International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

Innovative Protocol for the Synthesis of Acridine Derivatives using Ionic Liquid

Sangita Makone[1], Shreyas Mahurkar[2]

[1, 2] Chemical Sciences Research Laboratory, School of Chemical Sciences,
Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded, India

Abstract: ***Innovative protocol for the synthesis of acridine derivatives by reaction of dimedone, aromatic aldehyde and ammonium acetate is developed using ionic liquid 1-butyl-3-methylimidazolium perchlorate ([Bmim]ClO_4). The method provides several advantages such as simple work up, environmental friendliness and excellent yields in short reaction time. The ionic liquid [Bmim]ClO_4 used was recovered and reused for three times.***

Keywords: Aldehyde, dimedone, ammonium acetate, ionic liquid, acridine**.**

1. Introduction

Acridine 1,8-diones are an important class of heterocycles containing a 1,4-DHP parent nucleus, are induced with high efficiencies for several applications such as photo initiators, laser activity, fluorescence [1]-[4], laser dyes [5]-[7], electrochemical and photo-physical properties [8]. The 1,4-dihydropyridine are a common features of various pharmacological properties [9]. Dihydropyridine derivatives such as nifedipine, nicardipine, amlodipine are effective cardiovascular agents for the treatment of hypertension [10]-[12] (Fig. 1).

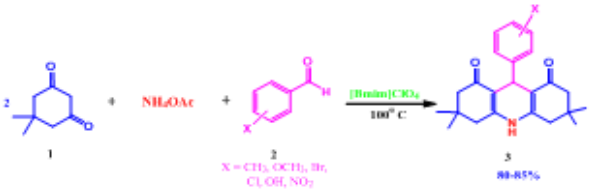
Figure 1: Representative antihypertensive compounds

Acridine derivatives have also been known for their calcium channel activity, moreover this heterocyclic ring constitutes variety of bioactive compounds these are vasodilator, bronchodilator, antiatherosentific, antidiabetic, antitumor, and anti-inflammatory agents [13] these compounds also exhibit diverse medical function such as neuroprotectus, platelet antiaggregaters and chemosensitizers [14].

The general synthesis of 1,4-DHP by Hantzsch method involves one pot cyclocondensation of aldehydes with dicarbonyls and ammonium acetate refluxing in ethanol [15]. There are several methods reported for the synthesis of 1,4-dihydropyridines from dimedone, aldehyde through different nitrogen sources like urea [16], methyl amine [17], different aniline or ammonium acetate [18] via traditional heating in organic solvent. The various catalyst such as [CMIM][CF_3COO] [19], TEBAC [20], DBSA [21], L-proline [22], Amberlyst-15 [23], metal triflates [24], iodine [25], CAN [26], MCM-41-SO_3H [27], tetrabutylammonium hexatungstate [28], $Zn(OAc)_2$ [29], SBSSA [30] trifluroethanol [31], HY-zeolite [32], p-TSA [33], silica sulfuric acid [34], $HClO_4$-SiO_2 [35] and methyltrioctylammonium chloride [36] are used for the synthesis of acridine derivatives.

However, most of the methods are blemished by aspects such as prolonged duration, inconvenient availability of reagent, toxic solvents and catalysts, tedious work up process and in some cases harmful to environmental because of their own limitations, the development of simple, efficient and environmentally benign method is still essential. For wide applicability and sustainable development there is a need of innovative protocol for synthesis of acridine derivatives using green alternatives.

Recently ionic liquids have been identified as green classes of solvents that offer opportunities to move away from traditional chemical processes to new green, clean technologies in which waste streams are minimized. Ionic liquids are salts composed of organic cations and organic or inorganic anions. Compared to conventional organic solvents, the use of ionic liquids for synthesis, catalysis and extraction has a number of advantages determined by the unique combinations of their properties. The use of ionic liquid was initially introduces as an alternative green reaction medium, today they have progressed far beyond this, having a significant role in controlling reactions as catalysts [37].



Scheme 1: Synthesis of acridine derivatives using [Bmim]ClO_4 ionic liquid.

2. Experimental

2.1 Materials

All the chemicals used are purchased from Aldrich, Spectrochem, Merck chemicals and were used without further purification. All melting points were measured on Veego digital melting point apparatus and are uncorrected. The NMR spectra were recorded on a Brucker Avance II spectrometer with TMS as internal standard ^{1}H NMR were run in deuteratd chloroform ($CDCl_3$). Chemical shifts (δ) are referred in terms of ppm.

