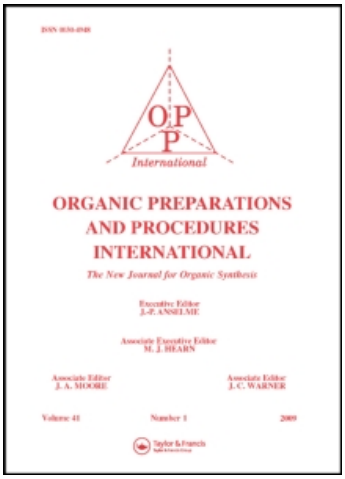


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SIMPLE AND RAPID PROCEDURE FOR THE SYNTHESIS OF SOME NEW 2*H*-CHROMENES

A. Zonouzi[a]; M. Sadeghi Googheri[a]; P. S. Miralinaghi[a]
[a] School of Chemistry, University College of Science University of Tehran, Tehran, IRAN

To cite this Article Zonouzi, A. , Googheri, M. Sadeghi and Miralinaghi, P. S.(2008) 'SIMPLE AND RAPID PROCEDURE FOR THE SYNTHESIS OF SOME NEW 2*H*-CHROMENES', Organic Preparations and Procedures International, 40: 5, 471 — 477
To link to this Article: DOI: 10.1080/00304940809458109
URL: http://dx.doi.org/10.1080/00304940809458109

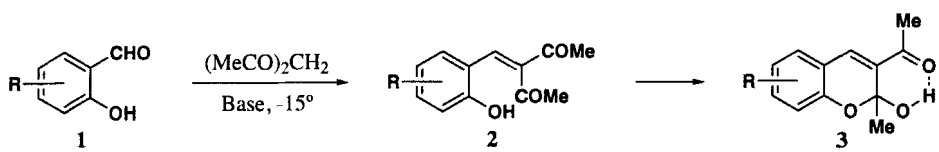
SIMPLE AND RAPID PROCEDURE FOR THE SYNTHESIS OF SOME NEW 2*H*-CHROMENES

Submitted by A. Zonouzi*, M. Sadeghi Googheri and P. S. Miralinaghi
(11/10/07)

School of Chemistry, University College of Science
University of Tehran, Tehran, IRAN
e-mail: zonouzi@khyam.ut.ac.ir

2*H*-Benzopyrans (2*H*-chromenes) are an important class of heterocyclic compounds which occur in many biological active products,[1] useful as antihypertensive,[2] hypoglycemic, cardio-protective agents,[3,4] and as insecticides.[5] Some of their derivatives are utilized in the synthesis of new macrocyclic ligands[6] and others have shown photochromic properties.[7] These interesting properties of 2*H*-chromenes led us to investigate a simple and efficient synthesis with the goal of obtaining more potent pharmacologically active compounds. Various methods are known to obtain 2*H*-chromene derivatives.[8-18] We now report a new and rapid method to obtain some 2*H*-chromene derivatives by the Knoevenagel reaction[19] employing cold and very dilute conditions.

Salicylaldehydes **1** and 2,4-pentanedione reacted to produce initially 3-(2-hydroxybenzylidene)-pentane-2,4-diones **2** which underwent deprotonation by piperidine followed by attack of the phenoxide ion on the carbonyl group of **2** to produce 1-(2-hydroxy-2-methyl-2*H*-chromene-3-yl)-1-ethanone derivatives **3** (*Scheme1*).



1 **2** **3**

a) R = H; b) R = 3-OMe; c) R = 4-OMe; d) R = 5-OMe; e) R = 6-OMe; f) R = 3-OH; g) R = 5-OH; h) R = 5-Br; i) R = 5-NO_2

Scheme 1

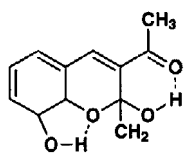
Although **3** is a cyclic hemiacetal and could be in equilibrium with **2**, equilibrium is essentially inhibited since spectroscopic evidence reveals the existence of hydrogen bonding that stabilizes structure **3** thus preventing interconversion to **2**. Crystals of **3** may be stored for a long time without any ring opening or any other changes. Different bases such as $NHEt_2$ (pK_a 11.5), NEt_3 (pK_a 10.70), piperidine (pK_a 11.21) and pyridine (pK_a 5.23)[20] were used. The best results were achieved with piperidine. When the base was used in equimolar amounts, yields were improved, most probably as a result of the dilute conditions.

