Pergamon

Tetrahedron Letters, Vol. 37, No. 11, pp. 1787-1790, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00132-3

A Two-Steps Benzotriazole-Assisted Synthesis of 3-Amino-2-Ethoxycarbonyl Imidazo [1,2-a] Pyridines and Related Compounds.

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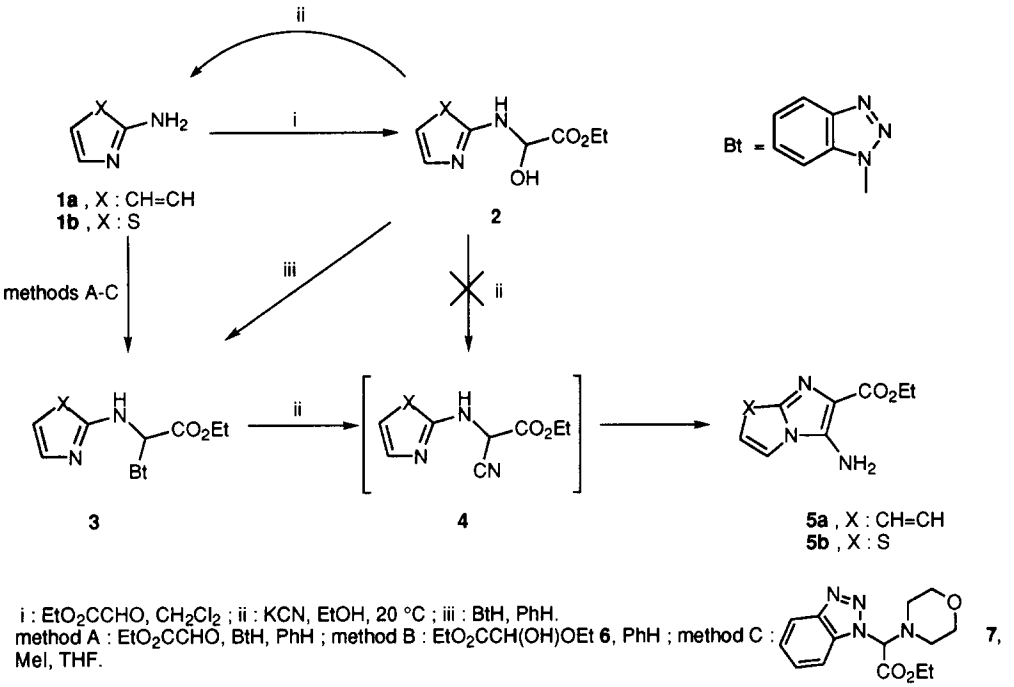
Abstract : Reaction of primary heterocyclic amidines with benzotriazole and ethyl glyoxylate or ethyl glyoxylate equivalents afforded the corresponding α-benzotriazolyl-α-amidino esters which, upon treatment with potassium cyanide yielded the corresponding 3-amino-2-ethoxycarbonyl imidazo [1,2-a] pyridines and related compounds.

The 3-amino-2-ethoxycarbonyl imidazo [1,2-a] pyridines **5a** and related compounds have been previously described as potential antibacterial agents,[1] and constitute valuable intermediates for the synthesis of purine derivatives.[2] These compounds were usually prepared in three steps from primary heterocyclic amidines **1**. This method needed a preliminary synthesis of the parent 3-unsubstituted imidazo heterocycle, followed by a two steps nitration/reduction procedure.[3,4] However this procedure was not regioselective, since nitration might occur at both the 3 position and the parent heterocycle.[5] The present communication deals with a new efficient two-steps synthesis of 3-amino-2-ethoxycarbonyl imidazo [1,2-a] pyridine **5a** and related compounds starting from primary heterocyclic amidines **1** by means of ethyl glyoxylate, benzotriazole and potassium cyanide (scheme 1).

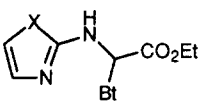
Reaction of primary heterocyclic amidines **1** and freshly distilled ethyl glyoxylate led to hydroxyaminals **2** in good yield (80-90 %).[6] However compounds **2** did not react with potassium cyanide, but underwent retroaldolisation affording quantitatively the starting amidines **1**. Thus hydroxyaminals **2** were reacted with benzotriazole (BtH), a highly efficient synthetic auxiliary described recently by Katritzky,[7] and afforded the benzotriazolylacetate **3**. Compound **3a** was also obtained directly from 2-amino pyridine **1a** by different ways using benzotriazole, and freshly distilled ethyl glyoxylate (method A), ethyl glyoxylate hemiacetal **6**[8] (method B), or the α-benzotriazolyl-α-morpholino acetate **7**[9] in presence of MeI (method C).[10]



