JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

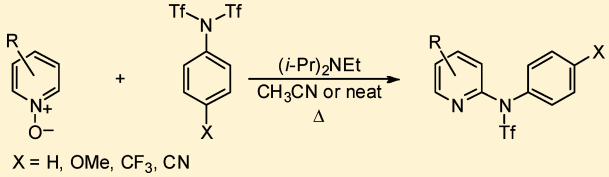
One-Step Conversion of Azine *N*-Oxides to α-*N*-Aryltriflamidoazines

John M. Keith*

Janssen Research and Development, LLC, 3210 Merryfield Row, San Diego, California 92121, United States

Supporting Information

ABSTRACT: Various pyridine, quinoline, isoquinoline, and pyrimidine *N*-oxides were converted to their corresponding α-*N*-aryltriflamidoheteroarenes in good yield by treatment with *N*-aryltriflimides, both neat and in solution, at temperatures ranging from rt to 100 °C.



Azine *N*-oxides have proven to be versatile synthetic intermediates for the drug discovery process. Methods allowing direct α-arylation[1,2] and substitution[3] as well as deoxygenative introduction of halide,[4] carbon,[5−7] oxygen,[8] sulfur,[9] and nitrogen[10−12] nucleophiles have all been developed. Our particular interest in *N*-oxides is with regard to deoxygenative substitutions reactions (Reissert−Henze approach)[13,14] with nitrogen nucleophiles. Recently, we have disclosed new or optimized methods for the introduction of azides,[15] imidazoles,[16] 1,2,3-triazoles, 1,2,4-triazoles, and electron-deficient pyrazoles[17] (Figure 1) utilizing such an approach. A key feature of the Reissert−Henze mechanism is that reactivity of the *N*-oxide is enhanced by the presence of suitably positioned electron-donating groups. This is in contrast to S_NAr and transition metal mediated couplings where the more electron-deficient ring-systems are expected to be more reactive. In this way, the Reisert−Henze approach is *mechanistically complementary* to S_NAr and transition-metal-mediated couplings and should be considered when the electronics of the system do not favor direct substitution or coupling.

More recently, we turned our attention to the possibility of introducing protected aniline functionality via a Reissert−Henze strategy. Methods exist for the introduction of unprotected anilines either through preactivation of the *N*-oxide (alkylation)[18] or the use of peptide coupling reagents[19] and for protected anilines using TsCl and PhNHTs.[20] We were interested in whether or not *N*-aryltriflimides, either preformed or prepared in situ, would be suitable reagents for the introduction of *N*-aryltriflamido functionality to the α-position of azines. We focused on triflimides because, in many instances, the same reagents can be used to affect the removal of triflamides as are used to remove other sulfonyl groups, but the reaction times tend to be much shorter when nucleophilic or reductive methods are utilized.[21]

We began our study using commercial *N*-phenyltriflimide and 4-phenylpyridine *N*-oxide as the substrate in the presence of an excess of diisopropylethylamine (DIPEA). The initial reactions were run both in solution (acetonitrile) and neat for comparison (Scheme1, Table 1). The neat reaction required a higher temperature (100 °C) simply to melt the solid components, but an excellent yield of product was obtained. The reaction conducted in acetonitrile took place at a lower temperature (50 °C), but the reaction time was significantly longer (8.5 h vs 3 h) and, in this particular example, the yield was a bit lower (74% vs 97%). With these promising results in hand, we expanded the scope of *N*-oxides subjected to our reaction conditions.

Simple electron neutral to slightly electron rich pyridine *N*-oxides were generally good substrates for this transformation (Table 1). Methyl groups in the 3-position neither hindered the reaction nor influenced the regioselectivity of nucleophilic attack (entries 3 and 4). Likewise, a 2-methyl (entry 5) was not noticeably detrimental to the reaction rate, although the reaction did slow somewhat with a 2-aryl ring (entry 8). Quinoline *N*-oxide (entry 6) and pyrimidine *N*-oxide (entry 7) both underwent this transformation, albeit under different conditions. Quinoline *N*-oxide reacted readily in heated acetonitrile solutions to give only one regioisomeric product (**7**), whereas pyrimidine *N*-oxide was unreactive in hot acetonitrile solutions. However, when heated neat in the presence of $PhN(Tf)_2$ and DIPEA, pyrimidine *N*-oxide gave a mixture of 2- and 4-substituted products (**8** and **9**, respectively), slightly favoring 2-substitution (1.35:1). The highly electron-deficient 3- and 4-cyanopyridine *N*-oxides were unreactive at moderate temperatures and yielded complex reaction mixtures at 130 °C (neat reaction).

Strongly electron-rich *N*-oxides are quite reactive in the presence of $PhNTf_2$. 4-Methoxypyridine *N*-oxide underwent reaction readily at rt, but not cleanly. It appears 4-methoxypyridine *N*-oxide reacts to a significant degree through a cationic mechanism (Scheme 2). There was evidence of solvent trapping, formation of the 2-triflate, dimerization of the substrate, and many other unidentifiable species. Running the reaction in a solvent with a lower dielectric constant (0.20 M in toluene, 50 °C, 2 h) yielded somewhat better, though still modest, results (42%). It may be that lower polarity solvents will be generally required for reactions involving highly electron-rich *N*-oxides.

