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Multicomponent Synthesis of Functionalized Tetrahydroacridinones: Insights into a Mechanistic Route

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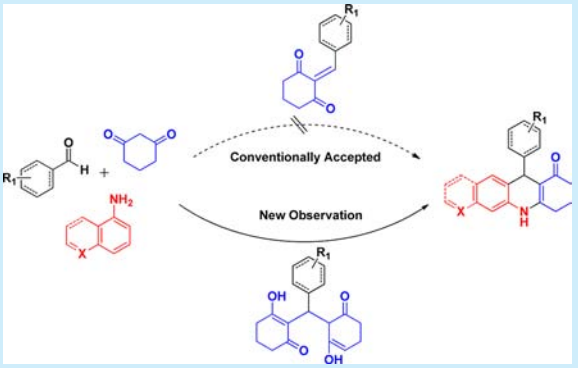
Supporting Information

ABSTRACT: A mechanistic study of three-component reactions of various aromatic amines with a number of aldehydes and 1,3-diones was achieved. The unprecedented reaction involved a nucleophilic attack of an aromatic amine on the in situ generated Michael adduct intermediate followed by six-electron ring cyclizations. It is contrary to the common belief that advocates involvement of coupling reactions between a Knoevenagel adduct and an aromatic amine to deliver substituted tetrahydroacridinones.



Multicomponent reactions (MCRs) play an important role in the synthesis of small organic molecules of biological importance. MCRs are chemical transformations that involve three or more reactants in a one-pot operation and yield compounds with high atom economy by incorporating all the reactants in the final product. MCRs also deliver products with a high degree of chemical and structural diversity. Their efficiency and the simplicity of the reaction procedures make MCRs cost-effective, time-efficient, and ecofriendly in comparison to conventional multistep synthesis.[1]

Over the years, three-component reactions of aromatic amines including 2-aminoimidazole with 1,3-dicarbonyl compounds and an aromatic aldehyde have been widely used for the synthesis of nitrogen-containing fused heterocycles owing to their diverse biological applications.[2] A number of heterocyclic compounds derived from these reactions are known for their important antibacterial, antimalarial, anti-inflammatory, and anticancer activities.[2,3] These acridine derivatives have also been found to have excellent electroluminescent properties and are widely used as pigments and dyes.[4] Recent examples of biologically active acridinones include the potential sirtuins inhibitor 1,8-dioxodecahydroacridine (**I**), the antimicrobial compound tetrahydrobenzo[*c*]acridin-8(9*H*)-one (**II**), and an aurora kinase inhibitor 1,4-dihydropyridine (**III**) (Figure 1).[5]

Researchers have developed a number of variants of three-component reactions utilizing microwave activation, ultrasonication, ionic liquid media, and solvent-free conditions.[6] Recent reports on diastereoselective reactions of 4-hydroxy-6-methyl-2*H*-pyran-2-one to produce pyrazolopyridinones and proline-promoted the regioselective synthesis of pyrimidoquinolinediones of barbaituric acid describe the power of multicomponent coupling reactions.[7] All of these transformations that involve 1,3-diketones, aldehydes, and amines were proposed to proceed through a Knoevenagel adduct, but no experimental proof of the mechanism is currently available.

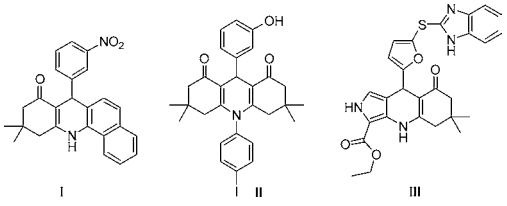


Figure 1. Biologically active dihydropyridines.

We recently attempted to synthesize a Knoevenagel adduct, 3-benzylidene-2,4-pentanedione (**K**), from benzaldehyde and 5,5-dimethylcyclohexane-1,3-dione under a number of reaction conditions. However, we found the Michael adduct **M1** is the sole product obtained rather than a Knoevenagel adduct. As all of the prior literature reports that three-component reactions of 1,3-diketones, benzaldehydes, and aromatic amines proceed via a mechanistic path involving the reactions of an amine with a Knoevenagel adduct intermediate, we decided to investigate these reactions in more detail.

