

Reactions of 4 or 3,4-Disubstituted-Coumarins With Nucleophilic Reagents

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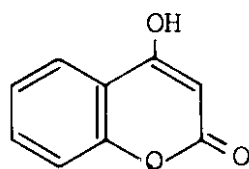
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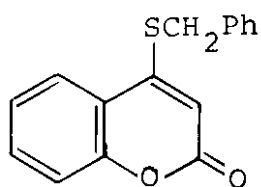
Summary: Reactions of 4-or 3,4-disubstituted-coumarins with nucleophilic reagents have been investigated. The reactions of 4-methoxy-coumarin with nucleophilic reagents were of limited success, however, 4-chloro-3-nitro-coumarin (III) with methanol, ethanol, benzyl alcohol or sodium acetate resulted in the formation of the corresponding 4-substituted-3-nitro-coumarins (IVa-d). 4-Alkoxy or chloro-3-nitro-coumarins (IVa, b or III) with benzyl mercaptan yielded 4-S-benzyl-3-nitro-coumarin (IVe) and 3,4-di-S-benzyl-coumarin (VIII). Analogous reaction of 3-acetyl-amino-4-methoxy-coumarin with benzyl-mercaptan gave (X). Attempts to cyclise (X) to coumarino-thiazole resulted in the formation of 3-diacetyl-amino derivative (XI). Reactions of the related 4-methoxy-6-methyl-2H-pyran-2-one and its thio-analogue with benzylmercaptan afforded (XIIa) and (XIIb) respectively.

Coumarins constitute one of the most important class of the oxygen heterocyclic compounds which occur in natural products¹ and possess vital pharmacological activity^{2,3a}, consequently the synthesis³ and properties of these compounds have been studied quite extensively. However, the reactions of the 4-or- 3,4-disubstituted-coumarins with nucleophilic reagents have been reported,^{4,5} to a limited extent due to the susceptibility of the pyrone ring to these reagents. In view of the synthetic importance and the occurrence of the coumarin derivatives in natural products, we have prepared a number of substituted-coumarins via nucleophilic displacement reactions, using 4-or 3,4-disubstituted-coumarins derived from 4-hydroxy-coumarin (I).

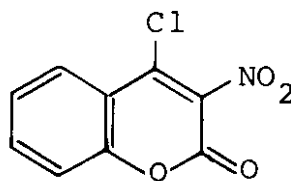
In preliminary experiments the reactions of 4-methoxy-coumarin with nucleophilic reagents (CN^- , CH_3COO^- , $\text{CH}(\text{COOEt})_2$) did not yield the anticipated products i.e. 4-substituted-coumarins and only benzyl mercaptan in the presence of sodium hydroxide on prolonged refluxing afforded 4-S-benzyl-coumarin (II). However, 4-chloro-3-nitro-coumarin (III) promised to provide a convenient route for nucleophilic substitution reactions.



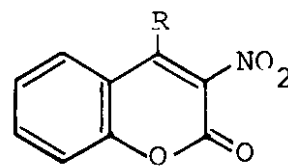
(I)



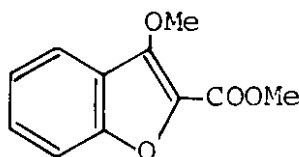
(II)



(III)



(IV)



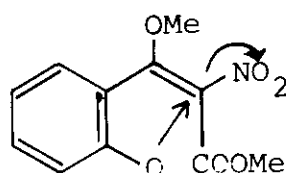
(V)