The effect of solvents was also examined. The results were poor using ether (bp. 35°C), tetrahydrofuran (bp. 66°C) and 1,4-dioxane (bp. 101°C), probably due to the interaction of

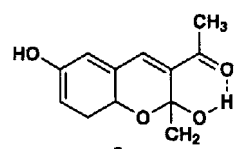
oxygen atoms with these solvents and the phenolic hydrogen in compounds **(2a-i)** which inhibited intramolecular cyclization and formation of products **(3a-i)**. Although the results were similar with benzene (bp. 80°C), toluene (bp. 110°C) and dichloromethane (bp. 44°C), dichloromethane was deemed the most suitable solvent. Removal of the solvent (dichloromethane) under reduced pressure without any heat, followed by washing the residues with solvents such as *n*-pentane or *n*-hexane several times and recrystallization from cyclohexane and drying under reduced pressure, is the optimized procedure.

This reaction is sensitive to heat; for example, if the reaction mixture was warmed up to 10°C, during the addition of base, the yield decreased to 70% and flash chromatography in the cold (ice bath) was required to separate **3a** from **2a**.

Structures **3** were assigned on the basis of their elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The mass spectra of these compounds **(3a-i)** displayed molecular ion peaks at appropriate m/z values. Initial fragmentation involved the loss of the chromene side-chains (CH_3, OH, H_2O, CH_3CO, R) and scission of the ring. Moreover, fragments 77 ($C_6H_5^+$) and 43 (CH_3CO^+) were the most intense fragments; for example, fragment 43 in **3g** is 100%. The mass spectrum of **3f** was different, the molecular ion peak (M^+) had the maximum intensity (100%) and M^+-1 appeared with the intensity (49%), probably due to interaction of the OH on C_8 and the oxygen atom in the chromene ring, which stabilized the molecular ion peak more than in the other compounds (*Scheme 2*). In compound **3g**, such an interaction was not possible and the molecular ion peak did not appear with high intensity.



3f



3g

Scheme 2

The ^{1}H NMR spectrum of **3a** showed two single sharp lines for the methyl groups (δ 1.86, 2.44). Structure **2** would be expected to show more closely spaced signals for two CH_3CO groups. The DNMR data for the rotational energy barrier of the carbon-carbon double bond in 3-(4-(dimethylamino)benzylidenepentane-2,4-dione) has already been reported.[21] The two methyls of the CH_3CO groups converged to one signal at above 180°C. The ^{1}H NMR spectrum of **3a** also showed a broad singlet for the OH proton at δ 5.35 and a multiplet for the phenyl protons as well as a sharp singlet for the olefinic proton at δ 7.45 (*see Experimental Section*).

The ^{1}H NMR spectra of **3b-i** were similar to that of **3a**, except for the signals of the R groups (OCH_3, OH) and for the changes in the multiplicity of signals of aromatic hydrogens resulting from the presence of the R groups (OCH_3, OH, Br, NO_2). The ^{1}H NMR spectrum of **3f** displayed two broad peaks for O-H (δ 5.25, 5.36) as a result of O-H -- O interaction (discussed

above). In **3g**, the O-H protons appeared at (δ 2.57, 4.77). The ^{13}C NMR spectrum of **3a** displayed resonances in agreement with structure **3a**, two different methyl groups at (δ 26.55, 27.61) and a signal at 98.78 for the C_2 between two oxygen atoms. The partial assignments of these resonances are given in the Experimental Section. The ^{13}C NMR spectral data for compounds **3b-i** confirm the proposed structures.

