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Unprecedented Bridged Annulation Approach to the Construction of 5,6-Dihydro-4*H*-benzo[*kl*]acridines†

Atul Goel,*,‡ Salil Pratap Singh,‡ Amit Kumar,‡ Ruchir Kant,§ and Prakas R. Maulik§

Divisions of Medicinal and Process Chemistry, Molecular and Structural Biology Central Drug Research Institute, CSIR, Lucknow 226001, India

atul_goel@cdri.res.in

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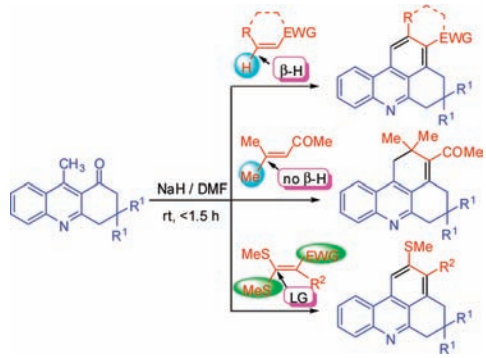
ABSTRACT



A general and novel "bridged annulation" methodology for the synthesis of 5,6-dihydro-4*H*-benzo[*kl*]acridines has been developed via Michael addition of a conjugate base of 9-methyl-3,4-dihydroacridin-1(2*H*)-one to various cyclic or acyclic α,β-unsaturated carbonyl/nitrile compounds under mild conditions at room temperature in a short time. To the best of our knowledge, such a general bridged annulation for the synthesis of fused N-heterocycles has not been reported in the literature.

Quinoline, acridine, and related N-heterocyclic systems like annulated phenanthridine are key structural motifs found in a large number of biologically important natural alkaloids isolated from plant and marine sources and represent privileged scaffolds in medicinal chemistry.[1,2] Among them, those bearing an acridine moiety display a wide range of pharmacological activities such as antiviral,[3] antimalarial,[4] antihelmintic,[5] antifungal,[6] antitumor,[7] stimulative,[8] and other activities.[9] As a consequence, numerous methods for the preparation of quinolines,[1,10,11] acridines,[12] and phenanthridines[13] have been described.

During our drug development program, we became interested in preparing novel quinolines, acridines, and their annulated compounds through our recently developed ring transformation strategy.[14] Our ring transformation approach involves the conversion of a 2-pyranone ring into an aromatic ring by reacting a pyranone with an active methylene

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‡ Division of Medicinal and Process Chemistry.
§ Division of Molecular and Structural Biology.

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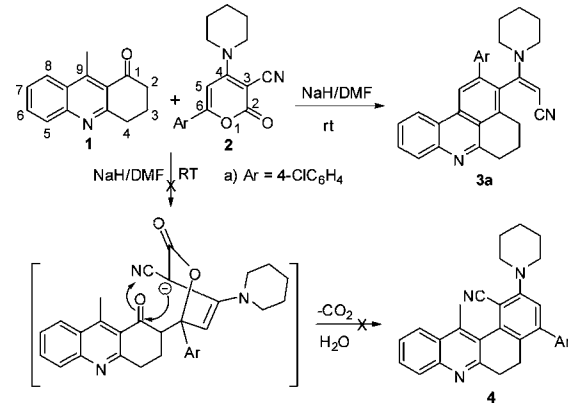
compound under mild basic conditions at room temperature.[15] Very recently, we have demonstrated that our methodology can be applied to prepare fluorescent blue materials for efficient organic light emitting diodes.[16] To prepare various N-heterocyclic compounds under a drug development program, various quinoline fused cyclic ketones were desirable that could enable us to perform unprecedented transformations.

