One-Pot DBU-Promoted Synthesis of Hydroacridinones and Spirohexahydropyrimidines

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Abstract: The potential hydroacridinone synthesis using simple and inexpensive starting materials, namely 1,3-dicarbonyl compounds, anilines, formaldehyde and DBU as a stoichiometric base was explored. As a result, from the reaction of 1,3-cyclohexanedione and dimedone tetrahydroacridinones were the main reaction products along with small yields of their oxidation products, the dihydroacridinones, whereas in the case of 2-acetylcyclohexanone spirohexahydropyrimidines were isolated in very good yields. Plausible mechanistic schemes for the formation of all products are proposed.

Key words: acridinones, aza-annulation, DBU as catalyst, 1,3-diones, spiropyrimidines

The vast majority of nature's molecules including proteins, nucleic acids and most biologically active compounds contain nitrogen. Consequently, developing new synthetic methods for the construction of nitrogenous molecules has defined the frontiers of organic synthesis since its very beginning.[3] Among them, acridine and its derivatives play an important role in medicinal chemistry. For example, tacrine is not only a well-known acridine drug, for the treatment of Alzheimer's disease[4] (AD) but also useful for the treatment of the central anticholinergic syndrome.[5] Velnacrine and suronacrine, structurally similar to tacrine (Figure 1), inhibit acetyl cholinesterase in vitro and are active in a model that may be predictive of AD, but have less acute toxicity in rats and mice.[6] Amsacrine is one of the first DNA-intercalating agents to be considered as a topoisomerase II inhibitor.[7] In addition, acridine derivatives display a wide range of antiviral,[8] antihelminthic,[9] and antitumor[10] activities. Moreover, acridine and acridinone are chemical families with derivatives demonstrating strong antimalarial activity.[11,12]

Concerning the synthesis of 1-acridinone derivatives no systematic study has been described, although some reports referring to the synthesis of 3,4-dihydro-1(2*H*)-acridinone or its 3,3-dimethyl derivative can be found in the literature,[13] using as starting materials either 2-amino- or 2-bromo-substituted aryl aldehydes and 1,3-cyclohexanediones. In addition, a microwave-assisted synthesis of some 9-aryl-3,3-dimethylhexahydro-1-acridinones has been reported.[14]

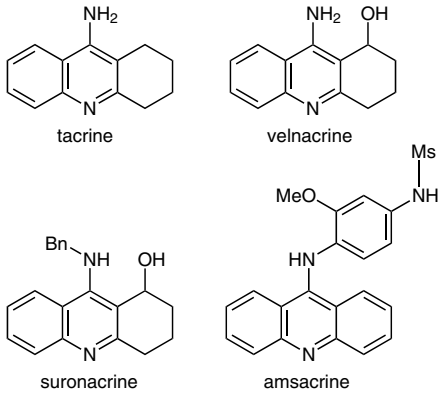

Figure 1 Selected examples of bioactive acridine derivatives

Among the various methods for the synthesis of such molecules, the initial step of a Knoevenagel condensation between 1,3-cyclohexanediones and aldehydes followed by reaction with an aniline would be a method of choice. Indeed, the method has been followed by using mainly heterocyclic amines leading to the synthesis of pyrazolo and triazolo heterocycles,[15] and also podophyllotoxin[16] derivatives. Naphthylamine and 6-aminoquinoline are also reported to follow an analogous reaction pathway leading to the isolation of phenanthroline derivatives.[17] In addition, recently the reaction between dimedone, aryl aldehydes and naphthylamine was reinvestigated by using L-proline, as an organocatalyst, whereupon tetrahydrobenzoacridinones were isolated.[18] To the contrary, from the reaction between anilines, formaldehyde and cyclic β-diketones 3,5-dispiropiperidines were isolated[19] in good yields, also when either homogeneous [$FeCl_3$, $In(OTf)_3$] or heterogeneous (silica tungstic acid) catalysts were used,[20] whereas formation of acridinones was not reported. When the same reaction was repeated in glycerol at 100 °C for two hours phenylaminocyclohexenyl cyclohexenones were formed through a Hantzsch reaction.[21] These results prompted us to re-examine the reaction between cyclic 1,3-diones, formaldehyde, and substituted anilines using DBU as a stoichiometric base reaction promoter, in an attempt to force the reaction to follow a pathway leading to the formation of hydroacridinones, since as it has been already mentioned that no systematic study leading to their synthesis has been reported.