Received: September 22, 2012
Published: December 7, 2012

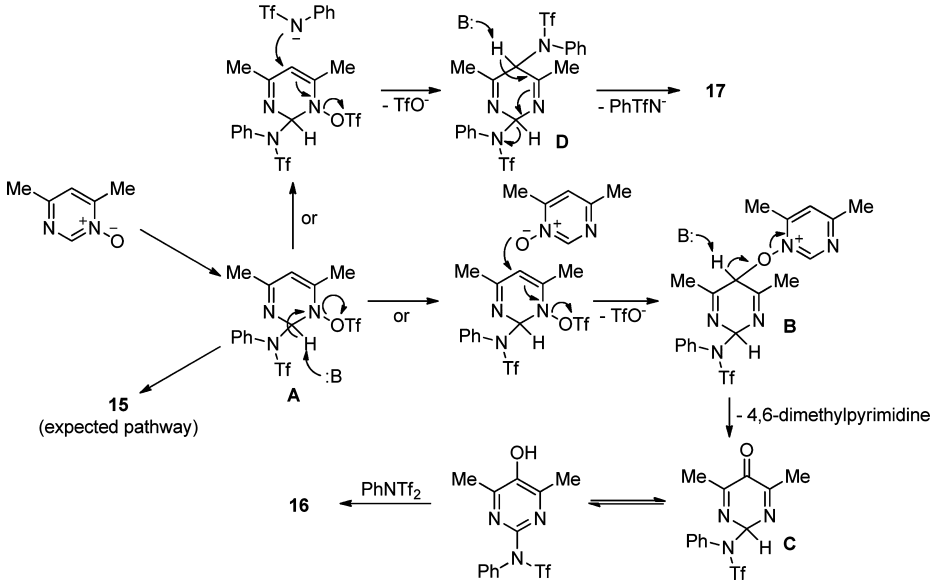
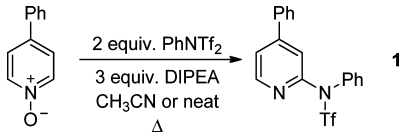


Figure 1. Possible mechanisms for generation of side products.

Scheme 1. Neat and Solution Reaction Conditions



Two other substrates, isoquinoline *N*-oxide and 4,6-dimethylpyrimidine *N*-oxide gave unusual products as well (Scheme 3). Isoquinoline *N*-oxide, in addition to the two expected regioisomeric products (**12** and **13**), gave a product that appeared to have undergone the desired substitution plus incorporation of a triflate moiety (**14**). This unusual substitution pattern was mirrored when 4,6-dimethylpyrimidine *N*-oxide was the substrate, although in this case, we also obtained the 5-substituted product (**17**).

Our suspicion is that the initial two steps of the reaction pathway (activation of the *N*-oxide and nucleophilic attack of the α-position) take place as expected, but from there, competing pathways intervene (Figure 1). Typically, the tetrahedral intermediate **A** would be deprotonated to eliminate triflate and afford the desired product, in this case **15**. However, one can imagine that in competition with deprotonation, a nucleophile, either *N*-oxide or $PhTfN^-$, could attack the 5-position, thereby eliminating triflate and giving an intermediate with two tetrahedral centers (intermediates **B** and **D**). What happens next depends on where deprotonation takes place and which nucleophile attacked the ring. If deprotonation takes place at the 2-position, then the desired product **15** should form. However, if deprotonation occurs at the 5-position, then intermediate **B** would be expected to eliminate 4,6-dimethylpyrimidine to give intermediate **C**. Intermediate **C** would tautomerize to the phenol, which would be rapidly converted to **16** under the reaction conditions. In contrast to the pathway proposed to be followed by intermediate **B**, deprotonation of intermediate **D** in the 5-position will likely lead to elimination of the 2-substituent to give **17**.

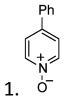
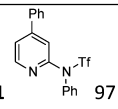
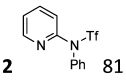
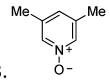
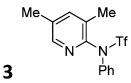
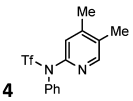
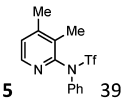
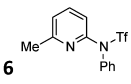
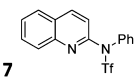
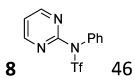
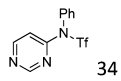
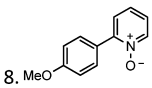
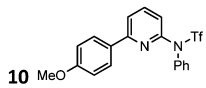
Having verified that $PhNTf_2$ is a competent reagent for converting azine *N*-oxides to α-phenyltriflamidoazines, we wanted to determine whether substituted variants of $PhNTf_2$ could be prepared and used in situ. Three substituted anilines were treated with 2 equiv of Tf_2O at 0 °C in the presence of DIPEA. After 2.5 h, the substrate was added and the mixture heated at 70 °C for 19 h (Scheme 4). Interestingly, the electron-rich aniline gave the highest yield of final product (**18**), whereas the yields of the other two decreased in step with their electron deficiency. HPLC and TLC analysis suggest the triflimides of the two electron-deficient anilines are not forming efficiently, and we thought this may be a limitation of preparing triflimides of electron-deficient anilines in situ.

