Tetrahedron Letters 53 (2012) 4573–4575

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An unexpected multicomponent reaction leading to 2-arylpyrrolo[2,3,4-*kl*]acridin-1(2*H*)-ones

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ARTICLE INFO

Article history:
Available online 19 June 2012

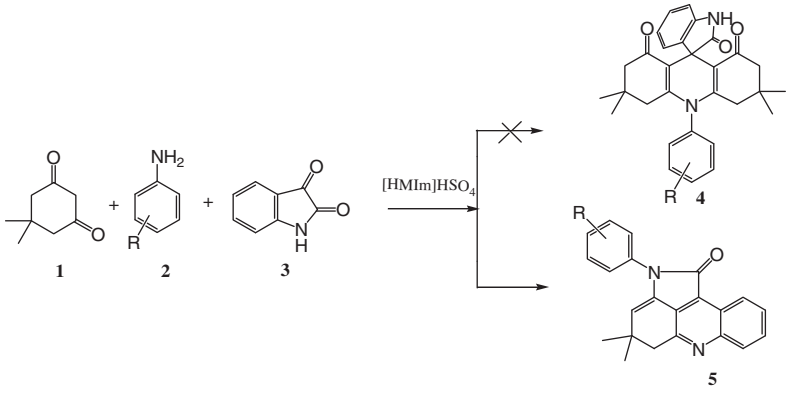
Keywords:
Multicomponent reaction
Pyrroloacridine
Ionic liquid
Dimedone
Isatin

ABSTRACT

An unexpected condensation profile was observed for the three-component reaction of 5,5-dimethyl-1,3-cyclohexadione (dimedone), various anilines, and isatin leading to the synthesis of novel 2-arylpyrrolo[2,3,4-*kl*]acridin-1(2*H*)-ones in the ionic liquid [HMIm]HSO_4. Regeneration of the enamine group after the initial condensation reaction associated with participation of the restored amine group in translactonization with the pyrrolidone ring are suggested as the main differentiating events being favored over addition of the second dimedone molecule, with respect to similar reported reactions.

Pyrroloacridines and pyrroloacridones show a wide spectrum of biological activities such as anthelmintic,[1] antitumor,[1,2] and antifungal.[3] Some of these compounds inhibit the growth of cancerous cells via binding to DNA,[4–6] whereupon they offer potential lead frameworks for developing novel anticancer drugs. Only a few reports[7] are available on the synthesis of pyrroloacridines and the majority of these compounds were found as the tetracyclic cores in metabolites from marine sources such as plakinidines A–C and alpkinidines.[8] Herein, we describe a novel multicomponent reaction providing an efficient approach to the synthesis of hitherto unreported 2-arylpyrrolo[2,3,4-*kl*]acridin-1(2*H*)-ones.

There are numerous methods available in the literature which describes reliable syntheses of acridines from dimedone, aldehydes, and aniline derivatives, or ammonium acetate via the



Scheme 1. The reaction leading to the synthesis of pyrroloacridones.

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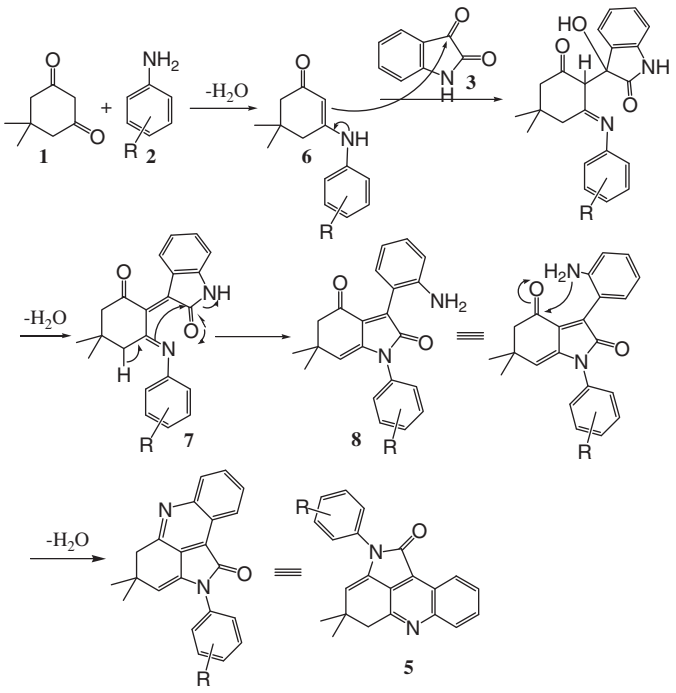
http://dx.doi.org/10.1016/j.tetlet.2012.06.070



Scheme 2. A proposed mechanism for the preparation of pyrroloacridones **5**.

