Efficient Synthesis of 2-Arylamino-2-imidazolines and 2-Aminobenzimidazoles with Aminoiminomethanesulfonic Acid Derivatives

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A highly efficient synthesis of 2-arylamino-2-imidazolines and 2-aminobenzimidazoles from aminoiminomethanesulfonic acid derivatives is described. The method is simple and practical, generating imidazoline and benzimidazoline derivatives in excellent isolated yields.

Keywords 2-arylamino-2-imidazoline, 2-aminobenzimidazole, synthesis, cyclization, heterocycle, aminoiminomethanesulfonic acid, ureas

Introduction

2-Arylamino-2-imidazolines have an interesting chemistry and they are effective pharmacophores in medicinal chemistry.[1-4] 2-Arylamino-2-imidazolines, in particular 2,6-dichlorophenylamino-2-imidazoline[5] (clonidine) have a pronounced, hypotensive action, which is coupled with a sedative action. Moreover, some of these compounds also have a more or less pronounced analgesic action which, however, because of the simultaneous existence of the hypotensive action and the depressant action on the central nervous system, was considered unexploitable.

Over the past years, a number of methods to produce aminoimidazolines from various materials have been reported in the literature for example, Chapleo *et al.*[6] have reported the synthesis of clonidine analogs by reacting an aromatic amine with 2-methylthio-2-imidazoline in the presence of pyridine. One of the most commonly used approaches entails a three-step protocol involving the conversion of an amine to the isothiocyanates, treatment of the isothiocyanate with thylenediamine, followed by a cyclization step using mercuric oxide or acetate to form the 2-amino-2-imidazoline.[7] There had also been reports in which a 2-chloro-2-imidazoline is coupled with an amine.[8] Also, Mundla *et al.*[9] have reported the synthesis of 2-arylamino-2-imidazolines by reacting an aromatic amine with *N*-acylated-2-methylthio-2-imidazoline.[10] Another methods for preparation of 2-arylamino-2-imidazolines are reaction of ethylenediamine with carbodiimide,[11] methyl *N*-arylthiocarbamate, and dimethyl *N*-aryldithiocarbonimidate.[12] Also, these compounds are prepared from reaction of cyanogens bromide with ethylenediamines.[13]

From our experience, many of the known methods have one or more limitations. For example, using toxic reagents like cyanogens bromide, low yields, hard reaction conditions, and the byproduct of many of these reactions is the noxious gas, methyl mercaptan; this foul smelling gas has a threshold of detection by humans of about 1 ppb.

In a note Maryanoff *et al.*[14] describe a convenient, cost-effective synthesis of guanidines from thioureas and amines. The key transformation involves activation of the sulfur in the thiourea through *S*-oxidation, followed by displacement of the activated sulfur group by amine nucleophiles. Aminoiminomethanesulfonic acid reacts with a variety of primary amines, including *t*-butylamine, to give 50%—80% yields of the corresponding guanidines. This reaction is more facile than guanidine synthesis starting with *S*-alkylisothioureas.[15] Reaction of primary and secondary amines with monosubstituted (phenylamino)- and (*n*-propylamino)iminomethanesulfonic acids also give good to excellent yields of the corresponding guanidines.[15]

Results and discussion

At the initiation of our work, we have prepared thioureas, according to literature procedure,[16] from reaction of amine with benzoyl chloride. Thiocarbamate oxidized to corresponding sulfonic acid by hydrogen peroxide and sodium molybdate.[14] Table 1 lists typical isolated yields for oxidation of several thioureas by 30% hydrogen peroxide in water using sodium molybdate as a catalyst. The molybdenum-promoted hydrogen peroxide oxidation of the thioureas to sulfonic acids proved

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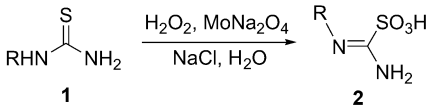
very exothermic. The rate of addition of H_2O_2 determined the internal temperature. The rate must be sufficiently slow to prevent the internal reaction temperature from rising above 0 ℃. Careful monitoring of the internal temperature afforded reproducible yields of the reagent.

Table 1 Conversion of thioureas to corresponding sulfonic acids at 0 ℃ in water



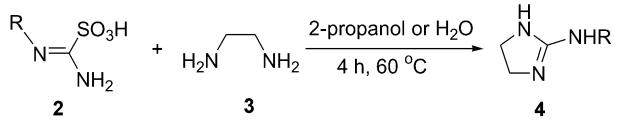
1 **2**

Compd.	R	Yield[a]/%
2a	H	65
2b	C_6H_5	78
2c	*p*-ClC_6H_4	80
2d	*p*-BrC_6H_4	83
2e	2,6-$Cl_2C_6H_4$	77

[a] Isolated yield.

