DOI 10.5012/bkcs.2009.30.12.2883

Articles

Microwave-Assisted Synthesis of 3-Styrylchromones in Alkaline Ionic Liquid

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Received June 15, 2009, Accepted July 10, 2009

A simple, highly efficient and environmentally benign method for the synthesis of 3-styrylchromones from 3-formylchromones and 4-nitrophenylacetic acid/4-nitrotolune in the presence of catalytic amount of basic ionic liquid 1-butyl-3-methylimidazolium hydroxide [(bmim)OH] carried out under the influence of microwave irradiation. This method gives remarkable advantages such as, short reaction times, simple work-up procedure and moderate to good yields. The ionic liquid was successfully reused for four cycles without significant loss of activity.

Key Words: 3-Styrylchromone, 3-Formylchromone, [Bmim]OH, Microwave irradiation

Introduction

Styrylchromones constitute a small but significant group of oxygenated heterocyclic compounds which have shown marked biological activities.[1-4] Synthetic 2-styrylchromone derivatives exhibit potent cytotoxic, *anti*-allergic, *anti*-viral, and *anti*-cancer activity.[5] Hormathamnione is exceptionally cytotoxic to P388 lymphocytic leukemia and HL-60 promyelocytic leukemia cell lines *in vitro* and appears to be a selective inhibitor of RNA synthesis[6a] and 6-Desmethoxyhormothamnione showed cytotoxicity to 9 KB cell lines.[6b] Despite the relationship of 3-styrylchromones with the well-studied 2-styrylchromones very little is known about their biological activities; only *anti*-fungal and *anti*-bacterial activities have been reported.[7]

Due to great importance, many synthetic strategies have been employed for the synthesis of 3-styrylchromone. In 2002, Shingare and coworkers reported the condensation of 3-formylchromones with 2,4-dinitrotoluene in the presence pyridine.[7] A modification of this method[8] which consists of the condensation of 3-formylchromones with 4-nitrophenylacetic acid followed by decarboxylation reaction, allowed the synthesis of new 3-styrylchromone derivatives. The synthetic method for 3-styrylchromones involves the Wittig reaction of 3-formylchromones with benzylic yields[9] and gives an isomeric mixture of (*E*) and (*Z*) 3-styrylchromones. The obtained isomers have been separated by thin layer chromatography. Also, Samat *et al.*[10] reported the synthesis of novel 3-styrylchromones which can also be regarded as 3-styrylflavones. These compounds have been obtained from the reaction of 1-(2-hydroxyphenyl)-3-phenylpropan-1,3-diones and phenyl acetaldehydes under a mild acid-catalyzed condition. These methods have not been entirely satisfactory, owing to such drawbacks as low yields, long reaction time, expensive and toxic catalysts.

Chromones and their derivatives of different oxidation level are well known naturally occurring oxygen-containing heterocyclic compounds which perform important biological functions in nature. It is known that certain natural and synthetic derivatives possess important biological activities[11-13] such as *anti*-tumor, *anti*-hepatotoxic, *anti*-oxidant, *anti*-inflammatory, *anti*-spasmolytic, oestrogenic and *anti*-bacterial.

In recent years, application of ionic liquids in organic synthesis have attracted considerable attention due to their special properties such as good solvating capability, wide liquid range, negligible vapor pressure, easy recycling, high thermal stability and rate enhancers.[14-16] Nowadays, much attention has been focused on organic reactions catalyzed by ionic liquids.[17-19] Particularly, imidazolium ionic liquids have been successfully used in many organic transformations includes Diels-Alder,[20a] Wittig,[20b] Hantzsch condensation.[20c]

The science of green chemistry is developed to meet the increasing demand of environmentally benign chemical processes. The application of microwaves (MWs), as an efficient heating source for organic reactions and it has been reported in the literature.[21] The main advantage of microwave assisted organic synthesis is the shorter reaction time using only small amount of energy.[21] Many microwave-assisted transformations offer additional convenience in the field of organic synthesis because of simple experimental procedure and high yields.

