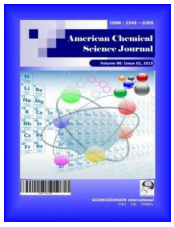

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N-Monobenzoylation (acetylation, arylsulfonation), N-, C- di- and N-, C-, O- tribenzoylation of 5H(chloro, nitro)-2-methyl(ethyl)benzimidazoles

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Authors' contributions

The work was carried out in collaboration between the authors. Authors TUD, UMY carried out the synthesis. Author AAM provided analysis of the study, and spectroscopic evaluation. Author GEB helped to isolate of reaction products. Author KMS offered the idea of researches did the collation of the date and editing of the write-up. All authors read approved the final manuscript.

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ABSTRACT

The interaction of 2-methyl(ethyl)-5H(chloro, nitro)benzimidazoles with benzoyl (acetyl) chloride, and *p*-toluenesulfonyl chloride in the presence of triethylamine in tetrahydrofuran or chloroform was studied. It was found that the reaction proceeds in three stages with the formation of N-monobenzoyl (acetyl, *p*-toluenesulfonyl), N-, C-dibenzoyl- and N-, C-, O-tribenzoyl benzimidazoles depending on the ratio of reagents, the nature of the substituent in the aromatic ring, α-methylene group, and acid chlorides. It was revealed that in the case of acetyl, *p*-toluenesulfonyl chloride reaction is stopped at the first stage with formation of N-monoacetyl (*p*-toluenesulfonyl) derivatives. The method for HPLC analysis for separation, identification and determination of the ratio of obtained compounds was developed. It was found that 1-acetyl (benzoyl)-2-methylbenzimidazoles

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were decomposed at the standing. The crystalline form of 1-acetyl-2-methylbenzimidazole is decomposed to the 2-methylbenzimidazole: 25% (7 days), 50% (15 days), 100% (30 days) and decomposition of 1-benzoyl-2-methylbenzimidazole to the 2-methylbenzimidazole (50%) occurs within 2 months.

Keywords: 1H-2-methyl-; ethyl-; 1-benzoyl-; p-toluenesulfonyl-; 2-acetyl-; methyl-; ethyl-; 5H-;-chloro; -nitrobenzoyl benzimidazoles; benzoyl chloride; p-toluenesulfonyl chloride; acylation; N-mono -; N; C-di-; N-; C-; O-tribenzoylation.

1. INTRODUCTION

Among the benzimidazole derivatives were found many drugs for medicine (*dibazol*, *medamin*, *mebendazole*, *albendazole*) and agriculture (*olgin*, *benomyl*, *benleyt*) [1-10]. Furthermore, these compounds are also interesting of a chemical point of view, since in their molecule there are some reactive centers (nitrogen atoms at N-1, N-3, aromatic ring and alkyl group at the α-carbon atom in the 2-alkylbenzimidazoles). In the literature many information about reactions of nitrogen atom (or nitrogen atoms) and aromatic rings of these compounds (alkylation, carboxyalkylation, acylation) were reported [8,9,11,12]. In these literatures given only a few information concerning to the reaction of 2-alkylbenzimidazole with electrophilic reagents, that occur by the α-methylene group. Thus, it was shown that, 2-methylbenzimidazole is reacted with benzoyl chloride, leading to mono- and dibenzoyl derivatives [13-15]. Similarly, the benzoylation goes on the methylene group of 1-ethyl-2-methylbenzimidazole [15]. In these previously reported literatures were not discussed the important issues such as the possibility formation of enol forms of obtained 2-phenacylbenzimidazole, that occur during the acylation of tricyclic quinazoline-4-ones [16-22]. Furthermore, it is known that a methylene group of their quinazoline analogues are also reacted with aldehydes, formamides, bromine, and others electrophilic reagents [22-31]. In our opinion, the interests are represented for the broader applications of the acylation reaction of 2-methylbenzimidazole, and their derivatives which have various substituents (Cl, NO_2, etc.) in the aromatic ring and α-methylene group, also studying their influence to reaction course and direction.

2. MATERIALS AND METHODS

2.1 General Conditions

^{1}H-NMR spectra were recorded in $CDCl_3$ and CCl_4+DMSO on Varian 400-MR spectrometer operating accordingly at 400 MHz. Tetramethylsilane (TMS) was used as internal standard, chemical shifts δ of ^{1}H were recorded in ppm.

Mass spectra were acquired on a Kratos MS-30 (UK) spectrometer. Mps were measured on a Boetius and MEL-TEMP apparatus manufactured by Branstead international (USA) and were uncorrected. IR spectra were recorded on Shimadzu FTIR-8400 and IR Fury System 2000 (Perkin-Elmer) as KBr pellets.

HPLC analysis was acquired on a Agilent 1200 series. The reaction process was monitored by TLC on Sorbfil and Whatman UV-254 percoated aluminum plates using C_6H_6/CH_3OH (3:1 and 5:1) solvent system and developed plates were visualized under UV lamp, and/or iodine tank where necessary. Solvents were purified by standard procedures. Organic solutions were dried over anhydrous Na_2SO_4 or with the dried $CaCl_2$.

2.2 Synthesis

The starting compound (1-4) was synthesized according to the method [8].

2.2.1 N-Monoacetylation of 2-methyl(ethyl)benzimidazoles

2.2.1.1 1-Acetyl-2-methylbenzimidazole (5)

2-Methylbenzimidazole 2.64 g (0.02 mol) (1) in 20 ml of chloroform was added 4 ml (0.04 mol) of acetic anhydride. The reaction mixture was heated at 50-60ºC for 40 min. Solvent was distilled off and the residue washed with water and dried. Compound 5 was recrystallized from hexane. Yield: 2.4 g (70%), mp 83-85ºC, R_f 0.68 (C_6H_6/CH_3OH - 3:1, at RT). IR (KBr), ν, cm^{-1}: 1725 (C=O, amide), 1660 (C=N), 1554 (C-N).

2.2.1.2 1-Acetyl-2-ethylbenzimidazole (6).

From 2.92 g (0.02 mol) 2-ethylbenzimidazole (2) analogously to the above mentioned method was obtained 1-acetyl-2-ethylbenzimidazole.

Yield: 2.3 g (63%), mp 170-172ºC (hexane). R_f 0.71 (C_6H_6/CH_3OH - 3:1, at RT). IR (KBr), v,cm^{-1}: 1723 (C=O, amide), 1656 (C=N), 1599 (C-N).

