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Condensations of aryl trifluoromethyl ketones with arenes in acidic media

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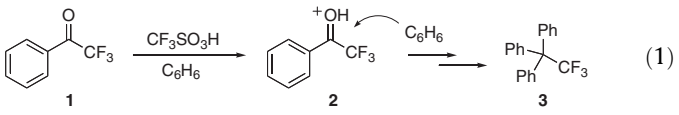
ABSTRACT

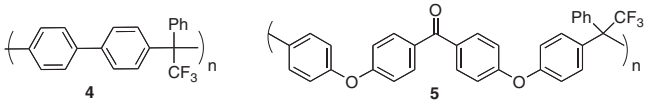
The chemistry of trifluoromethyl ketones has been studied. The work examines the condensation reactions of trifluoromethyl ketones with arenes in the superacid, including both synthetic and mechanistic aspects.

The hydroxyalkylation reaction involves the acid-catalyzed condensations of aldehydes and ketones with arenes.[1] Although the reaction is often limited to activated, electron-rich arenes, it has been shown in many instances that aldehydes and ketones bearing electron-withdrawing groups may react with benzene and even deactivated arenes.[2] For example, acetophenone will not react with benzene in CF_3SO_3H (triflic or trifluoromethanesulfonic acid), despite being protonated in the superacid.[3] As shown by Kray and Rosser,[2a] 2,2,2-trifluoroacetophenone (**1**) does however react in high yield with benzene to give the condensation product (**3**, Eq. 1). The inductive effects of the



1 2 3 (1)

trifluoromethyl group activate the carboxonium ion intermediate (**2**) and this leads to enhanced electrophilic reactivity. The hydroxyalkylation reaction has had an important role in polymer chemistry, as it is the reaction used to make bis-phenol-A and many condensation polymers with phenols. Recently, this chemistry has been applied in the synthesis of several novel condensation polymers (**4** and **5**) through the reactions of compound **1**



4 5

with biaryl substrates.[4] The step-growth polymerizations of electron-deficient ketones continue to be an active area of research in polymer synthesis.[5] As such, there is renewed interest in the hydroxyalkylation reaction of ketones and aldehydes. In the following Letter, we describe our studies of superacid-promoted hydroxyalkylation chemistry.

The condensation chemistry of a variety of trifluoromethyl ketones was studied, including acetophenones, biaryl, and heterocyclic systems (Table 1).[6] In condensation reactions with substituted acetophenones (**6–12**), generally good conversions were observed from benzene and CF_3SO_3H. The 4-(trifluoroacetyl)benzoic acid (**10**) reacts cleanly to form the benzoyl-substituted product (**17**), indicating that Friedel–Crafts chemistry occurs at both the ketone and acid functional groups. In the case of 2,2,2-trifluoro-4-methylacetophenone (**8**), the condensation does take place, however the reaction is complicated by formation of major impurities from transmethylation (the intermolecular exchange of methyl groups) at 25 °C. If the reaction is done at low temperature (−10 °C), the expected product **15** is formed in good yield and is relatively pure. The reaction of 2,2,2,4′-tetrafluoroacetophenone (**9**) forms the expected condensation product (**16**) however, it is accompanied by the formation of ca. 5% of an impurity identified as 1,1,1-trifluoro-2,2,2-triphenylethane (**3**). When the 2-(trifluoroacetyl)biphenyl (**11**) is reacted with CF_3SO_3H and C_6H_6, the condensation involves intra- and intermolecular reaction steps to produce a fluorene ring system (**18**). A similar transformation is seen with the quinoline derivative **12**.

Previous results have shown that the condensation reactions of trifluoromethyl ketones will occur with activated, electron-rich arenes and with benzene.[2a,4a] As such, ketone **7** condenses in good yield with the activated arene, benzo-18-crown-6 (Scheme 1). With reaction of precisely 2.0 equiv of arene to 1.0 equiv of **7**, the crown-derivative (**20**) is prepared cleanly. We have also found that this electrophile will react with somewhat deactivated arenes. When compound **7** is reacted with *o*-dichlorobenzene, the condensation product (**21**) is formed in reasonable yield.