Experimental

Melting points were obtained on a melting point apparatus with capillary tubes and are uncorrected. IR spectra were recorded on Perkin-Elmer FTIR Spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on Varian 300 MHz spectrophotometer in $CDCl_3$ as a solvent and TMS as an internal standard. Microwave irradiation was carried out in a microwave oven (BPL, 800T, 2450 MHz) with power output of 800 W.

Synthesis of substituted 3-styrylchromone 3 (a-j). A mixture of substituted 3-formylchromone (1 mmol), 4-nitrophenyl-

acetic acid/4-nitrotolune (1 mmol), [bmim]OH (5 mol%) were taken in a beaker (50 mL). The reaction mixture was mixed properly with the help of glass rod and irradiated (180 Watt) for a period of 5 sec at a time. The progress of reaction was monitored by TLC. After completion of reaction, the reaction content cooled to room temperature. The product was extracted with diethyl ether (2 × 20 mL) and the insoluble ionic liquid [bmim]OH directly recycled in subsequent runs. The organic layer was washed by brine (2 × 10 mL), dried over anhydrous $NaSO_4$ and solvent removed on rotary evaporator under reduced pressure. The crude solid compounds were crystallized by acetic acid to afford the desired products **3** (**a-j**). All the products were characterized by IR, ^{1}H NMR and mass spectra and by comparison of their physical characteristics with those of the authentic compounds.

Spectral data of principal compounds. Compound (**3a**): ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 2.25 (s, 3H), 6.70 (s, 1H), 7.60 (s, 1H), 7.23 (s, 1H), 7.10 (d, 1H, *J* = 12 Hz), 6.80 (d, 1H, *J* = 12 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 8.20 (d, 2H, *J* = 8.1 Hz). Compound (**3b**): ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 2.70 (s, 6H), 6.90 (s, 1H), 7.26 (s, 1H), 7.21 (s, 1H), 7.10 (d, 1H, *J* = 12 Hz), 6.80 (d, 1H, *J* = 12 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 8.20 (d, 2H, *J* = 8.1 Hz) Compound (**3d**): ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 6.79 (d, 1H, *J* = 8 Hz), 7.40 (d, 1H, *J* = 8 Hz), 7.70 (s, 1H), 7.21 (s, 1H), 7.10 (d, 1H, *J* = 12 Hz), 6.80 (d, 1H, *J* = 12 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 8.20 (d, 2H, *J* = 8.1 Hz) Compound (**3e**): ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 6.92 (s, 1H), 7.70 (s, 1H), 7.26 (s, 1H), 7.10 (d, 1H, *J* = 12 Hz), 6.80 (d, 1H, *J* = 12 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 8.20 (d, 2H, *J* = 8.1 Hz) Compound (**3f**): ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 2.28 (s, 3H), 6.80 (s, 1H), 6.90 (d, 1H, *J* = 8 Hz), 7.80 (d, 1H, *J* = 8 Hz), 7.20 (s, 1H), 7.10 (d, 1H, *J* = 12 Hz), 6.80 (d, 1H, *J* = 12 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 8.20 (d, 2H, *J* = 8.1 Hz) Compound (**3h**): ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 2.30 (s, 6H), 6.68 (s, 1H), 7.40 (s, 1H), 7.21 (s, 1H), 7.10 (d, 1H, *J* = 12 Hz), 6.80 (d, 1H, *J* = 12 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 8.20 (d, 2H, *J* = 8.1 Hz) Compound (**3j**): ^{1}H NMR ($CDCl_3$, 300 MHz, δppm): 2.27 (s, 3H), 6.83 (d, 1H, *J* = 8 Hz), 7.31 (d, 1H, *J* = 8 Hz), 7.60 (s, 1H), 7.20 (s, 1H), 7.10 (d, 1H, *J* = 12 Hz), 6.80 (d, 1H, *J* = 12 Hz), 7.50 (d, 2H, *J* = 8.1 Hz), 8.20 (d, 2H, *ss* = 8.1 Hz).

