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Regioselective synthesis of 5-ethoxycarbonyl-, 5-acetyl- and 5-trifluoroacetyl-6-trifluoromethylsalicylates by one-pot cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-alkoxy-2-alken-1-ones

Simone Ladzik [a], Mathias Lubbe [a], Nazken K. Kelzhanova [a,b], Zharylkasyn A. Abilov [b], Holger Feist [a], Peter Langer [a,c,*]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[b] Al-Farabi Kazakh National University, Al-Farabi ave. 71, 050040 Almaty, Kazakhstan
[c] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

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ABSTRACT

5-Ethoxycarbonyl-, 5-trifluoroacetyl-, and 5-acetyl-6-trifluoromethylsalicylates were prepared by one-pot cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-alkoxy-2-alken-1-ones. The reactions proceeded with very good regioselectivity by conjugate addition of the terminal carbon atom of the diene to the enone and subsequent cyclization. The cyclization proceeded in most cases via the trifluoroacetyl group.

1. Introduction

Organofluorine compounds play an important role in medicinal and agricultural chemistry. Due to the stereoelectronic properties of the carbon–fluorine bond, organofluorine compounds show an excellent solubility, bioavailability and metabolic stability [1]. A number of fluorinated molecules are clinically used. For example, 5-fluorouracil exhibits antineoplastic activity [2] and ciprofloxacin and flurithromycin are important antibiotics. Fluoxetine (prozac) shows antidepressant activity, while faslodex and efavirenz exhibit antitumor and antiviral activity, respectively [3,4]. Amphiphilic and liquid crystalline properties have been reported for a number of perfluoroalkyl-substituted compounds [5]. Last but not the least, fluoroalkylated compounds are also used as ligands [6] in catalytic reactions, as organocatalysts [7], and as substrates in palladium catalyzed reactions [8].

Two principal strategies for the synthesis of fluorinated molecules are possible. Firstly, direct fluorination reactions and, secondly, the application of a building block strategy. Fluorination reactions of arenes and heteroarenes are often limited by their low chemo- and regioselectivity and by multiple fluorination. These drawbacks can be circumvented when fluorine-containing substrates are employed in cyclization reactions (building block strategy). Aryl fluorides have been prepared by [4 + 2] cycloaddition reactions of fluorinated dienes [9]. The synthesis of fluorophenols by annulation reactions of 2,2-difluoro-1,5-diketones has been developed by Portella and coworkers [10]. In recent years, we have studied [11,12] the synthesis of fluorinated arenes based on cyclocondensation reactions of 1,3-bis(trimethylsilyloxy)-1,3-butadienes [13]. Herein, we report what are, to the best of our knowledge, the first regioselective syntheses of 5-ethoxycarbonyl-, 5-acetyl- and 5-trifluoroacetyl-6-trifluoromethylsalicylates by one-pot cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-alkoxy-2-alken-1-ones. Salicylates containing a trifluoromethyl function located at the aromatic ring have been reported in the literature. [14] Some of these derivatives show interesting biological activities like inhibition of protein syntheses [15], inhibition of nuclear factor κB (NF-κB) activity [16] and antithrombotic activity [17]. In case of the known trifluoromethylsalicylates, besides the three characteristic groups (carboxylate, hydroxy, and trifluoromethyl), at maximum one further functional group is present. The highly substituted trifluoromethylated derivatives reported the present manuscript have not been prepared so far. Due to the high degree of functionalization and substitution of these molecules, it can be anticipated that they are not readily available by other methods.

* Corresponding author at: Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany. Fax: +49 381 4986412.
E-mail address: peter.langer@uni-rostock.de (P. Langer).

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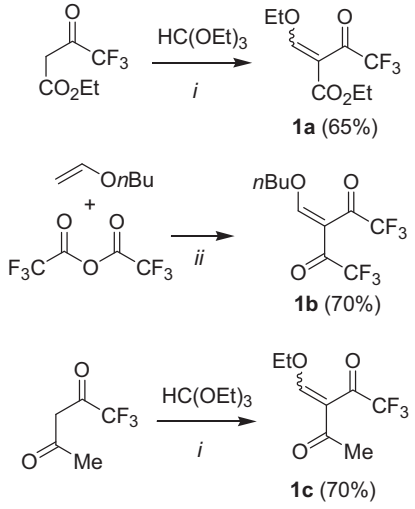
2. Results and discussion

Enones **1a–c** were synthesized by known procedures [18–20] (Scheme 1).