The IR spectra of compounds **3a-i** showed O-H absorptions (3330-3465 cm^{-1}), and did not change upon dilution with CCl_4, which is evidence for intramolecular hydrogen bonding; for compounds **3f**, **3g** there were other O-H absorptions (3200, 3151 cm^{-1}). The IR spectra of compounds **3a-i**, displayed carbonyl absorptions (1625-1666 cm^{-1}) which was low for C=O groups as a result of intramolecular O-H bonding, there were also three sharp C-O absorptions for **3a, h, i** and four in compounds **3b-g.**

Although the conditions reported here are similar to the Knoevenagel reaction, the reported procedure is not the same. It is a new modification of Knoevenagel reaction. In addition, the newly produced chromene derivatives (**3a-i**) have interesting structures (stable hemiacetals). The hemiacetal structures of **3a-i** are stabilized by intramolecular H-bonding so they can be isolated as pure compounds and their crystals can be stored for a long time without any changes. The procedure described here represents a simple and efficient entry into the synthesis of new 2*H*-chromene derivatives with potential biological activities. Further investigations of the present method are currently in progress to establish its scope and utility.

EXPERIMENTAL SECTION

Chemicals and solvents were obtained from Merck (Germany) and Fluka (Switzerland) and were used without further purification. Column chromatography was performed on silica gel (0.015-0.04 mm, mesh-size) and TLC on precoated plastic sheets ($25DC_{UV-254}$) respectively. Melting points were measured on a Gallenkamp melting point apparatus and are not corrected. Elemental analysis for C, H and N were performed using a Heraeus-CHN-O-rapid analyzer.IR spectra were measured on a Shimadzu FT-IR-4300 spectrophotometer as KBr discs. ^1H and ^{13}CNMR spectra were recorded on a Bruker 500 MHz spectrometer in $CDCl_3$ and DMSO- d_6 solutions and chemical shifts were recorded in ? units by using $SiMe_4$ as internal standard. Mass spectra were acquired on a Finnegan-MAT 8430 spectrometer at an ionization potential of 70ev.

1-(2-Hydroxy-2-methyl-2*H*-chromene-3-yl)-1-ethanone (3a). Typical Procedure.- To a stirred (magnetic stirrer) mixture of 2-hydroxybenzaldehyde (0.610g, 5mmol) and 2,4-pentanedione (0.52 g, 5 mmol) in dichloromethane (500 mL) at –15°C was added piperidine (0.49 g, 5mmol). The solution stirred for 2 h and then was allowed to stand in the refrigerator for two days. The solvent was removed under reduced pressure without heat, then was allowed to stand in the refrigerator overnight. The orange residue was purified by washing several times with *n*-hexane and dried. The product (0.826 g, 81%) was obtained as yellow crystals, mp, 135–136°C. The same procedure was used to prepare **3b-i.**

Table1. Yields, mps and Elemental Analysis of **3a-i**

Cmpd	Yields (%)	mp. (°C)	Color	Elemental Analysis (Found) C	H	N	Formula (M.W.)
3a	81	135-136	Yellow	70.57(70.53)	5.92(5.93)	----	$C_{12}H_{12}O_3$(204.22)
3b	85	168-169	Pale yellow	66.66(66.63)	6.02(6.01)	----	$C_{13}H_{14}O_4$(234.25)
3c	78	159-161	Orange	66.66(66.58)	6.02(5.99)	----	$C_{13}H_{14}O_4$(234.25)
3d	84	167-169	Yellow	66.66(66.60)	6.02(5.97)	----	$C_{13}H_{14}O_4$(234.25)
3e	74	168-170	White	66.66(66.63)	6.02(6.00)	----	$C_{13}H_{14}O_4$(234.25)
3f	76	164-165	Orange	65.64(64.45)	5.45(5.48)	----	$C_{12}H_{12}O_4$(220.22)
3g	79	165-166	Yellow	65.45(64.45)	5.49(5.50)	----	$C_{12}H_{12}O_4$(220.22)
3h	85	100-102	Pale yellow	50.91(.50.98)	3.92(3.90)	----	$C_{12}H_{12}BrO_3$(283.12)
3i	61	171-173	Reddish orange	57.83(57.82)	4.45(4.46)	5.62(5.66)	$C_{12}H_{11}NO_5$(249.22)

