

Alkylative coupling of enaminones and benzimidazole

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Abstract

N-Acyliminium reagents derived from benzimidazole have been used successfully in C-C bond forming reactions with β -enaminones. The new 2-substituted derivatives of 2,3-dihydrobenzimidazole are interesting both from synthetic point of view and as potential bioactive compounds.

Keywords: *N*-Acyliminium, α -amidoalkylation, enaminones

Introduction

The α -amidoalkylation of carbon nucleophiles with *N*-acyliminium compounds is a long-established method for C-C bond formation.¹⁻⁴ This reaction can be used for the synthesis of various heterocyclic derivatives.

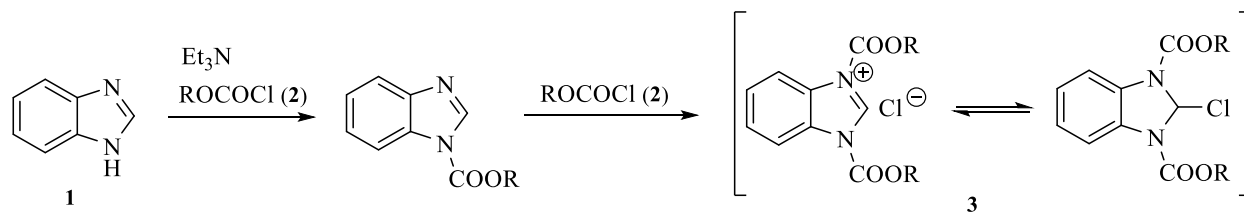
Benzimidazole ring is an important heterocyclic pharmacophore in drug discovery. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities - antiviral,^{5,6} antitumor,^{7,8} anticancer,⁹ antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Candida albicans*,¹⁰ antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis* and fungicidal activity against *Candida albicans* and *Asperigillus*.¹¹⁻¹³ Benzimidazoles are potential enterovirus inhibitors.¹⁴

We have previously used adducts of cyclic imines and acyl chlorides as electrophilic reagents in an intermolecular α -amidoalkylation reaction toward aromatics and methylene active carbonyl compounds.¹⁵⁻¹⁸ Now the same strategy has been successfully applied for coupling of benzimidazole and cyclic enaminones.

Results and Discussion

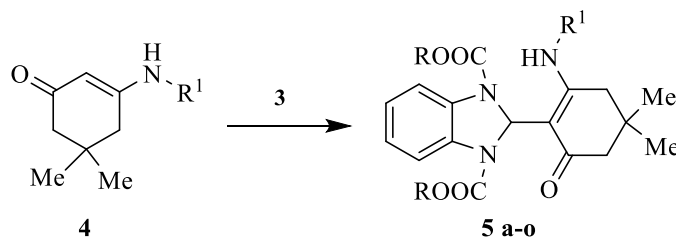
Enaminones, as defined by Greenhill, are monoenamines of 1,3-dicarbonyl compounds¹⁹ which combine the ambident electrophilicity of enones and the ambident nucleophilicity of enamines. The enaminones **4** necessary for this study were prepared by condensation of dimedone and various primary amines. The reactions were carried out in dichloroethane (or toluene for **4e**) at reflux temperature and the water was removed with Dean-Stark trap. With low-boiling amines such as methyl- and ethylamine the reaction was carried out at room temperature for 24 h in the presence of Na₂SO₄.

The *N*-acyliminium reagents **3** were obtained after initial *N*-acylation of benzimidazole **1** with alkyl chloroformates **2** (R Me, Et) in the presence of Et₃N, acting as hydrogen chloride acceptor (Scheme 1). The initial acylation took place at 0 °C for 15 minutes. Then the reaction mixture was brought to room temperature and second equivalent of alkyl chloroformate was added. In this manner we got the acyliminium reagents **3** (Scheme 1).



Scheme 1. Preparation of the acyliminium reagents from benzimidazole and alkylchloroformates.

The reactions of the acyliminium reagents **3** with enaminones were carried out in the same reaction vessel for 1 h at r.t. and in all cases led to a single product (**5 a–o**). The substituent R₁ was varied in the series of enaminones as indicated in Table 1. Attempts to amidoalkylate acyclic enaminones were not successful even at elevated temperature. The yields with cyclic enaminones **4** were from 11% (R¹ = CH₃) to 58% (R¹ = C₆H₅CH₂) and all of the studied examples proceeded regioselectively at the α-carbon of the enaminone as indicated by the disappearance of the characteristic vinyl signal in the ¹H-NMR spectra. No reaction at *N* or *O* was detected. The main problem limiting the yields was the formation of HCl salts of the enaminones in the course of the reaction. Attempts to use stronger bases as HCl scavengers were not successful, as they proved incompatible with the acyliminium reagent. The structure of the products **5** was determined by NMR spectroscopy. The resolution of all NMR spectra of **5** at 25 °C was very poor, which we assumed to be due to hindered rotation around the newly formed C-C bond. Indeed, when the NMR spectra were measured in DMSO at 80 °C their quality improved dramatically and assignment of peaks became possible.