R	
a	OEt
b	OMe
c	OCH ₂ ph
d	OCOMe
e	SCH ₂ ph

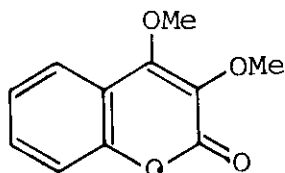
4-Chloro-3-nitro-coumarin (III) was obtained in quantitative yields by refluxing a mixture of 4-hydroxy-3-nitro-coumarin and phosphorus oxy chloride in the presence of pyridine. Reaction of 4-chloro-3-nitro-coumarin (III) with appropriate sodium alkoxide in the corresponding alcohol yielded 4-alkoxy-3-nitro-coumarins (IVa,b). Methyl-3-methoxy-coumarilate (V) was also isolated as a by-product alongwith (IVb) in the reaction of methoxide with (III). However, when 4-chloro-3-nitro-coumarin (III) was refluxed with pure methanol or ethanol in the presence of catalytic amount of corresponding alkoxide then only 4-alkoxy-3-nitro-coumarins (IVa,b) were obtained in almost quantitative yields. Repetition of these experiments without the presence of alkoxide also gave an appreciable yield of (IVa,b)

thus showing the facile character of the 4-chloro atom as a leaving group. The products (IVa,b) were characterised on the basis of spectral data and their syntheses from 4-hydroxy-3-nitro-coumarin and appropriate alkyl iodide in the presence of potassium carbonate using acetone as the solvent.

Formation of coumarilate (V) presumably involves the initial displacement of the chloro group (4-position) of (III) by the methoxy groups followed by the nucleophilic attack at carbonyl (2-position) to form the phenoxide ion (VI) which subsequently cyclises to the coumarilate (V) with the loss of nitro group. The characterisation of coumarilate (V) is complicated due to the possibility of the formation of the isomeric 3,4-dimethoxy-coumarin (VII). Newman⁵ et.al. on the basis of a detailed study of the spectral data has established that the coumarilates invariably show absorption maxima below 300 nm. In conformity with its structure the coumarilate (V) showed ultraviolet absorption maxima at 288 and 225 nm. The structure (V) is further substantiated by the comparison of absorption data, m.p. and mixed m.p. with an authentic sample.



(VI)

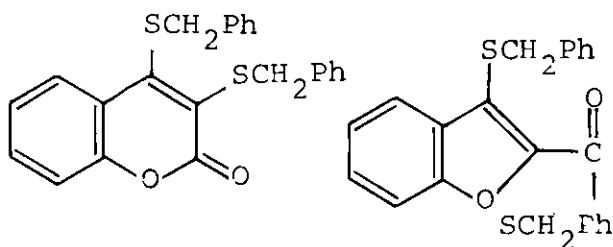


(VII)

Analogous reactions of 4-chloro-3-nitro-coumarin (III) with benzyl alcohol, sodium acetate and benzyl mercaptan yielded 4-substituted-3-nitro-coumarin (IVc) (IVd) and (IVe) respectively. Structure of these products was established on the basis of elemental analysis and spectral data. Reaction of 4-alkoxy-3-nitro-coumarin with benzyl mercaptans in the presence of sodium hydroxide also gave (IVe) in fairly good yield. In addition the products (IVc) and (IVd) were also obtained by other synthetic route, thus establishing their structure unambiguously.

Reactions of 4-alkoxy or chloro-3-nitro-coumarin with excess of benzyl mercaptan in the presence of sodium ethoxide or NaOH afforded 3,4-di-S-benzyl-coumarin (VIII) in appreciable yields. The structure is supported by the spectral data. The possibility of the formation of the isomeric coumarilate (IX) is eliminated by the ultraviolet absorption maxima at 325 nm, a

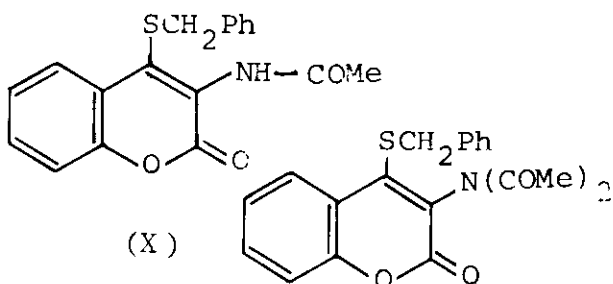
characteristic of coumarin ring. Product (VIII) was also obtained when 4-S-benzyl-3-nitro-coumarin (IVe) was refluxed with one equivalent of benzyl mercaptan in the presence of sodium ethoxide.



