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A New Mild Method for the Synthesis of Amidines

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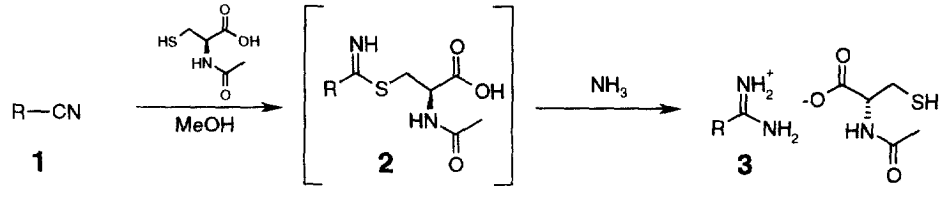
Abstract: *A new method for the synthesis of amidines is presented using N-acetylcysteine as a catalyst. The key advantage of this new method is that it is compatible with a large number of functional groups. It allows the synthesis of amidines in complex molecules containing acid-labile groups, base-labile centers of asymmetry or functional groups sensitive to hydrogenation.* © 1999 Elsevier Science Ltd. All rights reserved.

Key words: amidines, amination, homogeneous catalysis, nitriles.

Amidines are valuable intermediates in the synthesis of heterocyclic compounds,[1] characteristic structural features of many natural substances[2] and important pharmacophores in the active ingredients of drugs.[3] Numerous synthetic methods have been developed for their preparation which are documented comprehensively in a number of review articles.[4]

Many of the synthetic methods for the preparation of amidines described in the literature[5-16] involve highly acidic,[5, 6] alkaline[12-15] or strongly reducing[9, 11] reaction conditions or require high temperatures[16] and are less suitable for the synthesis of highly functionalized amidines.

We therefore developed a new method for the synthesis of amidines which does not have the above mentioned drawbacks. Starting from nitriles it uses *N*-acetylcysteine[17] as a catalyst. In the first step *N*-acetylcysteine adds to the nitrile **1** forming an imino-thioether intermediate **2**. In the second step the catalyst is released from the intermediate **2** by displacement with ammonia forming amidine **3**. The transformation is mechanistically related to the Thio-Pinner reaction.[6, 18, 19]



The reaction exhibits a marked dependence on the reaction temperature. At elevated temperature the reaction rate increases in spite of the reduced solubility of ammonia. The addition of *N*-acetylcysteine to the nitrile **1** is presumably the rate determining step of the reaction. The product obtained is the amidinium acetylcysteinate. Thus in addition to its

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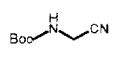
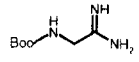
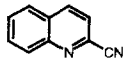
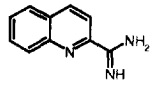
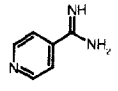
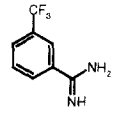
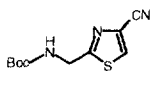
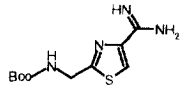
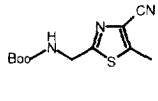
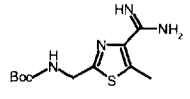
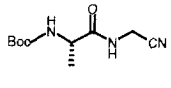
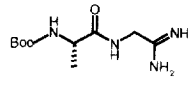
catalytic activity the *N*-acetylcysteine also has the function of stabilizing the amidine formed since the latter decomposes through loss of ammonia in basic media.[20]

Best results are obtained with electron-deficient aromatic, heteroaromatic and aliphatic nitriles as substrates. They react to form amidines in high to very high yields [table 1]. When the reaction is run catalytically or on a small scale ammonium acetate is used preferentially as an alternative to gaseous ammonia [table 1, method B].

Table 1: *N*-acetylcysteine-catalyzed conversion of nitriles to amidines

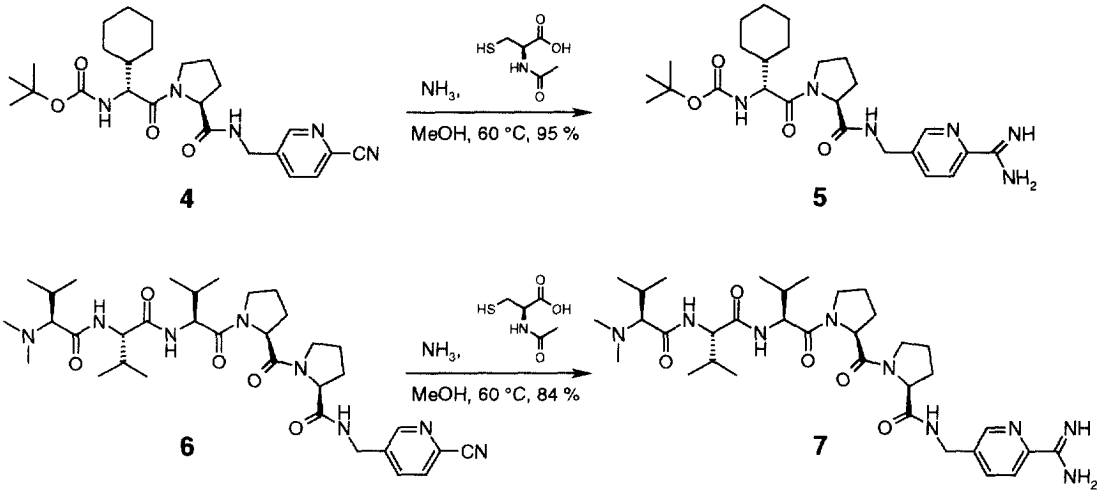
Entry	Reactant	Product	Method[a]	Eq. *N*-acetyl-cysteine	Temp. °C	Time h	Yield %
1			A	1	60	7	89
2			B	1	50	48	73
3			A	1.1	60	3.5	92
4			B	1	50	6.5	94
5			B	0.1	50	14	68
6			A	1	35	15	90
7			A	1	60	10	73
8			A	1.3	40	4	80
9			A	1.2	60	22	66
10			A	1.05	60	7.5	91[b]

