

A facile tandem synthesis of α -benzyl benzimidazole acetonitriles

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Abstract

An efficient and convenient tandem method for the synthesis of α -benzylbenzimidazoleacetonitriles has been developed. In this method, a benzimidazoleacetonitrile **1** was condensed with an aromatic aldehyde in the presence of basic alumina under solvent-free conditions by simple physical grinding of reactants using a mortar and pestle. Subsequent reduction of the *in situ* formed acrylonitrile derivative with NaBH₄ in 95% ethanol at room temperature gives the corresponding 2-(1*H*-benzimidazol-2-yl)-3-aryl-propionitrile **3** by regiospecific reduction of the double bond.

Keywords: Benzimidazoleacetonitriles, aromatic aldehydes, basic alumina, solvent-free, NaBH₄

Introduction

In recent years considerable attention has been paid to the reactions done under solvent-free conditions^{1,2}. NaBH₄ is a frequently used hydride in reduction processes and it is known to reduce polar carbonyl groups such as aldehydes and ketones³ and esters⁴. It is also known to reduce, selectively, carbonyl groups in α , β -unsaturated ketones⁵ and nitriles under certain conditions⁶.

Benzimidazole derivatives are useful intermediates/subunits for the development of molecules of pharmaceutical or biological interest⁷ and substituted benzimidazole derivatives have found applications in diverse therapeutic areas such as anti-ulcer agents, anti-cancer agents, and anthelmintic species to name just a few^{8,9}. The widespread interest in benzimidazole-containing systems has promoted extensive studies of their syntheses. Substituted-2-(α -cyanostyryl)benzimidazoles are useful intermediates for the syntheses of fused heterocyclic ring systems¹⁰.

In continuation of our earlier work^{11,12} on the synthesis of new benzimidazole derivatives with potential biological activity, we have been interested in the synthesis of 2-(α -

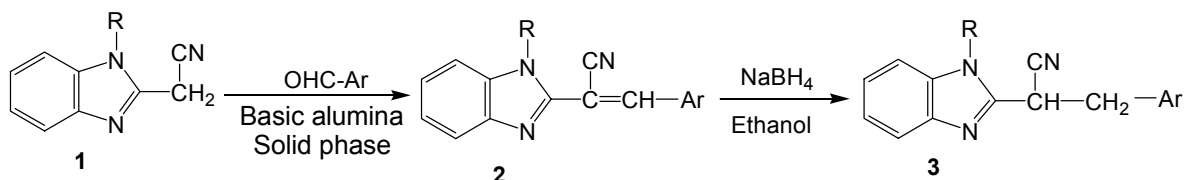
cyanostyryl)benzimidazoles and their further reactions with various reagents. The results of our studies in this direction are presented in this communication.

Results and Discussion

Literature reports^{13,14} indicate that the Knoevenagel condensation of 1-alkyl-2-(1*H*-benzimidazol-2-yl)acetonitriles **1** with aromatic aldehydes has been carried out with pyridine, piperidine, piperidine acetate, acetic acid, anhydrous ZnCl₂ and NaOH in methanol as catalysts.

In our earlier communication¹⁴, we reported that the condensation of **1** with aromatic aldehydes in methanolic NaOH solution gave isolated 1-alkyl-2-(1*H*-benzimidazol-2-yl)-3-arylacrylonitrile **2**, which, by subsequent reduction with NaBH₄ in ethanol, resulted in the formation of **3** in 74-82% yields. Now we wish to report a more selective method for the synthesis of monobenzylated derivatives of benzimidazole acetonitrile following a two-reaction sequence. The first step is a Knoevenagel condensation between benzimidazole acetonitriles and aromatic aldehydes under solvent-free conditions in the presence of basic alumina. The intermediate 2-(α -cyanostyryl)benzimidazoles **2** are then reduced in the second step to afford the desired α -benzylated benzimidazole acetonitrile derivatives in a tandem method.

Thus, condensation of 2-(1*H*-benzimidazol-2-yl)acetonitrile¹⁵ **1a** with *p*-tolualdehyde in the presence of basic alumina under solvent-free conditions was carried out by simple physical grinding using a mortar and pestle at room temperature for 10-15 min. The progress of the reaction was monitored by TLC analysis of the reaction mixture for the disappearance of **1a** using hexane and ethyl acetate (8:2) as eluent. Upon completion of the first step, the crude product was transferred into a round bottom flask and charged with 95% ethanol and the reaction mixture was cooled to 0 °C before introducing the NaBH₄. After complete addition of NaBH₄, slowly the reaction mixture was brought to room temperature, maintained at room temperature for 2-2.5 h, followed by an aqueous work-up to yield, 2-(1*H*-benzimidazol-2-yl)-3-tolylpropionitrile **3a**, by reduction of the double bond. The nitrile group remained totally unaffected under these conditions.



