JOC Article

An Efficient Procedure for the Preparation of 4-Substituted 5-Aminoimidazoles

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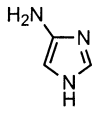
The preparation of *O*-methylimidates from α-aminonitriles and their subsequent co-cyclization with primary amines to afford 4-substituted 5-aminoimidazoles was studied. It was found that the mildly acidic pyridinium *p*-toluenesulfonate efficiently catalyzed each stage of the reaction sequence: (a) the formation of the *O*-methylimidates, (b) their co-cyclization with a variety of primary amines, and (c) certain derivatizations of the resultant heterocycles. The developed reaction conditions tolerate a wide variety of α-aminonitriles and primary amine co-reactants. Thus, it is possible to easily prepare a diverse array of substituted heterocyclic compounds in good yield. The requisite α-aminonitriles were synthesized either from amino acids or by phase-transfer alkylation of a glycine anion equivalent. The unstable free 5-aminoimidazoles were normally protected in situ to provide derivatives (methyl imidates or *N*,*N*-dimethylamidines) that were amenable to characterization.

Introduction

Aminoazoles are a class of heterocyclic molecules that display a range of stabilities and reactivity patterns that are exemplified by the parent members of the various families.[1] For example, 5-aminotetrazole monohydrate[2] is a commercially available white crystalline solid (mp 203 °C) that is frequently used as a building block for pharmaceuticals.[3] The aminotriazoles display similar stability; 3-amino-1,2,4-triazole[4] and 4-amino-1,2,3-triazole[5] are also both stable crystalline solids, the former melting at 152−156 °C and the latter at 74−75 °C. At the opposite end of the scale, the extremely electron-rich 2- and 3-aminopyrroles are highly reactive species and have never been isolated. Last, enjoying intermediate stability, are the aminoazole systems that contain two nitrogen atoms in the azole ring, certain of which are the subject of this paper. The free bases of 3-aminopyrazole[6] and 4-aminopyrazole[7] have been characterized, but to date, two of the parent aminoimidazoles **1** and **2** have evaded isolation, although they have been trapped as simple salts.[8] The low stability of these 4- and 5-aminoimidazoles is perhaps one reason these molecules have received relatively little attention from synthetic chemists over the years. However, despite this instability, 5-aminoimidazole ribonucleotide (AIR, **3**) is a biosynthetic intermediate in the pathway leading to purine ribonucleotides in prokaryotic and eukaryotic systems[9] and a precursor of the pyrimidine fragment of thiamin in some prokaryotic organisms.[10] Recent studies[11] by others in this area of biosynthetic chemistry have generated renewed interest in aminoimidazoles, and consequently, we became interested in the development of efficient synthetic routes into this intriguing class of heterocycles.



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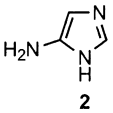

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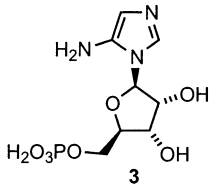

3

The preparation of *O*-alkylimidates **5** from α-aminonitriles **4** and subsequent co-cyclization of such imidates with primary amines to afford 4-substituted 5-aminoimidazoles **6** (Scheme 1) was previously documented in the literature.[12] However, in all reported cases there were some rather strict limitations with respect to the substrate scope, and the yields of these somewhat unstable[1]

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‡ Deceased 6 March 2002.

(1) For a review, see: Lythgoe, D. J.; Ramsden, C. A. *Adv. Heterocycl. Chem.* **1994**, *61*, 1, and references therein.

(2) Butler, R. N. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 5, p 802.

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(9) (a) Schrimsher, J. L.; Schendel, F. J.; Stubbe, J. *Biochemistry* **1986**, *25*, 4356. (b) Schrimsher, J. L.; Schendel, F. J.; Stubbe, J.; Smith, J. M. *Biochemistry* **1986**, *25*, 4366.

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(11) (a) Humphries, M. J.; Ramsden, C. A. *Synthesis* **1999**, 985. (b) Humphries, M. J.; Ramsden, C. A. *Synlett* **1995**, 203.

