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On the Synthesis of Substituted 2,2-Dimethyl-4-Chromanones and Related Compounds+1

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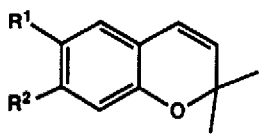
Abstract : **A systematic study of the reaction of a series of monosubstituted phenols 3 and 3-methylbut-2-enoic acid 4 in phosphorus oxychloride/zinc chloride revealed that the formation of 4-chromanones was strongly influenced by the substituents and their position on the aromatic ring of the starting phenols.**

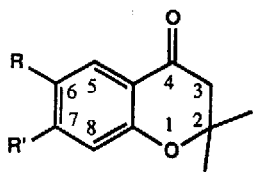
Substituted 2,2-dimethylchromene derivatives, e.g. precocene I **1a** and precocene II **1b** are natural products isolated by Bowers[2] from *Ageratum houstonianum*. These compounds are also known from various other natural sources.[3] Although precocenes are nature-friendly in the general sense, they cause precocious metamorphosis, sterility and other pronounced adverse biological effects in various insects.[2]

There are methods[4,5] for the synthesis of these compounds and analogues *via* the corresponding chromanones **2**. However, a truly systematic study of the acylation, Fries-rearrangement, and subsequent cyclization sequence has not yet been reported.[6]



1a $R^1 = H$, $R^2 = OMe$

1b $R^1 = R^2 = OMe$

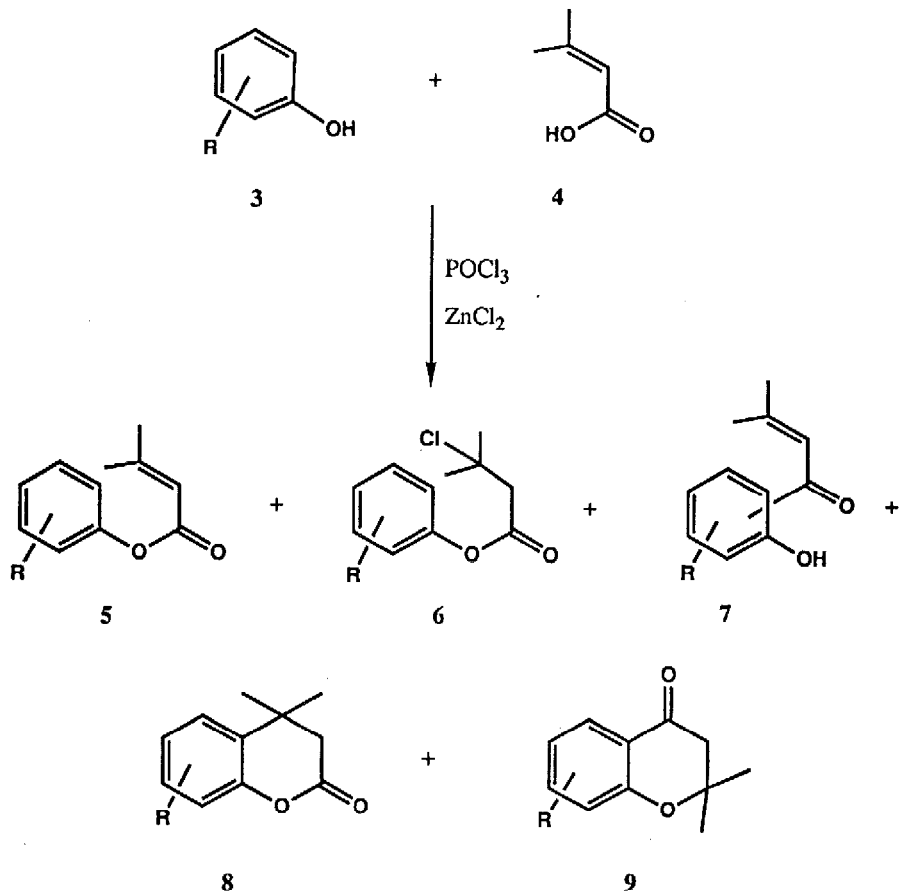


2

Since these chromanones are valuable intermediates in the synthesis of potentially useful modern pesticides and other bioactive compounds, such a study was warranted and justified.

+Dedicated with affection and appreciation to Professor Sir Derek Harold Richard Barton, FRS on the occasion of his 74th birthday.

We have shown earlier that the use of the $POCl_3/ZnCl_2$ reagent system can be very efficient in the synthesis of substituted chromanones.[4] We used these reagents in the systematic study of the reaction of monosubstituted phenols **3** with 3-methylbut-2-enoic acid **4** (Scheme 1).



Scheme 1

Thus, phenol and various monosubstituted phenols were reacted in $POCl_3/ZnCl_2$ and the progress of the reaction was monitored by glc and tlc. After all the starting **3** was consumed, an aqueous work-up followed that resulted in the crude mixtures of the corresponding **5-9** (Table 1). The data in Table 1 show that while the yield of the crude mixtures is high in all cases, the outcome of the reaction is very dependent on the substitution (substituent and position) of the starting phenol. The **5-7-9** sequence is desirable for the synthesis of substituted 2,2-dimethyl-4-chromanones in acidic systems. In those cases when the formation of the HCl addition products **6** dominates[10], the reaction leading to chromanones **9** are suppressed and the **5-6-(8)** alternative pathway is operational. We have found, however, that the formation of the corresponding coumarins **8** is either undetectable or this conversion is a very low yielding process.