Results and Discussion

In continuation of our research interest in microwave-assisted

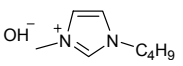
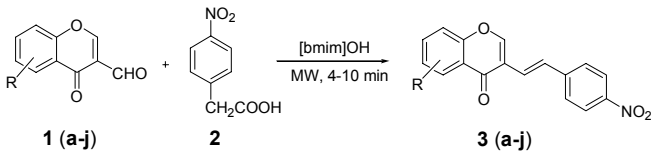
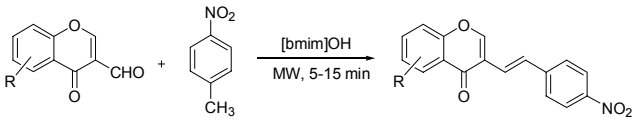


Figure 1. 1-Butyl-3-methylimidazolium hydroxide [(bmim)OH].



1 (**a-j**) **2** **3** (**a-j**)

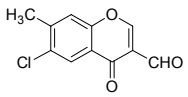
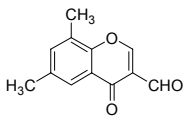
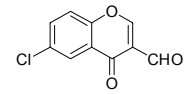
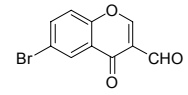
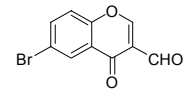
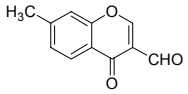
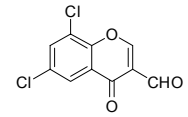
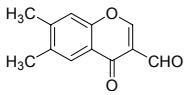
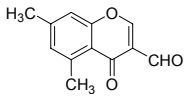
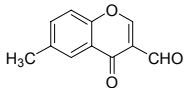
Scheme 1



1 (**a-j**) **4** **3** (**a-j**)

Scheme 2

Table 1. Synthesis of 3-styrylchromones in the presence of [bmim]OH under microwave irradiation.[a]

Entry	Aldehyde	4-nitrophenyl-acetic acid Yield (%)[b]	4-nitrotolune Yield (%)[b]	M.P. (°C)
3a		59	50	250 - 252
3b		56	53	232 - 234
3c		65	37	202 - 204
3d		67	35	258 - 260
3e		68	34	260 - 262
3f		64	30	262 - 264
3g		70	39	269 - 271
3h		60	30	250 - 252
3i		60	45	232 - 234
3j		54	34	240 - 242

[a]All the products were characterized by IR, ^{1}H NMR and mass spectra and by comparison of their physical characteristics with those of the authentic compounds; [b]Isolated yield.

Table 2. Recycling of [bmim]OH for the synthesis of 3-(4-nitrostyryl)-6-chloro-*4H*-chromen-4-one **3c**.[a]

Entry	Cycle[b]	Yield (%)[c]
1	Fresh	65
2	1st	62
3	2nd	61
4	3rd	59
5	4th	59

[a]Reaction condition: **1a** (1 mmol), **2** (1 mmol) and [bmim]OH (5 mol%) under microwave irradiation; [b]Reaction time-5 min; [c]Isolated yield.

synthesis[22] and the development of novel synthetic methodology,[23] herein, we would like to report a simple, efficient and rapid method for the synthesis of 3-styrylchromone (Scheme 1 and 2).

In order to find out the optimum reaction conditions, the reaction of 6-chloro-4-oxo-*4H*-chromene-3-carbaldehyde **1c** and 4-nitrophenylacetic acid **2** under the influence of microwave irradiation has been selected as model to investigate the effect of different amount of [bmim]OH on the yield. The best result was obtained by carrying out the reaction with 1 : 1 mol ratios of 6-chloro-4-oxo-*4H*-chromene-3-carbaldehyde : 4-nitrophenylacetic acid and 5 mol% of [bmim]OH (Figure 1) under microwave irradiation. Under this condition, 3-(4-nitrostyryl)-6-chloro-*4H*-chromene-4-one **3c** was obtained 65% yield after 5 min (Table 1, entry 3c). The same reaction was carried out in the absence of [bmim]OH under the same conditions, which resulted in no product formation within 30 min. This result indicates that [bmim]OH exhibit a high catalytic activity towards this organic transformation.