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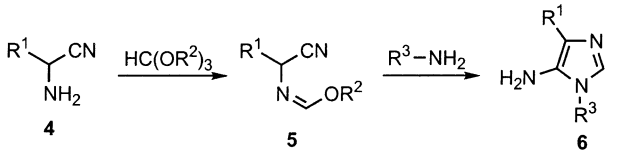
SCHEME 1



heterocycles were generally only moderate: the substituent on the α-aminonitrile (R^1) was restricted to an electron-withdrawing group (e.g., CN, CO_2Et, and $CONH_2$). It seems likely that having an electron-withdrawing group on such electron-rich heterocycles helped to provide at least a degree of stability that enabled their isolation and characterization.

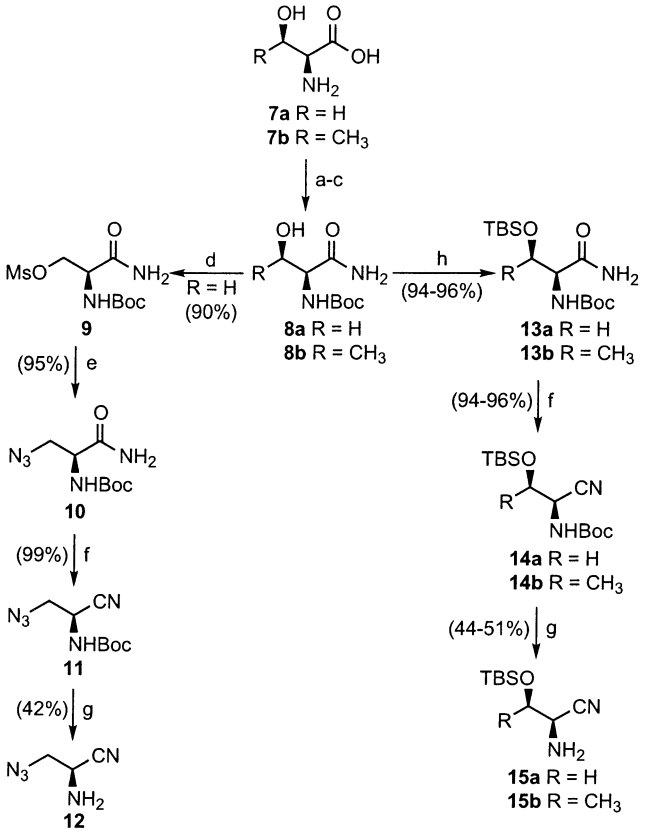
Given the frequent appearance of imidazole fragments in pharmaceutical compounds we sought to expand the scope of this potentially useful cyclization method and optimize its efficiency. The present work has established a simple pyridinium *para*-toluenesulfonate (PPTS) catalyzed procedure by which α-aminonitriles **4** can be transformed into 4-substituted 5-aminoimidazoles **6** in good yields. Moreover, the range of substituents (R^1 and R^3) tolerated by this new method has been explored and found to include a broad variety of functionality that could be utilized for further elaboration into more complex bicyclic heterocycles.

Results and Discussion

Synthesis of α-Aminonitrile Substrates. The requisite α-aminonitriles were prepared following two general routes, the first of which was based on the transformation of amino acid starting materials. The core sequence comprised protection, side-chain manipulation, conversion of the acid to a nitrile and then deprotection of the nitrogen. α-Aminonitriles featuring functionalized side-chains were of interest because of the potential to perform further interesting chemistry on the imidazoles they were expected to afford. In particular, we envisaged that aminoimidazoles bearing an alkyl chain terminated by an azide group might possibly be utilized for the formation of interesting bicyclics (e.g. dihydropurines), via Staudinger reduction[13] and further subsequent manipulations. Consequently, we attempted the synthesis of azido-substituted α-aminonitrile **12** starting from the naturally occurring (*S*)-serine **7a** (Scheme 2).

