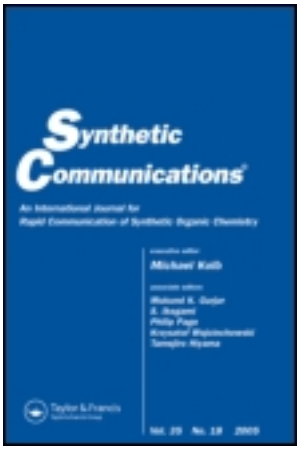

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α-Amidoalkylation Reactions and Oxidation of Adducts of Benzimidazoles and Acyl Chlorides

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α-AMIDOALKYLATION REACTIONS AND OXIDATION OF ADDUCTS OF BENZIMIDAZOLES AND ACYL CHLORIDES

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Abstract: Adducts **4** of benzimidazoles and acyl chlorides were successfully used as electrophilic reagents in an intermolecular α-amidoalkylation reaction toward ketones for synthesis of 2-(2-oxoalkyl)-1,3-diacyl-2,3-dihydrobenzimidazoles **6** and oxidized with $KMnO_4$ to 1,3-diacyl-2,3-dihydrobenzimidazol-2-ones **7**.

In the last few years, the reactivities of quaternary salts of N-hetero-aromatic compounds as pyridine, thiazole, imidazole and their benzoderivatives toward some C-electrophiles have been extensively studied. The reactions of organocopper and organotin reagents, sillyl enol ethers and titanium enolates with N-alkoxycarbonylpirydinium salts were used for synthesis of 4-substituted N-alkoxycarbonyl-1,4-dihydropirydines.[1] The reaction of quaternary salts of as N-ethoxycarbonylthiazolium chloride with lithium carbanions of esters, Grignard reagents, sillyl enol ethers was applied for preparation of 2-substituted N-ethoxycarbonylthiazolines[2] and with 2-trimethylsilylthiazole, or 4-methyl-2-trimethylsilyloxazole afforded the corresponding adducts.[3] Imidazole and benzimidazole were found out to react with acyl chlorides in the presence of triethylamine to form triacylimidazolinylimiadazoles and benzimidazoles.[4] An one-pot reaction of imidazole, thiazoles, oxazoles and their benzoderivatives with

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allyltributyltin in the presence of alkyl chloroformate was used for the synthesis of 2-alyl-1,3-bis (alkoxycarbonyl)-4-imidazolines, thiazolines and oxazolines.[5] It was reported recently that imidazole and thiazole reacted with sillyl enol ethers in the presence of an alkyl chloroformate and triethylamine to give 3-substituted derivatives.[6] It was found also that the adduct of 1-benzoylbenzamidazole with benzoyl chloride reacted with KCN to afford 2-cyano-1,3-dibenzoyl-2,3-dihydrobenzimidazole as a Reissert compound.[7a,b]

The last several years we used successfully the adducts of 3,4-dihydroisoquinolines and acyl chlorides as electrophilic reagents in an intra- and intermolecular α-amidoalkylation reaction toward aromatics[8], methylene active carbonyl compounds[9] and Grignard reagents[10] for synthesis of 1-substituted 2-acyltetrahydroisoquinolines and dibenzo[a,h]quinolizines.

Now we report the investigations on the preparation of adducts of benzimidazoles **1** with acyl chlorides and their application as α-amidoalkylation reagents toward some ketones. It was found that 1-ethoxycarbonylbenzoimidazole **3** reacted with ethyl chloroformate in anhydrous solvents as dichloroethane or acetonitrile at reflux for 3 h to afford an adduct **4** (R=H, R^1=OEt). The same adduct was obtained directly from benzimidazole and two equivalents of ethyl chloroformate in acetonitrile at reflux for 2 h. The adduct, after evaporation of the solvent, was stable enough and can be isolated and characterized. ^{1}H-NMR spectra of **3** (R=H, R^1=OEt) in $CDCl_3$ showed a singlet for the methine proton of C-2 at δ 8.47 ppm, while for **4a** (R=H, R^1=OEt) it was shifted to 7.05 ppm. Treatment of **4a** with 1 equiv. of $BF_3.OEt_2$ in $CDCl_3$ after overnight at room temperature afforded **4b** since a distinct singlet appeared at 10.07 ppm. Similar adducts **4** were obtained from 5,6-dimethylbenzimidazole and ethyl chloroformate as well as with benzoyl chloride and acetyl chloride but especially with acetyl chloride they were not enough stable to be isolated and characterized. It was found that the obtained adducts **4** reacted further with ketones as acetone, acetophenone, or benzalacetone and afforded the corresponding 2-(2-oxoalkyl)-1,3-diacyl-2,3-dihydrobenzimidazo-