Scheme 1

The above reaction has been found to be a general one and has been extended to other 1-alkyl-2-(1*H*-benzimidazol-2-yl)acetonitriles **1** (R=H & CH₃) (Table 1) with aromatic aldehydes,

followed by reduction with NaBH₄. The products thus obtained were assigned structure **3** on the basis of comparison of their spectral and analytical data with those reported¹⁴.

It may be mentioned here that Robert *et al.*¹⁶ first used this method for preparing mono alkylated derivatives of malononitrile by condensation of malononitrile with carbonyl compounds in the absence of alumina. In our work, it was found that condensation of **1** with aromatic aldehydes did not take place when the reaction between the two was attempted in the solid phase in the absence of alumina.

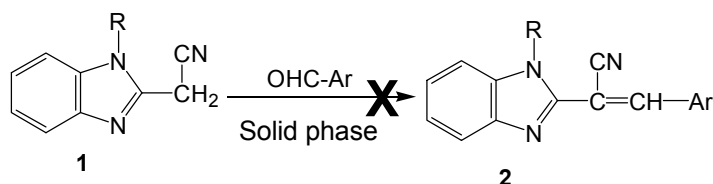
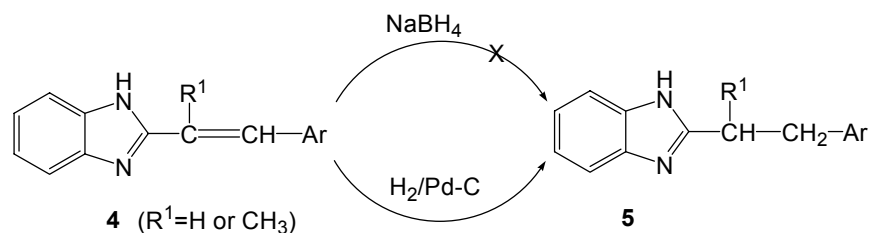


Table 1. Representation of compounds 1- 3 (R & Ar)

Entry	Substrate	Ar	Product
a	1a (R=H)	-C ₆ H ₄ CH ₃ - <i>p</i>	3a
b	1b (R=H)	-C ₆ H ₅	3b
c	1c (R=H)	-C ₆ H ₄ OCH ₃ - <i>p</i>	3c
d	1d (R=H)	-C ₆ H ₄ N(CH ₃) ₂ - <i>p</i>	3d
e	1e (R=H)	-C ₆ H ₃ (OCH ₃)- <i>m</i> -(OCH ₃)- <i>p</i>	3e
f	1f (R=H)	-C ₆ H ₄ Cl- <i>p</i>	3f
g	1g (R=H)	-C ₆ H ₄ F- <i>p</i>	3g
h	1h (R= CH ₃)	-C ₆ H ₄ CH ₃ - <i>p</i>	3h
i	1i (R= CH ₃)	-C ₆ H ₅	3i
j	1j (R= CH ₃)	-C ₆ H ₄ OCH ₃ - <i>p</i>	3j
k	1k (R= CH ₃)	-C ₆ H ₄ N(CH ₃) ₂ - <i>p</i>	3k
l	1l (R= CH ₃)	-C ₆ H ₃ (OCH ₃)- <i>m</i> -(OCH ₃)- <i>p</i>	3l

When, the reaction of 2-styrylbenzimidazole¹⁷ **4** (R=H or CH₃) (Scheme-2) with NaBH₄ in 95% ethanol at room temperature was attempted, it led to the recovery of starting material. However, shaking a solution of **4** with H₂ gas over Pd-C at room temperature gave the corresponding reduced product **5** involving saturation of the double bond. Based on the above findings, it may be inferred that the C=C is reduced selectively by NaBH₄ when it is in conjugation with an electron withdrawing group like a nitrile, due to the increase in the polarization of the double bond.



Scheme 2

In conclusion, we have developed a simple, novel, efficient and highly selective preparation of α -benzylated benzimidazoleacetonitriles by using basic alumina and NaBH₄ in a tandem method.

Experimental Section

General Procedures. Melting points are uncorrected and were determined in open capillary tubes in a sulphuric acid bath. TLC was performed on silica gel-G and visualization was done using iodine or UV-light. IR spectra were recorded with a Perkin-Elmer 1000 instrument in the KBr phase. ¹H-NMR spectra were obtained on a VARIAN 200MHz instrument and Mass spectra were recorded on an Agilent-LC-MS instrument giving only M⁺ values using the Q+1 mode.

