# Montmorillonite K-10 mediated Erlenmeyer synthesis of 4-arylmethylene-2-phenyl-5(4*H*)-oxazolones

**N.N. Karade[a]*, S.G. Shirodkar[b], B.M. Dhoot[b] and P.B. Waghmare[b]**

[a]*School of Chemical Sciences, S. R. T. M. University, Nanded 431 606, India*

[b]*Netaji Subhash Chandra Bose College, Nanded 431 601, India*

Aromatic aldehydes and hippuric acid in acetic anhydride undergoes classical Erlenmeyer synthesis in the presence of a catalytic amount of Montmorillonite K-10 to afford the corresponding azlactones in excellent yields with high selectivity. The azlactone formation does not proceed in the absence of either acetic anhydride or Montmorillonite.

**Keywords:** Montmorillonite K-10, hippuric acid, azlactones, dehydration, acetic anhydride

4-Arylmethylene-2-phenyl-5(4*H*)-oxazolones form an important class of valuable intermediates useful in the synthesis of many natural products[1] and medicinal agents such as antitumor or antimicrobial drugs.[2] Furthermore, the amino acids containing an aromatic side chain are also accessible from azlactones by treatment with red phosphorus and aqueous hydriodic acid.[3]

The Erlenmeyer synthesis is one of the most common reactions to produce azlactones.[4] The process consists of cyclodehydration-condensation of different arylaldehydes with hippuric acid in acetic anhydride, in the presence of anhydrous sodium acetate as a homogeneous basic catalyst. The literature reveals a variety of synthetic modification of this classical Erlenmeyer reaction in relation to the substitute for sodium acetate and the stoichiometric use of acetic anhydride, under homogeneous as well as heterogeneous catalytic conditions. The homogeneous reaction conditions employ various toxic reagents like polyphosphoric acid[5], lead acetate[6], $ZnCl_2$[7] and $SO_3$ in DMF.[8] The inexpensive and ecofriendly Bi(III) salts are good catalysts but the reaction requires acetic anhydride as the solvent.[9] The heterogeneous catalysis brought about by inorganic reagents like KF/NaOAc[10] and $H_3BO_3$[11] supported on solid calcinated $Al_2O_3$ requires special procedures for the catalyst preparation. However, these methods have not been entirely satisfactory, owing to drawbacks such as the use of commercially unavailable catalysts, low yields, long reaction time, inconvenient preparation of the catalyst at very high temperature (400 °C), difficulty in product isolation, corrosiveness and effluent pollution.

The last two decades have witnessed an explosive growth in the application of heterogeneous catalysis brought about by inorganic solids such as Montmorillonite K-10.[12-14] The commercially available Montmorillonite K-10 is an inexpensive and nontoxic inorganic solid material possessing both Brønsted and Lewis acidity.[15] In continuation of our interest[16] in Montmorillonite K-10, here we report its use in the classical Erlenmeyer azlactone synthesis (Scheme 1).

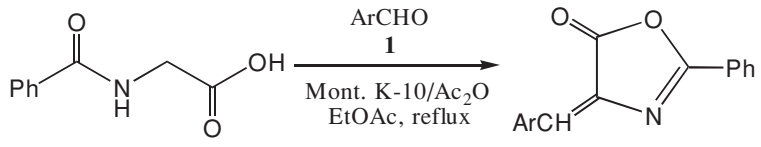
To study this process, we have examined the model reaction of benzaldehyde (10 mmol), hippuric acid (**2**) (10 mmol) and acetic anhydride (15 mmol) using Montmorillonite K-10 (20 % wt. w.r.t. **2**). This mixture was refluxed in ethyl acetate and indeed, 4-benzylidene-2-phenyl-5(4*H*)-oxazolone (**3**, Ar = Ph) was formed after 4 hours in 89 % yield. This reaction was also found to be successful in acetonitrile as solvent but in lower yield (61%). It is noteworthy that azlactone formation is not observed in the absence of either acetic anhydride or Montmorillonite K-10. Similarly, other aromatic aldehydes containing electron releasing (entries 2–5) and withdrawing (entries 8–9) groups gave the corresponding azlactones in good purity. The excellent yields demonstrate the efficiency of the Montmorillonite K-10 clay catalyst (Table 1). It is noteworthy that a hydroxy group (entries 6–7) is simultaneously acetylated during the reaction.[17] This is in contrast to the polyphosphoric acid catalysed azlactone synthesis.[5] Cinnamaldehyde (entry 10) also gives the azlactones in 62% yield without any side products formed due to double bond participation. However, the reaction was found to be unsuccessful with aliphatic aldehydes such as butyraldehyde and isobutyraldehyde (entries 11–12) in forming any azlactones.

