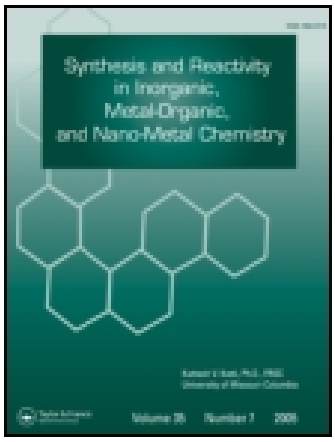

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Calcium Hydroxide Is an Efficient Catalyst for Synthesis of Polyhydroxy Chalcones

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Calcium hydroxide was found to be an efficient catalyst for synthesis of polyhydroxy chalcones. This method has been employed to synthesize various 2′,4′-dihydroxychalcones having various substituents on the B ring. The merits of this method include shorter reaction time, inexpensive and easily available catalyst, high yield, and easy workup compared to other reported methods.

Keywords aldehyde, calcium hydroxide, condensation, polyhydroxy chalcone, 2,4-dihydroxyacetophenone

INTRODUCTION

Polyphenols represent one of the most ubiquitous classes of compounds found in our daily diet.[1] Chalcones have continued to attract attention because of their interesting biological activities such as anticancer,[2] antimalarial,[3] antimicrobial,[4] anti-inflammatory,[5] and antioxidants,[6] and they constitute an important group of natural compounds that are especially abundant in fruits (e.g., citruses, apples), vegetables (e.g., tomatoes, shallots, bean sprouts, potatoes), and various plants species (e.g., licorice), many of which have been used for centuries in traditional herbal medicine.[7,8] The majority of naturally occurring chalcones contain polyhydroxy functional groups. Chemically chalcones are open chain flavanoids bearing two aromatic rings linked by a three carbon enone moiety. These polyhydroxy chalcones are involved as the intermediates for the synthesis of other flavonoids.[9,10] The classical approach for synthesis of chalcones involve Clasein-Schmidt condensation between aryl aldehydes and acetophenone in the presence of alkali metal hydroxides.[11] Several catalysts such as basic alumina,[12] zinc chloride,[13] Lewis acids such as BF_3, $AlCl_3$,[14] and Mg-Al-OBu hydrotalcite[15] have also been explored to effect this transformation and other reagents studied for the same include use of strong alkali catalyst under phase transfer conditions,[16] barium hydroxide in ethanol,[17] calcine $NaNO_3$/natural phosphate,[18] potassium phosphate,[19] the use of ultrasonic conditions,[20] C-200 as solid support under grinding conditions,[21] *via* Suzuki coupling reaction.[22] All these reported methods were used for the synthesis of 2′-hydroxy chalcones. However, these methods suffer when condensation reaction is sought between dihydroxy ketone and aldehyde in terms of yield, oily product, tedious extraction procedure, and longer reaction time. In most of the cases synthesis of polyhydroxy chalcones require protection and deprotection of the hydroxyl group and involve two additional steps. Hence, we felt there is a need to develop a new method for the synthesis of polyhydroxy chalcones by an eco-friendly approach in short time using inexpensive catalyst involving easy isolation procedure and the same has been realized with calcium hydroxide as basic catalyst to effect the Claisen-Schmidt condensation.

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EXPERIMENTAL

All purchased chemicals were of analytical grade and used without further purification. Melting point is determined by open capillary method and uncorrected. The ^{1}H NMR spectra were obtained on a Bruker DRX-300 Avance instrument (Pune, India) using $CDCl_3$ as solvent and TMS as internal standard at 300 MHz. All products are known.

