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N,N-Dimethylbenzimidazolium Iodide as an Efficient Catalyst for a Green Reaction of Intermolecular Stetter Reaction in Water

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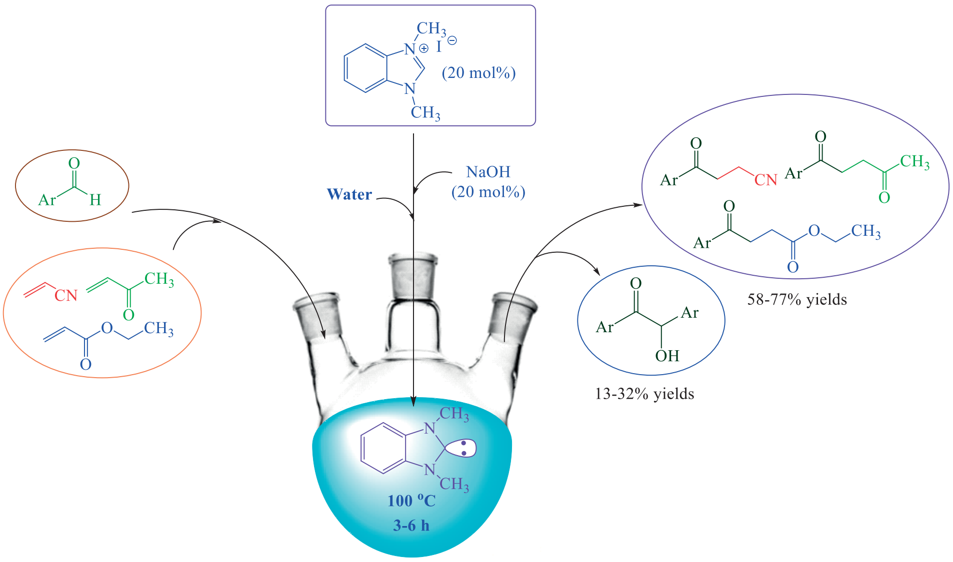
Abstract: The development of greener methodologies is an important field in the framework of green chemistry. In this research study, *N,N*-dimethylbenzimidazolium iodide in NaOH was developed as an efficient catalyst for intermolecular stetter reaction in the greenest solvent (water) to afford the desired 1,4-addition products in good yields of 58-77%. Moreover, the benzimidazolium salt catalyst and NaOH mixture can be reused for at least 4 additional reactions with a consistent yield of 65%.

Keywords: 1,4-Addition; *N,N*-Dimethylbenzimidazolium iodide; Stetter reaction; Water

Graphical Abstract:



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1. Introduction

The use of water as a reaction has been intensively investigated in recent years owing to water reputation as the greenest solvent with nontoxicity, safety, and nature's solvent, mild conditions and possesses distinguished physical and chemical properties [1-2]. Besides, it exhibits powerful hydrogen bonding and a wide temperature range to remain in the liquid state. Many organic compound transformations have been carried out in water [3-4]. Many organic solvents like methylene chloride, dimethylformamide, acetone, benzene, methanol, toluene are carcinogenic and toxic to human health, which causes an environmental issue by polluting the atmosphere. For this reason, the organic reaction in an aqueous medium has become a new way of thinking about chemistry, as is the case for green chemistry.

Over the past decade, various organic reactions have been found to perform successfully synthesis in water of 2-amino-1,3,4-thiadiazoles [5], pyrimido[4,5-d]pyrimidine [6], pyrano[2,3-c]pyrazoles [7], substituted 3,4-dihydropyrimidin-2(1H)-ones [8], 2-amino-4-(5-hydroxy-3-methyl-1H-pyra¬zol-4-yl)-4H chromene-3-carbonitrile derivatives [9], spiroindoline-pyranopyrazoles [10] 2-aminothiazoles [11] and benzoin condensation [12].Type of *N*-heterocyclic carbenes (NHCs) (Figure 1) has attracted considerable interest in recent years due to their ability to reverse aldehydes' normal mode of reactivity, rendering them nucleophilic at the carbonyl carbon. Especially stetter reaction has received significant interest in organocatalyzed reactions due to their special electronic characteristics [13-16]. The utilization of organocatalytic activation of NHC for new bond-formation between aldehyde and electrophilic double bond opens up a new avenue for the synthesis of 1,4-dicarbonyl compounds, which are useful building blocks for the synthesis of a wide range of heterocyclic and carbocyclic compounds, including furans, thiophene, pyridazines, and pyrrole derivatives [17]. For example, the use of thiamine as a catalyst in Stetter reaction [18] and the catalytic reaction of NHC of enals [19] have been well-documented.

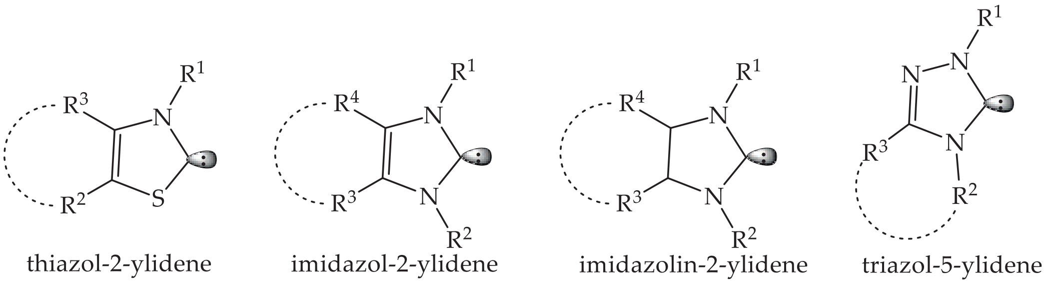


Figure 1. General types of N-heterocyclic carbenes

In the past, stetter reactions had to be carried out in aprotic solvents and conventional organic solvents such as dimethylformamide [20-21], ethanol [22] and dioxane [23]. Therefore, this reaction has also been carried out in ionic liquid catalyzed by thiazolium [24] and benzimidazolium salts [24], respectively. In our previous work, *N*,*N*-dimethylbenzimidazolium iodide was used as an effective and recyclable catalyst for stetter reaction in ionic liquid [Bmim]OH [25]. Herein, we report our extended investigation of greener aspects of stetter reaction in an aqueous medium catalyzed by *N*,*N*-dimethylbenzimidazolium iodide and NaOH.

