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SYNTHESIS OF BIS-HETEROCYCLIC COMPOUNDS BY α-AMIDOALKYLATION REACTION

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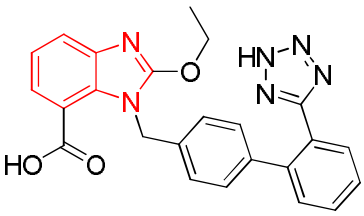
Abstract

*N-acyliminium ions **3**, formed in the reaction of benzimidazole and alkyl chloroformates, were successfully used as α-amidoalkylating reagents towards ketoamides **4 a - d**. The products **5**, obtained in this way, can be further elaborated to bis-heterocyclic compounds. To demonstrate this, product **5 a** was transformed to the corresponding amidoalcohol **6** by reduction with $NaBH_4$ in methanol and then it underwent cyclization to the corresponding 2-isoquinolylbenzimidazole **7**.*

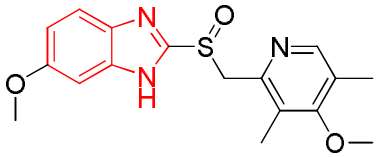
Key words: *α-amidoalkylation reaction, ketoamides, bis-heterocyclic compounds, benzimidazole*

1. INTRODUCTION

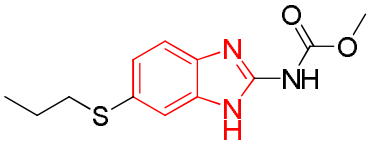
Benzimidazole ring plays an important role as pharmacophore in a number of pharmaceutically active compounds[1]. Benzimidazole derivatives show a wide range of significant antiviral activities, such as anti-HIV, anti-RSV, anti-HCV, anti-HBV and anti-HCMV activities[2-4]. A considerable number of drugs used in different therapeutic areas contain the benzimidazole ring, such as antihypertensives (candesartan, telmisartan), proton pump inhibitors (omeprazole), antihelmintics (albendazole, mebendazole), antihistaminics (astemizole), antifungal[5-7] as well as antitumor agents[8-12] some of which are potential agents against leukemia[13, 14].



Candestartan



Omeprazole



Albendazole

Benzimidazole-2-methylthiopyrimidines were found to have high antitumor activity against lung cancer, ovarian cancer and leukemia[15]. 2-substituted benzimidazoles, containing five-membered heterocycles at the 2-position, showed *in vitro* and *in vivo* antitumor activity[16]. Some new benzimidazole linked pyrrolobenzodiazepine conjugates show significant *in vitro* cytotoxicity against a number of human cancer cell lines[17].

Tiabendazole is a fungicide and parasiticide. It is used as a prophylactic treatment for Dutch Elm disease[18]. It is also a chelating agent used in medicine to bind metals in cases of metal poisoning, such as lead poisoning, mercury poisoning or antimony poisoning. In general, benzimidazoles with

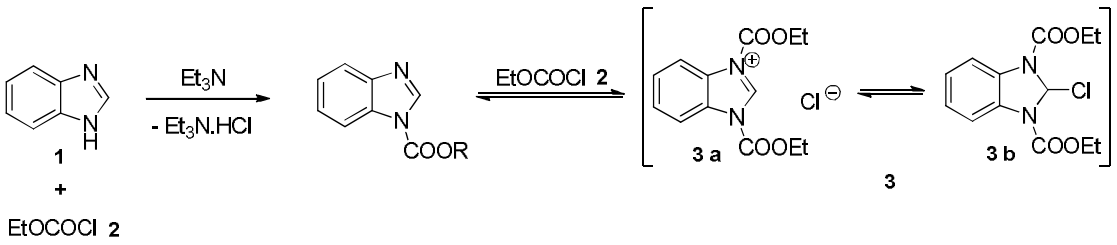
chelating substructure are potent inhibitors of E. coli MetAP. Binding to an auxiliary transition metal ion is important for the activity of benzimidazoles, irrespective of the enzyme subtype. Methionine aminopeptidases (MetAPs) are ubiquitous enzymes that are pursued as drug targets in the context of various pharmacological interventions, including the treatment of parasitic and bacterial infections and the therapy of cancer[19].

