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Lithium bromide catalyzed solvent free method for synthesis of 2-substituted benzimidazoles and imidazopyridines

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Abstract

The first successful lithium bromide mediated solvent free condensation of arylenediamine and esters to obtain 2-substituted benzimidazole and imidazopyridine in good to excellent yields is described.

Keywords: Benzimidazoles; Arylenediamine; Aliphatic esters; Lithium bromide; Imidazopyridines

The benzimidazole moiety is an important heterocyclic nucleus which has been used extensively in medicinal chemistry. Current clinical examples include the antihistamine astemizole [1], the anti-ulcerative esomeprazole [2] and albendazole [3], which is used to treat parasitic diseases. Benzimidazoles are a component of vitamin B12 and are related to the DNA base purine and the stimulant caffeine. Bisbenzimidazoles are being developed as DNA minor groove binding agents with antitumor activity [4] and can act as ligands to transition metals for modeling biological systems [5].

Due to their great importance, many synthetic strategies have been developed. The most popular synthetic approach generally involves the condensation of an arylenediamine with a carboxylic acid or its derivative under harsh dehydrating reaction conditions [6]. Another method is the condensation of an aldehyde with arylenediamine [7]. Some methods using transition metal catalyzed coupling reactions to construct the benzimidazole nucleus have also been reported. Those involved a palladium-catalyzed intramolecular *N*-arylation of (*O*-bromophenyl)-amidine [8]. A method starting from arylenediamine and orthoester in the presence of $Yb(OTf)_3$ [9], zeolite [10], or KSF clay [11] at high temperature was also used for the synthesis of benzimidazole derivatives. Very recently, literature survey reveals several methods for synthesis of benzimidazole and its derivatives using hypervalent iodine as oxidant [12], oxalic acid [13], H_2O_2/HCl [14], $TiCl_4$ [15], PPA [16], $SOCl_2/SiO_2$ [17], (bromodimethyl)sulfonium bromide[18], L-proline [19], sulfamic acid [20], and $FeBr_3$ [21]. However, in many of these methodologies, acids and aldehydes were used to condense with arylenedimine and suffer from one or more disadvantages, such as low yields, lack of easy availability

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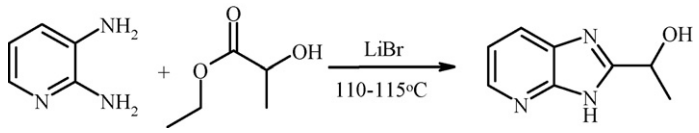


Scheme 1.

of the starting materials, use of high boiling corrosive solvents, requirement of excess of catalysts, special apparatus, and harsh reaction conditions. Thus, there is a need for simple and efficient processes for the synthesis of benzimidazole derivatives using starting materials other than acids and aldehyde.

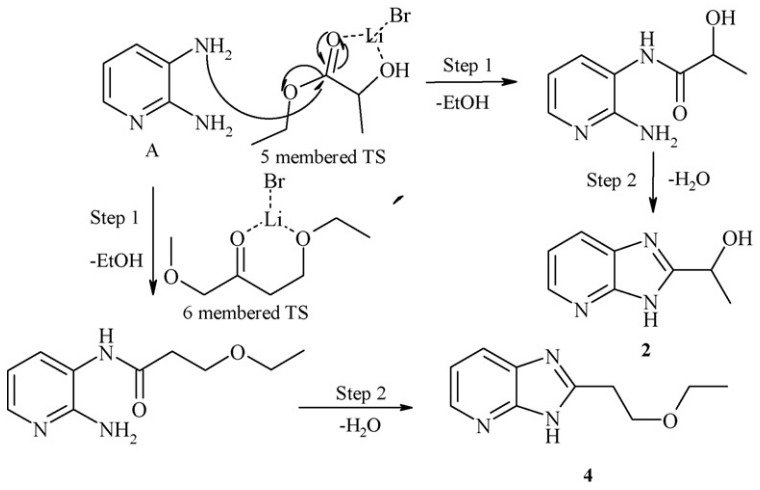
Another important retro-synthetic approach for synthesis of benzimidazole is condensation of substituted esters with arylenediamine, this has not been explored effectively till date. We therefore took this opportunity to explore this aspect of chemistry as an alternative method for synthesis of 2-substituted benzimidazoles and imidazopyridines.

In our ongoing project for synthesis of 2-substituted imidazopyridines as antihistamine compounds, we started as per the method for reported example [22]. Condensation of neat ethyl lactate with 2,3-diaminopyridine gave very less yield, reaction was incomplete after 48 h heating at 110–115 °C. In order to improve in both the parameters we employed the addition of Lewis acids to enhance the nucleophilicity of amine by polarizing the ester as given in the proposed mechanism (Scheme 1). The various different Lewis acids were used to catalyze a solvent free condensation of ethyl lactate with 2,3-diaminopyridine. This brought us to conclusion that lithium bromide was the best among different Lewis acids used (Table 1).

Lithium bromide is a versatile reagent often used basically as nucleophilic brominating reagent [23]. It has also been used as Lewis acid catalyst [24] and also as mediator in various other different reactions [25].

In a typical experiment arylenediamine was heated at 110–115 °C in neat substituted ethyl or methyl esters. Alcohol, nitriles and etheral esters were easily condensed (Table 2). The yields obtained were more in case of alcohol esters than nitrile and ethereal esters. Nitrile esters react slowly in absence of lithium bromide (Table 2, entry 5, 8), addition of lithium bromide increases the rate of reaction but various different side products were observed. Plane aliphatic esters without second hetero atom failed to give the required product (Table 2, entry 10), this suggest the requirement of another hetero atom oxygen, nitrogen for proper chelation of lithium ion in cyclic five-membered or six-membered transition state supporting the idea of proposed mechanism (Scheme 2) in first step. Further cyclisation where aromatization and removal of water molecule is the driving force.