2.2.2 N-Monobenzoylation of 2-substituted benzimidazoles (ratio of benzimidazole:benzoyl chloride - 1:1)

2.2.2.1 N-Monobenzoylation of the 2-methylbenzimidazole. Synthesis of 1-benzoyl-2-methylbenzimidazole (7)

To a solution of 1.32 g (0.01 mol) of 2-methylbenzimidazole in 40 ml chloroform were added 1.4 ml (0.012 mol) of benzoyl chloride and 1.66 ml (0.012 mol) of triethylamine. Reaction mixture was heated at 60-65ºC for 15 min, and formed precipitate was filtered off. The solvent was distilled off and the residue washed with water, and recrystallized from hexane.

Yield: 2 g (85%), mp 85ºC, R_f 0.87 (C_6H_6/CH_3OH, 3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 2.6 (3H, s, CH_3), 7.24 (4H, m, C_6H_4), 7.26 (1H, s, CH benzimidazole), 7.75 (5H, m, C_6H_5). IR (KBr), v, cm^{-1}: 1704 (C=O amide), 1598 (C=N), 2998 (CH_3).

By above mentioned method, to the 1.32 g (0.01 mol) of 2-methylbenzimidazole in 40 ml of tetrahydrofuran were added 1.4 ml (0.012 mol) of benzoyl chloride and 1.66 ml (0.012 mol) of triethylamine. 1.89 g (80%) of compound 7 was obtained, mp 85ºC (hexane), R_f 0.87 (C_6H_6/CH_3OH - 3:1, at RT).

2.2.2.2 N-Monobenzoylation of 2-ethylbenzimidazole. Synthesis of 1-benzoyl-2-ethylbenzimidazole (8)

Reaction carried out analogously to the synthesis method of compound 7. From 1.46 g (0.01 mol) of 2-ethylbenzimidazole, 1.4 ml (0.012 mol) of benzoyl chloride, 1.66 ml (0.012 mol) of triethylamine in 40 ml chloroform was obtained compound 8.

Yield: 2 g (80%), mp 82ºC (benzene-hexane - 1:1), R_f 0.86 (C_6H_6/CH_3OH - 3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 2.8 (3H, t, CH_3), 1.42 (2H, s, CH_2), 7.40 (1H, s, C=O amide), 7.45 (4H, m, C_6H_4), 7.54 (5H, m, C_6H_5), IR (KBr), v, cm^{-1}: 1701 (C=O amide), 1599 (C=N), 2975-2938 (CH_3CH_2).

Similarly of above mentioned method, from 1.46 g (0.01 mol) of 2-ethylbenzimidazole, 1.4 ml (0.012 mol) of benzoyl chloride, 1.66 ml (0.012 mol) of triethylamine in tetrahydrofuran was obtained compound 8.

Yield: 1.75 g (70%), mp 82ºC (benzene-hexane - 1:1), R_f 0.85 (C_6H_6/CH_3OH - 3:1, at RT).

2.2.2.3 N-Monobenzoylation of 2-methyl-5-chlorobenzimidazole. Synthesis of 1-benzoyl-2-methyl-5-chlorobenzimidazole (9)

The reaction carried out analogously to the above mentioned methods; from 1.66 g (0.01 mol) of 2-methyl-5-chlorobenzimidazole, 1.4 ml (0.012 mol) of benzoyl chloride, 1.66 ml (0.012 mol) of triethylamine in 40ml of chloroform was obtained compound 9.

Yield: 1.89 g (70%), mp 78-80ºC (hexane), R_f 0.84 (C_6H_6/CH_3OH-3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 2.54 (3H, s, CH_3), 7.1-8.15 (9H, m, C_6H_5+C_6H_4). IR (KBr), v, cm^{-1}: 1705 (C=O amide), 1600 (CN), 2927 (CH_3).

Analogously, from 1.66 g (0.01 mol) of 2-methyl 5-chlorobenzimidazole, 1.4 ml (0.012 mol) of benzoyl chloride and 1.66 ml (0.012 mol) of triethylamine in 40 ml of tetrahydrofuran was obtained the product 9 in moderate yield.

Yield: 1.62 g (60%), mp 78-80ºC (hexane), R_f 0.84 (C_6H_6/CH_3OH - 3:1, at RT).

2.2.2.4 N-Monobenzoylation of 2-methyl-5-nitrobenzimidazole. Synthesis of 1-benzoyl-2-methyl-5-nitrobenzimidazole (10)

From 1.77 g (0.01 mol) of 2-methyl-5-nitrobenzimidazole, 1.4 ml (0.012 mol) of benzoyl chloride and 1.66 ml (0.012 mol) of triethylamine in 40 ml of chloroform was obtained product 10.

Yield: 1.6 g (57%), mp 142-144ºC (benzene), R_f 0.85 (C_6H_6/CH_3OH - 3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 2.52 (3H, s, CH_3), 7.5-8.1 (8H, m, C_6H_5+C_6H_3). IR (KBr), v, cm^{-1}: 1703 (C=O amide), 1600 (C=N), 3063 (CH_3). ESI-MS in m/z (rel. %): 281 ($[M+H]^+$, 35), 177(100), 161(12), 105(63), 76(41).

Analogously, from 1.77 g (0.01 mol) of 2-methyl-5-nitrobenzimidazole, 1.4 ml (0.012 mol) of benzoyl chloride and 1.66 ml (0.012 mol) of triethylamine in 40 ml of tetrahydrofuran was obtained compound 10 in moderate yield.

Yield: 1.54 g (55%), mp 142-144ºC (benzene), R_f 0.85 (C_6H_6/CH_3OH - 3:1, at RT).

2.2.3 Reactions of 1-benzoyl-, acetyl-, 2-alkylbenzimidazoles with benzoyl (acetyl) chloride

2.2.3.1 Synthesis of 1,3-dibenzoyl-2-methylbenzimidazolium chloride (12)

To a solution of 2.36 g (0.01 mol) of 1-benzoyl-2-methyl benzimidazole (7) in 40 ml of absolute benzene 1.4 ml (0.012 mol) of benzoyl chloride was added. The reaction mixture was heated on a water bath at 50-60ºC. When clouding occurred and appeared a white precipitate, the reaction mixture was left for 10-15 min, and the precipitate filtered, washed with absolute benzene and dried. Yield: 3 g (80%), mp 258-260ºC. IR (KBr), v, cm^{-1}: 1798 (N(1)-C=O, carbonyl), 1668 (N(3)-C=O, carbonyl), 1624 (C=N), 1578 (C-N).