The notion that the triflimide reagents were not being formed efficiently in situ was at least partially supported by the yields obtained in the preparation and isolation of **21** and **22** (Scheme 5). But the yields of **21** and **22** *did not* explain the yields of **19** and **20**. When 4-phenylpyridine *N*-oxide was treated with **21** or **22** in CH_3CN at rt or 70 °C, the only product obtained in either case was the triflate **23**. It would appear that in CH_3CN, formation of the triflate is faster when there is not a large excess of $ArTfN^-$ present as would be the case if the reaction to form the reagents in situ did not go to completion. Interestingly, the product distribution could be changed to favor the pyridyltriflamide simply by utilizing a low dielectric solvent. Yields of 65% and 59% were obtained for **19** and **20**, respectively, when toluene[22] was used as the solvent at rt, though there was still some **23** generated under these conditions. Running the reactions neat (with heating) did not afford any advantage over the use of toluene.

In conclusion, we have developed a simple procedure for the introduction of *N*-aryltriflimides to the α-position of azine nitrogens starting from the corresponding azine *N*-oxides. The method is complementary to transition metal mediated and S_NAr reactions because it favors electron-neutral to moderately electron-rich *N*-oxide substrates. A highly electron-rich substrate appeared to yield products suggestive of cationic mechanisms in acetonitrile but gave a moderately improved yield in the less polar solvent toluene. Substituted *N*-phenyltriflimides can be prepared and used in situ, but when the substituent is electron-withdrawing, preformed and isolated triflimide reagents appear to be more efficient, especially in

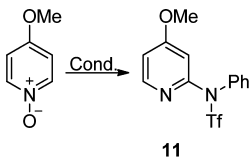
dx.doi.org/10.1021/jo302014c | J. Org. Chem. 2012, 77, 11313−11318

Table 1. Substrate Scope[a]

Substrate (entry)	Temp. °C	Reaction time and conditions	Product(s) & yield (%)[a]
 1.	100	3 h, neat	 **1** 97
	50	8.5 h, 0.1 M in CH_3CN	**1**, 74 (72)[b]
 2.	100	1.5 h, neat	 **2** 81
	50	10 h, 0.1 M in CH_3CN	**2**, 66
 3.	50	4.25 h, 0.1 M in CH_3CN	 **3** 89
 4.	50	40 min, 0.1 M in CH_3CN	 **4** 36  **5** 39
 5.	100	1 h, neat	 **6** 72
	50	10 h, 0.1 M in CH_3CN	**6**, 80
 6.	70	21.5 h, 0.1 M in CH_3CN	 **7** 87
 7.	90	24 h, neat	 **8** 46  **9** 34
	70	0.1 M in CH_3CN	N.R.
 8. MeO	70	24 h, neat	 **10** MeO 83

[a]Reaction conditions: (a) isolated; (b) 58.6 mmol (10 g) scale.

Scheme 2. Reaction of 4-Methoxypyridine *N*-Oxide with $PhN(Tf)_2$



11

Results:
A 6% **11** + complex mixture of side-products
B 42% **11**

Conditions:
A: 2 equiv. $PhNTF_2$, 0.1 M CH_3CN, 1.5 h, rt
B: 2 equiv. $PhNTF_2$, 0.2 M $PhCH_3$, 2 h, 50 °C

nonpolar solvents. Strongly electron-poor *N*-oxides are not productively reactive under the described reaction conditions.

EXPERIMENTAL SECTION

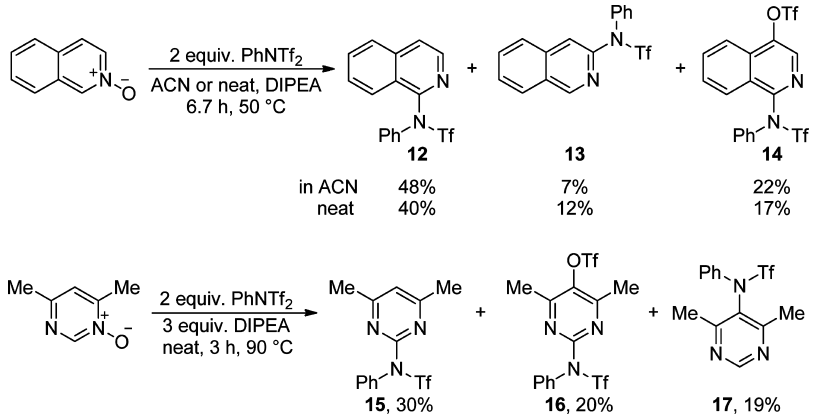
General Method for Preparing α-Phenyltriflamidoazines in Solution. To a round-bottomed flask were added a stirbar, azine *N*-oxide substrate (limiting reagent), 2 equiv of $PhNTf_2$, dry acetonitrile (0.1 M in substrate), and DIPEA (3.0 equiv). The flask was purged with nitrogen and the mixture warmed until reaction progression was evident by TLC or HPLC. Once the *N*-oxide was consumed, the mixture was diluted with Et_2O and washed with 1 N NaOH followed by brine. The ethereal solution was dried over $MgSO_4$, filtered, and evaporated to dryness to give the crude product. Chromatographic purification on silica gel was typically performed using a low polarity gradient of EtOAc/hexanes. For those samples not analytically pure after silica gel chromatography, an additional HPLC purification step was performed using a preparative (250 mm × 50 mm) C_{18} column, eluting with 25−100% acetonitrile/water with 0.05% trifluoroacetic acid at 80 mL/min. High-resolution mass spectra were obtained using a quadrupole detector.