Scheme 2. Amidoalkylation of cyclic enaminones with benzimidazole-derived acyliminium reagents.

Table 1. Yields of compounds **5** obtained according to Scheme 2

5	R	R¹	Yield (%)
a	C ₂ H ₅	3,4-(MeO) ₂ C ₆ H ₃ CH ₂ CH ₂	55
b	C ₂ H ₅	C ₆ H ₅ CH ₂ CH ₂	40
c	C ₂ H ₅	C ₆ H ₅ CH ₂	44
d	C ₂ H ₅	4-ClC ₆ H ₄ CH ₂	44
e	C ₂ H ₅	C ₆ H ₅	28
f	C ₂ H ₅	C ₃ H ₇	32
g	C ₂ H ₅	C ₂ H ₅	17
h	C ₂ H ₅	CH ₃	11
i	CH ₃	3,4-(MeO) ₂ C ₆ H ₃ CH ₂ CH ₂	21
j	CH ₃	C ₆ H ₅ CH ₂ CH ₂	33
k	CH ₃	C ₆ H ₅ CH ₂	58
l	CH ₃	4-ClC ₆ H ₄ CH ₂	38
m	CH ₃	C ₆ H ₅	35
n	CH ₃	C ₃ H ₇	36
o	CH ₃	C ₂ H ₅	41

In conclusion, the scope of application of the intermolecular reaction of α -amidoalkylation has been studied and series of cyclic enamino ketones were selectively amidoalkylated at the α -carbon atom in reactions with acyliminium reagents derived from benzimidazole.

Experimental Section

General. Commercial solvents and reagents, such as benzimidazole and alkyl chloroformate were purchased from Sigma-Aldrich and were used without further purification. β -Enaminones were prepared according to a procedure described in the literature.¹⁹ Melting points were determined on a Boetius PHMKO5 hot stage apparatus and are uncorrected. ¹H-NMR and ¹³C-NMR spectra were measured on Bruker DRX250 and AV600 apparatus in DMSO as solvent.

Chemical shifts are given in part per million (ppm) relative to TMS and coupling constants are indicated in Hz. All the NMR spectra were taken at 80 °C. TLC was done on precoated 0.2 mm Fluka silica gel 60 plates. Silica gel was used for column chromatographic separation.

General experimental procedure for preparation of compounds 5a-o: To a suspension of benzimidazole (1 mmol) in 1,2-dichloroethane (5 mL) cooled to 0 °C were added Et₃N (1 mmol) and alkyl chloroformate (1 mmol). The reaction mixture was stirred for 15 min at 0 °C. To the same reaction mixture was added second equivalent of alkyl chloroformate (1 mmol) and the mixture was stirred for 30 min at rt. Without isolation and purification of the formed *N*-acyliminium reagent, to the reaction mixture was added equivalent amount of β-enaminone **4**. After 1 h water (20 mL) was added and the mixture was extracted with 3×20 ml CHCl₃. The combined organic layers were dried (Na₂SO₄) and concentrated. After evaporation of the solvent the products were purified by column chromatography on silica gel using mixtures of petroleum and diethyl ether as eluents.

Diethyl 2-(2-((3,4-dimethoxyphenethyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1*H*-benzo[*d*]imidazole-1,3(2*H*)-dicarboxylate (5a). Mp 171–172 °C; ¹H-NMR: 0.95 (s, 6H), 1.23 (t, 6H, *J* 7.1), 1.91 (s, 2H), 2.31 (s, 2H), 2.71 (t, 2H, *J* 6.9), 3.48 (m, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 4.14 (q, 4H, *J* 7.1), 6.54 (br. s, 1H), 6.78 (d, 1H, *J* 8.0), 6.87–6.95 (m, 5H), 7.47–7.54 (m, 2H); ¹³C-NMR: 14.67, 28.29, 31.29, 36.36, 45.08, 51.01, 56.48, 56.63, 61.77, 71.42, 104.99, 113.29, 113.74, 114.24, 121.48, 122.67, 131.97, 133.52, 148.62, 149.91, 151.43, 162.39, 191.01; *Anal.* Calcd. for C₃₁H₃₉N₃O₇: C, 65.82; H, 6.95; N, 7.43. Found: C, 65.60; H, 7.01; N, 7.38.