To evaluate the effect of MW for the model reaction (Table 1, entry 3c), we first examined the reaction without MW at 100 °C. We found low yield (35%) with prolonged reaction time (110 min) and using MW amazingly we found excellent yield (65%) with short reaction time (5 min). Therefore, we chose this method to perform the synthesis of all derivatives of 3-styrylchromone under MW irradiation.

The results of this study are summarized in Table 1. With the optimized reaction condition in hand, we have synthesized various 3-styrylchromone derivatives from substituted 3-formylchromone in the presence of [bmim]OH under influence of microwave irradiation. The condensation of 3-formylchromones with 4-nitrophenylacetic acids followed by decarboxylation reaction, allowed the synthesis of new 3-styrylchromone derivatives and gave only the (*E*) isomer. The successful synthesis of 3-styrylchromone derivatives in shorter reaction times (5 - 15 min) with moderate to good yields. It is found that condensation of 3-formylchromones with 4-nitrophenyl acetic acid (Scheme 1) required less time as compared to 4-nitrotolune (Scheme 2). Moreover, yields with 4-nitrophenyl acetic acid (54 - 70%) are found to be good as compared to 4-nitrotolune (30 - 53%). This methodology avoids the use of strong base, hazardous solvents and requires only catalytic amount of the basic ionic liquid to promote the reaction.

In view of economical and environmental friendly methodologies, recovery and reuse of the ionic liquid is highly preferable. As indicated in Table 2 (entry 3c), recycled ionic liquid shows no loss of efficiency with regard to reaction time and yield after four successive runs.

Conclusion

In conclusion, we have emphasized a new and effective methodology for the synthesis of 3-styrylchromone derivatives. The notable merits of the present methods are short reaction times, simple work-up procedure and moderate to good yield of products. Moreover, the [bmim]OH was successfully reused for four cycles without significant loss of activity. Thus a rapid, convenient and environmentally benign method for the synthesis of compounds of type **3** (**a-j**) have been achieved. To the best of our knowledge this is first report on synthesis of 3-styrylchromones derivatives in basic ionic liquid.

Acknowledgments. The authors are thankful to the Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431 004, MS, India for providing the laboratory facility.