(VIII)

(IX)

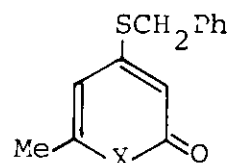
3-Acetylamino-4-methoxy-coumarin with benzyl mercaptan gave 3-acetylamino-4-S-benzyl-coumarin (X) and its attempted cyclisation to coumarino-thiazole using acetic anhydride or acetic anhydride/perchloric acid mixture resulted in the formation of 3-diacetylamino-4-S-benzyl-coumarin (XI).



(X)

(XI)

The reaction of the related 4-methoxy-6-methyl-2H-pyran-2-one⁶ and 4-methoxy-6-methyl-2H-pyran-2-thione⁷ with benzylmercaptan yielded the 4-S-benzyl derivatives (XIIa) and (XIIb) respectively. However, in both cases the reaction occurred under vigorous conditions as compared to the reactions of 4 or 3,4-disubstituted-coumarins with benzyl mercaptan.



(XII)

XIIa X = O

XIIb X = S

Experimental

Ultraviolet spectra were recorded on a Unicam SP800 spectrophotometer in ethanol, infrared spectra on Unicam SP200 for mulls in Nujol and NMR spectra were measured with a Perkin-Elmer R10 (60 MHz) spectrophotometer, with deuterio-chloroform as solvent and TMS as internal reference, unless otherwise stated. Melting points were determined on Gallenkamp melting point apparatus and are uncorrected.

4-Hydroxy-coumarin used in the present work was from Koch light (London). 4-Methoxy-coumarin m.p. 125°C (lit.⁵, m.p. 125°C), 4-Hydroxy-3-nitro-coumarin m.p. 177°C (lit.⁹, m.p. 177°C) and 3-acetyl-amino-4-methoxy-coumarin m.p. 170°C (lit.⁸, m.p. 170°C) were prepared by the methods as given in literature.

I. 4-S-benzyl-coumarin (II):

4-Methoxy-coumarin (1.8 g.) was added to a solution of benzyl mercaptan (1.25 g.) in ethanol and the mixture was refluxed for 5 hours on cooling the reaction mixture the resulting thick solid mass was filtered out and washed with small quantity of ethanol. Crystallisation from methanol gave long white needles (35%) m.p. 175°C (lit.¹⁰, m.p. 171-172°C) ν max. 1720, 1605, 1595, 1550 cm^{-1} λ max. 330 nm (Log. ϵ 3.57), 315 nm (log ϵ 3.84), 298 nm (log ϵ 4.02), 275 nm (log ϵ 3.98), 215 nm (Log. ϵ 4.31); nmr δ 4.25 (2H), 6.25 (1H) 7.45-7.85 (9H aromatic); (Found C, 71.58; H, 4.70; S, 11.65, $\text{C}_{16}\text{H}_{12}\text{O}_2\text{S}$ requires: C, 71.64; H, 4.48; S, 11.94%).

4-Chloro-3-nitro-coumarin (III):—

A mixture of 4-hydroxy-3-nitro-coumarin (1 g.), phosphorus oxychloride (8ml) and pyridine (2 ml) was refluxed for one hour. After cooling the reaction mixture was poured into ice-cold water (100 ml) with stirring. The solid product was filtered off and recrystallised from benzene-pet.ether (60-80°C) mixture as off white microcrystalline solid (84%) m.p. (160-162°C) ν max. 1750, 1690, 1550, 1190 cm^{-1} λ max. 325 nm (Log. ϵ 3.68), 286 nm (Log. ϵ 4.02), 215 nm (Log. ϵ 4.23), nmr δ 6.2 (1H) 7.4-7.8 (4H, aromatic); (Found: C, 48.0, H, 1.5; Cl, 15.52; $\text{C}_9\text{H}_4\text{O}_4\text{NCl}$ requires C, 47.89; H, 1.77, Cl, 15.7%).

