84 g (40 mmol) of benzyl bromide (**1g**). The stirred reaction mixture was heated, under nitrogen, at 90 °C in an oil bath and maintained at this temperature for 6 h. After cooling, GPC analysis indicated a 91% yield of **2g**. The reaction mixture was then filtered and concentrated under reduced pressure. The solid obtained was recrystallized in a mixture of water and methanol (1:3 v/v), washed with an aqueous solution of sodium thiosulfate and dried under vacuum. Pure **2g** (6.43 g) was thus obtained (72% yield).

Under solid–liquid phase-transfer conditions

In the same apparatus as above were introduced consecutively 4.68 g (30 mmol) of sodium triflinate, 0.46 g (2.8 mmol) of potassium iodide, 25 ml of toluene, 1.58 g (4.9 mmol) of tris-(3,6-dioxaheptyl)amine and 4.28 g (25 mmol) of **1g**. The mixture was vigorously stirred and, under nitrogen, maintained at 80 °C for 10 h. After reaction and filtration, GPC and ^{19}F NMR analyses indicated a 72% yield of **2g**. The same work-up as above afforded 3.00 g of pure **2g** (54% yield).

Benzyl triflone (**2g**): M.p. 104 °C (H_2O–MeOH). ^1H NMR δ: 4.41 (s, 2H, CH_2) (lit. value [6]: 4.49); 7.4 (m, 5H, C_6H_5) ppm. ^{13}C NMR δ: 56.2 (s, CH_2); 119.7 (q, CF_3, $^2J(C-F)$ = 328 Hz); 123.2 (s, C−CH_2); 129.2 (s, C *meta*); 130.0 (s, C *para*); 131.2 (s, C *ortho*) ppm. IR (cm^{-1}): 3000; 2960; 1500; 1460; 1415; 1400; 1360; 1350; 1325; 1290; 1225; 1200; 1190; 1120; 1075; 1030; 780; 720; 700; 640; 560; 525; 505. MS *m/z*: 224 ($M^{+\cdot}$).

Reaction of 2a with tetrabutylammonium bromide

In the same apparatus as described above for its preparation, 0.51 g (2.3 mmol) of **2a** were mixed with a solution of 0.78 g (2.4 mmol) of tetrabutylammonium bromide in 5 ml of DMAc. This medium was kept at 100 °C, under nitrogen, for 1.5 h. After the usual work-

up, 0.35 g of a crude mixture was obtained and analysed by ^1H and ^{19}F NMR spectroscopy, with benzotrifluoride as internal standard. By comparison with the spectra of isolated compounds, **2a** (45 mg), **3** (125 mg), **5** (19 mg) and ethyl fumarate (**4**) (42 mg) were found.

Reaction of sodium triflinate with ethyl bromoacetate in the presence of diisopropylethylamine (DIEA)

The procedure was the same as that already described for reactions between **1a** and CF_3SO_2Na, except that DIEA was added just after the other components, prior to heating, and the reaction medium was hydrolysed with 30 ml of 10% aqueous hydrochloric acid instead of pure water. The experimental data are given in Table 6.

Entry 1: From the whole crude product, compounds **6**, **7** and **10** were separated by flash chromatography, in the following order of elution: 0 g $BrCH_2CO_2Et$ (**1a**); 0.30 g (14%) $CF_3SO_2-CH(CO_2Et)-CH_2CO_2Et$ (**6**) (PE/E = 96:4); 0.13 g (7%) $CF_3SO_2-CH(CO_2Et)-(CH_2CO_2Et)_2$ (**10**) (PE/E = 96:4); and 0.61 g (48%) (*E*)-$EtO_2CCH_2-C(CO_2Et)=CHCO_2Et$ (**7**) (PE/E = 96:4).

Diethyl 2-(trifluoromethanesulfonyl)succinate (**6**); ^1H NMR δ: 1.35 (t, 6H, OCH_2CH_3, $^3J = 7$ Hz); 3.25 [dd, 2H, $CH_a-H_b-CH_c$, $^3J(H_a-H_c) = 6$ Hz, $^3J(H_b-H_c) = 9$ Hz]; 4.20 (q, 4H, OCH_2CH_3, $^3J = 7$ Hz); 4.57 [dd, 1H, $CH_c-CH_aH_b$, $^3J(H_c-H_a) = 6$ Hz, $^3J(H_c-H_b) = 9$ Hz] ppm. ^{19}F NMR (56.4 MHz) δ: −76.0 (s) ppm.

Ethyl aconitate (**7**): ^1H NMR δ: in accordance with the literature [20]. IR (cm^{-1}): 2988; 2949; 1755; 1738; 1653; 1472; 1418; 1371; 1321; 1273; 1171; 1097; 1040; 968.

Diethyl 3-(ethoxycarbonyl)-3-(trifluoromethanesulfonyl)pentane-1,5-dioate (**10**): ^1H NMR δ: 1.35 (t, 9H, OCH_2CH_3, $^3J = 7$ Hz); 3.70 (s, 4H, CH_2CO); 4.00 (q, 6H, OCH_2CH_3, $^2J = 7$ Hz) ppm. ^{19}F NMR (56.4 MHz) δ: −71.3 (s) ppm.