Our initial studies were conducted with dimedone, formaldehyde and *p*-anisidine (**2c**) as follows: a mixture of *p*-anisidine (1 equiv), formaldehyde (9 equiv, 36% aqueous

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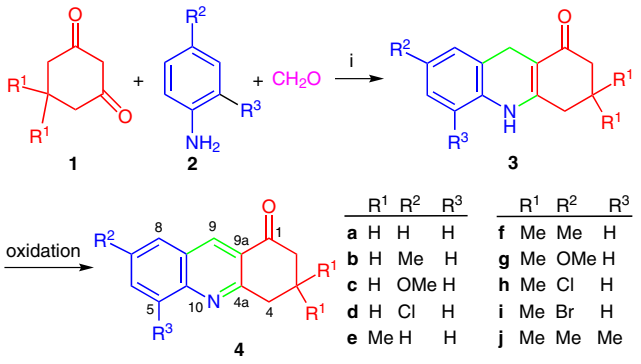
solution), dimedone (1 equiv) and DBU (1 equiv) in ethanol (20 mL) was refluxed for 10 minutes to dissolve all the reactants and then the reaction mixture was stirred at room temperature for three hours (Scheme 1). The product, which was isolated after purification on column chromatography, was identified as acridinone **3g**. This result prompted us to examine the generality of the reaction and the results summarized in Table 1 show that the reaction has a broad applicability. Indeed, by following the same experimental procedure, acridinones **3** were isolated from all studied reactions in good yields (55–73%, Table 1). Sometimes, small amounts (5–10%) of their air-oxidized derivatives, namely the dihydroacridinones **4**, were also isolated. In all cases compounds **3** could be easily oxidized quantitatively to the dihydro derivatives **4** with *p*-benzoquinone. All compounds **3** and **4** are novel with the exception of compounds **4a** and **4f**, which were prepared from 2-amino- or 2-bromo-substituted aryl aldehydes and 1,3-cyclohexanediones.[13]

Table 1 Reactions of Cyclohexane-1,3-diones with *p*-Substituted Anilines and Aqueous Formaldehyde[22]

Entry	R^1	R^2	R^3	Product (%)	
1	H	H	H	**3a** (69)	**4a** (–)
2	H	Me	H	**3b** (70)	**4b** (4)
3	H	OMe	H	**3c** (73)	**4c** (6)
4	H	Cl	H	**3d** (65)	**4d** (–)
5	Me	H	H	**3e** (70)	**4e** (–
6	Me	Me	H	**3f** (73)	**4f** (5)
7	Me	OMe	H	**3g** (69)	**7g** (7)
8	Me	Cl	H	**3h** 61)	**4h** (–)
9	Me	Br	H	**3i** (55)	**4i** (–)
10	Me	Me	Me	**3j** (62)	**4j** (10)

Conclusively, as shown in Scheme 2, the reaction between dimedones, formaldehyde and anilines greatly depends on the reaction conditions.



Scheme 1 DBU-promoted reaction of cyclohexan-1,3-diones with substituted anilines and formaldehyde. *Reagents and conditions*: (i) DBU, EtOH, reflux for 10 min followed by stirring at r.t. for 3 h.

