

## A New Synthesis for Substituted Coumarins

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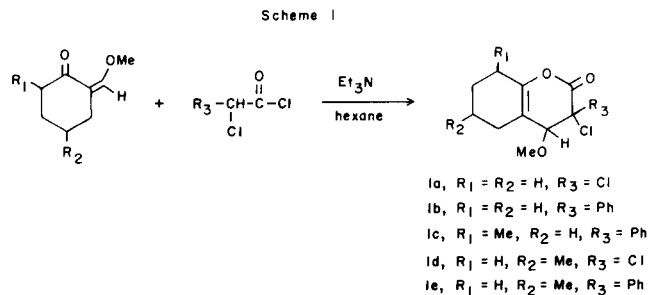
A new general synthesis of substituted coumarins is described. The *in situ* cycloaddition of chloroketenes with  $\alpha$ -methoxymethylenecyclohexanones yields (4 + 2) cycloaddition products, 3,4-dihydro-2-pyranones. The chlorine atom is reductively removed and methanol is spontaneously eliminated to yield the 5,6,7,8-tetrahydrocoumarins. Dehydrogenation of these compounds results in good yields of the substituted coumarins.

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Coumarins are derivatives of 2-pyranones which are widespread in nature being found primarily in the plant kingdom. Both natural and synthetic coumarins are known to exhibit useful and varied physiological activities [1-3] as well as enjoying much interest as fluorescent whiteners [4,5], dyes [6,7] and photographic sensitizers [8]. The synthesis of coumarins have been mostly through the traditional von Pechmann [9,10] and Knoevenagel [11-15] methods, however, there have recently appeared some varied methods for the synthesis of these important compounds [16-18].

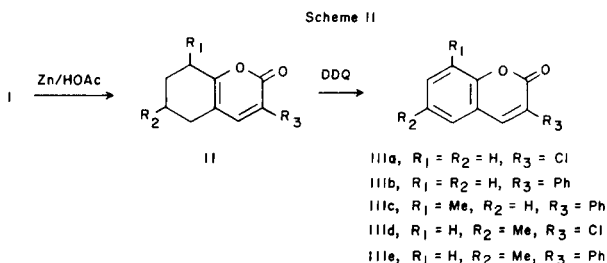
In our continuing studies in the development of new synthetic methodology utilizing cycloaddition reactions of ketenes, we have recently reported on the (4 + 2) cycloaddition of ketenes and  $\beta$ -methoxy- $\alpha,\beta$ -unsaturated ketones to yield 2-pyranones [19]. This paper describes a utilization of these (4 + 2) cycloaddition reactions in the development of a general synthetic route to substituted coumarins.

The *in situ* generation of dichloro- and phenylchloroketenes from freshly distilled dichloroacetyl chloride and phenylchloroacetyl chloride respectively with triethylamine in refluxing hexane in the presence of  $\alpha$ -methoxymethylenecyclohexanone resulted in the formation of the (4 + 2) cycloaddition product, the 3,4-dihydro-2-pyranone, Ia-e. The cycloaddition products were formed in up to 80%

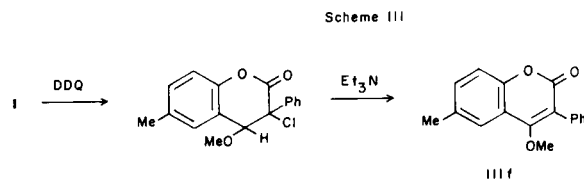


yields but were generally not isolated but treated with zinc in moist acetic acid [20]. The reductive removal of a chlorine atom resulted in the spontaneous elimination of methyl alcohol to yield the 3-substituted-5,6,7,8-tetrahydro-

coumarins, II, in yields of about 50%. These compounds were isolated and then dehydrogenated by refluxing in chlorobenzene with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DDQ, to yield the substituted coumarins, IIIa-e. An alternate method for accomplishing this dehydrogenation is the treatment of compounds II with *N*-bromosuccinimide with the spontaneous loss of two moles of hydrogen bromide. The substituted coumarins were obtained in overall yields of about 30% for all three steps of this synthesis.