It was anticipated that this route would involve a few relatively simple transformations, however the tendency of this amino acid to undergo elimination of its alcohol group caused several revisions in our original plan. Thus, beginning with serine **7a**, the functional groups were protected using standard methods and primary amide **8a**

SCHEME 2[a]



[a] Key: (a) HCl, MeOH; (b) $(Boc)_2O$, $NaHCO_3$, 1,4-dioxane/H_2O; (c) NH_3, MeOH, 50 °C; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) NaN_3, DMF, 25 °C; (f) TsCl, pyr, CH_2Cl_2; (g) TFA, −15 °C then NH_4OH; (h) TBSCl, imidazole, DMAP (1 mol %), CH_2Cl_2.

was generated simply by the action of anhydrous ammonia on the methyl ester. It is possible that this step could have affected the stereochemical integrity of **8a** but the extent of this was not investigated here because the stereocenter would ultimately be destroyed upon imidazole formation. From amide **8a** it was possible to form mesylate **9**, which was subjected to S_N2 displacement by azide anion in DMF to give compound **10**. Dehydration led to nitrile **11** and removal of the carbamate protecting group with cold trifluoroacetic acid yielded **12**. Key to the success of this chemistry was the conversion of the methyl ester to the primary amide prior to forming the mesylate; an earlier attempt to form the mesylate on the methyl ester resulted in elimination. Clearly, the lower acidity of the protons adjacent to an amide carbonyl, relative to those of an ester, was sufficient to suppress this elimination problem. As an alternative to this route, it was also possible to utilize Mitsunobu chemistry[14] (HN_3/DEAD/PPh_3) on the way to α-aminonitrile **12**, however this necessitated laborious chromatographic separations and required the use of the less attractive *N*-trityl protecting group if the unwanted elimination was to be completely avoided.

Several other α-aminonitriles were prepared according to this general route. Two others, **15a** and **15b**, were prepared in straightforward fashion from intermediates **8a** and **8b** (Scheme 2). Additionally, (*S*)-phenylalanine

(12) For examples, see: (a) Peinador, C.; Quintela, J. M.; Moreira, M. J. *Tetrahedron* **1997**, *53*, 8269. (b) Corelli, F.; Summa, A. B.; Brogi, A.; Monteagudo, E.; Botta, M. *J. Org. Chem.* **1995**, *60*, 2008. (c) Birkett, P. R.; King, H.; Chapleo, C. B.; Ewing D. F.; MacKenzie, G. *Tetrahedron* **1993**, *49*, 11029. (d) Agathocleous, D. C.; Shaw, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2555. (e) Al-Shaar, A. H.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2779. (f) Cristalli, G.; Eleuteri, A.; Franchetti, M.; Vittori, S.; Lupidi, G. *J. Med. Chem.* **1991**, *34*, 1187. (g) Mackenzie, G.; Wilson, H. A.; Shaw, G.; Ewing, D. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2541. (h) Kadir, K.; Shaw, G.; Wright, D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2728.

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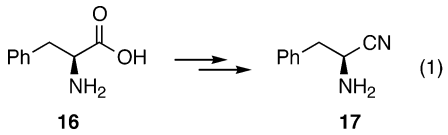
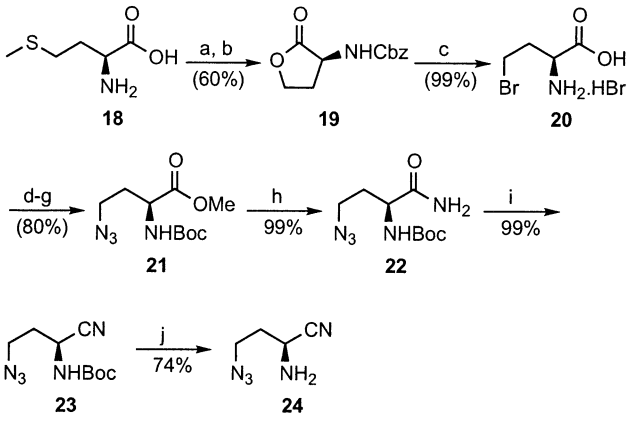
16 was used to prepare α-aminonitrile **17** following similar chemistry (eq 1).



