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Methyltrioctylammonium chloride catalysed sonochemical synthesis of acridine diones

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Abstract. The greener, clean and efficient protocol for the synthesis of acridine diones derivatives has been achieved by reacting aromatic aldehyde, dimedone and amines using methyltrioctylammonium chloride (Aliquate 336) as a catalyst under ultrasonic irradiations.

Keywords. Ultrasound irradiation; methyltrioctylammonium chloride; acridine diones derivatives.

1. Introduction

Ultrasound irradiation in organic synthesis is considered as a clean and energy conserving protocol as compared to the traditional methods and has been established as a versatile technique in synthetic organic chemistry.[1–4] It has been well established that ultrasound, when compared with conventional methods enhance the rate of reactions and product yields in addition to sometimes changing the reaction pathway.[5,6] In recent years, acridine diones have attracted keen interest of the researchers because of their use as drugs for cardiovascular diseases, such as angina pectoris,[7] hypertension,[8] antitumour agents,[9–11] DNA-binding moieties and DNA-intercalating anticancer drugs.[12,13] Therefore, the synthesis of acridine diones derivatives is an important and principal task in organic chemistry. A straightforward method for the synthesis of these compounds involve a condensation between aldehydes, dimedone and amines that is catalysed by various compounds such as poly-phosphoric acid,[14] (cetyltrimethylammonium bromide CTAB),[15] L-proline,[16] zeolite,[17] N-propyl sulphamic acid,[18] ionic liquids,[19] microwave irradiations.[20] They often suffer from the draw backs of long reaction times, harsh reaction conditions, toxicity, and difficulty in product separation, which limits its uses in the synthesis of complex molecules. Ionic liquids have attracted extensive research interest in recent years as environmentally benign solvents due to their favourable properties like non-inflammability, negligible vapour pressure, reusability and high thermal stability.[21,22] Combining these unique properties of ionic liquids they are emerging as a 'green reaction media' (catalyst + solvent). The use of ionic liquids as reaction medium may offer a convenient solution to both the solvent emission and catalytic recycling problem.[23–25]

To the best of our knowledge, acridine diones derivatives involving catalytic amount of ionic liquid methyltrioctylammonium chloride (Aliquate 336) under ultrasonication is unprecedented. In continuation of our interest in developing novel synthetic methodologies and use of ionic liquid as catalyst under ultrasonic irradiation for organic synthesis,[26–28] here, we have developed methodology for the synthesis of acridine diones derivatives in the presence of methyltrioctylammonium chloride under ultrasonication.

2. Experimental

2.1 *General*

All melting points were recorded in open capillary measurements, using sulphuric acid bath and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin–Elmer spectrophotometer. NMR spectra were recorded on AL-300F (Bruker) FT NMR spectrophotometer using $CDCl_3$ as internal standard. Sonication was performed in ELMA, Transonic T 310/H Ultrasonic cleaner (with a frequency of 40 KHz), Hans Schmidbauer GmbH and Co., Germany. The reactions were performed in open vessels.

2.2 *General procedure for the synthesis of acridine diones derivatives*

In a beaker a mixture of aromatic aldehyde (1 mmol), dimedone (2 mmol), ammonium acetate/aromatic

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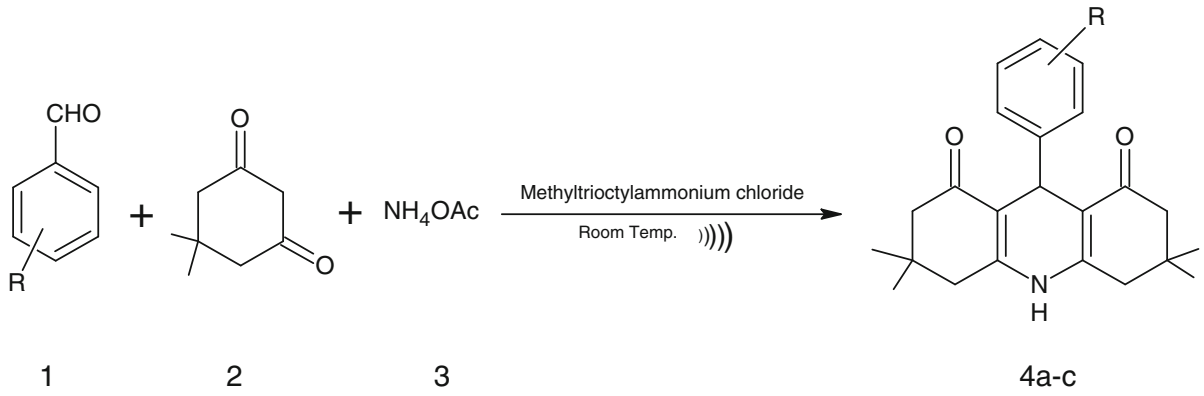