2.2 General procedure

The mixture of dimedone (10 mmol) ammonium acetate (7.5 mmol) and aldehyde (5 mmol) in 1-butyl-3-methyl imidazolium perchlorate ([Bmim]ClO_4) ionic liquid (4 mmol) was taken in 50 ml round bottom flask and stirred at 100^{o}C using heating magnetic stirrer. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was cooled to room temperature and to it water (5 ml) was added, solid separated was filtered. The crude product filtered was recrystallized from ethanol to give the pure product. The ionic liquid was recovered by distillation and reused for further three cycles.

3. Result and discussion

To a mixture of 3-nitro benzaldehyde (2mmol), dimedone (4mmol) and ammonium acetate (3mmol) and [Bmim]ClO_4 (4mmol) was added in 50ml round bottom flask and was stirred at 100^{o}C. This reaction is considered as model reaction. The progress of the reaction was monitored by TLC After completion of the reaction the reaction mixture was cooled to room temperature and water (5 ml) was added, solid separated was filtered and product was characterized by IR, ^{1}H NMR, ^{13}C-NMR and mass. We focused our initial investigation of the effect of various solvent on model reaction at different temperatures (**table 1**).

Table 1: Solvent study of synthesis of acridine 1,8-diones derivatives.

Sr. No.	*Solvent*	*Temp.(^{o} C)*	*Time (h)*	*Yield (%)*
1	Water	Reflux	6	54
2	Ethanol	78	4	58
3	Methanol	64	4	51
4	Acetone	60	4	33
5	Dichloromethane	40	4	47
6	Acetonitrile	80	4	45
7	[Bmim]Cl	100	4	71
8	[Bmim]Br	100	3	78
9	[Bmim]ClO_4	100	1.4	85

From the study of different solvent we observed that the formation of acridine 1,8-diones takes place with 54% yield in water at reflux condition up to 6 hr. while other solvent such as ethanol, methanol, acetone and dichloromethane gives the moderate yields. After study of organic solvents, ionic liquids were also exploited as solvents for the model reaction and we observe excellent result as compare to previous solvent used.

From this study we observe that ionic liquid was suitable media for the reaction model reaction which shows the dual role of ionic liquids as both reaction media and promoters.

As far as reaction temperature is concern we studied the reaction from temperature 60-110^{o}C in the gap of 10^{o}C. The best result in terms of time and yield for the reaction has been observed at 100^{o}C (as shown in table 2). The study was carried out at optimized temperature to carry similar type of reaction for various aromatic aldehydes.

Table 2: Optimization of reaction temperature for synthesis of acridine

Entry	*Temperature (^{o} C)*	*Time (Hrs.)*	*Yields (%)*
1	60	6.30 hrs	43
2	70	5.20 hrs	52
3	80	4.40 hrs	73
4	90	3.5 hrs	79
5	100	1.4 hrs	85
6	110	1.4 hrs	85

To evaluate the scope of this reaction a range of acridine derivatives were prepared by the reaction of dimedone, various aromatic aldehydes and ammonium acetate under optimized reaction conditions. The results are summarized in the table [**table 3**]. The result shows that the formation of acridine 1,8-diones proves to be general and quite efficient for aryl aldehydes and tolerate a variety of functional groups on the phenyl ring despite of whether electron donating or electron withdrawing in character.

The reuse of the ionic liquid was easily done up to 3 times with excellent yields without considerable loss in the reactivity (as shown in figure 2). After 3rd cycle we observe sudden decreases in the yield for the 4th reuse.