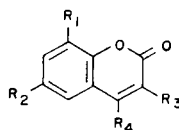
The phenylchloroketene cycloaddition products, Ib, Ic and Ie could be dehydrogenated with DDQ and then dehydrochlorinated with triethylamine in refluxing benzene to yield the 4-methoxy substituted coumarins as demonstrated below with Ie.



Dehydrogenation of the dichloroketene cycloaddition products with DDQ prior to loss of methanol were not successful.

Methylchloro- and other alkylchloroketenes will undergo the analogous (4 + 2) cycloaddition reaction with substituted  $\alpha$ -methoxymethylenecyclohexanone thus providing for a variation of the substituent in the 4-position of coumarin. Since 3-substituted derivatives of coumarins are particularly of much interest, the synthesis of the 3-chloro-

Table I  
Substituted Coumarins



| Compound | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub> | R <sub>4</sub> | Mp °C     | Molecular Formula                               | Analyses %     |              |
|----------|----------------|----------------|----------------|----------------|-----------|-------------------------------------------------|----------------|--------------|
|          |                |                |                |                |           |                                                 | Calcd./Found C | H            |
| IIIa     | H              | H              | Cl             | H              | 129.5-131 | C <sub>9</sub> H <sub>5</sub> ClO <sub>2</sub>  | 59.83<br>59.43 | 2.77<br>2.73 |
| IIIb     | H              | H              | Ph             | H              | 107.5-109 | C <sub>15</sub> H <sub>10</sub> O <sub>2</sub>  | 79.51<br>79.28 | 6.02<br>6.26 |
| IIIc     | Me             | H              | Ph             | H              | 112-114   | C <sub>16</sub> H <sub>12</sub> O <sub>2</sub>  | 81.34<br>81.78 | 5.11<br>5.34 |
| IIId     | H              | Me             | Cl             | H              | 121-122   | C <sub>10</sub> H <sub>7</sub> ClO <sub>2</sub> | 61.70<br>61.87 | 3.60<br>3.63 |
| IIIe     | H              | Me             | Ph             | H              | 147-147.5 | C <sub>16</sub> H <sub>12</sub> O <sub>2</sub>  | 81.34<br>81.10 | 5.11<br>4.87 |
| IIIf     | H              | Me             | Ph             | OMe            | 156.5-158 | C <sub>17</sub> H <sub>14</sub> O <sub>3</sub>  | 76.69<br>76.64 | 5.26<br>5.11 |

IR, <sup>1</sup>H and <sup>13</sup>C NMR Spectral Data

| Compound | IR, cm <sup>-1</sup><br>(Deuteriochloroform) |      | <sup>1</sup> H NMR (Deuteriochloroform) | <sup>13</sup> C NMR                                                                                                                                       |
|----------|----------------------------------------------|------|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
|          | C=O                                          | C=C  |                                         |                                                                                                                                                           |
| IIIa     | 1700                                         | 1600 | 7.20-7.67 (m) 4H, 7.88 (s) 1H           | 116.5 (d), 118.7 (s), 122.1 (s), 124.9 (d), 127.2 (d), 131.7 (d), 139.8 (d), 152.5 (s), 156.9 (s)                                                         |
| IIIb     | 1695                                         | 1600 | 7.23-7.70 (m) 9H, 7.80 (s) 1H           | 116.3 (d), 119.6 (d), 124.4 (d), 127.8 (d), 128.3 (d), 160.3 (s), 128.4 (d), 128.7 (d), 131.2 (s), 134.6 (s), 139.2 (d), 153.4 (s), 160.3 (s)             |
| IIIc     | 1695                                         | 1595 | 7.02-7.70 (m) 9H, 2.47 (s) 3H           | 15.3 (q), 119.3 (s), 140.1 (d), 124.0 (d), 125.6 (d), 125.7 (d), 151.8 (s), 128.0 (s), 128.4 (d), 128.5 (d), 128.6 (d), 132.6 (d), 134.8 (s), 160.4 (s)   |
| IIId     | 1720                                         | 1600 | 7.0-7.5 (m) 3H, 7.7 (s) 1H, 2.3 (s) 3H  | 20.44 (q), 116.0 (d), 118.3 (s), 121.8 (s), 126.8 (d), 132.7 (d), 134.8 (s), 139.8 (d), 150.5 (s), 157.0 (s)                                              |
| IIIe     | 1695                                         | 1595 | 7.0-7.9 (m) 9H, 2.3 (s) 3H              | 20.49 (q), 115.79 (d), 119.2 (s), 127.5 (d), 127.8 (d), 128.1 (d), 128.3 (d), 128.5 (d), 132.2 (d), 133.9 (s), 134.6 (s), 139.5 (d), 151.4 (d), 160.4 (s) |
| IIIf     | 1685                                         | 1595 | 7.0-7.6 (m) 6H, 3.45 (s) 3H, 2.4 (s) 3H | 20.66 (q), 60.85 (q), 110.8 (s), 115.8 (d), 117.1 (s), 123.3 (d), 127.9 (d), 130.7 (d), 132.3 (s), 132.6 (d), 133.5 (d), 150.4 (s), 162.7 (s), 163.2 (s)  |