2. Materials and Methods

All chemicals in the experiment were analytical grade and used directly without further purification. Melting points were determined in capillary tubes in a Buchi B 545 apparatus. The products were identified by comparing their melting points and spectral data (FTIR, ^1H & ^{13}C NMR) with those in the authentic samples. FT-IR spectra were obtained as KBr disks on a Shimadzu spectrometer which scans from 400 to 4000 wavenumber. The ^1H and ^{13}C NMR data were recorded on a Varian Mercury plus spectrometer (400 MHz). $CDCl_3$ was used as a solvent and internal standard. Coupling constant (*J*) are reported in Hertz (Hz) and the multiplicity abbreviations used are singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m).

2.1 General procedure for intermolecular stetter reaction between either acrylonitrile (2), ethyl acrylate (6) or methyl vinyl ketone (7) and aromatic aldehydes 1 catalysed by *N*,*N*-dimethylbenzimidazolium iodide (3) in water

N,*N*-dimethylbenzimidazolium iodide (**3**) (0.20 mmol) and NaOH (0.20 mmol) in water (5 mL) was added to either acrylonitrile (**2**), ethyl acrylate (**6**) or methyl vinyl ketone (**7**) (2.00 mmol) and aromatic aldehyde **1** (1.00 mmol) at a temperature range of room temperature to 100 °C under magnetic stirring for 3-6 h. After the completion of the reaction indicated by TLC (100% dichloromethane), the reaction mixture was extracted with ethyl acetate (3×30 mL). The combined organic extract was dried (anh. $\mathrm{Na_2SO_4}$), and the solvent was removed under reduced pressure. The residue was purified using preparative thin-layer chromatography (silica gel, elution with dichloromethane). The purified corresponding 1,4-addition products **4a**-**l**, acyloin products **5a**-**d** with their physical data were listed below. The aqueous phase consists of catalyst, NaOH, and water was used as a recycling condition for the new reaction without purification.

4-Phenyl-4-oxobutanenitrile (4a): White crystals; Yield 75%; R_f = 0.51 (100% dichloromethane); m.p. 74-76 °C (lit. 74-76 °C) [26]; IR (KBr) ν_{max}: 3069, 2925, 2889, 2251, 1678, 1607, 1522 and 1413 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$): δ 7.97 (2H, d, *J* = 7.2 Hz, 2-*H* and 6-*H*), 7.63 (1H, t, *J* = 7.6 Hz, 4-*H*), 7.51 (2H, t, *J* = 7.6 Hz, 3-*H* and 5-*H*), 3.39 (2H, t, *J* = 7.2 Hz, $\mathrm{CH_2C}H_2\mathrm{CN}$) and 2.79 (2H, t, *J* = 7.2 Hz, $\mathrm{C}H_2\mathrm{CH_2CN}$); ^{13}C NMR ($\mathrm{CDCl_3}$): δ 11.9, 34.3, 119.2, 128.0, 128.7, 133.9, 135.7 and 195.4

4-(4′-Chlorophenyl-4-oxobutanenitrile (4b): White crystals; Yield 77%; R_f = 0.45 (100% dichloromethane); m.p. 72-73 °C (lit. 72-73 °C) [27]; IR (KBr) ν_{max}: 3090, 3061, 2928, 2253, 1677, 1588, 1489, 1401 and 775 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$): δ 7.88 (2H, d, *J* = 8.4 Hz, 2-*H* and 6-*H*), 7.46 (2H, d, *J* = 8.4 Hz, 3-*H* and 5-*H*), 3.36 (2H, t, *J* = 7.2 Hz, $\mathrm{CH_2C}H_2\mathrm{CN}$) and 2.78 (2H, t, *J* = 7.2 Hz, $\mathrm{C}H_2\mathrm{CH_2CN}$); ^{13}C NMR ($\mathrm{CDCl_3}$):δ 11.7, 34.3, 119.2, 129.3, 129.3, 133.9, 140.5 and 194.2

4-(4′-Tolyl)-4-oxobutanenitrile (4c): White crystals; Yield 71%; R_f = 0..52 (100% dichloromethane); m.p. 75-77 °C (lit. 75-77 °C) [28]; IR (KBr) ν_{max}: 3044, 2927, 2855, 2250, 1681, 1673, 1609 and 1425 cm^{-1}; ^{1}H NMR ($\mathrm{CDCl_3}$): δ 7.87 (2H, d, *J* = 8.0 Hz, 2-*H* and 6-*H*), 7.29 (2H, d, *J* = 8.0 Hz, 3-*H* and 5-*H*), 3.38 (2H, t, *J* = 7.2 Hz, $\mathrm{CH_2C}H_2\mathrm{CN}$), 2.78 (2H, t, *J* = 7.2 Hz, $\mathrm{C}H_2\mathrm{CH_2CN}$) and 2.42 (3H, s, Ar-C*H*$_3$); ^{13}C NMR ($\mathrm{CDCl_3}$): δ 11.8, 29.8, 34.1, 119.4, 128.1, 129.6, 133.2, 144.9 and 201.3