Table 2 Investigation of Base-Promoted Mannich-Type Reaction Conditions on 2-Acetylcyclohexanone leading to the Formation of Spirohexahydropyrimidines **12**

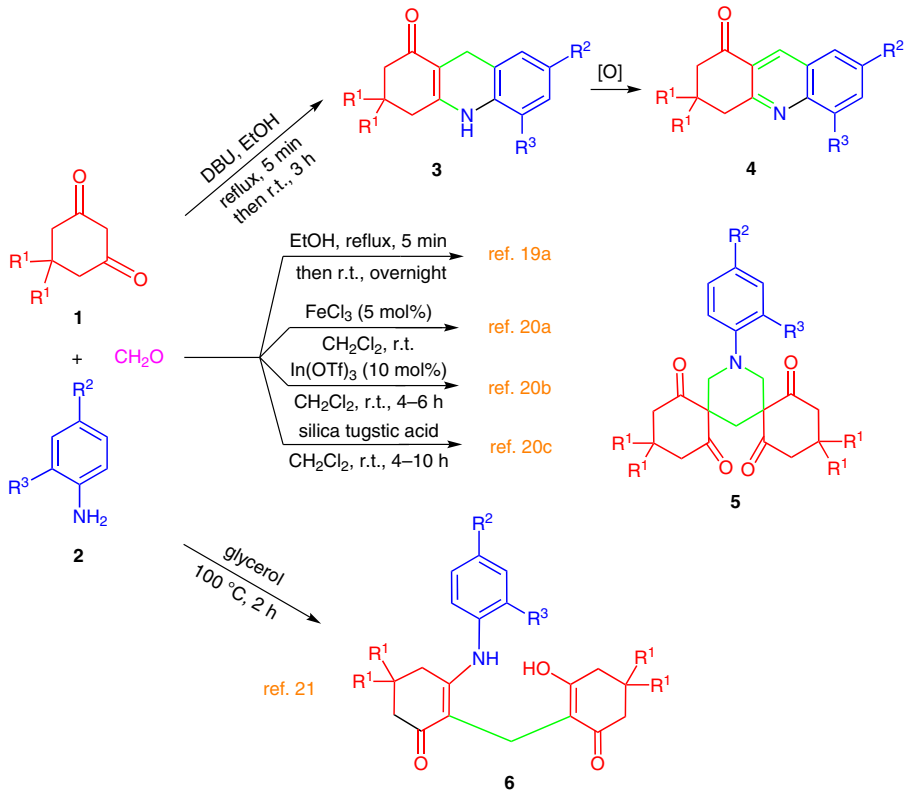
Entry	Amine	Catalyst	Yield (%)
1	**2c**	DBU	**12c** (79)
2	**2c**	K_2CO_3	**12c** (77)
3	**2c**	DABCO	–
4	**2a**	DBU	**12a** (68)
5	**2b**	DBU	**12b** (70)
6	**2d**	DBU	**12d** (61)

A possible mechanism for the formation of the acridinone system is outlined in Scheme 3. Initially, the DBU-catalyzed Knoevenagel condensation leads to the formation of adduct **7**, which suffers a nucleophilic addition of the aniline to one of the carbonyl carbons. Most probably, the abstraction of the labile hydroxyl group of intermediate **8** is the driving force for the facile cyclization reaction without any dismutation reaction.

Thus, after water elimination, the intermediate imine adduct **9** undergoes an electrocyclic ring closure to intermediate **10**, and through hydrogen shift and aromatization of one ring compound **3** is formed. Finally, air oxidation of **3** leads through aromatization of one more ring to the more stable core of dihydroacridinone **4**.

