



An Efficient One-Pot Synthesis of 1,8-dioxo-Decahydroacridines by Ionic Liquid with Multi-SO₃H Groups Under Ambient Temperature in Water

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ABSTRACT

Ionic liquid with multi-SO₃H groups was employed as a catalyst for facile preparation of 1,8-dioxo-decahydroacridines via the one-pot condensation of various aldehydes, 1,3-diketones with aromatic amines or ammonium acetate. Various aromatic aldehydes were utilized in the reaction and in all situations the desired product were synthesized successfully. The described novel synthesis method propose several advantages of safety, mild condition, short reaction times, high yields, simplicity and easy workup compared to the traditional method of synthesis.

Key words: Ionic liquid with multi-SO₃H groups, 1,8-dioxo-decahydroacridines, One-pot synthesis, Three component, Water solvent, Chemoselective.

INTRODUCTION

Acridine and acridine-1,8-dione derivatives are polyfunctionalized 1,4-dihydropyridine derivatives. They have a wide range of pharmacological properties such as antimalarial,¹ antitumor,² anticarcinogenic,³ anticancer,⁴ fungicidal,⁵ and widely prescribed as calcium b-blockers.⁶ Also, 1,8-dioxo-decahydroacridines were created to act as laser dyes,⁷ and used as photoinitiators.⁸

Many procedures were explained the synthesis of acridine derivatives containing 1,4-

dihydropyridines, from dimedone, aldehydes and different nitrogen sources such as urea,⁹ hydroxylamine,¹⁰ ammonium acetate on basic alumina,¹¹ and different appropriate amines or ammonium acetate,¹² via conventional heating in organic solvents, in the presence of Amberlyst-15,¹³ p-dodecylbenzenesulfonic acid (DBSA),¹⁴ triethylbenzylammonium chloride (TEBAC),¹⁵ and using ionic liquids,¹⁶ such as bronsted acidic imidazolium salts containing perfluoroalkyl tails,¹⁷ 1-methylimidazolium trifluoroacetate ([Hmim]TFA).¹⁸

However, some of these reported methods have one or more disadvantages such as moisture

sensitive, using the excess of catalysts, prolonged reaction time, low yields, toxic organic solvents, a microwave oven and unpleasant experimental procedure and reagents which are expensive.

Performing organic reactions in aqueous media has attracted much attention because of wonderful water properties. It would be significantly safe, cheap, non-toxic and environmentally friendly compared to organic solvents.¹⁹ Additionally, the catalyst system can be recycled using the water soluble catalyst and the insoluble products can be separated by simple filtration. So, development of a mild and efficient catalyst system for the synthesis of 1,8-dioxo-decahydroacridines is highly desirable. It should not only be stable in water but also should be completely soluble in it.

In recent years, ionic liquids have attracted much attention as a new class of green solvent and catalyst.²⁰ These aqueous media is utilized for organic synthesis due to their astonishingly properties, such as wide liquid range, favorable solvating capability, low temperature requirement, tunable polarity, high thermal stability, and ease of recyclability.²¹ Ionic liquids also have negligible vapor pressure, which facilitates product separation by distillation. Moreover, they are the cheapest and most environmentally friendly solvents, because water exhibits unique reactivity and selectivity, which differs from those in conventional organic solvents. The appropriate property of the ionic liquids lead to the development and application of so-called "task-specific" ionic liquids to synthesize the desirable products.

Recently, Jianguo et al.²² introduced a new ionic liquid with multi-SO₃H groups (Scheme 1) which have much higher activity than other reported catalysts with the additional advantage of reusability.

In continuation of our investigations on the development of new synthetic methodologies,²³ we herein report a new, convenient, mild and efficient procedure for the synthesis of 1,8-dioxo-decahydroacridines from one-pot condensation of various aromatic aldehydes, 1,3-diketones with aromatic amines or ammonium acetate using this non-volatile ionic liquid with multi-SO₃H groups under ambient temperature.