16 **17** (1)

An α-aminonitrile **24**, a homologue of **12**, was also targeted for synthesis using a procedure slightly modified from the literature for the initial steps (Scheme 3). Starting with (*S*)-methionine **18**, this cheaply available amino acid was first *N*-protected as the carbobenzyloxy-derivative[15] before *δ*-lactone **19**[16] was generated by the formation of the dimethyl sulfonium salt in a highly polar media followed by expulsion of dimethyl sulfide during ring closure. Next, a one-pot ring-opening/substitution reaction[17] was accomplished under strongly acidic conditions to afford the hydrobromide salt **20** in quantitative yield. Protection of the amino acid, introduction of the azide by displacement and final steps similar to those described for compound **12**, were then required to secure α-aminonitrile **24**.

SCHEME 3[a]

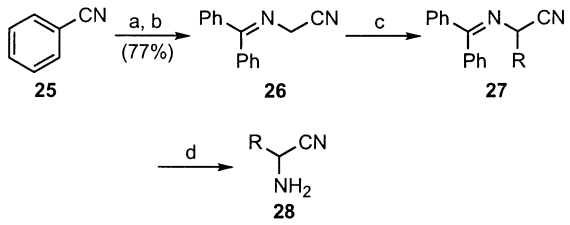


[a] Key: (a) CbzCl, $NaHCO_3$, 1,4-dioxane/H_2O; (b) MeI, AcOH, HCO_2H then pH 7, 100 °C; (c) HBr, AcOH, 85 °C; (d) HCl, MeOH; (e) $(Boc)_2O$, $NaHCO_3$, 1,4-dioxane/H_2O; (f) NaI, acetone, 56 °C; (g) NaN_3, DMF, 90 °C; (h) NH_3, MeOH, 50 °C; (i) TsCl, pyr, CH_2Cl_2; (j) TFA, −15 °C then NH_4OH.

Although the amino acid route to the aminonitriles was reasonably efficient it was clear that more simple chemistry was required if the imidazole-forming cyclization under study was to become generally useful. As such, recourse was made to the phase-transfer chemistry of O'Donnell in which glycine anion equivalents can be alkylated using a wide variety of electrophiles.[18] This technique was successfully applied to a number of compounds and provided extremely versatile and rapid access to different side chains.

The benzophenone imine of α-aminoacetonitrile **26** is commercially available. However, for the present work, it was easily synthesized in multigram quantities following a literature preparation.[19] Thus, the reaction of phenylmagnesium bromide with benzonitrile **25** followed by a methanol quench afforded benzophenone imine, which was subjected to salt metathesis conditions with the hydrochloride salt of α-aminoacetonitrile to yield **26** as a stable crystalline solid. Glycine anion equivalent **26** was then alkylated using various electrophiles under phase-transfer conditions, slightly modified from the O'Donnell procedure,[20] using benzyltriethylammonium chloride as the catalyst and concentrated sodium hydroxide as the base. Hydrolysis of the imines **27a**−**h** was facile using dilute aqueous acid in THF and furnished the α-aminonitriles **28a**−**g** in excellent overall yields.

SCHEME 4[a]



Entry	R-group	Yield of **27**	Yield of **28**
1	R = *p*-$CH_2(C_6H_4)OMe$	**27a** (82%)	**28a** (87%)
2	R = *p*-$CH_2(C_6H_4)NO_2$	**27b** (93%)	**28b** (89%)
3	R = *n*-C_6H_{13}	**27c** (88%)	**28c** (94%)
4	R = *i*-Pr	**27d** (83%)	**28d** (92%)
5	R = $(CH_2)_2CO_2Et$	**27e** (99%)	**28e** (77%)
6	R = $(CH_2)_3CO_2Et$	**27f** (95%)	**28f** (78%)
7	R = $(CH_2)_3Cl$	**27g** (92%)	
8	R = $(CH_2)_3N_3$	**27h** (95%)	**28g** (80%)

[a] Key: (a) PhMgBr, Et_2O; (b) $Cl^-H_3N^+CH_2CN$, CH_2Cl_2; (c) RX, $BnNEt_3^+\ Cl^-$ (10 mol %), 11 M aq NaOH, CH_2Cl_2; (d) 1 M aq HCl, THF then NH_4OH; (e) NaN_3, DMF, 80 °C.