In the next, we report the use of sulfonic acids as novel reagent for synthesis of 2-arylamino-2-imidazolines **4** from diamines under mild and neutral conditions (Scheme 1). Treatment of ethylenediamine with amino(phenylimino)methanesulfonic acid in water or 2-propanol solvent for 4 h afforded *N*-phenyl-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)amine with 90% yield. Encouraged by the results obtained with amino(phenylimino)-methanesulfonic acid, we examined several other diamines (Table 2). Various sulfonic acids reacted smoothly with diamines under similar reaction conditions to produce the corresponding 2-arylamino-2-imidazolines **4** in excellent yields.

Scheme 1 Preparation of imidazolines



2 **3** **4**

Table 2 Preparation of 2-arylamino-2-imidazolines from ethylenediamine with thioureas

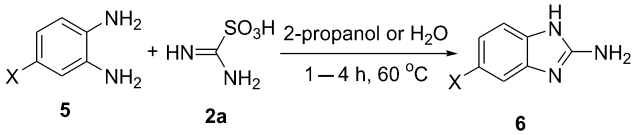
R	Thioureas **2**	Product **4**[a]	Solvent	Yield[b]/%
H	**2a**	**4a**	2-Propanol	80
			Water	77
C_6H_5	**2b**	**4b**	2-Propanol	90
			Water	76
p-ClC_6H_4	**2c**	**4c**	2-Propanol	92
			Water	68
p-BrC_6H_4	**2d**	**4d**	2-Propanol	93
			Water	65
2,6-$Cl_2C_6H_4$	**2e**	**4e**	2-Propanol	91
			Water	54

[a] All products are known compounds and characterized by ^{1}H NMR, IR, and m.p. [b] Isolated yield.

In order to directly compare the performance of reaction in 2-propanol with similar reactions in water, the conversion after 4 h was determined for similar amount of solvent. As can be seen from Table 2, the conversion after 4 h in 2-propanol is better than that in water.

The reaction of *o*-phenylenediamines with sulfonic acids was also investigated and found that *o*-phenylenediamines reacted with sulfonic acids at 60 ℃ in high yields (Scheme 2). The results are shown in Table 2.

Scheme 2 Preparation of 2-aminobenzimidazoles



5 **2a** **6**

Table 3 Preparation of 2-aminobenzimidazole from aminosulfonic acid with phenylenediamine

X	Phenylenediamine **5**	Product **6**[a]	Solvent	Yield[b]/%
H	**5a**	**6a**	2-Propanol	95
			Water	87
NO_2	**5b**	**6b**	2-Propanol	90
			Water	45
Cl	**5c**	**6c**	2-Propanol	97
			Water	80
CH_3	**5d**	**6d**	2-Propanol	93
			Water	82

[a] All products are known compounds and characterized by ^{1}H NMR, IR and m.p. [b] Isolated yield.

In conclusion, we have described a novel and efficient method for the synthesis of 2-arylamino-2-imidazoline and 2-aminobenzimidazole using 2-propanol or water as reaction medium. This method is simple, high yielding, and avoids the use of toxic reagents and harsh reaction conditions.

Experimental

^{1}H NMR spectra were recorded on a Bruker Fourier 300 NMR spectrometer using tetramethylsilane as the internal standard. IR spectra were taken on a Perkin-Elmer 267 spectrophotometer. Thin layer chromatography was performed on silica gel (Macerey-Nagel Co., plygram Sil G/uv).

All organic solutions were dried over $MgSO_4$ or Na_2SO_4 and solvents were removed under reduced pressure on a Buchi evaporator. All thioureas, aminoiminomethanesulfonic acids, 2-arylamino-2-imidazolines and 2-aminobenzoimidazoles are known compounds, and they were identified by comparison of their spectral (IR, NMR) and physical data with those of authentic samples.

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Synthesis of amino(phenylimino)methanesulfonic acid

Typical procedure A reaction vessel was charged with 1-phenylthiourea (1.97 g, 0.013 mol), water (6 mL), sodium chloride (0.29 g, 0.005 mol) and sodium molybdate dihydrate (0.0484 g, 0.0002 mol), and cooled to 0 ℃ with efficient stirring. Hydrogen peroxide (30%, 4.65 g, 0.041 mol) was added drop wise to the cooled suspension at a rate to minimize decomposition (followed the reaction by TLC). After addition of H_2O_2, the reaction mixture was allowed to warm up to 30 ℃ and stirred for 1 h. The product was isolated by cooling the reaction to 5 ℃ and collecting the solid sulfonic acid by filtration (2.33 g, 90%). m.p. 157.5—158.5 ℃ (Lit.[14] 157—158 ℃); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.52 (s, 1H, NH), 7.12—7.85 (m, 4H, ArH), 10.23 (br s, 1H); IR (KBr) v: 3340 (NH amine), 3350 (OH), 1670 (C=N stretching), 1590 (N—H bending), 1170 (asy SO_2), 1040 (sym. SO_2), 650 (SO) cm^{-1}.

Amino(4-chlorophenylimino)methanesulfonic acid: m.p. 147—148 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.52 (s, 1H, NH), 7.02—7.90 (m, 4H, ArH), 10.22 (br s, 1H); IR (KBr) v: 3340 (NH amine), 3345 (OH), 1668 (C=N stretching), 1595 (N—H bending), 1170 (asy SO_2), 1040 (sym. SO_2), 655 (SO) cm^{-1}.