4-(Pyridin-4-yl)-4-oxobutanenitrile (4d): Yellow crystals; Yield 73%; R_f = 0.53 (100% dichloromethane); m.p. 135-137 °C (lit. 135-137 °C) [29]; IR (KBr) ν_{max}: 3070, 2954, 2925, 2257, 2681, 1690, 1581, 1450, 1332, 1216 and 1000 cm^{-1}; ^{1}H NMR δ 8.76 (2H, d, *J* = 8.4 Hz, 2′-*H* and 6′-*H*), 7.89 (2H, d, *J* = 8.4 Hz, 3′-*H* and 5′-*H*), 3.01 (2H, t, *J* = 7.2 Hz, $\mathrm{CH_2C}H_2\mathrm{CN}$) and 2.75 (2H, t, *J* = 7.2 Hz, $\mathrm{C}H_2\mathrm{CH_2CN}$); ^{13}C NMR δ 14.9, 38.9, 119.6, 122.6, 135.0, 135.3, 150.5 and 198.9

1-Phenyl-1,4-pentanedione (4e): Yellow crystals; Yield 73%; R_f = 0.56 (100% dichloromethane); m.p. 70-72 °C; IR (KBr) ν_{max}: 3417, 3050, 2900, 1718, 1676, 1596, 1446, 1353, 1211, 1162 and 1068 cm^{-1}; ^{1}H NMR δ 7.84 (2H, d, *J* = 7.2 Hz, 2-*H* and 6-*H*), 7.71 (1H, t, *J* = 7.6 Hz, 4-*H*), 7.44 (2H, t, *J* = 7.6 Hz, 3-*H* and 5-*H*), 3.23 (2H, t, *J* = 13.1 Hz, $\mathrm{CH_2C}H_2\mathrm{COCH_3}$), 2.84 (2H, t, *J* = 13.1 Hz, $\mathrm{C}H_2\mathrm{CH_2COCH_3}$) and 2.17 (3H, s, $\mathrm{CH_2CH_2COC}H_3$); ^{13}C NMR δ 29.8, 32.3, 36.9, 127.8, 128.4, 132.9, 136.6, 198.3 and 206.9

1-(4′-Chlorophenyl)-1,4-pentanedione (4f): Yellow crystals; Yield 75%; R_f = 0.50 (100% dichloromethane); m.p. 71-73 °C; IR (KBr) ν_{max}: 3100, 2902, 1718, 1673, 1590, 1355, 1317, 1214 and 1089 cm^{-1}; ^{1}H NMR δ 7.90 (2H, d, *J* = 8.8 Hz, 2′-*H* and 6′-*H*), 7.41 (2H, d, *J* = 8.8 Hz, 3′-*H* and 5′-*H*), 3.21 (2H, t, *J* = 13.2 Hz, $\mathrm{CH_2C}H_2\mathrm{COCH_3}$), 2.75 (2H, t, *J* = 13.2 Hz, $\mathrm{C}H_2\mathrm{CH_2COCH_3}$) and 2.18 (3H, s, $\mathrm{CH_2CH_2COC}H_3$); ^{13}C NMR δ 29.7, 32.1, 36.8, 128.1, 128.8, 134.9, 139.3, 197.1 and 206.8

1-(4′-Tolyl)-1,4-pentanedione (4g): Yellow crystals; Yield 70%; R_f = 0.48 (100% dichloromethane); m.p. 83-85 °C; IR (KBr) ν_{max}: 3091, 2914, 1708, 1679, 1584, 1390, 1321, 1217 and 1109 cm^{-1}; ^{1}H NMR δ 7.88 (2H, d, *J* = 8.4 Hz, 2′-*H* and 6′-*H*), 7.31 (2H, d, *J* = 8.4 Hz, 3′-*H* and 5′-*H*), 3.22 (2H, t, *J* = 13.2 Hz, $\mathrm{CH_2C}H_2\mathrm{COCH_3}$), 2.78 (2H, t, *J* = 13.2 Hz, $\mathrm{C}H_2\mathrm{CH_2COCH_3}$) and 2.16 (3H, s, $\mathrm{CH_2CH_2COC}H_3$); ^{13}C NMR δ 11.9, 29.6, 32.2, 36.7, 128.9, 130.1, 134.5, 138.7, 198.1 and 206.7

1-(Pyridin-4-yl)-1,4-pentanedione (4h): Yellow crystals; Yield 72%; R_f = 0.42 (100% dichloromethane); m.p. 99-101 °C; IR (KBr) ν_{max}: 3111, 2969, 1711, 1679, 1593, 1375, 1319, 1214, 1111 and 1089 cm^{-1}; ^{1}H NMR δ 8.72 (2H, d, *J* = 8.8 Hz, 2′-*H* and 6′-*H*), 7.85 (2H, d, *J* = 8.8 Hz, 3′-*H* and 5′-*H*), 3.25 (2H, t, *J* = 13.2 Hz, $\mathrm{CH_2C}H_2\mathrm{COCH_3}$), 2.81 (2H, t, *J* = 13.2 Hz, $CH_2CH_2COCH_3$) and 2.17 (3H, s, $CH_2CH_2COCH_3$); ^{13}C NMR δ 29.9, 32.5, 36.9, 120.4, 134.6, 140.6, 198.3 and 206.8

Ethyl 4-phenyl-4-oxobutanoate (4i): Yellow liquid; Yield 62%; R_f = 0.54 (100% dichloromethane); IR (neat) ν_{max}: 3030, 2949, 1723, 1640, 1569, 1448, 1389, 1260 and 1183 cm^{-1}; ^{1}H NMR δ 7.97 (2H, d, *J* = 7.6 Hz, 2′-*H* and 6′-*H*), 7.55 (1H, t, *J* = 7.6 Hz, 4′-*H*), 7.46 (2H, t, *J* = 7.6 Hz, 3′-*H* and 5′-*H*), 4.17 (2H, q, *J* = 7.6 Hz, OCH_2CH_3), 3.32 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.73 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$) and 1.26 (3H, t, *J* = 7.6 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ 14.3, 28.5, 33.5, 60.6, 128.2, 128.6, 133.4, 136.6, 172.9 and 198.2.