2.2.3.2 Synthesis of 1-benzoyl-3-acetyl-2-methylbenzimidazolium chloride (13)

To a solution of 2.36 g (0.01 mol) of 1-benzoyl-2-methylbenzimidazole (7) in 40 ml of absolute benzene 0.94 ml (0.012 mol) of acetyl chloride was added. When appeared turbidity and occurred the formation of a white precipitate the reaction mixture was left for 10-15 min, then the precipitate filtered, washed with absolute benzene and dried. Yield: 3.2 (85%), mp 278-280ºC. IR (KBr), v, cm^{-1}: 1798 (N(1)-C=O, carbonyl), 1668 (N(3)-C=O, carbonyl), 1620 (C=N), 1574 (C-N).

2.2.3.3 Synthesis of 1,3-diacetyl-2-methylbenzimidazolium chloride (14)

To a solution of 1.74 g (0.01 mol) of 1-acetyl-2-methylbenzimidazole in 40 ml of absolute benzene 0.85 ml (0.012 mol) of acetyl chloride was added. It was observed the turbidity of reaction mixture and a white precipitate begins to precipitate. The reaction mixture was left for 10-15 min, and the precipitate filtered, washed with absolute benzene and dried.

Yield: 2.27 g (90%), mp 338-340ºC. IR (KBr), v, cm^{-1}: 1798 (N(1)-C=O, carbonyl), 1670 (N(3)-C=O, carbonyl), 1625 (C=N), 1579 (C-N).

2.2.3.4 Synthesis of 1,3-dibenzoyl-2-ethylbenzimidazolium chloride (15)

From 2.5 g (0.01 mol) of 1-benzoyl-2-ethylbenzimidazole (8) and 1.4 ml (0.012 mol) of benzoyl chloride in 40 ml of absolute benzene 1,3-dibenzoyl-2-ethylbenzimidazolium chloride (15) was obtained in yield 3.5 g (90%), mp 218-220ºC. IR (KBr), v, cm^{-1}: 1795 (N(1)-C=O, carbonyl), 1656 (N(3)-C=O, carbonyl), 1623 (C=N), 1574 (C-N).

2.2.3.5 Synthesis of 1-benzoyl-3-acetyl-2-ethylbenzimidazolium chloride (16)

From 2.5 g (0.01 mol) of 1-benzoyl-2-ethylbenzimidazole (8) and 0.85 ml (0.012 mol) acetyl chloride 1-benzoyl-3-acetyl-2-ethylbenzimidazole chloride 16 was synthesized. Yield: 2.79 g (85%), mp 223-225ºC. IR (KBr), v, cm^{-1}: 1790 (N(1)-C=O, carbonyl), 1670 (N(3)-C=O, carbonyl), 1623 (C=N), 1574 (C-N).

2.2.3.6 Synthesis of 1,3-dibenzoyl-2-methyl-5-chlorobenzimidazolium chloride (17)

Analogously from 2.71 g (0.01 mol) of 1-benzoyl-2-methyl-5-chlorobenzimidazole and 1.4 ml (0.012 mol) of benzoyl chloride 1,3-dibenzoyl-2-methyl-5-chlorobenzimidazolium chloride 17 was obtained in yield 3.3 g (80%), mp 218-220ºC. IR (KBr), v, cm^{-1}: 1796 (N(1)-C=O, carbonyl), 1660 (N(3)-C=O, carbonyl), 1624 (C=N), 1574 (C-N).

2.2.3.7 Synthesis of 1-acetyl-3-benzoyl-2-methyl-5-chlorobenzimidazolium chloride (18)

From 2.08 g (0.01 mol) of 1-acetyl-2-methyl-5-chlorobenzimidazole and 1.4 ml (0.012 mol) of benzoyl chloride compound 18 was synthesized. Yield: 2.97 g (85%), mp 222-225ºC. IR (KBr), v, cm^{-1}: 1792 (N(1)-C=O, carbonyl), 1668 (N(3)-C=O, carbonyl), 1620 (C=N), 1574 (C-N).

2.2.3.8 Synthesis of 1-benzoyl-3-acetyl-2-methyl-5-chlorobenzimidazolium chloride (19)

Similarly from 2.70 g (0.01 mol) of 1-benzoyl-2-methyl-5-chlorobenzimidazole and 0.85 ml (0.012 mol) of acetyl chloride 2.6 g (75%) of 1-benzoyl-3-acetyl-2-methyl-5-chlorobenzimidazolium chloride (19) was obtained, mp 243-245ºC. IR (KBr), v, cm^{-1}: 1796 (N(1)-C=O, carbonyl), 1665 (N(3)-C=O, carbonyl), 1621 (C=N), 1573 (C-N).

2.2.3.9 Synthesis of 1,2-dimethyl-3-benzoylbenzimidazolium chloride (20)

Analogously from 1.46 g (0.01 mol) of 1,2-dimethylbenzimidazole and 1.4 ml (0.012 mol) of benzoylchloride 2 g (70%) of 1,2-dimethyl-3-benzoylbenzimidazolium chloride 20 was

synthesized, mp 203-205ºC. IR (KBr), ν, cm^{-1}: 1772 (N(1)-C=O, carbonyl), 1628 (C=N), 1595 (C-N).

2.2.3.10 Synthesis of 1,2-dimethyl-3-acetylbenzimidazolium chloride (21)

From 1.46 g (0.01 mol) of 1,2-dimethylbenzimidazole and 0.94 ml (0.012 mol) acetyl chloride in 40 ml of benzene 1.68 g (75%) of compound 21 was obtained, mp 218-220ºC. IR (KBr), ν, cm^{-1}: 1770 (N(1)-C=O, carbonyl), 1630 (C=N), 1580 (C-N).

2.2.3.11 Synthesis of 1-methyl-2-ethyl-3-benzoylbenzimidazolium chloride (22)

Analogously from 1.6 g (0.01 mol) of 1-methyl-2-ethylbenzimidazole and 1.4 ml (0.012 mol) of benzoyl chloride 2.25 g (75%) of 1-methyl-2-ethyl-3-benzoylbenzimidazolium chloride (22) was synthesized, mp 206-208ºC. IR (KBr), ν, cm^{-1}: 1769 (N(1)-C=O, carbonyl), 1625 (C=N), 1590 (C-N).

2.2.3.12 Synthesis of 1-methyl-2-ethyl-3-acetylbenzimidazolium chloride (23)

From 1.6 g (0.01 mol) of 1-methyl-2-etylbenzimidazole, and 0.94 ml (0.012 mol) acetyl chloride was obtained 1.68 g (70%) of 1-methyl-2-ethyl-3-acetylbenzimidazolium chloride (23), mp 205-207ºC. IR (KBr), ν, cm^{-1}: 1771 (N(1)-C=O, carbonyl), 1627 (C=N), 1585 (C-N).

