Green Chemistry Letters and Reviews, 2014
Vol. 7, No. 1, 95–99, http://dx.doi.org/10.1080/17518253.2014.895867

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

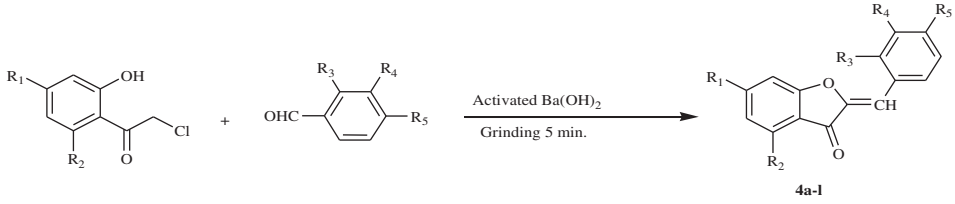
An improved one-pot and eco-friendly synthesis of aurones under solvent-free conditions

Suresh Kumar*

Department of Chemistry, Kurukshetra University, Kurukshetra-136119, India

(*Received 18 November 2013; final version received 6 February 2014*)

An efficient and eco-friendly approach for the synthesis of aurones including hydroxyaurones and their methyl ethers has been achieved directly from substituted 2-hydroxyphenacylchloride in a single pot just by grinding with aryl aldehydes using activated barium hydroxide as solid base and support.



Keywords: aurones; 2-hydroxyphenacylchloride; activated barium hydroxide; grinding; solvent free

Introduction

Aurones, i.e. 2-benzylidenebenzofuran-3(*2H*)-ones, constitute a subclass of naturally occurring compounds which are structurally isomeric to flavones, biogenetically related to chalcones, and are responsible for imparting beautiful yellow colors to some of the flower petals (*1–4*). Recent investigations have shown that these compounds have potent and promising biological activities, in some cases even more potent than chalcones and flavones (*5–7*), thus attracting the attention of the chemists.

Various approaches have been reported for the synthesis of aurones in the literature such as oxidative cyclisation of 2′-hydroxychalcones using A.F.O. reaction (*8–9*), or as an additional product during the alkaline cyclisation of 2′-hydroxychalcone dihalides along with flavones (*10*). Synthesis of aurones from 2′-acetoxychalcones in a two-step process has also been reported in the literature (*11*). Recently Au (I)-catalyzed cyclisation of 2-(1-hydroxyprop-2-ynyl) phenols has also been used for the synthesis of aurones (*12*). But all these methods suffer a serious limitation of formation of side products thus reducing the yield. Other approach which is more convenient and of much practical use involves the condensation of benzofuran-3(*2H*)-ones with aryl aldehydes using various acidic or basic catalysts (*13*) under different conditions such as $KOH/CH_3OH/H_2O$ (*14*), HCl/CH_3COOH (*15*), Al_2O_3/CH_2Cl_2 (*16*), $KF\text{-}Al_2O_3/CH_2Cl_2/MW$ (*17*), $EDDA/CH_3CN$/Ultrasound (*7*), and acetic anhydride (*18*). Benzofuran-3(*2H*)-ones required for this reaction, are generally obtained, either by cyclisation of 2-hydroxyphenacylchloride (*5*) or phenoxyacetic acid (*7*). But this method of synthesizing aurones from Benzofuran-3(*2H*)-ones, suffers a severe limitation in the synthesis of hydroxyl-substituted aurones and their partial methyl ethers as these are either very difficult to obtain using this method or require a very longer period for completion of the reaction. For obtaining the hydroxyl-substituted aurones, hydroxy group in benzofuran-3(*2H*)-ones is first protected before condensation, and then after condensation it is deprotected (*5*, *19*, *20*) while the partial methyl ethers of hydroxyl-substituted aurones are even more difficult to prepare by partial deprotection. So this approach is not compatible with the compounds containing labile functional groups under these conditions (*5*, *19*). Moreover for obtaining aurones from 2-hydroxyphenacylchloride is a two-step and two-pot route (*5*, *19*, *20*). In first step, 2-hydroxyphenacylchloride is cyclised

*Email: suresh_dua47@rediffmail.com

to give benzofuran-3(2*H*)-one, which is then condensed in another pot with aryl aldehyde in second step to give aurone.