Table 1
Effect of temperature variation and amount of dimedone on the yield and time of the model reaction

Entry	Dimedone (mmol)	*T* (°C)	Time (min)	Yield (%)
1	2	60	40	70
2	2	70	30	81
3	2	80	30	91
4	2	90	25	91
5	1.5	80	50	65
6	1	80	60	53

Hantzch reaction in the presence of various catalysts.[9–14] In this context, and in line with our interest in the synthesis of spiro-heterocyclic compounds,[15] we planned to employ isatin instead of an aldehyde in a similar reaction with dimedone (2 equiv) and aniline (1 equiv) in order to produce spiro[oxindole-acridine] compounds. However, when the reaction was conducted in the presence of the Brønsted-acidic ionic liquid, 1-methylimidazolium hydrogensulfate, [HMIm]HSO_4,[16] at 80 °C, a powdery product was obtained with spectral data and elemental analysis inconsistent with the expected structure **4a** (R = H). Indeed, the data were in good agreement with the structure of an unprecedented product, **5a** (R = H) being assembled via ring-opening of isatin followed by formation of a pyridine ring[17] (Scheme 1).

The mass spectrum of **5a** showed a molecular ion peak at *m*/*z* = 326, which was consistent with the mass of a 1:1:1 condensation product of the three components having released three molecules of water. The ^{1}H NMR spectrum of the product exhibited a singlet integrating for six protons at δ 1.35 corresponding to the two methyl groups and clearly indicating that only one molecule of dimedone had participated in the formation of the product **5a**. There were also two additional singlets in the spectrum at δ 3.22 (2H) and 5.63 (1H) that were assigned to the resonances of the methylene and olefinic methine protons, respectively. The aromatic region of the spectrum displayed separate signals for all the aromatic protons at the expected chemical shifts and with appropriate integral values. Further support for the structures of compounds **5** was obtained from the ^{13}C NMR spectra of the products where a downfield resonance (e.g., 166.7 for **5a**) was apparent corresponding to the presence of one carbonyl group in the molecule. Based on these features the product was identified as 2-phenyl-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (**5a**).

We have not established the exact mechanism for the formation of pyrroloacridines **5**, however, a reasonable suggestion is offered in Scheme 2. It is thought that, the reaction proceeds via a cascade of condensation reactions involving formation of the intermediate **7**, which is formed in situ by reaction of isatin **3** with intermediate enamine **6**, derived in turn from condensation of dimedone and aniline. Loss of a proton from intermediate **7** induces an intramolecular translactamization (arrows on **7**) to give the intermediate **8**. This intermediate undergoes a cyclocondenzation reaction to afford the corresponding 2-aryl-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one **5** (Scheme 2).

Optimization of the reaction conditions for the synthesis of **5a**, chosen as the model in [HMIm]HSO_4 under conventional heating, by exploring the effect of varying the temperature and amount of reactants revealed that the best yield was obtained with two equivalents of dimedone (Table 1).

The substrate scope of this protocol for the synthesis of a variety of pyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one derivatives was next studied by applying various anilines to the reaction and, as shown in Table 2, aniline derivatives **2a–i**, including those bearing electron-donating or electron-withdrawing as well as sterically demanding substituents, reacted efficiently with dimedone and isatin to afford

Table 2
Synthesis of pyrroloacridinones

Product	R	Method A[a]		Method B[b]		Mp (°C)
		Time (min)	Yield (%)	Time (min)	Yield (%)	
5a	H	30	91 (90,88,85)[c]	7	93 (91,90,88)[c]	196–197
5b	4-Cl	35	88	7	91	189–190
5c	4-Br	35	88	7	90	191–192
5d	4-I	35	90	7	90	204–205
5e	4-NO_2	45	83	10	86	181–182
5f	3-Cl	35	86	7	89	179–180
5g	4-OCH_3	25	92	5	95	185–186
5h	4-CH_3	25	90	5	92	220–221
5i	4-NO_2, 2-CH_3	50	85	10	89	185–186