Diethyl 2-(4,4-dimethyl-6-oxo-2-(phenethylamino)cyclohex-1-en-1-yl)-1*H*-benzo[*d*]imidazole-1,3(2*H*)-dicarboxylate (5b). Mp 140–141 °C; ¹H-NMR: 0.95 (s, 6H), 1.23 (t, 6H, *J* 7.0), 1.91 (s, 2H), 2.33 (s, 2H), 2.79 (t, 2H, *J* 7.5), 3.51 (m, 2H), 4.14 (q, 4H, *J* 7.0), 6.57 (br. s, 1H), 6.90–6.97 (m, 3H), 7.21–7.35 (m, 5H), 7.48–7.55 (m, 2H); ¹³C-NMR: 14.69, 28.27, 31.32, 36.84, 44.89, 51.02, 61.76, 71.37, 105.06, 113.27, 122.67, 126.78, 128.86, 129.11, 133.54, 139.10, 151.41, 162.32, 191.05; *Anal.* Calcd. for C₂₉H₃₅N₃O₅: C, 68.89; H, 6.98; N, 8.31. Found: C, 68.72; H, 7.03; N, 8.28.

Diethyl 2-(2-(benzylamino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1*H*-benzo[*d*]imidazole-1,3(2*H*)-dicarboxylate (5c). Mp 165–166 °C; ¹H-NMR: 0.39 (s, 6H), 0.70 (t, 6H, *J* 7.0), 1.39 (s, 2H), 1.84 (s, 2H), 3.63 (q, 4H, *J* 7.0), 3.99 (d, 2H, *J* 4.2), 6.33–6.40 (m, 2H), 6.44 (s, 1H), 6.63 (br. s, 1H), 6.74 - 6.80 (m, 1H), 6.84 (d, 4H, *J* 7.5), 6.93–7.00 (m, 2H); ¹³C-NMR: 14.75, 28.24, 31.41, 46.79, 51.05, 61.77, 71.37, 105.19, 113.24, 122.60, 127.39, 127.55, 128.86, 133.58, 139.42, 151.43, 162.49, 191.24; *Anal.* Calcd. for C₂₈H₃₃N₃O₅: C, 68.41; H, 6.77; N, 8.55. Found: C, 68.23; H, 6.81; N, 8.59.

Diethyl 2-(2-((4-chlorobenzyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1*H*-benzo[*d*]imidazole-1,3(2*H*)-dicarboxylate (5d). Mp 168–169 °C; ¹H-NMR: 0.93 (s, 6H), 1.24 (t, 6H, *J* 7.0), 1.93 (s, 2H), 2.35 (s, 2H), 4.17 (q, 4H, *J* 7.0), 4.52 (d, 2H, *J* 5.3), 6.90–6.93 (m, 2H), 6.97 (s, 1H), 7.42 (s, 4H), 7.49 (br. s, 2H); ¹³C-NMR: 14.75, 28.23, 31.45, 39.50, 46.05, 51.03, 61.80,

71.33, 105.25, 113.23, 122.59, 128.82, 129.30, 132.35, 138.59, 151.41, 162.39, 191.35; *Anal.* Calcd. for $C_{28}H_{32}ClN_3O_5$: C, 63.93; H, 6.13; N, 7.99. Found: C, 63.90; H, 6.21; N, 8.03.

Diethyl 2-(4,4-dimethyl-6-oxo-2-(phenylamino)cyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5e). Mp 184–187 °C; 1H -NMR: 0.96 (s, 6H), 1.30 (t, 6H, J 7.1), 2.03 (s, 2H), 2.42 (s, 2H), 4.24 (q, 4H, J 7.1), 6.91–6.98 (m, 2H), 7.13 (s, 1H), 7.17 - 7.22 (m, 2H), 7.27 (d, 1H, J 7.3), 7.42 - 7.48 (m, 2H), 7.50–7.55 (m, 2H), 8.84 (br. s, 1H); ^{13}C -NMR: 14.35, 27.48, 31.84, 51.09, 61.43, 70.83, 107.54, 112.76, 122.10, 125.00, 125.18, 129.10, 133.31, 139.27, 150.98, 159.42, 192.24; *Anal.* Calcd. for $C_{27}H_{31}N_3O_5$: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.95; H, 6.60; N, 7.78.

