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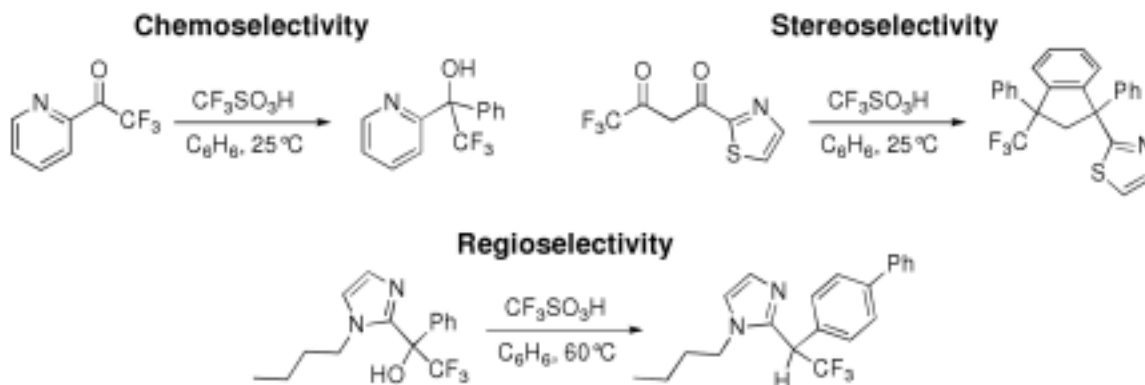
Superelectrophiles and the effects of trifluoromethyl substituents

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Abstract



Trifluoromethyl-substituted superelectrophiles were generated in superacid ($\text{CF}_3\text{SO}_3\text{H}$) and their chemistry was examined. The strong electron withdrawing properties of the trifluoromethyl group are found to enhance the electrophilic character at cationic sites in superelectrophiles. This leads to greater positive charge-delocalization in the superelectrophiles. These effects are manifested by the superelectrophiles showing unusual chemo-, regio-, and stereoselectivity in reactions.

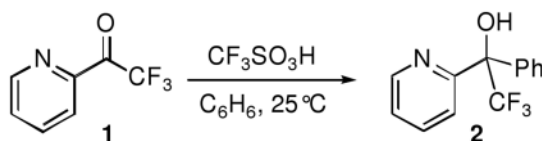
The trifluoromethyl ($-\text{CF}_3$) group is one of the most powerful electron withdrawing groups in structural organic chemistry.¹ This property is often manifested by increasing reactivities of adjacent acidic or electrophilic functional groups. The $-\text{CF}_3$ group primarily activates electrophilic 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, based on their high electrophilic reactivities.³ In this communication, we report the results of our studies on 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). In contrast to 2-acetylpyridine (**3**; eq 2), which gives the

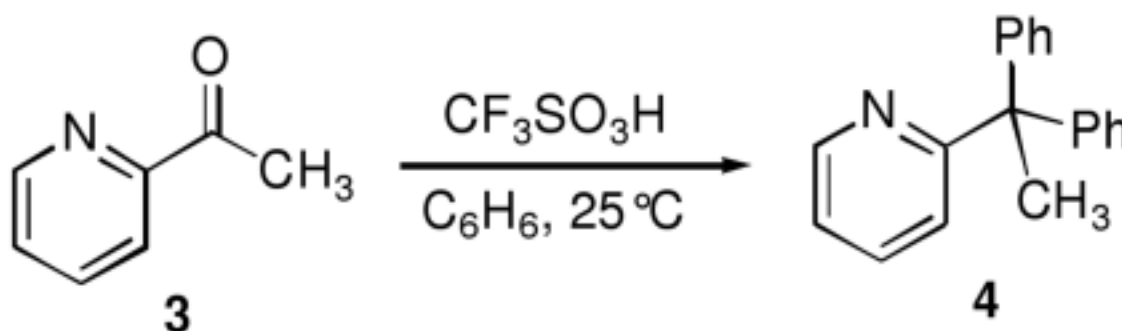
Correspondence to: Douglas A. Klumpp, dklumpp@niu.edu.

