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Preparation and Utility of Trihaloethyl Imidates: Useful Reagents for the Synthesis of Amidines

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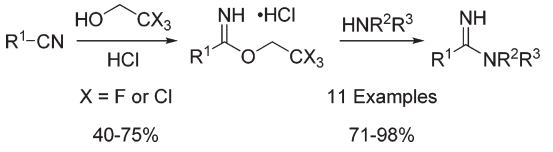
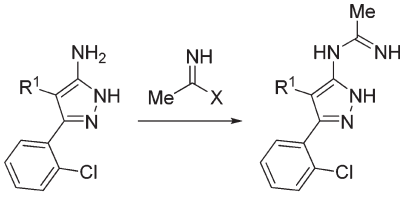


2,2,2-Trifluoro- and trichloroethyl imidates, which are easily prepared by reaction of a nitrile and a trihaloethanol in the presence of HCl, have proven to be excellent reagents for the preparation of amidines under mild reaction conditions. Depending on the nature of the amine nucleophile, the imidates can react either as the free-base or the hydrochloride salt in a telescoped process. In several cases, the *p*-bromobenzoate salt of the desired product was directly isolated from the reaction mixture.

Amidines are an important class of compounds that have demonstrated utility in the fields of catalyst design,[1] material science,[2] and medicinal chemistry.[3,4] Recent studies have demonstrated their capacity to fix carbon dioxide.[5,6]

The preparation of amidines has been reviewed[7] and generally originates from either nitrile or amide starting materials. As part of the development of a cannabinoid-1 (CB_1) receptor antagonist clinical candidate, the preparation of an amidine was necessary as an intermediate (**2**) to a pyrazolotriazinone.[8] We were surprised to find that while the formation of the amidine from the monosubstituted aminopyrazole **1a** proceeded in near quantitative yield with the ethoxyimidate, only 10% of the desired product was obtained from the corresponding disubstituted derivative **1b**. Gratifyingly, the analogous thioimidate[9] gave the desired product in 63% yield showing the importance in the selection of the leaving group based on the nature of the nucleophile (Table 1).

TABLE 1. Preparation of Amidines from Aminopyrazoles



1 **2**

entry	SM	R^1	X	% yield
1	**1a**	H	OEt	95
2	**1b**	4-ClPh	OEt	10
3	**1b**	4-ClPh	SCH_2Napth	63
4	**1b**	4-ClPh	OCH_2CF_3	50

While this method proved effective, we sought a superior and more cost-effective reagent for this transformation. Herein, we report that 2,2,2-trifluoroethyl and 2,2,2-trichloroethyl imidates are effective reagents for the preparation of amidines. Indeed, the preparation of **2** with 2,2,2-trifluoroethyl acetimidate provided a 50% yield without optimization (entry 4, Table 1).

We believed that a more general class of reagents for the formation of amidines would require a leaving group superior to the nitrogen nucleophile, leading to a productive collapse of the tetrahedral intermediate. More importantly, the inductive effect of the leaving group should provide increased reactivity at the electrophilic carbon, especially in the case of hindered substrates. On the basis of our initial results outlined above, we estimated that trifluoroethanol (pK_a = 23.1)[10] and trichloroethanol (pK_a = 19.5) could provide this advantage (EtOH pK_a = 29.5).[11]

Both 2,2,2-trifluoroethyl acetimidate and 2,2,2,-trichloroethyl acetimidate have previously been prepared and their stability evaluated.[12−14] The rate of aminolysis of

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TABLE 2. Preparation of Imidate Hydrochlorides

3

entry	compd	R	X	method[a]	% yield
1	**3a**	Me	F	A	65
2	**3b**	Me	Cl	A	75
3	**3c**	Et	F	B	46
4	**3d**	*i*-Pr	F	B	40
5	**3e**	Ph	F	A	64

[a]Method A: HCl gas. Method B: 4 N HCl/dioxane.

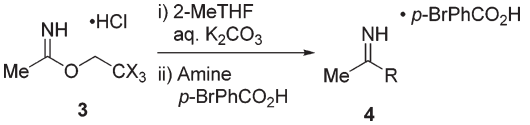
2,2,2-trifluoroethyl benyzimidate has also been studied.[15,16] However, the potential utility of these reagents for the formation of amidines has not been reported.

The desired reagents were prepared through a Pinner reaction with use of either HCl gas (Method A) or 4 N HCl in dioxane (Method B). The resulting imidate salts were directly isolated in good to moderate yields and were not individually optimized (Table 2). In general, Method A provided higher yields than Method B, although the latter has the advantage of being operationally simpler. All of these compounds are crystalline solids that proved to be stable at room temperature on the benchtop for a few months provided that they were kept away from moisture. The methyl derivatives **3a** and **3b** proved to be more prone to hydrolysis then the ethyl (**3c**) and isopropyl (**3d**) reagents while the benzimidate (**3e**) was the fastest to undergo hydrolysis. Efforts to prepare the *tert*-butyl derivative proved to be unsuccessful. In the case of the acetimidates, the trichloro reagent was preferred due to the higher yield obtained in its preparation (Table 2, entries 1 and 2).