General experimental method

A mixture of **1** (10 mmol), basic alumina (1.0 g) and aromatic aldehydes (10 mmol) was taken in a mortar and ground with a pestle. The progress of the reaction was monitored by TLC. After complete depletion of the starting material, the crude mass was transferred into a round bottom flask for reduction. To the crude mass, ethanol (50 mL) was added and the mixture was cooled to 0°C in a salt-ice bath. NaBH₄ (0.378 g, 10 mmol) was then introduced in one portion and the reaction mass was brought to RT slowly and stirred for 2.0-2.5 h. After completion of the reaction, the ethanol (20-25 mL) was distilled off and the reaction mixture was poured into ice-cold water (100 mL) and extracted into ethyl acetate (2x25 mL). The combined organic layers were dried with anhyd. Na₂SO₄ and evaporated to give pure product **3** without any further purification.

2-(1H-Benzimidazol-2-yl)-3-*p*-tolylpropionitrile (3a). Yield: 94%, mp: 208-10°C, IR (KBr) cm⁻¹: 3084 (-NH), 2254 (-CN) ; ¹H NMR (200MHz, DMSO-d₆): δ 2.24 (s, 3H, -CH₃), 3.33 (m, 2H, -CH₂-), 4.85 (t, 1H, -CH-), 7.08-7.60 (m, 8H, Ar-H), 12.70 (s, 1H, -NH-, D₂O exchangeable). M/z (M⁺+1): 262. Anal. Calcd. for (C₁₇H₁₅N₃) requires: C, 78.13; H, 5.79; N, 16.08; Found: 78.10; H, 5.75; N, 15.98 %.

2-(1H-Benzimidazol-2-yl)-3-phenylpropionitrile (3b). Yield: 92%, mp: 176-78°C, IR (KBr) cm⁻¹: 3057 (-NH), 2252 (-CN). ¹H NMR (200MHz, DMSO-d₆): δ 3.35(m, 2H, -CH₂-), 4.90(t,

1H,-CH-), 7.12-7.63(m, 9H, Ar-H), 12.70(s, 1H, D₂O exchangeable -NH). M/z (M⁺+1): 248. Anal. Calcd. for (C₁₆H₁₃N₃) requires: C, 77.71; H, 5.30; N, 16.99; Found: C, 77.72; H, 5.28; 16.96%.

2-(1H-Benzimidazol-2-yl)-3-(4-methoxyphenyl)propionitrile (3c). Yield: 95%, mp: 196-98 °C, IR (KBr) cm⁻¹: 3081 (-NH), 2242 (-CN). ¹H NMR (200MHz, DMSO-d₆): δ 3.33(m, 2H, -CH₂-), 3.70(s, 3H, -OCH₃), 4.83(t, 1H,-CH-) 6.8-7.6(m, 8H, Ar-H), 12.69(s, 1H, D₂O exchangeable -NH). M/z (M⁺+1): 278. Anal. Calcd. for (C₁₇H₁₅N₃O) requires: C, 73.63; H, 5.45; N, 15.15; Found: C, 73.61; H, 5.47; N, 15.14%.

2-(1H-Benzimidazol-2-yl)-3-(4-dimethylaminophenyl)propionitrile (3d). Yield: 90%, mp: 206-08 °C, IR (KBr) cm⁻¹: 3081 (-NH), 2245 (-CN). ¹H NMR (200MHz, DMSO-d₆): δ 2.83(s, 6H,-N(CH₃)₂), 3.29(m, 2H, -CH₂-), 4.76(t, 1H,-CH-), 6.6-7.6(m, 8H, Ar-H), 12.68(s, 1H, D₂O exchangeable -NH). M/z (M⁺+1): 291. Anal. Calcd. for (C₁₈H₁₈N₄) requires: C, 74.46; H, 6.25; N, 19.30; Found: C, 74.42; H, 6.24; N, 19.26%.

2-(1H-Benzimidazol-2-yl)-3-(3,4-dimethoxyphenyl)propionitrile (3e). Yield: 92%, mp: 186-88 °C, IR (KBr) cm⁻¹: 3075 (-NH), 2238 (-CN). ¹H NMR (200MHz, DMSO-d₆): δ 3.33(m, 2H, -CH₂-), 3.59(s, 3H, -OCH₃), 3.69(s, 3H, -OCH₃), 4.85(t, 1H,-CH-), 6.78-7.62 (m, 7H, Ar-H), 12.68(s, 1H, D₂O exchangeable-NH). M/z (M⁺+1): 308. Anal. Calcd. for (C₁₈H₁₇N₃O₂) requires: C, 70.34; H, 5.58; N, 13.67; Found: 70.36; H, 5.56; 13.63%.

