Efficient Synthetic Method of 1,2-substituted benzimidazoles

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ABSTRACT: The benzimidazole exhibits widespread activities, and the benzimidazole nucleus is found in a variety of drugs. In this paper, we research a new and efficient synthetic method of 1,2-disubstituted benzimidazole. o-phenylenediamine and ketone form schiff bases having one free amine group with microwave, and then schiff bases condensed with different aldehydes to give five 1,2-substituted benzimidazoles. The mechanism of reaction involves 1,3 shift of negative hydrogen ion.

KEY WORDS: benzimidazole; dischiff base; 1,3 shift

1,2二取代苯并咪唑化合物的一种高效合成方法

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摘要:苯并咪唑是一类具有广泛生理活性的化合物,许多药物分子中都含有苯并咪唑结构。笔者研究苯并咪唑化合物新的高效合成方法。以邻苯二胺和酮为原料,在微波条件下,经缩合,形成单席夫碱,然后再与其他醛反应,高产率的得到了5个1位、2位接有不同取代基的苯并咪唑化合物。单席夫碱生成咪唑过程中,发生1,3负氢迁移。

关键词:苯并咪唑;席夫碱;1,3迁移

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The benzimidazole exhibits widespread activities, and the benzimidazole nucleus is found in a variety of drugs such as vitamin B_{12}[1], albendazole[2-3] and omeprazole[4], and is also a key feature in cardiotonic agents such as potential antitumor agents[5]. Moreover, the benzimidazole was used as antiseptic and inhibiting nucleic acid synthesis[6]. Thus, they have

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received a considerable amount of attention in diverse areas

Traditional synthesis of the benzimidazole nucleus involves coupling of carboxylic acid 1, 2-phenylenediamine By their methods, 2-substituted benzimidazole was obtained But activities of the benzimidazoles are associated with 1, 2-substituted group and X, -OH group[6-8] In this paper, we wish to develop a new and simple approach for the synthesis of 1, 2-disubstituted benzimidazole including of X, and OH groups

Scheme 1

In scheme 1, the synthesis was commenced with benzoyl choride and 3, 5-dichlorbenzophenol to give the ether **2** in 93% yield The ether **2** was then carried out with anhydron $AlCl_3$ for 3 hour under 100℃ to afford benzophenone **3** in 90% yield With microwave to head up, the mixture of compound **3** and o-phenylenediamine melted to form schiff base **4** having one free amine group Then, compound **4** condensed with different aldehydes to give five 1, 2-substituted benzimidazoles **1** (Analysis date shown in table 1).

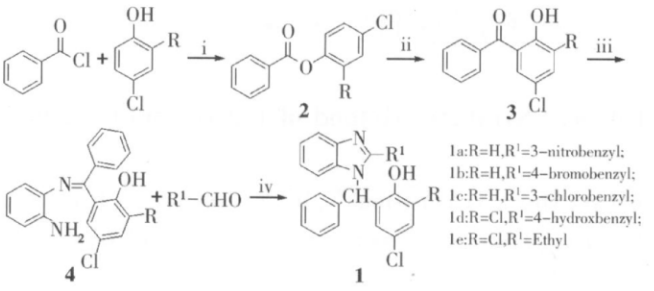

Fig 1 The synthetic route of Benzimidazoles

1- ether, pydinine, 4 h; 2- $AlCl_3$, 110 ℃, 6 h; 3. o-phenylenediamine, 700 W microwave, 15 s; 4- toluene, acetic acid, reflux, 36 h

图 1 苯并咪唑的合成路线

Tab 1 Analysis date of benzimidazoles 1a~ 1e

表 1 苯并咪唑 1a~ 1e的分析数据

Number	Formula	Mp/℃	Anal Calcd	MS(m/z, %)	^{1}HNMR (d^6-DMSO, δ_{ppm})
1a	$C_{26}H_{18}O_3N_3Cl_1$	160-161	C 68.56, H 3.98, N 9.17	455 (M^+, 1.3), 404 (3.8), 306 (6.9), 265 (54.7), 239 (100)	6.73-7.71(m, 17H, Ar-H and N-CH), 10.1(s, 1H, -OH)
1b	$C_{26}H_{18}ON_2BrCl$	273-275	C 63.81, H 3.66, N 5.77	488 (M^+, 0.5), 272 (72.8), 215 (100), 152(21.4)	6.73-7.71(m, 17H, Ar-H and N-CH), 10.1(s, 1H, -OH)
1c	$C_{26}H_{18}ON_2Cl_2$	233-234	C 70.06, H 4.10, N 6.31	444 (M^+, 1.2), 228 (100), 215 (82), 152(19)	6.72-7.75(m, 17H, Ar-H and N-CH), 10.1(s, 1H, -OH)
1d	$C_{26}H_{18}O_2N_2Cl_2$	240-242	C 67.65, H 3.96, N 6.12	460(M^+, 22), 340 (39), 51(100)	6.85-8.05(m, 16H, Ar-H and N-CH)
1e	$C_{26}H_{18}O_3N_2Cl$	237-238	C 68.45, H 3.91, N 9.15	455(M^+, 52), 378 (37), 306(53), 215(100)	1.37(t, 3H, J = 7.4Hz, $-CH_3$), 2.97(q, 2H, J = 7.4Hz, $-CH_2$-), 6.70-7.48(m, 12H, Ar-H and N-CH)

As shown in scheme 2, the mechanism of benzimidazole synthesis involves 1, 3 shift of negative hydrogen ion Firstly, compound **4** and aldehyde condensed to give dishiff base **5**, then compound **5** is treated with general acid to bring about the buildling of five ring and 1, 3 shift of negative hydrogen ion and benzimidazoles **1** were obtained

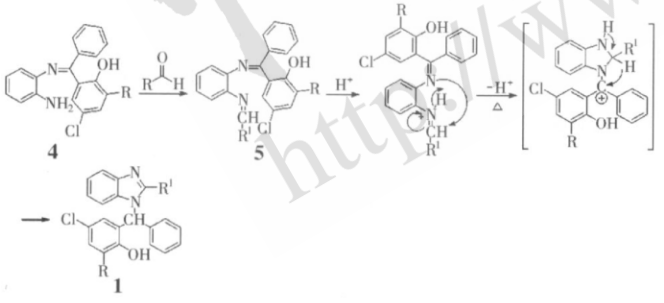

Fig 2 Mechanism of Benzimidazole synthesis

图 2 苯并咪唑合成机制

Scheme 2

In conclusion, we research an effective synthesis method of 1, 2-disubstituted benzimidazole By four steps, five new 1, 2-substituted benzimidazoles were obtained, their biological activity is being studied on

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