In view of the above, we have longstanding interest in the development of new methodologies providing access to potentially bioactive benzimidazoles. Our approach to the synthesis of these compounds relies on the fact that the core benzimidazole moiety can exhibit the characteristics of a cyclic imine and under appropriate conditions it can give iminium ions susceptible to nucleophilic attack. In our previous studies *N*-acyliminium ions, formed in the reaction of benzimidazole and alkyl chloroformates, were successfully used in α-amidoalkylation reaction with methyl ketones [21]. A new series of 1,2,3-trisubstituted 2-(2-oxoalkyl)-2,3-dihydrobenzimidazoles were synthesized and evaluated for their cytotoxic activity. Some of the compounds showed selective antiproliferative properties *in vitro* against the human metaststic melanoma cells at 10^{-4} M concentration[20]. Also, the synthesis of bis-heterocyclic compounds in the molecule of which there is isoquinoline or beta-carboline ring, was studied. The intermolecular α-amidoalkylation reaction was applied to indole, pyrole, thiophene, pyrazine etc[22]. Comparative study on the reactivity of the N-acyliminium electrophilic reagents showed that the reaction outcome depends both on the type of acyl chloride and on the type of the hetero ring and its substitutes. Of all studied reagents, those obtained from benzimidazole and alkyl chloroformates were found to be the most stable. One of them was isolated and spectrally characterized[23].

2. RESULTS AND DISCUSSION

The aim of this study is to investigate the possibility of α-amidoalkylation reaction between *o*-acylated 2-phenylethylamides and N-acyliminiun ions of benzimidazole. The resulting compounds could be used to obtain 1-(2-benzimidazolyl-methyl)-2-acyl-tetrahydroisoquinolines. Similar approach was already successfully used for synthesis of substituted tetrahydroisoquinolines with contractile activity[24].

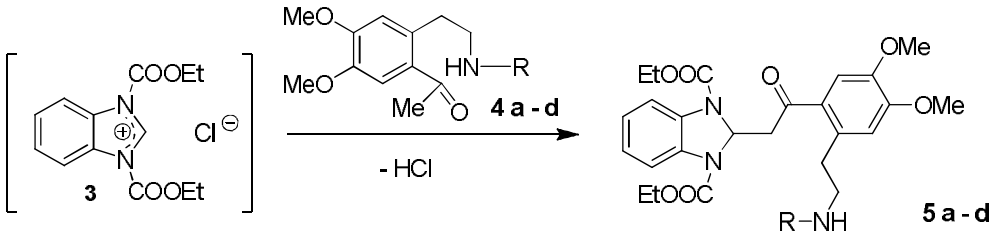
The necessary starting compounds, namely ortho-*N*-acyl-2-phenylethylamines, were obtained by known methods[25]. *N*-acyliminium reagent **3** was obtained after the initial *N*-acylation of benzimidazole **1** with ethyl chloroformate **2** in the presence of Et_3N, acting as hydrogen chloride acceptor (Scheme 1).



Scheme 1.

It was found that the amidoalkylation reaction of ketoamides **4 a - d** took place at room temperature. Adding the ketoamides **4 a - d** to *N*-acyliminium reagent **3** led to one product **5 a – d**. After aqueous

work up of the reaction mixture to remove unreacted benzimidazole and $Et_3N.HCl$, the products were purified by column chromatography on neutral alumina. The structures of the products were determined on the basis of NMR analysis, which showed that amides **4 a - d** were selectively α-amidoalkylated at the methyl group, giving compounds **5 a – d** (Scheme 2).



