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Mild method for the synthesis of amidines by the electrophilic activation of amides

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Abstract

The synthesis of amidines was achieved by the addition of amines to amides that were previously activated with trifluoromethanesulfonic anhydride (triflic anhydride) and pyridine. Various disubstituted and trisubstituted amidines were prepared in yields up to 84%. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: amides; amidines.

Amidines have long been regarded as useful intermediates in the synthesis of heterocyclic compounds. Accordingly, the condensation of amidines with α-halo ketones or α-hydroxy ketones yields imidazole rings, while heating amidine salts with ethylene diamine yields dihydroimidazoles.[1] Pyrimidine derivatives have also been prepared from amidines using a vast array of β-dicarbonyl compounds, β-dinitriles, β-cyano esters, β-keto nitriles as well as α,β-unsaturated esters, nitriles and carbonyls.[1]

Conventional strategies for amidine synthesis include: (1) the addition of metal amides or amines to nitriles;[2] (2) the addition of amines to imido ester intermediates;[3] and (3) the condensation of amides with amines in the presence of halogenating reagents.[4] In the latter strategy, harsh conditions are generally used in order to activate the amide and make it more prone to nucleophilic attack.

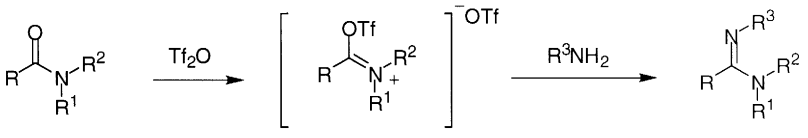

Fig. 1.

Recently, we have demonstrated that secondary and tertiary amides can be activated with trifluoromethanesulfonic anhydride (triflic anhydride)[5] to generate the corresponding iminium salts

* Corresponding author. Tel: (514) 343-6283; fax: (514) 343-5900; e-mail: andre.charette@umontreal.ca (A. B. Charette)

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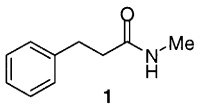
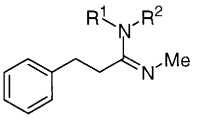
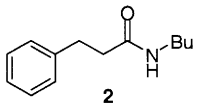
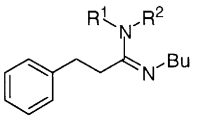
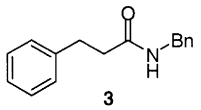
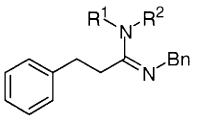
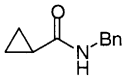
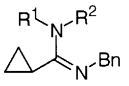
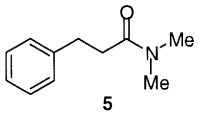
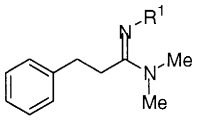
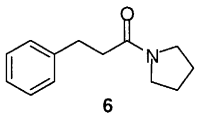
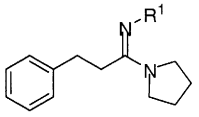
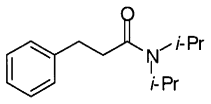
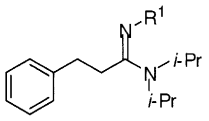
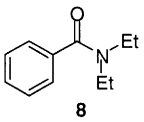
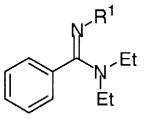
Table 1
Synthesis of amidines from secondary and tertiary amides

Entry	Substrate	Amine[a]	Product[b]	Yield (%)[c]
1	 **1**	Me_2NH		**9** 68% (R^1 = R^2 = Me)[d]
2		$EtNH_2$		**10** 77% (R^1 = H, R^2 = Et)[e]
3		$BnNH_2$		**11** 84% (R^1 = H, R^2 = Bn)
4	 **2**	Me_2NH		**12** 64% (R^1 = R^2 = Me)[d]
5		$EtNH_2$		**13** 83% (R^1 = H, R^2 = Et)
6	 **3**	Me_2NH		**14** 73% (R^1 = R^2 = Me)
7		$EtNH_2$		**15** 77% (R^1 = H, R^2 = Et)
8		$BnNH_2$		**16** 61% (R^1 = H, R^2 = Bn)
9	 **4**	Me_2NH		**17** 74% (R^1 = R^2 = Me)[e]
10		$EtNH_2$		**18** 82% (R^1 = H, R^2 = Et)
11		$BnNH_2$		**19** 63% (R^1 = H, R^2 = Bn)
12	 **5**	$EtNH_2$		**20** 75% (R^1 = Et)
13		$BnNH_2$		**21** 64% (R^1 = Bn)
14	 **6**	Me_2NH		**22** 55% (R^1 = Et)[f]
15		$EtNH_2$		**23** 48% (R^1 = Bn)
16	 **7**	$EtNH_2$		**24** 55% (R_1 = Et)[e]
17		$BnNH_2$		**25** 53% (R_1 = Bn)[e]
18	 **8**	$EtNH_2$		**26** 45% (R_1 = Et)[f]
19		$BnNH_2$		**27** 34% (R_1 = Bn)