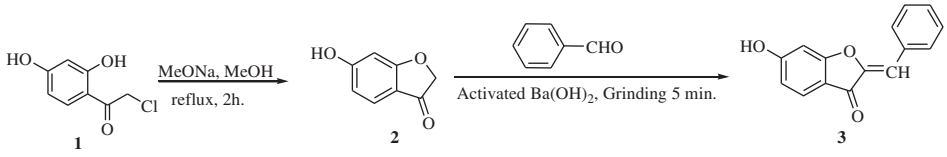
Results and discussion

Working on the line of the development of novel, greener, and milder routes for the synthesis of biologically active compounds of natural origin and their synthetic analogs using new techniques (*21*–*23*), herein we report a facile and solid phase, green synthesis of aurones in a single pot by a grinding procedure using activated barium hydroxide as the solid base catalyst (*24*). This method not only provides aurones in high yield within a few minutes, just by acidification of the ice-cold reaction mixture, but also avoids the use of toxic organic solvents at any stage of the reaction.

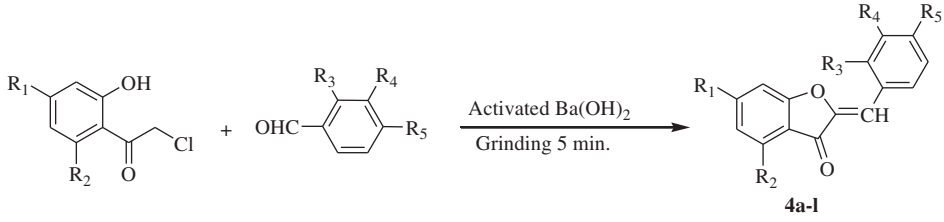
In the first experiment, 6-hydroxybenzofuran-3(2*H*)-one, obtained from cyclisation of 2,4-dihydroxyphenacylchloride by a reported method (*20*), was ground well with benzaldehyde and activated barium hydroxide in a china mortar with pestle for 5 minutes (Scheme 1). The reaction mixture turned yellow and it was kept at room temperature for 10 minutes for completion of the reaction (TLC). Acidification of ice-cooled reaction mixture gave 6-hydroxyaurone in 95% yield, whose structure was confirmed by comparison with an authentic sample (*25*) and spectral data.

In the next experiment, a mixture of 2,4-dihydroxyphenacylchloride, benzaldehyde and activated barium hydroxide was ground for 5 minutes in a mortar and pestle, the result was of much practical use and important one, compared to the previous one, as 6-hydroxyaurone was obtained in a single pot with the same yield (95%) after work-up of the reaction mixture in the same period of time (Scheme 2). When 2,4-dihydroxyphenacylchloride was ground alone with activated barium hydroxide, for the same period of time, it underwent cyclisation to produce 6-hydroxybenzofuran-3(2*H*)-one (**2**, Scheme 1), as confirmed from spectral data and comparison with an authentic sample (*25*). So in this procedure the reaction is taking place in two steps but in a single pot. The scope of this procedure was further extended successfully by synthesizing various substituted hydroxyaurones and their methyl ethers by condensing various substituted aryl aldehydes with hydroxyl- and methoxy-substituted 2-hydroxyphenacylchlorides, which are otherwise very difficult to synthesize by reported routes (Table 1).

Barium hydroxide is a very good solid base catalyst because of its crystalline texture properties (*26*) and its use has been reported in various organic transformations (*21*, *24*). Here in this reaction, when we used hydrated barium hydroxide or other strong bases like NaOH and KOH in place of activated barium hydroxide under these conditions, results were not as good as with activated barium hydroxide. With hydrated barium hydroxide, the reaction could not be completed even after one hour, whereas with NaOH and KOH the product could not be isolated. When the present catalyst was compared with other reported catalyst for this reaction in literature, it was found to be a superior solid base catalyst, in terms of yield, time and mildness of reaction conditions (Table 2). With activated barium hydroxide, the present method is equally applicable for the synthesis of hydroxyl-substituted aurones and their completely or partially methyl ether. Here in this reaction, best results were obtained when 3–4 mole equivalents of barium hydroxide, relative to phenacylchloride, were used.