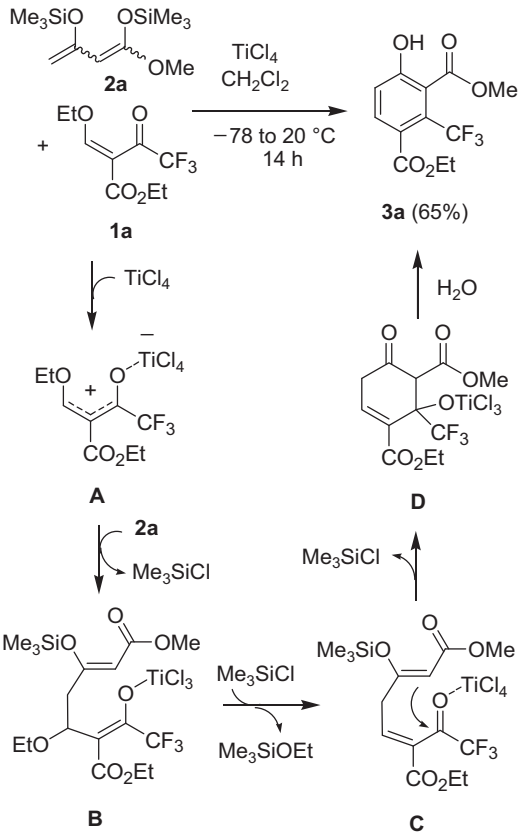
The $TiCl_4$-mediated cyclization of enone **1a** with 1,3-bis(silyloxy)-1,3-butadiene **2a** (Chan's diene) [21] afforded 5-ethoxycarbonyl-6-trifluoromethyl-salicylate **3a** (Scheme 2). The formation of **3a** can be explained by reaction of **1a** with $TiCl_4$ to give intermediate **A**, regioselective attack of the terminal carbon atom of **2a** to **A** to give intermediates **B** and **C**, cyclization (to give intermediate **D**) and aromatization (before or during the aqueous work-up). Product **3a** was formed with excellent regioselectivity. Only the isomer containing the CF_3 group located *ortho* to the ester group was formed (inspection of the crude product). The formation of the other regioisomer, containing the CF_3 group located *para* to the ester group, was not observed. The regioselectivity can be explained by steric and electronic effects.

The $TiCl_4$-mediated cyclization of enones **1a,b** with 1,3-bis(silyloxy)-1,3-butadienes **2a–u**, prepared from the corresponding 1,3-dicarbonyl compounds in one or two steps [21,22], afforded the 5-ethoxycarbonyl-6-trifluoromethyl-salicylates **3a–r** and the 5-trifluoroacetyl-6-trifluoromethyl-salicylates **3s–ai** (Scheme 3, Table 1). The best yields for compounds **3** were obtained when the reactions were carried out in highly concentrated solutions. For **3a,b,s,t** a 1.0/2.0/1.0 ratio of **1**/**2**/$TiCl_4$ gave the best yields. In case of **3c–r** and **3u–ai**, the best yields were obtained using a 1.0/1.5/1.0 ratio. The yields decreased when the stoichiometric ratio was 1.0/1.0/1.0. The reason for the change remains unclear at present. The temperature had to slowly warm from −78 to 20 °C.

Products **3a–r** were isolated in 30–79% yield. The best yields were obtained for **3a** and **3b**. Salicylates **3s–ai** were isolated in 32–69% yields. No clear trend was observed for the yields. All reactions proceeded with excellent regioselectivity by initial attack of the terminal carbon atom of the diene to the double bond. A first attack to the carbonyl group was not observed. The cyclization step proceeded by attack of the central carbon atom of the diene to the CF_3CO group. The moderate yields of all products can be explained by practical problems during the chromatographic purification. The formation of regioisomers as a reason for the moderate yields can be excluded because the crude product mixtures (before chromatographic purification) were analyzed by ^1H NMR and no



Scheme 1. Synthesis of **1a-c**: Reagents and conditions: *i*: $CF_3CO–CH_2–CO_2Et$ (1.0 equiv.), $HC(OEt)_3$ (1.5 equiv.), Ac_2O (3.0 equiv.), 120 °C, 2 h, then 140 °C, 5 h; *ii*: $H_2C = CH(OnBu)$ (1.0 equiv.), pyridine (3.0 equiv.), $CHCl_3$, $(F_3CCO)_2O$ (3.0 equiv.), 50 °C, 20 h.

