

AZOLIUM SALTS AS EFFECTIVE CATALYSTS FOR BENZOIN CONDENSATION AND RELATED REACTIONS ¹

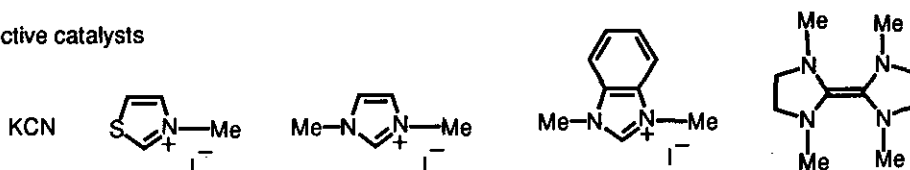
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Abstract—A catalytic ability of several azolium salts for benzoin condensation, the benzoylation of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine, and oxidative aroylation was examined. We found that azolium salts having an imidazolium moiety, such as 1,4-dimethyl-1,2,4-triazolium iodide (3), and 2-methylpyrido[1,2-*c*]- (4), dipyrdo[1,2-*c*:2',1'-*e*]- (5), naphtho[1,2-*c*]- (10), and phenanthro[9,10-*c*]imidazolium iodide (11) can be used as effective catalysts for benzoin condensation and related reactions.

During our continuous study of the catalytic action of azolium salts, our interest in benzoin condensation ² and related reactions ³ was focused to find new catalysts. The discovery of new catalysts and the definition of the structural requirements for effective catalysts are useful and interesting in organic synthesis. For benzoin condensation, it is well known that cyanide ion is the original catalyst.² Moreover, it has been reported that several compounds, such as thiazolium salts,⁴ imidazolium salts,⁵ benzimidazolium salts,⁵ and electron-rich olefins (imidazolines)⁶ can be used as effective catalysts. However, the structural requirements for these compounds, which have the ability as a catalyst, are still not clear. We considered that the discovery of new compounds as an effective catalyst for benzoin condensation and related reactions will clarify this situation.

Effective catalysts

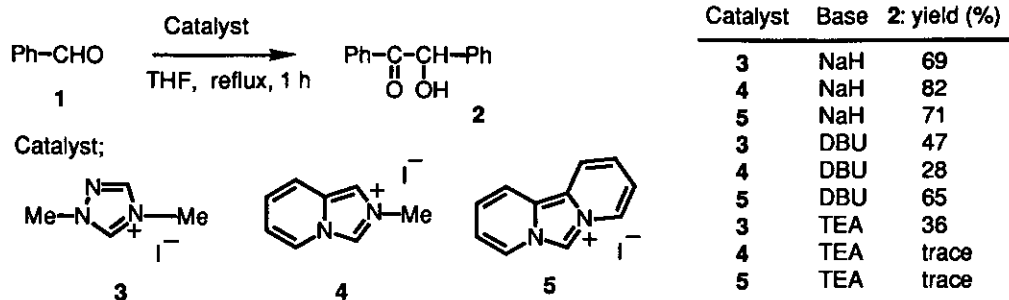


Scheme 1

In this paper, we wish to report newly finding azolium salts having the catalytic ability for benzoin condensation and related reactions.

We have already reported that chemical behavior of azolium ylides, which are derived from azolium salts, is similar to that of cyanide ion.⁷ This results and reported results ⁸ indicate that quaternary ammonium salts can be used as the catalyst.²⁻⁵ To clarify the structural requirement of an effective catalyst for benzoin condensation and related reactions, various azolium salts and azinium salts,⁹ except thiazolium, imidazolium, and benzimidazolium salts, were examined for producing benzoin (2) by self-condensation of benzaldehyde (1).

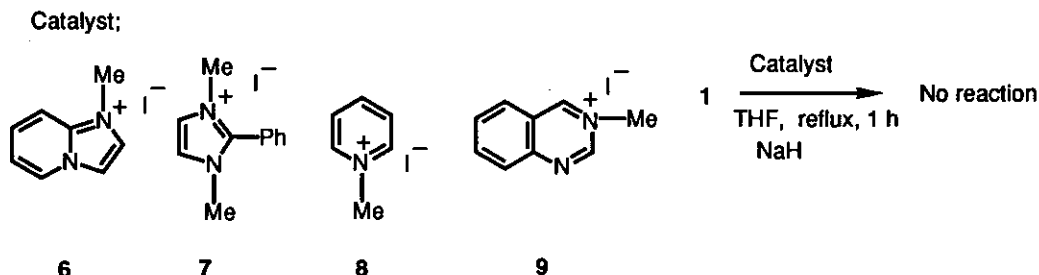
As shown in Scheme 2, in the presence of 1,4-dimethyl-1,2,4-triazolium iodide (3), self-condensation of benzaldehyde (1) proceeded to give benzoin (2) in good yield.¹⁰ A similar catalytic effect was observed for 2-methylpyrido[1,2-*c*]imidazolium iodide (4) and dipyrdo[1,2-*c*:2',1'-*e*]imidazolium iodide (5). On the