Scheme 1. Two pot synthesis of 6-hydroxyaurone.



Scheme 2. One pot synthesis of aurones.

Table 1. One pot solvent-free synthesis of aurones using grinding procedure.

Product	R^1	R^2	R^3	R^4	R^5	Yield[a] (%)	Obs. mp (Lit.) °C	References
2	–	–	–	–	–	96	237–38 (239–40)	(25)
3	–	–	–	–	–	95	260–61 (261–62)	(25)
4a	OH	H	H	H	H	95	260–62 (261–62)	(25)
4b	OH	H	H	H	OCH_3	94	255–56	
4c	OH	H	H	OCH_3	OCH_3	92	205–06	
4d	OCH_3	H	H	H	H	93	142–43 (145)	(27)
4e	OCH_3	H	H	H	OCH_3	92	134–35 (134)	(27)
4f	OCH_3	H	H	OCH_3	OCH_3	94	188–89 (189)	(27)
4g	OH	OH	H	H	H	88	250–51 (252–53)	(14)
4h	OH	OH	H	H	OCH_3	90	237–38 (240–41)	(2)
4i	OH	OH	H	OCH_3	OCH_3	91	221–22 (220–21)	(2)
4j	OCH_3	OCH_3	H	H	H	93	155–56 (157)	(14)
4k	OCH_3	OCH_3	H	H	OCH_3	92	166–67 (167–68)	(11)
4l	OCH_3	OCH_3	H	OCH_3	OCH_3	90	167–68 (169–70)	(19)

[a]Isolated yield of aurones.

Experimental

All the reactions were carried out in simple china mortar and pestle. In each case, reaction mixture was ground for 5 minutes and then kept at room temperature for 10 minutes, when reaction was completed as monitored on TLC. Melting points were taken in an open capillary on an electrically heated metal block and are uncorrected. The ^{1}H nuclear magnetic resonance (NMR) spectra were recorded on Bruker Avance II 400 spectrometer at 400 MHz in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in ppm and coupling constant in Hz. The IR spectra were recorded using Perkin Elmer spectrometer (KBr pellets). Activated barium hydroxide was obtained by heating commercial $Ba(OH)_2{\cdot}8H_2O$ in an oven at 200°C for 3 hours. 2-Hydroxyphenacylchlorides used in these reactions were synthesized by Houben–Hoesch reaction of chloroacetonitrile with phenolic compounds.

General procedure

A mixture of substituted 2-hydroxyphenacylchloride (4 mmol) and aryl aldehyde (4.1 mmol) was ground

Table 2. Comparison of the catalyst used for condensation of benzofuran-3(2*H*)-one with aryl aldehyde to give aurones.

S. No.	Catalyst	Nature of benzofuran-3(2*H*)-one	Time	Temperature	% Yield	References
1	KOH/ CH_3OH/H_2O	4,6-Dihydroxybenzofuran-3(2*H*)-one	20 hours	Room temperature	60–70	(14)
2	KOH/ CH_3OH/H_2O	4,6-Dimethoxybenzofuran-3(2*H*)-one	1 hour	Room temperature	62–95	(28)
3	Conc. HCl/ CH_3COOH	Mehtoxy-substituted and hydroxyl-substituted benzofuran-3(2*H*)-one	3–5 hours	Room temperature	–	(15)
4	EDDA/CH_3CN/ stirring	Methoxy-substituted benzofuran-3(2*H*)-one	30–300 minutes	Room temperature	58–90	(7)
5	EDDA/CH_3CN/ Ultrasound	Methoxy-substituted benzofuran-3(2*H*)-one	5–30 minutes	Ultrasound	85–96	(7)
6	Al_2O_3/CH_2Cl_2/ stirring	Unsubstituted benzofuran-3(2*H*)-one	10 minutes–4 hours	Room temperature	86–93	(16)
7	Al_2O_3/CH_2Cl_2/ stirring	4,6-Dimethoxybenzofuran-3(2*H*)-one	24 hours	Room temperature	73	(19)
7	KF-Al_2O_3/ CH_2Cl_2	Naphthofuranone	5 + 10 minutes	MW/40 W	57–96	(17)
8	Activated Ba $(OH)_2$/grinding	Hydroxy-substituted and methoxy-substituted benzofuran-3(2*H*)-one	5 + 10 minutes	Room temperature/ grinding	88–95	Present method

with activated barium hydroxide (2.5 g, 14.59 mmol) in china pestle mortar for 5 minutes when the reaction mixture turned yellow. It was then kept for 10 minutes at room temperature. Completion of the reaction was checked on TLC. After completion of the reaction, ice-cold water (30 ml) was added to the reaction mixture and acidified with conc. HCl. Yellow-colored solid that separated out was filtered, washed with water, and recrystallized from ethanol.