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>.

condensation product (**4**),⁴ compound **1** gives an intermediate alcohol product (**2**). Rather than enhancing the electrophilic



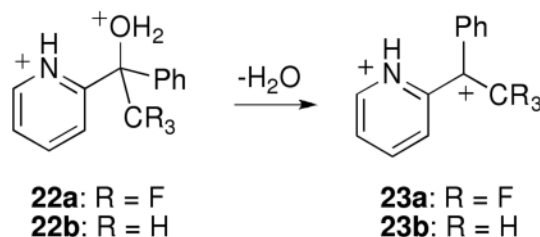
(1)



(2)

condensation with benzene, the $-\text{CF}_3$ group slows the final substitution step and the hydroxy group is relatively stable in the superacid. For this type of condensation (the hydroxyalkylation reaction⁵), selective formation of the intermediate alcohol is rare. Other *N*-heterocyclic systems (Table 1, entries 1-3) were studied and the heterocyclic alcohols (**13-15**) were obtained as the only major products in reactions at 25°C .

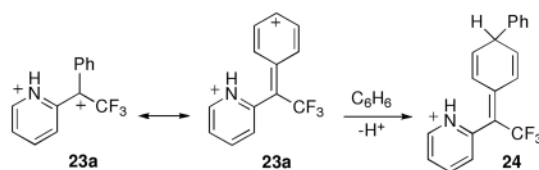
We propose that the $-\text{CF}_3$ derivatives show this chemoselectivity due to the increased reactivities of the intermediate carbenium-based superelectrophiles, leading to strengthening of carbon-oxygen bond. In the case of 2-(trifluoroacetyl)pyridine (**1**), reaction with benzene leads to formation of the pyridinium-oxonium dication **22a** (eq 3). Loss of water from **22a** is inhibited, because cleavage of the carbon-oxygen bond requires separation of a relatively strong



(3)

nucleophile (H_2O) from a very powerful electrophile (**23a**). This effect is similar to the well-known kinetic stabilities of uncharged, $-\text{CF}_3$ 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 $-\text{CF}_3$ group in **22a** is apparent, as the closely related system (from 2-acetylpyridine) **22b** cleaves rapidly at 25°C to the carbocationic superelectrophile (**23b**). Thus, the observed chemoselectivity is the result of a strengthening of the carbon-oxygen bond by the $-\text{CF}_3$ group in the pyridinium-oxonium dication.

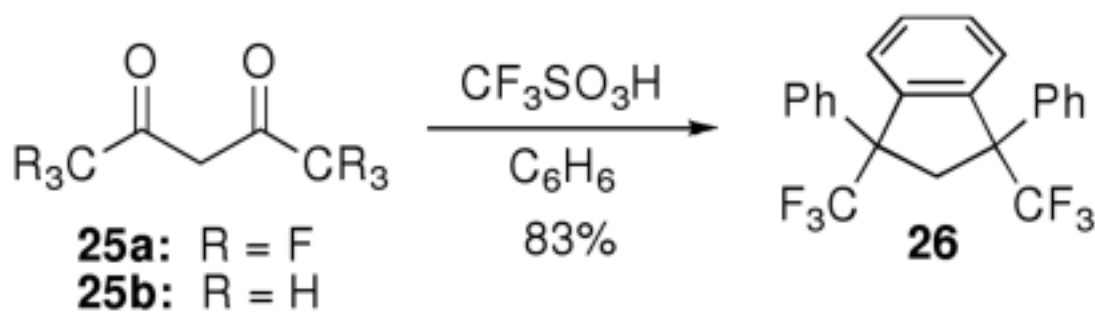
With heating in superacid, the *N*-heterocyclic alcohols do lead to formation of a condensation product with benzene, however it is not the expected product from the hydroxyalkylation reaction. Instead, regioselective functionalization at a remote site is observed (Table 1, entries 4-6). Reactions of alcohols **2**, **8-9** in $\text{CF}_3\text{SO}_3\text{H}$ 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 $-\text{CF}_3$ group. In compound **2**, ionization of the alcohol group leads to **23a** and delocalization of the π -electrons lead to positive charge accumulating in the 4-position of the phenyl group (eq 4).