Our study began with the synthesis of Knoevenagel adduct 3-benzylidene-2,4-pentanedione (**K**) from an equimolar quantity

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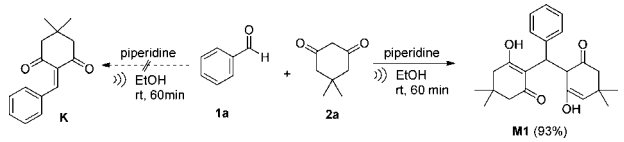
of benzaldehyde (**1a**) and 5,5-dimethylcyclohexane-1,3-dione (**2a**) in the presence of piperidine under ultrasonic activation for 60 min (Scheme 1).

Scheme 1. Reaction of Aldehyde and 1,3-Diketone



However, the only product isolated from the reaction mixture was a Michael adduct **M1** in 93% yield. In order to trap the reaction at 3-benzylidene-2,4-pentanedione stage, we used excess amount of benzaldehyde (2 equiv) to react with 5,5-dimethylcyclohexane-1,3-dione, and it was unfruitful. The only product observed was still Michael adduct **M1**, as suggested by a broad singlet at δ 11.80 (−OH) and singlet at δ 5.50 (Ph-CH) in the proton NMR of the isolated product. Our observation was further supported by a literature report on Knoevenagel condensation.[8] The structure of Michael adduct **M1** was further confirmed by single-crystal X-ray analysis (Figure 2). The "Y" shape of the three-dimensional structure of

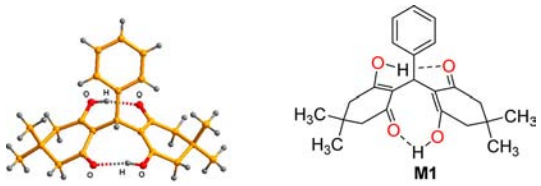


Figure 2. X-ray crystal structure and intramolecular hydrogen bonding of **M1**.

M1 is characterized by strong intramolecular hydrogen bonding between the hydroxyl groups of enol with a carbonyl group on the neighboring ring. It is clear that the benzylidene enone **K** is too short-lived and instantly undergoes 1,4-conjugate addition with enolizable ketone, i.e., 1,3-dione.

We reacted several aromatic aldehydes with 5,5-dimethylcyclohexane-1,3-dione to yield the corresponding Michael adducts (**M1**−**M5**) in the presence of piperidine under ultrasonication (Figure 3). Aliphatic aldehyde and cyclohexane carbaldehyde also reacted smoothly to give Michael adduct **M6**. To synthesize a Knoevenagel adduct, we treated several aromatic aldehydes to react with 5,5-dimethylcyclohexa-1,3-dione, following precedents in the literature.[9] However, the

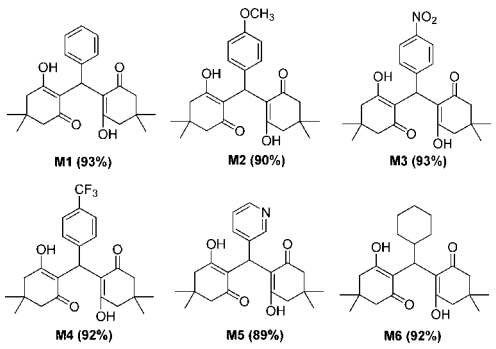
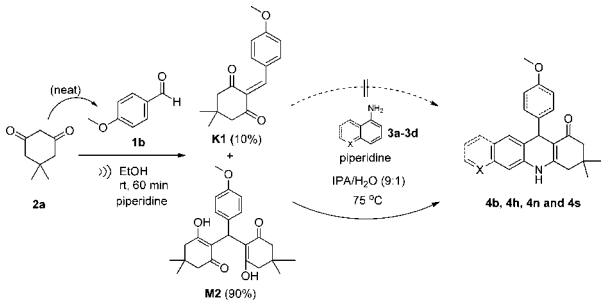


Figure 3. Preparation of Michael adducts **M1**−**M6**.

only products obtained using these prior studies were the corresponding Michael adducts.

Finally, we successfully synthesized a Knoevenagel adduct in 10% yield through the slow addition of 5,5-dimethylcyclohexane-1,3-dione (1 equiv) into an ethanolic solution of 4-methoxybenzaldehyde (1.2 equiv). Once the Knoevenagel adduct was rescued, we treated it immediately with various aromatic amines such as 3,4-(methylenedioxy)aniline (**3a**), 5-aminoindazole (**3b**), 5-aminoindole (**3c**) and 5-aminoquinoline (**3d**) in aqueous 2-propanol with piperidine under reflux conditions. To our surprise, none of the coupling reactions yielded MCR products and the intermediate Knoevenagel adduct was decomposed to aldehydes and 1,3 diketones in all cases (Scheme 2). The very fast formation of Michael adduct

Scheme 2. Reaction of Knoevenagel Adduct K1 and Substituted Aniline 3a−d



led us to speculate that it might play some roles in the three-component reactions. This prompted us to test the feasibility of a reaction between Michael adduct and an aromatic amine. Heating an equimolar solution of **M1** and 3,4-(methylenedioxy)aniline (**3a**) under the same reaction conditions to give 10-phenyl-6,7,8,10-tetrahydro[1,3]dioxolo-[4,5-*b*]acridin-9-(5*H*)-one (**4a**) smoothly as the single product.