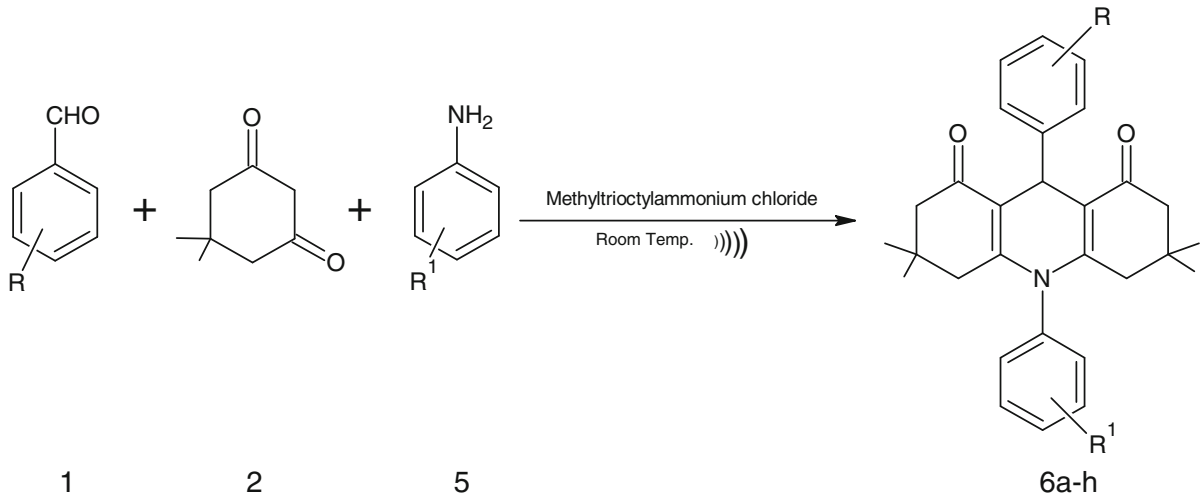
Scheme 1. Synthesis of tetrahydroacridine-1,8 (2H,5H,9H,10H)-diones.

amine (1+) was mixed with methyltrioctylammonium chloride (10 mol%) (schemes 1 and 2) which was irradiated under ultrasonic waves at the room temperature for an appropriate time (see table 2). The progress of the reaction was monitored by TLC. After the completion of reaction the solid product was filtered. This solid product was recrystallized from ethanol.

2.2a *3,3,6,6-Tetramethyl-9-(3-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione* (***4a***): mp 273–275°C; ^{1}H–NMR ($CDCl_3$) δ 0.89 (s, 6H), 1.03 (s, 6H), 2.0 (d, J = 16.3 Hz, 2H), 2.15 (d, J = 16.3 Hz, 2H), 2.28 (d, J = 17.1 Hz, 2H), 2.38 (d, J = 17.1 Hz, 2H), 5.01 (s, 1H), 7.30 (t, J = 7.86 Hz, 1H), 7.60 (d, J = 6.9 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 8.02 (s, 1H), 8.90 (s, br., 1H); ^{13}C–NMR ($CDCl_3$) δ 27.4, 29.9, 32.9, 34.4, 51.1, 112.2, 121.2, 123.1, 130.0, 135.2, 148.4, 149.6, 150.2, 195.6; IR (cm^{-1}) 3380, 3060, 2960, 1645, 1610, 1520, 1480, 1360, 1340, 1220, 1140.

2.2b *3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione* (***4b***): mp 282–283°C; ^{1}H–NMR ($CDCl_3$) δ 0.87 (s, 6H), 1.05 (s, 6H), 2.08 (d, J = 16.3 Hz, 2H), 2.18 (d, J = 16.3 Hz, 2H), 2.24 (d, J = 17.0 Hz, 2H), 2.38 (d, J = 17.0 Hz, 2H), 5.08 (s, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 6.9 Hz, 2H), 8.47 (s, 1H); ^{13}C–NMR ($CDCl_3$) δ 27.4, 29.9, 32.9, 34.9, 51.0, 112.3, 123.5, 129.4, 146.3, 149.8, 154.9, 195.6; IR (cm^{-1}) 3384, 3070, 2956, 1643, 1515, 1479, 1342, 1218, 1166.

2.2c *3,3,6,6-Tetramethyl-9-(2-chlorophenyl)-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione* (***4c***): mp 217–219°C; ^{1}H–NMR ($CDCl_3$) δ 1.08 (s, 6H), 1.03 (s, 6H), 2.030–2.30 (m, 4H), 2.48–2.62 (m, 4H), 5.04 (s, 1H), 7.08 (t, J = 7.2 Hz, 1H), 7.03–7.039 (m, 1H), 7.25 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 6.4 Hz, 1H); ^{13}C–NMR ($CDCl_3$) δ 27.8, 29.7, 32.5, 41.2, 51.2, 114.2, 126.8, 127.6, 128.2, 130.6, 133.9, 149.4, 163.5, 197.0; IR (cm^{-1}) 3400, 2980,1660, 1620, 1465, 1350, 1200.