Diethyl 2-(4,4-dimethyl-6-oxo-2-(propylamino)cyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5f): Mp 110–113 °C; 1H -NMR: 0.92 (t, 3H, J 7.4), 1.01 (s, 6H), 1.24 (t, 6H, J 7.1), 1.49 (sxt, 2H, J 7.1, 7.3), 1.95 (s, 2H), 2.39 (s, 2H), 3.18 - 3.26 (m, 2H), 4.16 (q, 4H, J 7.1), 6.42 (br. s, 1H), 6.91–6.98 (m, 3H), 7.50–7.57 (m, 2H); ^{13}C -NMR: 10.91, 14.16, 23.15, 27.82, 30.89, 44.68, 50.51, 61.21, 70.86, 104.33, 112.77, 122.18, 133.01, 150.92, 161.96, 190.36; *Anal.* Calcd. for $C_{24}H_{33}N_3O_5$: C, 64.99; H, 7.50; N, 9.47. Found: C, 65.07; H, 7.53; N, 9.41.

Diethyl 2-(2-(ethylamino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5g). Mp 168–171 °C; 1H -NMR: 1.01 (s, 6H), 1.13 (t, 3H, J 7.1), 1.25 (t, 6H, J 7.1), 1.94 (s, 2H), 2.40 (s, 2H), 3.36–3.37 (m, 2H), 4.15 (q, 4H, J 7.1), 6.56 (br. s, 1H), 6.92–6.97 (m, 3H), 7.50–7.56 (m, 2H); ^{13}C -NMR: 14.16, 15.31, 27.80, 30.91, 37.55, 50.55, 61.18, 70.80, 104.20, 112.64, 122.10, 133.15, 150.86, 161.92, 190.40; *Anal.* Calcd. for $C_{23}H_{31}N_3O_5$: C, 64.32; H, 7.27; N, 9.78. Found: C, 64.19; H, 7.30; N, 9.71.

Diethyl 2-(4,4-dimethyl-2-(methylamino)-6-oxocyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5h). Mp 198–200 °C; 1H -NMR: 1.00 (s, 6H), 1.24 (t, 6H, J 7.1), 1.91 (s, 2H), 2.39 (s, 2H), 2.95 (d, 3H, J 4.8), 4.14 (q, 4H, J 7.1), 6.80 (s, 1H), 6.89–6.94 (m, 2H), 7.10 (br. s, 1H), 7.46–7.54 (m, 2H); ^{13}C -NMR: 14.09, 27.87, 29.81, 30.82, 50.62, 61.16, 70.87, 104.20, 112.41, 121.85, 133.39, 150.79, 162.88, 190.38; *Anal.* Calcd. for $C_{22}H_{29}N_3O_5$: C, 63.60; H, 7.04; N, 10.11. Found: C, 63.57; H, 7.13; N, 10.05.

Dimethyl 2-(2-((3,4-dimethoxyphenethyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5i). Mp 168–173 °C; 1H -NMR: 0.95 (s, 6H), 1.91 (s, 2H), 2.32 (s, 2H), 2.74 (t, 2H, J 7.1), 3.47 - 3.55 (m, 2H), 3.70 (s, 6H), 3.77 (s, 3H), 3.80 (s, 3H), 6.63 (br. s, 1H), 6.80 (d, 1H, J 8.1), 6.89–6.98 (m, 5H), 7.46–7.51 (m, 2H); ^{13}C -NMR: 27.67, 30.74, 35.98, 44.48, 50.48, 52.38, 55.98, 56.13, 71.05, 104.29, 112.77, 113.25, 113.79, 121.01, 122.23, 131.54, 132.91, 149.41, 151.36, 162.15, 190.58; *Anal.* Calcd. for $C_{29}H_{35}N_3O_7$: C, 64.79; H, 6.56; N, 7.82. Found: C, 64.75; H, 6.68; N, 7.80.

Dimethyl 2-(4,4-dimethyl-6-oxo-2-(phenethylamino)cyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5j). Mp 139–141 °C; 1H -NMR: 0.95 (s, 6H), 1.92 (s, 2H), 2.34 (s, 2H), 2.81 (t, 2H, J 7.3), 3.50 - 3.58 (m, 2H), 3.70 (s, 6H), 6.66 (br. s, 1H), 6.90 (s, 1H), 6.93–6.98 (m, 2H), 7.25–7.37 (m, 5H), 7.47–7.54 (m, 2H); ^{13}C -NMR: 28.16, 31.26, 36.93, 44.79, 50.98, 52.88, 71.50, 104.86, 113.27, 122.73, 126.75, 128.86, 129.13, 133.42, 139.17, 151.84,

162.58, 191.12; *Anal.* Calcd. for C₂₇H₃₁N₃O₅: C, 67.91; H, 6.54; N, 8.80. Found: C, 67.72; H, 6.61; N, 8.69.