Although the reaction conditions have not been fully optimized, we have found that the reaction is best done with an excess of CF_3SO_3H and that weaker acids do not promote the condensation. Using the condensation of 2,2,2-trifluoroacetophenone (**1**) with benzene as a test reaction, the quantity of CF_3SO_3H was varied (25 °C and 24 h reaction). While the reaction proceeds with 1 equiv of acid, product **3** was isolated in just 58% yield. Using 5 equiv of

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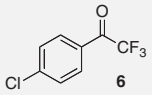
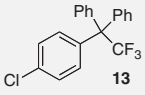
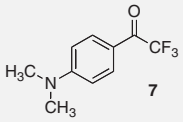
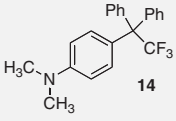
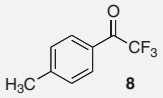
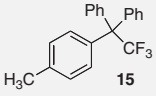
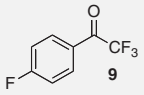
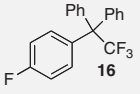
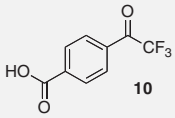
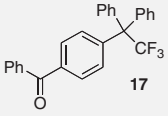
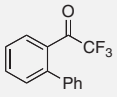
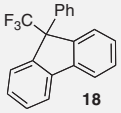
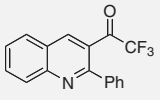
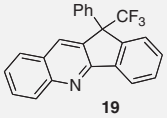
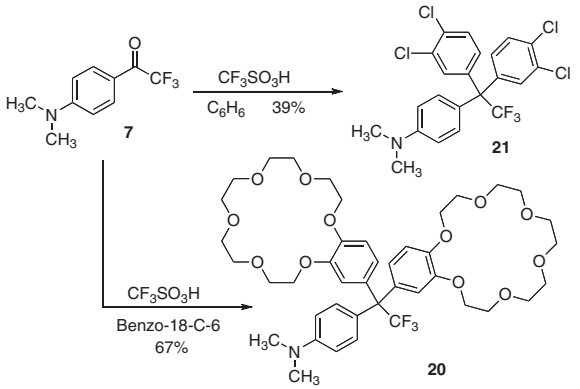
Table 1
Products and yields from the reactions of ketones **6**–**13** with C_6H_6 in CF_3SO_3H

Substrate	Product	Yield[a] (%)
 **6**	 **13**	96[c]
 **7**	 **14**	89[c]
 **8**	 **15**	90[b]
 **9**	 **16**	86[c]
 **10**	 **17**	73[c]
 **11**	 **18**	99[c]
 **12**	 **19**	71[d]

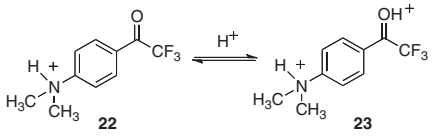
[a] Isolated yield.
[b] Reaction done at −10 °C.
[c] Reaction done at 25 °C.
[d] Reaction done at 50 °C.



Scheme 1.

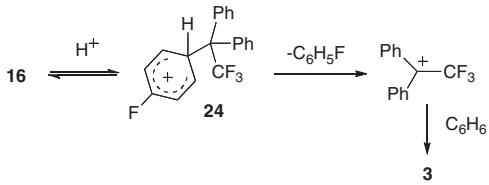
CF_3SO_3H, the reaction quantitatively produces compound **3**. Reactions were also done with large excesses of H_2SO_4 and CF_3CO_2H (20 equiv), but no condensation product was detected. These results are consistent with the need for very strong acids, or superacids, to effectively promote the condensations of trifluoromethyl ketones.

The mechanism of the hydroxyalkylation reaction is generally thought to proceed through a carboxonium ion intermediate, or protonated carbonyl group. In order to further examine the carboxonium ions involved in the condensation reactions, ^{13}C NMR studies were done with the 2,2,2-trifluoroacetophenone derivatives in CF_3SO_3H solution (Table 2). It has been known for some time that ^{13}C NMR chemical shift values are extremely sensitive to electron density and charge formation. With closely related structures, ^{13}C NMR chemical shift values are useful in characterizing the nature of carbocationic intermediates.[7] By comparing the ^{13}C NMR spectra from $CDCl_3$ and CF_3SO_3H solutions, we sought to gain insight regarding the structures of protonated ketones in CF_3SO_3H. When 2,2,2-trifluoroacetophenone (**1**) is examined in the two solutions, it is remarkable to note the large downfield shifts of the carbonyl carbon (δ 180.6→187.7) and *ortho, para* carbons (δ 130.2, 135.5→132.9, 140.5). Similar results are seen for ketone **8**. These data suggest a fairly high equilibrium concentration of the carboxonium ions (i.e., **2**). Formation of the protonated ketone is favorable due to the good electron-donating abilities of the phenyl and 4-methylphenyl groups. With ketone **7**, the carboxonium group ^{13}C resonances are shifted downfield, although to a less extent than with compounds **1** and **8**. This is likely due to lower equilibrium concentration of the carboxonium ion (**23**). The 4-(*N,N*-dimethylammonium) phenyl group is