References

1. Desideri, N.; Conti, C.; Mastropaolo, F. *Antiviral Chem. Chemother.* **2000**, *11*, 373.
2. Peixoto, F.; A. Barros, I. R. N. A.; Silva, A. M. S. *J. Biochem. Mol. Toxicol.* **2002**, *16*, 220.
3. Fernandes, E.; Carvalho, M.; Carvalho, F.; Silva, A. M. S.; Santos, C. M. M.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Bastos, M. L. *Arch. Toxicol.* **2003**, *77*, 500.
4. Filipe, P.; Silva, A. M. S.; Morlière, P.; Brito, C. M.; Patterson, L. K.; Hug, G. L.; Silva, J. N.; Cavaleiro, J. A. S.; Mazière, J.-C.; Freitas, J. P.; Santus, R. *Biochem. Pharmacol.* **2004**, *67*, 2207.
5. (a) Doria, G.; Romero, C.; Forgione, A.; Sberze, P.; Tibolla, N.; Corno, M. L.; Cruzzola, G.; Cadelli, G. *Eur. J. Med. Chem.* **1979**, *14*, 347. (b) Brion, J. D.; Le Baut, G.; Zammattio, F.; Pierre, A.; Atassi, G.; Belachmi, L. *Eur. Pat. Appl.* **1991**, EP 454, 587; *Chem. Abstr.* **1992**, *116*, 106092K.
6. (a) Gerwick, W. H.; Lopez, A.; Van Duyne, G. D.; Clardy, J.; Ortiz, W.; Baez, A. *Tetrahedron Lett.* **1986**, *27*, 1979. (b) Gerwick, W. H. *J. Nat. Prod.* **1989**, *52*, 252.
7. Sonawane, S. A.; Chavan, V. P.; Karale, B. K.; Shingare, M. S. *Ind. J. Heterocyclic Chem.* **2002**, *12*, 65
8. (a) Karale, B. K.; Gill, C. H.; Shingare, M. S. *Ind. J. Heterocycl. Chem.* **2003**, *12*, 267. (b) Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *Aveiro.* **2003**, *PO102*, 148.
9 Sandulache, A.; Silva, A. M. S.; Pinto, D. C. G. A.; Almeida, L. M. P. M.; Cavaleiro, J. A. S. *New J. Chem.* **2003**, *27*, 1592.
10. Lokshin, V.; Heynderickx, A.; Samat, A.; Pèpe, G.; Guglielmetti, R. *Tetrahedron Lett.* **1999**, *40*, 6761.
11. Atassi, G.; Briet, P.; Berthelon, J. P.; Collonges, F. *J. Med. Chem. Chim. Ther.* **1985**, *20*, 393.
12. Middleton, Jr., E.; Kandaswami, C. *The Flavonoids Advances in Research Since* 1986; Harborne, J. B., Ed.; Chapman: Hall, London, 1994; p 619.
13. Harborne, J. B.; Williams, C. A. *Phytochemistry* **2000**, *55*, 481.
14. Thomas, W. *Chem. Rev.* **1999**, *99*, 2071.
15. Sheldon, R. *Chem. Commun.* **2001**, 2399.
16. Zhao, D.; Wu, M.; Kou, Y.; Min, K. *Catal. Today* **2002**, *2654*, 1.
17. Peng, J.; Deng, Y. *Tetrahedron Lett.* **2001**, *42*, 403.
18. Shen, Z. L.; Zhou, W. J.; Liu, Y. T.; Ji, S. J.; Loh, T. P. *Green Chem.* **2008**, *10*, 283.
19. Gong, K.; He, Z.-W.; Xu, Y.; Fang, D.; Liu, Z.-L. *Monatsh.*

Chem. **2008**, *139*, 913.
20. (a) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793. (b) Le Boulaire, V. R. *Chem. Commun.* **2000**, 2195. (c) Ji, S. J.; Jiang, Z. Q.; Lu, J.; Loh, T. P *Synlett* **2004**, *5*, 831.
21. Kahveci, B.; Ozil, M.; Serdar, M. *Heteroatom Chem.* **2008**, *19*, 38.
22. (a) Karale, B. K.; Chavan, V. P.; Mane, A. S.; Hangarge, R. V.; Gill, C. H.; Shingare, M. S. *Synth. Comm.* **2002**, *32*, 497. (b) Shindalkar, S. S.; Madje, B. R.; Shingare, M. S. *Mendeleev Commun.* **2007**, *17*, 43. (c) Sapkal, S. B.; Shelke, K. F.; Shingate, B. B.; Shingare, M. S. *Tetrahedron Lett.* **2009**, *50*, 1754.
23. (a) Pawar, S. S.; Dekhane, D. V.; Shingare, M. S.; Thore, S. N. *Tetrahedron Lett.* **2008**, *49*, 4252. (b) Sadaphal, S. A.; Shelke, K. F.; Sonar, S. S.; Shingare, M. S. *Central Euro. J. Chem.* **2008**, *6*, 622. (c) Diwakar, S. D.; Bhagwat, S. S.; Shingare, M. S.; Gill, C. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4678. (d) Shelke, K. F.; Sapkal, S. B.; Shingare, M. S. *Chie. Chem. Lett.* **2009**, *20*, 283. (e) Shelke, K. F.; Sapkal, S. B.; Sonar, S. S.; Madje, B. R.; Shingate, B. B.; Shingare, M. S *Bull. Korean Chem. Soc.* **2009**, *30*, 1057. (f) Shelke, K. F.; Madje, B. R.; Sapkal, S. B.; Shingate, B. B.; Shingare, M. S. *Green Chem. Lett. Rev.* **2009**, *2*, 3. (e) Shelke, K. F.; Sapkal, S. B.; Kategaonkar, A. H.; Shingate, B. B.; Shingare, M. S. *S. Afr. J. Chem.* **2009**, *62*, 109.