[a] method A: NH_3; method B: NH_4OAc.

[b] isolated as *N*-acetylcysteinate.

The reaction can be carried out at very high concentrations (> 50%) and this has a positive effect on the reaction time. Sterically demanding nitriles can likewise be converted to the corresponding amidines, but they react more slowly [table 1, entries 8 and 9]. In accord with the mechanism postulated above catalytic quantities of *N*-acetylcysteine can be used, but this results in prolonged reaction times [table 1, entries 4 and 5].

The method proves to be particularly advantageous when introducing the amidine moiety to highly functionalized molecules since strong bases (racemization), strong acids (cleavage of acid-labile protecting groups) and strongly reducing reaction conditions (reduction of functional groups) are avoided. Thus it was possible to transform the nitriles **4** and **6**, intermediates in the synthesis of thrombin inhibitors or cytostatics, into the corresponding amidines **5**[21] and **7** in good yields without racemization of the stereocenters or cleavage of the protecting groups.



These examples clearly demonstrate the scope of the reaction in terms of functional group compatibility. Furthermore, the catalyst is not toxic or olfactorially unpleasant. Additionally, *N*-acetylcysteine has a stabilizing effect on the product of the reaction. The catalyst can be recycled after simple separation from the crude product by means of ion exchange chromatography. The method also exhibits good atom economy since it avoids the formation of salts which, above all in industrial processes, are unwanted.

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Typical Procedures:

tert-Butyl 2-amino-2-iminoethylcarbamate × AcOH [method A]

N-Boc-aminoacetonitrile (4.1 g, 26 mmol) and *N*-acetylcysteine (4.2 g, 26 mmol) were dissolved in 30 mL of methanol at 60 °C and ammonia is passed through for 7 h. The solvent was removed in vacuo. After ion exchange chromatography tert-butyl 2-amino-2-iminoethylcarbamate × AcOH was obtained (5.4 g, 23 mmol, 89%).^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.45 (s, 9 H, t-Bu) 1.95 (s, 3 H, CH_3), 4.0 (d, J = 7 Hz, 2 H, CH_2), 6.9 (broad s, 1 H, NH). ^{13}C NMR ([D_6]DMSO, 25 °C, TMS): δ = 24.5 (Q), 28.1 (Q), 42.9 (t), 78.7 (S), 155.7 (S), 169.1 (S), 176.1 (S). - MS (CI, 120 eV): m/z (%): 174 (70) $[M + H]^+$, 132 (35), 118 (100). Anal. for $C_9H_{19}N_3O_4$, found (calc.): C 46.0 (46.3), H 8.1 (8.2).

2-Amidinoquinoline × AcOH [method B]

2-Cyanoquinoline (477 mg, 3.0 mmol) and *N*-acetylcysteine (56 mg, 0.34 mmol) were dissolved in methanol (2.5 mL) and ammonium acetate (280 mg, 3.60 mmol) was added. The reaction mixture was heated at 50 °C under an atmosphere of nitrogen for 14 h. The *N*-acetylcysteine was separated *via* an ion exchanger charged with acetate. The methanol was removed in vacuo, the residue was taken up in water and washed with dichloromethane. The aqueous phase was lyophilized and 2-amidinoquinoline × AcOH was obtained (0.47 g, 2.0 mmol, 68%, colorless solid). ^{1}H NMR (360 MHz, [D_6]DMSO, 25 °C, TMS): δ = 1.80 (s, 3H), 7.77 (t, J = 8.4 Hz, 1H), 7.92 (t, J = 8.4 Hz, 1H), 8.12 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.67 (d, J = 8.4 Hz, 1H). ^{13}C NMR ([D_6]DMSO, 25 °C, TMS): δ = 23.8 (Q), 118.3 (D), 127.9 (D), 128.5 (S), 128.7 (D), 129.3 (D), 130.8 (D), 138.0 (D), 146.2 (S), 147.2 (S), 161.9 (S), 175.5 (S). Anal. for $C_{12}H_{13}N_3O_2$, found (calc.): C 62.0 (62.3), H 5.7 (5.7), N 18.0 (18.2).