2,3-Diaminopyridine showed slow condensation with substituted esters without LiBr, whereas orthodiamino-benzene remain unreacted in absence of LiBr. This concludes that LiBr improves the reactivity of 2,3-diaminopyridine, whereas orthodiaminobenzene reacts easily with substituted esters to get respective condensed product. The excess unreacted alcohol, ethereal esters used can be easily recovered by high vacuum distillation of the reaction mixture.



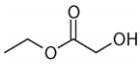
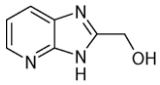
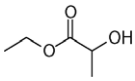
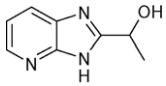
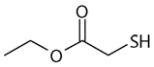
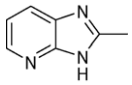
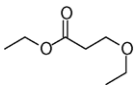
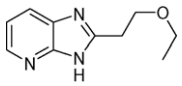
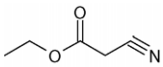
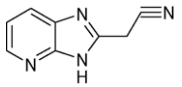
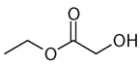
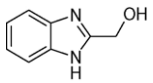
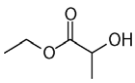
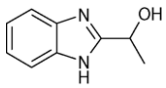
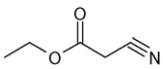
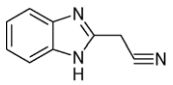
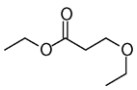
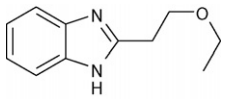
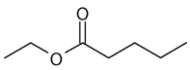
Scheme 2. Proposed mechanism.

Table 1
Effect of Lewis acid (1 mole) on condensation of ethyl lactate with 2,3-diaminopyridine.[a]

Entry	Lewis acid	Time (h)	Yield (%)[b]
1	BF_3-ethrate	12	35
2	$FeCl_3$	15	47
3	$SnCl_4$	13	–
4	ZnBr	12	40
5	$TiCl_4$	18	–
6	LiBr	6	80

[a] 2,3-Diaminopyridine (1 mole), ethyl lactate (10 mole), solvent free, 115 °C.
[b] Isolated yield.

Table 2
Lithium bromide catalyzed synthesis of 2-substituted imidazopyridines and benzimidazoles. Using 2,3-diaminopyridine and orthodiaminobenzene as reactants with different esters.[a]

Entry	Ester	Product	Yield[b]	Time (h)
1			85	7
2			80	6
3			55	8
4			75	9
5			70	14[c]
6			85	8
7			83	8
8			70	18[c]
9			70	10
10		No reaction	–	–

[a] Standard conditions: (1 mole) arylenediamine, (10 mole) ester, and (1 mole) LiBr. 110–115 °C.
[b] Isolated yields based upon starting 2,3-diaminopyridine.
[c] Reaction without addition of LiBr.

Thiols and keto esters failed to give required product which is one of the drawbacks of this methodology. Surprisingly reaction of ethyl thioglycolate with 2,3-diaminopyridine gave 2-methylimidazopyridine as product (Table 2, entry 3).

In conclusion we report a unique method for solvent free condensation of esters with arylenediamine using lithium bromide as catalyst to obtain benzimidazoles and imidazopyridines in good to excellent yields.

General procedure for synthesis of 2-substituted benzimidazoles and imidazopyridines: Arylenediamine (1 mole), substitued ester (10 mole), LiBr (1 mole) were taken in single neck round bottom flask. Reaction mixture was heated to 110–115 °C. Progress of the reaction was monitored on TLC. After completion of reaction crude product was purified by flash chromatography to obtain corresponding 2-substituted benzimidazoles and imidazopyridines compounds these were characterized by ^{1}H NMR and mass [26].

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[26] Selected spectral data: *1-(3-H-Imidazo[4,5-b]pyridin-2-yl)-ethanol.* (entry 2): off-white solid; mp °C: 155–157; ^{1}H NMR (D_2O, 400 MHz): δ 1.530–1.513 (d, 3H), 5.08–5.029 (q, 1H), 7.22–7.18 (q, 1H, 4 Hz, 8 Hz), 7.88–7.86(d, 1H, 8 Hz), 8.21–8.20 (2d, 1H, 4 Hz); MS (EI, 70 eV): *m/z* 163.9 (M+H). *(2-Ethoxy-ethyl)-3H-imidazo [4,5-b]pyridine.* (entry 4): yellow solid. mp °C: 95–97; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (t, 3H), 3.22 (t, 2H), 3.62 (q, 2H), 3.84 (t, 2H), 7.20–7.17 (q, 1H, 4 Hz, 8 Hz), 7.97–7.95 (d, 1H, 8 Hz), 8.30–8.29 (d, 1H, 4 Hz); MS (EI, 70 eV): *m/z* 192.1 (M+H). *1-(1H-Benzoimidazol-2-yl)-ethanol.* (entry 7): yellow solid. mp °C: 173–175; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.73 (d, 3H), 5.22 (d, 1H), 7.26–7.24 (q, 2H, 4 Hz, 8 Hz), 7.60–7.57 (q, 2H, 4 Hz, 8 Hz); MS (EI, 70 eV): *m/z* 163.0 (M+H).