General Method for Preparing α-Phenyltriflamidoazines (Neat Reaction). To a microwave vial were added a small stirbar, azine *N*-oxide substrate (limiting reagent), 2 equiv of $PhNTf_2$, and 3.0 equiv of DIPEA. The vial was purged with nitrogen and then heated in an oil bath until the solids melted (the mixture never became homogeneous; DIPEA is immiscible with the melted solids). The reaction progress was monitored by TLC or HPLC and the temperature adjusted to optimize reaction rate. Once the *N*-oxide was consumed, the workup and purification procedures described above were used.

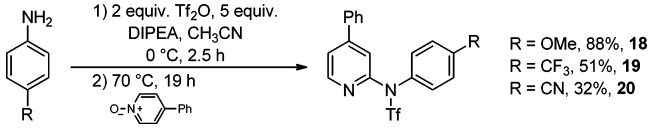
1,1,1-Trifluoro-*N*-phenyl-*N*-(4-phenylpyridin-2-yl)methanesulfonamide (1): neat reaction 228 mg, 97%; solution reaction 169 mg, 74%; 10 g scale solution reaction 16.005 g, 72%; white solid; mp =

dx.doi.org/10.1021/jo302014c | J. Org. Chem. 2012, 77, 11313−11318

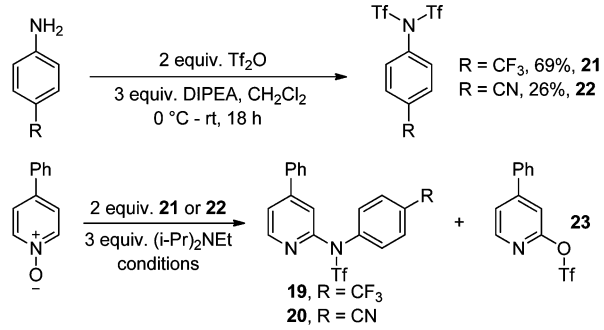
Scheme 3. Products Derived from Isoquinoline *N*-Oxide and 4,6-Dimethylpyrimidine *N*-Oxide



Scheme 4. In Situ Generation and Use of *N*-Aryltriflimides



Scheme 5. Evaluation of 4-Cyanophenyl and 4-Trifluoromethyl Triflimides



triflimide	reaction cond.	% yield (sulfonamide)	% yield **23**
21	0.1 M CH_3CN, rt, 30 min	0	35
22	0.1 M CH_3CN, rt, 30 min	0	92
21	0.1 M CH_3CN, 70 °C, 24 h	0	40
22	0.1 M CH_3CN, 70 °C, 24 h	0	36
21	0.1 M $PhCH_3$, rt, 2 h	65 (**19**)	25
22	0.1 M $PhCH_3$, rt, 2 h	59 (**20**)	33
21	neat, 70 °C, 15 min	44 (**19**)	40
22	neat, 60 °C, 15 min	27 (**20**)	66

120−121 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.59 (d, J = 5.4 Hz, 1H), 7.86 (d, J = 1.2 Hz, 1H), 7.78−7.75 (m, 4H), 7.74−7.73 (dd, J = 1.8, 5.4 Hz, 1H), 7.53−7.46 (m, 6H); ^{13}C NMR (151 MHz, acetone-d_6) δ 155.1, 153.4, 151.6, 140.2, 138.5, 131.6, 131.5, 131.4, 131.1, 128.9, 125.6−119.1 (q, J = 321.9 Hz), 123.6, 121.6; MS (ESI$^+$), found 379.1 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{18}H_{14}F_3N_2O_2S$ 379.0728 (M + H)$^+$, found 379.0735.

1,1,1-Trifluoro-*N*-phenyl-*N*-(pyridin-2-yl)methanesulfonamide (2): neat reaction 298 mg, 81%; solution reaction 210 mg, 66%; white solid; mp = 114−116 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.54−8.53 (m, 1H), 7.94−7.91 (dt, J = 1.8, 8.4 Hz, 1H), 7.69−7.68 (m, 2H), 7.53−7.46 (m, 4H), 7.44−7.41 (ddd, J = 1.2, 4.8, 7.2 Hz, 1H); ^{13}C NMR (151 MHz, acetone-d_6) δ 154.3, 151.0, 141.3, 140.1, 131.5, 131.4, 125.8, 125.5−119.1 (q, J = 321.8 Hz), 123.8; MS (ESI$^+$), found 303.1 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{12}H_{10}F_3N_2O_2S$ 303.0415 (M + H)$^+$, found 303.0421.