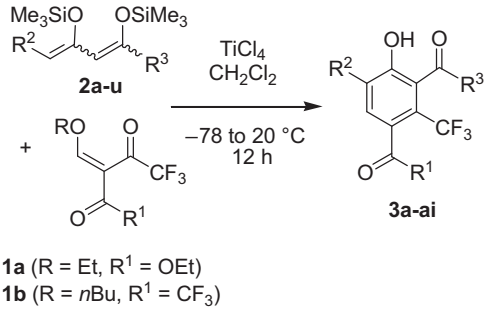


Scheme 2. Possible mechanism of the formation of **3a**.

Table 1
Synthesis of **3a–ai**.

1	2	3	R^1	R^2	R^3	% (**3**)[a]
a	**a**	**a**	OEt	H	OMe	65
a	**b**	**b**	OEt	Me	OMe	79
a	**c**	**c**	OEt	iPr	OEt	36
a	**d**	**d**	OEt	$(CH_2)_2CH(Me)_2$	OMe	67
a	**e**	**e**	OEt	nBu	OEt	33
a	**f**	**f**	OEt	nPent	OEt	40
a	**g**	**g**	OEt	nHex	OEt	37
a	**h**	**h**	OEt	nHept	OEt	30
a	**i**	**i**	OEt	nOct	OMe	35
a	**j**	**j**	OEt	nNon	OMe	30
a	**k**	**k**	OEt	nDec	OEt	30
a	**l**	**l**	OEt	nDodec	OMe	36
a	**m**	**m**	OEt	nHexadec	OMe	52
a	**n**	**n**	OEt	nOctadec	OEt	45
a	**o**	**o**	OEt	Allyl	OMe	51
a	**p**	**p**	OEt	$Cl(CH_2)_4$	OMe	52
a	**q**	**q**	OEt	$Cl(CH_2)_3$	OMe	43
a	**r**	**r**	OEt	$Ph(CH_2)_2$	OMe	50
b	**s**	**s**	CF_3	H	Me	60
b	**t**	**t**	CF_3	H	OEt	40
b	**u**	**u**	CF_3	H	OiPr	40
b	**c**	**v**	CF_3	iPr	OEt	52
b	**d**	**w**	CF_3	$(CH_2)_2CH(Me)_2$	OMe	61
b	**f**	**x**	CF_3	nPent	OEt	35
b	**g**	**y**	CF_3	nHex	OEt	43
b	**h**	**z**	CF_3	nHept	OEt	32
b	**i**	**aa**	CF_3	nOct	OMe	44
b	**j**	**ab**	CF_3	nNon	OMe	50
b	**k**	**ac**	CF_3	nDec	OEt	30
b	**l**	**ad**	CF_3	nDodec	OMe	33
b	**m**	**ae**	CF_3	nHexadec	OMe	52
b	**o**	**af**	CF_3	Allyl	OMe	46
b	**p**	**ag**	CF_3	$Cl(CH_2)_4$	OMe	69
b	**q**	**ah**	CF_3	$Cl(CH_2)_3$	OMe	62
b	**r**	**ai**	CF_3	$Ph(CH_2)_2$	OMe	44

[a]Yields of isolated products.



Scheme 3. Synthesis of **3a–ai**.

regioisomers were observed. However, hydrolysis of the 1,3-bis(silyloxy)-1,3-butadienes (to give 3-oxoalkanoates) and $TiCl_4$-mediated oxidative dimerization of the dienes (to give 3,6-dioxooctane-1,8-dioates) were observed as side reactions. Such products were found in the crude mixture in small amounts.