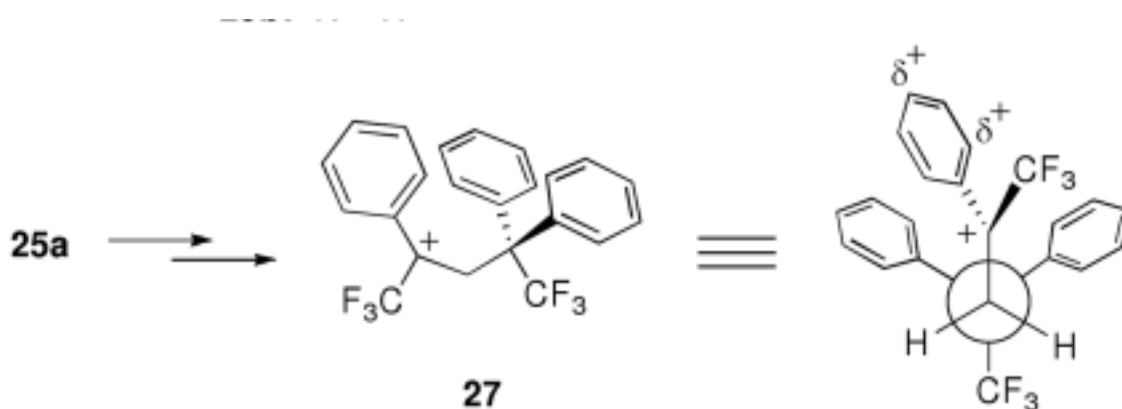
(4)

Nucleophilic attack by benzene gives **24** and proton transfer steps give the final product **16**. The present results suggest that $-\text{CF}_3$ substituents can increase the importance of charge-charge repulsive effects in superelectrophiles.

Besides effecting chemoselectivity and regioselectivity, we have found evidence that $-\text{CF}_3$ substituents may also influence the stereoselectivity in superelectrophilic condensation reactions. Trifluoromethyl-substituted 1,3-diketones (**10-12**) were reacted with benzene in superacidic $\text{CF}_3\text{SO}_3\text{H}$ and 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). NMR spectroscopy and



(5)



(6)

X-ray crystallography indicates exclusive formation of the *syn* stereoisomer (**26**). The influence of the $-\text{CF}_3$ groups is clearly significant, as 2,4-pentanedione (**25b**) in $\text{CF}_3\text{SO}_3\text{H}$ does not react with benzene.⁹ The preference for *syn* stereochemistry is also thought to be a consequence of the $-\text{CF}_3$ 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** eq 6). With cyclization of the carbocation, the indane ring system is formed. The observed stereochemistry suggests conformer **27** is strongly preferred and dictates the stereochemical outcome of the reaction (cyclization into either of the adjacent phenyl rings will give the observed *syn* stereochemistry). Cationic π -stacking is known for its ability to produce ordered structures and to even influence stereochemistry.¹⁰ Evidently, the $-\text{CF}_3$ 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 $-\text{CF}_3$ 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 they 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.

Supplementary Material

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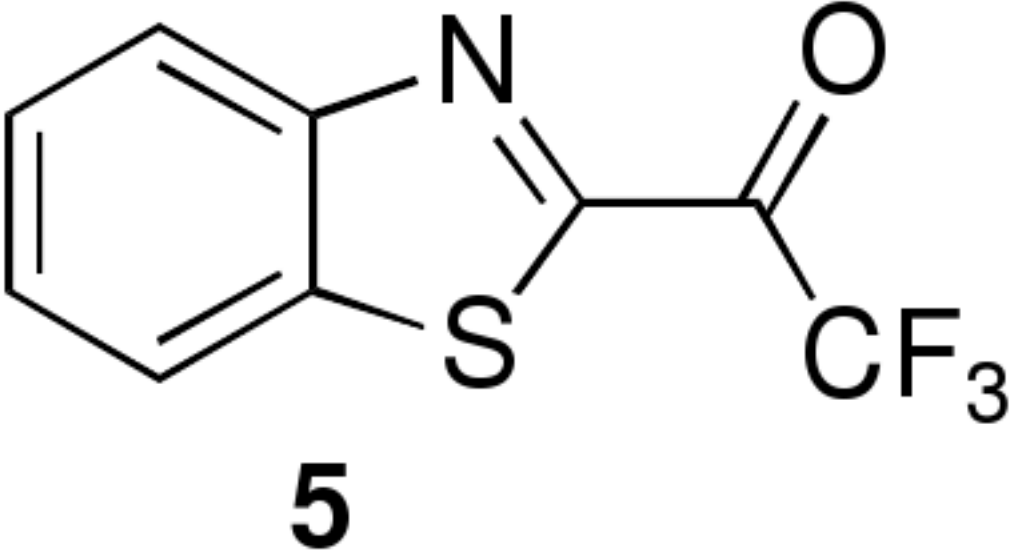
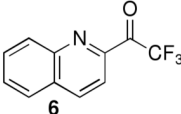
Acknowledgments