Among various approaches reported for the synthesis of these N-heterocycles, Friedlaender annulation is one of the most effective and simplest protocols.[17] In this approach, an aromatic amine having an ortho-tethered enal or enone functionality is involved in an intramolecular cyclization reaction to furnish the desired N-heterocycles. We found the Brønsted acid-catalyzed Friedlaender annulation protocol to be suitable for preparing various N-heterocyclic substrates such as 9-methyl-3,4-dihydroacridin-1(2*H*)-one (**1**, **5**).[18] These reactions are advantageous since they include important "green" chemistry factors such as atom economy,[19] reduction of synthetic steps, and minimization of solvents and waste.[20]

When we applied our ring transformation strategy[14] to prepare 5,6-dihydrobenzo[*a*]acridine (**4**) using substrate 9-methyl-3,4-dihydroacridin-1(2*H*)-one (**1**, 1 mmol) and 6-(4-chlorophenyl)-2-oxo-4-(piperidin-1-yl)-2*H*-pyran-3-carbonitrile[14] (**2a**, 1 mmol) in the presence of NaH (1.5 mmol) in DMF at room temperature for 1 h, we unexpectedly obtained 3-(2-(4-chlorophenyl)-5,6-dihydro-4*H*-benzo[*kl*]acridin-3-yl)-3-(piperidin-1-yl)acrylonitrile (**3a**) in 54% yield (Scheme 1).

Scheme 1. Synthesis of 5,6-Dihydro-4*H*-benzo[*kl*]acridine (**3a**)



The structure of the compound **3a** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1). The

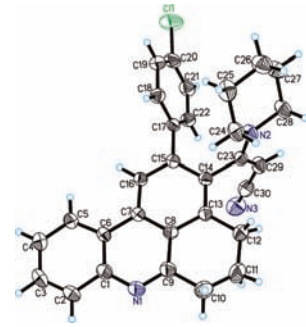


Figure 1. ORTEP diagram of compound **3a**.

formation of the compound **3a** in lieu of **4** revealed that the reaction proceeded through a carbanion generated from a methyl group at position 9 instead of a methylene group at position 2 of a ketone **1** as shown in Scheme 1.

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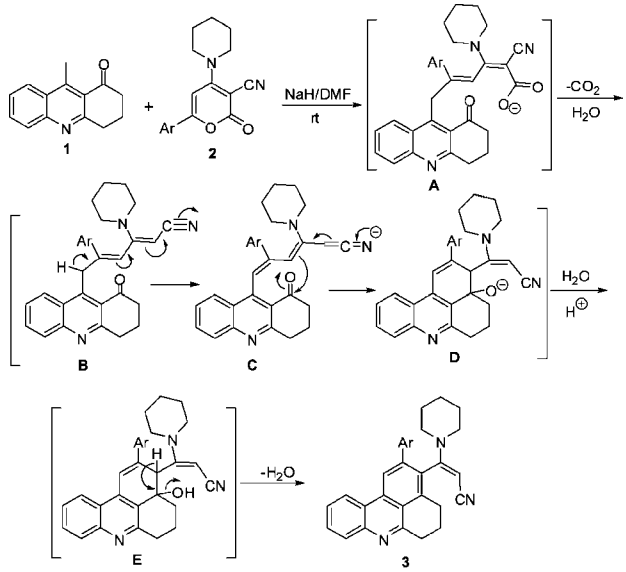
To generalize the reaction, various functionalized 2*H*-pyran-2-ones[14,15] (**2b**−**e**) were reacted with the cyclic ketone **1** to furnish 5,6-dihydro-4*H*-benzo[*kl*]acridines (**3b**−**e**) in a single step at room temperature (Scheme 2). A plausible

Scheme 2. Synthesis of 5,6-Dihydro-4*H*-benzo[*kl*]acridines (**3a**−**e**)



mechanism for the formation of **3a**−**e** is depicted in Scheme 2, which revealed that reaction is possibly initiated by the attack of a carbanion of **1** at the C-6 position of 2-pyranone (**2**) followed by ring opening, decarboxylation, and intramolecular cyclization involving the C-5 position of 2-pyranone and carbonyl functionality of the ketone (**1**) to afford 5,6-dihydro-4*H*-benzo[*kl*]acridines (**3a**−**e**). It is interesting to note that only C-5 and C-6 positions of the 2-pyranone (**2**) are involved in the construction of an aromatic bridged ring.

With the success of this new protocol, we thus envisaged that this unexpected new "bridged annulation" approach would allow us to prepare a wide selection of N-heterocyclic compounds using readily available functionalized α,*β*-unsaturated electron-withdrawing compounds. Accordingly, several α,*β*-unsaturated compounds (**6a**−**d**) having electron-withdrawing carbonyl or nitrile functionality were treated with 9-methyl-3,4-dihydroacridin-1(2*H*)-ones (**1**, **5**) in the presence of NaH in DMF at room temperature, which furnished 5,6-dihydro-4*H*-benzo/naphtho[*kl*]acridines (**7a**−**f**) in good yields (Scheme 3).