Next, in continuation of the above studies an analogous DBU-promoted reaction was conducted with 2-acetylcyclohexanone (**11**), formaldehyde and *p*-anisidine (Scheme 4). The product, which was isolated after purification on column chromatography, was identified as 2,4-bis(4-methoxyphenyl)-2,4-diazaspiro[5.5] undecan-7-one (**12c**) in 79% yield. The reaction proceeded analogously affording **12c** in 77% yield, when K_2CO_3 was used as a base. In contrast, when 1,4-diazabicyclo[2.2.2]octane (DABCO) was used, minor amounts of some unidentified products were formed, whereas in the absence of a base the anilinomethylcyclohexanone derivative **13c** was isolated. These results prompted us to use other amines (Table 2) and in all cases, the corresponding spirohexahydropyrimidines **12** were isolated as the only reaction products in very good yields (61–79%). It is noteworthy that the formation of the same spirohexahydropyrimidines **12** via proline-catalyzed condensation of cyclohexanone with anilines and aqueous formaldehyde has been reported.[23] Moreover, recently we have studied the acid-catalyzed reaction between 2-acetylcyclohexanone, formaldehyde and anilines, whereupon by a double-Mannich annulation the azabicyclononanones **14** were isolated[24] (Scheme 4). In this way, it is established that the reaction pathway greatly depends on the reaction conditions.

Concerning a tentative reaction mechanism, it should be noticed that most probably, due to the lack of a methylene group between the two carbonyls, the reaction prefers to follow a different pathway (Scheme 5). Thus, 2-acetylcy-



Scheme 2 Reaction of cyclohexan-1,3-diones with substituted anilines and formaldehyde under various conditions

clohexanone after initial aminomethylation to the Mannich product **13** is deacetylated by DBU,[25] possibly through intermediate **15** to intermediate **17**, which is subjected to a second aminomethylation to give the intermediate propane-1,3-diamine **18**. Next, subsequent condensation of **18** with the excess of formaldehyde leads to the isolated 1,3-diaryl-5-spirohexahydropyrimidine **12**.

The structural characterization of all compounds **3**, **4**, and **12** was based on rigorous spectroscopic analysis IR, NMR (^{1}H, ^{13}C, DEPT, COSY, NOESY, HMQC and HMBC), mass spectra and elemental analysis data. In Figure 2, the HMBC correlations between protons and carbons via $^2J_{C–H}$ and $^3J_{C–H}$ in compounds **3f** and **4f** are depicted.

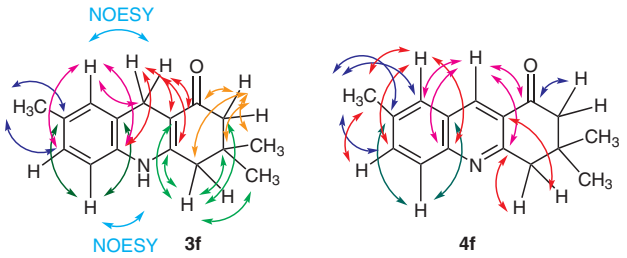
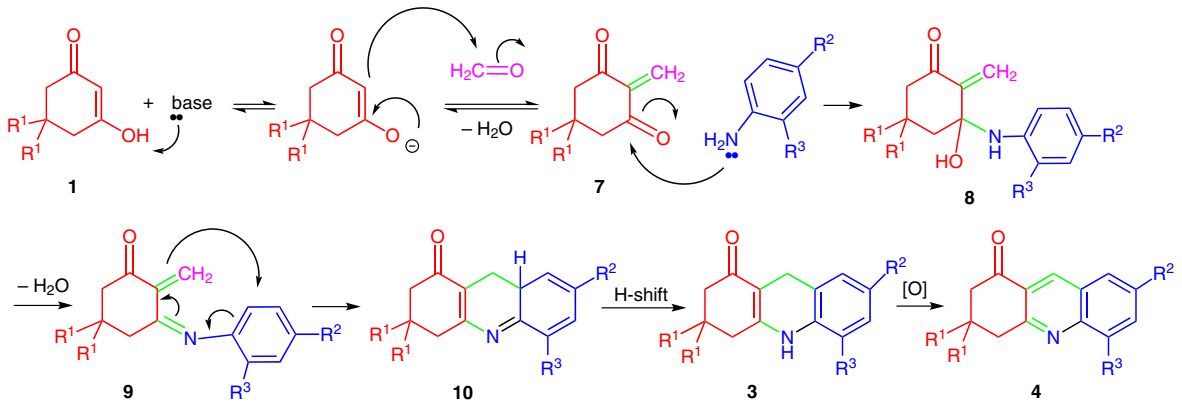
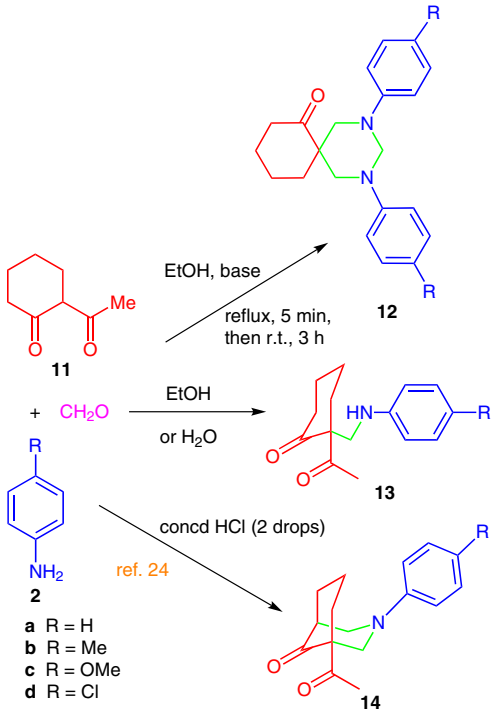