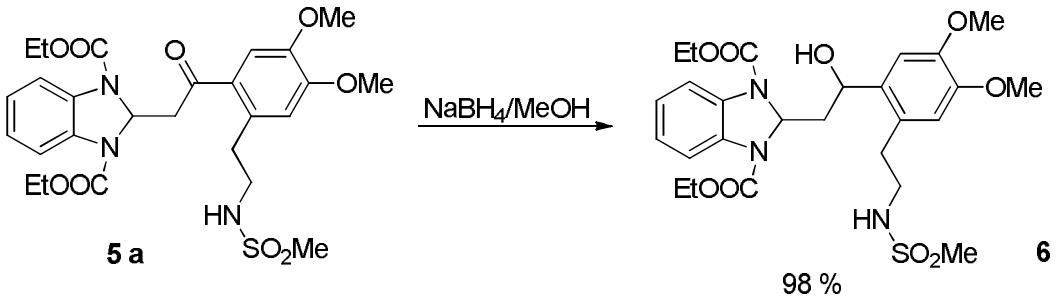
Scheme 2.

First we carried out the α-amidoalkylation reaction with ketosulfamide **4 a**. The reaction proceeded quickly at room temperature and gave **5 a** in 62% yield after only 15 minutes. This result prompted us to amidoalkylate other *N*-acyl derivatives of homoveratrylamine **4 b - d** (Scheme 2). The reactions with ketoamides **4 b - d** were also successful, but the yields were somewhat lower and longer reaction time was neccessary (Table 1).

Table 1.

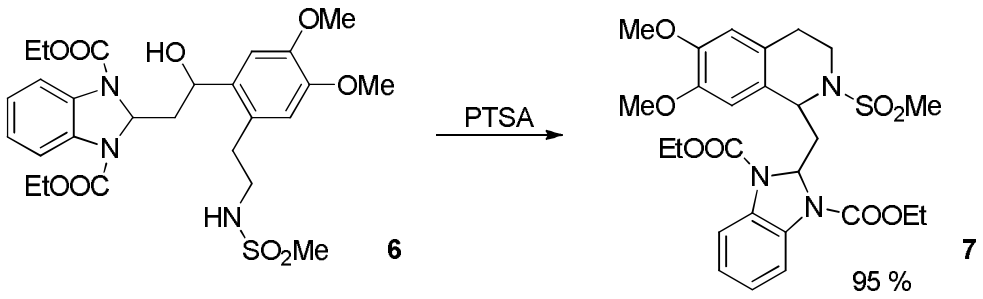
5	R	Reaction time	Yield, %
a	SO_2CH_3	15 min	62
b	$COOC_2H_5$	5 h	34
c	$COCH_3$	24 h	55
d	COC_6H_5	24 h	24

The newly obtained 2-substituted benzimidazoles **5 a - d** are good structural blocks for the synthesis of isoquinolines. For this purpose, product **5 a** was transformed to the corresponding amidoalcohol **6** by reduction with $NaBH_4$ in methanol at room temperature (Scheme 3).



Scheme 3.

The obtained amidoalcohol **6**, after purification and spectral characterization by ^{1}H- and ^{13}C-NMR spectroscopy, was treated with protic acid in anhydrous media and underwent cyclization to the corresponding 2-isoquinolylbenzimidazole **7** (Scheme 4). The reaction took place at room temperature for 20 minutes in dichloromethane and in the presence of catalytic amount of *p*-toluensulfonic acid (PTSA).



Scheme 4.

3. EXPERIMENTAL SECTION

Commercial solvents and reagents, such as benzimidazole and ethyl chloroformate were purchased from Sigma-Aldrich and were used without further purification. Amides were prepared according to a procedure described in the literature[25]. Melting points were determined on a Boetius PHMKO5 hot stage apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were taken in $CDCl_3$ on Bruker DRX250 apparatus. Chemical shifts are given in part per million (ppm) relative and are referenced to TMS (δ=0.00ppm) as an internal standard and coupling constants are indicated in Hz. All the NMR spectra were taken at rt (ac. 295 K). TLC was carried out on precoated 0.2 mm Fluka silica gel 60 plates. Aluminium oxide was used for column chromatographic separation.

Synthesis of compounds 5 a – d. Reaction of N-[2-(2-acyl-4,5-dimetoxyphenyl)-ethyl] amides (4 a – d) with adducts of benzimidazole and ethyl chloroformate (3) – typical procedure.