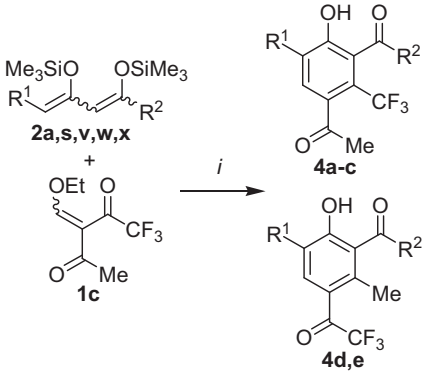
The structures of the products were established by spectroscopic methods (2D NMR, HMBC, NOESY, analysis of the C–F coupling constants). For example, the structure of **3a** was easily proven by inspection of the ^{1}H NMR spectrum which exhibits two characteristic doublets for the aromatic protons (J = 8.7 Hz). Analysis of the ^{13}C NMR shows quartets for the carbon atoms attached to the ester groups, due to carbon–fluorine coupling ($^3J_{C,F}$ = 2 and 3 Hz). For the other regioisomer, a singlet would be expected. In the ^{13}C NMR spectra of isophthalates **3a,b**, a typical quartet (J = 275 Hz) is observed at approx. 123 ppm for the CF_3 group attached to the benzene moiety. A singlet at approx. −54 ppm is observed in the ^{19}F NMR spectrum. For the 5-trifluoroacetyl-6-trifluoromethyl-salicylates **3s,t** two quartets (^{13}C NMR) and singlets (^{19}F NMR) are observed. The CF_3 group located at the benzene ring appears at −52 ppm while the CF_3 group located at the carbonyl group appears at approx. −75 ppm. The structures of all other derivatives were established by similar observations. In addition, NOESY and HMBC experiments were carried out for specific derivatives which further support the structures. The structure of **3m** was independently confirmed by X-ray crystal structure analysis (Fig. 1) [23].

The $TiCl_4$-mediated cyclization of 1,3-bis(silyloxy)-1,3-butadienes **2s**, **2v** and **2w** with enone **1c** afforded the 5-acetyl-6-trifluoromethyl-salicylates **4a–c**, respectively (Scheme 4, Table 2). The formation of the regioisomeric 5-triluoroacetyl-6-methyl-salicylates was not observed. Interestingly, the cyclization of **1c** with dienes **2a** and **2x** resulted in a complete change of the regioselectivity and formation of the 5-trifluoroacetyl-6-methyl-salicylates **4d,e**, respectively. Inspection of the crude products showed that a small amount (less than 10%) of the other regioisomer was present which could be separated. The moderate

Table 2
Synthesis of **4a–e**.

2	4	R^1	R^2	% (**4**)[a]
s	**a**	H	Me	55
v	**b**	OMe	OMe	47
w	**c**	H	Ph	48
a	**d**	H	OMe	56
x	**e**	Et	OEt	62

[a]Yields of isolated products.



Scheme 4. Synthesis von **4a–e**: *i*: $TiCl_4$, CH_2Cl_2, −78 → 20 °C, 14 h.

yields can again be explained by practical problems during the chromatographic purification. As side-reactions, hydrolysis and oxidative dimerization of the diene was observed.

In all reactions, the first step proceeds by conjugate addition of the terminal carbon atom of the diene to the enone. The regioselectivity of the subsequent cyclization step seems to depend on the substitution pattern of the diene. The nucleophilicity of dienes **2s,v,w** is lower than the nucleophilicity of **2a** and **2x**. This is a result of the fact that dienes **2s** and **2w** are derived from 1,3-diketones, while dienes **2a** and **2x** are derived from β-ketoesters (which possess an additional π-donating alkoxy group located at carbon atom C-1 of the diene). The decreased nucleophilicity of diene **2v** can be explained by the electron-withdrawing effect of the methoxy group located at carbon C-4 of the diene. The cyclizations of the less reactive dienes proceed via the more reactive trifluorocarbonyl group, while the cyclizations of the more reactive dienes proceed via the less reactive acetyl group. The exact reason for this change of the regioselectivity remains unclear at present. Obviously, steric effects (presence of a substituent R^1) do not play a role.