Spectral data of the selected compounds

6-Hydroxybenzofuran-3(2*H*)-one 2: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.29 (s, 2H, $-OCH_2-$), 6.51 (d, 1H, H-7, *J*=1.96 Hz), 6.59 (dd, 1H, H-5, *J* = 2.04, *J* = 8.56 Hz), 7.46–7.48 (m, 1H, H-4 *J*=4.44, *J*=8.48 Hz.).

2-Benzylidene-6-hydroxybenzofuran-3(2*H*)-one 3: IR (KBr) 3420 cm^{-1} (ν_{OH}); 1678 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.70– 6.74 (m, 3H, H-5, H-7, =CH-Ph), 7.34–7.47 (m, 3H, H-3′, H-4′, H5′), 7.60 (d, 1H, H-4, *J* = 8.0 Hz), 7.87–7.89 (dd, 2H, H- 2′, H-6′, *J* = 1.32, *J* = 8.52 Hz).

6-Hydroxy-2(4-methoxybenzylidene)benzofuran-3(2*H*)-one 4b: IR (KBr) 3412 cm^{-1} (ν_{OH}); 1674 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H, OCH_3), 6.69– 6.73 (m, 3H, H-5, H-7, =CH-Ph), 6.98 (dd, 2H, H-3′, H-5′, *J* = 1.96, *J* = 8.88 Hz), 7.60 (s, 1H, H-4), 7.85 (dd, 2H, H-2′, H-6′, *J* = 1.88, *J* = 8.84 Hz).

6-Hydroxy-2(3,4-dimethoxybenzylidene)benzofuran-3(2*H*)-one 4c: IR (KBr) 3410 cm^{-1} (ν_{OH}); 1677 cm^{-1} ($\nu_{C=O}$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.92, 3.97 (each s, 6H, 2 × OCH_3), 6.70–6.73 (m, 3H, H-5, H-7, =CH-Ph), 6.95 (d, 1H, H-5′, *J* = 8.28 Hz), 7.46–7.49 (m, 2H, H-2′, H-6′), 7.62 (d, 1H, H-4, *J* = 8.96 Hz) (See Supplementary material for spectral details of selected compounds).

Conclusion

Thus, this method provides a very convenient, one-pot solid phase, environmentally benign synthesis of aurones including hydroxyaurones and their completely or partial methyl ethers directly from substituted 2-hydroxyphenacylchloride within few minutes and avoids the prior preparation of benzofuran-3(2*H*)-ones by cyclisation of corresponding 2-hydroxyphenacylchloride. No solvent was needed during reaction or in extraction process, for isolating the product from reaction mixture, thus making it an eco-friendly procedure. Moreover, this procedure also avoids the complications arising from the protection and deprotection of hydroxy group. Transition in color, of the reaction mixture during grinding, from colorless to yellow, itself indicates the progress of the reaction. Thus, it is a very simple one-pot, mild, efficient, and eco-friendly synthesis of aurones at room temperature. To my knowledge, this is the first report of synthesizing aurone directly from 2-hydroxyphenacylchloride in one-pot under solid-phase conditions.

Acknowledgments

The author is extremely thankful to Prof. J. K. Makrandi for his valuable suggestions in this work.