4-Alkoxy-3-nitro-coumarin (IVa, IVb)

A solution of 4-chloro-3-nitro-coumarin (1.1g.) in ethanol (10ml) and sodium ethoxide (0.12 g. sodium, 2ml ethanol) was left at room temperature for 12 hours.

Evaporation of the reaction mixture under reduced pressure and crystallisation of solid residue from benzene-petroleum ether gave 4-ethoxy-3-nitro-coumarin (IVa) m.p. 140°C ν max. 1720, 1705, 1610, 1570 cm^{-1} max. (nm) 315 (Log. ϵ 3.62), 304 (Log. ϵ 3.45), 277 (Log. ϵ 3.82); nmr δ 2.2 (3H); 4.52 (2H) 7.46-8.0 (4H, aromatic), (Found: C, 56.0, H, 3.6; N, 5.85; $\text{C}_{11}\text{H}_9\text{O}_5\text{N}$ requires C, 56.17; H, 3.82; N, 5.95%).

Under the analogous conditions the reaction of 4-chloro-3-nitro-coumarin (III) with sodium methoxide in methanol gave 4-methoxy-3-nitro-coumarin (IVb) m.p. 98-99°C (benzene-pet.ether 60-80°C— ν max. 1720, 1705, 1628, 1565 cm^{-1} λ max. (nm) 306 (Log. ϵ 3.63) 280 (Log. ϵ 3.93), 270 (Log. ϵ 3.94), 213 (Log. ϵ 4.23); nmr δ 4.5 (3H), 7.52-8.15 (4H, aromatic); (Found: C, 54.00; H, 3.15; N, 6.30, $\text{C}_{10}\text{H}_7\text{O}_5\text{N}$ requires C, 54.29; H, 3.17; N, 6.34%). The mother liquor from the crystallisation of (IVb), on evaporation yielded methyl-3-methoxy-coumarilate (V) m.p. 75-76°C (lit.⁵, m.p. 75.4-76.8°C) λ max. 288, (Log. ϵ 4.25), 225 (Log. ϵ 4.01), 215 (Log. ϵ 4.0). The identity of product (V) was established by the comparison of spectral data m.p. and mixed m.p. with an authentic sample prepared by the method of Newman et al.⁵

4-Chloro-3-nitro-coumarin (III) on refluxing (0.4 hr.) with appropriate alcohol in the presence of catalytic amount of corresponding sodium alkoxide yielded 4-methoxy or 4-ethoxy-3-nitro-coumarin (IV) in quantitative yields. The identity of the products with that obtained by the preceding method was established by m.p., mixed m.p. and comparison of spectral data. Repetition of these experiments even without the addition of catalytic amount of sodium alkoxide and refluxing the mixture for 1 hour also gave (IVa, b) in good yields (60-70%).

Products (IVa, b) were also obtained by refluxing (8-10 hours) a mixture of 4-hydroxy-3-nitro-coumarin (1.5 g.) methyl iodide or ethyl iodide (1ml), and anhydrous potassium carbonate (8 g.) in ethyl methyl ketone (40 ml).

4-Benzyloxy-3-nitro-coumarin (IVc)

4-Chloro-3-nitro-coumarin (III) on refluxing with benzyl alcohol as described in the previous experiment gave 4-benzyloxy-3-nitro-coumarin m.p. 140-143°C (benzene-pet.ether— λ max. 1715, 1610, 1590 cm^{-1} ; λ max. (nm) 325 (Log. ϵ 3.8), 280 (Log. ϵ 4.1); nmr δ , 4.1 (2H), 7.4-8.1 (9H, aromatic); (Found: C, 64.5; H, 3.52; N, 4.5 $\text{C}_{16}\text{H}_{11}\text{O}_5\text{N}$ requires C, 64.64; H, 3.70; N,

4.73%). The same product was also obtained when a mixture of 4-hydroxy-3-nitro-coumarin (1 g.) benzyl chloride (1 ml) and anhydrous potassium carbonate (8 g.) in acetone (40ml) was refluxed for 8 hours.