In conclusion, we have reported the synthesis of 5-ethoxycarbonyl-, 5-acetyl- and 5-trifluoroacetyl-6-trifluorosalicylates by regioselective one-pot cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 3-alkoxy-2-alken-1-ones. The use of enones

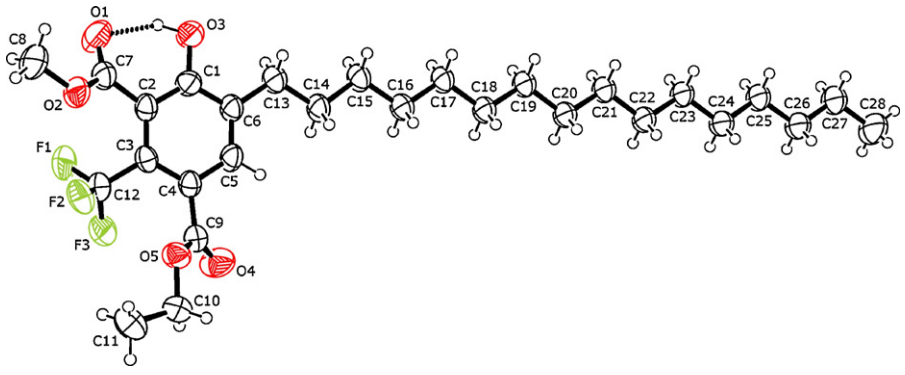


Fig. 1. Crystal structure of **3m**.

derived from 1,1,1-trifluoroacetylacetone resulted, depending on the substitution pattern of the diene, in the formation of two different regioisomers. The products are not readily available by other methods.

3. Experimental

General comments: All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. Melting points were determined with a Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus), Leitz Labolux 12 Pol with heating table Mettler FP 90. Melting points are uncorrected. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker ARX 300 spectrometer (300.1 MHz, 75.5 MHz, and 235 MHz, respectively). For ^{1}H, ^{13}C and and ^{19}F NMR spectra the deuterated solvents indicated were used. Mass spectra were recorded with Varian MAT CH 7, MAT 731 (EI, 70 eV) and Intecta AMD 402 (EI, 70 eV and CI). For ^{19}F NMR, $CFCl_3$ was used as external standard (0.0 ppm). Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For HRMS Varian MAT 311 and Intecta AMD 402 were used. IR spectra were detected with Nicolet 205 FT-IR and Nicolet Protége 460 FT-IR. Elemental analyses were performed with a LECO CHNS-932, Thermoquest Flash EA 1112. X-ray data collections were performed with a Bruker X8Apex diffractometer with CCD camera (Mo K_α radiation and graphite monochromator, λ = 0.71073 Å). The space group is determined by the XPREP program and the structures were solved via the SHELX-97 program package. Refinements were carried out according to the minimum square error method. For preparative scale chromatography, silica gel (60–200 mesh) was used. The synthesis of enones **1a**, [14] **1b**, [15] and **1c** [16] and of dienes **2** [17,18] were carried out following known procedures.

General procedure for the synthesis of **3a–ai** *and* **4a–4e**. Compound **1a**, **1b** or **1c** was solved in 3 mL of dry CH_2Cl_2 under inert atmosphere. To the solution was added diene **2**. The solution was cooled to −78 °C and $TiCl_4$ was added. The mixture was allowed to warm to room temperature during 14 h with stirring. The solution was poured into an aqueous solution of hydrochloric acid (10%, 50 mL) and the mixture was extracted with CH_2Cl_2 three times. The combined organic layers were dried with Na_2SO_4, filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel) to give products **3a–ai**.

1-Ethyl-3-methyl-4-hydroxy-2-(trifluoromethyl)- isophthalate (**3a**): Starting with **1a** (241 mg, 1.0 mmol), **2a** (521 mg, 2.0 mmol) and $TiCl_4$ (190 mg, 1.0 mmol) in 2 mL of dry CH_2Cl_2, **3a** was isolated as a yellow oil (190 mg, 65%); R_f 0.34 (*n*-heptane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.51 (s, 1H, OH), 7.68 (d, ^{3}J = 8.7 Hz, 1H, CH), 7.19 (d, ^{3}J = 8.7 Hz, 1H, CH), 4.36 (q, ^{3}J = 7.1 Hz, 2H, OCH_2), 3.98 (s, 3H, OCH_3), 1.37 (t, ^{3}J = 7.2 Hz, 3H, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.9, 167.1 (C=O), 160.1 (C–O), 134.0 (CH), 129.5 (q, $J_{C,F}$ = 33 Hz, C-2), 126.1 (q, $J_{C,F}$ = 3 Hz C-1), 122.7 (q, $J_{C,F}$ = 275 Hz, CF_3), 120.9 (CH), 114.4 (q, $J_{C,F}$ = 2 Hz, C-3), 62.2 (CH_2), 53.3 (OCH_3), 13.8 (CH_2CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −54.3 (CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 3350 (br m), 2986 (m), 2958 (w), 2910 (m), 1725 (s), 1597 (s), 1446 (s), 1369 (m). MS (EI, 70 eV): *m/z* (%) = 292 (M^+, 36), 260 (47), 232 (28), 227 (42), 212 (100). Anal. Calcd. for $C_{12}H_{11}F_3O_5$ (292.21): C, 49.32; H, 3.79. Found: C, 49.48; H, 4.05.

