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COMMUNICATIONS

Superelectrophiles and the Effects of Trifluoromethyl Substituents

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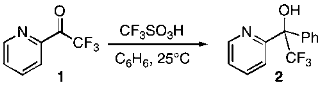
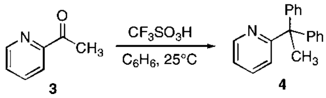
The trifluoromethyl ($-CF_3$) group is one of the most powerful electron-withdrawing groups in structural organic chemistry.[1] This property is often manifested by increased reactivities of adjacent acidic or electrophilic functional groups. The $-CF_3$ group primarily activates electrophilic sites by inductive electron-withdrawing effects. Similar electrophilic activation has been observed from cationic functional groups and structures.[2] Depending on the cationic group, very strong electron-withdrawing effects may occur via inductive, resonance, or other electrostatic effects. Multiply charged cationic electrophiles (i.e., dications or trications) have even been described as superelectrophiles on the basis of their high electrophilic reactivities.[3] In this communication, we report the results of our studies of trifluoromethyl-substituted superelectrophiles. Despite their high electrophilic reactivities, these species exhibit well-defined chemo-, regio-, and stereoselectivities in their reactions.

Our initial experiments examined the superacid-promoted reaction of 2-(trifluoroacetyl)pyridine (**1**) with benzene (eq 1):



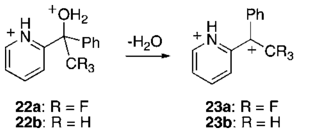
(1)



(2)

In contrast to 2-acetylpyridine (**3**), which gives the condensation product **4** (eq 2),[4] compound **1** gives intermediate alcohol product **2**. Rather than enhancing the electrophilic condensation with benzene, the $-CF_3$ group slows the final substitution step, and the hydroxy group is relatively stable in the superacid. For this type of condensation (the hydroxyalkylation reaction[5]), selective formation of the intermediate alcohol is rare. Other N-heterocyclic systems (Table 1, entries 1−3) were studied, and heterocyclic alcohols (**13**−**15**) were obtained as the only major products in the reactions at 25 °C.

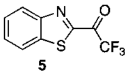
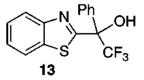
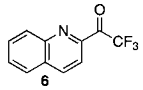
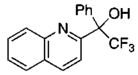
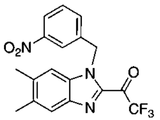
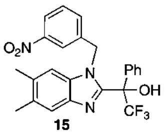
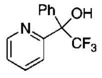
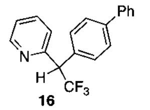
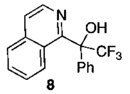
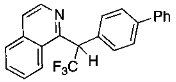
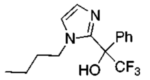
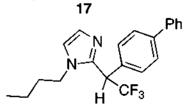
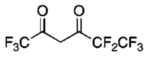
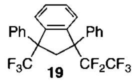
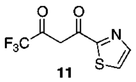
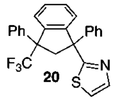
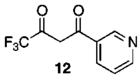
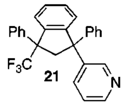
We propose that the $-CF_3$ derivatives show this chemoselectivity because of the increased reactivities of the intermediate carbenium-based superelectrophiles, which lead to strengthening of the carbon−oxygen bond. In the case of **1**, reaction with benzene leads to formation of the pyridinium−oxonium dication **22a**. Loss of water from **22a** via eq 3:



(3)

is inhibited because cleavage of the carbon−oxygen bond requires separation of a relatively strong nucleophile (H_2O) from the very powerful electrophile **23a**. This effect is similar to the well-known kinetic stabilities of uncharged $-CF_3$-substituted systems.[6] Likewise, several reports have described chemistry with small, highly charged ions and their tendencies to retain good leaving groups (i.e., halogens or protonated hydroxy groups) even in superacidic media.[7] The effect of the $-CF_3$ group in **22a** is apparent, as the closely related system **22b** (from 2-acetylpyridine) cleaves rapidly at 25 °C to give the carbocationic superelectrophile **23b**. Thus, the observed chemoselectivity is the result of a strengthening of the carbon−oxygen bond by the $-CF_3$ group in the pyridinium−oxonium dication.