2.2.4 Reaction of 2-methylbenzimidazole with benzoyl chloride (ratio 1:2)

To a solution of 1.32 g (0.01 mol) of 2-methylbenzimidazole in 60 ml of chloroform were added 3.32 ml (0.024 mol) of triethylamine and 2.8 ml (0.024 mol) of benzoyl chloride and reaction mixture was boiled for 15 min, was cooled, and the precipitate of triethylamine hydrochloride was filtered. Chloroform was distilled off and the residue consists of a mixture of several compounds. The composition of the compounds was determined by HPLC. It was determined that the mixture contains 1-benzoyl-2-methylbenzimidazole (**7**, 41.2%), 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24, 22.7%) and 1-benzoyl-2-(benzoylmethylidene)-1H-benzimidazole (25, 22.5%).

Reaction of 2-methylbenzimidazole with benzoyl chloride (ratio 1:3)

From 1.32 g (0.01 mol) of 2-methylbenzimidazole, 4.2 ml (0.036 mol) of benzoyl chloride and 4.98 ml (0.036 mol) of triethylamine in 90 ml of chloroform was obtained analogously to the above mentioned method a mixture, which contain of N-benzoyl-2-methylbenzimidazole (7, 24.8%), 1-benzoyl-2-(benzoylmethylidene)-1H-benzimidazole (25, 32.1%) and 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24, 19.67%).

2.2.5 Benzoylation of 2-methylbenzimidazole with benzoyl chloride (ratio 1:4)

2.2.5.1 Synthesis of 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24)

Method A: the reaction mixture of 1.32 g (0.01 mol) of 2-methylbenzimidazole in 60 ml of chloroform, 5.563 ml (0.048 mol) of benzoyl chloride and 6.66 ml (0.048 mol) of triethylamine was boiled for 10 min and 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24) was obtained.

Yield: 3.24 g (73%), mp 157-159^{0}C (hexane), R_f 0.89 (C_6H_6/CH_3OH - 3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 6.8-7.83 (19H, m, $3C_6H_5$+C_6H_4), 6.8 (1H, s, CH). IR (KBr), ν, cm^{-1}: 1670 (C=C), 1715 (C=O amide), 1745 (C=O ester). ESI-MS in m/z (rel. %): 444 ($[M+H]^+$, 85), 339 (27), 235(5), 105 (100), 76 (62).

Carrying out the reaction of 1.32 g (0.01 mol) of 2-methylbenzimidazole, 5.56 ml (0.048 mol) of benzoyl chloride and 6.66 ml (0.048 mol) of triethylamine in 60 ml of tetrahydrofuran gives 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24) in good yield. Yield: 3.1 g (70%), mp 157-159ºC (hexane).

Method B: the mixture of 1.32 g (0.01 mol) of 2-methylbenzimidazole and 5.56 ml (0.048 mol) of benzoyl chloride, 6.66 mL (0.048 mol) of triethylamine was heated in the absence of solvent at 172-178ºC for 1 h. After cooling, to the reaction mixture 50 ml of water was added and extracted with chloroform. The chloroform layer was dried over anhydrous Na_2SO_4. The solvent was distilled off and the residue was recrystallized from hexane. Yield: 3.55 g (80%), mp 157-159ºC.

2.2.6 Benzoylation of 1-benzoyl-2-methylbenzimidazole with benzoyl chloride (ratio 1:3)

2.2.6.1 Synthesis of 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24)

To a solution of 2.36 g (0.01 mol) of 1-benzoyl-2-methylbenzimidazole in 60 ml of chloroform 3.32 ml (0.024 mol) of triethylamine and 2.8 ml (0.024 mol) of benzoyl chloride were added and the mixture was boiled for 15 min, and after cooling the formed precipitate of triethylamine hydrochloride was filtered. To the reaction mixture 50 ml of water was added and extracted with chloroform. The chloroform layer was dried over anhydrous Na_2SO_4, the solvent was distilled off and the residue recrystallized from hexane.
Yield: 3.1 g (70%), mp 157-159ºC, R_f 0.89 (C_6H_6/CH_3OH - 3:1, at RT).

2.2.6.2 Synthesis of 1-benzoyl-2-(benzoylmethylidene)-1H-benzimidazole (25)

The mixture of 4.44 g (0.01 mol) of 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24) and 1.22 g (0.01 mol) of benzoic acid was heated at 175-180ºC for 30 min. To the reaction mixture was added 25 ml of benzene. After cooling, the obtained precipitate was filtered and washed with benzene.

Yield: 3 g (90%), mp 254-256ºC (in the literature [13] mp 256-257.5ºC), R_f 0.68 (C_6H_6/CH_3OH-3:1, at RT). 1H-NMR (DMSO-d_6-$CDCl_3$) δ: 7.0-7.66 (14H, C_6H_4 +2 C_6H_5), 13.08 (1H, NH). IR (KBr), ν, cm^{-1}: 3360, 3390 (NH), 1620 (C=O, C=C), 1715 (C=O amide).

2.2.7 Benzoylation of 2-ethylbenzimidazole (ratio 1:4)

2.2.7.1 Synthesis of 1-benzoyl-2-(β-benzoyloxy-β-phenylpropenyl)-1H-benzimidazole (26)

Method A: analogously to the above mentioned synthesis method of compound 24 (method A), from 1.46 g (0.01 mol) of 2-ethylbenzimidazole, 5.56 ml (0.048 mol) of benzoyl chloride and 6.66 ml (0.048 mol) of triethylamine in 60 ml of chloroform 2.75 g (60%) of 1-benzoyl-2-(β-benzoyloxy-β-phenylpropenyl)-1H-benzimidazole (26) was obtained, mp 138-140ºC (hexane), R_f 0.69 (C_6H_6/CH_3OH - 3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 6.9-8.1 (15H, m, $3C_6H_5$), 6.64 (4H, m, C_6H_4), 2.14 (3H, t, CH_3). IR (KBr), ν, cm^{-1}: 2980 (CH_3), 1750 (C=O ester), 1692 (C=O amide), 1656 (C=C), 1598 (C=N). ESI-MS in m/z (rel. %): 458 ($[M]^+$, 100), 368 (10), 263 ($[M-C_6H_5CO]^+$, 15), 105 (C_6H_5CO, 57).