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References

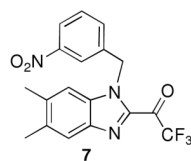
1. a Olah, GA.; Chambers, RD.; Prakash, GKS. *Synthetic Fluorine Chemistry*. Wiley & Sons; New York: 1992. b Schlosser M. *Angew Chem Int Ed* 1998;37:1496. c Olah, GA.; Prakash, GKS.; Molnar, A.; Sommer, J. *Superacid Chemistry*. 2nd. Wiley & Sons; New York: 2009.
2. Klumpp, DA.; Activation of Electrophilic Sites by Adjacent Cationic Groups. Recent Developments in Carbocation and Onium Ion Chemistry. In: Laali, K., editor. *ACS Symposium Series*. Vol. 395. American Chemical Society; Washington, DC: 2007. p. 144-159.
3. Olah, GA.; Klumpp, DA. *Superelectrophiles and Their Chemistry*. Wiley & Sons; New York: 2008.
4. Klumpp DA, Garza G, Sanchez GV, Lau S, DeLeon S. *J Org Chem* 2000;65:8997. [PubMed: 11149842]
5. Prakash GKS, Panja C, Shakhmin A, Shah E, Mathew T, Olah GA. *J Org Chem* 2009;74:8659. and reference cited therein. [PubMed: 19863094]
6. a Allen AD, Kanagasabapathy VM, Tidwell TT. *J Am Chem Soc* 1986;108:3470. b Allen AD, Fujio M, Mohammed N, Tidwell TT, Tsuji Y. *J Org Chem* 1997;62:246. [PubMed: 11671396] c Creary X. *Chem Rev* 1991;91:1625. d Begue JP, Benayoud F, Bonnet-Delpon D, Allen AD, Cox RA, Tidwell TT. *Gazz Chim Ital* 1995;125:399.
7. a Olah GA, Prakash GKS, Shih JG, Krishnamurthy VV, Mateescu GD, Liang G, Sipos G, Buss V, Gund TM, Schleyer PvR. *J Am Chem Soc* 1985;107:2764. b Prakash GKS, Krishnamurthy VV, Arvanaghi M, Olah GA. *J Org Chem* 1985;50:3985. c Olah GA, Comisarow MB. *J Am Chem Soc* 1966;88:3313.
8. For somewhat related examples of biphenyl group formation, see: a Ohwada T, Okabe K, Ohta T, Shudo K. *Tetrahedron* 1990;46:7539. b Shudo K, Ohta T, Ohwada T. *J Am Chem Soc* 1981;103:645. c Nakamura S, Sugimoto H, Ohwada T. *J Am Chem Soc* 2007;129:1724. [PubMed: 17249674]
9. The exact role of dicationic superelectrophiles in the condensation of **25a** has not been determined, however by analogy to other diketones (reference 3, pp 140-142), 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.
10. a Cakir SP, Stokes S, Sygula A, Mead KT. *J Org Chem* 2009;74:7529. [PubMed: 19725504] b Ma JC, Dougherty DA. *Chem Rev* 1997;97:1303. [PubMed: 11851453]

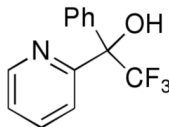
Table 1Products and yields for reactions of trifluoromethyl substrates with CF₃SO₃H and C₆H₆.