Ethyl 4-(4′-dichlorophenyl)-4-oxobutanoate (4j): White crystals; Yield 66%; R_f = 0.55 (100% dichloromethane); mp 55-57 °C (lit. 56-58 °C) [30]; IR (KBr) ν_{max}: 3013, 2961, 1745, 1687, 1600, 1446, 1330 and 1273 cm^{-1}; ^{1}H NMR δ 7.86 (2H, d, *J* = 8.8 Hz, 2′-*H* and 6′-*H*), 7.36 (2H, d, *J* = 8.8 Hz, 3′-*H* and 5′-H), 4.09 (2H, q, *J* = 7.8 Hz, $CO_2CH_2CH_3$), 3.21 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.68 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$) and 1.22 (3H, t, *J* = 7.8 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ 14.2, 28.3, 33.3, 60.8, 128.9, 129.5, 134.7, 139.6, 172.7 and 197.1.

Ethyl 4-(4′-tolyl)-4-oxobutanoate (4k): White crystals; Yield 58%; R_f = 0.49 (100% dichloromethane); mp 64-65 °C; IR (KBr) ν_{max}: 3059, 2971, 1748, 1690, 1596, 1451, 1323, 1179, 1005 and 763 cm^{-1}; ^{1}H NMR δ 7.87 (2H, d, *J* = 8.4 Hz, 2′-*H* and 6′-*H*), 7.38 (2H, d, *J* = 8.4 Hz, 3′-*H* and 5′-*H*), 4.09 (2H, q, *J* = 7.6 Hz, $CO_2CH_2CH_3$), 3.21 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.68 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.13 (3H , s, CH_3Ar) and 1.23 (3H, t, *J* = 7.6 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ 14.1, 28.4, 30.9, 33.2, 60.7, 128.9, 129.6, 134.8, 139.7, 172.9 and 196.9.

Ethyl 4-(pyridin-4-yl)-4-oxobutanoate (4l): Yellow liquid; Yield 64%; R_f = 0.47 (100% dichloromethane); IR (neat) ν_{max}: 3100, 2983, 2911, 1735, 1680, 1590, 1453, 1361, 1223, 1165 and 1042 cm^{-1}; ^{1}H NMR δ 8.76 (2H, d, *J* = 8.8 Hz, 2′-*H* and 6′-*H*), 7.88 (2H, d, *J* = 8.8 Hz, 3′-*H* and 5′-*H*), 4.13 (2H, q, *J* = 7.6 Hz, $CO_2CH_2CH_3$), 3.01 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$), 2.72 (2H, t, *J* = 6.8 Hz, $CH_2CH_2CO_2CH_2CH_3$) and 1.15 (3H, t, *J* = 7.6 Hz, $CO_2CH_2CH_3$); ^{13}C NMR δ 14.2, 27.8, 33.4, 60.7, 122.9, 135.0, 150.3, 173.0 and 196.7.

Benzoin (5a): White crystals; Yields 14-23%; R_f = 0.25 (100% dichloromethane); m.p. 133-135 °C (lit. 134-136 °C) [31]; IR (KBr) ν_{max}: 3412, 3050, 3025, 2929, 1676, 1595, 1450, 1260, 1209 and 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.91(2H, d, *J* = 7.6 Hz, 2-*H* and 6-*H*), 7.52 (1H, t, *J* = 7.6 Hz, 4-*H*), 7.39 (2H, t, *J* = 7.6 Hz, 3-*H* and 5-*H*), 7.24-7.34 (5H, m, Ar-*H*), 5.97 (1H, s, C*H*) and 4.52 (1H, br s, O*H*); ^{13}C NMR ($CDCl_3$) δ 76.4, 127.9, 128.7, 128.7, 129.1, 133.7, 133.9, 139.2 and 198.8

4,4′-Dichlorobenzoin (5b): White crystals; Yields 15-26%; R_f = 0.23 (100% dichloromethane); m.p. 87-88 °C (lit. 87-88 °C) [29]; IR (KBr) ν_{max}: 3421, 3063, 2927, 1679, 1595, 1479, 1408, 1262, 1207 and 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.76 (2H, d, *J* = 8.8 Hz, 2-*H* and 6-*H*), 7.34 (2H, d, *J* = 8.8 Hz, 3-*H* and 5-*H*), 7.24 (2H, d, *J* = 8.8 Hz, 3′-*H* and 5′-*H*), 7.18 (2H, d, *J* = 8.8 Hz, 2′-*H* and 6′-*H*) and 5.81 (1H, s, C*H*); ^{13}C NMR ($CDCl_3$): δ 75.5, 129.1, 129.2, 129.5, 130.5, 131.6, 134.9, 137.3, 140.8 and 197.4

