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Synthesis and Protection of Some Amidines

Kadir DABAK
İstanbul Technical University, Faculty of Sciences, Department of Chemistry,
Maslak 80626 İstanbul-TURKEY
e-mail: kadird@eczacibasi.com.tr

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A series of benzamidine derivatives were synthesized from substituted benzonitrile compounds and protected with the *tert*-butoxycarbonyl group.

Introduction

Amidines, especially benzamidine derivatives and their protected forms, are used very often in pharmacological and medicinal applications[1−5].

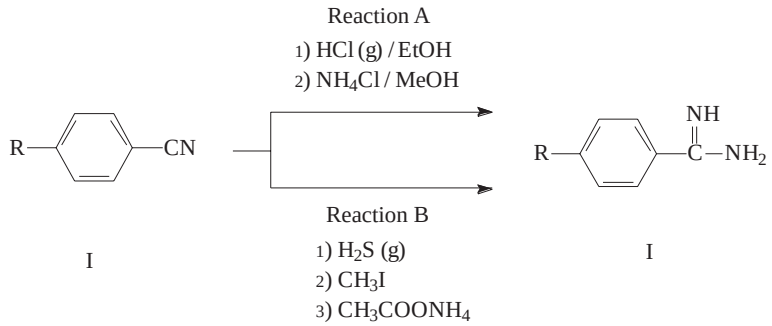
Amidines are usually prepared from nitrile compounds. There are several methods available for transformation of the nitrile group to the amidine group in the literature[6−8]. However, for the protection of the amidine group, there are only limited examples. In particular, for *tert*-butoxycarbonyl protection, only a few examples are reported[9].

In this study, the synthesis of some amidines and their protection with the *tert*-butoxycarbonyl group were investigated.

Results and Discussion

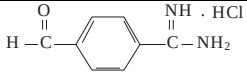
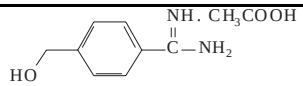
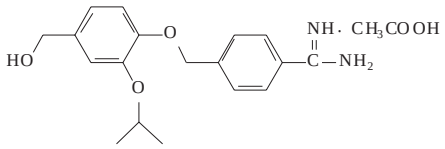
Recently, we described[10] an efficient synthesis of a 1,2,4-trisubstituted benzene templated potential peptidomimetic of SNX111[11]. SNX111, which is also known as "ω-Conotoxin MVIIA", from the venom of the cone shell *Conus magus*[12,13], is one of the most promising new drugs for the treatment of severe neuropathic pain[14,15]. Compound **IIc** (Table 1) was designed and synthesized in our previous study[10] as a potential peptidomimetic of SNX111. On this compound, there are three amino acid side chain mimicking groups. Leucine, tyrosine and arginine amino acid side chain mimetics were attached on a central core. The arginine side chain was mimicked by the benzamidine group on this compound.

In this study, amidine derivatives (**II**) (Table 1) were synthesized from nitrile compounds (**I**) by two different methods. The Pinner reaction[7] (Scheme 1, Reaction A) and the thioimidate route[8] (Scheme 1, Reaction B) are the methods studied. The reaction yields and spectroscopic data for the synthesized amidines are given in Table 1.



Scheme 1.

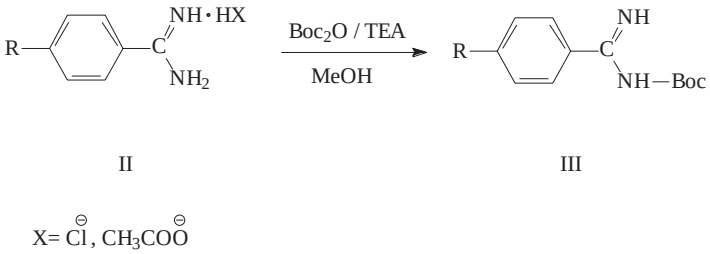
Table 1. Synthesized amidines

	Amidine	Yield (%)	Spectroscopic data
IIa		20[a]	^{1}H NMR (270 MHz, $CDCl_3$)δ 7.95 (d, 2H, J=8.6 Hz), 8.04 (d, 2H, J=8.2 Hz), 9.36 (s, 2H), 9.58 (s, 2H), 10.12 (s, 1H).
IIb		45[b]	^{1}H NMR (270 MHz, $CDCl_3$)δ 1.71(s, 3H), 4.58 (s, 2H), 7.49 (d, 2H, J=8 Hz), 7.74 (d, 2H, J=8 Hz).
IIc		50[b]	^{1}H NMR (270 MHz, $CDCl_3$)δ 1.37 (d, 6H, J=6.1 Hz), 1.72 (s, 3H), 3.35 (broad), 4.35 (s, 2H), 4.59 (septet, 1H), 5.20 (s, 2H), 6.78 (d, 1H), 6.85 (d, 2H), 7.61 (d, 2H, J=8 Hz), 7.78 (d, 2H, J=8 Hz). MS (EI) m/e (relative intensity) 311 (9), 297 (28), 139 (58), 116 (100), 93 (40), 43 (35).