Table 2. Spectroscopic Data of **3a-i**

Cmpd	^{1}H NMR (δ:ppm)	^{13}C NMR (δ:ppm)	MS (m/z Fragment)
3a	1.86,2.44(2s,6H,2CH_3)	26.55,27.61(2CH_3)	204(M^+,33)
	5.35(brs,1H,OH proton)	98.78(C-OH)	189(M^+-CH_3,100)
	6.9-7.38(m,4H,Ar protons)	116.71,118,86,121.59	187(M^+-OH,73)
	7.45 (s,1H,olefinic proton)	132.79,132.2, 128.96 (Ar carbons)	171(M^+-CH_3,H_2O,48)
		135.03(^{13}CH=C), 153.02 (^{13}C-C=O)	161(M^+-CH_3CO,43)
		198.07(C=O)	
3b	1.93,2.45(2s,6H,2CH_3)	27.29,28.48(2CH_3)	234(M^+,17)
	3.87(1s,3H,OCH_3)	56.91(OCH_3)	219(M^+-CH_3,100)
	4.5(brs,1H,OH proton)	99.95(^{13}C-OH)	217(M^+-OH,41)
	6.83-7.39(m,3H,Ar protons)	115.09,120.01,121.47	203(M^+-OCH_3, 25)
	7.4 (s,1H,olefinic proton	122.06,138.2,162.08(Ar carbons)	201(M^+-CH_3,H_2O,50)
		135.54(^{13}CH=C)	
		152.04(^{13}C-C=O), 198.34(C=O)	191(M^+-CH_3CO,49)
3c	1.78,2.43(2s,6H,2CH_3)	26.69,28.35(2CH_3)	234(M^+,23)
	3.81(1s,3H,OCH_3)	56.05(OCH_3)	219(M^+-CH_3,100)
	4.5(brs,1H,OH proton)	102.04(^{13}C-OH)	217(M^+-OH,52)
	6.49-6.61,	109.72,112.70,120.17	203(M^+-OCH_3,29)
	7.08-7.28(2m,3H,Ar protons)	121.26,130.74,164.63 (Ar carbons)	201(M^+-CH_3,H_2O,58)
	7.37 (s,1H,olefinic proton)	136.01(^{13}CH=C)	191(M^+-CH_3CO,53)
		155.51(^{13}C-C=O), 198.34(C=O)	
3d	1.73,2.35(2s,6H,2CH_3)	27.01,27.94(2CH_3)	234(M^+,28)
	3.66(1s,3H,OCH_3)	56.26(OCH_3)	219(M^+-CH_3,69)
	4.67(brs,1H,OH proton)	99.16(^{13}C-OH)	217(M^+-OH,100)
	6.66-6.8 (m,3H,Ar protons)	112.92,118.14,119.69	203(M^+-OCH_3,40)
	7.29 (s,1H,olefinic proton)	119.96,134.23, 147.64 (Ar carbons)	201(M^+-CH_3,H_2O,31)
		135.43(^{13}CH=C)	191(M^+-CH_3CO,49)
		154.67(^{13}C-C=O), 198.61(C=O)	77(ph^+,55)

Table 2. Continued...