***N*-(3,5-Dimethylpyridin-2-yl)-1,1,1-trifluoro-*N*-phenylmethanesulfonamide (3):** solution reaction 502 mg, 89%; colorless oil; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.301−8.297 (m, 1H), 7.79−7.77 (m, 2H), 7.562−7.558 (m, 1H), 7.47−7.44 (m, 2H), 7.41−7.38 (m, 1H), 2.38 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (151 MHz, acetone-d_6) δ 149.4, 148.3, 142.3, 138.9, 136.4, 133.0, 130.2, 129.9, 129.4, 121.6 (q, J = 322.8 Hz), 17.8, 17.7; MS (ESI$^+$), found 331.2 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{14}H_{13}F_3N_2O_2S$ 331.0723 (M + H)$^+$, found 331.0719.

***N*-(4,5-Dimethylpyridin-2-yl)-1,1,1-trifluoro-*N*-phenylmethanesulfonamide (4):** 199 mg, 36%; white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (br s, 1H), 7.57−7.55 (m, 2H), 7.40−7.34 (m, 3H), 7.15 (s, 1H), 2.26 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.5, 149.5, 149.3, 138.6, 133.2, 129.7, 129.39, 129.37, 123.0, 120.6 (q, J = 322.3 Hz), 19.6, 16.2; MS (ESI$^+$), found 331.2 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{14}H_{13}F_3N_2O_2S$ 331.0723 (M + H)$^+$, found 331.0723.

***N*-(3,4-Dimethylpyridin-2-yl)-1,1,1-trifluoro-*N*-phenylmethanesulfonamide (5):** 216 mg, 39%; white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.28 (d, J = 4.8 Hz, 1H), 7.71−7.69 (m, 2H), 7.37−34 (m, 2H), 7.33−7.29 (m, 1H), 7.12 (d, J = 4.8 Hz, 1H), 2.33 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 150.8, 150.0, 146.4, 138.3, 132.1, 129.4, 128.8, 128.4, 126.5, 120.7 (q, J = 323.5 Hz), 20.2, 14.3; MS (ESI$^+$), found 331.2 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{14}H_{13}F_3N_2O_2S$ 331.0723 (M + H)$^+$, found 331.0721.

1,1,1-Trifluoro-*N*-(6-methylpyridin-2-yl)-*N*-phenylmethanesulfonamide (6): neat reaction 201 mg, 72%; solution reaction 251 mg, 80%; white solid; mp = 91−92 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.75 (t, J = 7.8 Hz, 1H), 7.66−7.65 (m, 2H), 7.51−7.45 (m, 3H), 7.27 (d, J = 7.2 H, 1H), 7.22 (d, J = 7.8 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (151 MHz, acetone-d_6) δ 160.5, 153.7, 141.3, 140.3, 131.4, 131.3, 125.7−119.2 (q, J = 322.0 Hz), 125.0, 120.3, 25.0; MS (ESI$^+$), found 317.3 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{13}H_{11}F_3N_2O_2S$ 317.0566 (M + H)$^+$, found 317.0570.

1,1,1-Trifluoro-*N*-phenyl-*N*-(quinolin-2-yl)methanesulfonamide (7): 192 mg, 87%; white solid; mp = 57−59 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.39 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.83−7.80 (m, 1H), 7.71 (d, J = 7.8 Hz, 2H), 7.64−7.62 (m, 1H), 7.55−7.48 (m, 3H), 7.37 (d, J = 9.0 Hz, 1H); ^{13}C NMR (151 MHz, acetone-d_6) δ 152.5, 147.5, 140.7, 138.9, 131.7, 130.74, 130.66, 130.62, 129.6, 128.8, 128.4, 128.1, 121.6 (q, J = 322.3 Hz), 119.3; MS (ESI$^+$), found 353.2 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{16}H_{11}F_3N_2O_2S$ 353.0566 (M + H)$^+$, found 353.0563.

1,1,1-Trifluoro-*N*-phenyl-*N*-(pyrimidin-2-yl)methanesulfonamide (8): 147 mg, 46%; white solid; mp = 114−115 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.75 (d, J = 4.8 Hz, 2H), 7.55−7.48 (m, 5H), 7.44 (t, J = 4.8 Hz, 1H); ^{13}C NMR (151 MHz, acetone-d_6) δ 159.95, 159.92, 138.2, 131.2, 130.5, 130.4, 121.4 (q, J = 322.3 Hz), 120.4; MS (ESI$^+$), found 304.1 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{11}H_8F_3N_3O_2S$ 304.0362 (M + H)$^+$, found 304.0358.

dx.doi.org/10.1021/jo302014c | *J. Org. Chem.* 2012, 77, 11313−11318

1,1,1-Trifluoro-*N*-phenyl-*N*-(pyrimidin-4-yl)methanesulfonamide (9): 109 mg, 34%; white solid; mp = 69−71 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.04 (s, 1H), 8.81 (br s, 1H), 7.62−7.59 (m, 5H), 7.14 (d, J = 5.4 Hz, 1H); ^{13}C NMR (151 MHz, acetone-d_6) δ 160.8, 159.9, 158.8, 137.1, 131.33, 131.25, 131.0, 121.2 (q, J = 322 Hz), 114.6; MS (ESI$^+$), found 304.1 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{11}H_8F_3N_3O_2S$ 304.0362 (M + H)$^+$, found 304.0361.

