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A Straightforward and Efficient Catalyst-free One-pot Synthesis of *N*-Acyl-1,3-diaryl-2-azaphenalene Derivatives via Multicomponent Reactions

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A novel, one-pot multicomponent reaction of two molecules of aldehydes with 2,7-naphthalenediol and ammonium carboxylates is described as an efficient and direct procedure for the preparation of *N*-acyl-1,3-diaryl-2-azaphenalene derivatives in EtOH under reflux conditions. *N*-Acyl-1,3-diaryl-2-azaphenalene derivatives were obtained in good to high yields without any catalyst or activation.

Multicomponent reactions (MCRs), with three or more reactants combining in a one-pot procedure to give a single product, are a promising and vital field of chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient, and time-saving manner without the isolation of any intermediate.[1–4] As a result, it requires minimum effort, which minimizes the environmental loading and is acceptable from a "Green Chemistry" point of view. MCRs are perfectly suited for combinatorial library synthesis, and thus are finding increased use in the discovery process for new drugs and agrochemicals.[5,6] Therefore, the design of novel MCRs has attracted great attention from research groups working in medicinal chemistry, drug discovery, and materials science. The Biginelli,[7] Ugi,[8] Passerini,[9] and Mannich[10] reactions are some example of MCRs. Nevertheless, development and discovery of new MCRs is still in demand.

In this context, recently we have reported[11] the reaction of 2-naphthol and aldehydes (2:1) in the presence of *p*-toluenesulfonic acid (*p*-TSA) to form dibenzoxanthenes. The reaction proceeds through the in situ formation of *ortho*-quinone methides (*o*-QMs) and 2-naphthol acts as a nucleophile. To expand this type of tandem process that would permit the condensation of the in situ generated *o*-QMs with nucleophiles other than phenols, we utilized urea, amides, and semicarbazide hydrochloride (to work as nucleophiles) to produce corresponding amidoalkyl and semicarbazonoalkyl naphthols.[12]

In the present study, we report our results on a new type of multicomponent reaction where five molecules react to form a piperidine ring. Thus, aromatic aldehydes, ammonium carboxylates, and 2,7-naphthalenediol are directly transformed into *N*-acyl-1,3-diaryl-4,9-dihydroxy-2,3-dihydro-2-azaphenalenes (Figure 1).

First, to evaluate the synthetic potential of the proposed procedure and to optimize the reaction conditions, the reaction of benzaldehyde, 2,7-naphthalenediol, and ammonium acetate was examined in different solvents such as ethanol, chloroform, acetonitrile, tetrahydrofuran, dimethyl formamide, and toluene under reflux conditions. As shown in Table 1, ethanol gave the most satisfactory results in comparison with other solvents.

A slight excess of the ammonium acetate was found to be advantageous and hence the molar ratio of 2,7-naphthalenediol to benzaldehyde and ammonium acetate was kept at 1:2:1.2.

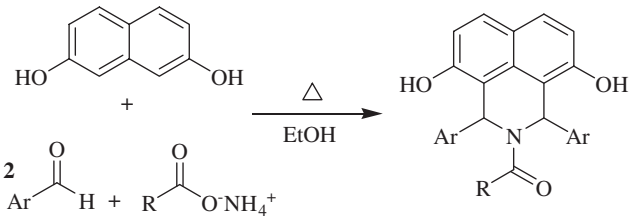

Figure 1. Synthesis of *N*-acyl-1,3-diaryl-2-azaphenalene derivatives.

Table 1. Solvent effect on the reaction of benzaldehyde, ammonium acetate, and 2,7-naphthalenediol

Entry	Solvent	Time/h	Yield/%[a]
1	Ethanol	6	91
2	Chloroform	15	<10
3	Acetonitrile	15	<10
4	Tetrahydrofuran	15	20
5	Dimethyl formamide	15	0
6	Toluene	15	0

[a]Isolated yields.

Encouraged by this result, the reaction of 2,7-naphthalenediol with various aromatic aldehydes, bearing electron-withdrawing groups (such as nitro and halide), electron-donating groups (such as methyl and methoxy), and ammonium acetate was carried out in ethanol under reflux conditions and afforded the corresponding *N*-acyl-1,3-diaryl-2-azaphenalene derivatives in good to high yields (Table 2).[14] To extend the preparative utility and generality of this multicomponent reaction, a variety of aromatic aldehydes were treated with 2,7-naphthalenediol and ammonium benzoate under the same experimental conditions, and the corresponding products were obtained in good to high yields without any difficulties (Table 2).[14] On the other hand, aliphatic aldehydes such as propionaldehyde or butyraldehyde and heterocyclic aldehydes such as 2-pyridinecarbaldehyde or furfural were also examined under the same conditions, but the corresponding products were isolated only in trace amounts.