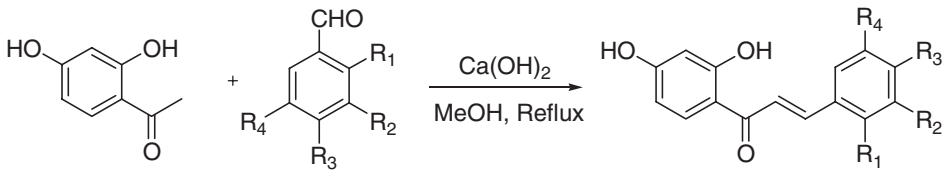
General Procedure for Synthesis of Polyhydroxy Chalcone

To a mixture of dihydroxy acetophenone (5 mmol, 0.760 g) and substituted benzaldehyde (5 mmol, 0.525 g) dissolved in 10 mL of methanol, calcium hydroxide (15 mmol, 1.11 g) was added and subjected to reflux conditions. The progress of the reaction was monitored by TLC and after completion of the reaction, it was cooled, poured into cold water, and neutralized with dil. HCl. The solid precipitated was filtered and washed with water, and then with cold ethanol. Recrystallization from ethanol afforded pure chalcone.

Spectral Data for Selected Sample

(2E)-1-(2, 4-dihydroxyphenyl)-3-(4-methylphenyl) prop-2-en-1-one (3b)

IR (KBr) cm^{-1}: 3372 (−OH str.), 1693 (C=O str.), 3041 (Ar C−H str.), 1588, (C=C ring str), 1225 (C−O str.), ^{1}HNMR ($CDCl_3$): δ = 2.12 (s, 3H, $–CH_3$), 6.72–6.84 (m, 3H, $–C_6H_3$), 6.74 (d, J = 15 Hz, 1H, =CH), 7.24–7.46 (m, 4H, $–C_6H_4$), 7.40



1 2 3

SCH. 1. Synthesis of polyhydroxy chalcone by calcium hydroxide.

(d, J = 15 Hz, 1H, =CH), 11.65 (s, 1H, −OH), 12.40 (s, 1H, −OH).

(2E)-1-(2, 4-dihydroxyphenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (3c)

IR (KBr) cm^{-1}: 3383 (−OH str.), 1690 (C=O str.), 3041 (Ar C−H str.), 1587, (C=C ring str), 1226 (C−O str.), ^{1}HNMR ($CDCl_3$): $\delta = 3.88$ (s, 3H, 4-OCH_3), 6.57–7.02 (m, 3H, $-C_6H_3$), 7.41 (d, J = 15 Hz, 1H, =CH), 7.87–8.04 (m, 4H, $-C_6H_4$), 7.92 (d, J = 15 Hz, 1H, =CH), 12.74 (s, 1H, −OH), 13.52 (s, 1H, −OH).

(2E)-1-(2, 4-dihydroxyphenyl)-3-(3, 4-dihydroxyphenyl)prop-2-en-1-one (3d)

IR (KBr) cm^{-1}: 3372 (−OH str.), 1680 (C=O str.), 3041 (Ar C−H str.), 1590 (C=C ring str), 1220 (C−O str.), ^{1}H-NMR ($CDCl_3$): $\delta = 6.42$(d, $J = 15$ Hz, 1H, =CH), 6.86–6.97 (m, 3H, $-C_6H_3$), 7.21–7.26 (m, 3H, $-C_6H_3$), 7.61 (d, $J = 15$ Hz, 1H, =CH), 10.49 (s, 1H, −OH), 13.54 (s, 1H, −OH).

(2E)- 3-(2, 4-dichlorophenyl)-1-(2, 4-dihydroxyphenyl)-prop-2-en-1-one (3e)

IR (KBr) cm^{-1}: 3483 (−OH str.), 1692 (C=O str.), 3048 (Ar C−H str.), 1587 (C=C ring str), 1222 (C−O str.), ^{1}H-NMR ($CDCl_3$): $\delta = 6.52–6.56$ (m, 3H, $-C_6H_3$), 7.48 (d, J = 15 Hz, 1H, =CH), 7.66–7.79 (m, 3H, $-C_6H_4$), 8.13 (d, J = 15 Hz, 1H, =CH), 12.74 (s, 1H, −OH), 13.20 (s, 1H, −OH).