From 1.46 g (0.01 mol) of 2-ethylbenzimidazole, 5.56 ml (0.048 mol) of benzoyl chloride and 6.66 ml (0.048 mol) of triethylamine in 60 ml of tetrahydrofuran 2.66 g (58%) compound **26** was obtained, mp 138-140ºC (hexane).

Method B (solvent free): Reaction carried out analogously to the method B of 2-methylbenzimidazole. From 1.32 g (0.01 mol) of 2-ethylbenzimidazole, 5.56 ml (0.048 mol) of benzoyl chloride and 6.66 ml (0.048 mol) of triethylamine 3.2 g (69.8%) product 26 was synthesized, mp 138-140ºC (benzene-hexane, 1:1).

2.2.8 Benzoylation of 2-methyl-5-chlorobenzimidazole

2.2.8.1 Synthesis of 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-5-chlorobenzimidazole (27)

Method A: similarly benzoylation of 2-methylbenzimidazole provided using by the method A: from 1.66 g (0.01 mol) of 2-methyl-5-chlorobenzimidazole, 5.56 ml (0.048 mol) of benzoyl chloride and 6.66 ml (0.048 mol) of triethylamine in 60 ml of chloroform was obtained compound 27 in yield 3.49 g (73%), mp 178-180ºC (hexane), R_f 0.81 (C_6H_6/CH_3OH-3:1, at RT). ^{1}H-NMR (DMSO-d_6-$CDCl_3$) δ: 7.3 (2H, q, C_6H_3), 6.9 (1H, d, C_6H_3), 6.7-7.8 (15H, m, $3C_6H_5$). IR (KBr), ν, cm^{-1}: 1736 (C=O ester), 1702 (C=O amide), 1649 (C=C). ESI-MS in m/z (rel. %): 478.5 ($[M+H]^+$, 100), 372(5), 105(90), 76(57).

Provided the reaction in tetrahydrofuran of 1.66 g (0.01 mol) of 2-methyl-5-chlorobenzimidazole, 5.56 ml (0.048 mol) of benzoyl chloride and 6.66 ml (0.048 mol) of triethylamine and synthesized the product 27 in good yield. Yield: 3.35 (70%), mp 178-180ºC (benzene-hexane 1:1).

Method B: from 1.66 g (0.01 mol) of 2-methyl-5-chlorobenzimidazole, 5.56 ml (0.048 mol) of benzoyl chloride, 6.66 ml (0.048 mol) triethylamine 3.35 g (70%) product 27 was obtained, mp 178-180ºC (benzene-hexane = 1:1).

2.2.9 Arylsulfonation of 2-methyl(ethyl)-5H(chloro, nitro)benzimidazoles

2.2.9.1 1-(p-Tolylsulfonyl)-2-methylbenzimidazole (28)

A mixture of 1.32 g (0.01 mol) 2-methylbenzimidazole, 1.9 g (0.01 mol) *p*-toluenesulfonyl chloride and 1.4 ml (0.01 mol) of triethylamine in 40 ml chloroform was heated in water bath for 1 h and chloroform was distilled off. The formed salt was washed with water and recrystallized from mixture - hexane: benzene 1:1. Yield: 2.38 g, 80%, R_f 0.7, mp 128-130ºC.

^{1}H-NMR ($CDCl_3$) δ: 7.95 (1H, dd, *J*=8.5, *J*=2.1, H-4), 7.74 (2H, m, H-5,6), 7.56 (1H, dd, *J*=8.3, *J*=2.1, H-7), 7.24 (4H, m, C_6H_4-SO_2), 2.75 (3H, s, CH_3-2), 2.32 (3H, s, C_6H_4-CH_3). IR (KBr), v, cm^{-1}: 1372 (SO_2-*asym.*), 1171 (SO_2-*sym.*).

2.2.9.2 1-(p-Tolylsulfonyl)-2-ethylbenzimidazole (29)

Analogously from 1.46 g (0.01mol) 2-ethylbenzimidazole in 40 ml of chloroform, 1.9 g (0.01 mol) *p*-toluenesulfonyl chloride and 1.4 ml (0,01 mol) of triethylamine product 29 was synthesized and recrystallized from hexane: benzene 1:1.

Yield: 2.34 g, 78%, R_f 0.88, mp 144-145ºC. ^{1}H-NMR ($CDCl_3$) δ: 7.94 (1H, dd, *J*=8.3, *J*=2.2, H-4), 7.72 (2H, m, H-5,6), 7.58 (1H, dd, *J*=8.2, *J*=2.2, H-7), 3.10 (2H, m, CH_2-2), 2.32 (3H, s, C_6H_4-CH_3), 1.38 (3H, t, CH_2CH_3-2). IR (KBr), v, cm^{-1}: 1374 (SO_2-*asym.*), 1167 (SO_2-*sym.*).

2.2.9.3 1-(p-Tolylsulfonyl)-2-methyl-5-chlorobenzimidazole (30)

From 1.66 g (0.01 mol) 2-methyl-5-chlorobenzimidazole in 40 ml of chloroform, 1.9 g (0.01 mol) *p*-toluenesulfonyl chloride and 1.4 ml (0.01 mol) of triethylamine compound 30 was obtained and recrystallized from hexane: benzene 1:1.

Yield: 2.6 g, 83%, R_f 0.8 (C_6H_6/CH_3OH - 3:1), mp 123-125ºC. ^{1}H-NMR ($CDCl_3$) δ: 7.96 (1H, s, H-4), 7.53 (2H, m, H-6,7), 7.7 (4H, m, C_6H_4-SO_2), 2.73 (3H, s, CH_3-2), 2.34 (3H, s, C_6H_4-CH_3). IR (KBr), v, cm^{-1}: 1375 (SO_2-*asym.*), 1174 (SO_2-*sym.*).

2.2.9.4 1-(p-Tolylsulfonyl)-2-methyl-5-nitrobenzimidazole (31)

From 1.77 g (0.01 mol) of 2-methyl-5-nitrobenzimidazole in 40 ml of chloroform, 1.9 g (0.01 mol) *p*-toluenesulfonyl chloride and 1.4 ml (0.01 mol) of triethylamine was synthesized product 31 and recrystallized from hexane: benzene 1:1.

Yield: 2.82 g, 85%, R_f 0.85 (C_6H_6/CH_3OH - 3:1), mp 150-152ºC. ^{1}H-NMR ($CDCl_3$) δ: 8.88 (1H, s, H-4), 8.18 (2H, m, H-6,7), 7.8 (4H, m, C_6H_4-SO_2), 2.81 (3H, s, CH_3-2), 2.36 (3H, s, C_6H_4-CH_3). IR (KBr), v, cm^{-1}: 1371 (SO_2-*asym.*), 1177 (SO_2-*sym.*).