Delighted with this observation, we treated a series of Michael adducts (**M1**−**M6**) with aromatic amines 3,4-(methylenedioxy)aniline (**3a**), 5-aminoindazole (**3b**), 5-amino-imidazole (**3c**), and 5-aminoquinoline (**3d**), which yielded the corresponding tetrahydroacridines **4a**−**u**. The results of this study are summarized in Table 1. The reaction time required for completion varied with the reactivity of the amines from 16 h for 3,4-(methylenedioxy)aniline to 5 days for 5-aminoquinoline (Table 1). All reactions produced yields as shown in Table 1, including those involving Michael adduct **M6**, synthesized from cyclohexane carbaldehyde, which resulted in moderate yields of 42−66%. The structures of the obtained MCR products were further confirmed using X-ray crystallographic studies of **4j** and **4l** (Figure 4).

The success of these transformations posed a question regarding the validity of the widely proposed and accepted mechanism of three-component reactions (Scheme 3).[10] This widely accepted mechanistic pathway involves formation of 3-benzylidene-2,4-pentanedione (**K**) via Konevengel condensation of an aldehyde with 1,3-dicarbonyl compound. Piperidine promotes the transformation by forming an iminium hydroxide intermediate with the aldehyde. Nucleophlic attack of amine nitrogen on β-carbon of enone **K** yields intermediates **8a**−**c** that subsequently undergo cyclization to generate hydroxyl-amine, which leads to observed product **4** after dehydration. The failure of a coupling reaction between a Knoevenagel

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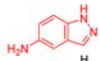
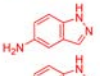
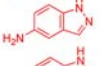
Table 1. Coupling Reactions of Aromatic Amines with Michael Adducts

product	Amine	M1-M6	time (h)	yield[b] (%)	product	Amine	M1-M6	time (h)	yield[b] (%)
4a		M1	16	79	4l		M6	16	49
4b		M2	16	82	4m		M1	12	91
4c		M3	24	92	4n		M2	24	70
4d		M4	30	75	4o		M3	24	56
4e		M5	12	89	4p		M4	24	85
4f		M6	24	42	4q		M5	24	85
4g		M1	16	81	4r		M1	120	70
4h		M2	16	86	4s		M2	120	86
4i		M3	24	78	4t		M4	120	81
4j		M4	30	92	4u		M6	120	66
4k		M5	18	76					

[a]Reactions were performed in the presence of piperidine (2 equiv). [b]Isolated yield after column purification.

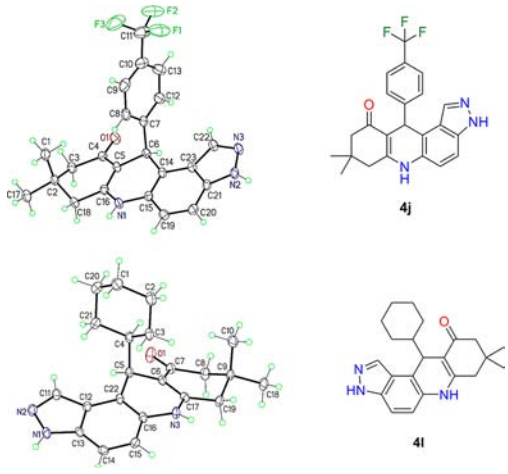
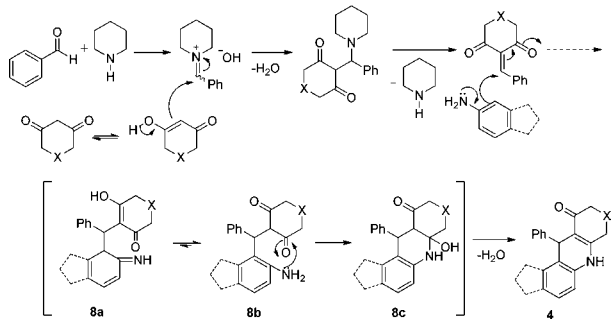


Figure 4. X-ray crystal structures of **4j** and **4l**.

adduct and aromatic amines authenticated our proposal that the Michael adduct is a key intermediate in this MCR reaction.

