A Novel One-pot Synthesis of 2*H*-4-Chlorochromenes via the Vilsmeier Reaction of 2′-Hydroxychalcones

Kalvi Hemanth Kumar and Paramasivan Thirumalai Perumal*
Organic Chemistry Division, Central Leather Research Institute, Adayar, Chennai-20, India

(Received June 24, 2005; CL-050817)

A novel versatile one-pot synthesis of 2*H*-4-chlorochromenes from 2′-hydroxychalcones have been developed. This method has been investigated for the synthesis of 2*H*-4-chlorochromen-2-ylpyrazoles.

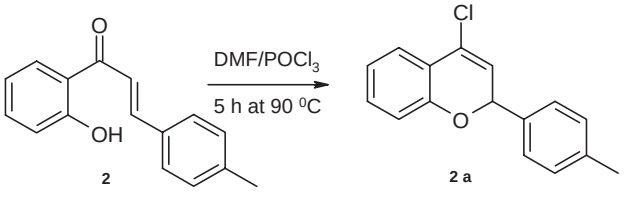
Functionalized chromenes are important intermediates in the synthesis of several natural products and medicinal agents.[1] These compounds have assumed greater importance as a result of their health promoting effects.[2] In the literature 2*H*-4-chlorochromenes can principally be realized either by modification of the pre-constructed chromonone nucleus[3] or through the construction of the 4-chlorochromene ring from γ-chloropropargyl aryl ethers[4] which have involved tedious procedures. Nevertheless, it is still of continued interest and great significance to explore novel and efficient synthetic approaches for this class of compounds.

The wide synthetic potential of the versatile Vilsmeier reaction has been known for years and its utility for achieving different synthetic transformations has been amply demonstrated.[5] Although the Vilsmeier reaction is known for formylation, haloformylation, halogenation, and ring annulation reactions, this has not been used for the synthesis of 2*H*-4-chlorochromenes. To the best of our knowledge the Vilsmeier reaction had never been studied with 2′-hydroxychalcones. As a continuation of our studies on the synthesis of heterocyclic compounds with potential medicinal values from 2′-aminochalcones and 2′-hydroxychalcones[6] and the Vilsmeier reaction,[7] in this letter we wish to report a one-pot synthesis of substituted 2*H*-4-chlorochromenes directly from the Vilsmeier reaction of 2′-hydroxychalcones which are easily accessible starting materials.

In the present work, the initial studies were performed on the reaction of 2′-hydroxychalcone 2 (Scheme 1) with the Vilsmeier reagent[8] $POCl_3$–DMF(6 equiv.) at 90 °C. Subsequent basic hydrolysis gave 2*H*-4-chlorochromene in moderate yield.

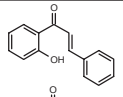
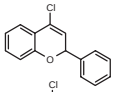
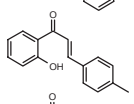
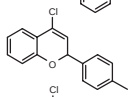
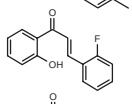
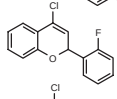
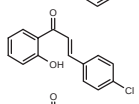
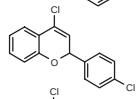
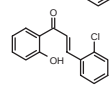
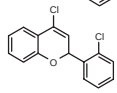
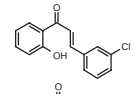
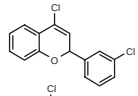
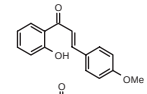
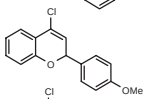
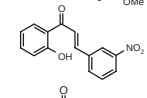
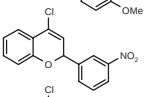
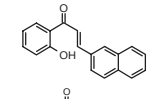
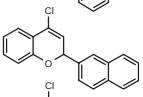
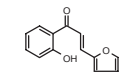
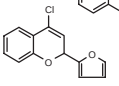
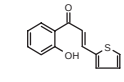
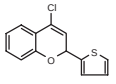
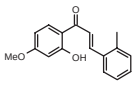
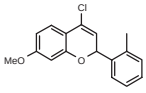
To extend the scope of this reaction, a wide range of substituted and structurally diverse 2′-hydroxychalcones were subjected to this reaction. The reaction proceeded in a similar fashion. Subsequently, substituted chromenes were obtained in moderate yields. The results are summarized in Table 1.[9]