Scheme 2

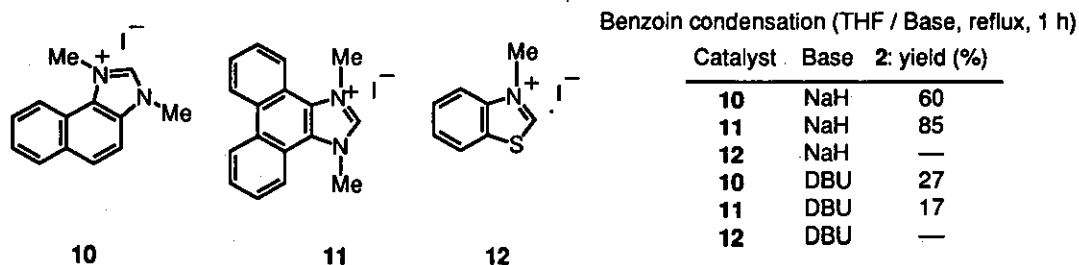
other hand, attempts at the benzoin condensation catalyzed by 1-methylpyrido[1,2-*b*]imidazolium iodide (6), 1,3-dimethyl-2-phenylimidazolium iodide (7), 1-methylpyridinium iodide (8), and 3-methylquinazolinium iodide (9) were unsuccessful.

These results and reported results^{4,5} suggested that in order to act as an effective catalyst, the catalysts require an imidazolium moiety or a thiazolium moiety with no substituent at the 2-position. In fact, the self-condensation of benzaldehyde (1) catalyzed by 6 and 7, whose structures include an imidazolium moiety but substituted at the 2-position of the imidazole, did not produce benzoin (2).



Scheme 3

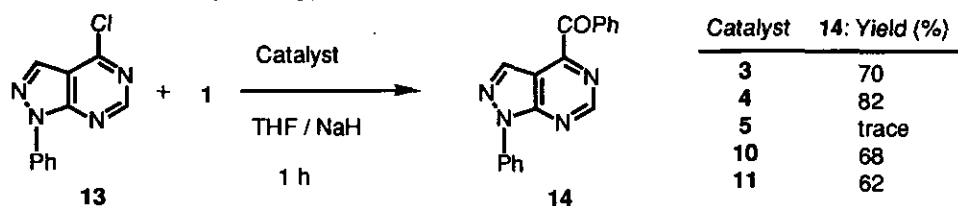
The self-condensation of benzaldehyde (1) in the presence of several azolium salts having an imidazolium moiety or a thiazolium moiety were examined. In the presence of 10 and 11, which include an imidazolium moiety, the self-condensation proceeded to give benzoin (2) in moderate yields, but, upon similar treatment in the presence of 1-methylbenzothiazolium iodide (12), which includes a thiazolium moiety, the condensation failed to proceed.¹¹ In spite of the effective catalyst of thiazolium salt,⁴ it is not clear yet why the catalytic action of 12 could not be exhibited.



Scheme 4

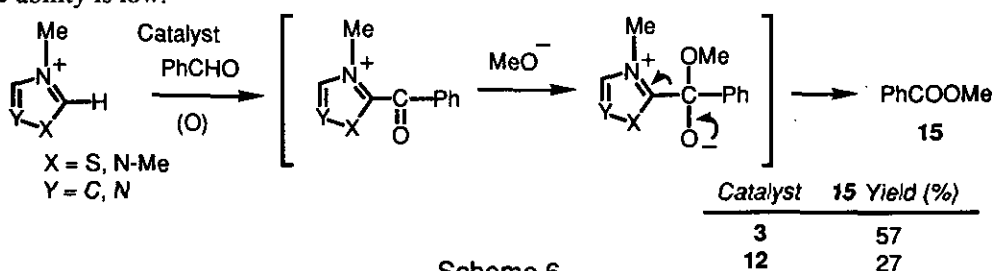
The catalytic action of the azolium salts was used to produce 4-aryl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine by the benzylation of 4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (13).¹² In the

presence of **3**, upon treatment of **13** with benzaldehyde (**1**), 4-benzoyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**14**) was produced in moderate yield. A similar catalytic action was observed in **4**, **10**, and **11**. However, it was not easy to produce benzoylpyrazolopyrimidine (**14**) by catalytic action of **5**. In a manner similar to that observed during benzoin condensation, the benzoylation of **13** catalyzed by **6**, **7**, **8**, **9**, and **12** failed to produce benzoylpyrazolopyrimidine (**14**).



