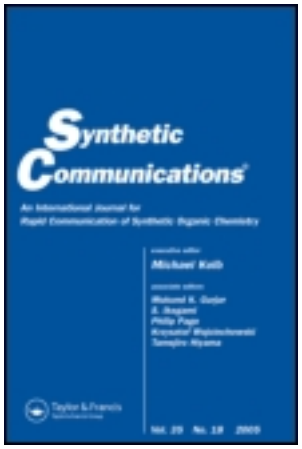

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$TiCl_4$-CATALYZED FRIEDEL–CRAFTS REACTION OF TRIFLUOROACETALDEHYDE ETHYL HEMIACETAL (TFAE)

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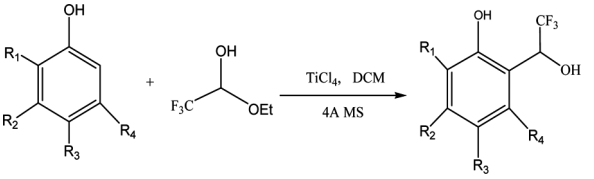
GRAPHICAL ABSTRACT



Abstract *The $TiCl_4$-catalyzed Friedel–Crafts reaction with trifluoroacetaldehyde ethyl hemiacetal is shown to serve as an efficient route for the synthesis of CF_3-substitituted compounds of biological and synthetic importance, producing 2,2,2-trifluoroethyl phenols in good yields under mild conditions.*

Keywords Friedel–Crafts reaction; phenol; $TiCl_4$; trifluoroacetaldehyde ethyl hemiacetal (TFAE)

INTRODUCTION

The unique behavior of fluorinated compounds makes them suitable for numerous applications. Organofluorine compounds play an important role in several scientific disciplines, and the synthesis of compounds containing fluorine is an important field of chemistry.[1] One of the important fluorine-containing groups is the trifluoromethyl group, which has been found to have unique physical and biological properties.[2] In particular, the lipophilicity attached to the trifluoromethyl moiety makes trifluoromethylated molecules of great interest, especially for biological purposes. However, their preparation by direct introduction of a nucleophilic CF_3 moiety on organic substrates, which is the most promising general route, still suffers from a limited number of efficient reagents that are able to stabilize the very unstable $-CF_3$ anion.[3] Trifluoromethylated compounds continue to be of great industrial interest,[4]

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and therefore the development of new methods to incorporate the trifluoromethyl group into organic compounds remains an important area of research.[5]

The Friedel–Crafts alkylation of aromatic and heteroaromatic compounds is one of the most fundamental carbon–carbon bond-forming reactions in organic synthesis.[6–8] We have reported the Friedel–Crafts reactions of *N*,*N*- and *N*,*O*-acetals with phenols promoted by $TiCl_4$.[9] To continue progress in Friedel–Crafts alkylation, we reasoned that if trifluoroacetaldehyde ethyl hemiacetal (TFAE) is used in a similar reaction, we might be able to prepare *ortho*- or *para*-(2,2,2-trifluoro-1-hydroxyethyl)phenol in one step.

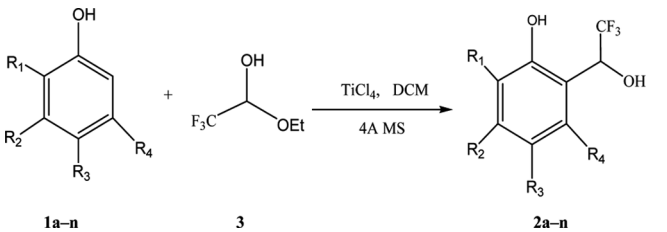
Trifluoroacetaldehyde has always been recognized as a potentially very useful precursor to trifluoromethyl compounds.[10] However, because of its volatility, high reactivity, and commercial unavailability, trifluoroacetaldehyde is almost never used directly; we chose its hydrate hemiacetal as an electrophilic agent. Because of our continuing interest in organofluorine chemistry, we studied the reaction and herein report our results.

RESULTS AND DISCUSSION

Trifluoroacetaldehyde was chosen as an electrophile in the Friedel–Crafts reaction of phenols. In attempts to determine the most advantageous conditions, optimization experiments were carried out using 4-*tert*-butyl phenol (**1a**) as the substrate. The reaction of 4-*tert*-butyl phenol with trifluoroacetaldehyde ethyl hemiacetal (**3**) was studied for different catalysts under the same reaction conditions (Scheme 1); the different conversion yields obtained in the presence of various Lewis acids are given in Table 1.