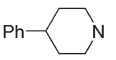
The reactivity of acetimidate **3a** was first evaluated with use of aniline as a nucleophile. It was determined that it was preferable to first neutralize the hydrochloride salt to the free base to increase reactivity. 2-Methyltetrahydrofuran (2-MeTHF) proved to be an acceptable solvent for performing both the salt break (aqueous K_2CO_3) as well as the subsequent amidine formation. While the reaction proceeded rapidly, the resulting amidine proved to be an oil that was difficult to isolate and purify. Several salts were prepared (HCl, HBr, AcOH, $PhCO_2H$) and it was discovered that the *p*-bromobenzoate provided a crystalline solid of high purity. Furthermore, the amidine formation proceeded in the presence of the acid to afford the desired salt directly in a single operation.

Acetimidates **3a** and **3b** reacted in a similar fashion (entries 1 and 2, Table 3) and the reaction was performed with use of the trichloro derivative with several amines. The reaction proceeded in high yield with a variety of anilines (entries 2−6) and only in the case of the more sterically demanding 2,4-xylidine (entry 6) was the yield below 90%. Condensation with more nucleophilic primary amines also proved to be high yielding (entries 7 and 8). In the case of 4-phenylpiperidine, the amine was sufficiently reactive that the desired product (**4h**) could be accessed directly in 92% yield from the HCl salt of the amidine, thereby avoiding the need to generate the free base of the reagent (entry 9).

TABLE 3. Preparation of Amidines As *p*-Bromobenzoate Salts

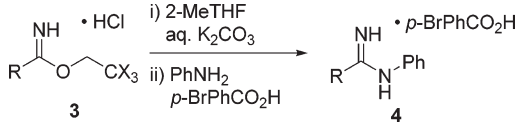


3 **4**

Entry	Reagent	Product	R	Yield(%)
1	**3a**	**4a**	PhNH	92
2	**3b**	**4a**	PhNH	96
3	**3b**	**4b**	4-MePhNH	93
4	**3b**	**4c**	4-ClPhNH	96
5	**3b**	**4d**	4-MeOPhNH	98
6	**3b**	**4e**	2,4-Me_2PhNH	74
7	**3b**	**4f**	$PhCH_2NH$	91
8	**3b**	**4g**	$PhCH_2CH_2NH$	98
9	**3b**	**4h**		92[a]

[a]Prepared and isolated directly as the HCl salt without free basing.

TABLE 4. Preparation of *N*-Phenylamidine *p*-Bromobenzoate Salts



3 **4**

entry	product	reagent	R	% yield
1	**4a**	**3a**	Me	92
2	**4i**	**3c**	Et	91
3	**4j**	**3d**	*i*-Pr	88
4	**4k**	**3e**	Ph	71[a]

[a]Prepared in EtOH without neutralization of **3e** and isolated as the free base after extractive workup.

Substitution on the imidate reagent was also evaluated by using aniline as the nucleophile, and the trifluoroethyl derivatives were used for comparison. In the first three cases, using the protocol leading to isolation of the *p*-bromobenzoate, the overall yield obtained was high and consistent (Table 4, entries 1−3). Because of concerns about hydrolysis of the benzimidate reagent (**3e**), it was reacted with aniline in ethanol followed by an extractive workup to provide the desired *N*-phenyl imidate (**4k**) in 71% yield (entry 4). As a comparison, preparation of **4k** from the nitrile proceeds in 80% yield but requires the use of the pyrophoric $AlMe_3$[17] and has not been previously reported with use of either the methyl or ethyl imidate reagents.

In summary, the versatility and utility of trifluoroethyl and trichloroethyl imidates has been demonstrated for the preparation of amidines. Formation of the *p*-bromobenzoate salts is a convenient method for isolation and purification of the products when the HCl salt of the starting imidate cannot be used directly. These reagents offer the advantage of being readily prepared in a single step from inexpensive starting materials, display reasonale stability, and react under mild process-friendly conditions. Reports on our evaluation of

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the addition of other nucleophiles on this class of imidates will be reported in due course.

Experimental Section

Representative Examples of Reagent 3 Preparation. Method A: 2,2,2-Trichloroethyl Acetimidate Hydrochloride (3b). To a mixture of trichloroethanol (200 mL, 2.08 mol) and acetonitrile (130 mL, 2.48 mol) at 0 °C was bubbled HCl gas for 7 h. The mixture was sealed and stored in a freezer for 72 h. The product was isolated by filtration, washed with cold acetonitrile (3 × 150 mL), and dried to provide 2,2,2-trichloroethyl acetimidate hydrochloride (**3b**) (354 g, 75%). Mp 201−203 °C. ^{1}H NMR (DMSO) δ 2.54 (s, 3), 5.36 (s, 2), 12.38 (br s, 2). ^{13}C NMR δ 19.3, 80.1, 93.6, 177.8.