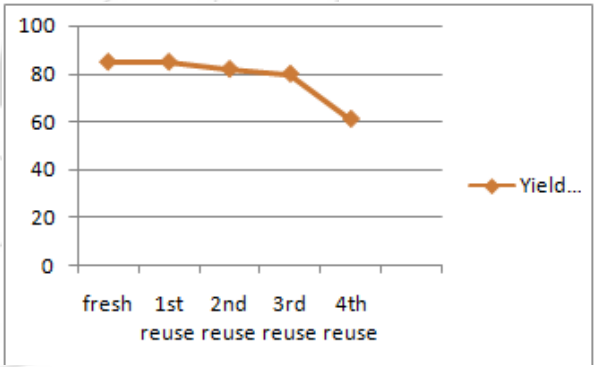


Figure 2: Reuse of ionic liquid

3.1 Structural determination of isolated compound

Primary elucidation of the structure for the optimized reaction isolated product was examined. Authentication of product was carried out by spectral analysis. FT-IR spectra illustrate narrow band at 3345 cm^{-1} represent the presence of N-H stretch, a medium band obtained at 2954 cm^{-1} represents the presence of alkanes (4 x CH_3 groups), a band at 1719 cm^{-1} represents the presence of general carbonyl group (C=O stretch) a medium band at 1379 cm^{-1} for alkanes (C-H bending), a medium band at 1064, 1103 cm^{-1} confirms the presence of amine (C-N stretching). The determination of structure for the product was further confirmed by ^{1}H NMR spectra. A singlet obtained at 5.54 (s, 1H, -CH) and broad singlet at 8.87 (s, 1H, -NH) authenticate the formation of product.

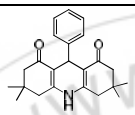
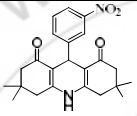
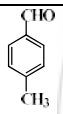
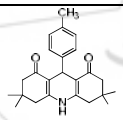
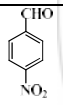
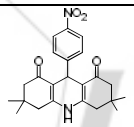
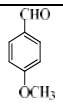
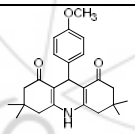
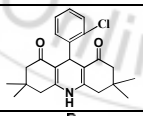
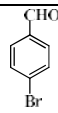
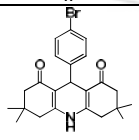
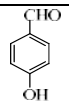
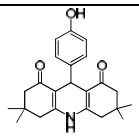
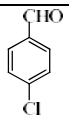
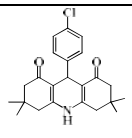
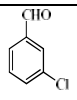
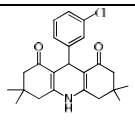
3.2 Spectral data

3,3,6,6-tetramethyl-9-phenyl-3,4,6,7,9,10 hexahydroacridine-1,8(2H,5H)-dione (Table 3, entry 1). IR (cm-1): 3435, 3275, 2951, 2885, 1624, 1474, 1366, 1227, 1150; ^{1}H NMR (δ): 0.96 (s, 6H), 1.01 (s, 6H), 2.18 (d, 2H), 2.28 (d, 2H), 2.39 (d, 2H), 2.42 (d, 2H), 4.81(s, 1H), 7.15-7.23 (m, 5H), 9.37 (s, 1H). ^{13}C NMR: 196.37, 162.29, 143.63, 129.89, 129.73, 128.31, 115.03, 50.70, 40.86, 32.18, 31.83, 29.24, 27.27; Mass: 349.5

3,3,6,6-tetramethyl-9-(3-nitrophenyl)-3,4,6,7,9,10 hexahydroacridine-1,8 (2H,5H)-dione (Table 3, entry 2). IR (cm^{-1}): 3345, 3189, 2954, 2872, 1719, 1607, 1465, 1379, 1224, 1103, 1064, 933, 758, 688, 656; ^{1}H NMR (δ): 1.12 (s, 6H), 1.27 (s, 6H), 2.40 (q, 4H), 2.48 (s, 4H), 5.54 (s, 1H), 7.44 (d, 2H), 8.02 (d, 2H), 8.87 (s, 1H); ^{13}C NMR: 196.40, 163.02, 148.33, 146.28, 135.81, 128.80, 122.48, 121.69, 114.55, 50.62, 40.81, 32.26, 32.06, 29.20, 27.31; Mass: 395 (M+1)

9-(4-methoxyphenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydroacridine-1,8 (2H, 5H)-dione (Table 3, entry 5). IR (cm-1): 3273, 3203, 3068, 2954, 1640, 1602, 1476, 1394, 1361, 1218, 1139, 832, 724, 662; ^{1}H NMR (δ): 0.99 (s, 2H), 1.09 (s, 6H), 2.20 (q, 4H), 2.45 (s, 4H), 3.73 (s, 3H), 4.69 (s, 1H), 6.75 (d, 2H), 7.19 (d, 2H) 8.11 (s, 1H); ^{13}C NMR: 196.59, 162.08, 144.01, 136.42, 120.02, 115.79, 113.91, 112.27, 55.87, 50.75, 40.85, 32.16, 29.26, 27.26; Mass: 380 (M+1)