We observed that both cyclic and acyclic α,*β*-unsaturated compounds (**2a**−**e**, **6a**−**d**) displayed appreciable reactivity under these reaction conditions delivering acridine-fused polycycles in a single step. To the best of our knowledge, such bridged annulation has not been reported in the literature prior to this study.

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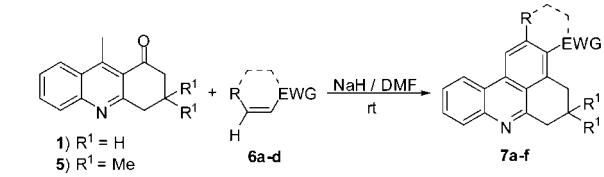
Scheme 3. Synthesis of N-Heterocycles (**7a**−**f**) Using Cyclic or Acyclic α,*β*-Unsaturated Electron-Withdrawing Compounds



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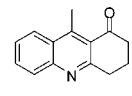
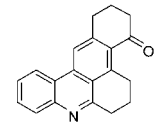
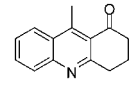
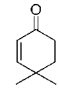
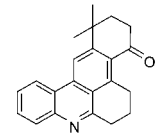
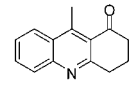
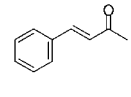
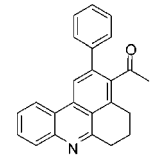
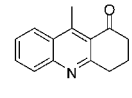
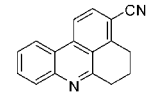
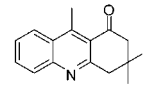
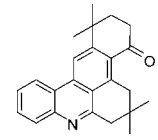
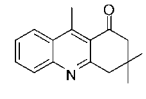
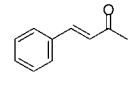
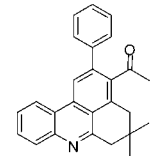
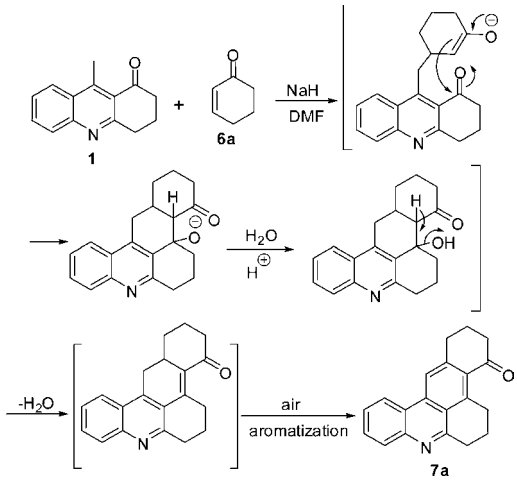
a				64
b				72
c				88
d				55
e				60
f				64

The plausible mechanism for the formation of one of the compounds **7a** is depicted in Scheme 4. Reaction is possibly initiated by Michael addition of a conjugate base of **1** at the *β*-position of cyclohexenone (**6a**) followed by intramolecular cyclization involving the α-position of **6a** and carbonyl functionality of the ketone (**1**) and further aromatization in air to afford 2,3,6,7-tetrahydro-1*H*-naphtho[1,2,3-*kl*]acridin-4(5*H*)-one (**7a**).

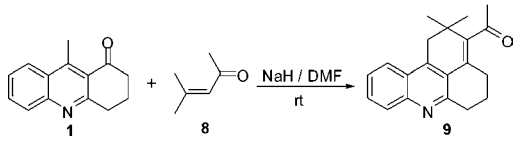
From the proposed mechanism, it is evident that an "H-atom" at the α- and *β*-positions of the Michael acceptor is involved in the aromatization of a newly formed bridged ring, and the presence of *β*-H favors aerial oxidation as shown in Scheme 4. To test this observation, an independent reaction was attempted with 4-methylpent-3-en-2-one (**8**) having no "*β*-H" as shown in Scheme 5.