Figure 2 HMBC correlations between protons and carbons via $^2J_{C–H}$ and $^3J_{C–H}$ in compounds **3f** and **4f**

In conclusion, by using DBU as a base reaction promoter, we have developed a simple and efficient one-pot condensation of substituted anilines, aqueous formaldehyde and



Scheme 3 Mechanistic rationalization for the formation of acridinones **3** and **4**



Scheme 4 Reaction of 2-acetylcyclohexanone with substituted anilines and formaldehyde, under various reaction conditions; for bases used to obtain compounds **12**, see Table 2

1,3-dicarbonyl compounds leading to the synthesis of tetrahydro- and dihydroacridinones, belonging to a class of pharmacologically interesting compounds. Simplicity of operation, high yields, easy workup and a wide range of substrate applicability are the key advantages of the methodology. Moreover, it should be pointed out that all of the previously described methodologies involving condensation of anilines, aqueous formaldehyde and 1,3-dicarbonyl compounds without a base reaction promoter resulted in the formation of dispiropiperidines. By using 2-acetylcyclohexanone, through an unexpected reaction, spirohexahydropyrimidines were isolated and it is well known that various natural products and pharmaceutical agents containing the hexahydropyrimidine moiety exhibit a broad range of biological activities.[26]

References and Notes

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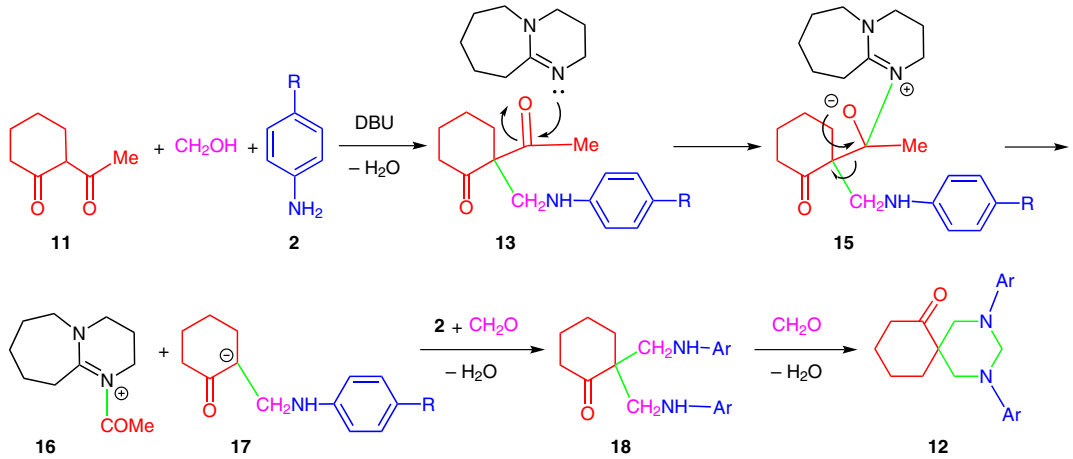

