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New synthesis of 2-benzimidazoleacetates and study of their Knoevenagel reaction

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Abstract To obtain 2-benzimidazolyl acrylate **2**, a new efficient synthesis of 2-benzimidazoleacetate, involving esterification of 2-benzimidazole acetic acid at low temperature as the crucial step, was developed. The generality and efficiency of the process was illustrated by the high-yield synthesis of methyl, ethyl, *i*-propyl, and *n*-butyl 2-benzimidazoleacetate. The Knoevenagel reaction of 2-benzimidazoleacetate with aromatic aldehydes was studied. It was found that only in the presence of a catalytic amount of morpholine could the Knoevenagel reaction proceed to give the expected 3-aryl-2-benzimidazolyl acrylate. A mechanism for the morpholine-catalyzed reaction is suggested.

Keywords Benzimidazoleacetate · Synthesis · Knoevenagel reaction · Catalysis

Introduction

2-Benzimidazolyl acrylonitriles are important derivatives of benzimidazoles. In 2004, the Bednarski [1] group reported that some 2-benzimidazolyl acrylonitrile derivatives had cytotoxic activity in vitro and were, on average, 10 and 3-fold more potent than cisplatin and etoposide, respectively. In 2007, the Botta group identified 2-benzimidzolyl acrylonitrile derivatives as HIV-1 integrase-binding inhibitors [2]; In 2010, Refaat [3] reported 2-benzimidazolyl acrylonitrile derivatives had antitumor activity; the same year the Hranjec [4] group reported 2-benzimidzolyl acrylonitrile derivatives had antitumor activity in vitro.

Structure–activity relationships (SAR) indicated that the nitrile group is not an absolute requirement for cytotoxic activity [1]. Here we are interested in the ester analogue of 2-benzimidazolyl acrylonitrile derivatives, i.e. 2-benzimidazolyl

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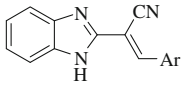
Scheme 1 2-Benzimidazolyl acrylonitrile and 2-benzimidazolyl acrylate



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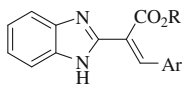


2

acrylate **2**, as shown in Scheme 1. 2-Benzimidzolyl acrylate also **2** may have antitumor activity, and serve as a key intermediate in the preparation of fused heterocyclic ring systems. To obtain these compounds, we have developed a new efficient synthesis of 2-benzimidazoleacetate and studied the Knoevenagel reaction of 2-benzimidazoleacetate with aromatic aldehydes. The results are presented in this communication.

Results and discussion

3-Aryl-2-benzimidazolyl acrylate **2** can be synthesized by the Knoevenagel reaction of 2-benzimidazoleacetate with aromatic aldehydes. First, 2-benzimidazoleacetate should be synthesized. Careful investigation of the literature revealed two general methods for synthesis of 2-benzimidazoleacetate starting from 2-cyanomethylbenzimidazole. One is Allan's synthesis [5]; the other is Dubey's synthesis [6], which involves the hydrolysis of 2-cyanomethylbenzimidazole to give 2-benzimidazole acetic acid and esterification of the acid with alcohols in the presence of catalytic amount of conc. H_2SO_4 to give 2-benzimidazoleacetate. Because we found that preparation of 9% alcoholic hydrogen chloride in Allan's synthesis was troublesome in the laboratory, we decided to adopt Dubey's synthesis of 2-benzimidazoleacetate.

2-Cyanomethylbenzimidazole was hydrolyzed in alkaline solution to give 2-benzimidazoleacetic acid in 96% yield. Esterification of the acid with alcohols in the presence of a catalytic amount of conc. H_2SO_4, however, gave 2-benzimidazoleacetate in poor yield. The main product was identified as 2-methylbenzimidazole, formed by decarboxylation of 2-benzimidazole acetic acid (Scheme 2). Esterification with alcohols in the presence of a catalytic amount of phosphoric acid or hydrochloric acid gave similar results. Unexpectedly, esterification performed in the presence of a catalytic amount of PTSA under Dean–Stark trap conditions resulted in complete decomposition of 2-benzimidazole acetic acid. After several setbacks, it was found that to obtain a high yield of 2-benzimidazoleacetate, the esterification must be carried performed at low temperature. Thionyl chloride met this requirement and was an efficient reagent for esterification of 2-benzimidazole acetic acid affording 2-benzimidazoleacetate in high yield. The generality and efficiency of the process was illustrated by the high yield synthesis of methyl, ethyl, *i*-propyl and *n*-butyl 2-benzimidazoleacetate, as shown in Table 1.