2.2.9.5 1-(p-Tolylsulfonyl)-2-ethyl-5-nitrobenzimidazole (32)

From 1.91 g (0.01 mol) of 2-ethyl-5-nitrobenzimidazole in 40 ml of chloroform, 1.9 g (0.01 mol) *p*-toluenesulfonyl chloride and 1.4 ml (0.01 mol) of triethylamine compound 32 was obtained and recrystallized from mixture of hexane: benzene - 1:1.

Yield: 2.85 g, 82%, R_f 0.88 (C_6H_6/CH_3OH-3:1), mp 143-145ºC. IR (KBr), v, cm^{-1}: 1378 (SO_2-*asym.*), 1177 (SO_2-*sym.*).

2.2.9.6 1-(p-Tolylsulfonyl)-2-benzylbenzimidazol (33)

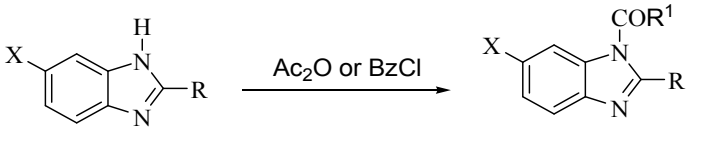
From 2.08 g (0.01 mol) 2-benzylbenzimidazol in 40 ml of chloroform, 1.9 g (0.01 mol) *p*-toluenesulfonyl chloride and 1.4 ml (0.01 mol) of triethylamine was synthesized product 33 and recrystallized from mixture of hexane: benzene - 1:1.

Yield: 2.9 g (80%), R_f 0.77 (C_6H_6/CH_3OH - 3:1), mp 135-138ºC. IR (KBr), v, cm^{-1}: 1378 (SO_2-*asym.*), 1178 (SO_2-*sym.*).

3. RESULTS AND DISCUSSION

3.1 Chemistry

Acetylation of 2-methyl(ethyl)-benzimidazoles (1,2) were carried out with acetic anhydride in chloroform without catalyst at 50-60ºC and 1-acetyl-2-methyl(ethyl)-benzimidazoles (5, 6) were synthesized in 63-70% yields. Benzoylation of 2-alkyl (methyl, ethyl)-5H(chloro, nitro)-benzimidazoles (1-4) with benzoyl chloride provided in the presence or absence of triethylamine in different ratios: 1:1:1, 1:2:2, 1:3:3, 1:4:4. However, reaction in the ratio 1:1:1 gives the corresponding 1-benzoylbenzimidazole derivatives (7-10):

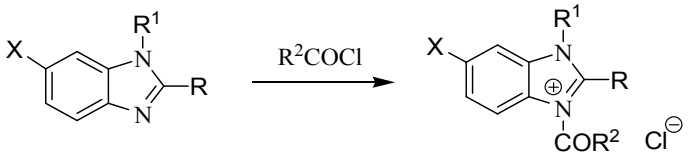


1-4 **5-10**

1 X= H, R=CH_3, **2** X= H, R=C_2H_5
3 X= Cl, R=CH_3, **4** X= NO_2, R=CH_3

5 X= H, R=R^1=CH_3
6 X= H, R=C_2H_5, R^1=CH_3
7 X= H, R=CH_3, R^1=C_6H_5
8 X= H, R=C_2H_5, R^1=C_6H_5
9 X= Cl, R=CH_3, R^1=C_6H_5
10 X= NO_2, R=CH_3, R^1=C_6H_5

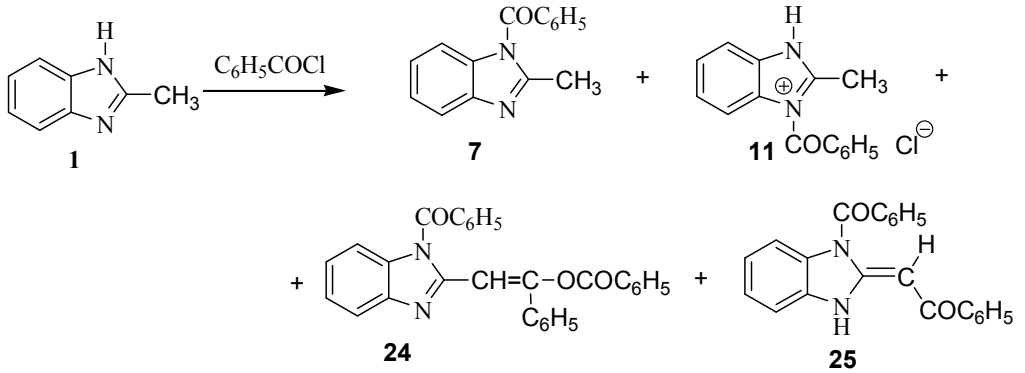
Detection of chloride 3-benzoyl-2-methylbenzimidazolium chlorode (11) in the reaction mixture leads us to thought that in the second stage of benzoylation reaction goes in presence both nitrogen atoms. Therefore, we decided to provide a reaction of 1-benzoyl(acetyl)-2-methyl(ethyl) benzimidazole with benzoyl (acetyl) chloride in the absence of triethylamine. It is showed that by adding benzoyl(acetyl)chloride to a solution of 1-methyl-, -benzoyl(acetyl)-2-methyl(ethyl)-benzimidazoles in absolute benzene at room temperature leads to obtain of 1,3-dialkyl-, -dibenzoyl(diacetyl, 1-benzoyl-3-acetyl) benzimidazole chlorides (12-23):



12-23

12, R=CH_3, R^1=C_6H_5CO, R^2=C_6H_5, X=H
13, R=R^2=CH_3, R^1=C_6H_5CO, X=H
14, R=R^2=CH_3, R^1=CH_3CO, X=H
15, R=C_2H_5, R^1=C_6H_5CO, R^2=C_6H_5, X=H
16, R=C_2H_5, R^1=C_6H_5CO, R^2=CH_3, X=H
17, R=CH_3, R^1=C_6H_5CO, R^2=C_6H_5, X=Cl
18, R=CH_3, R^1=CH_3CO, R^2=C_6H_5, X=Cl
19, R=R^2=CH_3, R^1=C_6H_5CO, X=Cl
20, R=R^1=CH_3, R^2=C_6H_5, X=H
21, R=R^1=R^2=CH_3, X=H
22, R=C_2H_5, R^1=CH_3, R^2=C_6H_5, X=H
23, R=C_2H_5, R^1=R^2=CH_3, X=H