2-(1H-Benzimidazol-2-yl)-3-(4-chlorophenyl)propionitrile (3f). Yield: 90%, mp: 206-08 °C, IR (KBr) cm⁻¹: 3024 (-NH), 2249 (-CN). ¹H NMR (200MHz, DMSO-d₆): δ 3.43 (m, 2H, -CH₂-), 4.85 (t, 1H, -CH-), 7.12-7.62 (m, 8H, Ar-H), 12.7 (s, 1H, D₂O exchangeable-NH). M/z (M⁺+1): 282. Anal. Calcd. for (C₁₆H₁₂ClN₃) requires: C, 68.21; H, 4.29; N,14.91; Found: C, 68.20; H, 4.26, N, 14.93%.

2-(1H-Benzimidazol-2-yl)-3-(4-fluorophenyl)propionitrile (3g). Yield: 88%, mp: 170-72 °C, IR (KBr) cm⁻¹: 3085 (-NH), 2252 (-CN). ¹H NMR (200MHz, DMSO-d₆): δ 3.30(m, 2H, -CH₂-), 4.9 (t, 1H, -CH-), 7.12-7.7 (m, 8H, Ar-H), 12.65 (s, 1H, D₂O exchangeable-NH). M/z (M⁺+1): 266. Anal. Calcd. for (C₁₆H₁₂FN₃) requires: C, 72.44; H, 4.56; N, 15.84; Found: C, 72.40; H, 4.58; N, 15.82 %.

2-(1-Methyl-1H-benzimidazol-2-yl)-3-p-tolylpropionitrile (3h). Yield: 96%, mp: 134-36 °C, IR (KBr) cm⁻¹: 2247 (-CN). ¹H NMR (200MHz, CDCl₃): δ 2.33(s, 3H, -CH₃), 3.50(m, 2H, -CH₂-), 3.59(s, 3H, -NCH₃), 4.35(t, 1H, -CH-), 7.12-8.0(m, 8H, Ar-H). M/z (M⁺+1): 276. Anal. Calcd. for (C₁₈H₁₇N₃) requires: C, 78.52; H, 6.22; N, 15.26; Found: C, 78.49; H, 6.21; 15.28%.

2-(1-Methyl-1H-benzimidazol-2-yl)-3-phenylpropionitrile (3i). Yield: 92%, mp: 142-44 °C, IR (KBr) cm⁻¹: 2245 (-CN). ¹H NMR (200MHz, CDCl₃): δ 3.55(m, 2H, -CH₂-), 3.58(s, 3H, -NCH₃), 4.36(t, 1H, -CH-), 7.21-7.82(m, 9H, Ar-H). M/z (M⁺+1): 262. Anal. Calcd. for (C₁₇H₁₅N₃) requires: C, 78.13; H, 5.79; N, 16.08; Found: C, 78.10; H, 5.80; N, 16.02%.

3-(4-Methoxyphenyl)-2-(1-methyl-1H-benzimidazol-2-yl)propionitrile (3j). Yield: 95%, mp: 148-50 °C, IR (KBr) cm⁻¹: 2247 (-CN). ¹H NMR (200MHz, CDCl₃): δ 3.47(m, 2H, -CH₂-), 3.50(s, 3H, -NCH₃), 3.78(s, 3H, -OCH₃), 4.32(t, 1H, -CH-), 6.82-7.70 (m, 8H, Ar-H). M/z (M

$^{\dagger}+1$): 292. Anal. Calcd. for (C₁₈H₁₇N₃O) requires: C, 74.20; H, 5.88; N, 14.42; Found: C, 74.18; H, 5.85; N, 14.40%.

3-(4-Dimethylaminophenyl)-2-(1-methyl-1H-benzimidazol-2-yl)propionitrile (3k). Yield: 91%, mp: 120-22°C, IR (KBr) cm⁻¹: 2244 (-CN). ¹H NMR (200MHz, CDCl₃): δ 2.9(s, 6H, -N(CH₃)₂), 3.42(m, 2H, -CH₂-), 3.50(s, 3H, -NCH₃), 4.3(t, 1H, -CH-), 6.6-7.8(m, 8H). M/z (M[†]+1): 305. Anal. Calcd. for (C₁₉H₂₀N₄) requires: C, 74.97; H, 6.62; N, 18.41; Found: C, 74.96; H, 6.60; N, 18.44%.

3-(3,4-Dimethoxyphenyl)-2-(1-methyl-1H-benzimidazol-2-yl)propionitrile (3l). Yield: 90%, mp: 128-30°C, IR (KBr) cm⁻¹: 2246 (-CN). ¹H NMR (200MHz, CDCl₃): δ 3.5(s, 3H, -OCH₃), 3.6(s, 3H, -OCH₃), 3.8(m, 2H, -CH₂-), 3.82(s, 3H, -NCH₃), 4.3(t, 1H, -CH-), 6.6-7.8(m, 8H, Ar-H). M/z (M[†]+1): 322. Anal. Calcd. for (C₁₉H₁₉N₃O₂) requires: C, 71.01; H, 5.96; N, 13.08; Found: C, 70.98; H, 5.98; N, 13.06%.

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