EXPERIMENTAL

A mixture of 1,3-diketone (2.0 mmol), aromatic aldehyde (1.0 mmol), aromatic amine or ammonium acetate (1.0 mmol) and ionic liquid (1 mol%) in water (2 mL) were stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC (n-hexane/ethyl acetate 4:1). After completion of the reaction, the resulting solid (crude product) was filtered and then recrystallized from ethanol-water to obtain pure product. The physical data (mp, NMR, IR) of these known compounds were found to be identical with those reported in the literature.

The spectral data for selected products

(Table 3, entry 6): m.p. 290-291 °C. yield: 94 %; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 0.85 (s, 6H), 1.02 (s, 6H), 1.82-2.49 (m, 8H), 4.81 (s, 1 H), 7.00-7.16 (m, 5H), 9.41 (br s, 1H, NH); ¹³C NMR (DMSO-*d*₆, 100 MHz) δ: 22.2, 26.4, 29.0, 30.1, 30.5, 30.9, 32.1, 32.7, 50.2, 11.4, 114.3, 123.2, 125.3, 126.7, 127.4, 127.5, 146.4, 149.3, 194.2; IR (KBr) ν: 3745, 3054, 2958, 2873, 1589, 1486, 1371, 1261, 765.

(Table 3, entry 18): m.p. 244-246 °C. yield: 96 %, ¹H NMR (DMSO-*d*₆, 400 MHz): δ=0.81 (s, 6H), 0.95 (s, 6H), 1.80-2.24 (m, 8H), 5.25 (s, 1H), 7.22-7.28 (m, 4H), 7.38-7.59 (m, 5H); ¹³C NMR (DMSO-*d*₆, 100 MHz): δ=22.2, 26.7, 29.7, 31.2, 32.4, 32.5, 38.1, 41.8, 50.1, 53.4, 59.5, 114.2, 115.5, 119.0, 128.2, 129.3, 129.4, 129.7, 131.5, 138.9, 144.7, 149.8, 195.8; IR (KBr) ν: 3783, 3693, 2952, 2360, 1633, 1583, 1365, 1222, 837.

(Scheme 3, entry 2): m.p. 267-268 °C. yield 93 %; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 0.73 (s, 9H, 3 * CH₃), 0.87 (s, 12H, 4 * CH₃), 1.01 (s, 3H, CH₃), 1.758-1.83 (m, 4H, 2 * CH₂), 2.03-2.18 (m, 8H, 4 * CH₂), 2.33-2.47 (m, 4H, 2 * CH₂), 3.57 (s, 6H, 2 * OCH₃), 4.66 and 5.21 (2 * d, 2H, J = 12.2 Hz, 2 * CH), 6.77-7.09 (m, 4H, ArH), 7.33-7.64 (m, 4H, ArH), 7.78-7.98 (m, 2H, ArH), 8.10-8.31 (m, 2H, ArH); IR (KBr) ν: 1225, 1583, 1646, 2957, 3044 cm⁻¹.

(Scheme 3, entry 4): m.p. 229-231 °C. yield 95 %; ¹H NMR (DMSO-*d*₆, 400 MHz) δ: 0.86 (s, 9H, 3 * CH₃), 0.95 (s, 12H, 4 * CH₃), 0.99 (s, 3H,

CH₃), 1.89–2.04 (m, 10H, 5 * CH₂), 2.21–2.33 (m, 4H, 2 * CH₂), 2.42–2.45 (m, 2H, CH₂), 3.61 (s, 6H, 2 * OCH₃), 4.89 and 5.43 (2 * d, 2H, J = 12.3 Hz, 2 * CH), 6.31–6.77 (m, 8H, ArH), 6.89–6.93 (m, 2H, ArH), 7.02–7.05 (m, 2H, ArH); IR (KBr) ν : 1224, 1571, 1663, 2958, 3043 cm⁻¹.