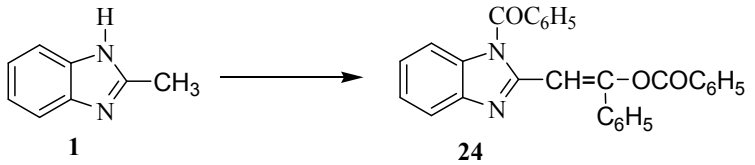
Carrying out reaction in a ratio 1:2:2 give compound 7 (for example, 2-methylbenzimidazole, 1). At the end of the reaction at boiling temperature the formed salt drops out. After separation the mixture (salt) was analyzed by HPLC, and found that the mixture contained of 1-benzoyl-2-methylbenzimidazole (7, 41.2%), 3-benzoyl-2-methylbenzimidazolium chloride (11), 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24, 22.7%) and 1-benzoyl-2-(benzoylmethylidene)-1H-benzimidazole (25, 22.5%):



1 **7** **11** **24** **25**

Conducting the reaction in a ratio of reagents 1:3:3 gives a mixture of benzoylation products: 1-benzoyl-2-methylbenzimidazole (7), 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24) and 1-benzoyl-2-(benzoylmethylidene)-1H-benzimidazole (25). Benzoylation of 2-

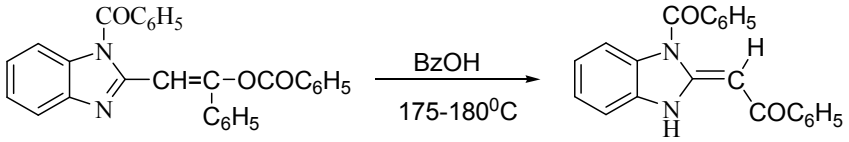
methylbenzimidazole with benzoylchloride in a ratio 1:4:4 in chloroform or tetrahydrofuran leads to formation only of 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24):



1 **24**

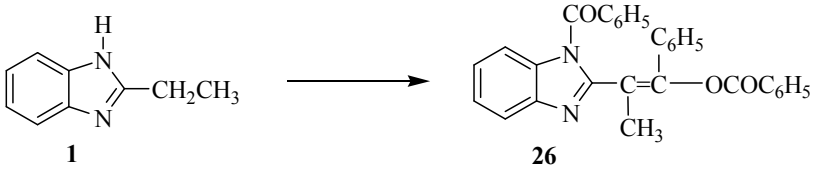
1-Benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (24) has been synthesized by interaction of compound 1 and benzoyl chloride in the presence of triethylamine (without solvent) at 172-178ºC. Compound 24 was obtained from 1-benzoyl-2-methylbenzimidazole, benzoyl chloride and triethylamine (ratio 1:3:3) in 70% yield. These data are confirmed indirectly by initial formation of a product 7 at benzoylation of 1 with benzoyl chloride in the presence of triethylamine in a ratio of reagents 1:4.

Compound 25 is formed at heating of compound 24 with benzoic acid in a ratio 1:1 at 175-180ºC for 30 min in excellent (90%) yield:



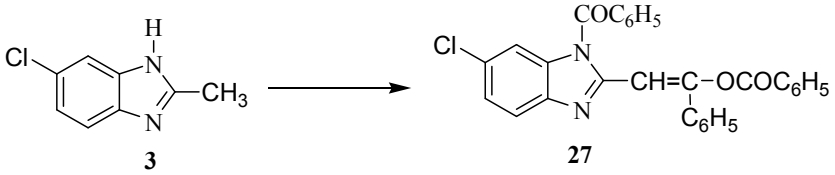
24 **25**

Similarly benzoylation provide of 2-ethylbenzimidazole with benzoyl chloride in the presence of triethylmine in tetrahydrofuran or chloroform, and was obtained a 1-benzoyl-2-(β-benzoyloxy-β-phenylpropenyl)-1H-benzimidazole (26) (60% in the case of chloroform and 58% in tetrahydrofuran):



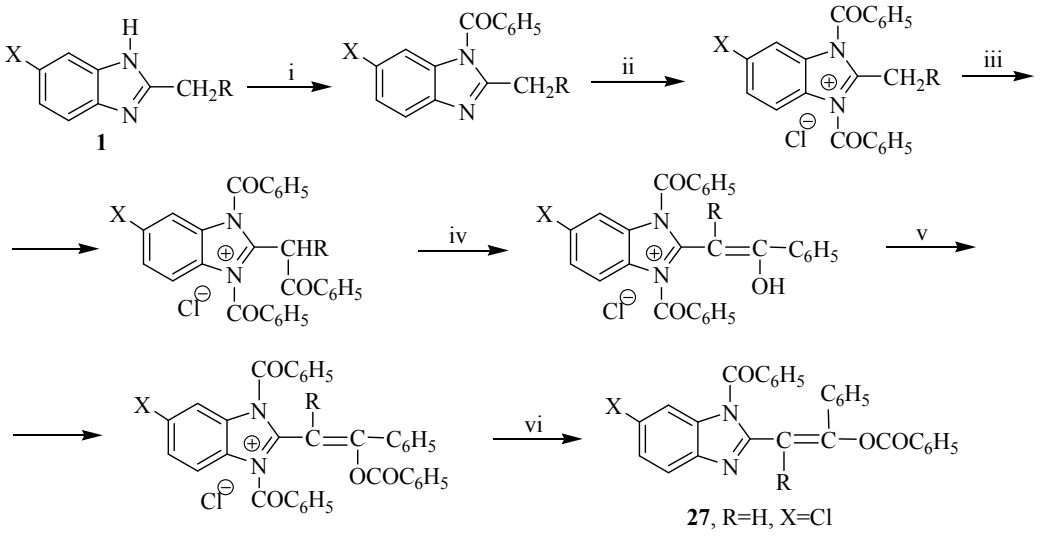
1 **26**

Benzoylation of 2-methyl-5-chlorobenzimidazole with benzoyl chloride in the presence of triethylamine in chloroform or tetrahydrofuran at 60-65ºC in a ratio 1:4:4 gives the 5-chloro-1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole (27) in 73% and 70% yields, respectively:



3 **27**

Based on the experimental results can be recommended a conversion scheme of 2-methyl(ethyl)-1-benzoyl-5H(chloro, nitro)-1H-benzimidazoles to 1-benzoyl-5H(chloro, nitro)-2- (β-benzoyloxy-β-phenylvinyl- or -β-phenylpropenyl)-1H-benzimidazoles (27):