Next we turned our attention to study the mechanistic aspect of this multicomponent reaction. Thus, the reaction of benzaldehyde with 2,7-naphthalenediol and ammonium acetate was chosen as a model reaction for this study. First, we attempted to explain the reaction with formation of acetamide from ammonia and ethyl acetate that can be formed from ethanol and acetic acid. Therefore, the reaction of 2,7-naphthalenediol with benzaldehyde and acetamide was carried out in ethanol or 1,2-dichloroethane similar to 2-naphthol in the synthesis of amidoalkyl naphthols,[12] but the reaction was unsuccessful. On the other hand, the reaction of 2,7-naphthalenediol, benzaldehyde, ammonia, and ethyl acetate was also examined and it was

Table 2. Synthesis of *N*-acyl-1,3-diaryl-4,9-dihydroxy-2,3-dihydro-2-azaphenalenes[13]

Entry	Ar (aldehyde)	R	Time/h	Yield/%[a]
1	C_6H_5	Me	5	86
2	4-MeC_6H_4	Me	5	84
3	4-FC_6H_4	Me	6	82
4	3-BrC_6H_4	Me	6	90
5	4-ClC_6H_4	Me	6	89
6	3-$MeOC_6H_4$	Me	7	86
7	3-$NO_2C_6H_4$	Me	10	86
8	2-ClC_6H_4	Me	8	78
9	4-HOC_6H_4	Me	7	81
10	C_6H_5	Ph	7	87
11	4-MeC_6H_4	Ph	6	85
12	4-$MeOC_6H_4$	Ph	8	83
13	3-ClC_6H_4	Ph	8	85
14	4-ClC_6H_4	Ph	6	88
15	4-BrC_6H_4	Ph	7	94

[a]Isolated yields.

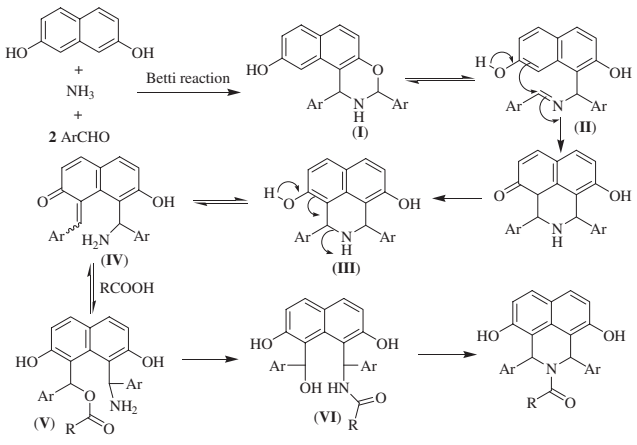

Figure 2. The most probable mechanism for synthesis of *N*-acyl-1,3-diaryl-2-azaphenalene derivatives.

found that 1,3-diaryl-2-azaphenalene derivatives **III** was obtained as an isolable intermediate. Also, remarkable solvent effect of ethanol can be explained by the fact that reactions involving imines and iminium ions, such as the Biginelli and the Ugi reactions are strongly favored by protic solvents.[15]

From these observations, the formation of product can be explained by the Betti reaction.[16] 2,7-Naphthalenediol can be reacted with benzaldehyde and ammonia in a molar ratio of 1:2:1 to yield naphthoxazine **I** or isomeric Schiff base **II** similar to 2-naphthol in the Betti reaction. In view of tautomeric capability of these condensation products,[17] the Schiff base intermediate furnished the 1,3-diaryl-2-azaphenalene derivatives upon an intermolecular cyclization and keto–enol tautomerization (Figure 2).

This intermediate **III** can be converted to intermediate **IV** and reacted with acetic acid to produce intermediate **V** (an explanation for this behavior might be the fact that the aromatic Mannich reaction is a reversible reaction[18]).

Finally, *N*-acyl-1,3-diaryl-2-azaphenalene derivatives can be obtained from intermolecular acylation of **IV** and intermolecular ring closure reaction of intermediate **VI**.

In conclusion, we have described a novel, efficient, and one-pot procedure for the preparation of *N*-acyl-1,3-diaryl-4,9-dihydroxy-2,3-dihydro-2-azaphenalenes from five-component condensation reactions of aromatic aldehydes, 2,7-naphthalenediol, and ammonium carboxylates in ethanol under reflux conditions. In addition to the efficiency and simplicity provided by this catalyst-free procedure, ease of workup, high yields of products, and environmental friendliness make the method advantageous.

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13 *General procedure:* A mixture of 2,7-naphthalenediol (1 mmol), aldehyde (2 mmol), and ammonium carboxylate (1.2 mmol) in ethanol (5 mL) was stirred under reflux conditions for an appropriate time as indicated in Table 2. The progress of the reaction was monitored by TLC. After completion of the reactions, the organic solvent evaporated and saturated aqueous NaCl (20 mL) was added to it, the suspension was stirred for 30 min and the precipitate filtered, washed with water and air-dried. The crude products were washed with mixture of ethyl acetate/*n*-hexane, (20 mL, 1:4) to afford the pure products.
14 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.
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