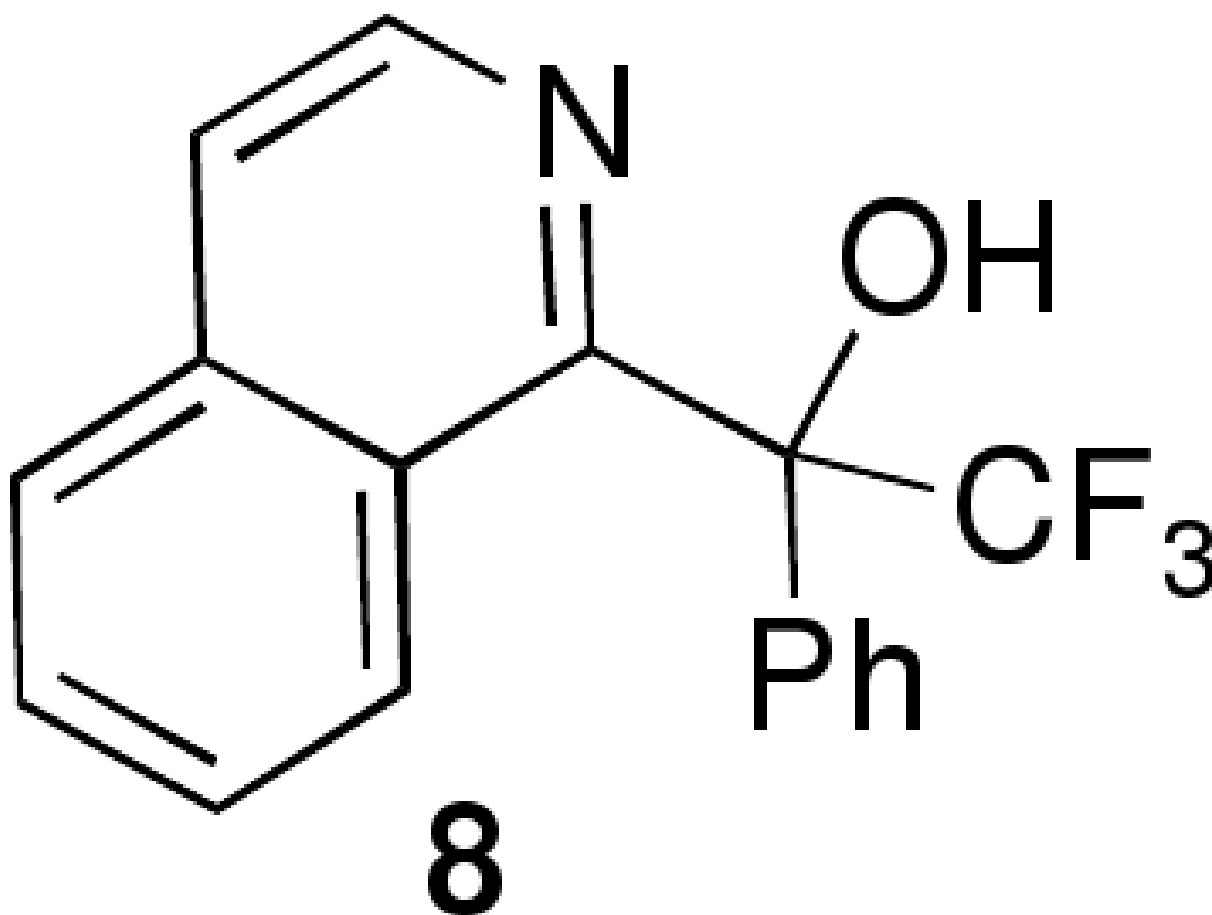
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2	 6