To a suspension of benzimidazole (1 mmol) in 1,2-dichloroethane (5 ml) cooled to 0 °C were added Et_3N (1 mmol) and ethyl chloroformate (1 mmol). The reaction mixture was stirred for 15 min at rt. After that to the same reaction mixture was added second equivalent of ethyl 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 ketoamides **4 a – d**. The reaction time is presented in Table 1. After completion of the reaction, 20 ml of water was added and the mixture was extracted with 3x20 ml CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated. The products, after evaporation of the solvent, were purified by column chromatography on neutral Al_2O_3 using mixtures of petroleum and diethyl ether as eluents.

Diethyl 2-(2-(4,5-dimetoxy-2-(2-(methylsulfonamido)ethyl)phenyl)-2-oxoethyl)-1*H*-benzo[d]imidazole-1,3(2*H*)-dicarboxylat (5 a)

mp = 105 - 107 °C

^{1}H-NMR: 1.33 (t, *J* = 7.1, 6H, $CO_2CH_2\underline{CH_3}$), 2.67 (t, *J* = 6.1, 2H, $\underline{CH_2}CH_2NH$), 2.77 (s, 3H, SO_2CH_3), 3.30 (m, 2H, $CH_2\underline{CH_2}NH$), 3.52 (br. s, 2H, $\underline{CH_2}CO$), 3.92 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.22 –

4.34 (m, 4H, $CO_2\underline{CH_2}CH_3$), 5.11 (t, J = 5.4, 1H, CH), 6.48 (t, J = 4.3, 1H, NH), 6.66 (s, 1H, Ar), 6.91 – 6.98 (m, 2H, Ar), 7.17 – 7.65 (m, 3H, Ar); ^{13}C-NMR: 14.39, 33.70, 39.84, 44.51, 44.78, 56.07, 56.22, 62.59, 113.22, 114.22, 123.56, 129.55, 134.10, 147.00, 152.15, 181.64, 197.89.

Diethyl 2-(2-(2-(2-((ethoxycarbonyl)amino)ethyl)-4,5-dimethoxyphenyl)-2-oxoethyl)-1*H*-benzo[d]imidazole-1,3(2H)-dicarboxylate (5 b)

mp = 93 - 94 °C

^{1}H-NMR: 1.20 (t, J = 7.1, 3H, $NHCO_2CH_2\underline{CH_3}$), 1.31 (t, J = 7.0, 6H, $CO_2CH_2\underline{CH_3}$), 2.68 (t, J = 6.7, 2H, $\underline{CH_2}CH_2NH$), 3.32 (m, 2H, $CH_2\underline{CH_2}NH$), 3.50 (d, J = 3.7, 2H, $\underline{CH_2}CO$), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.06 (q, J = 7.1, 2H, $NHCO_2\underline{CH_2}CH_3$), 4.29 (m, 4H, $CO_2\underline{CH_2}CH_3$), 5.28 (br. s, 1H, NH), 6.51 (t, J = 4.4, 1H, CH), 6.64 (s, 1H, Ar), 6.91 – 6.98 (m, 2H, Ar), 7.21 – 7.55 (m, 3H, Ar); ^{13}C-NMR: 14.38, 14.67, 33.30, 41.84, 44.85, 55.96, 56.21, 60.42, 62.52, 73.73, 114.14, 114.74, 123.59, 129.45, 135.09, 146.73, 151.94, 156.78, 171.02.

Diethyl 2-(2-(2-(2-acetamidoethyl)-4,5-dimethoxyphenyl)-2-oxoethyl)-1*H*-benzo[d]imidazole-1,3(2H)-dicarboxylate (5 c)

mp = 103 - 105 °C

^{1}H-NMR: 1.34 (t, J = 7.1, 6H, $CO_2CH_2\underline{CH_3}$), 1.86 (s, 3H, $COCH_3$), 2.61 (t, J = 4.3, 2H, $\underline{CH_2}CH_2NH$), 3.40 (m, 2H, $CH_2\underline{CH_2}NH$), 3.56 (br. s, 2H, $COCH_2$), 3.91 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.20 – 4.39 (m, 4H, $CO_2\underline{CH_2}CH_3$), 6.51 (t, J = 4.3, 1H, CH), 6.59 (br. s, 1H, NH), 6.64 (s, 1H, Ar), 6.92 – 6.99 (m, 2H, Ar), 7.20 – 7.56 (m, 3H, Ar); ^{12}C-NMR: 14.44, 23.19, 32.21, 41.35, 44.93, 56.03, 56.21, 62.59, 112.91, 113.95, 114.71, 123.61, 129.70, 135.18, 146.77, 152.16, 170.23, 198.49.