expected to destabilize the carboxoniun ions due to inductive and electrostatic effects. Despite an apparently lower equilibrium concentration of the carboxonium ion **23**, the condensation product with benzene (**14**) is formed in good yield. This suggests relatively high electrophilic reactivity for carboxonium ion (**23**), a feature that is confirmed by its reaction with *o*-dichlorobenzene. While strong electron-withdrawing aryl groups may tend to further activate carboxonium electrophiles, it should be noted however that the basicity of the carbonyl group could drop-off and the formation of the carboxonium ion may not be possible. This may be similar to the experimental observation that 1,1,1-trifluoroacetone readily forms condensation polymers with biaryl substrates, but hexafluoroacetone does not form polymers.[4a,5a]

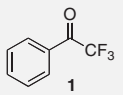
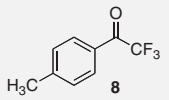
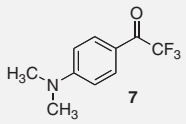
Besides the role of the carboxonium ion, there are other mechanistic considerations with this hydroxyalkylation chemistry. In the reactions of ketones **8** and **9**, by-products were observed. For example, reaction of **9** produces the major product **16**, but compound **3** is also produced in small amounts (5%). The formation of by-product **3** can be explained by an aryl-group exchange involving *ipso*-protonation of the fluorophenyl group (Eq. 2). The very

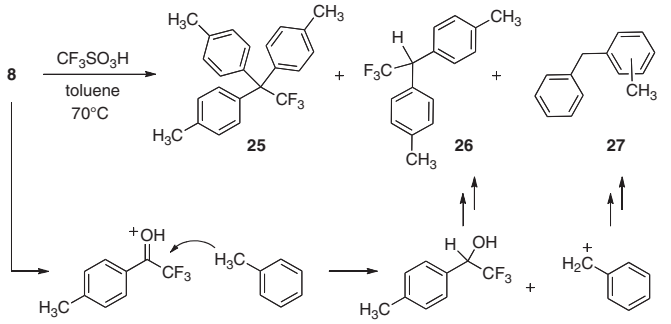


(2)

high acidity of CF_3SO_3H facilitates this chemistry.[8] The undesired by-product (**3**) tends to form in greater quantities under conditions of excess acid and elevated temperature. In the case of 2,2,2-trifluoro-4-methylacetophenone (**8**), transmethylation is observed, but another side-reaction also occurs. When compound **8** was reacted with toluene at 70 °C in CF_3SO_3H (5 equiv), three types of products were detected by GC–MS and NMR analysis (Scheme 2). As reported previously by Kray and Rosser,[2a] the condensation product **25** is formed as a major product. However, the diarylethane (**26**) is also formed as a major product (ratio of **25**/**26** is 4:1).

Table 2
^{13}C NMR spectral data from trifluoromethyl ketones in $CDCl_3$ and CF_3SO_3H (q, quartet)

	Solvent (temp)	^{13}C NMR signals, δ
 **1**	$CDCl_3$ (25 °C) CF_3SO_3H (−20 °C)	116.8 (q), 129.2, 130.1, 130.2, 135.5, 180.6 (q) 116.5 (q), 127.3, 129.9, 132.9, 140.5, 187.7 (q)
 **8**	$CDCl_3$ (25 °C) CF_3SO_3H (−20 °C)	21.9, 116.8 (q), 127.5, 129.8, 130.2, 147.0, 180.1 (q) 22.4, 118.3 (q), 123.0, 132.1, 136.4, 162.2, 187.5 (q)
 **7**	$CDCl_3$ (25 °C) CF_3SO_3H (−20 °C)	40.0, 110.9, 117.4, 117.5 (q), 132.7, 154.7, 177.9 (q) 47.7, 116.2 (q), 122.1, 131.0, 134.0, 147.6, 183.9 (q)



Scheme 2.

Formation of this product can be explained by the involvement of a hydride transfer step.

