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Synthesis of 3-methyl-coumarins, -thiacoumarins and -carbostyrils

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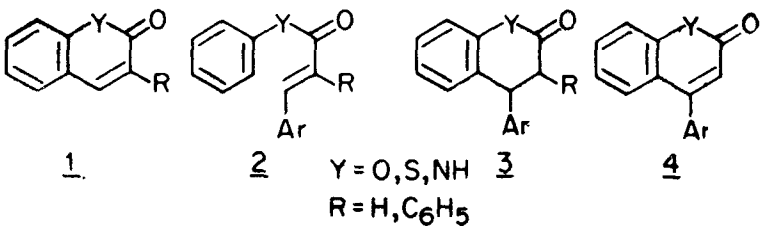
Abstract. Reaction of 3,6-dimethyl-4-phenyl-3,4-dihydrocoumarin 5*a* with anhydrous aluminum chloride gave 3,6-dimethyl-coumarin (6*a*); likewise, 6-chloro-3-methyl-coumarin (6*b*) was obtained from 5*b*. Substituted 3-methyl-thiacoumarins (8*a*, *b*) and 3-methyl-carbostyrils (10*a*–*e*) were prepared from the reactions of the respective α-methyl-cinnamoyl derivatives (7*a*, *b*) and (9*a*–*e*), of thiophenols and anilines.

Keywords. 4-Aryl-3,4-dihydrocoumarins; 3-methyl-coumarins; 3-methyl-thia-coumarins; 3-methyl-carbostyrils; dearylation by aluminum chloride.

1. Introduction

We have reported (Manimaran *et al* 1975) the synthesis of coumarins, thiacoumarins and carbostyrils (1) by the treatment of the cinnamoyl derivatives (2) of phenols, thiophenols and anilines respectively with anhydrous aluminum chloride. In these reactions, 4-aryl-3, 4-dihydro-coumarin and -carbostyril (3, Y = O, NH; R = H) have been proposed as intermediates through their independent synthesis and further conversion to the end product (1) by dearylation with aluminum chloride. Eventhough the dihydrocompound in the sulphur system (3, Y = S) has not been isolated, such entity is considered as an intermediate by its similarity of reactions with the other two ring systems (2, Y = O, NH)

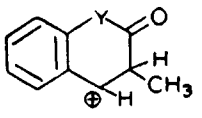


Similar studies (Manimaran *et al* 1979) with the α-phenyl-cinnamoyl derivatives (2, R=C_6H_5) have also been carried out which resulted in the synthesis of 3-phenyl-coumarins, -thiacoumarins and -carbostyrils (1, R = C_6H_5). Here again representative dihydrosystems (2, R = C_6H_5; Y = O, NH) have been studied. Considering the dihydro system as the intermediate with the phenyl substituent at the 3-position (3, R = C_6H_5), the dearylation could occur by the loss of the C_4-aryl group resulting in 3-phenyl system (1, R = C_6H_5) or by the elimination of the phenyl group at position-3 affording the 4-aryl substituted system (4). In all the reactions, only the C_4-aryl group got eliminated ultimately resulting in the synthesis of 3-phenyl-coumarins and related systems (1, R = C_6H_5).

2. Results and discussion

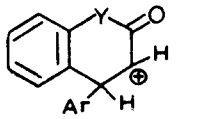
From the above results, one could draw out a method of synthesising 3-substituted coumarins and other systems (1) from the cinnamoyl compound 2 with the appropriate substituent at the α-position. The results of such a study with α-methyl-cinnamoyl system (2, R = CH_3) are reported here. This study was taken up on two main reasons. One factor was to effect the synthesis of 3-methyl-coumarins, -thiacoumarins and -carbostyrils (1, R = CH_3), involving the dearylation of the C_4-aryl group from the dihydrointermediate (3, R = CH_3); the other reason was to find out whether any dealkylation occurs from such a dihydro system which would yield 4-aryl-coumarins, -thiacoumarins and -carbostyrils (4), since aluminum chloride is known to effect dealkylation (Olah 1973; Ross and Barclay 1964).