Entry 2: The crude product was analysed by ^1H and ^{19}F NMR spectroscopy as well as by IR spectroscopy coupled with GPC. The results were as follows: 0 g ethyl bromoacetate (**1a**); 0.09 g (8%) ethyl fumarate (**4**); 0.48 g (40%) ethyl aconitate (**7**); 0.36 g (30%) ethyl succinate (**8**); and 0.23 g (19%) ethyl tricarballylate (**9**).

Entry 3: NMR analysis and flash chromatography of the whole crude product indicated complete conversion of ethyl bromoacetate and afforded **4** and **7** in the following yields: ethyl fumarate (**4**): crude 0.21 g (19%), isolated 0.11 g (10%) (PE/E = 90:10); and ethyl aconinate (**7**): crude 0.84 g (77%), isolated 0.65 g (60%) (PE/E = 80:20).

Entry 4: The same procedure indicated complete conversion of **1a** and provided the following results: ethyl aconitate (**7**): crude 0.73 g (47%), isolated 0.73 g (47%) (PE/E = 80:20); ethyl succinate (**8**): crude 0.15 g (10%), isolated 0.10 g (6%) (PE/E = 80:20); and ethyl tricarballylate (**9**): crude 0.37 g (24%), isolated 0.37 g (24%) (PE/E = 80:20). The ^1H NMR spectra of ethyl succinate (**8**) and tricarballylate **9** were in accordance with the literature [20].

Entry 5: NMR analysis of the crude product indicated again complete conversion of **1a** and delivered the following figures: 0.15 g (9%) ethyl fumarate (**4**) and 1.11 g (67%) ethyl aconinate (**7**).

Synthesis of triflone 6 and triflone 10 from ethyl (trifluoromethanesulfonyl)acetate (2a)

In order to confirm the structures of triflones **6** and **10**, isolated from **1a**, sodium triflinate and DIEA (Table 6, entry 1), these compounds have been prepared via another route from **2a** and ethyl bromoacetate (**1a**). Thus, 0.161 g (6.7 mmol) of sodium hydride, washed with 3×5 ml of petroleum ether, were added to 6 ml of *N*,*N*-dimethylformamide (DMF). Compound **2a** (1.06 g, 4.8 mmol) was dropped, under stirring, onto this suspension at −10 °C within 10 min. The reaction mixture was stirred at room temperature for 14 h then 0.60 g (3.6 mmol) of ethyl bromoacetate, dissolved in 5 ml of DMF, was added. Stirring was continued at room temperatures for 24 h. After addition of 30 ml of water, extraction with 3×30 ml of ether and decantation, the organic phase was washed twice with 20 ml of water, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting material (1.04 g) was separated by flash chromatography to yield: 0.62

TABLE 6. Experimental data for the reaction of CF_3SO_2Na with ethyl bromoacetate (**1a**) in the presence of DIEA

Entry No.	CF_3SO_2Na [g (mmol)]		**1a** [g (mmol)]		KI [g (mmol)]		DIEA [g (mmol)]		DMAc (ml)	θ (°C)	Time (h)	Crude product (g)	Unconverted CF_3SO_2Na [g (%)] (^{19}F NMR)	
1	2.38	(15.3)	2.60	(15.6)			2.20	(17.1)	25	60	4	1.07	0.71	(30)
2	1.08	(6.9)	2.33	(14.0)			2.00	(15.5)	10	100	9	1.30	0.40	(35)
3	0.98	(6.3)	2.11	(12.6)	0.20	(1.2)	1.93	(15.0)	15	100	9	1.41	0.60	(61)
4	0.92	(5.9)	3.00	(18.0)	0.20	(1.2)	2.44	(18.9)	15	100	14.5	1.77	0.48	(52)
5	1.00	(6.4)	3.24	(19.4)	0.25	(1.5)	2.74	(21.2)	15	80	14.5	1.66	0.72	(72)

g triflone **6** (PE/E = 95:5); 0.13 g triflone **10** (PE/E = 95:5); 0.13 g ethyl bromoacetate (**1a**) (PE/E = 94:6); and 0.07 g triflone **2a** (PE/E = 94:6).

The ^{19}F and ^{1}H NMR spectra of triflones **6** and **10** prepared in this way were identical with those of the triflones obtained from ethyl bromoacetate, sodium triflinate and DIEA (Table 6, entry 1).

The new compounds described in this paper are as follows: methyl 2-(trifluoromethanesulfonyl)propionate (**2b**), ethyl 3-(trifluoromethanesulfonyl)propionate (**2c**), 1-(trifluoromethanesulfonyl)-3,3-dimethyl-2-butanone (**2e**), α-(trifluoromethanesulfonyl)propiophenone (**2f**), diethyl 2-(trifluoromethanesulfonyl)succinate (**6**) and diethyl 3-(ethoxycarbonyl)-3(trifluoromethanesulfonyl)-pentane-1,5-dioate (**10**).

Conclusions

Though primary triflones can be obtained cleanly in acetonitrile from potassium triflinate and alkyl bromides, this reaction is very slow and not suitable for the preparation of secondary triflones. The use of the readily available sodium triflinate in a more basic aprotic solvent such as *N*,*N*-dimethylacetamide allows the preparation of primary as well as secondary triflones under mild conditions. Such an improvement widens the synthetic usefulness of triflones.

The unique properties of the trifluoromethanesulfonyl group also allows the one-pot synthesis of ethyl aconitate from ethyl bromoacetate with sodium triflinate as a catalyst, provided that a stoichiometric amount of a non-nucleophilic tertiary amine like diisopropylethylamine is used.

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