The results in Scheme 4 show that O'Donnell's method proved to be well suited to the rapid synthesis of the various α-aminonitrile substrates required for this work. An experimental detail worthy of mention in connection with these phase-transfer reactions regards the choice of solvent used for the organic phase. Previous literature examples utilized either toluene or dichloromethane with equal efficiency[18] but, for small scale experiments, we found that the latter solvent provided a significant rate enhancement. This was ascribed to the physical properties of the two-phase systems obtained with each of these two solvents, in particular the densities of each phase. The similarity between the density of dichloromethane and concentrated aqueous sodium hydroxide resulted in the easy formation of a true liquid−liquid emulsion when the mixture was subjected to standard magnetic stirrer/flea agitation. Clearly these conditions generated a high surface area for phase-transfer and the alkylation reactions proceeded rapidly. Alternatively, when toluene was used as the organic phase the difference in density from that of the aqueous phase made efficient mixing difficult

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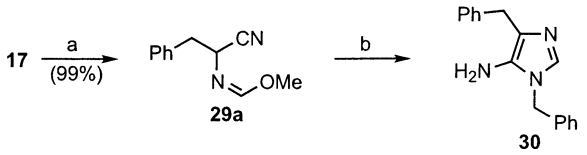
(18) For a review see: O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3.
(19) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.
(20) O'Donnell, M. J.; Eckrich, T. M. *Tetrahedron Lett.* **1978**, 4625.

SCHEME 5[a]



[a] Key: (a) $HC(OMe)_3$, PPTS (0.2 mol %), 65 °C; (b) $BnNH_2$ (100 mol %), PPTS (1 mol %), $CHCl_3$, 67 °C.

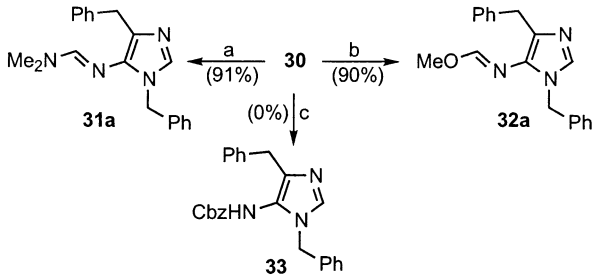
to achieve on a small scale and the alkylation reactions required several days to reach approximately 85% completion.

Imidazole Synthesis. Having established efficient routes to a number of substituted α-aminonitriles our attention was then turned toward formation of the imidates and their cyclization to the imidazoles. We chose to use α-aminonitrile **17** for the optimization of these reaction conditions because of its lack of possible interfering functionality and ease of synthesis. A known method for the formation of the methyl or ethyl imidate from α-aminonitriles involves boiling in the appropriate orthoformate with, or without, distillative removal of the product alcohol.[12] In the present work it was found that this method was not reproducible and often resulted in mixtures of product and starting material. Prolonged heating normally led to complete consumption of the α-aminonitrile **17**; however, this also caused significant decomposition of the product and a concomitant low yield. Given the unattractiveness of requiring to purify the relatively reactive imidate more efficacious conditions were sought.

During this work on imidate formation it was observed that the incomplete conversion was exacerbated when base-washed glassware was utilized. This suggested that deliberate addition of an acid catalyst might assist imidate formation. Initially, 2,2,2-trifluoroethanol was tested as an additive in these reactions but this was found to be ineffective. Next, the more acidic PPTS was used and this was found to be an excellent catalyst for the formation of methyl imidate **29a**. Following optimization, formation of imidate **29a** was routinely accomplished by heating α-aminonitrile **17** in trimethyl orthoformate at 65 °C for 1 h with 0.2 mol % of PPTS as catalyst. Concentration in vacuo yielded microanalytically pure imidate **29a** in almost quantitative yield (Scheme 5). The lower temperature and reduced reaction time employed in these new conditions avoids the decomposition problems that were previously experienced. With easy access to pure imidate **29a** secured, it was then possible to examine its co-cyclization with an amine to the heterocycle.