Scheme 4. Plausible Reaction Mechanism for **7a**



The isolated compound was characterized as 1-(2,2-dimethyl-2,4,5,6-tetrahydro-1*H*-benzo[*kl*]acridin-3-yl) ethanone **9**, which indicated that β-H is essential for aromatization of the newly formed bridged ring. On the contrary, if

Scheme 5. Reaction of **1** with **8** Having No β-H



we look at the case in Scheme 2, where there is no "H" at position 6 of the pyranone ring, we obtained the aromatized products (**3a**−**f**). The proposed mechanism revealed that a good "leaving group (LG)" may lead to aromatization of the bridged ring.

Thus, a few Michael acceptors (**10**−**12**)[21] with a good leaving group at the β-position of α,β-unsaturated carbonyl compounds were prepared to confirm this bridged annulation reaction, and results are shown in Scheme 6. The reaction is possibly initiated by addition of a conjugate base of **1** (or **5**) to the β-position of a Michael acceptor (**10**−**12**), followed by elimination of the methylsulfanyl anion and intramolecular cyclization to furnish intermediate A. This intermediate A in the presence of the methylsulfanyl anion may undergo elimination of thiolester to afford 2-(methylsulfanyl)-5,6-dihydro-4*H*-benzo[*kl*]acridines (**13**−**15**) in good yields.

This new bridged annulation under mild basic conditions provides simple access to compounds with functional group diversity by changing the substitution pattern either on 9-methyl-3,4-dihydroacridin-1(2*H*)-one (**1**, **5**) or taking different Michael acceptor groups. The procedure may be

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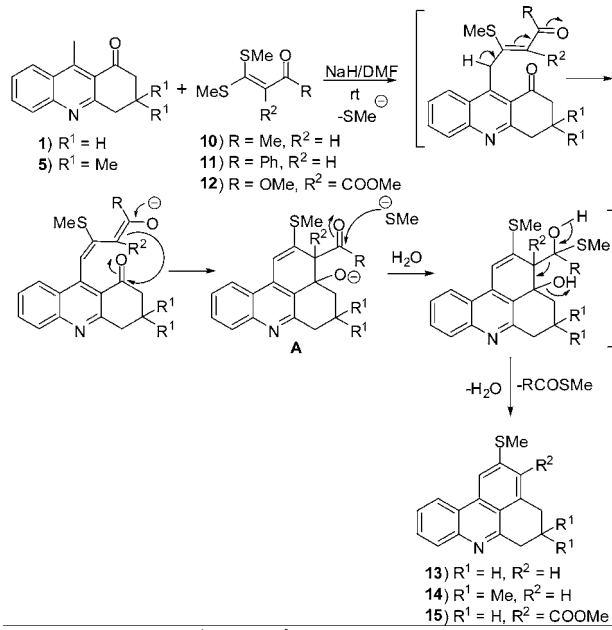
Scheme 6. Synthesis of 2-Methylsulfanyl-5,6-dihydro-4*H*-benzo[*kl*]acridines (**13**−**15**)



entry	R	R^1	R^2	isolated compound	reaction time(min)	yield (%)
1	Me	H	H	**13**	10	65
2	Ph	H	H	**13**	20	60
3	Me	Me	H	**14**	15	72
4	Ph	Me	H	**14**	22	65
5	OMe	H	COOMe	**15**	30	52

applied to the synthesis of quinoline or acridine-based alkaloids for drug development perspectives.

In summary, we have developed a novel and efficient bridged annulation strategy for the synthesis of a variety of 5,6-dihydro-4*H*-benzo[*kl*]acridines by the base-assisted Michael addition of a conjugate base of **1** (or **5**) to the β-position of the Michael acceptor. It is demonstrated that an H-atom at the α- and β-positions of the Michael acceptor is involved in the aromatization of a newly formed bridged ring, and the presence of β-H favors aerial oxidation. In the absence of β-H at the Michael acceptor, a good leaving group at the β-position facilitates the reaction toward aromatization of a newly formed bridged ring. This general methodology may be useful to synthesize a variety of N-heterocyclic compounds from readily available starting materials.

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Supporting Information Available: Complete experimental details, characterization data of the compounds **3a**−**e**, **7a**−**f**, **9**, and **13**−**15** and X-ray data of **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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