In this context, several reactions were carried out with α-methyl-cinnamoyl systems. In all the experiments, only 3-methylderivatives (1, R = CH_3) were obtained involving the cyclization and dearylation steps, instead of the 4-aryl-derivatives 4 which would result by dealkylation of 3 (R = CH_3). Such a selectivity in these reactions could be explained by considering the two ion-pairs *A* and *B*, in the transition state, similar to such ion-pairs suggested for the 3-phenyl system. (Johnston *et al* 1972; Gopalan *et al* 1975). The ion-pair *A* is having resonance



$ArAlCl_3^{\ominus}$

A



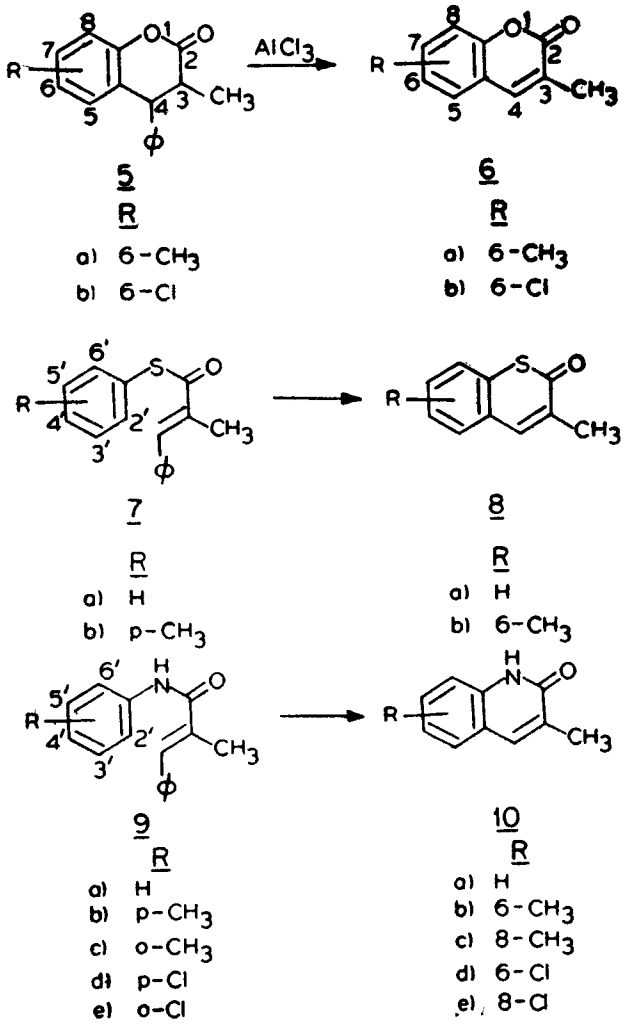
$CH_3AlCl_3^{\ominus}$

B

stability whereas *B*, in addition to not having such stabilization contributions, has the positive charge at the unfavourable α-position of the carbonyl group. Hence the dearylation is the preferred path than the dealkylation in the ring system 3 (R = CH_3). The various 3-methylcoumarins 6,3-methyl-thiacoumarins 8 and 3-methyl-carbostyrils 10 synthesised by this method are listed in the chart.

2.1. *Preparation of* 3,6-*dimethyl*-4-*phenyl*-3,4-*dihydrocoumarin* (5*a*)

A mixture of *p*-cresol (2·64 g) and α-methyl-cinnamic acid (4·0 g) was heated at 130° with 2 ml of conc. sulphuric acid for 1 hr. The reaction mixture was extracted



with chloroform and washed several times with water. The organic layer was dried ($MgSO_4$) and concentrated and the residue was chromatographed over a silica gel column. On elution with benzene, the dihydrocoumarin (5*a*) was obtained. Yield: 1·21 g. mp 148–9°. IR (KBr): 1750–60 cm^{-1}. NMR ($CDCl_3 + CCl_4$) : δ (ppm) 1·1 (d, 3H, 3–CH_3, J = 7Hz), 2·27 (s, 3H, 6–CH_3), 3·1 (m, 1H, 3–CH, J ≈ 6Hz), 4·03 (d, 1H, 4–CH, J = 6Hz) and 6·8–7·4 (m, 8H, aromatic).