1,1,1-Trifluoro-*N*-(6-(4-methoxyphenyl)pyridin-2-yl)-*N*-phenylmethanesulfonamide (10): 206 mg, 83%; white solid; mp = 82−83 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.09 (dd, J = 2.1, 6.7 Hz, 2H), 7.89 (t, J = 7.8 Hz, 1H), 7.84 (dd, J = 0.9, 7.8 Hz, 1H), 7.74−7.72 (m, 2H), 7.54−7.51 (m, 2H), 7.49−7.47 (m, 1H), 7.26 (dd, J = 0.8, 7.8 Hz, 1H), 7.07 (dd, J = 2.1, 6.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (151 MHz, acetone-d_6) δ 162.3, 157.5, 153.2, 141.1, 139.3, 131.2, 130.65, 130.60, 130.5, 129.3, 121.6 (q, J = 322.2 Hz), 119.8, 119.6, 115.2, 55.8; MS (ESI$^+$), found 409.5 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{19}H_{15}F_3N_2O_3S$ 409.0828 (M + H)$^+$, found 409.0824.

1,1,1-Trifluoro-*N*-(4-methoxypyridin-2-yl)-*N*-phenylmethanesulfonamide (11): in CH_3CN 16 mg, 6%; in $PhCH_3$ 119 mg, 42%; colorless film; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.03 (d, J = 7.2 Hz, 1H), 7.04 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 4.2, 7.2 Hz, 1H), 4.02 (s, 3H); ^{13}C NMR (151 MHz, acetone-d_6) δ 172.4, 158.7, 138.9, 122.0 (q, J = 321.0 Hz), 107.0, 99.7, 57.3; MS (ESI$^+$), found 333.1 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{13}H_{11}F_3N_2O_3S$ 333.0515 (M + H)$^+$, found 333.0512.

1,1,1-Trifluoro-*N*-(isoquinolin-1-yl)-*N*-phenylmethanesulfonamide (12): neat reaction 101 mg, 40%; solution reaction 243 mg, 48%; white solid; mp = 118−119 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.56 (d, J = 6.0 Hz, 1H), 8.51−8.50 (m, 1H), 8.05−8.03 (m, 1H), 7.97 (d, J = 5.4 Hz, 1H), 7.94−7.93 (m, 2H), 7.83−7.79 (m, 2H), 7.48−7.46 (m, 2H), 7.41−7.40 (m, 1H); ^{13}C NMR (151 MHz, acetone-d_6) δ 152.0, 143.2, 140.8, 140.1, 133.3, 131.4, 131.2, 131.1, 130.3, 129.2, 127.7, 126.4, 125.9−119.4 (q, J = 322.0 Hz), 125.2; MS (ESI$^+$), found 353.3 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{16}H_{11}F_3N_2O_2S$ 353.0566 (M + H)$^+$, found 353.0568.

1,1,1-Trifluoro-*N*-(isoquinolin-3-yl)-*N*-phenylmethanesulfonamide (13): neat reaction 31 mg, 12%; solution reaction 34 mg, 7%; white solid; mp = 126−127 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.42 (s, 1H), 9.05 (s, 1H), 8.44 (d, J = 8.4 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 8.02−8.00 (m, 1H), 7.91 (d, J = 7.8 Hz, 2H), 7.82−7.79 (m, 1H), 7.52−7.48 (m, 2H), 7.44−7.41 (m, 1H); ^{13}C NMR (151 MHz, acetone-d_6) δ 156.5, 146.2, 141.3, 135.4, 134.3, 133.5, 131.74. 131.70, 131.1, 130.4, 130.3, 130.1, 125.6−119.2 (q, J = 321.9 Hz), 123.8; MS (ESI$^+$), found 353.3 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{16}H_{11}F_3N_2O_2S$ 353.0566 (M + H)$^+$, found 353.0569.

1-(1,1,1-Trifluoro-*N*-phenylmethylsulfonamido)isoquinolin-4-yl trifluoromethanesulfonate (14): neat reaction 62 mg, 17%; solution reaction 156 mg, 22%; white solid; mp =116−117 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.78 (s, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.18−8.15 (m, 1H), 8.06−8.04 (m, 1), 7.93−7.92 (d, J = 8.4 Hz, 2H), 7.52−7.49 (m, 2H), 7.47−7.44 (m, 1H); ^{13}C NMR (151 MHz, acetone-d_6) δ 151.6, 145.0, 139.6, 135.7, 135.6, 133.6, 133.0, 131.64, 131.58, 130.4, 129.0, 127.5, 122.5 (q, J = 323.0 Hz), 122.5, 120.2 (q, J = 318.7 Hz,); ^{19}F NMR (376 MHz, acetone-d_6) δ −71.4, −73.9; MS (ESI$^+$), found 501.3 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{17}H_{10}F_6N_2O_5S_2$ 501.0008 (M + H)$^+$, found 500.9990.

N-(4,6-Dimethylpyrimidin-2-yl)-1,1,1-trifluoro-*N*-phenylmethanesulfonamide (15): 162 mg, 30%; tan solid, mp = 88−89 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.52−7.47 (m, 5H), 7.15 (s, 1H), 2.39 (s, 6H); ^{13}C NMR (151 MHz, acetone-d_6) δ 170.1, 159.3, 138.4, 131.1, 130.3, 121.5, (q, J = 322.6 Hz), 119.0, 23.6; MS (ESI$^+$), found 332.2 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{13}H_{12}F_3N_3O_2S$ 332.0675 (M + H)$^+$, found 332.0668.