No detectable substitution product was found by thin-layer chorromatography (TLC) using $Zn(OTf)_3$ or $La(OTf)_3$ as the Lewis acid. Although Lewis acids such as $Zn(OTf)_3$ and $La(OTf)_3$ were not effective, use of either $Sc(OTf)_3$ or $AlCl_3$ afforded an adduct (**2a**) in good yield. $TiCl_4$ exhibited the greatest activity and afforded **2a** in 79% yield. Meanwhile, we found that the yields were notably improved by the addition of molecular sieves 4 Å (4 Å MS) when $TiCl_4$ was employed as the Lewis acid. The temperature also affected the reaction. Lowering the reaction temperature (below room temperature) was not successful because the amount of adduct (**2a**) was diminished when the reaction was carried out at −20 °C. The yield of the adduct (**2a**) was improved to 93% when the reaction was carried out at a slightly elevated temperature (40 °C).

Once we had established the optimal conditions for the reaction, various phenols (**1a–o**) were investigated in the presence of $TiCl_4$ in dichloromethane (DCM) (Scheme 1, Table 2).



Scheme 1. Friedel–Crafts reaction of 4-*tert*-butyl phenol and trifluoroacetaldehyde ethyl hemiacetal.

Table 1. Screening Lewis acids by reaction of trifluoroacetaldehyde ethyl hemiacetal (**3**) with **1a**

Entry	Lewis acid[a]	Substrate	Temp. (°C)	Time (h)	Yield (%)[b]
1	$Sc(OTf)_3$	**1a**	25	8	68
2	$AlCl_3$	**1a**	25	8	75
3	BF_3	**1a**	25	8	25
4	$TiCl_4$	**1a**	25	8	79
5	$TiCl_4$	**1a** (4A MS)	40	8	93
6	$Y(OTf)_3$	**1a**	25	24	Trace
7	$Zn(OTf)_3$	**1a**	25	24	None
8	$La(OTf)_3$	**1a**	25	24	None
9	None	**1a**	25	24	None

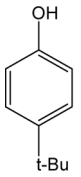
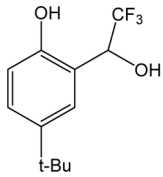
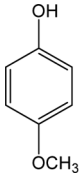
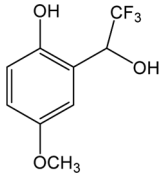
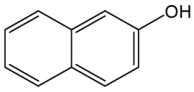
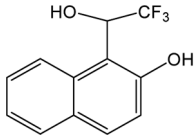
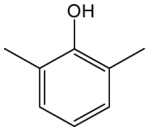
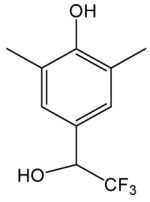
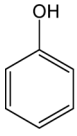
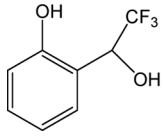
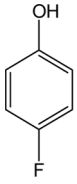
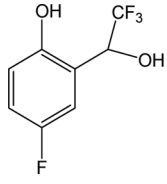
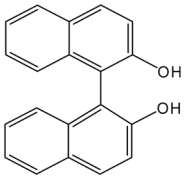
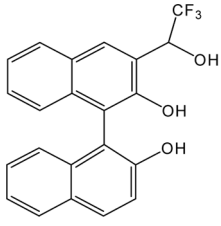
[a]Lewis acids were added as equimolar amounts of phenol and TFAE.
[b]Conversion yields were determined after isolation by flash chromatography on silica gel.

The $TiCl_4$-promoted Friedel–Crafts reactions all afforded the desired products (**2a–h**) in moderate to good yields (50.7–93%). Some observations are worthy of specific comments. The products showed that the Friedel–Crafts alkylation of phenols has excellent *ortho* regioselectivity. Substituents on the phenols such as halogen, OMe, and alkyl, and aryl, have no significant effect on the regioselectivity of the Friedel–Crafts reaction (entries 1–18). The Friedel–Crafts reaction occurs exclusively at the α-position (**2c**, entry 3), for β-naphthol (**1c**) and at the β-position (**2h,** entry 9). for α-naphthol (**1h**). For 1,1′-binaphthol (BINOL, **1g**), the mono-Friedel–Crafts product (**2g**) at the 3-position was obtained in 50.7% yield when triple-fold of TFAE and $TiCl_4$ were used (entry 8). The indole compounds do not have an available lone pair of electrons, because of their delocalization into the aromatic ring, so coordination to the titanium is not a strong interaction. In addition, the indole compounds were unstable when $TiCl_4$ was added in a blank reaction, TLC and ^1H NMR clearly showing that very complicated adducts were produced.