(2E)- 3-(4-chlorophenyl)-1-(2, 4-dihydroxyphenyl)-prop-2-en-1-one (3f)

IR (KBr) cm^{-1}: 3375 (−OH str.), 1690 (C=O str.), 3039 (Ar C−H str.), 1592 (C=C ring str), 1224 (C−O str.), ^{1}H-NMR ($CDCl_3$): $\delta = 6.47–6.50$ (m, 3H, $-C_6H_3$), 7.50 (d, J = 15 Hz, 1H, =CH), 7.68–7.82 (m, 4H, $-C_6H_4$), 8.01 (d, J = 15 Hz, 1H, =CH), 12.68 (s, 1H, −OH), 13.14 (s, 1H, −OH).

(2E)-1-(2, 4-dihydroxyphenyl)-3-(4-nitrophenyl)prop-2-en-1-one (3i)

IR (KBr) cm^{-1}: 3382 (−OH str.), 1681 (C=O str.), 3037 (Ar C−H str.), 1589 (C=C ring str), 1221 (C−O str.), ^{1}H-NMR ($CDCl_3$): $\delta = 6.71–6.93$ (m, 3H, $-C_6H_3$), 7.29 (d, $J = 15$ Hz, 1H, =CH), 7.71–7.77 (m, 4H, $-C_6H_4$), 8.02 (d, $J = 15$ Hz, 1H, =CH), 10.08 (s, 1H, −OH), 10.52 (s, 1H, −OH).

(2E)-1-(2, 4-dihydroxyphenyl)-3-(4-hydroxyphenyl)prop-2-en-1-one (3k)

IR (KBr) cm^{-1}: 3391(−OH str.), 1693(C=O str.), 3045 (Ar C−H str.), 1594 (C=C ring str), 1223 (C−O str.), ^{1}H-NMR ($CDCl_3$): $\delta = 7.75–7.80$ (m, 3H, $-C_6H_3$), 7.95 (d, J = 15 Hz, 1H, =CH), 8.27–8.35 (m, 4H, $-C_6H_4$), 8.21 (d, J = 15 Hz, 1H, =CH), 10.56 (s, 1H, −OH), 12.51 (s, 1H, −OH).

(2E)-1-(2, 4-dihydroxyphenyl)-3-(4-hydroxy-3-methoxyphenyl) prop-2-en-1-one (3o)

IR (KBr) cm^{-1}: 3373(−OH str.), 1686 (C=O str.), 3039 (Ar C−H str.), 1586 (C=C ring str), 1223 (C−O str.), ^{1}H-NMR ($CDCl_3$): $\delta = 3.27$ [s, 6H, 4-$N(CH_3)_2$], 6.50–6.81 (m, 3H, $-C_6H_3$), 6.73 (d, J = 15 Hz, 1H, =CH), 7.73–7.85 (m, 4H, $-C_6H_4$), 8.01(d, J = 15 Hz, 1H, =CH), 10.48 (s, 1H, −OH), 11.49 (s, 1H, −OH).

RESULTS AND DISCUSSION

Calcium hydroxide is a solid, water-stable base, obtained through calcination of calcium carbonate. It is a white powder with a high pH (12.6) and is slightly soluble in water (solubility of 1.2 g/L at a temperature of 25°C).[23] Use of calcium hydroxide in organic synthesis is very rare; it has been used in selective C-4 acylation of pyrazolones[24] and synthesis of benzopyrans.[25,26] The effect of calcium regents on Aldol reactions of phenolic enolates with aldehydes is well studied.[25] In the present study this concept has been extended for the synthesis of polyhydroxy chalcones. It is well documented in literature that diphenolate anions of resorcinol chelates with divalent metal to form chelates and thus act as bidentate ligand and calcium is divalent in nature.

Thus it was anticipated that the two phenolic hydroxyl groups in dihydroxy acetophone under basic conditions should form chelate with divalent calcium and hence reduce the positive mesomeric effect of phenolic dianions responsible for the reduced electrophilicity of carbonyl group and acidity of methyl group.