This proposed mechanism is supported by the observation of diarylmethane by-product (**27**).[9] These data suggest that good hydride donors may be unsuitable as substrates in hydroxyalkylations that utilize trifluoromethyl ketones. These undesirable side reactions may however be suppressed by using lower reaction temperatures (vide supra).

In conclusion, we have found that substituted trifluoroacetophenones condense with benzene and substituted arenes in superacidic CF_3SO_3H.[10] While the strength of this acid facilitates rapid condensations of the ketones with arenes, it can also lead to undesirable side reactions, such as aryl-group exchange and side reactions in alkyl-substituted arenes. Depending on the structure of the trifluoromethyl ketone, intramolecular reactions may compete with intermolecular reactions.

Acknowledgments

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6. Typical procedure: the trifluoromethyl ketone (1 mmol) is dissolved in 2 mL of C_6H_6, and CF_3SO_3H (2 mL, 23 mmol) is added with stirring. After 4 h, the mixture is poured onto ice. If the substrate contains a strong base site (amino group or *N*-heterocycle), then the solution is neutralized with 10 M NaOH. The aqueous solution is then extracted twice with $CHCl_3$ (2×30 mL) and the organic phase is washed with water and twice with brine. The solution is then dried over $MgSO_4$ and isolated by column chromatography or recrystallization. In the case of compound **20**, 2 mmol of benzo-18-crown-6 is reacted with 1 mmol of compound **7**.
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9. Alternatively, hydride transfer might occur after arylation and formation of the carbocation intermediate. Products **25**–**27** could not be separated; their identities and relative yields were established by GC–MS, GC-FID, and ^1H NMR analysis of the crude product mixture.
10. Characterization of data of new compounds. Compound **13**: ^1H NMR, δ, $CDCl_3$: 7.12 (d, J = 9 Hz, 2H), 7.16–7.17 (m, 3H), 7.33 (d, J = 9 Hz, 2H), 7.34–7.38 (m, 7H). ^{13}C NMR, δ, $CDCl_3$: 64.9 (q, J_{C-F} = 24 Hz), 127.8 (q, J_{C-F} = 285 Hz), 127.9, 128.2, 128.3, 129.9, 131.4, 133.9, 138.7, 139.7. LR MS: 348/346 (M+), 279/277, 201/199, 165. HRMS, $C_{20}H_{14}F_3Cl$ calcd 346.07361, found 346.07434. Compound **14**: ^1H NMR, δ, $CDCl_3$: 3.03 (s, 6H), 6.73 (d, J = 8.3 Hz, 2H), 7.06 (d, J = 8.6 Hz, 2H), 7.27–7.28 (m, 4H), 7.37–7.39 (m, 6H). ^{13}C NMR, δ, $CDCl_3$: 40.3, 64.5 (q, J_{C-F} = 23 Hz), 111.6, 127.5, 128.0, 128.4, (q, J_{C-F} = 285 Hz), 130.1, 130.8, 140.9, 149.5. LR MS: 355 (M+), 286, 165. HRMS, $C_{22}H_{20}NF_3$ calcd 355.15478, found 355.15586. Compound **15**: ^1H NMR, δ, $CDCl_3$: 2.47 (s, 3H), 7.16 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 7.30–7.37 (4H), 7.40–7.48 (m, 6H). ^{13}C NMR, δ, $CDCl_3$: 21.0, 65.0 (q, J_{C-F} = 94 Hz), 127.7, 128.1, 128.2 (q, J_{C-F} = 284 Hz), 128.9, 130.0, 130.0, 137.4, 137.6, 140.4. LR MS: 326 (M+), 257, 165. HRMS, $C_{21}H_{17}F_3$ calcd 326.12824, found 326.12735. Compound **16**: ^1H NMR, δ, $CDCl_3$: 7.04–7.08 (m, 2H), 7.18–7.22 (m, 6H), 7.37–7.42 (m, 6H). ^{13}C NMR, δ, $CDCl_3$: 64.8 (q, J_{C-F} = 94 Hz), 115.0 (d, J_{C-F} = 21 Hz), 127.8, 128.0 (q, J_{C-F} = 285 Hz), 128.2, 129.9, 131.8 (d, J_{C-F} = 30 Hz), 136.0, 140.1, 162.1 (d, J_{C-F} = 247 Hz). LR MS: 330 (M+), 261, 183, 165. HRMS, $C_{20}H_{14}F_4$ calcd 330.10316, found 330.10356. Compound **17**: ^1H NMR, δ, $CDCl_3$: 7.19–7.23 (m, 2H), 7.35–7.40 (m, 2H), 7.51–7.54 (m, 1H), 7.62–7.65 (m, 8H), 7.82 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 7.4 Hz, 2H). ^{13}C NMR, δ, $CDCl_3$: 65.3 (q, J_{C-F} = 24 Hz), 127.8 (q, J_{C-F} = 284 Hz), 128.0, 129.9, 129.9, 129.9, 132.7, 136.8, 137.3, 139.4, 139.5, 143.6, 144.7, 146.2, 196.2. LR MS: 416 (M+), 347, 165, 105. HRMS, $C_{27}H_{19}OF_3$ calcd 416.13881, found 416.13955. Compound **18**: ^1H NMR, δ, $CDCl_3$: 7.28–7.32 (m, 3H), 7.35–7.38 (m, 4H), 7.50–7.53 (m, 2H), 7.58 (d, J = 12 Hz, 2H), 7.84 (d, J = 8 Hz, 2H). ^{13}C NMR, δ, $CDCl_3$: 63.8 (q, J_{C-F} = 26 Hz), 120.3, 126.3, 126.8 (q, J_{C-F} = 281 Hz), 126.3, 127.3, 127.3, 127.7, 128.1, 128.7, 129.2, 137.5, 141.4, 144.3. LR MS: 310 (M+), 241, 183, 119. HRMS, $C_{20}H_{13}F_3$ calcd 310.09694, found 310.09619. Compound **19**: ^1H NMR, δ, $CDCl_3$: 7.31–7.34 (m, 3H), 7.39–7.41 (m, 2H), 7.55–7.58 (m, 2H), 7.62–7.67 (m, 2H), 7.78–7.84 (m, 2H), 8.22–8.28 (m, 2H), 8.36–8.40 (m, 1H). ^{13}C NMR, δ, $CDCl_3$: 61.4 (q, J_{C-F} = 281 Hz), 122.4, 126.5, 126.5, 126.6 (q, J_{C-F} = 26 Hz), 127.4, 127.5, 128.0, 128.5, 128.9, 129.3, 129.9, 130.2, 131.1, 133.4, 136.4, 137.2, 140.4, 145.7, 149.1, 160.5. LR MS: 361 (M+), 292, 234, 145. HRMS, $C_{23}H_{14}NF_3$ calcd 361.10783, found 361.10910. Compound **20**: ^1H NMR, δ, $CDCl_3$: 2.94 (s, 6H), 3.65–3.78 (m,