4,6-Dimethyl-2-(1,1,1-trifluoro-*N*-phenylmethylsulfonamido)pyrimidin-5-yl trifluoromethanesulfonate (16): 158 mg, 20%; white solid; mp = 116−116.5 °C (needles obtained from slow evaporation of acetone); ^{1}H NMR (600 MHz, acetone-d_6) δ 7.56−7.53 (m, 3H), 7.50−7.48 (m, 2H), 2.53 (s, 6H); ^{13}C NMR (151 MHz, acetone-d_6) δ 163.6, 156.7, 141.2, 137.7, 131.1, 130.7, 130.4, 121.3 (q, J = 292.4 Hz), 119.2 (q, J = 287.2 Hz), 20.0; HRMS (ESI$^+$) m/e calcd for $C_{14}H_{11}F_6N_3O_5S_2$ 480.0117 (M + H)$^+$, found 480.0101.

***N*-(4,6-Dimethylpyrimidin-5-yl)-1,1,1-trifluoro-*N*-phenylmethanesulfonamide (17):** 163 mg, 19%; pale yellow solid, mp = 76.5−78 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.0 (s, 1H), 7.53−7.50 (m, 2H), 7.46−7.44 (m, 2H), 7.42−7.39 (m, 1H), 2.59 (s, 6H); ^{13}C NMR (151 MHz, acetone-d_6) δ 168.4, 158.1, 139.6, 131.0, 128.8, 124.8, 122.9 (q, J = 321.4 Hz), 22.2; MS (ESI$^+$), found 332.2 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{13}H_{12}F_3N_3O_2S$ 332.0675 (M + H)$^+$, found 332.0679.

1,1,1-Trifluoro-*N*-(4-methoxyphenyl)-*N*-(4-phenylpyridin-2-yl)methanesulfonamide (18): 451 mg, 88%; viscous oil; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.55 (d, J = 5.4 Hz, 1H), 7.81 (d, J = 0.6 Hz, 1H), 7.73−7.70 (m, 4H), 7.63 (dd, J = 1.2, 4.8 Hz, 1H), 7.49−7.44 (m, 3H), 7.04−7.01 (m, 2H), 3.78 (s, 3H); ^{13}C NMR (151 MHz, acetone-d_6) δ 161.4, 154.5, 152.4, 150.5, 137.6, 132.0, 131.6, 130.6, 130.1, 127.9, 122.3, 121.5 (q, J = 322 Hz), 120.2, 115.6, 55.9; MS (ESI$^+$), found 409.2 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{19}H_{15}F_3N_2O_3S$ 409.0828 (M + H)$^+$, found 409.0815.

1,1,1-Trifluoro-*N*-(4-phenylpyridin-2-yl)-*N*-(4-(trifluoromethyl)phenyl)methanesulfonamide (19): 337 mg, 51%; waxy solid, mp = 83−85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.61 (dd, J = 0.6, 5.4 Hz, 1H), 7.73−7.69 (m, 5H), 7.64−7.62 (m, 3H), 7.55−7.50 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 153.7, 151.7, 149.3, 141.1, 136.4, 131.7 (q, J = 33.0 Hz), 130.6, 129.71, 129.66, 127.4, 127.1 (q, J = 3.6 Hz), 123.6 (q, J = 270.9 Hz), 122.7, 120.9, 120.4 (q, J = 321.9 Hz); MS (ESI$^+$), found 447.1 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{19}H_{12}F_6N_2O_2S$ 447.0596 (M + H)$^+$, found 447.0583.

***N*-(4-Cyanophenyl)-1,1,1-trifluoro-*N*-(4-phenylpyridin-2-yl)-methanesulfonamide (20):** 204 mg, 32%; tan solid; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.61 (dd, J = 0.6, 5.4 Hz, 1H), 7.97−7.93 (m, 5H), 7.78−7.75 (m, 3H), 7.54−7.48 (m, 3H); ^{13}C NMR (151 MHz, acetone-d_6) δ 153.4, 152.9, 151.0, 143.1, 137.5, 134.6, 131.2, 130.9, 130.3, 128.1, 123.2, 121.4 (q, J = 321.8 Hz), 121.2, 118.2, 114.2; MS (ESI$^+$), found 404.1 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{19}H_{12}F_3N_3O_2S$ 404.0675 (M + H)$^+$, found 404.0666.