Cmpd	^{1}H NMR (δ:ppm)	^{13}C NMR (δ:ppm)	MS (m/z Fragment)
3e	1.77,2.47(2s,6H,2CH_3)	26.94,28.20(2CH_3)	234(M^+,14)
	3.89(1s,3H,OCH_3)	56.41(OCH_3)	219(M^+-CH_3,100)
	4.96(brs,1H,OH proton)	99.56(^{13}C-OH)	217(M^+-OH,32)
	6.41-6.621	107.74,109.74,110.19	203(M^+-OCH_3,20)
	7.16-7.37(2m,3H,Ar protons)	130.93,131.58,157.58 (Ar carbons)	201(M^+-CH_3,H_2O,43)
	7.61 (s,1H,olefinic proton)	134.19(^{13}CH=C)	191(M^+-CH_3CO,47)
		154.59(^{13}C-C=O)	43($CH3CO^+$, 88)
		199.26(C=O)	
3f	1.95,2.45(2s,6H,2CH_3)	26.71,28.83(2 CH_3)	220(M^+, 100)
	5.25-5.36(2brs, OH proton)	99.42(^{13}C-OH)	219(M^+-H,49)
	6.76-7.42(m,3H,Ar protons)	118.29,119.02,119.58	205(M^+-CH_3,95)
	7.55 (s,1H,olefinic proton)	120.61,133.81,140.64(Ar carbons)	203(M^+-OH,56)
		134.186(^{13}CH=C)	187(M^+-CH_3, H_2O,80)
		144.96 (^{13}C-C=O)	
		196.10(C=O)	
3g	1.61,2.37(2s,6H,2CH_3)	25.49,26.62(2CH_3)	220(M^+,12)
	2.57,4.77(2brs, OH proton)	96.95(^{13}C-OH)	205(M^+-CH_3,58)
	6.62-7.32(m,3H,Ar protons)	113.42,116.33,118.91	203(M^+-OH,18)
	7.71 (s,1H,olefinic proton)	119.15,133.98,145.48 (Ar carbons)	187(M^+-CH_3,H_2O,32)
		133.75(^{13}CH=C)	177(M^+-CH_3CO,19)
		150.83 (^{13}C-C=O)	43 (CH_3CO^+,100)
		195.78(C=O)	
3h	1.82,2.45(2s,6H,2CH_3)	27.20,28.48(2CH_3)	282,284(M^+, M^+_+ 2 ,38,40)
	4.1(brs,1H,OH)	99.69(^{13}C-OH)	267, 269(M^+-CH_3,23,24)
	6.77-7.35(m,3H,Ar proton)	114.30,119.30,121.20	249,251(M^+-CH_3OH,24,26)
	7.48 (s,1H,olefinic proton)	131.64, 134.68,136.05 (Ar carbons)	126,128(M^+-Br,CH_3CO, CH_3OH,100,96)
		133.92(^{13}CH=C)	
		154.14 (^{13}C-C=O)	
		198.62(C=O)	
3i	1.94,2.5(2s,6H,2CH_3)	27.17,27.55(2CH_3)	249(M^+,13)
	5.5(brs,OH)	101.78(^{13}C-OH)	234(M^+-CH_3,100)
	6.95-7.3	117.25,119.20,124.52	216(M^+- CH_3H_2O,52)
	8.1-8.21(2m,3H,Ar protons)	127.22,132.13,141.52 (Ar carbons)	206(M^+- CH_3CO_3,39)
	7.45 (s,1H,olefinic proton)	135.82(^{13}CH=C)	203(M^+-NO_2, 20)
		155.52(^{13}C-C=O)	160(M^+-NO_2, CH_3CO ,32)
		196.50(C=O)	

Acknowledgements.- We thank the Research Council of Tehran University for the financial support through Grant No. 514/1/466.

REFERENCES

1. Y. Kang, Y. Mei, Y. G. Du and Z. Jin, *Org. Lett.*, **5**, 4481 (2003) .

2. F. Cassidy, J. M. Evan, M. S. Hadel, A. H. Halodij, P. E. Leach, and G. Stemp, *J. Med. Chem.*, **35**, 1623 (1992).

3. D. W. Roberston and M. I. Steinberg, *J. Med. Chem.*, **33**,1529 (1900).

4. B. H. Lee, H. W. Seo and S. E. Yoo, *Pharmacology*, **70**, 74 (2004).

5. *US Patent*, 4, 716, 238, Dec, 29 (**1987**), *Chem. Abstr.*, **102** : 45779b (1985).

6. (a) P. Brun, R. Guglielmetti, G. Pepe and S. J. Anguille, *Photochem. Photobiol. A. Chem.*,**156**, 77 (2003); (b) *US Patent*, 4, 990, 287, Feb, 5 (**1991**), *Chem. Abstr.*, **108**, 158841h (1988).

7. S-e.Yoo, I-C. Jeon Yi, and K. Y. K. S. Kim, *Bull. Korean. Chem. Soc.*, **22**, 917 (2001), *Chem. Abstr.*, **136** : 69798k (2002).

8. H. Saiomoto, Y. Ogo, M. Komoto, M. Morimoto and Y. Shigemasa, *Heterocycles*, **55**, 2051 (2001).

9. C. D.Gabbutt, D. J. Hartley, J. D. Hepworth, B. M. Heron, M. Kanjia and M. M. Rahman, *Tetrahedron*, **50**, 2507 (1994).