4-Acetyloxy-3-nitro-coumarin (IVd)

A mixture of 4-chloro-3-nitro-coumarin (III) (1 g.) and sodium acetate (1 g.) in water-ethanol (10ml) was refluxed for one hour and evaporated to dryness. Residue was extracted with chloroform. The chloroform extracts on evaporation gave viscous residue which on crystallisation from (benzene-pet.ether) (60-80°) mixture gave solid m.p. 60-65°C ν max. 1750 (CO) 1725 (CO of ring). λ max. (nm) 310; 288; nmr 4.5 (3H), 7.5-8.1 (4H, aromatic); (Found: C, 53.01; H, 2.81; N, 5.61%). The same product was also obtained by the treatment of 4-hydroxy-3-nitro-coumarin (1 g.) with acetic anhydride (2ml) in pyridine (20-25ml) at room temperature (10-12 hours).

4-S-benzyl-3-nitro-coumarin (IVe)

To a solution of benzyl mercaptan (0.3 g) and sodium hydroxide (0.03 g) in ethanol (3ml) was added 4-chloro-3-nitro-coumarin (0.3 g) and the mixture refluxed for 10 minute. After cooling the solid product was filtered out and washed with ether. Crystallisation from benzene gave needles m.p. 153-155°C (60%). ν max. 1719, 1610, 1590, 1540 cm^{-1} . λ max. (nm) 325 (Log ϵ 3.75), 286 (Log ϵ 4.03), 212 (Log ϵ 4.32); nmr δ 4.2 (2H, 7.4-8.2 (9H, aromatic); (Found: C, 61.13; H, 3.65; S, 10.0; N, 4.70 $\text{C}_{16}\text{H}_{11}\text{SO}_4\text{N}$ requires C, 61.34; H, 3.51; S, 10.2; N, 4.47%). The same product was also obtained when 4-methoxy-3-nitro-coumarin (IVa) or 4-ethoxy-3-nitro-coumarin (IVb) was used instead of 4-chloro-3-nitro-coumarin (III) in this experiment.

3,4-di-S-benzyl-coumarin (VIII)

4-Chloro-3-nitro-coumarin (III) or 4-alkoxy-3-nitro-coumarin (IVa, b; 1.1 g) and benzyl mercaptan (1 g) was added to the sodium ethoxide solution made by adding sodium (0.1 g) in ethanol (25 ml). After refluxing for one hour, the reaction mixture was evaporated to dryness under reduced pressure. Solid residue on recrystallisation (twice) from ethanol-pet.ether (60-80°C) gave white needles m.p. 90°C. ν max. 1715, 1603, 1585 cm^{-1} . λ max. (nm) 325 (Log ϵ 3.86), 285 (Log ϵ 3.91), 242 (Log ϵ 4.16); nmr δ 3.95 (2H, 4.39 (2H), 7.38-8.1

(14H aromatic); (Found: C, 71.14; H, 4.53; S, 16.4 $\text{C}_{23}\text{H}_{18}\text{O}_2\text{S}_2$ requires C, 70.26; H, 4.61; S, 16.41%).