We have extended this 2*H*-4-chlorochromene methodology to synthesize 2*H*-4-chlorochromen-2-ylpyrazoles by the cyclization of pyrazole analogues of 2′-hydroxychalcones (Scheme 2) under the Vilsmeier reaction conditions, and the results are summarized in Table 2. We carried out this reaction with different equiv. of $POCl_3$ in DMF and found out that 6 equiv. was suitable for achieving the chlorochromenes.[8] None of the chlorochromenes were obtained when the reaction was carried out in $POCl_3$ alone. In summary, the note–worthy features of the present investigation are the easy accessibility of the starting materials and procedure involves a simple, inexpensive, safe, and efficient

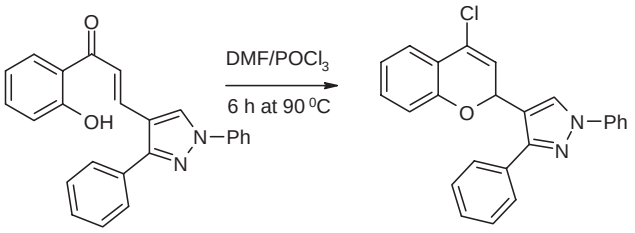


Scheme 1.

Table 1. Cyclization of 2′-hydroxychalcones under the Vilsmeier reaction conditions

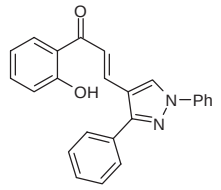
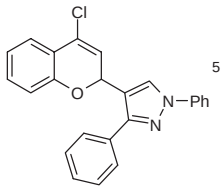
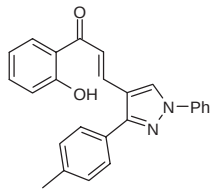
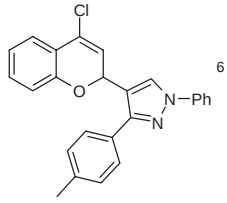
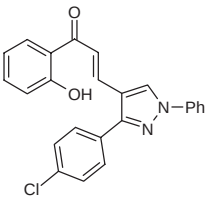
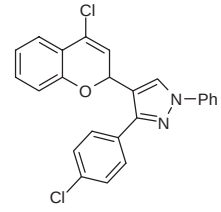
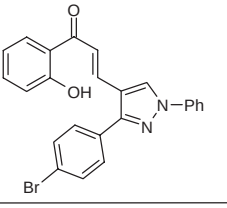
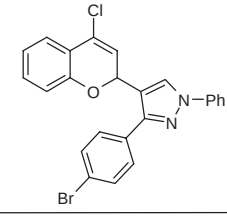
Entry	Substrate	Product[a]	Time/h	Yield[b]/%
1			5	56
2			5	65
3			6	58
4			6	66
5			6	62
6			6	60
7			4	68
8			8	30
9			8	48
10			6	45
11			6	52
12			6	55

[a]All products were characterized by ^{1}H NMR and mass spectra and by elemental analysis. [b]Yield of isolated products.



Scheme 2.

Table 2. Cyclization of pyrazole analogues of 2′-hydroxychalcones under the Vilsmeier reaction conditions

Entry	Substrate	Product[a]	Time/h	Yield[b]/%
1			5	58
2			6	62
3			8	58
4			8	52

[a]All products were characterized by ^{1}H NMR and mass spectra and by elemental analysis. [b]Yield of isolated products.

one-pot synthesis of substituted chromenes.

We believe that this procedure will provide a better scope for synthesizing 2*H*-4-chlorochromenes as the starting materials are easily accessible and more practical alternative to the existing procedures. Even though it is limited to 2′-hydroxychalcones and pyrazole analogues of 2′-hydroxychalcones.

We thank the Council of Scientific and Industrial Research, New Delhi, India for financial support.

