

Study on the Reaction of Benzimidazolium Salt with Amine Compounds

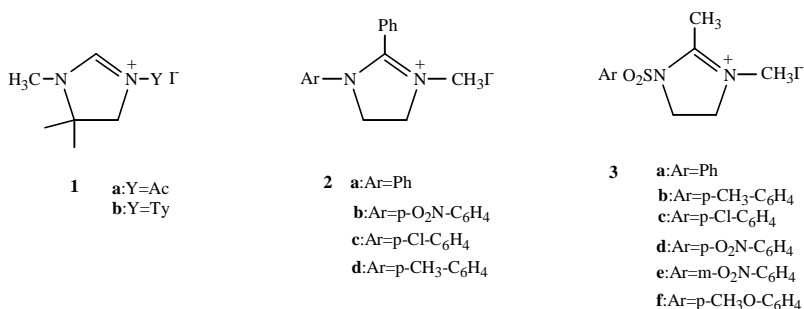
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Abstract: The addition-hydrolysis reaction of benzimidazolium salt with some mono- and bifunctional amine nucleophiles is reported, and a novel method of biomimetic synthesis for formamides and heterocycle compounds is provided.

Keywords: Tetrahydrofolate coenzyme model, benzimidazole methiodide salt, amine compound, biomimetic synthesis.

The metabolic interconversions of tetrahydrofolate coenzymes involve the transfer of one-carbon units at different oxidation levels, that is the level of formate, formaldehyde and methanol. Many suitable coenzyme models have been developed for potential utilization in the biomimetic transfer of one-carbon units at the formyl level. Pandit *et al.* has synthesized the compound **1** as the models of coenzyme [5,10-(CH⁺)-THF], and studied the reactions of the models with a variety of nucleophiles, the results demonstrated that in many reactions the isolated product represented a net one carbon transfer, in others the intermediate prior to this overall process¹; Zhi Zhong XIA *et al.* has synthesized the compounds **2** and **3** as the models of [5,10-(CH⁺)-THF], the reaction results of the two models with diverse nucleophiles are the same with model **1**².

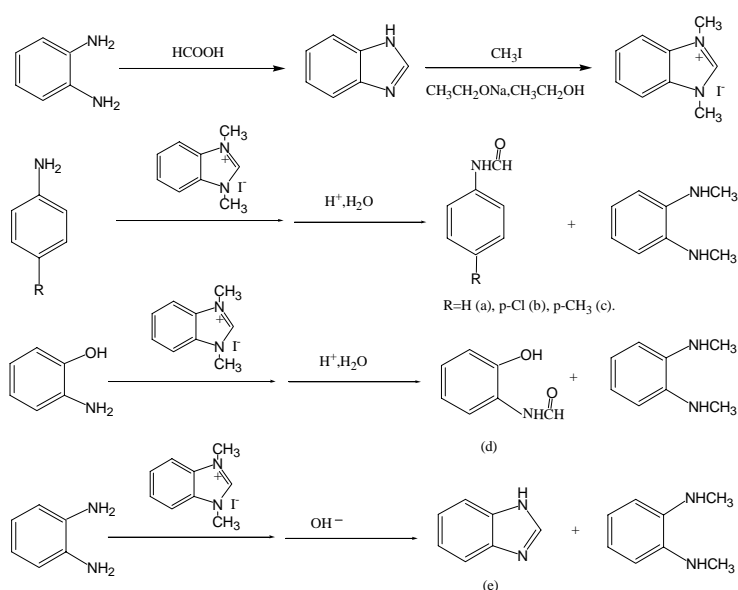


Based on the one-carbon unit transfer reaction of tetrahydrofolate coenzymes, we reported the addition-hydrolysis reaction of benzimidazole methiodide salts with nucleophiles such as Grignard reagents and ethyl malonate, and the new methods for the

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preparation of aldehydes, ketones and β -keto acid were provided^{3,4}. In this paper, the reaction of benzimidazolium salt with amine nucleophiles was studied, and a novel method of biomimetic synthesis of formamides and heterocycle compounds is presented. Benzimidazolium salt was used as tetrahydrofolate coenzyme model at formic acid oxidation level and amine compounds as nucleophiles to which one-carbon unit was transferred (**Scheme 1**).

Scheme 1



Experimental

Synthesis of benzimidazolium iodide:

Benzimidazolium iodide was prepared according to our previous paper³.

Synthesis of compounds a-d:

5.5 g (0.02 mol) Benzimidazolium iodide and 0.03 mol amine compounds were dissolved in 30 mL dry DMF, and the mixture was refluxed for 30 hr. After cooling to room temperature, the mixture was added dilute HCl to make its pH 2. Then the mixture was stirred at room temperature for another 2 hr. DMF was removed and the residue was purified by chromatography (SiO₂, petroleum ether and ethyl acetate).