Diethyl 2-(2-(2-(2-benzamidoethyl)-4,5-dimethoxyphenyl)-2-oxoethyl)-1*H*-benzo[d]imidazole-1,3(2H)-dicarboxylate (5 d)

mp = 148 - 149 °C

^{1}H-NMR: 1.31 (t, J = 7.0, 6H, $CO_2CH_2\underline{CH_3}$), 2.69 (br. s, 2H, CH_2CO), 3.61 (m, 4H, CH_2), 3.85 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.27 (q, J = 7.0, 4H, $CO_2\underline{CH_2}CH_3$), 6.51 (t, J = 4.2, 1H, CH), 6.65 (s, 1H, Ar), 6.94 (m, 2H, Ar), 7.33 – 7.47 (m, 4H, Ar), 7.60 (d, J = 3.7, 1H, NH), 7.71 (s, 2H, Ar), 7.74 (s, 2H, Ar); ^{12}C-NMR: 14.44, 31.74, 55.99, 56.19, 62.63, 112.72, 114.00, 114.72, 123.66, 126.96, 128.41, 131.17, 134.39, 135.08, 146.77, 167.62, 199.05.

Synthesis of diethyl 2-(2-(4,5-dimethoxy-2-(2-(methylsulfonamido)ethyl)phenyl)-2-hydroxyethyl)-1*H*-benzo[d]imidazole-1,3(2H)-dicarboxylate (6)

To the solution of 0.300 g of compound **5 a** (Scheme 2) in methanol (50 ml), at room temperature was added $NaBH_4$. The reaction was monitored by TLC and went to completion in the course of 20 – 30 min. The solvent was distilled under vacuum and the mixture was diluted in 20 ml $CHCl_3$ and extracted with water. The resulting amidoalcohol **6** was purified by column chromatography on neutral Al_2O_3.

mp = 145 - 146 °C

^{1}H-NMR: 1.38 - 1.47 (m, 6H, $CO_2CH_2\underline{CH_3}$), 2.14 – 2.56 (m, 2H, CH_2), 2.71 (s, 3H, CH_3), 2.80 (br. s, 2H, $\underline{CH_2}CH_2NH$), 3.31 - 3.34 (m, 2H, $CH_2\underline{CH_2}NH$), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.32 - 4.45 (m, 4H, $CO_2\underline{CH_2}CH_3$), 5.05 (br. s, 1H, CH), 5.24 (br. s, 1H, CH), 6.39 (br. s, 1H, NH), 6.64 (s, 1H, Ar), 6.92 (s, 1H, Ar), 7.03 – 7.06 (m, 2H, Ar), 7.37 - 7.62 (m, 2H, Ar); ^{13}C-NMR: 14.44, 30.87, 32.19, 39.90, 43.30, 44.62, 55.98, 62.67, 63.15, 74.01, 109.68, 112.98, 123.59, 127.44, 133.68, 134.24, 147.87, 148.39, 190.36.

Synthesis of diethyl 2-((6,7-dimethoxy-2-(methylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)methyl)-1H-benzo[d]imidazole-1,3(2H)-dicarboxylate (7)

The amidoalcohol **6** (0,030 g) was dissolved in dichloromethane (50 ml) in an open flask and *p*-toluensulfonic acid (0.005 g) was added (Scheme 2). The reaction mixture was stirred for 20 min at rt. and then was filtered through a short column on neutral Al_2O_3 to give practically clean **7**.

CONCLUSION

A new reaction scheme was developed, combining the *C-C* bond forming capability of the intermolecular α-amidoalkylation reaction with an intramolecular *N*-alkylation approach for the synthesis of tetrahydroisoquinolines. The utility of this approach was demonstrated with the synthesis of new bis-heterocyclic compounds.

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