Initially, the reaction was explored between 2, 4-dihydroxyacetophenone, and benzaldehyde with 3 equiv. calcium hydroxide in methanol at room temperature. After 36 h, the condensation went to completion as observed by TLC and work up afforded the desired chalcone in 87% yield. With a view to reduce the reaction time the transformation was studied at reflux

TABLE 1
Synthesis of polyhydroxy chalcone

Entry	R^1	R^2	R^3	R^4	Product (3)	%Yield[b]	M. P. °C [Ref]
1	H	H	H	H	**3a**	87	130[28]
2	H	H	CH_3	H	**3b**	83	154[27]
3	H	H	OMe	H	**3c**	85	168[29]
4	H	OH	OH	H	**3d**	82	215[29]
5	Cl	H	Cl	H	**3e**	77	156[29]
6	H	H	Cl	H	**3f**	88	135[29]
7	Cl	H	H	H	**3g**	73	179[29]
8	H	H	F	H	**3h**	89	129[29]
9	H	H	NO_2	H	**3i**	90	178[29]
10	H	NO_2	H	H	**3j**	89	212[29]
11	H	H	OH	H	**3k**	67	183[29]
12	H	OH	H	H	**3l**	65	181[29]
13	OH	H	H	H	**3m**	70	130[28]
14	H	H	NMe_2	H	**3n**	64	181[29]
15	H	OMe	OH	H	**3o**	59	210 [27]
16	NO_2	H	H	H	**3p**	61	200[29]

[a]Reaction conditions: (5 mmol, 0.760 g) of 2,4-dihydroxyacetophenone (5 mmol, 0.525 g) of substituted benzaldehyde (3 mmol, 1.11 g) of calcium hydroxide reflux in 10 mL methanol. [b]Isolated yield.

temperature and the reaction proceeds to completion in 12 h in good yield. Having set the optimum conditions for smooth conversion, the scope of the reaction was studied with various substituted aldehydes bearing different functional groups such as CH_3, OMe, Cl, NO_2, NMe_2, and OH groups on the aromatic ring and the results are summarized in Table 1.

As is obvious from the results obtained the reaction proceeds well with different substituted aromatic aldehydes subjected to the reaction conditions and afford the corresponding chalcones in good yield and moderate yields were obtained with aldehydes bearing substituents at ortho position, which may be attributed to steric effect. As expected aldehydes bearing electron withdrawing substituents gave better yields compared to ones with electron donating substituents.

CONCLUSION

In conclusion, here in we report an inexpensive, eco-friendly synthesis of polyhydroxy chalcone using calcium hydroxide as a catalyst. The merits of the protocol include short reaction time, easy work up procedure and is devoid of additional protection/deprotection steps. Further the method should find wide spread usage in the synthesis of naturally occurring polyhydroxy chalcones such as butein and naringenin, and the attributes of the catalyst such stability to air, water, non toxic nature and cost make it attractive to the existing procedures reported.