1,1,1-Trifluoro-*N*-(4-(trifluoromethyl)phenyl)-*N*-((trifluoromethyl)sulfonyl)methanesulfonamide (21). To a 250 mL round-bottomed flask were added a stir bar, 2.734 g (17.0 mmol) of 4-trifluoromethylaniline, 70 mL of dry DCM, and 12.0 mL (69.6 mmol) of diisopropylethylamine. The mixture was then cooled to 0 °C and slowly treated with 10.0 g (35.4 mmol) of Tf_2O over the course of 5 min. The resultant mixture darkened considerably. The mixture was stirred for 19 h with gradual warming to rt after which time the solvent was removed in vacuo and the residue subjected to silica gel chromatography (eluting with 0−10% EtOAc/hexanes) to give the desired product as a crystalline white solid (4.979 g, 69%): mp = 95−96 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82−7.78 (m, 1H), 7.58−7.54 (d, J = 8.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.08, 134.3 (q, J = 33.2 Hz), 131.78, 127.3 (q, J = 3.0 Hz), 123.0 (q, J = 271.8 Hz), 119.5 (q, J = 324.7 Hz); MS (ESI$^+$), found 423.9 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_9H_3F_9NO_4S_2$ 423.9365 (M − H)$^-$, found 423.9365.

***N*-(4-Cyanophenyl)-1,1,1-trifluoro-*N*-((trifluoromethyl)-sulfonyl)methanesulfonamide (22).** Compound **22** was prepared under conditions identical to those used to prepare compound **21** and was isolated as a crystalline white solid (1.686 g, 26%): mp = 70.5−71.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86−7.81 (m, 2H), 7.58−7.53 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 135.6, 133.8, 132.1, 119.4 (q, J = 324.7 Hz), 116.9, 116.6. MS (ESI$^+$), found 382.9 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_9H_5F_6N_2O_4S_2$ 382.9595 (M + H)$^+$, found 382.9580.

4-Phenylpyridin-2-yl trifluoromethanesulfonate (23): pale yellow semisolid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.46−8.41 (dd, J = 5.2, 0.6 Hz, 1H), 7.67−7.62 (m, 2H), 7.61−7.58 (dd, J = 5.1, 1.5 Hz, 1H), 7.56−7.48 (m, 3H), 7.38−7.35 (dd, J = 1.5, 0.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.9, 154.3, 149.0, 136.4, 130.3, 129.6, 127.3, 122.5, 118.8 (q, J = 321.6 Hz), 112.9; MS (ESI$^+$), found 304.0 (M + H)$^+$; HRMS (ESI$^+$) m/e calcd for $C_{12}H_9F_3NO_3S$ 304.0255 (M + H)$^+$, found 304.0249.

dx.doi.org/10.1021/jo302014c | J. Org. Chem. 2012, 77, 11313−11318

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and HPLC chromatograms for all described compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jkeith@its.jnj.com

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) Campeau, L.-C.; Stuart, D. R.; Leclerc, J.-P.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.-Y.; Lasserre, S.; Guimond, N.; Lecavallier, M.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 3291−3306.
(2) Mai, W.; Yuan, J.; Li, Z.; Sun, G.; Qu, L. *Synlett* **2012**, 145−149.
(3) Andersson, H.; Sainte-Luce Banchelin, T.; Das, S.; Olsson, R.; Almqvist, F. *Chem. Commun.* **2010**, *46*, 3384−3386.
(4) Jung, J.-C.; Jung, Y.-J.; Park, O.-S. *Synth. Commun.* **2001**, *31*, 2507−2512.
(5) Shoji, T.; Okada, K.; Ito, S.; Toyota, K.; Morita, N. *Tetrahedron Lett.* **2010**, *51*, 5127−5130.
(6) Gualo-Soberanes, N.; Ortega-Alfaro, M. C.; Lopez-Cortes, J. G.; Toscano, R. A.; Rudler, H.; Alvarez-Toledano, C. *Tetrahedron Lett.* **2010**, *51*, 3186−3189.
(7) Fife, W. K. *J. Org. Chem.* **1983**, *48*, 1375−1377.
(8) Katada. *Yakugaku Zasshi* **1947**, *67*, 51.
(9) The methods used in the following reference allow for the introduction of a variety of nucleophile types in addition to thiols: Storz, T.; Bartberger, M. D.; Sukits, S.; Wilde, C.; Soukup, T. *Synthesis* **2008**, 201−214.
(10) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554−4557.
(11) Abramovitch, R. A.; You-Xiong, W. *Heterocycles* **1987**, *26*, 2065−2068.
(12) Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341−1344.
(13) Katritzky, A. R.; Lagowski, J. M. *Chemistry of the Heterocyclic N-Oxides*; Academic Press: London, 1971; p 300.
(14) Abramovitch, R. A.; Smith, E. M. *Chem. Heterocycl. Compd.* **1974**, *14*, 114−117.
(15) Keith, J. M. *J. Org. Chem.* **2006**, *71*, 9540−9543.
(16) Keith, J. M. *J. Org. Chem.* **2008**, *73*, 327−330.
(17) Keith, J. M. *J. Org. Chem.* **2010**, *75*, 2722−2725.
(18) Lee, C.-S.; Ohta, T.; Shudo, K.; Okamoto, T. *Heterocycles* **1981**, *16*, 1081−1084.
(19) Londregan, A. T.; Jennings, S.; Wei, L. *Org. Lett.* **2010**, *12*, 5254−5257.
(20) Kurbatov, Yu. V.; Solekhova, M. A. *Khim. Geterotsikl. Soedin.* **1986**, 936−938.
(21) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: Hoboken, 2006.
(22) There still appears to have been some degree of ionic character of the reactions run in toluene as evidenced by the presence of small amounts, ∼2%, of solvent-trapped products.