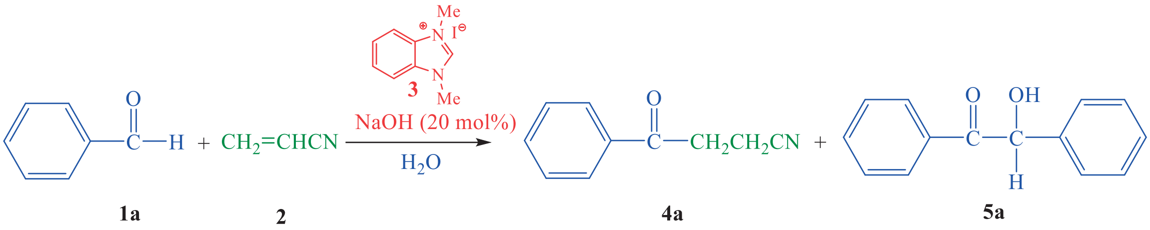
4,4′-Dimethylbenzoin (5c): White crystals; Yields 21-32%; R_f = 0.22 (100% dichloromethane); m.p.: 75-77 °C (lit. 75 °C) [32]; IR (KBr) ν_{max}: 3442, 3044, 2929, 1678, 1607, 1520, 1449, 1374 and 1191 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.81 (2H, d, *J* = 8.8 Hz, 2-*H* and 6-*H*), 7.22 (2H, d, *J* = 8.8 Hz, 3-*H* and 5-*H*), 7.19 (2H, d, *J* = 8.4 Hz, 2′-*H* and 6′-*H*), 7.10 (2H, d, *J* = 8.4 Hz, 3′-*H* and 5′-*H*), 5.89 (1H, s, C*H*), 2.34 (3H, s, Ar-CH_3) and 2.30 (3H, s, Ar-CH_3); ^{13}C NMR ($CDCl_3$): δ 21.3, 21.8, 75.8, 127.8, 129.3, 129.4, 129.9, 131.1, 136.4, 138.5, 144.9 and 198.7

4,4′-Pyridoin (5d): Yellow crystals; Yields 13-25%; R_f = 0.20 (100% dichloromethane); m.p. 153-155 °C; IR (KBr) ν_{max}: 3464, 3068, 2981, 2850, 1668, 1591, 1513, 1472, 1319, 1275, 1170, 1081, 819 cm^{-1}; ^{1}H NMR δ 8.77 (2H, d, *J* = 8.8 Hz, 2-*H* and 6-*H*), 8.55 (2H, d, *J* = 8.8 Hz, 3-*H* and 5-*H*), 7.94 (2H, d, *J* = 8.4 Hz, 2′-*H* and 6′-*H*), 7.20 (2H, d, *J* = 8.4 Hz, 3′-*H* and 5′-*H*), 6.09 (1H, s, C*H*); ^{13}C NMR ($CDCl_3$) δ: 75.6, 122.2, 122.6, 135.1, 137.5, 145.2, 150.5, 197.8

3. Results and Discussion

To investigate this intermolecular stetter reaction, the simple substrate benzaldehyde (**1a**) and acrylonitrile (**2**) were firstly surveyed, which was carried out under similar conditions as reported in the literature [24] by using 20 mol% of catalyst **3** and in the presence of 20 mol% of different bases and temperature with water as the solvent. The screening of the optimized base, including temperature control, was carried out, and the results are summarized in Table 1.

Table 1. Optimization condition of intermolecular stetter reaction between benzaldehyde (**1a**) and acrylonitrile (**2**) catalyzed by *N*,*N*-dimethylbenzimidazolium iodide (**3**) in the presence of various bases in water



Entry	Base	Temp.	Time (h)	Yield **4a** (%)	Yield **5a** (%)
1	TEA	r.t.	12	n.d.	12
2	DBU	r.t.	12	n.d.	14
3	NaOH	r.t.	6	25	21
4	TEA	100	10	15	14
5	DBU	100	10	46	17
6	NaOH	100	4.5	75	18

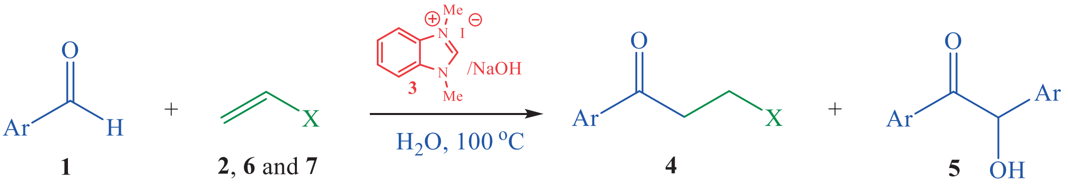
Under this situation, when benzimidazolium salt **3** under the conditions of organic bases of triethylamine (TEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature in the water was used, the reaction proceeded not smoothly and afforded only product of α-hydroxy ketone **5a** in 12 and 14%, respectively (Table 1, entries 1, 2). Unfortunately, desired 4-phenyl-4-oxobutanenitrile (**4a**) was low yield when the reaction was run with an ionic base of NaOH at room temperature in water (Table 1, entries 3).

The reaction between benzaldehyde (**1a**) and acrylonitrile (**2**) by using 20 mol% of *N*,*N*-dimethylbenzimidazolium iodide (**3**) and different base in water at 100 ^{o}C was carried out, and the resulting was listed in Table 1. In the case of this stetter reaction catalyzed by benzimidazolium salt **3** with NaOH in water provided 1,4-addition product **4a** in 75% yield that was higher than organic bases of TEA and DBU due to it being a strong base for better deprotonation of the catalyst. Moreover, NaOH provided more advantages than the organic base (TEA and DBU) because it is the inorganic base dissolved in an aqueous phase and easily separated from the products and reused. The increasing temperature from room temerature to 100 oC can increase the reaction rate, as shown in Table 1 that the reaction was faster at high temerature and increased the product. This result is consistent with previously reported studies [33]. The side product **5a** was still obtained in 14, 17, and 18% yields, respectively (Table 1, entries 4 to 6).

With the optimal reaction conditions established (Table 1), the extension of these reaction conditions between either acrylonitrile (**2**) or methyl vinyl ketone (**6**) and aldehydes **1a-d** was conducted with good yields (70-77%) of corresponding 1,4-addition products **4b-h** (Table 2, entries 1-7). In each case, small amounts of acyloins **5a-d** (13 to 23%) were also formed in these reactions.