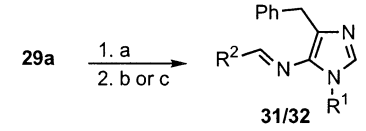
Benzylamine was chosen initially as the amine coreactant and pleasingly it was found that the use of PPTS as an additive in this step again led to efficient catalysis of the desired reaction. Optimum conditions involved the use of 1 mol % PPTS, one equivalent of benzylamine and boiling chloroform as the solvent (Scheme 5). Under these mild conditions the intermediate formed from the reaction between the imidate and benzylamine, an amidine, cleanly cyclized in situ. Simple evaporation of the solvent then furnished the rather unstable crude 5-aminoimidazole **30** as a crystalline solid, which was judged to be > 95% pure by ^{1}H NMR spectroscopy. A ^{13}C NMR spectrum

SCHEME 6[a]



[a] Key: (a) $Me_2NCH(OMe)_2$, PPTS (1 mol %), 80 °C; (b) $HC(OMe)_3$, PPTS (1 mol %), 80 °C; (c) *N*-Cbz-*N*′-methylimidazolium triflate, CH_3CN, 0 °C.

SCHEME 7[a]



Entry	R^1	R^2	Imidazole derivative
1	R^1 = *n*-Pr	R^2 = NMe_2	**31b** (89%)
2	R^1 = cyclopentyl	R^2 = NMe_2	**31c** (80%)
3	R^1 = Ph	R^2 = OMe	**32b** (67%)

[a] Key: (a) RNH_2 (100 mol %), PPTS (1 mol %), $CHCl_3$, 67 °C; (b) $HC(OMe)_3$, PPTS (1 mol %), 80 °C; (c) $Me_2NCH(ONe)_2$, PPTS (1 mol %), 80 °C.

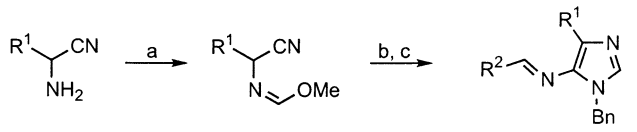
of the crude free amine could also be obtained but it was not possible to obtain an accurate elemental analysis of the crude product. Furthermore, the previously documented instability[1] and unusual reactivity[2g] of this class of heterocyclic compound was then observed when attempts were made to purify **30**; recrystallization and silica/alumina chromatography all failed to improve the situation and actually returned material of lower quality.

The instability of **30** prompted attempts to form more stable and easily characterizable derivatives in which the free amino-group was protected however, as anticipated from the literature,[2g] this also proved to be nontrivial. It was hoped that reaction of **30** with the reactive Cbz-introducing reagent *N*-carbobenzyloxy-*N*′-methylimidazolium triflate[21] would afford the *N*-Cbz-derivative **33** but unfortunately this led only to decomposition (Scheme 6). However, it was possible to prepare and isolate in high yield either the *N, N*-dimethylamidine **31a** (91%) or the methyl imidate **32a** (90%) under similar PPTS-catalyzed conditions to those used for the previous two steps. These derivatives were stable enough to be purified by standard silica chromatography and properly characterized.

Having developed optimized reaction conditions using benzylamine, the use of other amines in this cyclization was then examined (Scheme 7). Somewhat expectedly, it was found that *n*-propylamine was well behaved in this reaction and cleanly afforded the desired *N*-propylimidazole **31b** in 89% yield. Perhaps not so anticipated were the results obtained with cyclopentylamine and aniline; the steric bulk of the former might have been expected

(21) Watkins, B. E.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 4471.