2.2. 6-*Chloro*-3-*methyl*-4-*phenyl*-3,4-*dihydrocoumarin* (5*b*)

From the sulphuric acid reaction of *p*-chlorophenol (3·16 g) and α-methyl-cinnamic acid (4 g), by the above procedure, the dihydrocoumarin 5*b* (2·92 g) was obtained; mp 145–6°. IR (KBr): 1750–70 cm^{-1}. NMR ($CDCl_3 + CCl_4$): δ 1·1 (d, 3H, CH_3, J = 7Hz), 2·7–3·3 (m, 1H, 3–CH), 4·07 (d, 1H, 4–CH, J = 6Hz) and 6·8–7·6 (m, 8H, aromatic).

2.3. 3,6-*Dimethyl-coumarin* (6*a*)

The dihydrocoumarin 5*a* (500 mg) was heated at 120° in chlorobenzene (30 ml) with anhydrous aluminum chloride (1·5 g), for 1 hr. The reaction mixture was treated with ice and dilute hydrochloric acid and extracted with chloroform. The dried ($MgSO_4$) organic layer was concentrated and the residue chromatographed over a column of silica gel and eluted with benzene to isolate 3,6-dimethyl-coumarin (6*a*) (0·245 g; 71%); mp 114–5° [lit. (Gopalan *et al.* 1975) mp 116°]. IR (KBr): 1700–10 cm^{-1}. Mixed mp with authentic sample (Gopalan *et al* 1975) undepressed.

2.4. 6-*Chloro*-3-*methyl-coumarin* (6*b*)

By a reaction similar to that of 5*a*, treatment of the dihydrocoumarin 5*b* (500 mg) with aluminum chloride (1·5 g) in chlorobenzene (30 ml) at 120° for 6 hrs, gave 6-chloro-3-methyl-coumarin (6*b*) (0·243 g, 68%). mp 158–9° [lit. (Gopalan *et al* 1975) mp 159°]; mixed mp with authentic sample (Gopalan *et al* 1975) undepressed. IR (KBr): 1710–20 cm^{-1}. The attempt to prepare the 3-methyl-coumarins (6) directly from the ester yielded only the corresponding phenols.

2.5. 3-*Methyl-thiacoumarin* (8*a*) *and* 3,6-*dimethyl-thiacoumarin* (8*b*)

Thiophenyl α-methyl-cinnamate (7*a*) was prepared from α-methyl-cinnamoyl chloride (from 3·0 g of the acid) and thiophenol (2·0 g). Yield: 2·93 g (63%): mp 63–4°. NMR ($CDCl_3$): δ 2·37 (s, 3H, CH_3), 7·4–7·8 (m, 10H, aromatic) and 7·9 (s, 1H, β–H). Found: C, 75·64; H, 5·50. $C_{16}H_{14}OS$ requires: C, 75·58; H, 5·55%.

p-Thiocresyl α-methyl-cinnamate (7*b*) was prepared from *p*-thiocresol (3·0 g) and the acid chloride from α-methyl-cinnamic acid (4·0 g). Yield: 5·8 g (87%); mp 66–7°. IR ($CHCl_3$): 1630–50 cm^{-1}. NMR ($CDCl_3 + CCl_4$) : δ 2·2 (s, 3H, CH_3), 2·4 (s, 3H, CH_3), 7·2–7·6 (m, 9H, aromatic) and 7·7 (s, 1H, β–H) Found: C, 76·38; H, 6·26. $C_{17}H_{16}OS$ requires: C, 76·10; H, 6·01%.

3-Methyl-thiacoumarin (8*a*) was obtained by the treatment of the thiol ester 7*a* (2·0 g) with aluminum chloride at 95° for 4 hr followed by work-up as in the oxygen analog. Yield: 0·52 g (40%); mp 79–80° [lit. mp 80°]. IR ($CHCl_3$): 1630–40 cm^{-1}. NMR ($CDCl_3$) : δ 2·2 (s, 3H, CH_3) and 7·2–7·8 (m, 5H, aromatic and C_4–H).