In contrast, acyloins became the competitive side reaction when a less electrophilic double bond of ethyl acrylate (**7**) was used due to the Breslow intermediate reacted with more reactive aldehydes than less reactive ethyl acrylate, the desired product was provided with a lower yield of 1,4-additions **4i-l** in 62, 66, 58 and 64% yields, respectively. The less electrophilic double bond of ethyl acrylate (**7**) slightly decreased the yields of 1,4-additions **4i-l** and slightly increased reaction times (Table 2, entries 8-11).

Table 2. Intermolecular stetter reaction of aromatic aldehydes **1a**-**d** with acrylonitrile (**2**), ethyl acrylate (**6**) and methyl vinyl ketone (**7**) catalysed by *N*,*N*-dimethylbenzimidazolium iodide (**3**) (20 mol%) and NaOH (20 mol%) in water at 100 °C



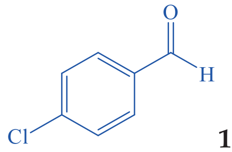
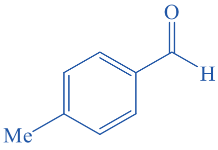
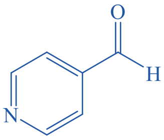
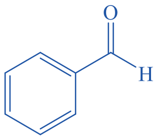
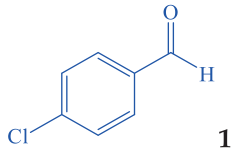
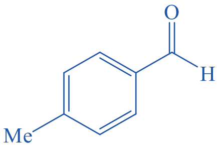
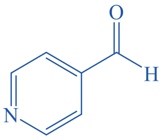
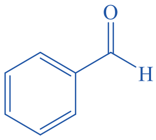
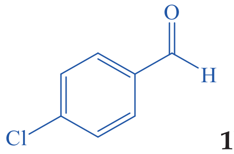
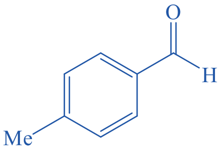
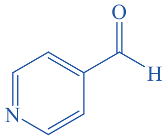
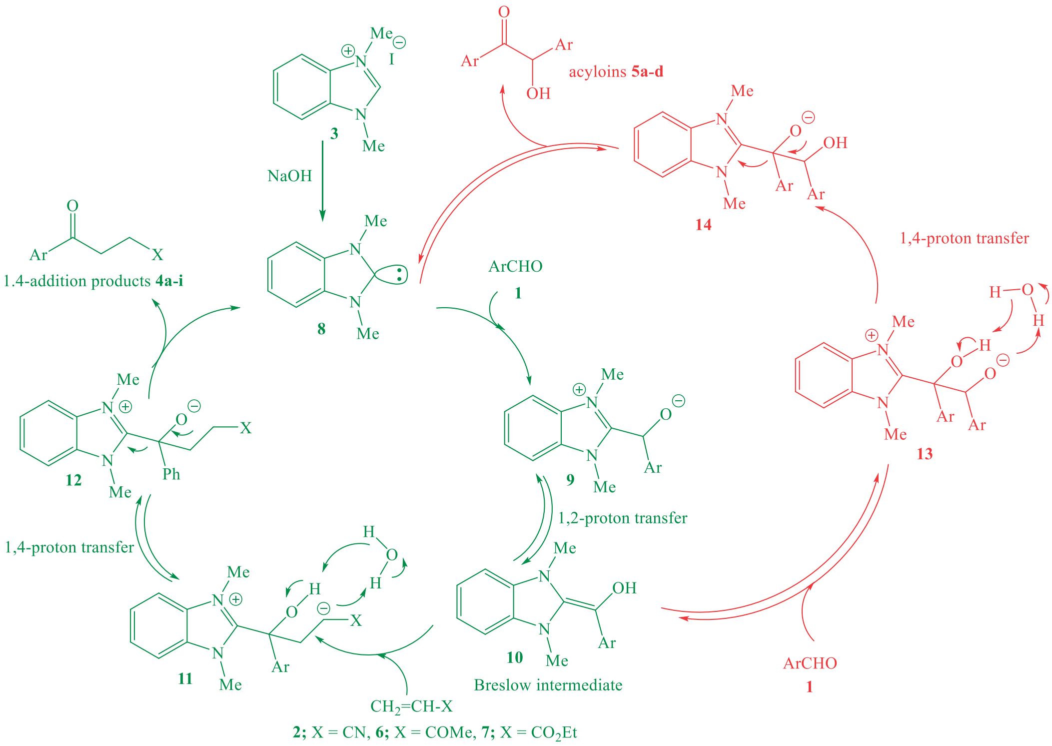
Entry	Aldehyde	X	Time (h)	Yield (%)	Yield (%)
1	 **1b**	CN (**2**)	3	77 (**4b**)	15 (**5b**)
2	 **1c**	CN (**2**)	5	71 (**4c**)	21 (**5c**)
3	 **1d**	CN (**2**)	3.5	73 (**4d**)	13 (**5d**)
4	 **1a**	COCH3 (**6**)	4.5	73 (**4e**)	14 (**5a**)
5	 **1b**	COCH3 (**6**)	3.5	75 (**4f**)	16 (**5b**)
6	 **1c**	COCH3 (**6**)	5	70 (**4g**)	23 (**5c**)
7	 **1d**	COCH3 (**6**)	4	72 (**4h**)	15 (**5d**)
8	 **1a**	CO2CH2CH3 (**7**)	5	62 (**4i**)	23 (**5a**)
9	 **1b**	CO2CH2CH3 (**7**)	4	66 (**4j**)	26 (**5b**)

Table 2. Intermolecular stetter reaction of aromatic aldehydes **1a-d** with acrylonitrile (**2**), ethyl acrylate (**6**) and methyl vinyl ketone (**7**) catalysed by *N*,*N*-dimethylbenzimidazolium iodide (**3**) (20 mol%) and NaOH (20 mol%) in water at 100 °C (Continued)