Dimethyl 2-(2-(benzylamino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5k). Mp 180–184 °C; ¹H-NMR: 0.90 (s, 6H), 1.92 (s, 2H), 2.37 (s, 2H), 3.70 (s, 6H), 4.55 (d, 2H, *J* 6.0), 6.88 - 6.94 (m, 2H), 6.96 (s, 1H), 7.26–7.34 (m, 2H), 7.37–7.39 (m, 4H), 7.45–7.51 (m, 2H); ¹³C-NMR: 28.13, 31.37, 46.68, 51.02, 52.88, 71.52, 104.93, 113.20, 122.64, 127.25, 127.52, 128.92, 133.54, 139.62, 151.86, 162.79, 191.33; *Anal.* Calcd. for C₂₆H₂₉N₃O₅: C, 67.37; H, 6.31; N, 9.07. Found: C, 67.31; H, 6.40; N, 9.12.

Dimethyl 2-(2-((4-chlorobenzyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5l). Mp 172–175 °C; ¹H-NMR: 0.92 (s, 6H), 1.94 (s, 2H), 2.36 (s, 2H), 3.73 (s, 6H), 4.56 (d, 2H, *J* 6.1), 6.91 - 6.94 (m, 2H), 6.97 (s, 1H), 7.34 (s, 1H), 7.42–7.45 (m, 4H), 7.47–7.52 (m, 2H); ¹³C-NMR: 27.83, 30.89, 45.52, 50.39, 52.42, 70.95, 104.64, 112.71, 122.16, 128.39, 128.63, 131.83, 133.01, 138.18, 151.33, 162.37, 190.81; *Anal.* Calcd. for C₂₆H₂₈ClN₃O₅: C, 62.71; H, 5.67; N, 8.44. Found: C, 62.59; H, 5.73; N, 8.39.

Dimethyl 2-(4,4-dimethyl-6-oxo-2-(phenylamino)cyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5m). Mp 203–204 °C; ¹H-NMR: 0.94 (s, 6H), 2.01 (s, 2H), 2.37 (s, 2H), 3.78 (s, 6H), 6.91–6.98 (m, 2H), 7.09 (s, 1H), 7.17 - 7.29 (m, 3H), 7.42 - 7.45 (m, 2H), 7.49–7.52 (m, 2H), 8.86 (br. s, 1H); ¹³C-NMR: 27.89, 32.30, 51.59, 53.00, 71.50, 107.90, 113.18, 122.66, 125.92, 129.66, 133.70, 139.80, 151.85, 160.34, 192.74; *Anal.* Calcd. for C₂₅H₂₇N₃O₅: C, 66.80; H, 6.05; N, 9.35. Found: C, 66.73; H, 6.17; N, 9.31.

Dimethyl 2-(4,4-dimethyl-6-oxo-2-(propylamino)cyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5n). Mp 43–45 °C; ¹H-NMR: 0.92 (t, 3H, *J* 7.2), 1.00 (s, 6H), 1.50 (sxt, 2H, *J* 7.1, 7.5), 1.95 (s, 2H), 2.40 (s, 2H), 3.20 - 3.28 (m, 2H), 3.71 (s, 6H), 6.52 (br. s, 1H), 6.92–6.98 (m, 3H), 7.48–7.54 (m, 2H); ¹³C-NMR: 10.83, 23.27, 27.70, 30.85, 44.55, 50.48, 52.34, 71.00, 104.11, 112.77, 122.24, 132.89, 151.34, 162.24, 190.45; *Anal.* Calcd. for C₂₂H₂₉N₃O₅: C, 63.60; H, 7.04; N, 10.11. Found: C, 63.68; H, 7.13; N, 10.17.

Dimethyl 2-(2-(ethylamino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (5o). Mp 84–87 °C; ¹H-NMR: 1.00 (s, 6H), 1.12 (t, 3H, *J* 7.2), 1.94 (s, 2H), 2.40 (s, 2H), 3.27–3.37 (m, 2H), 3.71 (s, 6H), 6.60 (br. s, 1H), 6.92–6.98 (m, 3H), 7.47–7.54 (m, 2H); ¹³C-NMR: 15.48, 27.70, 30.85, 37.48, 50.52, 52.32, 70.98, 104.11, 112.68, 122.18, 132.99, 151.31, 162.13, 190.43; *Anal.* Calcd. for C₂₁H₂₇N₃O₅: C, 62.83; H, 6.78; N, 10.47. Found: C, 62.75; H, 6.83; N, 10.39.

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