[a)] By Reaction A (Scheme 1)

[b)] By Reaction B (Scheme 1)

Amidine groups of synthesized compounds (**II**) were protected with Boc_2O (Scheme 2). The reaction yields and spectroscopic datas are given in Table 2.

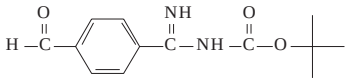
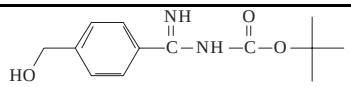
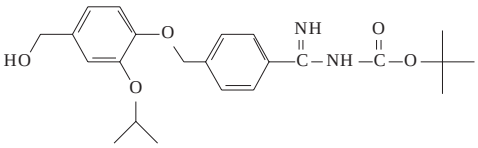


Scheme 2.

Experimental

^{1}H NMR spectra were recorded at 300 MHz on a Varian Gemini-2000 NMR spectrometer and at 270 MHz on a Jeol JNM EX270 machine; ^{13}C spectra were recorded at 75.4 MHz on the Varian instrument and at 67.8 MHz on the Jeol. Me_4Si was used as an internal reference. Mass spectra were produced on a Kratos model MS25 magnetic sector mass spectrometer using electron impact ionization (70eV).

Table 2. Protected amidines.

	R	Yield (%)	Spectroscopic data
IIIa		75	^{1}H NMR (270 MHz, $CDCl_3$)δ 1.5 (s, 9H), 7.85 (d, 2H, J=8 Hz), 7.96 (d, 2H, J=8 Hz), 10.02 (s, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$)δ 27.8, 28.0, 80.0, 127.8, 128.3, 129.5, 138.2, 140.3, 162.4, 165.9, 191.4. MS (EI) m/e (relative intensity) 248 (M^+).
IIIb		78	^{1}H NMR (270 MHz, $CDCl_3$)δ 1.55 (s, 9H), 4.75 (s, 2H), 7.42 (d, 2 H, J=8 Hz), 7.85 (d, 2H, J=8 Hz), MS (EI) m/e (relative intensity): 250 (M^+).
IIIc		73	^{1}H NMR (270 MHz, $CDCl_3$)δ 1.36 (d, 6H, J=6 Hz), 1.54 (s, 9H), 4.54-4.57 (septet, 1H), 4.59 (s, 2H), 5.15 (s, 2H), 6.83 (s, 2H), 6.98 (s, 1H), 7.47 (d, 2H, J=8 Hz), 7.77 (d, 2H, J=8 Hz). MS (EI) m/e (relative intensity): 430 (M^+).

Synthesis of p-amidino benzaldehyde.HCl (*IIa*)

p-Cyano benzaldehyde (10.38 g) was dissolved in dry chloroform (200 ml), and absolute ethly alcohol (5.56 ml, 1.2 eq) was added to this solution. This mixture was saturated at 0°C with dry HCl and allowed to stand at 0°C for 24 hours. Then the solvent was removed under reduced pressure and 250 ml of diethy ether was added. Precipitated white crystals were filtrated. The crystals were dissolved in ice-cold water, 200 ml of 10% potassium carbonate was added and the mixture was stirred for 5 min at room temperature. Then extracted with 200 ml of ethyl acetate. The organic phase was dried over sodium sulphate, the solvent was removed under reduced pressure and an oil was obtained. This oil was refluxed for 5 h in the presence of ammonium chloride (1.1 eq.) in methanol/water (150 ml/20 ml). Solvent was removed under reduced pressure, acetone (200 ml) was added and filtration yielded the title compound. The yield and spectroscopic data are given in Table 1.

Synthesis of *IIb* and *IIc*

Hydrogen sulphide was bubbled through a solution of the benzonitrile (**I**) (8.4 mmol), in a pyridine-triethylamine mixture (20 ml-2 ml) for 15 min at room temperature. After 24 h at room temperature in a stoppered flask, the reaction mixture was concentrated under a steady stream of nitrogen. The residue was diluted with 100 ml of ethyl acetate, washed with 100 ml of $KHSO_4$ and 100 ml of saturated sodium chloride solution and dried over sodium sulphate. Concentration in vacuo afforded a quantitative yield of thioamide. The thioamide was dissolved in a solution of acetone-iodomethane mixture (30 ml-2 ml) and was warmed for 5 h to achieve reflux. Concentration in vacuo afforted the thioimidate as the HI salt. Residue was used directly in the next step without purification. The residue and ammomium acetate (2 g) in methanol (150 ml) was refluxed for 8 h. After cooling to room temperature, the reaction mixture was concentrated under a steady stream of nitrogen; then acetone (200 ml) was added and the precipitated product was filtrated. The yields and spectroscopic data are given in Table 1.

Synthesis of Compounds *III*

Amidine compound (**II**) (0.1 mmol) was dissolved in 40 ml methanol and 2 ml triethylamine was added. Then Boc_2O (3.3 eq) was added and the mixture was refluxed for 5 h. The solvent was removed under reduced pressure and the product was purified by column chromatography. The yields and spectroscopic data are given in Table 2.

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