Entry	Aldehyde	X	Time (h)	Yield (%)	Yield (%)
10	 **1c**	$CO_2CH_2CH_3$ (**7**)	6	58 (**4k**)	32 (**5c**)
11	 **1d**	$CO_2CH_2CH_3$ (**7**)	4.5	64 (**4l**)	22 (**5d**)

The catalytic cycle of the stetter reaction (green pathway) proposed similarly with a previous report [33], the *N*,*N*-dimethylbenzimidazolium iodide (**3**) is deprotonated by NaOH to form carbene **8,** which reacts with the aldehyde **1** to give the Breslow intermediate **10**. Then, subsequent nucleophilic attack of the Breslow intermediate **10** to the Michael acceptors **2**, **6** or **7** provides tetrahedral intermediate **11**. 1,4-Proton transfer by water and collapse of the tetrahedral intermediate **11** affords the 1,4-addition products **4a-i** and regenerates the carbene catalyst **8** (Scheme 1).

The side product **5a-d** is shown in the red pathway. The Breslow intermediate **10** is an acylation reagent, which reacts with another aldehyde **1** to provide an intermediate **13**. Water is deemed a proton shuttle in a 1,4-H shift process by simultaneously providing one proton to the oxygen and obtaining another from the hydroxyl group to give an intermediate **14** followed by the regeneration of the NHC catalyst and elimination of the acyloins **5a-d**.



Scheme 1. Catalytic cycles of intermolecular stetter reaction (blue pathway) and acyloin condensation (red pathway) catalysed by *N*,*N*-dimethylbenzimidazolium iodide (**3**) and NaOH in water

Recycling of *N*,*N*-dimethylbenzimidazolium iodide (**3**) were examined for the intermolecular stetter reaction between benzaldehyde (**1a**) and acrylonitrile (**2**) in water. After the first run, which gave 1,4-addition product **4a** in 75% yields, the benzimidazolium salt **3** and NaOH in water after the reaction and extraction separation was reused in the same type of reaction for at least 5 cycles.

The recovered benzimidazolium salt **3** and NaOH in water was subjected to a second cycle with 1 equiv. of benzaldehyde (**1a**) and 2 equiv. of acrylonitrile (**2**) gave 4-phenyl-4-oxobutanenitrile (**4a**) in a 73% yield. Similarly, in the third, fourth, and fifth cycles, the yield of 1,4-addition products was 70%, 68%, and 65%, respectively (Table 3). The slight decrease in the yield may be due to the reduction of NaOH and the increase of water or the decomposition of some amount of catalyst in the reaction because the recycle condition came from the aqueous phase after extraction of the product and used without purification.

Table 3. Intermolecular stetter reaction between benzaldehyde (**1a**) and acrylonitrile (**2**) in recycled catalysed of *N*,*N*-dimethylbenzimidazolium iodide (**3**) and NaOH with water as the solvent

Run	Yield 4a (%)	Yield 5a (%)
1	75	18
2	73	17
3	70	14
4	68	13
5	65	11

4. Conclusions

Intermolecular stetter reaction between either acrylonitrile or methyl vinyl ketone and aromatic aldehydes in the presence of 20 mol% of *N*,*N*-dimethylbenzimidazolium iodide (**3**) and NaOH performed well in water and as an efficient green method, giving a good yield of products with corresponding acyloins as side products. NaOH plays an important role in this stetter reaction due to its strong basicity and recycling ability. The increasing reaction temperature can increase the reaction rate and product yields. Moderate yields of 1,4-addition products were observed upon treating aromatic aldehydes with a less reactive acceptor (ethyl acrylate). The recycle reaction system containing benzimidazolium salt **3** and NaOH after the extraction can be reused five times without significant loss of efficiency.

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Conflicts of Interest: The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Pelissier, H. Recent developments in enantioselective organocatalytic michael reactions in aqueous media. *Current Organic Chemistry*. 2018, 22, 323-344.
2. Van Der Helm, M P.; Klemm, B.; Eelkema, R. Organocatalysis in aqueous media. *Nature Review Chemistry*. 2019, 3, 491-508.