Reaction conditions: dimedone (2 mmol), aniline (1 mmol), isatin (1 mmol), [HMIm]HSO_4 (0.5 mL).
[a] Conventional heating in an oil bath at 80 °C.
[b] Sonication (45 KHz frequency) in a water bath at 80 °C.
[c] The yields of reactions with recycled ionic liquid over three successive runs.

the desired products **5a–i** in good yields over short reaction times (Scheme 1 and Table 2).

We also examined the efficiency of the synthesis in terms of yields and reaction times under ultrasound irradiation, likewise at 80 °C in the ionic liquid [HMIm]HSO_4. In all the cases studied, the reaction proceeded smoothly to give better yields of products **5a–i** in shorter times with respect to standard heating (Table 2).

The ionic liquid (IL) was easily separated from the reaction medium by dissolving in distilled water, washing with diethyl ether, and evaporation at 80 °C under reduced pressure for 1 h. The recovered IL could be recycled in subsequent runs. Table 2 shows that no considerable change in the activity of the IL was observed when it was reused over three successive runs.

In conclusion, we have developed a novel, efficient, and clean route for the synthesis of a new class of pyrroloacridines via an unexpected three-component reaction between dimedone, various anilines, and isatin in the ionic liquid [HMIm]HSO_4. The products were successfully synthesized under classic reaction conditions in the ionic liquid, and alternatively in higher yields and reduced reaction times under ultrasound irradiation. The use of an inexpensive and reusable ionic liquid, short reaction times, high yields, simplicity of product isolation, and lack of problems connected with conventional solvents are advantages of the procedure.

Acknowledgment

Financial support by the Islamic Azad University, Rasht Branch is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.070.

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17. *General procedure for the preparation of 2-aryl-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-kl]acridin-1(2H)-ones* **5a–i**. **Method A**: Dimedone (0.28 g, 2 mmol), aniline (1 mmol), and isatin (0.15 g, 1 mmol) were added to the ionic liquid [HMIm]HSO_4 (0.5 mL). The thoroughly stirred mixture was then heated in an oil bath at 80 °C for the appropriate time according to Table 2. After completion of the reaction, as indicated by TLC, the mixture was allowed to cool to room temperature and then H_2O (5 mL) was added. The obtained precipitate was filtered and the crude product recrystallized from EtOH (96%). **Method B**: A mixture of dimedone (2 mmol), aniline (1 mmol), isatin (1 mmol), and [HMIm]HSO_4 (0.5 mL) was sonicated (45 KHz frequency) in a H_2O bath at 80 °C for the appropriate time according to Table 2. After completion of the reaction, H_2O (5 mL) was added. The obtained precipitate was filtered and crystallized from EtOH (96%).
2-Phenyl-4,5-dihydro-4,4-dimethylpyrrolo[2,3,4-*kl*]acridin-1(2*H*)-one (**5a**): Pale yellow powder, Mp 196–197 °C, IR (KBr): 3035, 2960, 1704, 1647, 1488, 1342, 1115, 1074, 819, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H 1.35 (s, 6H, 2 CH_3), 3.22 (s, 2H, CH_2), 5.63 (s, 1H), 7.32 (t, *J* 6.4 Hz, 1H), 7.51–7.59 (m, 4H), 7.65 (t, *J* 6.8 Hz, 1H), 7.78 (t, *J* 7.6 Hz, 1H), 8.20 (d, *J* 8.0 Hz, 1H), 8.75 (d, *J* 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 30.8, 37.1, 44.19, 118.3, 122.6, 124.2, 124.9, 126.3, 126.4, 127.4, 127.8, 129.3, 129.4, 129.5, 133.3, 134.7, 149.7, 154.5, 166.7; MS: *m/z* (%) = 327 (M+1, 7), 326 (M, 32), 311 (100), 296 (15), 268 (18), 192 (10), 167 (48), 149 (88), 77 (16); Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.91; H, 5.58; N, 8.65.