1-(3-Acetyl-4-hydroxy-2-trifluoromethylphenyl)-2,2,2-trifluor-oethanone (**3s**): Starting with **1b** (292 mg, 1.0 mmol), **2s** (489 mg, 2.0 mmol) and $TiCl_4$ (190 mg, 1.0 mmol) in 3 mL of CH_2Cl_2, **3s** was isolated as a red oil (179 mg, 60%); R_f 0.36 (*n*-heptane/EtOAc 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.45 (s, 1H, OH), 7.59 (d, ^{3}J = 9.0 Hz, 1H, CH), 7.22 (d, ^{3}J = 9.0 Hz, 1H, CH), 2.63 (q, $J_{H,F}$ = 1.4 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 203.7 (H_3C–C=O), 183.0 (q, $J_{C,F}$ = 37 Hz, F_3C–C=O), 157.2 (C–O), 130.7 (q, $J_{C,F}$ = 2 Hz, CH), 128.1 (q, $J_{C,F}$ = 33 Hz, C-2), 128.0 (q, $J_{C,F}$ = 2 Hz, C), 124.2 (q, $J_{C,F}$ = 2 Hz, C), 120.0 (CH), 119.5 (q, $J_{C,F}$ = 291 Hz, $COCF_3$), 118.8 (q, $J_{C,F}$ = 275 Hz, $ArCF_3$), 31.8 (q, $J_{C,F}$ = 3 Hz, CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −51.5 ($ArCF_3$), −74.0 ($COCF_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3391 (w), 1699 (m), 1591 (m), 1134 (w), 1001 (s), 968 (s). MS (EI, 70 eV): *m/z* (%) = 300 (M^+, 20), 265 (58), 231 (100), 215 (22), 191 (40). Anal. Calcd. for $C_{11}H_6F_6O_3$ (300.15): C, 44.02; H, 2.01. Found: C, 43.93; H, 2.36.

3-Acetyl-4-hydroxy-2-trifluoromethyl-acetophenone (**4a**). Starting with 1c (420 mg, 2.0 mmol), **2s** (489 mg, 2.0 mmol) and $TiCl_4$ (379 mg, 2.0 mmol) in CH_2Cl_2 (4 mL), **4a** was isolated as a colourless solid (270 mg, 55%); R_f 0.11 (*n*-heptane/EtOAc = 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.38 (s, 1H, OH), 7.36 (d, ^{3}J = 8.6 Hz, 1H, CH), 7.11 (d, ^{3}J = 8.6 Hz, 1H, CH), 2.59 (s, 3H, CH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 204.2 (C=O), 202.3 (C=O), 155.3 (C-4), 133.2 (q, $J_{C,F}$ = 3 Hz, C), 129.7 (CH), 127.6 (q, $J_{C,F}$ = 3 Hz, C), 125.0 (q, $J_{C,F}$ = 32 Hz, C-2), 123.1 (q, $J_{C,F}$ = 276 Hz, CF_3), 119.8 (CH), 31.7, 30.6 (CH_3). ^{19}F NMR ($CDCl_3$, 235 MHz): δ = −51.9 (CF_3). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3362 (s), 1709 (s), 1676 (s), 1585 (s). MS (EI, 70 eV): *m/z* (%) = 246 (M^+, 39), 231 (100), 211 (73), 191 (48), 43 (55). Anal. Calcd. for $C_{11}H_9F_3O_3$ (246.18): C, 53.67; H, 3.68; found: C, 53.82; H, 3.73.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2012.02.002.

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