Scheme 2. Synthesis of N-aryl-tetrahydroacridine-1,8 (2H,5H,9H,10H)-diones.

Table 1. Effect of amount of catalyst with or without ultrasonication for the synthesis of acridine diones at room temperature.

	Aliquat	With sonication		Without sonication	
Entry	336 (mol%)	Yield (%)	Time (min)	Yield (%)	Time (min)
1	2	Nil	190	Nil	350
2	4	40	150	Nil	350
3	6	85	95	20	350
4	8	89	85	22	350
5	10	98	40	28	350
6	12	96.5	50	30	350

2.2d *3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-10-phenyl-3,4,6,7,9,10-tetrahydroacridine-1,8-(2H,5H,9H,10H)-dione (**6b**)*: mp 278–280°C ^{1}H–NMR ($CDCl_3$): δ 0.75 (s, 6H), 0.89 (s, 6H), 1.75 (d, J = 17.5 Hz, 2H), 2.03 (d, J = 17.5 Hz, 2H), 2.03 (d, J = 16.3 Hz, 2H), 2.03 (d, J = 16.3 Hz, 2H), 5.29 (s, 1H), 7.03 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H), 7.54 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H); ^{13}CNMR ($CDCl_3$): δ 195.6, 153.6, 150.4, 146.2, 138.7, 129.7, 128.8, 123.5, 113.6, 50.03, 41.9, 33.6, 32.4, 29.6, 26.7; IR (KBr) (cm^{-1}) 2956, 1635, 1594, 1514, 1349, 1224, 1176, 1144, 1113, 1003, 864, 830, 703, 572, 513.

3. Results and discussion

The optimal condition for the synthesis of acridine diones derivatives was studied. The pilot reaction was carried out using benzaldehyde, aniline and dimedone. In a typical experiment a mixture of benzaldehyde (1 mmol), aniline (1 mmol) and dimedone (2 mmol) was placed under ultrasonic irradiation, at stirring and heating conditions. The results revealed that, when the reaction was carried at stirring and heating conditions it gave the lower yield of product even after prolonged reaction time. However, at the same time under ultrasonication we got the excellent yield of product in short span (table 1). The results in table 1 revealed that the ultrasonic irradiation was very simple and convenient for the synthesis of acridine diones derivatives at room temperature in the presence of ionic liquid using ultrasonic cleaner with a frequency of 40 KHz. In this experiment the ultrasonic technique represented a better procedure in terms of time and yields.

The catalytic activity of methyltrioctylammonium chloride was also studied. Methyltrioctylammonium chloride was added in varying amount. It was found that 10 mol% catalysts was optimum to carry out the reaction. Using more than 10 mol% of the catalyst did not affect the yield or time of the reaction to greater extent. Using less than 10 mol% of the catalyst results in the less amount of the percentage yield in prolonged reaction time. To express the generality of reaction various aromatic aldehydes and amines were reacted with dimedone using methyltrioctylammonium chloride as catalyst under ultrasonic irradiation. Here, we have found that the reaction of aromatic aldehydes having electron–withdrawing and electron donating groups are equally facile for the reaction (resulting in the formation of good yield). The results obtained in the current method are illustrated in table 2. All the products obtained were fully characterized by spectroscopic methods such as IR, ^{1}H NMR and also by comparison with the reference compounds.

Table 2. Methyltrioctylammonium chloride catalysed synthesis of acridine diones at room temperature under ultrasonication.

Entry	R	R^1/amine	Time (min)	Yield (%)	M.pt (°C)[ref.]
4a	3-NO_2	NH_4OAc	50	90	274–277[17]
4b	4-NO_2	NH_4OAc	40	93	283–285[17]
4c	2-Cl	NH_4OAc	35	94	215–217[17]
6a	C_6H_5	C_6H_5	50	96	223–225[15]
6b	4-Cl	C_6H_5	45	95	245–248[15]
6c	4-NO_2	C_6H_5	50	90	278–280[15]
6d	4-OCH_3	C_6H_5	50	92	293–295[15]
6e	C_6H_5	4-CH_3	45	94	267–270[15]
6f	4-NO_2	4-CH_3	45	90	>300[15]
6g	4-OCH_3	4-CH_3	55	92	132–135[15]
6h	3-NO_2	4-CH_3	55	93	279–282[15]

4. Conclusion

The methodology of the synthesis of a variety of acridine diones precursors under ultrasound irradiation conditions in the presence of the catalytic amount of an

ionic liquid, i.e., methyltrioctylammonium chloride has been developed. The present methodology gives significant advantages such as simple procedure, easy work up and clean reaction profile, use of inexpensive catalyst, excellent percentage yields, shorter reaction time, solvent free media and mild reaction conditions.

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