**Table 1** Montmorillonite K-10 mediated azlactone synthesis from hippuric acid and aromatic aldehydes

| Entry | Aldehyde RCHO R = | Reaction time /h | Yield[a] /% | M.p. of azlactone /°C Found | Reported |
|---|---|---|---|---|---|
| 1 | Ph- | 4 | 89 | 167 | 166[10] |
| 2 | *p*-$MeOC_6H_4$- | 6 | 83 | 154 | 157[10] |
| 3 | *p*-$Me_2NC_6H_4$- | 6 | 84 | 212 | 213[9] |
| 4 | *p*-$MeC_6H_4$- | 5 | 81 | 143 | 141[10] |
| 5 | *p*-$ClC_6H_4$- | 6 | 78 | 194 | 197[10] |
| 6 | *p*-$HOC_6H_4$- | 7 | 80[b] | 144 | 148[10] |
| 7 | *o*-$HOC_6H_4$- | 8 | 77[b] | 131 | 132[10] |
| 8 | *m*-$O_2NC_6H_4$- | 8 | 73 | 166 | 165[10] |
| 9 | *p*-$O_2NC_6H_4$- | 6 | 77 | 240 | 241[10] |
| 10 | PhCH=CH- | 7 | 69 | 149 | 151[10] |
| 11 | $CH_3CH_2CH_2$- | 24 | – | – | – |
| 12 | $(CH_3)_2CH$- | 24 | – | – | – |

[a]Isolated yield after crystallisation. All products show satisfactory spectral data.
[b]Products are *O*-acetylated at the phenolic group.

In conclusion, we have extended the use of the environmentally friendly inorganic solid acid Montmorillonite K-10 to the important classical Erlenmeyer azlactone synthesis. Advantages of Montmorillonite catalysis are the cleaner




**2** **3**

**Scheme 1**

* Correspondent. E-mail: nnkarade@rediffmail.com

reaction conditions and the reduced reaction time compared with 24 hours for the classical Erlenmeyer azlactone synthesis. Further advantages include high yields of the products, a simple product isolation technique, recoverability of the catalyst, and "green" reaction conditions.

## Experimental

Montmorillonite K-10 was purchased from Lancaster Chemicals and was used as received without any pretreatment or activation. The products were characterised by their melting points and/or IR and $^1$H NMR spectra and by comparison with literature data.

*General procedure for the synthesis of azlactones*

A mixture of the benzaldehyde **1** (10 mmol), hippuric acid **2** (10 mmol), acetic anhydride (15 mmol) and Montmorillonite K-10 (20 % by wt rel. to **2**) was refluxed in ethyl acetate (20 ml) with occasional stirring for 4–8 h. as indicated in Table 1. The reaction was monitored by TLC. The Montmorillonite K-10 was filtered off and washed with ethyl acetate. The solvent was removed under reduced pressure to afford the crude product. The crude product was recrystallised from acetone-water (2:1) to give the pure yellow crystalline azlactones **3**.[18]

The authors are thankful to UGC, New Delhi, for financial assistance.

*Received 13 June 2004; accepted 23 November 2004*
*Paper 04/2574*

## References

1 (a) F. Cavalier and J. Verducci, *Tetrahedron Lett*., 1995, 36, 4425; (b) S.N. Mitra, S. Dey, S. Karthikeyan and T.P. Singh, *Biopolymers*, 1997, 41, 1997; (c) R. Cannella, F. Clerici, M.L. Gelmi, M. Penso and D. Pocar, *J. Org. Chem*. 1996, 61, 1854; (d) R. Bossio, S. Marcaccini, R. Pepino and P. Paoli, *J. Heterocycl*. Chem., 1994, 31, 729.