RESULTS AND DISCUSSION

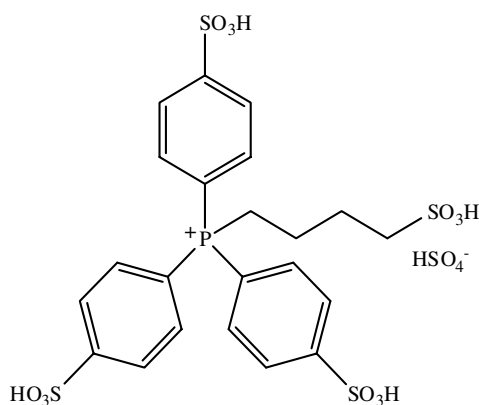
First, we studied three-component condensation of dimedone (2 mmol), 4-chlorobenzaldehyde (1 mmol) and *p*-toluidineiline (1 mmol) to optimize the reaction conditions with respect to temperature, time, solvent, molar ratio of catalyst to the substrate and reusability of catalyst. It was found that 1 mol% of catalyst was sufficient to obtain the desired 1,8-dioxo-decahydroacridines in 96% yield within 21 min at room temperature in water (Scheme 2).

The effect of solvent on the yield of 1,8-dioxo-decahydroacridines is given in Table 1. The reaction of between dimedone, aniline and

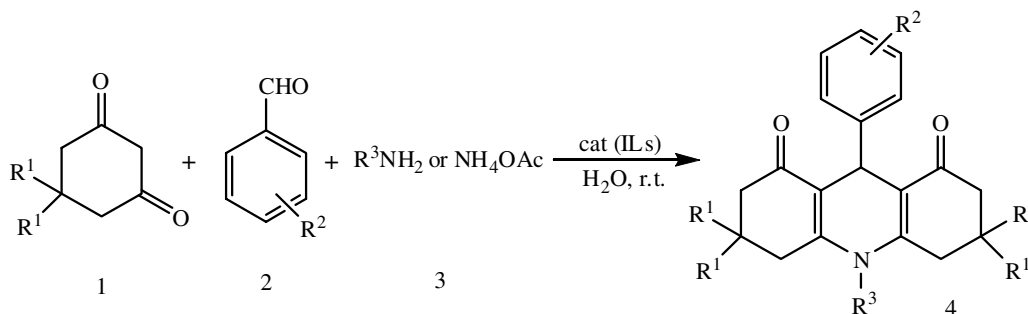
benzaldehyde was chosen as a model reaction for investigating the effect of solvent. Among the solvents examined, water was found to be the most effective solvent.

In order to show the merit of ILs in comparison with the other catalysts used for the similar reaction, some of the results are tabulated in Table 2. According to Table 2, the required ratio for the most catalysts used for this purpose is >1 mol% and also the required reaction times are much longer (5–6 h).