Second, to further demonstrate the utility of the hydroxyl-directed C-*ortho* Friedel–Crafts reaction, the reaction of phenol **1e** (1 eq.) with 1 eq. of TFAE in the presence of $TiCl_4$ (1.5 eq.) was carried out. The reaction afforded ortho-2,2,2-trifluoro-1-hydroxyethyl (**2e**) products in 86.2% yield (entry 6). Product analysis by ^1H NMR and ^{13}C NMR showed that the *ortho*-substituted compound was predominantly formed, and no detectable amount of 4-substituted compound was observed by ^1H or ^{13}C NMR, even after the reaction was carried out at reflux temperature (40 °C). However, the 2,6-dimethyl phenol (**1d**) can be treated with 1 eq. of TFAE in the presence of $TiCl_4$ (1 eq.) at reflux temperature to give the 4-(2,2,2-trifluoro-1-hydroxyethyl) product (**2d,** entry 4) in 56.2% yield. It was shown that the reaction can still occur when the α-position of the phenol was taken up; meanwhile, the regiochemistry of the reaction was controlled by the hydroxyl group. Although the explanation for this regiochemical result is not very clear, it could be due to multiple coordination with the hydroxyl group. According to the same procedure, the Friedel–Crafts reaction of **1n** (entry 15) with TFAE carried out in stepwise mode gave a yield of 34.2%.

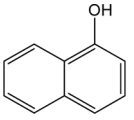
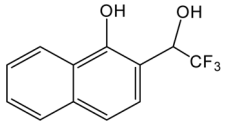
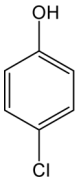
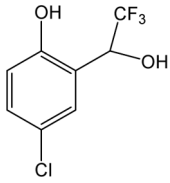
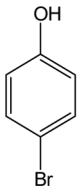
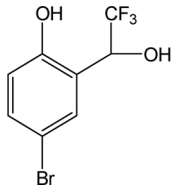
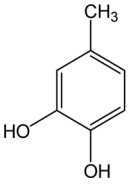
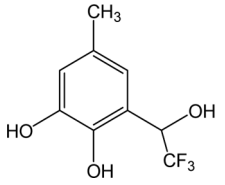
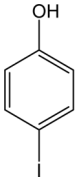
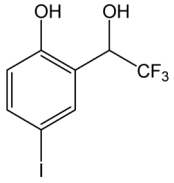
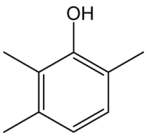
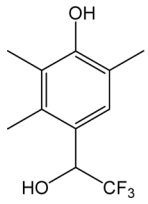
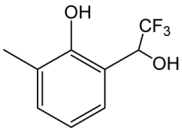
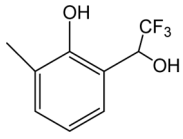
Furthermore, we found that the reaction of 4-fluorophenol and TFAE readily took place in the presence of $TiCl_4$, preferentially forming the *ortho*-substituted product, whereas we did not obtain any product in the reaction of *N*,*O*-hemiacetals

Table 2. Friedel–Crafts alkylation of phenols (**1a–n**) with TFAE (**3**)

Entry	Substrate	Molar ratio[a]	Product	Yield[b] (%)
1	 **1a**	1:1.1	 **2a**	89.0
2	 **1b**	1:1.1	 **2b**	81.2
3	 **1c**	1:1.0	 **2c**	78.1
4	 **1d**	1:1.5	 **2d**	56.2
5	 **1e**	1:1.1	 **2e**	86.2
6	 **1f**	1:3.0	 **2f**	68.1
7	 **1g**	1:1.0	 **2g**	50.7

(*Continued*)

Table 2. Continued

Entry	Substrate		Molar ratio[a]	Product		Yield[b] (%)
8		**1h**	1:1.1		**2h**	70.8
9		**1i**	1:1.1		**2i**	54.2
10		**1j**	1:2.0		**2j**	62.8
11		**1k**	1:1.5		**2k**	71.2
12		**1l**	1:1.1		**2l**	79.6
13		**1m**	1:1.1		**2m**	34.2
14		**1n**	1:1.1		**2n**	73.2

[a]Phenol/TFAE.
[b]Isolated yield by flash chromatography on silica gel.
[c]**1g**: racemic BINOL.

as electrophilic agents, even when a large amount of $TiCl_4$ was used. The obtained results are summarized in Table 2.