10. A. Alberola, A. González- Ortega, C. López, and F. Villafane, *Heterocycles*, **38**, 819 (1994).

11. (a) D. Bell, M. R. Davies, G. R. Geen and I. S. Mann, *Synthesis*, 707 (**1995**); (b) M. Harfenist and E. Thom, *J. Org. Chem.*, **37**, 841 (1972).

12. E. Geneive, H. Jacobs and H. Jacobs, *Tetrahedron*, **57**, 5335 (2001).

13. G. Pandey and A. Krishna, *J. Org. Chem.*, **53**, 2364 (1988).

14. M. A. Neirabeyeh, R. Koussini and G. Guillaumet, *Synth. Commun.*, **20**, 783 (1990).

15. V. K. Ahluwalia, F. M. Ghazanfari and K. K. Arora, *Synthesis*, 526 (**1981**).

16. R. K. Razdan, W. R. Thompson, H. G. Pars and F. E. Granchelli, *Tetrahedron Lett.*, 3405 (**1967**).

17. (a) S. J. Pastine, S. W. Youn and D. Sames, *Org. Lett.*, **5**, 1055 (2003); (b) *US Patent*, 6, 573, 219 B1, Jun. 3 (**2003**), *Chem. Abstr.*, **134**, 163055w (2001).

18. E. E. Schweizer, J. Liehr and D. J. Monaco, *J. Org. Chem.*, **33**, 2416 (1968).

19. (a) *Advanced Organic Chemistry*, M. B. Smith and J. March, 5th. Ed. Wiley Interscience, 1225 (**2001**); (b) *Comprehensive Organic Synthesis*, B. M. Trost, Pergamon Press, **2**, 34

(**1991**); (c) *Heterocyclic Chemistry*, T. L. Gilchrist, 2nd Ed. John Wiley & Sons Inc., 181 (1992).

20. R. G. Pearson, H. Sobel and J. Songstad, *J. Am. Chem. Soc.*, **90**, 319 (1968).

21. I. Yavari, A. Zonouzi and R. Hekmat- Shoar, *Tetrahedron Lett.*, **39**, 3841 (1998).

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AN EFFICIENT, ONE-POT SYNTHESIS OF ALKYL ARYLSELENOFORMATES USING THE ZINC-RUTHENIUM CHLORIDE SYSTEM IN AQUEOUS MEDIA

Submitted by Barahman Movassagh* and Ameneh Tatar
(09/02/07)

Department of Chemistry, K. N. Toosi University of Technology,
P. O. Box 16315-1618, Tehran, IRAN
E-mail: bmovass1178@yahoo.com

The chemistry of organoselenium compounds has been of growing interest because of the many synthetic applications of these compounds.[1] For example, selenoformates are used for the synthesis of γ- and δ-lactones through the intramolecular addition of alkoxycarbonyl radicals onto carbon-carbon multiple bonds.[2] Over the last three decades, many investigators have described important chemical transformations that were efficiently achieved using organoselenium reagents. Although numerous reports on the synthesis of organoselenium compounds have already been published,[3,4] most of them with the exception of three recent reports,[5] usually require the handling of unstable reagents, strongly acidic or basic reaction conditions, and two-step procedures. Hence, the development of a one-step synthetic method using stable reagents under neutral conditions would be useful. Among the methods for the introduction of selenium moiety into organic molecules, the use of selenide anions is especially convenient and common. In general, the methods for the preparation of selenide anions include reductive cleavage of the Se-Se bond by various reducing agents such as $NaBH_4$,[6] $LiAlH_4$,[7] Na/NH_3,[8] Bu_3SnH,[9] SmI_2,[10] reaction of Grignard reagents with selenium,[11] and of selenols with sodium hydride or even with aqueous sodium hydroxide under certain conditions.[12]

Much attention has been paid to organometallic reactions in aqueous media in recent years.[13] The aqueous medium offers a powerful tool for minimizing waste production and harmful organic solvent dispersal.[14] Some particular properties of water make this solvent very attractive (i.e. non-toxicity, non-inflammability, high heat capacity, possibility of controlling pH