With 2-benzimidazoleacetate available we began to study the Knoevenagel reaction of 2-benzimidazoleacetate with aromatic aldehydes. The catalyst is essential for the Knoevenagel reaction. In the model experiment, a mixture of 2-benzimidazoleacetate **2b** (1.0 eq), 2-chlorobenzaldehdye (1.2 eq), and the catalyst (0.3 eq) in ethanol was heated under reflux. The progress of reaction was monitored

Scheme 2 The decarboxylation of 2-benzimidazole acetic acid

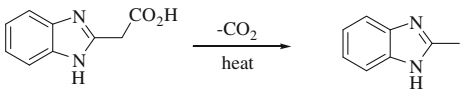
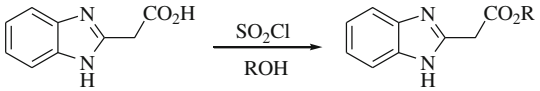


Table 1 Synthesis of 2-benzimidazoleacetates

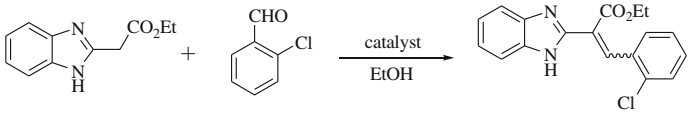


2a-2d

Entry	R	Product	Yield/%
1	Me	**2a**	85
2	Et	**2b**	85
3	*i*-Pr	**2c**	83
4	*n*-Bu	**2d**	81

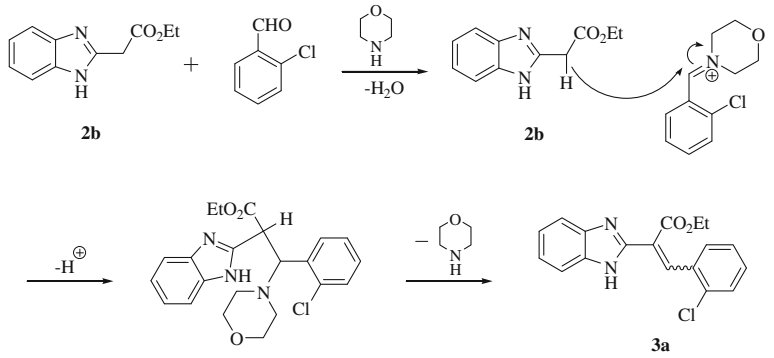
by TLC. A series of catalysts were tested for the reaction. The results are summarized in Table 2. Because of the weak electron-withdrawing nature of the benzimidazolyl group, the Knoevenagel reaction of 2-benzimidazoleacetate with aromatic aldehydes proceeded with difficulty compared with the ethyl acetoacetate or malonate counterparts. It was shown that the Knoevenagel reaction of 2-benzimidazoleacetate **2b** with 2-chlorobenzaldehdye did not proceed in the presence of catalytic amounts of Et_3N, sodium acetate, or K_2CO_3 [7]. Even the ionic liquid [bmim]OH [8] did not promote the reaction. Eventually it was found that only in the presence of a catalytic amount of morpholine could the Knoevenagel reaction

Table 2 Screening of the catalyst



2b **3a**

Entry	Catalyst	Product	Yield/%
1	Et_3N	**3a**	0
2	NaOAc	**3a**	0
3	AcOH	**3a**	0
4	NaOH	**3a**	0
5	K_2CO_3	**3a**	0
6	[bmim]OH	**3a**	0
7	Pyridine	**3a**	0
8	Morpholine	**3a**	57



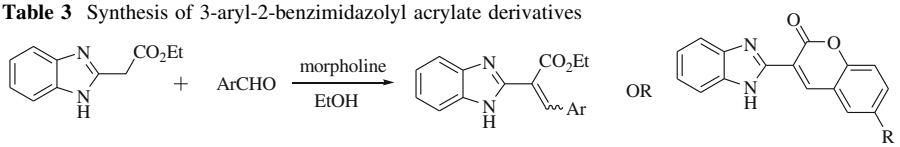
Scheme 3 Mechanism of the morpholine-catalyzed Knoevenagel reaction

proceed to give 3-aryl-2-benzimidazolyl acrylate in moderate yield as *Z*,*E* mixtures (Table 2, entry 8).