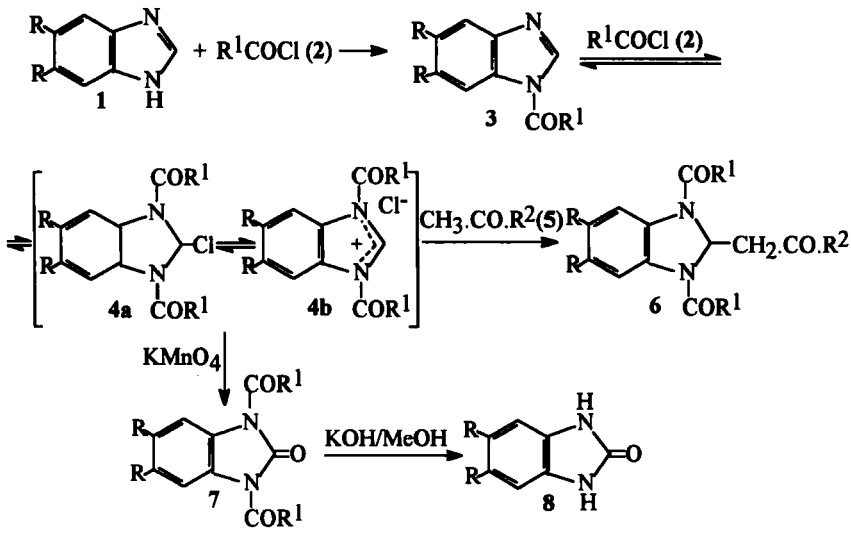

Table 1

Entry	R	R^1	R^2	Yield (%)		mp
				Method A	Method B	(°C)
6a	H	OEt	Me	80	56	55-56
6b	H	OEt	C_6H_5	84	62	89-90
6c	H	OEt	CH=CH C_6H_5	74	65	93-93.5
6d	Me	OEt	Me	53	30	131-132
6e	Me	OEt	C_6H_5	50	33	144-145
7a	H	OEt	-	70	-	126.5-127
7b	H	C_6H_5	-	53	-	213-213.5[a]
7c	H	Me	-	-	40	148-149[b]
7d	Me	OEt	-	65	-	191-191.5

[a]Lit. Mp 212-213°C (ref. 12); [b]Lit. Mp 149-151°C (ref. 13)

Table 2

Entry	^{1}H-NMR ($CDCl_3$/TMS), δ, J (Hz)	MS (70eV) m/z/M^+
6a	1.41(t,6H,J=7),2.21(s,3H),3.05(d,2H,J=3),4.37(q,4H, J=8),6.59(t,1H,J=3), 6.98-7.22(m,2H),7.50-7.89(m,2H)	320; (320.2) $C_{16}H_{20}N_2O_5$
6b	1.31(t,6H,J=7),3.58(d,2H,J=6),4.26(q,4H,J=8),6.68 (t,1H, J=5),6.98-7.21(m,2H),7.45-7.78(m,5H),8.01 and 8.15(d,d,2H,J=2)	382; (382.4) $C_{21}H_{22}N_2O_5$
6c	1.40(t,6H,J=7),3.25(d,2H,J=8),4.35(q,4H,J=8),6.61 (t,1H, J=3),6.70(d,1H,J=2),6.91(d,1H,J=2),7.00-7.25 (m,2H),7.41-7.62(m,5H),7.67 and 7.76(d,d,2H,J=2)	408; (408.4) $C_{23}H_{24}N_2O_5$
6d	1.45(t,6H,J=7),2.22(s,6H),2.28(s,3H),2.38(d,2H,J=5), 4.37(q,4H,J=8),6.50(t,1H,J=5),7.37(s,1H),7.45(s,1H)	348; (348.4) $C_{18}H_{24}N_2O_5$
6e	1.37(t,6H,J=7),2.17(s,6H),3.52(d,2H,J=6),4.22(q,4H, J=8),6.61(t,1H,J=5),7.33(s,1H),7.41((s,1H),7.45-7.64 (m,3H),8.01 and 8.13(d,d,2H,J=2)	410; (410.5) $C_{23}H_{26}N_2O_5$
7a	1.55(t,6H,J=7),4.60(q,4H,J=8),7.25-7.43(m,2H),7.87-8.18(m,2H)	278; (278.3) $C_{13}H_{14}N_2O_5$
7b	7.26-7.60(m,7H),7.71-8.05(m,7H)	342; (342.4) $C_{21}H_{14}N_2O_3$
7c	2.68(s,6H),7.21-7.42(m,2H),8.20-8.38(m,2H)	218; (218.2) $C_{11}H_{10}N_2O_3$
7d	1.53(t,6H,J=7),2.27(s,6H),4.57(q,4H,J=8),7.76(s,2H)	306; (306.3) $C_{15}H_{18}N_2O_5$