3-Acetylamino-4-S-benzyl-coumarin (X)

To a solution of 3-acetylamino-4-methoxy-coumarin⁸ (1.1 g) in ethanol (15ml) was added benzyl mercaptan (0.7 g) and sodium hydroxide (0.7 g) dissolved in ethanol (5ml). After refluxing (1 hour) and cooling, the solid product was filtered out and crystallised from ethanol as white shining needles m.p. 185-186°C. ν max. 3250, 1715, 1660, 1600 cm^{-1} ; λ max. (nm) 325 (Log ϵ 3.97), 300 (Log ϵ 3.94), 211 (Log ϵ 4.4); nmr δ 2.1 (3H), 4.0 (2H), 7.4-8.2 (9H, aromatic). (Found: C, 66.15; H, 4.29; N, 4.42; S, 9.6 $\text{C}_{18}\text{H}_{15}\text{NSO}_3$ requires C, 66.46; H, 4.61; N, 4.30; S, 9.8%).

3-Diacetylamino-4-benzyl mercaptanyl-coumarin (XI)

To mixture of 3-Acetylamino-4-benzyl mercaptanyl (X, 0.5g) and in acetic anhydride (5ml) was added a drop of 72% perchloric acid and then the mixture was allowed to stand at room temperature for 12 hours. The light brown solution was then poured into ice cold water. The resulting solid was filtered out which on crystallisation from ethanol-pet.ether (60-80°C) mixture gave white solid m.p. 150-152°C ν max. 1715; 1650, 1560 cm^{-1} , nmr δ 2.43 (6H), 4.33 (2H), 7.65-8.4 (9H, Aromatic); (Found: C, 65.1; H, 4.60; N, 3.90; S, 8.81 $\text{C}_{20}\text{H}_{17}\text{NSO}_4$ requires C, 65.39; H, 4.63; N, 3.81; S, 8.99%). The same product was also obtained by refluxing 3-acetylamino-4-benzyl mercaptanyl-coumarin (X) with acetic anhydride.

4-S-benzyl-6-methyl-pyran-2-one (XIIa)

4-Methoxy-6-methyl-2H-pyran-2-one⁵ (2.0 g) was added to solution of benzyl mercaptan (2.5 g) and sodium hydroxide (0.2 g) in ethanol (5ml). The reaction mixture was refluxed for 24 hours. Evaporation of the reaction mixture under reduced pressure yielded a thick oily liquid with a strong smell of mercaptan. Addition of pet.ether (60-80°C) to the chilled residue gave white solid m.p. 60-70°C. Which on fractional crystallisation from pet-ether (60-80°C) and ether mixture (3:1) gave 4-methoxy-6-methyl-2H-pyran-2-one (1g) m.p. (86-87°C) and 4-S-benzyl-6-methyl-2H-pyran-2-one (0.3g) m.p. 94-95°C. ν max. 1720, 1630, 1600, 1530 cm^{-1} . λ max. 300 (Log ϵ 3.84), 275 (Log ϵ 4.24), nmr δ 2.3 (3H), 4.28 (2H), 6.02 (2H), 7.6 (5H, aromatic) (Found: C, 67.48; H, 5.42; S, 13.41; $\text{C}_{13}\text{H}_{14}\text{O}_2\text{S}$ requires C, 67.24; H, 5.17; S, 13.78%).

4-S-benzyl-6-methyl-pyran-2-thione (XIIb)

A mixture of 4-Methoxy-6-methyl-pyran-2-thione⁷ (0.5 g), benzyl mercaptan (1 g) and sodium hydroxide (0.05 g) in ethanol (5ml) was refluxed for 16 hours. Evaporation of the reaction mixture under vacuum and recrystallisation of the residue from pet.ether (60-80°C) gave faint yellow plates (0.2 g) m.p. 108-109°C. ν max. 1620, 1580, 1520, 1190, 1065 cm^{-1} ; λ max. (nm) 345 (Log ϵ 3.71), 306 (Log ϵ 4.27), 239 (Log ϵ 4.24); nmr δ 2.3 (3H), 4.15 (2H), 6.25 (1H), 6.52 (1H), 7.42 (5H, aromatic) (Found: C, 63.03; H, 5.05; S, 25.63; $\text{C}_{13}\text{H}_{12}\text{OS}_2$ requires C, 62.90; H, 4.83; S, 25.8%).

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