2 (a) A.P. Martinez, W.W. Lee and L. Goodman, *Tetrahedron*, 1964, 20, 2763; (b) M. L. Gelmi, F. Clerici and A. Melis, *Tetrahedron*, 1997, 53, 1843.

3 (a) K. Gootwald and D. Seebach, *Tetrahedron*, 1999, 55, 723; (b) D. Seebach, G. Jaeschke, K. Gootwald, K. Matsuda, M. Breuning and G. Bringmann, Tetrahedron, 1997, 22, 7359; (c) F.M. Bautista, J.M. Campelo, D.L. Garcia and J.M. Marinas, *Aminoacids*, 1992, 2, 87.

4 (a) R. Filler, Adv. *Heterocyclic Chem*. 1954, 4, 75; (b) H.E. Carter, *Org. Reactions*, Wiley, New York, 1946, 3, 198; (c) S.P. Dhoubhadel, J. Indian Chem. Soc., 1986, 63, 757.

5 Y.S. Rao, J. Org. Chem., 1976, 41, 722.

6 (a) E. Galantay, A. Szabo and J. Fried, J. Org. Chem., 1963, 28, 98; (b) T. Wieland and V. Georgi, *Liebigs Ann. Chem*., 1966, 700, 133; (c) C. Cativiela and E. Melendez, *Synthesis*, 1978, 832; (d) C. Cativela, M.D. Diaz-de-Villegas and J.A. Galvez, *Tetrahedron Lett*., 1999, 40, 1027.

7 P.S. Rao and R.V. Venkatratnam, *Ind. J. Chem*., B, 1994, 33, 984.

8 E. Baltazzi and E.A. Davis, *Chem. Ind. (London)* 1962, 929.

9 (a) K.A. Monk, D. Sarapa and R.S. Mohan, *Synth. Commun*. 2000, 30, 3167; (b) M.M. Khodaei, A.R. Khosropour and S.J.H. Jomor, *J. Chem. Research (S)*, 2003, 638.

10 F.M. Bautista, J.M. Campelo, A. Garcia, D. Luna, J.M. Marinas and A.A. Romero, *J. Chem. Soc., Perkin Trans*. 2, 2002, 227.

11 (a) J. Kashyap, A.B. Chetry, P.J. Das, *Synth Commun*., 1998, 28, 4187; (b) H.J. Ringold, B. Loeken, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc*., 1956, 78, 816.

12 F. Bigi, L. Chesini, R. Maggi and G. Sartori, *J. Org. Chem*., 1999, 64, 1033.

13 S. Frere, V. Thiery and T. Besson, *Tetrahedron Lett*., 2001, 42, 2791.

14 S. Kanagasabapathy, A. Sudalai and B.C. Benicewicz, *Tetrahedron Lett*., 2001, 42, 3791.

15 (a) T.J. Pinnavia, *Science* 1983, 220, 4595; (b) P. Laszlo, *Science* 1987, 235, 1473.

16 (a) N.N. Karade, S.S. Kate and R.N. Adude, *Synlett*, 2001, 10, 1573; (b) N.N. Karade, S.G. Shirodkar and R.A. Potrekar, *J. Chem. Research (S)*, 2003, 652.

17 For acylation of alcohols, phenols, and amines catalyzed by Montmorillonite K-10, see: (a) T.-S. Li and A.-X. Li, *J. Chem. Soc., Perkin Trans*. 1, 1998, 1913. (b) A.-X. Li, T.-S. Li and T.-H. Ding, *Chem. Commun*., 1997, 1389.

18 Characterization of 4-benzylidene-2-phenyloxazol-5(4H)-one: IR (cm-1, nujol): 1797, 1654, 1551, 771, 700; 1H NMR (300 MHz; CDCl3): δ 7.27 (s,1H), 7.48-7.64 (m, 5H), 8.19-8.22 (m, 5H); m.p. 167 °C.