CONCLUSION

In summary, we have demonstrated a novel hydroxyl-directed Friedel–Crafts reaction of various phenols with TFAE that provides direct access to C-*ortho*, 2,2,2-trifluoro-1-hydroxyethyl phenols. This method leads to a simple synthetic procedure for the introduction of the $-CF_3$ anion. TFAE has been found to be a good electrophilic agent for use in a direct Lewis acid–catalyzed Friedel–Crafts reaction with phenol to form various 2,2,2-trifluoro-1-hydroxyethyl phenols of a general structure. The potential of this new Friedel–Crafts reaction is evident in Table 2, which contains highly valuable products that are employed in the synthesis of the analogs of natural products, and pharmaceutically interesting compounds can be easily obtained in good yields. Further studies on the scope and mechanism of the asymmetric reactions of TFAE are under active investigation.

EXPERIMENTAL

Typical Experimental Procedure

$TiCl_4$ (1.0 eq.) was added dropwise to a solution of phenol **1a** (1.0 eq.) and 4 Å molecular sieves (9 mg) in anhydrous dichloromethane at room temperature under nitrogen. After the mixture was stirred for 30 min, TFAE (1.1 eq.) was added. The reaction was completed within 8 h at room temperature (monitored by TLC). The usual workup furnished a residue that was separated and purified by flash chromatography on silica gel to give the pure product.

Data

4-*t*-Butyl-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2a). ^{1}H NMR ($CDCl_3$): δ 1.28 (s, 9H), 4.36 (s, 1H), 5.18 (m, 1H), 6.82 (d, $J = 8.5$ Hz, 1H), 7.17 (s, 1H), 7.29 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 73.8, 77.4,109.8, 120.1, 122.6, 123.8, 125.8, 126.0, 126.1, 127.7, 127.8, 135.2, 153.2. HRMS (FAB) calcd. for $C_{12}H_{15}O_2F_3$: 248.2425. Found: 248.2416.

4-Methoxy-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2b). ^{1}H NMR ($CDCl_3$): δ 3.78 (s, 3H), 5.15 (q, 1H), 6.73 (s, 1H), 6.80 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 56.2, 72.8, 77.4,114.9, 116.7, 118.4, 123.6, 125.9, 149.3, 153.8; MS-EI m/z (%): 176 (56.1), 204 (100), 223 (M^+, 31.2).

1-(2,2,2-Trifluoro-1-hydroxyethyl)-2-naphthol (2c). ^{1}H NMR ($CDCl_3$): δ 5.32 (q, 1H), 7.09 (d, $J = 8.49$ Hz, 1H), 7.37 (d, $J = 8.50$ Hz, 1H), 7.51 (m, 2H), 7.77 (m, 1H), 8.12 (s, 1H), 8.27 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 74.9, 77.4, 109.7, 120.1, 122.6, 123.8, 125.8, 126.1, 126.2, 127.8, 135.2, 153.2; MS-EI m/z (%): 196 (59.4), 224 (100), 243 (M^+, 15.7).

2,6-Dimethyl-4-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2d). ^{1}H NMR ($CDCl_3$): δ 2.22 (s, 6H), 4.74 (q, $J = 7.2$ Hz, 1H), 4.89 (s, 1H), 7.08 (s, 2H); ^{13}C NMR

($CDCl_3$): δ 16.3, 73.2, 77.4,123.6, 125.8, 126.1, 128.1, 129.7, 130.2, 152.2; HRMS (FAB) calcd. for $C_{10}H_{11}O_2F_3$: 220.0711. Found: 220.0709.

2-(2,2,2-Trifluoro-1-hydroxyethyl)phenol (2e). ^1H NMR ($CDCl_3$): δ 5.23 (q, $J = 5.2$ Hz, 1H), 6.92 (m, 2H), 7.17 (d, 1H), 7.29 (d, 1H); ^{13}C NMR ($CDCl_3$): δ 73.3, 77.4,117.7, 121.0, 123.7, 125.9, 130.0, 131.3, 155.7. HRMS (FAB) calcd. for $C_8H_7O_2F_3$: 192.0431. Found: 192.0420.

4-Fluoro-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2f). ^1H NMR ($CDCl_3$): δ 3.5 (s, 1H), 5.21 (q, $J = 5.2$ Hz, 1H), 6.53 (s, 1H), 6.84 (m, 1H), 7.0 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 72.3, 77.4, 117.7, 121, 123.7, 126.0, 130.0, 131.3, 155.7. MS-EI m/z (%): 180 (100), 198 (41.2), 211 (M^+, 21.5).