REFERENCES

1. Ullah, M. F.; Khan, M.W. *Asian Pac J. Cancer Prev.* **2008**, *9*, 187–195.
2. (a) Wattenberg, L.W.; Coccia, J.B.; Galbraith, A.R. *Cancer Lett.* **1994**, *83*, 165–169; (b) Dinkova-Kostova, A.T.; Abeygunaward, A.C.; Talalay, P. *J. Med. Chem.* **1998**, *41*, 5287–5296.
3. Ram, V.J.; Saxena, A.S.; Srivastava, S.; Chandra, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2159–2161.
4. Kidwai, M.; Sapra, P.; Misra, P.; Saxena, R.K.; Singh, M. *Bioorg. Med. Chem.* **2001**, *9*, 217–220.
5. Ballesteros, J.F.; Sanz, M.J.; Ubeda, A.; Miranda, M.A.; Iborra, S.; Paya, M.; Alcaraz, M.J. *J. Med. Chem.* **1995**, *38*, 2794–2797.
6. Mario, S.J.; Seiji, A.; Satoshi, T.; Hui, Y.; Kurt, R.A.; Margaret, B.J.; Roberto, G.R. *Food Chem.* **2008**, *107*, 813–819.
7. Orlikova, B.; Tasdemir, D.; Golais, F.; Dicato, M.; Diederich, M. *Genes Nutur.* **2011**, *6*, 125–147.
8. Di Carlo, G.; Mascolo, N.; Izzo, A.A.; Capasso, F. *Life Sci.* **1999**, *65*, 337–353.
9. Harborne, J.B.; Mabry, T.J.; Mabry, H. *The Flavonoids*; Chapman and Hall, London, **1975**.
10. Dhar, D.N. *The Chemistry of Chalcones and Related Compounds*; Wiley, New York, **1981**.
11. Dhar, D.N.; Lal, J.B. *J. Org. Chem.* **2008**, *23*, 1159–1161.
12. Rajender, S.V.; George, N.K.; Lau, T.; Richard, M. *Synth. Commun.* **1985**, *15*, 279–284.
13. Reddy, G.V.; Maitraie, D.; Narsaiah, B.; Rambabu, Y.; Rao, P.S. *Synth. Commun.* **2001**, *31*, 2881–1284.
14. (a) Breslow, D.S.; Hauser, C.R. *J. Am. Chem. Soc.* **1940**, *62*, 2385–2388; (b) Calloway, N.O.; Green, L.D. *J. Am. Chem. Soc.* **1937**, *59*, 809–811.
15. Kantam, M.L.; Prakash, V.B.; Reddy, C.V. *Synth. Commun.* **2005**, *35*, 1971–1978.
16. Pinkey, P.K.; Jain, S.K.; Grover, S.K. *Curr. Sci.* **1983**, *52*, 1185–1188.
17. Alcantara, D.R.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett.* **1987**, *28*, 1515–1518
18. Sebti, S.; Solhy, A.; Tahir, R.; Boulaajaj, S.; Mayoral, J.A.; Fraile, J.M.; Kossir, A.; Oumimoun, H. *Tetrahedron Lett.* **2001**, *42*, 7953–7955.
19. Pore, D.M.; Desai, U.V.; Thopte, T.S.; Wadganokar, P.P. *Russ. J. Org. Chem.* **1995**, *43*, 1088–1089.

20. (a) Fuentes, A.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett.* **1987**, *28*, 4541–4544; (b) Li, J.T.; Yang, W.Z.; Wang, S.X.; Li, S.H.; Li, T.S. *Ultrason. Sonochem.* **2002**, *9*, 237–239; (c) Calvino, V.; Picallo, M.; Lopez-Peinado, A.J.; Martin-Aranda, R.M.; Duranvalle, C.J. *Appl. Surf. Sci.* **2006**, *252*, 6071–6074.
21. Kumar, S.; Lamba, M.S.; Makrandi, J.K. *Green Chem. Lett. Rev.* **2008**, *1*, 123–125.
22. Eddarir, S.; Cotelle, N.; Bakkour, Y.; Rolando, C. *Tetrahedron Lett.* **2003**, *44*, 5359–5363.
23. Greenwood, N.N.; Earnshaw, A. *Chemistry of the Elements*; Pergamon Press, New York, **1984**.
24. Hari, S.G.; Lee, Y.R. *Bull. Korean Chem. Soc.* **2011**, *32*, 2949–2954.
25. Saimoto, H.; Yoshida, K.; Murakami, T.; Morimoto, M.; Sashiwa, H.; Shigemasa, Y. *J. Org. Chem.* **1996**, *61*, 6768–6769.
26. Jensen, B.S. *Acta. Chem. Scand.* **1959**, *13*, 1668–1670.
27. Dhar; D.N., Lal, J.B. *J. Org. Chem.* **1958**, *23*, 1159–1161.
28. Ameta, K.L.; Rathore, N.S.; Biresh, K. *Analele Universitatii din Bucuresti–Chimie* **2011**, *20*, 15–24.
29. Wu, Z.X.; Hai, Z.D.; Chun, Q.Y.; Peng, S.L.; Mei, Y.X.; Ping, G.L. *Med. Chem. Res.* **2010**, *19*, 403–412.