20H), 3.84–3.86 (m, 4H), 3.91–3.93 (m, 4H), 3.99–4.02 (m, 4H), 4.14–4.16 (m, 4H), 4.20–4.21 (m, 4H), 6.60–6.65 (m, 4H), 6.75–6.82 (m, 3H), 6.95–6.98 (m, 3H). ^{13}C NMR, δ, $CDCl_3$: 40.4, 63.5 (q, J_{C-F} = 19 Hz), 64.3, 64.4, 67.1, 68.9, 69.2, 69.6, 69.6, 70.7, 70.8, 70.9, 111.7, 112.7, 116.5, 119.8, 121.3, 128.3 (q, J_{C-F} = 278 Hz), 130.6, 133.7, 142.8, 148.0, 148.3. LR MS: 823 (M+), 754, 647, 578. HRMS, $C_{42}H_{56}O_{12}NF_3$ calcd 823.37548, found 823.37399. Compound **21**: ^{1}H NMR, δ, $CDCl_3$: 3.01 (s, 6H), 6.68 (d, J = 9.2 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H), 7.04 (dd, J = 8.4, 2.4 Hz, 2H), 7.28 (d, J = 2.4 Hz, 2H), 7.43 (d, J = 8.7 Hz, 2H). ^{13}C NMR, δ, $CDCl_3$: 40.1, 63.5 (q, J_{C-F} = 24 Hz), 111.8, 124.8, 127.1 (q, J_{C-F} = 284 Hz), 129.2, 130.1, 130.3, 131.8, 132.5, 132.7, 140.7, 150.4. LR MS: 495/493/491 (M+), 426/424/422, 175. HRMS, $C_{22}H_{16}NCl_4F_3$ calcd 490.99888, found 490.99808.