Amino(4-bromophenylimino)methanesulfonic acid: m.p. 153—156 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.40 (s, 1H, NH), 7.02—7.76 (m, 4H, ArH), 10.20 (br s, 1H); IR (KBr) v: 3340 (NH amine), 3348 (OH), 1668 (C=N stretching), 1590 (N—H bending), 1174 (asy SO_2), 1045 (sym. SO_2), 650 (SO) cm^{-1}.

Amino(2,6-dichlorophenylimino)methanesulfonic acid: m.p. 264—265 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.52 (s, 1H, NH), 7.02—8.10 (m, 3H, ArH), 10.18 (br s, 1H); IR (KBr) v: 3345 (NH amine), 3350 (OH), 1668 (C=N stretching), 1545 (N—H bending), 1173 (asy SO_2), 1046 (sym. SO_2), 650 (SO) cm^{-1}.

Synthesis of *N*-phenyl-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)amine

Typical procedure Amino(phenylimino)sulfonic acid (2 g, 0.01 mol) prepared above was added to the ethylenediamine (1.56 g, 0.026 mol) in 10 mL of 2-propanol or water at room temperature. The reaction mixture was heated at 60 ℃ for 4 h. The reaction was worked up by adjusting the pH to range 12—14 with 3 mol/L NaOH and the mixture was extracted with CH_2Cl_2 (20 mL×3), dried over Na_2SO_4 and concentrated. The concentrated residue was purified by column chromatography to afford pure compound (1.38 g, 86%). m.p. 115.5—117 ℃ (Lit.[12] m.p. 115—116 ℃); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.45 (s, 1H, NH), 3.70 (s, 4H, imidazoline CH_2), 6.28 (broad peak, 1H, imidazoline NH), 7.10—8.15 (m, 5H, ArH); IR (KBr) v: 3275 (imidazoline N—H stretching), 3254 (N—H stretching), 1660 (C=N stretching), 1539 (N—H bending) cm^{-1}.

N-(4-Chlorophenyl)-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)amine: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.48 (s, 1H, NH), 3.73 (s, 4H, imidazoline CH_2), 6.28 (broad peak, 1H, imidazoline NH), 7.12—8.34 (m, 4H, ArH); IR (KBr) v: 3270 (imidazoline N—H stretching), 3262 (N—H stretching), 1665 (C=N stretching), 1542 (N—H bending) cm^{-1}.

N-(4-Bromophenyl)-*N*-(4,5-dihydro-1*H*-imidazol-2-yl)amine: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.35 (s, 1H, NH), 3.68 (s, 4H, imidazoline CH_2), 6.04 (broad peak, 1H, imidazoline NH), 7.10—8.51 (m, 4H, ArH); IR (KBr) v: 3267 (imidazoline N—H stretching), 3253 (N—H stretching), 1667 (C=N stretching), 1547 (N—H bending) cm^{-1}.

2-Aminoimidazoline: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 3.50 (s, 2H, NH_2), 3.61 (s, 4H, imidazoline CH_2), 6.02 (broad peak, 1H, imidazoline NH); IR (KBr) v: 3258 (imidazoline N—H stretching), 3243, 3250 (NH_2 stretching), 1660 (C=N stretching), 1540 (N—H bending) cm^{-1}.

Synthesis of 2-amino-5-nitrobenzimidazole

Typical procedure Aminoiminomethanesulfonic acid (1.24, 0.01 mol) and 4-nitrophenylenediamine (1.53 g, 0.01 mol) were mixed in 10 mL of 2-propanol or water and stirred at room temperature for 5 min. The reaction mixture was heated at 60 ℃ for 1 h. The mixture was cooled and pH was adjusted between 12—14 with 3 mol/L NaOH. The resulting precipitate was filtered and washed with water. Crude product was recrystalized from methanol (1.6 g, 90%), m.p. 207—210 ℃ (Lit.[17] 207—211 ℃); ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.85 (s, 2H), 7.18 (d, J=8.7 Hz, 1H), 7. 87 (dd, J_{AB}=8.7 Hz, J_m=2.3 Hz, 1H), 7.95 (d, J=2.3 Hz, 1H).

2-Amino-5-methylbenzimidazole: m.p. 203—204 ℃; ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 2.31 (s, 3H), 6.85 (s, 2H), 7.18 (d, J=8.2 Hz, 1H), 7. 87 (dd, J_{AB}=8.2 Hz, J_m=2.2 Hz, 1H), 7.95 (d, J=2.2 Hz, 1H).

2-Amino-5-chlorobenzimidazole: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.79 (s, 2H), 7.15 (d, J=8.1 Hz, 1H), 7.80 (dd, J_{AB}=8.1 Hz, J_m=2.1 Hz, 1H), 7.90 (d, J=2.1 Hz, 1H).

2-Aminobenzimidazole: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 6.68 (s, 2H), 7.21—7.81 (m, 5H).

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