coumarins described above should be easily converted to important derivatives, *i.e.*, 3-chlorocoumarins are known to undergo conversion to the 3-alkoxy derivatives by reaction with metal alkoxides.

It is possible to modify this synthesis procedure by employing monosubstituted ketenes in the cycloaddition step, thus eliminating the reductive removal of the chlorine atom. However, the yields of chloroketene cycloadducts are generally significantly higher than monosubstituted ketenes. Nevertheless, the cycloaddition of monosubstituted ketenes with  $\alpha$ -methoxymethylenecyclohexanones yield dihydropyranones that may be dehydrogenated to 3-substituted-4-alkoxycoumarins, such as IIIf, as described above but by a different procedure.

The synthesis of  $\alpha$ -methoxymethylenecyclohexanone is easily accomplished from cyclohexanone and ethyl formate. Consequently, the availability of substituted cyclohexanones provides the opportunity to introduce substitution in the benzene ring of the coumarin system.

In summary we have described a three-step synthesis for coumarins which provides a various substitution in the 3-position, alkoxy substitution in the 4-position and the opportunity for substitution in the benzene ring of the coumarin system.

## EXPERIMENTAL

Proton nmr and <sup>13</sup>C nmr spectra were recorded on a Perkin-Elmer R-

24B and a JEOL FX-90Q FT respectively employing deuteriochloroform as the solvent with tetramethylsilane as the internal standard. The infrared spectra were obtained in a Beckmann 1330 spectrophotometer. Hexane and triethylamine were dried and purified by distillation from sodium-potassium alloy prior to use. All of the substituted  $\alpha$ -methoxymethylenecyclohexanones were prepared from the corresponding substituted cyclohexanones with ethyl formate (1:1.5) and sodium ethoxide (1:1) in excellent yield following literature procedures [21,22].

General Procedure for Chloroketene Cycloadditions with  $\alpha$ -Methoxymethylenecyclohexanones (3,4-Dihydro-2-pyranones).

A solution of 0.0125 mole of the freshly distilled chlorinated acetyl chloride in 50 ml of dry hexane was added over a 2 hour period to a stirred, refluxing solution of 0.0125 mole of the  $\alpha$ -methoxymethylenecyclohexanone and 0.0125 mole of triethylamine in 100 ml of dry hexane under a nitrogen atmosphere. The resulting mixture was stirred for an additional 30 minute period. The amine salt was then removed by filtration, and the filtrate was concentrated on a rotatory evaporator. The residue was then treated with zinc in acetic acid.

Zinc/Acetic Acid Reduction (Tetrahydrocoumarins).

To the concentrated residue was added 40 ml of acetic acid and 2 ml of water. The mixture was stirred at room temperature, and 4 g of powdered zinc was added in one portion. The mixture was stirred for 24 hours. Excess zinc and the zinc salt were filtered and washed with 40 ml of chloroform. The filtrate was placed in a separatory funnel and washed several times with water until the aqueous layer tested neutral with litmus paper. The chloroform layer was dried over magnesium sulfate and concentrated to give the substituted 2-pyranones.