Table 3: Synthesis of acridine derivatives using [Bmim]ClO_4 ionic liquid

Sr. No.	*Aldehyde*	*Product* [a]	*Time (h)*	*Yield* [b] *(%)*	*Mp. (°C)*
1			1.35	85	190-192
2			1.40	85	284-286
3			2.0	84	265-268
4			1.35	82	285-287
5			2.10	80	268-270
6			1.45	82	220-222
7			1.40	82	239-241
8			1.50	80	> 300
9			1.30	85	296-298
10			1.45	83	278-280

[a] All the product were characterized by IR spectral data and comparison of their melting point with those of the authentic samples. Also the structures of the some products were confirmed by ^{1}H NMR spectral data. [b] Isolated yield.

4. Conclusions

In conclusion, we have reported a simple innovative catalytic method for the synthesis of acridine derivatives by one-pot three-component reaction of dimedone, aromatic aldehydes and ammonium acetate using [Bmim]ClO_4 as an efficient, reusable and green solvent and catalyst. The catalyst can be recycled after a distillation work-up, and reused three times without substantial reduction in its catalytic activity. High yields, short reaction times and easy work-up are advantages of this protocol.

References

[1] V. Thiagarajan, P. Ramamurthy, D.V.T. Thirumalai, Ramakrishnan, Organic Letter, 7, pp.657–660, 2005.
[2] P. Shanmugasundaram, P. Murugan, V.T. Ramakrishnan, N. Srividya, P. Ramamurthy, Heteroatom Chemistry, 7, pp.17–22, 1996.
[3] H.J. Timpe, S. Ulrich, C. Decker, J.P. Fouassier, Macromolecules, 26, pp. 4560–4566, 1993.
[4] P. Shanmugasundarm, K.J. Prabahar, V.T. Ramakrishnan, Journal of. Heterocyclic Chemistry, 30, pp.1003–1007, 1993.
[5] P. Murugan, P. Shanmugasundaram, B. Venkatachalapathy, V.T. Ramakrishnan, N. Srividya, P. Ramamurthy, K. Gunasekaran, D. Velmurugan, J. Chem. Soc. Perkin Trans 2, pp. 999–1004, 1998.
[6] K.J. Prabahar, V.T. Ramakrishnan, D. Sastikumar, D. Selladurai, V. asilamani, Indian J. Pure Appl. Phys., 29, pp. 382–384, 1991.
[7] A. Islam, P. Murugan, K. C. Hwang, C. H. Cheng, Synth. Met., 139, pp. 347–353, 2003.
[8] H. Mohan, N. Srividya, P. Ramamurthy, J. P. Mittal, J Chem. Soc., Faraday Trans., 92, pp.2353–2359, 1996.
[9] V. Klusa, Drugs Future, 26, pp.135–138, 1995.
[10] J.L. Reid, P. A. Meredith, F. Pasanisi, J. Cardiovasc. Pharmacol., 7, pp.S18–S20, 1985.
[11] K.K. Pasunooti, C.N. Jensen, H. Chai, M.L. Leow, D.W. Zhang, X.W. Liu, J. Comb. Chem., 12, pp. 577–581, 2010.
[12] H.W. Lee, S.J. Shin, H. Yu, S.K. Kang, C.L. Yoo, Org. Proc. Res. Dev., 13, pp.1382–1386, 2009.
[13] R. Mannhold, B. Jablonka, W. Voigdt, Eur. J. Med. Chem., 27, pp.229–235, 1992.
[14] R.Boer, V. Gekeler, Drugs Future, 20, pp.499–509, 1995.
[15] A. Hantzsch, J. Liebigs, Ann. Chim., 215, pp. 1–82,1882.
[16] A.A. Bakibaev, V.D. Fillimonov, E.S. Nevgodova, Zh. Org. Khim., 27, pp.1512–1519, 1991.
[17] G.P. Hua, X.J. Zhang, F. Shi, S.J. Tu., J.N. Xu, Q. Wang, X.T. Zhu, J. P. Zang, S.J. Ji, Chin. J. Chem., 23, pp. 1646–1650, 2005.