Scheme 1

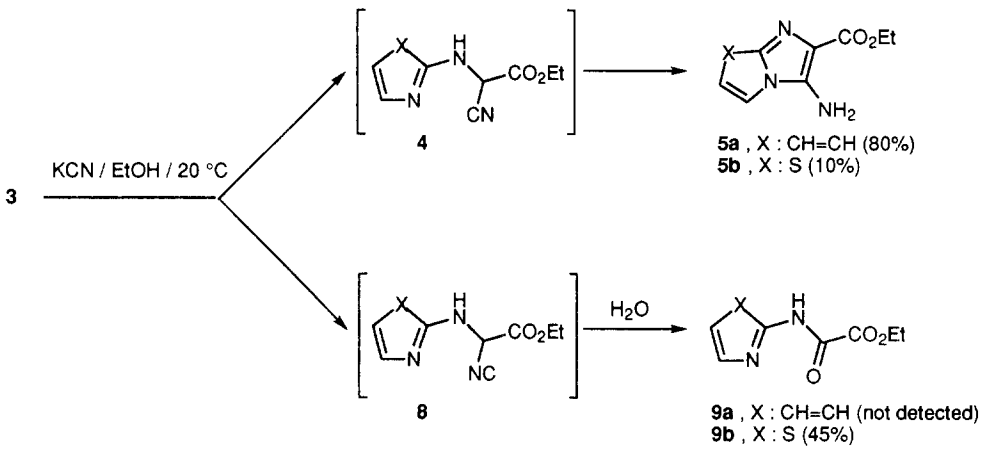
With 2-amino thiazole **1b**, method A gave only traces of **3b**, whereas method C led to **3b** in 40% yield (Table 1, entries 4 and 5). These results show the convenience of method C to produce compounds **3** in good yields (compare entries 1,2 and 3 and entries 4 and 5).

Table 1 : Preparation of compounds **3**.



entry	**3**	X	method	Yield %
1	**a**	CH=CH	A	49
2	**a**	CH=CH	B	59
3	**a**	CH=CH	C	70
4	**b**	S	A	trace
5	**b**	S	C	40

The resulting stable derivative **3a** was reacted smoothly with potassium cyanide in ethanol at 20 °C to afford directly 3-amino-2-ethoxycarbonyl imidazo [1,2-a] pyridine **5a** in 80% yield.[11] The reaction involves a substitution of the benzotriazole moiety by the cyanide anion[12] followed by an intramolecular cyclisation. However, when the same reaction conditions were employed with **3b**, both the expected amino imidazo thiazole **5b** and the α-ketoester **9b**[13] were isolated in 10 and 45% yield respectively (scheme 2). The predominant formation of compound **9b** is probably due to a preferential non classical addition of the cyanide ion to **3b** leading to the isocyanide adduct **8b**. It is noteworthy that the ambident nucleophilic character of the cyanide ion was previously reported for other displacement reactions.[14]



Scheme 2

The reaction of different heterocyclic amidines in presence of benzotriazole and ethyl glyoxylate, or equivalents of ethyl glyoxylate yielded α-benzotriazolyl-α-amidino esters. These compounds constitute valuable synthons capable of reacting with different nucleophiles. Particularly, when reacted with potassium cyanide, they lead directly to 3-amino imidazo heterocycles. The simplicity of the procedure coupled with the convenient availability of the starting material suggests a potential utility of this reaction in organic chemistry. Moreover it can be extended to other aldehydes and other cyclic, non cyclic amidines and isosteres.

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10 Typical procedure for method C : **3a**. Methyl iodide (1.1 g, 0.8 mmol) was added to a solution of ethyl 2-(benzotriazol-1-yl)-2-morpholinoacetate **7**[9] (2 g, 0.68 mmol) in dry THF (30 mL). The mixture was stirred at 20 °C for 10 min. and 2-aminopyridine (0.64 g, 0.68 mmol) was added. The mixture was refluxed for 3h, cooled at 20 °C and left for 16h. The heterogeneous solution was filtered and the resulting solution was evaporated in vacuo. A classical work-up afforded a residue, which was purified by flash chromatography on silica gel (EtOAc-hexane 2/3) to afford 1.4 g (70%) of white powder. mp 118-119 °C ; ^{1}H-NMR (200MHz, $CDCl_3$) δ : 1.18 (t, 3H, J = 7.2), 4.29 (m, 2H), 6.27 (d, 1H, J = 7.6), 6.62 (d, 1H, J = 8.3), 6.69 (ddd, 1H, J = 7.1, 5.0 and 0.6), 7.3-7.6 (m, 4H), 7.93 (d, 1H, J = 8.3), 8.05 (d, 1H, J = 8.3), 8.11 (dd, 1H, J = 5.0 and 0.6) ; ^{13}C-NMR (50MHz, $CDCl_3$) δ : 13.8, 63.2, 65.2, 109.0, 110.7, 115.5, 119.8, 124.1, 127.6, 132.5, 137.8, 145.9, 147.8, 154.8, 166.4.

11 Typical procedure for compounds **5** : 3-amino-2-ethoxycarbonyl imidazo [1,2-a] pyridine **5a**. Potassium cyanide (120 mg, 1.8 mmol) was added to a solution of **3a** (500 mg, 1.7 mmol) in absolute ethanol (15 mL). The mixture was stirred at 20 °C for 2h and the solvent was removed under reduce pressure. After classical work up, the crude product was crystallised from ether to afford 280 mg (80%) of a yellow powder. mp 210 °C (lit.[4] 210-212 °C) ; ^{1}H-NMR (200MHz, $CDCl_3$) δ : 1.42 (t, 3H, J = 7.3), 4.42 (q, 2H, J = 7.3), 5.07 (broad, 2H), 6.75 (ddd, 1H, J = 6.7, 6.6 and 1.0), 7.06 (ddd, 1H, J = 9.1, 6.6, and 1.3), 7.46 (ddd, 1H, J = 9.1, 1.0 and 0.9), 7.73 (ddd, 1H, J = 6.7, 1.3 and 0.9) ; ^{13}C-NMR (50MHz, $CDCl_3$) δ : 14.3, 60.5, 112.3, 115.8, 118.9, 121.7, 124.2, 136.7, 139.0, 165.2.

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(*Received in France* 30 *November* 1995; *accepted* 22 *January* 1996)