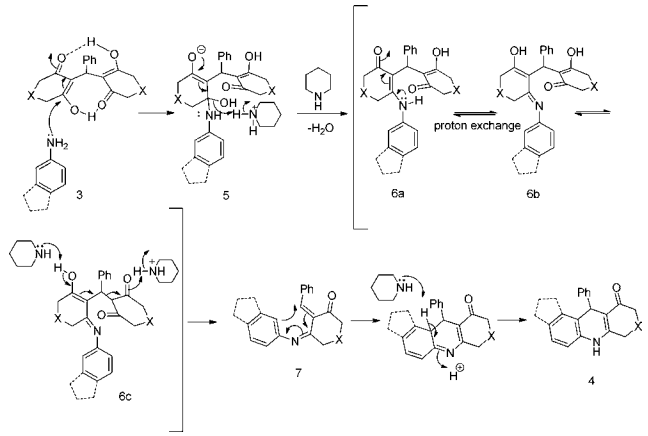
The reaction involves an initial nucleophilic attack of nitrogen of an aromatic amine on enol of **M1** to yield adduct **5** that, after dehydration, gives enaminone **6a**. The intramolecular hydrogen bonding in **M1** activates the enone toward nuleophilic attack. Imino enol **6b** undergoes a retro-aldol-type reaction via keto tautomer **6c** to produce aza-triene **7** and 1,3-diketone. The aza-triene **7** then undergoes six-electron thermal

Scheme 3. Commonly Proposed MCR Mechanism



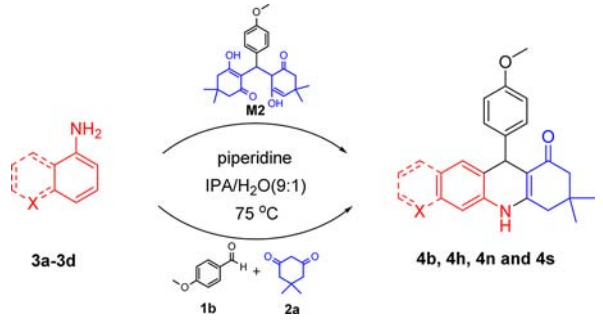
ring closure to produce the observed product **4** following aromatization (Scheme 4).

Scheme 4. Mechanistic Pathway for Reaction between Michael Adduct and Amine



Next, we performed competitive three-component reactions between 4-methoxybenzaldehyde, 5,5-dimethylcyclohexane-1,3-dione, and amines **3a−d**. The corresponding Michael adduct **M2** was also reacted with amines **3a−d**. The results of these reactions are summarized in Scheme 5 and Table 2. To our

Scheme 5. Competitive Three-Component Reactions Performed As Part of This Study



delight, the reactions produced comparable yields under identical conditions. These observations also support our claim regarding the mechanistic path of these reactions. This new understanding of reaction routes of three-compound reactions can be expected to enhance the design of new reaction methodologies and procedures that will allow the synthesis of interesting molecular scaffolds.

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Table 2. Competitive Reactions Using Michael Adducts M2 vs MCR

	Michael adducts (M2)		three-component	
product	reaction time (h)	yield (%)	reaction time (h)	yield (%)
4b	16	82	16	78
4h	16	86	16	80
4n	24	70	24	65
4s	120	86	120	84

We have presented the results of a novel mechanistic investigation of the three-component reactions involving a 1,3 dione, an aldehyde, and an aromatic amine to synthesize the corresponding acridine derivatives. The isolation of a Michael adduct by the reaction of an aldehyde with a 1,3-dicarbonyl compound and its subsequent reaction with an amine yielded the acridine accordingly. Our observations contradict the common belief that the key step in this MCR occurs through the formation of a Knoevenagel adduct. This mechanism study is expected to broaden the new understanding of this MCR that is proposed to involve highly reactive Knoevenagel adducts. It is hoped that this contribution will eventually lead to the development of better synthetic strategies for other biologically interesting compounds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02705.

Experimental details plus spectroscopic and other data for compounds **M1**−**M4**, **K1**, and **4a**−**u** (PDF)
X-ray data for **4c** (CIF)
X-ray data for **4d** (CIF)
X-ray data for **4e** (CIF)
X-ray data for **4j** (CIF)
X-ray data for **4l** (CIF)
X-ray data for **4r** (CIF)
X-ray data for **4s** (CIF)

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Notes

The authors declare no competing financial interest.

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