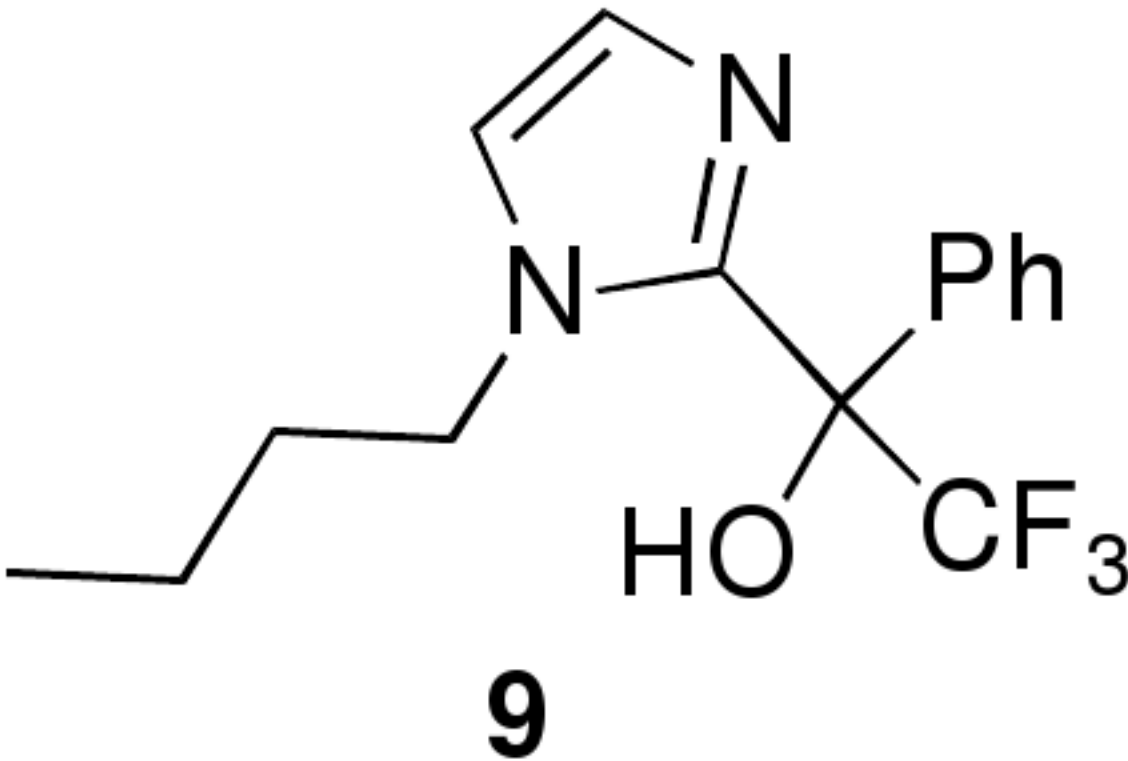
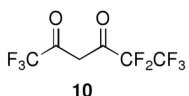
Entry	Substrate
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3



Entry	Substrate
4	 2

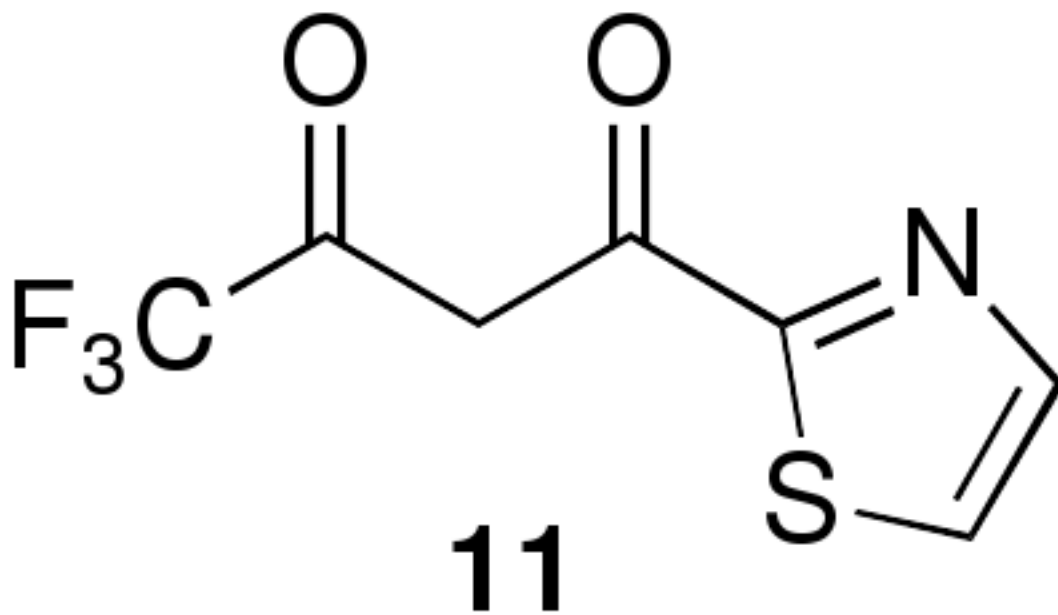
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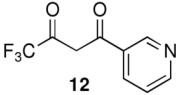
Entry	Substrate
6	 9
7	 10

Entry

Substrate

8



Entry	Substrate
9	 <chem>CC(=O)c1ccncc1C(=O)C(F)(F)F</chem> 12

^a Reaction done at 25°C;

^b reaction done at 60°C.