The fact that only morpholine catalyzed the Knoevenagel reaction could be rationalized as shown in Scheme 3. Morpholine condensed readily with aromatic aldehydes to give the iminium salt intermediate. 2-Benzimidazoleacetate **2b** added to the activated C=N double bond of iminium salt, then the adduct eliminated one molecule of morpholine to afford the 3-aryl-2-benzimidazolyl acrylate **3a**.

The morpholine catalyzed Knoevenagel reaction of 2-benzimidazoleacetate **2b** with other aromatic aldehydes was also performed. The results are summarized in Table 3. It should be pointed out that reaction of 2-benzimidazoleacetate **2b** with 2-hydroxylaldehdye proceeded smoothly via sequential Knoevenagel and intramolecular transesterification to give benzimidazolyl coumarin derivatives in high yield. The intramolecular transesterification process shifted the chemical equilibrium to the products. This constituted a new method for synthesis of coumarin derivatives.

Table 3 Synthesis of 3-aryl-2-benzimidazolyl acrylate derivatives



2b **3a-3b** **3c-3d**

Entry	Ar	Product	R	Yield/%
1	2-ClC_6H_4	**3a**	–	57
2	4-ClC_6H_4	**3b**	–	49
3	2-HOC_6H_4	**3c**	H	87
4	2,4-$(HO)_2C_6H_3$	**3d**	OH	71

Conclusions

To obtain 2-benzimidazolyl acrylate **2**, we have developed a new efficient synthesis of 2-benzimidazoleacetate which includes esterification of 2-benzimidazole acetic acid at low temperature as the crucial step. The generality and efficiency of the process were illustrated by the high yield synthesis of methyl, ethyl, *i*-propyl, and *n*-butyl 2-benzimidazoleacetate. The Knoevenagel reaction of 2-benzimidazoleacetate with aromatic aldehydes proceeded to give the expected 3-aryl-2-benzimidazolyl acrylate only in the presence of a catalytic amount of morpholine. A mechanism for the morpholine-catalyzed reaction has been suggested.

Experimental

Melting points were uncorrected and determined on a WRS-1A digital melting-point apparatus. IR spectra were measured in KBr on a Equinox-55 spectrometer. ^{1}H NMR spectra were recorded on an Inova-400, with TMS as internal reference. All reagents and solvents were obtained from commercial sources and were used without purification. The ionic liquid [bmim]OH was prepared by Ranu's procedure [9]; 2-benzimidazole acetic acid was prepared by Allan's procedure [5].

General procedure for preparing 2-benzimidazoleacetates **2a**–**2d**

Thionyl chloride (2.4 eq) was added, dropwise, to a rapidly stirred suspension of 2-benzimidazole acetic acid (1.0 eq) in alcohol cooled to 0 °C. The mixture was stirred overnight and the temperature was increased slowly to room temperature. The mixture was then heated under reflux for 1 h. When the mixture had cooled, it was poured into excess saturated sodium bicarbonate solution and extracted with dichloromethane. The extract was dried and evaporated. The residue was purified by flash column chromatography to afford the 2-benzimidazoleacetate as white solid.

*Methyl 2-benzimidazoleacetate (**2a**)*

Mp 106–108 °C, lit [6] 0.104–106 °C; ^{1}H NMR ($CDCl_3$) δ: 7.58–7.60 (m, 2H), 7.24–7.26 (m, 2H), 4.09 (s, 2H), 3.80 (s, 3H); IR (KBr) 1742, 1540, 1439, 1274, 745 cm^{-1}.

*Ethyl 2-benzimidazoleacetate (**2b**)*

Mp 128–130 °C, lit [5] 0.128–129 °C; ^{1}H NMR ($CDCl_3$) δ: 7.57–7.59 (m, 2H), 7.23–7.27 (m, 2H), 4.23–4.27 (m, 2H), 4.07 (s, 2H), 1.28–1.32 (m, 3H); IR (KBr) 1736, 1541, 1443, 1273, 1032, 745 cm^{-1}.