Method B: 2,2,2-Trifluoroethyl Propionimidate Hydrochloride (3c). To a mixture of trifluoroethanol (69.0 g, 0.689 mol) and propionitrile (32.0 g, 0.574 mol) at 0 °C was added 4 N HCl in dioxane (215 mL, 0.860 mol). The mixture was allowed to warm to rt and was stirred for 48 h. The volatiles were removed under reduced pressure and the crude product was triturated with MTBE (200 mL). The product was isolated by filtration and dried to provide 2,2,2-trifluoroethyl propionimidate hydrochloride (**3c**) (50.0 g, 46%). Mp 148−150 °C. ^{1}H NMR δ 1.28 (t, 3, J = 7.42 Hz), 2.80 (q, 2, J = 7.42 Hz), 5.10 (q, 2, J = 7.42 Hz). ^{13}C NMR δ 9.5, 26.8, 69.0 (q, J = 38 Hz), 121.3 (q, J = 278 Hz), 180.0.

Representative Examples of Amidine Preparation. *N*1-Phenylacetamidine 4-Bromobenzoate (4a). 2,2,2-Trifluororoethyl acetimidate hydrochloride (**3a**) (2.873 g, 16.18 mmol) was dissolved in H_2O (10 mL) and 2-MeTHF (5 mL) followed by addition of K_2CO_3 (4.14 g, 30.0 mmol). The layers were separated and the crude organic layer was added to aniline (0.940 g, 10.1 mmol) and *p*-bromobenzoic acid (2.02 g, 10.1 mmol) in 2-MeTHF (40 mL). The reaction mixture was stirred at rt overnight. The solids were filtered and washed with 2-MeTHF (3 × 10 mL) to afford *N*-phenylacetimidamide 4-bromobenzoate (**4a**) (3.10 g, 92%) as a white solid. Mp 178−179 °C. ^{1}H NMR (DMSO) δ 2.17 (s, 3), 7.15 (d, 2, J = 7.47 Hz), 7.24 (t, 1, J = 7.47 Hz), 7.39 (t, 2, J = 7.47 Hz), 7.51 (d, 2, J = 8.30 Hz), 7.79 (d, 2, J = 8.30 Hz), 8.59 (br s, 1), 11.14 (br s, 2). ^{13}C NMR (DMSO) δ 124.4, 125.5, 127.3, 130.1, 131.2, 131.9, 137.7, 138.5, 170.9. Anal. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.76; H, 4.27; N, 8.27. HREIMS m/z 135.0917 (calcd m/z 135.0917 for $C_{18}H_{10}N_2$ + H). The free base is known and has been characterized.[18,19]

1-(4-Phenylpiperidin-1-yl)ethanimine Hydrochloride (4h). 2,2,2-Trichloroethyl acetimidate hydrochloride (**3b**) (2.67 g, 11.8 mmol) and 4-phenylpiperidine (1.58 mL, 9.98 mmol) were added to EtOH (20 mL). The solution was stirred at rt overnight and concentrated under reduced pressure, then the crude solid was triturated with MTBE. The solids were filtered to afford 1-(4-phenylpiperidin-1-yl)ethanimine hydrochloride (**4h**) (2.20 g, 92%) as a white solid. Mp 223−225 °C. ^{1}H NMR (DMSO) δ 1.68 (dq, 1, J = 12.89, 3.90 Hz), 1.75 (dq, 1, J = 12.89, 3.90 Hz), 1.95−2.05 (m, 2), 2.45 (s, 3), 2.79 (dt, 1, J = 12.11, 3.51 Hz), 3.10−3.20 (m, 1), 3.26 (dt, 1, J = 12.89, 2.34 Hz), 3.94 (d, 1, J = 13.67 Hz), 4.85 (d, 1, J = 13.67 Hz), 7.13−7.28 (m, 5), 9.47 (br s, 1), 9.95 (br s, 1). ^{13}C NMR (DMSO) δ 20.0, 32.1, 33.3, 41.5, 47.7, 48.7, 126.7, 126.8, 128.7, 143.7, 162.4. HREIMS m/z 203.1544 (calcd m/z 203.1543 for $C_{13}H_{18}N_2$ + H).

***N*-Phenylbenzamidine (4k).** To 2,2,2-Trifluoroethyl benzimidate hydrochloride (**3e**) (0.48 g, 2.0 mmol) and aniline (0.55 g, 5.91 mmol) was added EtOH (10 mL). The mixture was stirred at 40 °C for 48 h. The mixture was concentrated and partitioned between MTBE (15 mL) and aq K_2CO_3 (10 mL). The MTBE layer was concentrated and the crude residue was triturated with heptanes to afford *N*-phenylpropionimidamide (**4k**) (0.28 g, 71%). HREIMS m/z 197.1074 (calcd m/z 197.1073 for $C_{13}H_{12}N_2$ + H). The ^{1}H NMR data were identical with the previously reported data.[17,20]

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Supporting Information Available: Complete experimental procedures and characterization data of the compounds prepared and ^{1}H and ^{13}C NMR spectra of compounds **3c**, **3d**, **4e**, **4g**, and **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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