Table 1. Reaction of monosubstituted phenols **3** with 3-methylbut-2-enoic acid **4** in $POCl_3/ZnCl_2$.

Compound 3	R	Reaction time (h)	Yield[a] (%)	Yield (%)[b]				
				5	**6**	**7**	**8**	**9**
3a	H	52	87	5[7,8]	80	9[c]	3[7]	3[8]
3b	2-OH	4	81	72	28			
3c	3-OH	3	92			76[d]		24[f]
3d	4-OH	6	91	92	8			
3e	2-Me	46	94		64	26[d]	4[g,7]	6[g,7]
3f	3-Me	46	93		37	9[e]	4[f,7]	50[f,7]
3g	4-Me	30	94		83		7[h,7]	10[h,11]
3h	2-MeO	4	89		68	31[d,6]		
3i	3-MeO	4	89	7[6]		38[d,6]	3[f]	52[f]
3j	4-MeO	26	85	55[6,9]	45			
3k	2-Cl	71	91	5	95			
3l	3-Cl	71	93	3	97			
3m	4-Cl	48	93		100			

[a]Yield of the isolated crude mixture of the corresponding **5-9**.
[b]Based on GC/MS and ^1H NMR identification and quantitative analysis by ^1H NMR.
[c]4-substituted product. [d]2-substituted product. [e]4.5% 2-substituted and 4.5% 4-substituted product.
[f]7-substituted chromanone derivative. [g]8-substituted chromanone derivative. [h]6-substituted chromanone derivative.

In the case of the 3-hydroxy and 3-methoxy starting compounds (**3c** and **3i**, respectively) the formation of the C-acylated products (**7c** and **7i**, respectively) causes no problem, since these can be either isolated or taken directly to the next step and cyclized in alkaline media to furnish the corresponding chromanones **9** in high yielding reactions. Our findings indicate, however, that despite of successful applications in the case of 3-hydroxy and 3-alkoxyphenols and further substituted derivatives[4,12], these conditions are unsuitable for transformation of cresols (**3e-g**) and chlorophenols (**3k-m**). Also, the 2 or 4-substituted phenols with an OH or OMe substituent fail to cyclize to the corresponding chromanones in this reagent system. This is in agreement with earlier observations.[13, 14]

Typical procedure :

To a stirred mixture of phosphoryl chloride (20 ml) and 3-methylbut-2-enoic acid (11 mmol , 1.1 g), zinc chloride (15 mmol, 2.04 g) and phenol (10 mmol) were added at room temperature. The reaction was monitored by TLC and GC. When the starting phenol disappeared (see Table 1) the mixture was poured onto crushed ice (200 g), extracted with ether (3 x 30 ml) and the ethereal solution was dried with sodium sulfate. The solvent was removed in vacuum and the residue was then studied by ^{1}H NMR and GC-MS.

References and notes :

1. Synthesis of Benzopyran Derivatives XIX. Part XVIII.: Jekö, J.; Timár, T.; Jaszberenyi, J. Cs. *J. Org. Chem.* **1991**, *56* , 6748. Part XVII. : Eszenyi, T.; Timár, T.; Sebök, P. *Tetrahedron Lett.* **1991**, *32*, 827. Part XVI.: Eszenyi,T.; Timár,T. *Synth. Commun.* **1990**, *20*, 3212.
2. Bowers, W. S.; Ohta, T.; Cleere, J. S.; Marsella, P.A. *Science* **1976**, *193*, 542.
3. Alertsen, A. R. *Acta Chem. Scand.* **1955**, *9*, 1725. Idem *Acta Polytechn. Scand., Chem. Incl. Metall. Ser.*, Chapter 13, **1961**, 1 and references cited therein..
4. Timár, T.; Hosztafi, S.; Jászberényi, J. Cs.; Kövér, K. E.; Batta, Gy. *Acta Chim. Hung.* **1988**, *125*, 303 . Timár, T.; Jászberényi, J. Cs. *J. Heterocycl. Chem.* **1988**, *25*, 871. Sebök, P.; Timár, T.; Jaszberenyi, J. Cs.; Batta, Gy. *Heterocycles* **1988**, *27* , 2595.
5. Lockhart, I. M. 4-Chromanones. In *Chromenes, Chromanones and Chromones* ; Ellis. G. P. Ed.; John Wiley and Sons, Inc.: New York, 1977; pp.207-428.
6. Camps, F.; Coll, J.; Colomina, O.; Messeguer, A. *J. Heterocycl. Chem.* **1985**, *22*, 363.
7. Cologne, J.; Chambard, R. *Bull. Soc. Chim. France*, **1953**, 573.
8. Baker, W.; Floyd, A.J.; McOmie, J. F. W.; Pope, G.; Weaving, A. S.; Wild, J. H. *J. Chem. Soc.* **1956**, 2010.
9. Primo, J.; Tormo, R.; Miranda, M. A. *Heterocycles* **1982**, *19*, 1819.
10. Mahajan, J. R.; Araújo, H. C. *Can. J. Chem.* **1987**, *65*, 224.
11. Auwers, K. v.; Lämmerhirt , E. *Chem. Ber.* **1920**, *53B*, 428.
12. Camps, F.; Coll, J.; Messeguer, A.; Pericás, M. A., Ricart, S.; Bowers, W. S.; Soderlund, D. M. *Synthesis* **1980**, 725.
13. Quilicio, A.; Cardani, C.; Panizzi, L.*Gazz. Chim. Ital.* **1950**, *80*, 325.
14. Ohta, T.; Bowers, W. S. *Chem. Pharm. Bull.* **1977**, *25*, 2788.

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