Supplementary material

All supplemental material is available alongside this article on www.tandfonline.com – go to http://dx.doi.org/10.1080/17518253.2014.895867

References

(1) Nakayama, T.; Sato, T.; Fukui, Y.; Sakakibara, K.Y.; Hayashi, H.; Tanaka, Y.; Kusumi, T.; Nishino, T. *FEBS Lett*. **2001**, *499*, 107–111.
(2) Jain, A.C.; Rohatagi, V.K.; Seshadri, T.R. *Indian J. Chem*. **1969**, *7*, 540–543.
(3) Nakayama, T. *J. Biosci. Bioeng*. **2002**, *94*, 487–491.
(4) Olesen, J.M.; Ronsted, N.; Tolderlund, U.; Cornett, C.; Molgaard, P.; Madsen, J.; Jones, C.G.; Olsen, C.E. *Nature*. **1998**, *393*, 529.
(5) Okombi, S.; Rival, D.; Bonnet, S.; Mariotte, A.M.; Perrier, E.; Boumendjel, A. *J. Med. Chem*. **2006**, *49*, 329–333.
(6) Haudecoeur, R.; Boumendjel, A. *Curr. Med. Chem*. **2012**, *19*, 2861–2875.
(7) Manjulatha, K.; Srinivas, S.; Mulakayala, N.; Rambabu, D.; Prabhakar, M.; Arunasree, K.M.; Alvala, M.; Rao, M.V.B.; Pal, M. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 6160–6165.
(8) Bonnett, M.; Burke, A.J.; Ivo O'Sullivan, W. *Tetrahedron*. **1996**, *52*, 7163–7168.
(9) Zhao, X.; Liu, J.; Xie, Z.; Li, Y. *Synthesis*. **2012**, *44*, 2217–2224.
(10) Donnelly, J.A.; Fox; M.J.; Sharma, T.C. *Tetrahedron*. **1979**, *35*, 875–879.
(11) Bose, G.; Mondal, E.; Khan, A.T.; Bordoloi, M.J. *Tetrahedron Lett*. **2001**, *42*, 8907–8909.
(12) Harkat, H.; Blanc, A.; Weibel, J.M.; Pale, P. *J. Org. Chem*. **2008**, *73*, 1620–1623.
(13) Levai, A. *Arkivoc*. **2004**, *vii*, 15–33.
(14) Grover, S.K.; Gupta, V.N.; Jain, A.C.; Seshadri, T.R. *J. Sci. Ind. Res*. **1960**, *19B*, 258–264.
(15) Geismann, T.A.; Harbone, J.B. *J. Am. Chem. Soc*. **1955**, *77*, 4622–4624.
(16) Varma, R.S.; Varma, M. *Tetrahedron Lett*. **1992**, *33*, 5937–5940.
(17) Villemin, D.; Martin, B.; Bar, N. *Molecules*. **1998**, *3*, 88–93.
(18) Farkas, L.; Nogardi, M.; Pallos, L. *Tetrahedron Lett*. **1963**, *4*, 1999–2000.

(19) Bolek, D.; Gutschow, M. *J. Hetrocyclic Chem*. **2005**, *42*, 1399–1403.
(20) Beney, C.; Mariotte, A.M.; Boumendjel, A. *Heterocycles*. **2001**, *55*, 967–972.
(21) Kumar, S.; Lamba, M.S.; Makrandi, J.K. *Green Chem. Lett. Rev*. **2008**, *1*, 123–125.
(22) Sharma D.; Kumar, S.; Makrandi, J.K. *Green Chem. Lett. Rev*. **2011**, *4*, 127–129.
(23) Kumar, P.; Meenakshi; Kumar, S.; Kumar, A.; Hussain, K.; Kumar, S. *J. Hetrocyclic Chem*. **2012**, *49*, 1243–1249.
(24) Jeanmart, S. *Synlett*. **2002**, *10*, 1739.
(25) Balkrishna, K.J.; Rao, N.P.; Seshadri, T.R. *Proc. Indian. Acad. Sci*. **1949**, *29A*, 394–403.
(26) Alcantara, A.R.; Marinas, J.M.; Sinisterra, J.V. *Tetrahedron Lett*. **1987**, *28*, 1515–1518.
(27) Geoghegan, M.; O'Sullivan, W.I.; Philbin, E.M.; Wheeler, T.S. *Tetrahedron*. **1966**, *22*, 3203–3208.
(28) Boumendjel, A.; Beney C.; Deka, N.; Mariotte, A.M.; Lawson, M.A.; Trompier, D.; Cortay, H.B.; Pietro, A.D. *Curr. Pharma. Bull*. **2002**, *50*, 854–856.