SCHEME 8[a]



Entry	Aminonitrile	Imidate (Yield)	Derivative (Yield)
1	**12** $R^1 = CH_2N_3$	**29b** (99%)	**32c** R^2 = OMe (0%)
2	**15a** $R^1 = CH_2OTBS$	**29c** (99%)	**31d** $R^2 = NMe_2$ (43%)
3	**15b** R^1 = CH(Me)OTBS	**29d** (99%)	**31e** $R^2 = NMe_2$ (0%)
4	**24** $R^1 = (CH_2)_2N_3$	**29e** (99%)	**32d** R^2 = OMe (90%)
5	**28a** $R^1 = p\text{-}CH_2(C_6H_4)OMe$	**29f** (99%)	**32e** R^2 = OMe (91%)
6	**28b** $R^1 = p\text{-}CH_2(C_6H_4)NO_2$	**29g** (99%)	**32f** R^2 = OMe (93%)
7	**28c** $R^1 = n\text{-}C_6H_{13}$	**29h** (99%)	**32g** R^2 = OMe (86%)
8	**28d** $R^1 = i$-Pr	**29i** (76%)	**32h** R^2 = OMe (85%)
9	**28e** $R^1 = (CH_2)_2CO_2Et$	**29j** (99%)	**32i** R^2 = OMe (84%)
10	**28f** $R^1 = (CH_2)_3CO_2Et$	**29k** (99%)	**32j** R^2 = OMe (81%)
11	**28g** $R^1 = (CH_2)_3N_3$	**29l** (99%)	**31f** $R^2 = NMe_2$ (92%)

[a] Key: (a) $HC(OMe)_3$, PPTS (0.2 mol %), 65 °C; (b) $BnNH_2$ (100 mol %), PPTS (1 mol %), $CHCl_3$, 67 °C; (c) $HC(OMe)_3$, PPTS (1 mol %), 80 °C or $Me_2NCH(OMe)_2$, PPTS (1 mol %), 80 °C.

to compromise the reaction efficiency and the different electronics of the latter likewise. Gratifyingly, imidazole **31c** was obtained in 80% yield and imidazole **32b** in 67% yield, both under the developed standard cyclization conditions. Compound **32b** is worthy of note because the preparation of such an *N*-arylimidazole would likely be difficult by other means.

Last, the scope of the new method with respect to the α-aminonitrile side-chain was studied using a wide variety of compounds, the synthesis of which was described above. In all but a few cases the PPTS-catalyzed procedure smoothly furnished the desired 4-substituted 5-aminoimidazoles in high yield and derivatization of these to the methyl imidates or *N*,*N*-dimethylamidines was equally straightforward (Scheme 8). Entries 5, 7, and 8 clearly demonstrate that α-aminonitriles bearing electroneutral/electron-rich side chains are efficiently cyclized and provide stable, characterizable derivatives. In particular, entry 8 shows that steric bulk on the α-aminonitrile does not interfere with the ring formation. α-Aminonitriles bearing more functionalized side-chains (e.g., entries 4 and 9−11) also fared well and there is potential for these products to undergo further reactions/cyclizations to more complex molecules. The three substrates that did not react cleanly in this process (entries 1−3) all contained heteroatoms in the *β*-positions of the α-aminonitriles. That it was possible to form the imidates from these substrates suggests that instability toward the mildly acidic reaction conditions was not the problem and analysis of reaction mixtures indicated that these imidates were rapidly consumed in the imidazole-forming step. It seems likely that an undesired elimination took place sometime after formation of the intermediate amidine and that this eventually led to total decomposition in the case of entries 1 and 3.

Conclusion

In conclusion, the three-step transformation of various α-aminonitriles into protected 4-substituted 5-aminoimidazoles, via intermediate amidines (formed and cyclized in situ), was examined. It was found that the mildly acidic PPTS efficiently catalyzed this process and, contrary to earlier reports,[12] using the new method it was possible to synthesize many compounds bearing electroneutral/electron-donating groups on the heterocyclic ring. The new method has wide substrate scope with respect to both the α-aminonitrile used and also the amine coreactant and generally affords almost pure 4-substituted 5-aminoimidazoles in high yield simply by evaporation of the reaction solvent. The instability of the 4-substituted 5-aminoimidazoles demanded their rapid derivatization, to either the methyl imidate or the *N*,*N*-dimethylamidine, in order that full characterization data could be obtained. Last, the use of the method established in the present work, in conjunction with the convenient glycine anion equivalent alkylation technique developed elsewhere,[18] should allow for the rapid production of a large array 4-substituted 5-aminoimidazole compounds if so desired.

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Supporting Information Available: Full experimental procedures and analytical and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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