*i-Propyl 2-benzimidazoleacetate (**2c**)*

Mp 157–159 °C; ^{1}H NMR ($CDCl_3$) δ: 7.57–7.59 (m, 2H), 7.23–7.27 (m, 2H), 5.10–5.13 (m, 1H), 4.04–4.05 (m, 2H), 1.26–1.31 (m, 6H); IR (KBr) 1730, 1441, 1273, 1195, 1037, 745 cm^{-1}.

*n-Butyl 2-benzimidazoleacetate (**2d**)*

Mp 66–68 °C; ^{1}H NMR ($CDCl_3$) δ: 7.57–7.59 (m, 2H), 7.23–7.27 (m, 2H), 4.16–4.20 (m, 2H), 4.06 (s, 2H), 1.63–1.67 (m, 2H), 1.37–1.41 (m, 2H), 0.91–0.96 (m, 3H); IR (KBr) 1740, 1541, 1443, 1274, 1193, 1030, 743 cm^{-1}.

General procedure for preparing 3-aryl-2-benzimidazolyl acrylate derivatives **3**

Morpholine (0.3 eq) was added to a solution of 2-benzimidazoleacetate (1.0 eq) and the aldehyde (1.2 eq) in anhydrous ethanol and the resulting mixture was heated under reflux. The progress of the reaction was monitored by TLC. When reaction complete, the solvent was removed under vacuum and the residue was purified by flash column chromatography or recrystallization to afford the 3-aryl-2-benzimidazolyl acrylate derivatives.

*3-(2-Chlorophenyl)-2-benzimidazolyl acrylate (**3a**)*

^{1}H NMR (DMSO) δ: 12.89 (s, 1H, NH), 7.89 (s, 1H), 7.66 (s, 1H), 7.60 (d, 1H, $J = 7.6$ Hz), 7.55 (s, 1H), 7.42–7.47 (m, 3H), 7.24 (s, 2H), 4.24 (q, 2H, $J = 6.8$ Hz), 1.10 (t, 3H, $J = 7.2$ Hz); IR (KBr) 1725, 1277, 1073, 745 cm^{-1}.

*3-(4-chlorophenyl)-2-benzimidazolyl acrylate (**3b**)*

^{1}H NMR (DMSO) δ: 12.60 (s, 1H, NH), 8.06 (s, 1H), 7.64 (s, 1H), 7.51 (s, 1H), 7.33 (d, 2H, $J = 8.8$ Hz), 7.23 (s, 2H), 7.14 (d, 2H, $J = 8.4$ Hz), 4.23 (q, 2H, $J = 7.2$ Hz), 1.21 (t, 3H, $J = 7.6$ Hz); IR (KBr) 1716, 1249, 1069, 745 cm^{-1}.

*3-(2-Benzimidazolyl)coumarin (**3c**)*

Mp246–248 °C (lit [10] 247 °C); ^{1}H NMR (DMSO) δ: 12.57 (s, 1H, NH), 9.16 (s, 1H), 8.02 (dd, 1H, J = 8.0 Hz, 1.6 Hz), 7.66–7.76 (m, 3H), 7.54 (d, 1H, $J = 8.4$ Hz), 7.46 (t, 1H, $J = 7.6$ Hz), 7.22–7.25 (m, 2H); IR (KBr) 3334, 1713, 1416, 1130, 760, 733 cm^{-1}.

*3-(2-Benzimidazolyl)-7-hydroxycoumarin (**3d**)*

Mp >270 °C (lit [11] >360 °C); ^{1}H NMR (DMSO) δ: 12.42 (s, 1H, NH), 10.91 (s, 1H, OH), 9.06 (s, 1H), 7.84 (d, 1H, $J = 8.8$ Hz), 7.62–7.67 (m, 2H), 7.17–7.22 (m, 2H), 6.90 (dd, 1H, $J = 8.8$ Hz, 2.4 Hz), 6.85 (d, 1H, $J = 1.6$ Hz), 7.22–7.25 (m, 2H); IR (KBr) 3329, 1712, 1597, 1251, 740 cm^{-1}.

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