les (Table 1, Method A, **6a-e**) as a result of an intermolecular α-amidoalkylation reaction. It was found also that the reaction can be carried as one-pot starting from benzimidazole, ethyl chloroformate and the corresponding ketones **5** (Table 1, Method **B**).

The application of adducts **4** as amidoalkylation reagents toward ketones showed the depends of the yields of **6** from the substituents in the aromatic ring of benzimidazole as well as of the nature of the used acyl chloride. The presence of donating groups (**4**, R=Me) decreased the yields of products **6** (Table 1, **6d,e**). The adducts of benzimidazole with acetyl and benzoyl chlorides don't react with ketones **5** at different reaction conditions probably because they formed only a salts but not the adducts with a covalent structure **4a**.

The adducts **4**, obtained from 1-acylbenzimidazole **3** and the corresponding acyl chloride in dichloroethane were successfully oxidized with $KMnO_4$ in the presence of 18-Crown-6 as a phase transfer catalyst to 1,3-diacyl-2,3-dihydro-benzimidazol-2-ones **7** in good yields (Table 1, **7a,b,d**). The oxidation of the same adducts, obtained from benzimidazole and acyl chlorides in acetonitrile with $KMnO_4$ led to unsatisfactory yields of **7** (30-40%). Only 1,3-diacetyl-2,3-dihydro-benzimidazol-2-one **7c** (Table 1) was obtained in a moderate yield by oxidation with $KMnO_4$ of adduct **4** (R=H, R^1=Me) obtained from benzimidazole and acetyl chloride in acetonitrile probably because it is in its salt form.

1,3-Diacyl-2,3-dihydrobenzoimidazol-2-ones **7** were easily hydrolysed to 1,2-dihydroimidazol-2-one **8** at treatment with 10% methanolic potassium hydroxide for 30 min at room temperature.

The above reactions of adducts **4** allow the synthesis of not easily accessible 1,2-dihydrobenzimidazoles with substitution at 1,2 and 3 positions with the routs available in the literature but they are attractive as potential pharmaceutical agents.

Experimental

Preparation of 1-ethoxycarbonylbenzimidazole 3 (R=H, R^1=OEt): To a stirred solution of benzimidazole **1** (10 mmol) and Et_3N (12 mmol) in dichloroethane (20 mL), cooled in an ice bath, was added dropwise ethyl chloroformate (12 mmol). The suspension was stirred for 6 h at room temperature, then washed with water (3x50 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under vacuum. The pure product was obtained as an oil in 80 % yield; ^{1}H-NMR ($CDCl_3$), δ, J (Hz): 1.55(t, 3H, J=6), 4.60(q, 2H, J=8), 7.31-7.57(m, 2H), 7.82(d, 1H, J=7), 8.07(d, 2H, J=7), 8.56(s, 1H).

1-Ethoxycarbonyl-5,6-dimethylbenzimidazole 3 (R=Me, R^1=OEt) was obtained by a procedure previously described for 1-benzoylbenzimidazole[7] in 85 % yield; mp 92-93°C; ^{1}H-NMR ($CDCl_3$), δ, J (Hz): 1.57(t, 3H, J=6), 2.37(s, 6H), 4.60(q, 2H, J=8), 7.61(s, 1H), 7.85(s, 1H), 8.47(s,1H).