[a]Added as its hydrochloride salt. [b]The amidines were isolated as the corresponding amidine salts (HX) where X = Cl and OTf; [c]Yields were calculated assuming that OTf is the counterion; [d]1.2 equiv of the amine salt added at 0 °C; [e]3.0 equiv of the amine salt added at 0 °C; [f]3.0 equiv of the amine salt added at -10 °C.

which can further react with ethanol, hydrogen sulfide, ^{18}O-labeled water, aminothiols or 1,1,1-tris(hydroxymethyl)ethane to give the corresponding ethyl esters, thioamides, ^{18}O-labeled amides, thiazolines and cyclic orthoesters, respectively.[6] Dossena and co-workers have also reported similar results using triflic anhydride and 2,6-di-*tert*-butylpyridine for the activation of simple amides (usually DMF and *N*,*N*-dimethylacetamide) and their subsequent conversion into thioimidates, esters and *O*-alkyl

thioesters.[7] They also reported the formation of amidine salts when an amine was added, but only two examples were reported and the yields were moderate (57% and 59%). Concurrently to their work, we also focused our attention to develop a general protocol to access amidines in high yields from both secondary and tertiary amides based on our previous findings and using pyridine as the base.

The general strategy that was envisioned is illustrated in Fig. 1 The addition of triflic anhydride to a secondary or tertiary amide and pyridine would generate the iminium triflate **A** that should be converted into the amidine **B** upon addition of the appropriate amine.

In our first attempt, amide **1** was activated with triflic anhydride and pyridine for two hours at 0°C, after which time a solution of methylamine in dichloromethane (5.0 equiv.) was added and allowed to react overnight at room temperature. The solvent was removed under reduced pressure and a ^{1}H NMR of the crude material revealed that a complex mixture of products was formed. Substitution of methylamine for diethylamine also resulted in complete decomposition. We then decided to add the amine as its hydrochloric salt assuming that the diminished nucleophilicity would prevent the extensive decomposition. Gratifyingly, amidine **9** was isolated in 68% yield when amide **1** was activated as mentioned above and allowed to react with dimethylamine hydrochloride (1.2 equiv.) (Table 1, entry 1). Following the same procedure, amide **2** and **3** were also smoothly converted into amidines **12** (64%) and **14** (46%). After optimization, we found that the addition of 3.0 equiv. of the amine hydrochloride salt at low temperature (between −30°C and −40°C) followed by the slow warming of the reaction to room temperature gave the best yields. Other amine hydrochloride salts reacted in a similar fashion to give the corresponding amidines in good to excellent yields (Table 1).[8] As outlined in Table 1, long chain *N*-alkylated secondary amides (**2**), *N*-benzylamides (**3**), and cyclopropanamides (**4**) were easily converted into the corresponding amidines. We then focused our attention on the activation of tertiary amides with triflic anhydride and found that they gave slightly lower yields of the desired products (see Table 1). The activation periods with tertiary amides are slightly longer than those required for secondary amides. Interestingly, very hindered amidines such as compounds **25** and **27** could also be synthesized.

In summary, we have shown that a wide variety of amidines can be easily prepared from amides. The reaction conditions are milder than the usual methods employing amides as starting material and the reagents used are all commercially available or readily accessible.

Acknowledgements

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8. To a solution of amide **3** (237.4 mg, 1.0 mmol) and pyridine (240 μL, 3.0 mmol) in CH_2Cl_2 (5.0 mL) at −40°C was slowly added Tf_2O (220 μL, 1.3 mmol). The mixture was allowed to warm to 0°C over 2.5 h. The solution was then cooled to −40°C and $Me_2NH{\cdot}HCl$ (250 mg, 3.0 mmol) was introduced in one portion. The reaction was then warmed to room temperature and stirred for ca. 20 h. The reaction was then diluted with CH_2Cl_2 and saturated aqueous $NaHCO_3$. The aqueous layer was washed with CH_2Cl_2 (3×), and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography using MeOH:EtOAc (0 to 10% MeOH) afforded 304.6 mg (73%) of the amidine salt as an off-white solid. Mp >200°C. ^{1}H NMR (400 MHz, CD_3OD) δ 7.14–7.43 (m, 10H), 4.52 (s, 2H), 3.24 (s, 3H), 3.21 (s, 3H), 2.93 (t, *J*=7.8 Hz, 2H), 2.76 (t, *J*=7.8 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.2, 139.8, 138.0, 130.2, 130.0, 129.5, 129.2, 128.2, 128.1, 120.3 (q, *J*=319 Hz), 48.5, 41.6, 39.8, 32.1, 30.4. HRMS calculated for $C_{18}H_{23}N_2$: 267.1861. Found: 267.1869. The free base could be isolated (>95%) by dissolving the amidinium salt in 4N NaOH and by washing the aqueous layer with ether (3×). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the analytically pure amidine as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.20 (m, 10H), 4.56 (s, 2H), 3.02 (s, 6H), 2.79–2.75 (m, 2H), 2.72–2.67 (m, 2H). HRMS calculated for $C_{18}H_{22}N_2$: 266.1783. Found: 266.1792.