Scheme 5

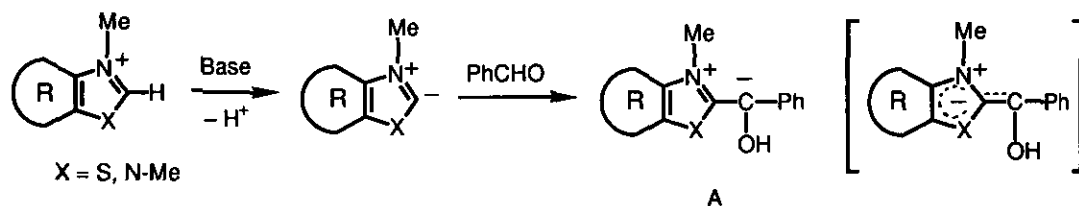
Furthermore, the azolium salt (**3**) catalyzed the oxidative aroylation.^{3d} When a solution of benzaldehyde (**1**), nitrobenzene, and DBU in the presence of **3** in MeOH was stirred at room temperature for 4 h, methyl benzoate (**15**) was obtained in 57% yield. A similar treatment catalyzed by **12** gave methyl benzoate (**15**) in 27% yield. This result indicated that the azolium salt (**12**) can behave as an effective catalyst. However, a catalytic ability is low.



Scheme 6

The catalytic behavior of the newly finding azolium salts is similar to that of the imidazolium and benzimidazolium salts.^{3a,13} In benzoin condensation and related reactions catalyzed by azolium salts, the formation of the intermediate(A) is an important step to achieve the aroylation. The key intermediate(A) is formed by benzaldehyde (**1**) and the ylide. For usable compounds as an effective catalyst for benzoin condensation and related reactions, we have determined that an important factor is the formation of ylide by expulsion of the C²-hydrogen.¹⁴ Another factor is the reactivity and stability of the ylide and the key intermediates(A).^{3e} It is clear that the azolium salts having an imidazolium moiety or a thiazolium moiety well meet the situation.

The acidity of the azolium salts at the C²-hydrogen of the imidazolium or the thiazolium moieties relates to the base effect for benzoin condensation.^{5b} In fact, the catalytic action of **3** can be shown under milder conditions compared with the imidazolium and benzimidazolium salts because of the higher acidity.^{4b,15} On the other hand, among the azolium salts, which have catalytic ability reported by us in this paper, the rate of deuterium-hydrogen exchange for **12** at the C²-position is rapid, but the catalytic ability is low. The reason for this is not clear yet. Further investigation of the properties and reactivities of the azolium salts will clarify the relationship between the structure and the catalytic ability.



Scheme 7

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7. A. Miyashita, Y. Matsuoka, K. Iwamoto, and T. Higashino, *Chem. Pharm. Bull.*, 1994, 42, 1960.
8. (a) R. K. Howe and K. W. Ratts, *Tetrahedron Lett.*, 1967, 4743; (b) K. W. Ratts, R. K. Howe, and W. G. Phillips, *J. Am. Chem. Soc.*, 1969, 91, 6115.
9. The azolium salts and the azinium salts described in this paper were prepared by treatment of the corresponding heteroarenes with methyl iodide.
10. A typical procedure: To a mixture of benzaldehyde (1, 1.06 g, 10 mmol) and azolium salt (1 mmol) in 50 ml of THF was added base (3 mmol) and the mixture was refluxed for 1 h. The reaction mixture was poured into H₂O, and extracted with CHCl₃. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with CHCl₃.
11. It was reported that the benzothiazolium salt (12) behaves as an effective catalyst in benzoin condensation; B. Lachmann, H. Steinmaus, and H. W. Wanzlick, *Tetrahedron*, 1971, 27, 4085. But, under our conditions, we could not obtain benzoin (2).
12. A typical procedure: To a mixture of benzaldehyde (1, 382 mg, 3.6 mmol), 4-chloro-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (13, 692 mg, 3 mmol) and azolium salt (1 mmol) in 30 ml of THF was added NaH (50% in oil, 173 mg, 3.6 mmol) and the mixture was refluxed for 1 h with stirring. The reaction mixture was poured into H₂O, and extracted with CHCl₃. The organic layer was washed with H₂O, dried over Na₂SO₄, and concentrated. The residue was purified by column chromatography on SiO₂ with CHCl₃.
13. (a) R. Breslow, *J. Am. Chem. Soc.*, 1958, 80, 3719; (b) R. Breslow and E. McNelis, *J. Am. Chem. Soc.*, 1959, 81, 3080.
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15. Rate constants (K) for the deuterium-hydrogen exchange of the azolium salts at the C²-position were determined by ¹H-nmr in CD₃OD at 27°C on the basis of the integration of the C²-hydrogen. 3; K = 23.6 × 10⁻⁴ min⁻¹, 1,3-dimethylimidazolium iodide; 1.5 × 10⁻⁴ min⁻¹, 1,3-dimethylbenzimidazolium iodide; 2.9 × 10⁻⁴ min⁻¹. Since the disappearance rate of the C²-hydrogen of 12 was fast, the rate constant could not be measured under these conditions. We believe that the chemical shifts of the C²-hydrogen for the azolium salts in ¹H-nmr are correlated with the acidities. Chemical shifts (DMSO-d₆) ppm: 3; 10.25, 4; 9.70, 12; 10.66, 1,3-dimethylimidazolium iodide; 9.20, 1,3-dimethylbenzimidazolium iodide; 9.85, 3-methylthiazolium iodide; 10.20.

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