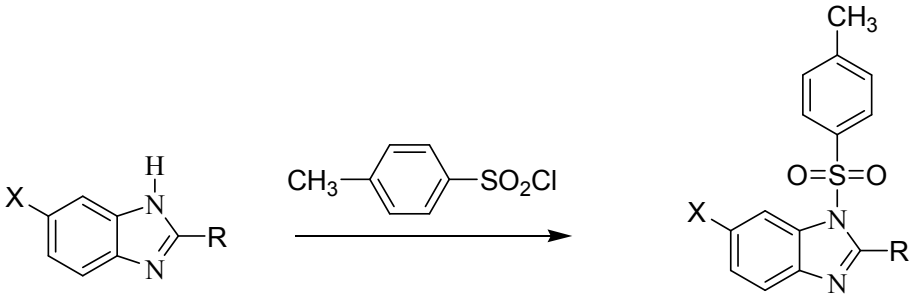
As noted above, benzoylation of 2-alkyl-1-benzoylbenzimidazoles (second step) are formed 1,3-dibenzoyl-2-alkylbenzimidazolium chlorides, that is accepted by data of obtained for 2-methyl-1H (benzoyl, acetyl)-5H(chloro) benzimidazole by reacting of 2-alkylbenzimidazoles with benzoyl chloride in the absence of triethylamine. This is followed by elimination of hydrogen chloride under the action of triethylamine and takes place a formation of 1,3-dibenzoyl-2-methylidene (ethylidene) benzimidazoles. More recently attack of another molecule of benzoyl chloride leads to the formation of 1,3-dibenzoyl-2-benzoylmethyl (ethyl) benzimidazoles, which can exist in an enol form. Benzoylation with the benzoyl chloride in the presence of triethylamine gives the 1,3-dibenzoyl-2-(β-benzoyloxy-β-phenylvinyl (propenyl)) benzimidazoles. Under the action of the water the reaction goes by the splitting off hydrogen chloride and benzoic acid and takes place formation of compound 27 (R=H, CH_3, R^1=H, Cl, NO_2).

This reaction scheme acknowledged firstly, that for the formation of 1,3-dibenzoyl-2-methylbenzimidazole chloride of the reaction of 1-benzoyl-2-methylbenzimidazole with benzoyl chloride provides in the absence of triethylamine. Formation of the mixture of the salt and 1-benzoyl-2-methylbenzimidazole, 1-benzoyl-2-(β-benzoyloxy-β-phenylvinyl)-1H-benzimidazole by the reaction of 2-methylbenzimidazole in a ratio 1:1:1 also indirectly supports it.

In the example of the reaction of 2-methylbenzimidazole with *p*-nitrobenzoyl chloride in various ratios (1:1:1, 1:2:2, 1:3:3, 1:4:4) was obtained exclusively 1-(*p*-nitrobenzoyl)-2-methylbenzimidazole. All attempts to acylation of its different acylating agents (acetyl-, benzoyl-, *p*-nitrobenzoyl chlorides) in the presence of triethylamine in chloroform and tetrahydrofuran was not successful. In all cases, the results return to the starting compounds. These data are explained, apparently reducing the base properties of nitrogen atom (s) under the influence of a strong electron withdrawing group of 1-*p*-nitrobenzene fragment of 2-methylbenzimidazole. The reduction of base properties in the principal atom (s) of nitrogen prevents the occurrence of a second molecule of *p*-nitrobenzoyl chloride, i.e. formation of chloride 1,3-di-(*p*-nitrobenzoyl)-2-methylbenzimidazole (for example *p*-nitrobenzoyl) or the salt of 1-*p*-nitrobenzoyl-3-aroyl(acyl)-2-methylbenzimidazole (example acetyl- or other arylchlorides). In according with this further any transformations are not for the corresponding chlorides.

According to the reaction products the alkyl group at the α-carbon atoms (methyl, ethyl) or at the position 5 (hydrogen, chlorine) has no substantial influence on the reaction.

The same results were obtained for the interaction of 2-methyl(ethyl)-5H(chloro, nitro) benzimidazole with *p*-toluenesulfonyl chloride. In all cases, the ratios of benzimidazole-sulfonylchloride-triethylamine - 1:1:1, 1:2:2, 1:3:3, 1:4:4 will produce products of monosulfonation: 1-(*p*-tolylsulfonyl)-2-methyl(ethyl)-5H(chloro, nitro)benzimidazoles (28-33):



28-33

It should be noted that the acylation of 2-methyl (ethyl)-5-nitro-, 1-(*p*-tolylsulfonyl)-2-methyl(ethyl) benzimidazol benzoyl- and acetylchloride with triethylamine goes nor changing of reaction condition neither changing of solvents.

In the case of 1-(*p*-tolylsulfonyl)-2-methylbenzimidazols we are expected to obtain arylsulfonation products of methylene group at C-2 - 2 -(*p*-tolylsulfonylmethylene)-1H-benzimidazole and 1-(*p*-tolylsulfonyl)-2-(β-tolylsulfonyloxy-β-phenylvinyl)-1H-benzimidazole. This is due, apparently, the impossibility of formation a quaternary salt of 1-(*p*-tolylsulfonyl)-3-(*p*-tolylsulfonyl)-benzimidazolium chloride.

4. CONCLUSION

The interaction of the 2-alkyl(methyl, ethyl)-1-(acetyl, benzoyl)-5H(chloro, nitro) benzimidazoles with benzoyl chloride in the presence of triethylamine in different ratios (1:1:1, 1:2:2, 1:3:3, 1:4:4) in chloroform or tetrahydrofuran under the mild conditions (60-65ºC) was studied. It was shown that depending on the ratio of reagents the 1-benzoyl (acetyl, *p*-tolylsulfonyl)-2-methyl(ethyl)-5H(chloro, nitro)benzimidazoles, 1,3-dibenzoyl-2-methylbenzimidazolium chlorides, 1-benzoyloxy-β-phenylvinyl (propenyl)-1H-benzimidazole were formed. The separating and determination methods are found for the obtained compounds. Recommended conversion circuit of 2-alkylbenzimidazoles, 1-benzoyloxy-β-phenylvinyl-1H-benzimidazoles and their derivatives by using HPLC analysis. The possibility of synthesis of 1-mono-, N-1, N-3-di-, N-, C-di- and N-, C-, O-tribenzoylation of 2-methyl(ethyl)-benzimidazoles are revealed. It was shown that a ratio of formed products depends on the ratio of reagents, the nature of the substituent of aromatic ring and the acylating agents.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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