Table 1. Products and Yields for Reactions of Trifluoromethyl Substrates with CF_3SO_3H and C_6H_6

Entry	Substrate	Product	Yield
1	 **5**	 **13**	91%[a]
2	 **6**	 **14**	79%[a]
3	 **7**	 **15**	80%[a]
4	 **2**	 **16**	78%[b]
5	 **8**	 **17**	86%[b]
6	 **9**	 **18**	96%[b]
7	 **10**	 **19**	88%[a]
8	 **11**	 **20**	98%[a]
9	 **12**	 **21**	94%[a]

[a] Reaction done at 25 °C. [b] Reaction done at 60 °C.

Heating the N-heterocyclic alcohols in superacid does lead to formation of condensation products with benzene, but they are not

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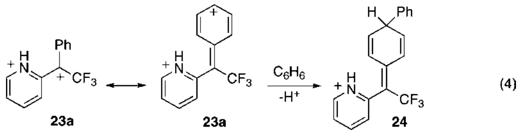
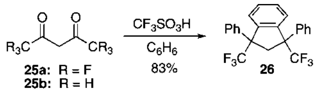
the products expected from the hydroxyalkylation reaction. Instead, regioselective functionalization at a remote site is observed (Table 1, entries 4−6). The reactions of alcohols **2**, **8**, and **9** in CF_3SO_3H and C_6H_6 at 60 °C lead to compounds **16**−**18**, respectively, as the only major products.[8] These conversions can be contrasted with the hydroxyalkylation product observed from 2-acetylpyridine, where nucleophilic attack by benzene occurs at the site of alcohol ionization (i.e., **22b**) and the *gem*-diphenyl group is produced (eq 2). This unusual regioselectivity is clearly the result of the inductive effects from the $-CF_3$ group. In compound **2**, ionization of the alcohol group leads to **23a**, and delocalization of the π electrons leads to an accumulation of positive charge at the 4-position of the phenyl group (eq 4):



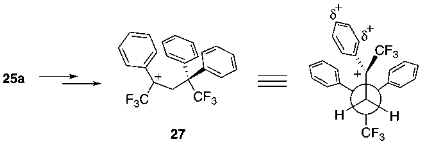
(4)

Nucleophilic attack by benzene gives **24**, and proton-transfer steps give the final product **16**. The present results suggest that $-CF_3$ substituents can increase the importance of charge−charge repulsive effects in superelectrophiles.

We have found evidence that in addition to effecting chemoselectivity and regioselectivity, $-CF_3$ substituents may also influence the stereoselectivity in superelectrophilic condensation reactions. Trifluoromethyl-substituted 1,3-diketones **10**−**12** were reacted with benzene in superacidic CF_3SO_3H, and the respective substituted indanes **19**−**21** were formed stereoselectively in excellent yields (Table 1, entries 7−9). For example, compound **25a** gives product **26** by reaction with three molecules of benzene (eq 5):



(5)



(6)

NMR spectroscopy and X-ray crystallography indicate the exclusive formation of the syn stereoisomer **26**. The influence of the $-CF_3$ groups is clearly significant, as 2,4-pentanedione (**25b**) in CF_3SO_3H does not react with benzene.[9] The preference for syn stereochemistry is also thought to be a consequence of the $-CF_3$ group(s). Condensation at one of the carbonyl centers produces a *gem*-diphenyl group, while the other carbonyl gives the intermediate carbocation (i.e., **27** in eq 6). With cyclization of the carbocation, the indane ring system is formed. The observed stereochemistry suggests that conformer **27** is strongly preferred and dictates the stereochemical outcome of the reaction (cyclization into either of the adjacent phenyl rings gives the observed syn stereochemistry). Cationic π-stacking is known for its ability to produce ordered structures and even influence stereochemistry.[10] Evidently, the $-CF_3$ group leads to significant charge delocalization into the phenyl group, and the resulting cationic π-stacking stabilizes conformer **27**.

In conclusion, the results indicate that $-CF_3$ groups (and presumably other perfluoroalkyl groups) can have profound effects on the chemistry of superelectrophiles. The strong electron-withdrawing properties lead to increased charge delocalization and greatly enhance the electrophilic reactivities of these ions. Despite the high electrophilic reactivities, these systems have shown interesting chemo-, regio-, and stereoselectivities in their conversions.

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Supporting Information Available: Experimental procedures, characterization data for new compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The exact role of dicationic superelectrophiles in the condensation of **25a** has not been determined, but by analogy to other diketones (see pp 140−142 of ref 3), the reaction may be initiated by protonation of both carbonyl groups. The final cyclization step occurs via the monocationic electrophile **27**. Substrates **11** and **12** react via distonic superelectrophiles.
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