[18] N. Martin, M. Quinteiro, C. Seoane, J.L. Soto, A. Mora, M. Suarez, A. Morales, E. Ochoa, J.D. Bosque, Journal of Heterocyclic Chemistry, 32, pp.235–238, 1995.
[19] D. Patil, D. Chandam, A. Mulik, P. Patil, S. Jagadale, R. Kant, V. Gupta, M. Deshmukh, Catalysis Letter, 2014, doi: 10.1007/s10562-014-1202-z
[20] X.S. Wang, D.Q. Shi, Y.F. Zhang, S.H. Wang, S.J. Tu, Chinese Journal of Organic Chemistry, 24, pp.430–432, 2004.
[21] T.S. Jin, J.S. Zhang, T.T. Guo, A.Q. Wang, T.S. Li, Synthesis, pp.2001–2005, 2004.
[22] K. Venkatesan, S.S. Pujari, K.V. Srinivasan, Synthetic Communication, 39, pp.228-241, 2009.
[23] B. Das, P. Thirupathi, I. Mahender, V. S. Reddy, Y.K. Rao, J. Mol. Catal. A, 247, pp.233–239, 2006.
[24] L.M. Wang, J. Sheng, L. Zhang, Tetrahedron Letters, 61, pp.1539–1543, 2005.
[25] S. Ko, M.N.V. Sastry, C. Lin, C.F. Yao, Tetrahedron Letters, 46, pp.5771–5774, 2005.
[26] Ko Sh., C.F. Yao, Tetrahedron Letters, 62, pp.7293–7299, 2006.
[27] S. Rostamizadeh, A. Amirahmadi, N. Shadjou, A.M. Amani, Journal of Heterocyclic Chemistry, 49, pp.111–115, 2012.
[28] A. Davoodnia, A. Zare-Bidaki, H. Behmadi, Chinese journal of catalysis, 33 (11), pp.1797-1801, 2012.
[29] S. Balalaie, F. Chadegani, F. Darviche, H.R. Bijanzadeh, Chin. J. Chem., 27, pp. 1953, 2009.
[30] K. Niknam, F. Panahi, D. Saberi, M. Mohagheghnejad, J. Heterocyclic Chem., 47, pp.292, 2010.
[31] C.O. Okoro, M.A. Ogunwale, T. Siddiquee, Appli. Sci, 2, pp. 368-374, 2012.
[32] M. Nikpassand, M. Mamaghani, K. Tabatabaeian, Molecules, 14, pp.1468-1474, 2009.
[33] a) S.R. Cherkupally, R. Mekela, Chem. Pharma Bull., 56, 1002-1004, 2008. b) A. Kumar, R.A. Maurya, Synlett, 6, pp. 883-885, 2008. c) A. Kumar, S. Sharma, V.D. Tripathi, R.A. Maurya, S.P. Srivastava, G. Bhatia, A.K. Tamrakar, A.K Srivastava, Bioorg. Med. Chem., 18, pp.4138-4148, 2010.
[34] A. Mobinikhaledi, N. Foroughifar, M.A. Bodaghifard, H. Moghanian, S. Ebrahimi, M. Kalhor, Synthetic Communication, 39, pp.1166-1174, 2009.
[35] M. Maheswara, V. Siddaiah, G.L.V. Damu, C.V. Rao, Arkivoc (ii), pp.201-206, 2006.
[36] B. Kaur, H. Kumar, J. Chem. Sci., 125 (5), 989–992, 2013.
[37] Q. Zhang, S. Zhang and Y. Deng, Recent advances in ionic liquid catalysis, Green Chem., 13, pp.2619-2637, 2011.

Author Profile

Dr. Mrs. Sangita S. Makone received M. Sc. from Dr. Babasaheb Ambedkar Marathwada University in 1991. She completed her M. Phil. in 1997 and Ph. D. in 2003 from Swami Ramanad Teerth Marathwada University, Nanded. Now she is working as Professor in the school of chemical sciences, in S.R.T.M. University, Nanded and incharge H.O.D. of physical chemistry. She completed one major research project on the topic "Organic reactions in an aqueous media" funded by DST New Delhi. She has number of publications on her record in national and international journal. She has also awarded for Best-teacher of S.R.T.M. University campus in 2012.