2-Chloro-1,3-diethoxycarbonyl-2,3-dihydrobenzimidazole 4a (R=H, R^1=OEt) was obtained from 1-ethoxycarbonylbenzimidazole **3**(3 mmol) and ethyl chloroformate (3 mmol) in dichloroethane at reflux for 3 h. The product was isolated from the starting compounds by column chromatography on neutral Al_2O_3 using p. ether, then p. ether/Et_2O (4:1) as eluents as white crystals; mp 120-120.5°C; ^{1}H-NMR ($CDCl_3$/TMS), δ, J (Hz): 1.43(t, 6H, J=7), 4.35 (q, 4H, J= 8), 7.05(d, 2H, J=6), 7.08(d, 2H, J=6), 7.22(s, 1H), 7.32-7.75(m, 2H); IR (KBr) 1723 cm^{-1} (CO).

Synthesis of 2-(2-oxoalkyl)-1,3-diacyl-2,3-dihydrobenzimidazoles (Table 1, **6a-e**); **Method A:** To a solution of 1-ethoxycarbonylbenzimidazole **3** (2 mmol) in dichloroethane (10 mL) were added ethyl chloroformate (2.1 mmol) and the corresponding ketone **5** [acetone (5 mL), or acetophenone (3 mmol), or benzalacetone (2 mmol)]. The reaction mixture was stirred at reflux for 3 h, then cooled to room temperature. Water (20 mL) and 10% aq.HCl (20 mL) were added and the solution was extracted with $CHCl_3$ (3x 20 mL). The combined extract was dried (Na_2SO_4), the solvents were evaporated under vacuum and the products were purified by column chromatography on neutral Al_2O_3, using p. ether, then p. ether/Et_2O (4:1) as eluents.

Method B: Ethyl chloroformate (4.2 mmol) and the corresponding ketone **5** (at amounts as in Method A) were added to a stirred solution of benzimidazole **1** (2 mmol) in CH_3CN (10 mL). The reaction mixture was reflux for 3 h, then was worked up as above and the products were purified as above.

Synthesis of 1,3-diacyl-2,3-dihydrobenzimidazol-2-ones (Table 1, **7a,b,d**); **Typical procedure:** Acyl chloride **2** (2.1 mmol) was added to a solution of 1-acylbenzimidazol **3** (2 mmol) in dichloroethane (10 mL) and the mixture was stirred for 2 h at reflux for preparation of **4**. The mixture was cooled to room temperature and 18-crown-6 (50 mg) was added. $KMnO_4$ (4 mmol) was then added portionwise to a stirred at room temperature mixture for 3 h. The colour of the mixture turned from violet to brown from the formed MnO_2. Saturated aqueous metabisulite solution (10 mL) was then carefully added. The resulting mixture was treated with aq. 10%

HCl (10 mL) and the solution was extracted with $CHCl_3$ (3x20 mL). The combined extract was dried (Na_2SO_4), the solvents evaporated under vacuum and the products were purified by recrystallization from p. ether/ether (1:1).

One-pot synthesis of 1,3-diacetyl-2,3-dihydrobenzimidazol-2-one (Table 1, **7c**): To a stirred and cooled in an ice-water bath solution of benzimidazole **1** (2 mmol) in acetonitrile (10 mL) was added dropwise a solution of acetyl chloride (4.2 mmol) in acetonitrile (2 mL) and the mixture was stirred for 1 h at room temperature. 18-Crown-6 (50 mg) was added and then $KMnO_4$ (4 mmol) was added portionwise for 3 h. The reaction mixture was worked up as above and the product was purified by recrystallization from Et_2O.

Hydrolysis of 1,3-dibenzoyl-2,3-dihydrobenzimidazol-2-one 7 to 1,2-dihydro-benzimidazol-2-one 8 (R=H). A solution of 1,3-dibenzoyl-2,3-dihydrobenz-imidazol-2-one **7b** (0,3 g) in 10% methanolic potassium hydroxide (5 mL) was stirred at room temperature for 30 min. Water (10 mL) was added and the solution was extracted with $CHCl_3$ (4x30 mL). The combined extract was dried (Na_2SO_4), the solvents evaporated to produce the product as white crysatls; mp 308-310°C (lit.[12] 310-312°C). ^{1}H-NMR ($CDCl_3$/DMSO-d_6), δ: 7.15-7.45 (m, 4H), 10.85 (s, 2H); IR (KBr) 1744 cm^{-1} (CO), 3176 cm^{-1} (NH).

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