Synthesis of compound e:

The procedure for the preparation of compound **e** was the same with that of **a-d** except

that the mixture was hydrolyzed by adding dilute NaHCO₃ to make the pH of the mixture being 9-10.

The spectral data and physical constants of compounds *a-e* are as follows:

- a** mp: 48-49°C(50°C)⁵, yellow solid, yield: 53.7%. IR(KBr), $\nu(\text{cm}^{-1})$: 3265~3134, 1681, 1549, 1314, 3078, 1598, 1491, 1439, 750, 686. MS m/z : 121(M⁺).
- b** mp: 100-102°C (102°C)⁵, yellow solid, yield: 60%. IR(KBr), $\nu(\text{cm}^{-1})$: 3330~3060, 1677, 1540, 1308, 3058, 1603, 1487, 828. MS m/z (%): 155(M⁺).
- c** mp: 51-52°C (52°C)⁵, yellow solid, yield: 67.7%. IR(KBr), $\nu(\text{cm}^{-1})$: 3444~3191, 1687, 1517, 3038, 2918, 2862, 1611, 1485, 1398, 811. MS m/z : 135(M⁺).
- d** mp: 127-128°C (129-129.5°C)⁵, purple solid, yield: 76.6%. IR(KBr), $\nu(\text{cm}^{-1})$: 3378, 3100, 1656, 1536, 1278, 1590, 1453, 751. MS m/z : 137(M⁺).
- e** mp: 169-170°C (170.5°C)⁶, white solid, yield: 67.8%. IR(KBr), $\nu(\text{cm}^{-1})$: 3050, 1618, 1585, 1456, 1769, 1407, 1301, 1269, 1244, 1196, 1129, 954, 745. MS m/z : 118(M⁺).

Results and Discussion

The mechanism for the reaction of benzimidazolium iodide with nucleophiles has been proposed in our earlier paper³. The reaction of the mono-functional amine nucleophiles with benzimidazolium iodide can be reasonably explained by a similar addition reaction of mono-functional amine nucleophiles with quaternary C=N bond of benzimidazolium iodide, and the obtained intermediate can be converted into the corresponding formamides *via* hydrolysis. The reaction of the bifunctional amine nucleophiles with benzimidazolium iodide can be reasonably explained as follows: the first intermediate obtained from the same addition reaction as the mono-functional amine nucleophiles also has polarized C=N bond being attacked by the other nucleophilic group of bifunctional amine compound, and the second intermediate is obtained, which can be hydrolyzed to give corresponding heterocycle compound. The probable mechanism of the reaction is as shown by **Scheme 2**.

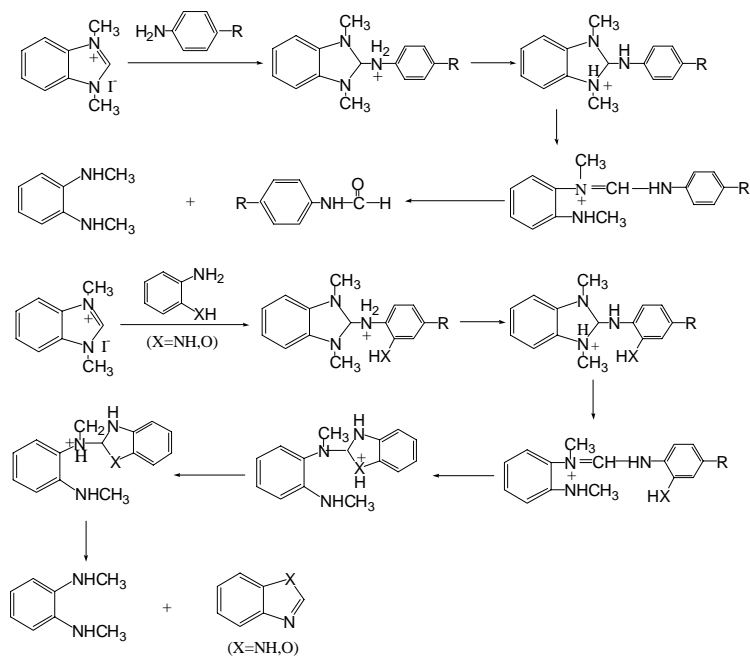
The isolation of 2-formamidophenol upon work-up of the reaction with bifunctional 2-aminophenol is consistent with the known ease of hydrolysis of the expected benzoxazole, which presumably is the primary product.

It is not necessary to separate the product of addition of benzimidazolium iodide salt with amine, the addition product is hydrolysed directly to the product after the addition reaction is finished.

Further studies of this reaction and the mechanism are being continued in our laboratory.

In conclusion, benzimidazolium is one kind of ideal tetrahydrofolate model at the oxidation level of formic acid according to its reaction with diverse nucleophiles.

Scheme 2



Acknowledgments

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