Scheme 5 Mechanistic rationalization for the formation of spirohexahydropyrimidines **12**

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(22) **General Experimental Procedure for the DBU-Promoted Mannich Reaction**: A mixture of 4-methylaniline (1.0 mmol), formaldehyde (9 equiv, 36% aq solution), DBU (1 equiv) and dimedone (1 equiv) in EtOH (20 mL) was refluxed for 10 min to dissolve all the reactants, and then the reaction mixture was stirred for 3 h at r.t. The solvent was distilled off and the resulting residue was subjected to column chromatography on silica gel using petroleum ether–EtOAc (10:1) as eluent, to give the product **3f** along with a small amount of **4f**. In an analogous manner, using 2-acetylcyclohexanone (2.0 mmol) product **10b** was isolated. (a) 3,3,7-Trimethyl-3,4,9,10-tetrahydroacridin-1(2*H*)-one (**3f**): white crystals; mp 230–232 °C; yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09 (s, 6 H, 2 × Me, 3-Me), 2.236 (s, 2 H, 4-H), 2.245 (s, 3 H, 7-Me), 2.27 (s, 2 H, 2-H), 3.67 (s, 2 H, 9-H), 5.87 (br s, 1 H, NH), 6.50 (d, *J* = 7.9 Hz, 1 H, 5-H), 6.85 (dd, *J* = 7.9, 1.7 Hz, 1 H, 6-H), 6.91 (d, *J* = 1.7 Hz, 1 H, 8-H). ^{13}C NMR (300 MHz, $CDCl_3$): δ = 20.7 (7-Me), 24.2 (C-9), 28.5 (2 × Me, 3-Me), 32.6 (C-3), 42.4 (C-4), 50.7 (C-2), 104.3 (C-9a), 114.6 (C-5), 122.8 (C-8a), 127.4 (C-6), 130.5 (C-8), 133.1 (C-7), 134.2 (C-10a), 151.3 (C-4a), 194.8 (C-1). LC–MS (ESI, 1.65 eV): *m*/*z* = 242 (100) $[M + H]^+$. Anal. Calcd for $C_{16}H_{19}NO$ (241.33): C, 79.63; H, 7.94; N, 5.80. Found: C, 79.78; H, 7.78; N, 5.96. (b) 3,3,7-Trimethyl-3,4-dihydroacridin-1(2*H*)-one (**4f**): white crystals; mp 95–97 °C; yield: 73%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.15 (s, 6 H, 2 × Me, 3-Me), 2.54 (s, 3 H, 7-Me), 2.64 (s, 2 H, 2-H), 3.18 (s, 2 H, 4-H), 7.62 (dd, *J* = 8.6, 1.7 Hz, 1 H, 6-H), 7.68 (d, *J* = 1.7 Hz, 1 H, 8-H), 7.94 (d, *J* = 8.6 Hz, 1 H, 5-H), 8.73 (s, 1 H, 9-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (7-Me), 28.4 (2 × Me, 3-Me), 32.8 (C-3), 47.2 (C-4), 52.6 (C-2), 125.4 (C-9a), 126.9 (C-8a), 128.36 (C-8), 128.42 (C-5), 134.6 (C-6), 135.8 (C-9), 136.7 (C-7), 148.8 (C-10a), 160.0 (C-4a), 198.1 (C-1). LC–MS (ESI, 1.65 eV): *m*/*z* = 240 (100) $[M + H]^+$. Anal. Calcd for $C_{16}H_{17}NO$ (239.31): C, 80.30; H, 7.16; N, 5.85. Found: C, 80.60; H, 7.18; N, 6.05.

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