General Procedure for Dehydrogenation (Substituted Coumarins) [23].

A solution of 1 g of the 5,6,7,8-tetrahydrocoumarin in 200 ml of chlorobenzene was refluxed with DDQ for 18 hours. The mixture was filtered and the solvent removed under reduced pressure. The residue was purified by chromatography on a column of acidic alumina upon elution with hexane/ethyl acetate (1:1) to yield the substituted coumarin.

6-Methyl-4-methoxy-3-phenylcoumarin (III<sub>f</sub>).

A 1 g portion of 1e was refluxed with 2.25 g of DDQ in chlorobenzene for 18 hours. The mixture was filtered and dried under reduced pressure. The residue was passed through a column of acidic alumina by elution with hexane/ethyl acetate (1:1) to yield 6-methyl-4-methoxy-3-chloro-3,4-dihydrocoumarin. This compound was refluxed with 2 ml of triethylamine 60 ml of benzene for 24 hours. The amine salt was removed by filtra-

tion and the solvent evaporated under reduced pressure. The residue was recrystallized from 95% ethanol and benzene to give 36 mg (41%) of III<sub>f</sub>.

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## REFERENCES AND NOTES

- [1] T. O. Soimae, *J. Pharm. Sci.*, **53**, 231 (1964).
- [2] R. B. Arora and C. N. Mathur, *Br. J. Pharmacol.*, **20**, 29 (1963).
- [3] H. Ichibagase, *J. Pharm. Soc. Japan*, **75**, 1475 (1955).
- [4] H. Schlaepfer, German Patent, 2,329,991 (1974); *Chem. Abstr.*, **81**, 51143d (1974).
- [5] A. Dorlars, C. W. Schellhammer and J. Schroeder, *Angew. Chem., Int. Ed. Engl.*, **14**, 665 (1975).
- [6] G. A. Reynolds, K. H. Drexhage, *Opt. Commun.*, **13**, 222 (1975).
- [7] K. H. Drexhage, G. R. Erikson, G. H. Hawks and R. C. Reynolds, *ibid.*, **15**, 399 (1975).
- [8] J. D. Kendall, H. R. J. Waddington and G. F. Duffin, British Patent 867,592 (1961); *Chem. Abstr.*, **55**, 21927c (1961).
- [9] S. Sethna and R. Phadke, *Org. React.*, **7**, 1 (1953).
- [10] For a review on coumarin syntheses see, S. Wawzonek, "Heterocyclic Compounds", Vol 2, R. C. Elderfield, ed, John Wiley and Sons, New York, 1951, pp 174-176.
- [11] A. Jujimoto and A. Sakurai, *Synthesis*, 871 (1977).
- [12] C. R. Jacobson, K. R. Brower and E. D. Amstutz, *J. Org. Chem.*, **18**, 1117 (1953).
- [13] E. C. Horning, M. G. Horning and D. A. Dimming, *Org. Synth.*, **35**, 165 (1955).
- [14] L. L. Woods and J. Sapp, *J. Org. Chem.*, **30**, 312 (1965).
- [15] H. Ichibagase, *J. Pharm. Soc. Japan*, **75**, 1477 (1955).
- [16] E. R. Bissel, *Synthesis*, 846 (1982).
- [17] G. A. Kraus and J. O. Pezzanite, *J. Org. Chem.*, **44**, 2480 (1979).
- [18] R. T. Taylor and R. A. Cassel, *Synthesis*, 672 (1982).
- [19] W. T. Brady and M. Agho, *J. Org. Chem.*, **48**, 5337 (1983).
- [20] Compounds Ib, Id, and 1e were isolated in about 80% yield and all the spectral data (H-nmr, C-nmr and ir) were consistent with the assigned structures.
- [21] C. Ainsworth, *Org. Synth.*, **39**, 27 (1959).
- [22] W. S. Johnson and H. Rosvic, *J. Am. Chem. Soc.*, **69**, 1361 (1947).
- [23] D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1965).