3. Ren, Y.; Cai, C. Iodine catalysis in aqueous medium: An improved reaction system for knoevenagel and nitroaldol condensation. *Catalysis Letter*. 2007, 118, 134–138.
4. Gong, K.; He, Z.W.; Xu, Y. Green synthesis of 5–benzylidene rhodanine derivatives catalyzed by 1–butyl–3–methyl imidazolium hydroxide in water. *Monatshefte für Chemie*. 2008, 139, 913–915.
5. Aryanasab, F.; Ziyaei, A.H.; Mohammad, S.R. Dithiocarbamate as an efficient intermediate for the synthesis of 2–amino–1,3,4–thiadiazoles in water. *Tetrahedron Letter*. 2010, 51, 790–792.
6. Kidwai, M.; Singhal, K.; Kukreja, S. One–pot green synthesis for pyrimido [4,5–d] pyrimidine derivatives. *Zeitschrift für Naturforschung B*. 2007, 62b, 732–736.
7. Pravin, V.; Shinde, J.B.; Gujar, B. Silica in water: A potentially valuable reaction medium for the synthesis of pyrano [2,3–c]pyrazoles. *Bulletin of the Korean Chemical Society*. 2012, 33, 1345–1348.
8. Polshettiwar, V.; Varma, R.S. Biginelli reaction in aqueous medium: A greener and sustainable approach to substituted 3,4–dihydropyrimidin –2(1H)–ones. *Tetrahedron Letter*. 2007, 48,7343–7346.
9. Kumaravel, K.; Vasuki, V. Four component catalyst–free reaction in water synthesis of novel 2–amino–4–(5–hydroxy–3–methyl–1H–pyrazol–4–yl)–4H chromene–3 carbonitrile derivatives. *Green Chemistry*. 2009, 11, 1945–1947.
10. Ahadi, S.; Yasaei, Z.; Bazgir, A. A clean and one–pot synthesis of spiroindoline–pyranopyrazoles. *Journal of Heterocycle Chemistry*. 2010, 47, 1090–1094.
11. Taterao, M.P.; Ingale, S.A.; Srinivasan, K.V. Catalyst–free efficient synthesis of 2–aminothiazoles in water at ambient temperature. *Tetrahedron*. 2008, 64, 5019–5022.
12. Iwamoto, K.I.; Hamaya, M.; Hashimoto, N.; Kimura, H.; Suzuki, Y.; Sato, M. Benzoin reaction in water as an aqueous medium catalyzed by benzimidazolium salt. *Tetrahedron Lett*er. 2006, 47, 7175–7177.
13. Nair, V.; Vellalath, S.; Poonoth, M.; Mohan, R.; Suresh, E. *N*-heterocyclic carbene catalyzed reaction of enals and 1,2-dicarbonyl compounds: Stereoselective synthesis of spiroγ-butyrolactones. *Organic Letter.* 2006, *8*, 507-509.
14. Wang, X.N.; Zhang, Y.Y.; Ye, S. Enantioselective synthesis of spirocyclic oxindole-β-lactones via *N*-heterocyclic carbene-catalyzed cycloaddition of ketenes and isatins. *Advanced Synthesis & Catalysis.* 2010, 352, 1892-1895.
15. Sun, L.H.; Shen, L.T.; Ye, S. Highly diastereo- and enantioselective NHC-catalyzed [3+2] annulation of enals and isatins. *Chemistry Communication.* 2011, 47, 10136-10138.
16. Jiang, K.; Bhoopendra, T.; Chi, Y. Access to spirocyclic oxindoles via *N*-heterocyclic carbene-catalyzed reactions of enals and oxindole-derived α,β-unsaturated imines. *Organic Letter.* 2012, 14, 2382-2385.
17. Zhang, F.; Du, P.; Chen, J.; Wang, H.; Luo, Q.; Wan, X. Co-catalyzed synthesis of 1,4-dicarbonyl compounds using TBHP oxidant. *Organic Letter.* 2014, 16, 19322-1935.
18. Stetter, H. Catalyzed addition of aldehydes to activated double bonds-A new aynthetic approach. *Angewandte Chem*ie *International Edition.* 1976, 15, 639-647.
19. Leong, W.W.Y.; Chen, X.; Chi, Y.R. NHC-catalyzed reactions of enals with water as a solvent. *Green Chemistry.* 2013, 15, 1505-1508.
20. Stetter, H.; Schreckenberg, M. Addition of aliphatic aldehydes to activated double bonds. *Chemische Berichte*. 1974, 107, 2453.
21. Stetter, H. Catalyzed addition of aldehydes to activated double bonds-A new synthetic approach. *Angewandte Chem*ie *International Edition in English*. 1976, 15, 639–647.
22. Stetter, H.; Kuhlmann, H. Addition von aldehyde an aktivierte doppelbindungen-XII. *Tetrahedron*. 1977, 33, 353-356.
23. Novak, L.; Baan, G.; Marosfalvi, J.; Szantay, C. Application of carbonyl umpolung to prostaglandin synthesis I. Synthesis of 11-deoxy prostaglandin intermediates. *Tetrahedron Letter*. 1978, 19, 487-490.
24. Anjaiah, S.; Chandrasekhar, S.; Gree, R. Stetter reaction in room temperature ionic liquids and application to the synthesis of haloperidol. *Advanced Synthesis & Catalysis* 2004, 346, 1329-1334.
25. Phungpis, B.; Hahnvajanawong, V.; Theramongkol, P. Benzoin condensation and stetter reaction catalysed by *N*,*N*-dimethylbenzimidazolium iodide in [Bmim][OH]. *Oriental Journal of Chemistry.* 2014, 30, 933–939.

26. Stetter, H.; Schreckenberg, M. A new method for addition of aldehydes to activated double bonds, *Angewandte Chemie International Edition*. 1973, 12, 81.
27. Reutrakul, V.; Nimgirawath, S.; Panichanun, S.; Ratananukul, P. Addition reactions of α-(dimethylamino) nitriles with acrylonitrile: A simple synthesis of γ-ketonitriles. *Chemistry Letter*. 1979, 399-400.
28. Herman, H.; Schreckenberg, M. 1977, Process for Preparing Ketones, US Patent NO. 4014889.
29. Breslow, R. On the mechanism of thiamine action. IV.[1] Evidence from studies on model systems. *Journal of American Chemical Society*. 1958, 80, 3719-3726.
30. Stetter, H.; Kuhlmann, H. The catalyzed nucleophilicaddition of aldehydes to electrophilic double bonds. *Organic Reaction*. 1991, 40, 434.
31. Phungpis, B.; Hahnvajanawong, V. 1-Butyl-3-methylimidazolium bromide as a solvent and precatalyst for stetter reaction. *Asian Journal of Chemistry*. 2020, 32, 2028-2032.
32. Corey, E.J.; Zhang, F.Y. Mechanism and conditions for highly enantioselective epoxidation of α,β-enones using charge-accelerated catalysis by a rigid quaternary ammonium salt. *Organic Letter*. 1999, 1, 1287-1290.
33. Debiais, M.; Hamoud, A.; Drain, R.; Barthélémy, P.; Desvergnes, V. Bio-inspired NHC-organocatalyzed Stetter reaction in aqueous conditions. *RSC Advanced*. 2020, 10, 40709-40718.