3-(2,2,2-Trifluoro-1-hydroxyethyl)-1,1′-binaphthol (2g). ^1H NMR ($CDCl_3$): δ 2.03 (s, 1H), 5.56 (q, 1H), 7.09–7.17 (m, 2H), 7.27–7.45 (m, 5H), 7.89–8.0 (m, 3H), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 70.4, 77.4,110.4, 112.7, 118.3, 122.5, 123.8, 124.3, 124.6, 124.7, 125.2, 126.1, 128.1, 128.8, 128.9, 129.3, 129.9, 131.6, 132.2, 133.6, 133.9, 150.8, 153.2. MS-EI m/z (%): 366 (100), 385 (M^+, 39.8)

2-(2,2,2-Trifluoro-1-hydroxyethyl)-1-naphthol (2h). ^1H NMR ($CDCl_3$): δ 5.35 (m, 1H), 7.12 (d, $J = 8.39$ Hz, 1H), 7.39 (d, $J = 8.39$ Hz, 1H), 7.53 (m, 2H), 7.80 (m, 1H), 8.1 (s, 1H), 8.28 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 75.1, 77.4, 109.8, 120.1, 122.6, 123.8, 125.8, 126.0, 126.1, 127.7, 127.8, 135.2, 153.2. HRMS (FAB) calcd. for $C_{12}H_9O_2F_3$: 242.1951. Found: 242.1943.

4-Chloro-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2i). ^1H NMR ($CDCl_3$): δ 5.18 (m, 1H), 6.81 (d, $J = 8.59$ Hz, 1H), 6.86 (s, 1H), 7.29 (s, 1H), 7.52 (d, $J = 8.59$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 72.8, 77.4, 112.9, 118.5, 121.1, 125.6, 128.8, 133.4, 134.1. MS-EI m/z (%): 196 (100), 214 (28.1), 227 (M^+, 15.3).

4-Bromo-2-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2j). ^1H NMR ($CDCl_3$): δ 5.20 (m, 1H), 6.80 (d, $J = 8.69$ Hz, 1H), 6.91 (s, 1H), 7.39 (s, 1H), 7.42 (d, $J = 8.69$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 72.4, 77.4, 112.8, 119.5, 121.1, 125.6, 127.8, 132.4, 134.1, 154.9. MS-EI m/z (%): 241 (100), 259 (36.5), 271 (M^+, 19.6).

2-Hydroxy-4-methyl-6-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2k). ^1H NMR ($CDCl_3$): δ 2.28 (s, 3H), 3.73 (s, 1H), 5.17 (s, 1H), 5.56 (s, 1H), 6.61 (d, $J = 7.93$ Hz, 1H), 6.72 (d, $J = 7.93$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 15.9, 73.9, 77.4, 115.1, 120.0, 122.4, 123.6, 125.9, 128.1, 143.4. HRMS (FAB) calcd. for $C_9H_9O_3F_3$: 222.1611. Found: 222.1609.

4-Indo-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2l). ^1H NMR ($CDCl_3$): δ 3.6 (s, 1H), 5.16 (q, $J = 5.2$ Hz, 1H), 6.68 (d, $J = 8.63$ Hz, 1H), 6.91 (s, 1H), 7.54 (s, 1H), 7.57 (d, $J = 8.63$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 75.4, 77.4, 82.3, 119.9, 123.3, 125.6, 138.3, 140.0, 155.8. HRMS (FAB) calcd. for $C_9H_9O_3F_3$: 318.1536. Found: 318.1601.

2,3,6-Trimethyl-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2m). ^1H NMR ($CDCl_3$): δ 2.20 (m, 9H), 4.67 (s, 1H), 4.80 (s, 1H), 5.32 (q, 1H), 7.01 (s, 1H). MS-EI m/z (%): 216 (100), 235 (M^+, 30.7)

2-Methyl-6-(2,2,2-trifluoro-1-hydroxyethyl)phenol (2n). ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H), 3.5 (s, 1H), 5.21 (q, 1H), 6.84 (t, 1H), 6.98 (d, $J = 7.36$ Hz, 1H), 7.20 (d, $J = 5.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.1, 73.2, 120.4, 123.7, 125.9, 126.2, 127.6, 132.5, 154.2. HRMS (FAB) calcd. for $C_9H_9O_2F_3$: 206.2157. Found: 206.2169.

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