References and Notes

1 B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, **120**, 9074 (1998).
2 J. Jankun, S. H. Selman, R. Swiercz, and E. Skrzypezak-Jankun, *Nature*, **56**, 387 (1997).
3 P. E. Brown, W. Y. Marcus, and P. Anastasis, *J. Chem. Soc., Perkin Trans. 1*, **1985**, 1127.
4 G. Ariamala and K. K. Balasubramanian, *Tetrahedron Lett.*, **29**, 3487 (1988).
5 a) O. Meth-Cohn and B. Tamowski, *Adv. Heterocycl. Chem.*, **31**, 207 (1982). b) C. M. Marson, *Tetrahedron*, **48**, 3659 (1992). c) A. D. Thomas and C. V. Asokan, *Tetrahedron*, **60**, 5069 (2004).
6 a) K. Hemanth Kumar, D. Muralidharan, and P. T. Perumal, *Syntheis*, **2004**, 63. b) K. Hemanth Kumar, S. Selvi, and P. T. Perumal, *J. Chem. Res.*, **2004**, 218. c) K. Hemanth Kumar, D. Muralidharan, and P. T. Perumal, *Tetrahedron Lett.*, **45**, 7903 (2004).
7 a) V. J. Majo and P. T. Perumal, *Tetrahedron Lett.*, **37**, 5015 (1996). b) V. J. Majo and P. T. Perumal, *J. Org. Chem.*, **61**, 6523 (1996). c) V. J. Majo and P. T. Perumal, *J. Org. Chem.*, **63**, 7136 (1998). d) R. R. Amaresh and P. T. Perumal, *Tetrahedron Lett.*, **38**, 7287 (1997).
8 Genaral procedure for the synthesis of chromenes: The Vilsmeier reagent was prepared by adding $POCl_3$ (1.4 mL 6 equiv.) dropwise to ice cold dry DMF (10 mL) under stirring. The reaction mixture was stirred for 10–15 min at 0 °C. To the above Vilsmeier reagent was added 2′-hydroxychalcone 2 (Entry 2 , Table 1) 0.6 g, 2.51 mmol as a solution in 5 mL dry DMF. The reaction mixture was stirred at room temperature for 30 min and maintained on a boiling water bath at at 90 °C for 5 h. The dark red solution was cooled and poured over 40 g, crushed ice and neutralized with 10% NaOH solution, after leaving it aside for 3–4 h. The reaction mixture was extracted with chloroform (20 mL 4 times) washed with 100 mL water and dried over anhydrous Na_2SO_4. Evaporation of the solvent, purification of the residue by using short silica gel column hexane as eluent gave **2a** as coloress oil, 0.42 g (65%). This procedure was followed for the synthesis of all the 2*H*-4-chlorochromenes and the results are summarized in Table 1 and Table 2.
9 Spectral data for the selected compounds: 2*H*-4-chloro-2-(4-methylphenyl)chromene (Entry 2, Table 1). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 5.92 (d, $J = 3.5$ Hz, 1H, H-2), 5.95 (d, $J = 4.0$ Hz, 1H, H-3), 6.81 (dd, $J = 1.15$, 8.0 Hz 1H, H-8), 6.95–6.98 (m, 1H, H-6), 7.18–7.21 (m, 3H, H-7, H′-3, H′-5), 7.33 (d, $J = 8.5$ Hz 2H, H′-2, H′-6), 7.48 (dd, $J = 1.15$, 8.0 Hz, 1H, H-5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.34, 77.98, 116.21, 120.35, 121.45, 122.09, 124.65, 127.21, 128.23, 129.54, 130.92, 136.82, 138.81, 153.59. MS: $m/z = 256$ (M^+). Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10%. Found: C, 75.05; H, 5.30%. 2*H*-4-Chloro-2-(2-thienyl)chromene (Entry 11, Table 1). colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.07 (d, $J = 4.5$ Hz, 1H, H-2), 6.14 (d, $J = 4.0$ Hz, 1H, H-3), 6.81 (d, $J = 8.0$ Hz, 1H, H-8), 6.96–6.99 (m, 2H, H-6, H′-4), 7.09 (d, $J = 3.4$ Hz, 1H, H′-3), 7.18–7.22 (m, 1H, H-7), 7.29 (d, $J = 5.15$ Hz, 1H, H′-5), 7.49 (dd, $J = 1.15$ Hz, 8.0 Hz, 1H H-5). ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.69, 116.61, 120.43, 120.96, 121.79, 124.76, 126.65, 126.87, 126.95, 129.12, 131.04, 142.49, 152.85. MS m/z 248.5 (M^+). Anal. Calcd for $C_{13}H_9ClOS$: C, 62.77; H, 3.65%. Found: C, 62.54; H, 3.69%.

Published on the web (Advance View) September 10, 2005; DOI 10.1246/cl.2005.1346