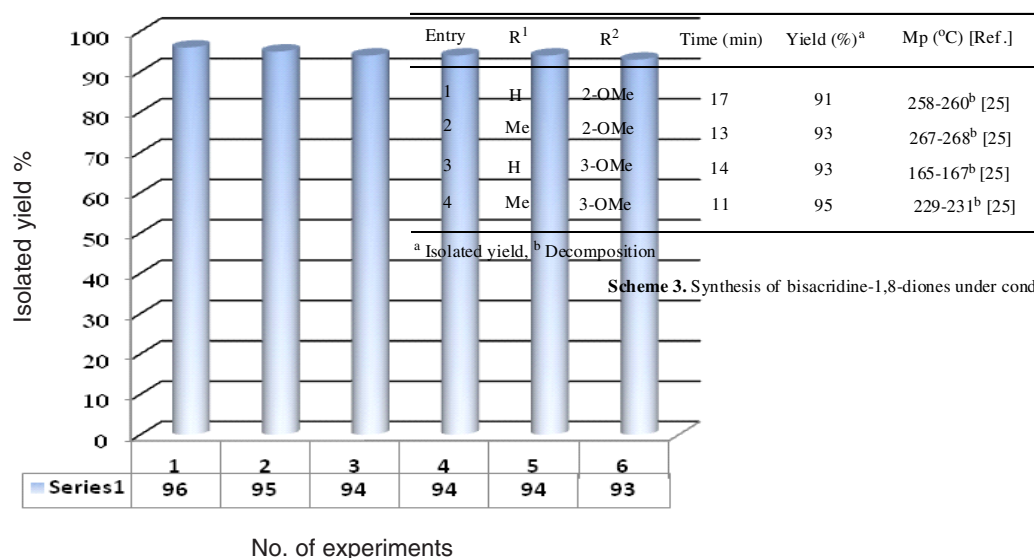
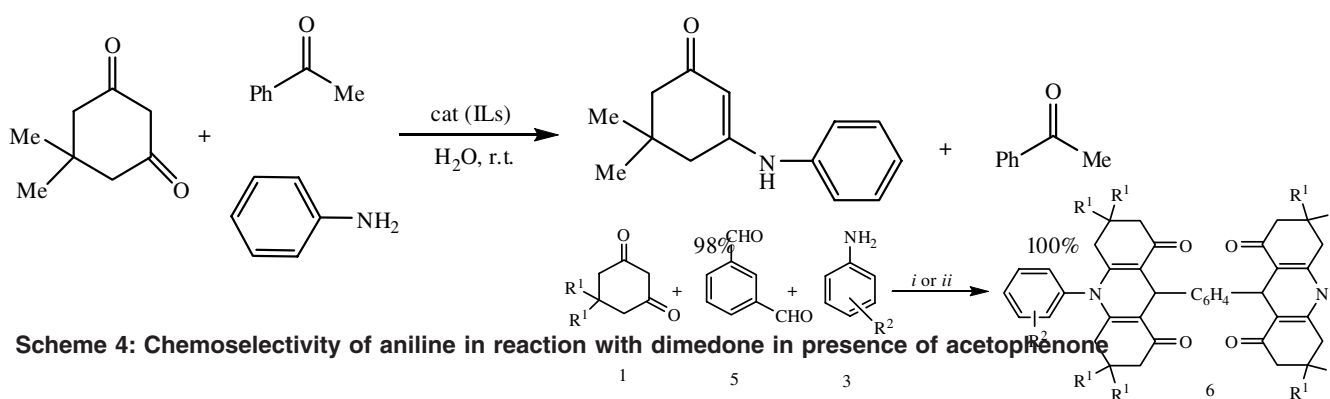
After finding the optimized reaction conditions, the investigation was preceded by performing the reaction between a series of aromatic aldehydes and primary amines or ammonium acetate with 1,3-diketones. To show the general applicability of this method, various aldehydes and amines were efficiently reacted with two equivalents of 1,3-diketones in the same conditions. These results encouraged us to investigate the scope and the generality of this new



Scheme 1: ILS with multi SO₃H groups



Scheme 2: Synthesis of 1,8-dioxo-decahydroacridines

Scheme 3: Synthesis of bisacridine-1,8-diones under condition of 1mol% ILS**Scheme 5: Reusability studies of the catalyst for synthesis of compound (Table 3, entry 22)**

protocol for various aldehydes and amines under optimized conditions. As shown in Table 3, a series of aromatic aldehydes and amines underwent electrophilic substitution reaction with 1,3-diketones to afford a wide range of substituted 1,8-dioxo-decahydroacridines in good to excellent yields. The nature and electronic properties of the substituents on the aromatic ring effect the conversion rate, and aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table 3, entries 2, 7,

13, 17, 21) react faster than electron-donating groups (Table 3, entries 4, 5, 9, 10, 25). Also, both aromatic amines and ammonium acetate similarly underwent well to the conversion.

Surprisingly, when isophthalaldehyde (5) was used with 4 molar equivalents of 1,3-diketones and 2 molar equivalents of aromatic amines, bisacridine-1,8-diones (6) was obtained in excellent yield²⁴ (Scheme 3).

Table 1: Solvent effect on the reaction of between dimedone, aniline and benzaldehyde^a

Entry	Solvent	Time (min)	Yield (%) ^b
1	H ₂ O	12	95
2	C ₂ H ₅ OH	12	93
3	CH ₃ CN	13	93
4	CH ₃ COOEt	17	91
5	PhCH ₃	21	89

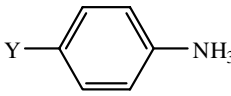
^a Reaction condition: 5,5-dimethyl-1,3-cyclohexenedione (2 mmol), aniline (1 mmol), bezaldehyde (1 mmol), catalyst (1 mol%), solvent (2 mL)

^b Isolated yield

Table 2: Reaction of between dimedone, 4-chlorobenzaldehyde and p-toluidineiline in presence of different catalyst

Entry	Catalyst	Catalyst (mol %)	Time (min)	Yield (%)	Ref.
1	IL with multi SO ₃ H groups	1	8	96	—
2	PTSA	2	360	18	[17]
3	C ₇ F ₁₅ COOH	2	360	31	[17]
4	DBSA	2	360	41	[17]
5	[HMIM]TFA	0.1 gr	300	84	[13]
6	TsOH	10	360	13.2	[14]
7	Sc(DS) ₃	10	360	78.3	[14]
8	C ₁₁ H ₂₃ COOH	10	360	26.8	[14]

Table 3: Synthesis of 1,8-dioxo-decahydroacridines under condition of 1 mol% ILs

Entry	R ¹	R ²	Amine	Time (min)	Yield (%)	Mp (°C) ^{Ref}
1	H	H	NH ₄ OAc	21	93	279-281 ^{24a}
2	H	3-NO ₂	NH ₄ OAc	14	97	283-284 ^{24a}
3	H	4-Cl	NH ₄ OAc	16	95	296-298 ^{24a}
4	H	4-OH	NH ₄ OAc	19	93	305-306 ^{24a}
5	H	4-OMe	NH ₄ OAc	16	93	303-305 ^{24a}
6	Me	H	NH ₄ OAc	19	94	290-291 ^{24b}
7	Me	3-NO ₂	NH ₄ OAc	11	98	307-309 ^{24c}
8	Me	4-Cl	NH ₄ OAc	13	96	299-300 ^{24a}
9	Me	4-OH	NH ₄ OAc	17	94	307-308 ^{24a}
10	Me	4-OMe	NH ₄ OAc	17	94	276-278 ^{24a}
11	Me	4-Me	NH ₄ OAc	15	95	279-281 ^{24d}
						
12	H	H	Y=H	15	94	274-276 ^{24e}
13	H	3-NO ₂	Y=H	7	97	278-279 ^{24f}
14	H	4-Cl	Y=H	11	96	291-293 ^{24f}
15	H	2-OMe	Y=H	13	94	270-271 ^{24f}
16	Me	H	Y=H	12	95	253-254 ¹³
17	Me	3-NO ₂	Y=H	6	98	295-297 ^{24f}
18	Me	4-Cl	Y=H	10	96	244-246 ^{24f}
19	Me	2-OMe	Y=H	11	94	210-222 ¹³
20	Me	H	Y=Me	11	95	262-264 ¹⁴
21	Me	3-NO ₂	Y=Me	5	98	284-286 ¹⁴
22	Me	4-Cl	Y=Me	8	96	272-273 ¹⁴
23	Me	2,4-Cl ₂	Y=Me	8	96	320-321 ¹⁴
24	Me	4-Me	Y=Me	9	96	296-298 ^{28c}
25	Me	4-OMe	Y=Me	10	95	282-284 ¹⁴

The high chemoselectivity of this reaction had also been verified by a competitive reaction between dimedone, acetophenone and aniline, as shown in Scheme 4. The result showed that aniline was carried out with dimedone in excellent yield and acetophenone observed with product under identical conditions. The high chemoselectivity of this reaction is the result of more reactivity 1,3-diketone with compared ketone.

The reusability of the catalysts was checked using dimedone, 4-chlorobenzaldehyde and *p*-toluidineiline as a model substrate. At the end of the reaction, CH₂Cl₂ was added to the mixture. The aqueous layer was separated and used without further purification. In this media, as shown in (scheme 5), the recovered catalyst can be reused at least six additional times in subsequent reactions without appreciable loss in the catalytic activity.

CONCLUSION

The objective of this paper is to describe green, simple and efficient ionic liquid with multi-SO₃H groups to catalyze one-pot method for the synthesis of 1,8-dioxo-decahydroacridines derivatives. The experimental procedure for this reaction is remarkably facile and requires no toxic organic solvents. The catalyst offers several advantages including mild reaction conditions, cleaner reactions, shorter reaction times, high yield of the products, lower catalytic loading as well as simple experimental and isolation procedures.

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