3,6-Dimethyl-thiacoumarin (8*b*) was obtained from 1·0 g of the ester 7*b* and 3·0 g of aluminum chloride at 95° for 1·5 hr. Yield: 0·2 g (28%); mp 95–6° [lit. mp 98°]. IR ($CHCl_3$): 1630–40 cm^{-1}. NMR ($CDCl_3$): δ 2·19 (s, 3H, CH_3), 2·41 (s, 3H, CH_3) and 7·08–7·60 (m, 4H, aromatic and C_4–H). Found: C, 69·72; H, 5·54. $C_{11}H_{10}OS$ requires: C, 69·46; H, 5·30%.

2.6. *Preparation of cinnamanilides* (9*a*–*e*)

The anilides were prepared by the treatment of the respective anilines with α-methyl-cinnamoyl chloride in the presence of pyridine by the standard method. α-Methyl-cinnamanilide (9*a*) : mp 98–9°. Yield : 65%. Found: C, 80·76; H, 6·54. $C_{16}H_{15}NO$ requires: C, 80·98; H, 6·37%.

4′,α-Dimethyl-cinnamanilide (9*b*) : mp 119–20°. Yield: 51%. Found: C, 81·40; H, 6·86. $C_{17}H_{17}NO$ requires: C, 81·24; H, 6·82%.

2′,α-Dimethyl-cinnamanilide (9*c*) : mp 90–1°. Yield: 79%. Found: C, 81·14; H, 7·0. $C_{17}H_{17}NO$ requires: C, 81·24; H, 6·82%.

4′-Chloro-α-methyl-cinnamanilide (9*d*) : mp 146–7°. Yield: 85%. Found: C, 70·48; H, 5·40. $C_{16}H_{14}ClNO$ requires: C, 70·66; H, 5·19%.

2′-Chloro-α-methyl-cinnamanilide (9*e*): mp 56–7°. Yield: 77%. NMR (CF_3CO_2H): δ 1·8 (s, 3H, CH_3) and 6·7–7·4 (m, 10H, aromatic and β-H).

2.7. *Synthesis of* 3-*methyl-carbostyrils* (10*a–e*)

α-Methyl-cinnamanilide (9*a*) (1·5 g) was heated with anhydrous aluminum chloride (4 g) in chlorobenzene (25 ml) at 95° for 3 hr. The reaction mixture was worked up as for the oxygen system (6) and purified by chromatography through a silica gel column to isolate 3-methyl-carbostyril (10*a*) (0·72 g, 73%); mp 235–6° [lit. (Effenberger and Hartmann 1969) mp 238°]. IR (KBr): 1640–50 cm^{-1}. NMR ($CDCl_3$): δ 2·33 (s, 3H, CH_3) and 7·2–8·0 (m, 5H, aromatic and C_4–H).

3, 6-Dimethyl-carbostyril (10*b*) was obtained (988 mg, 71%) from 2g of the anilide 9*b* by reaction with aluminium chloride (5 g) in chlorobenzene (30 ml) at 95° for 6 hr; mp 249–50°. Found: C, 76·18; H, 6·52. $C_{11}H_{11}NO$ requires C, 76·28; H, 6·40%. NMR (CF_3CO_2H): δ 2·2 (broad s, 6H, $2CH_3$), 7·3–7·5 (m, 3H, aromatic) and 8·07 (s, 1H, C_4–H).

Reaction of 2g of the anilide 9*c* with 5g of aluminum chloride in 25 ml of chlorobenzene at 120° for 2 hr afforded 3,8-dimethyl-carbostyril (10*c*) (918 mg, 65%): mp 177–8° [lit. (Effenberger and Hartmann 1969) mp 180°]. IR (KBr): 1640–55 cm^{-1}.

6-Chloro-3-methyl-carbostyril (10*d*) was obtained in 84% yield from 2 g of the anilide 9*d* with 5g of aluminum chloride in 30 ml of chlorobenzene at 95° for 6 hr; mp 252–3°. IR (KBr): 1640–60 cm^{-1}. NMR (CF_3CO_2H): δ 2·07 (s, 3H, CH_3), 7·2–7·6 (m, 3H, aromatic) and 7·9 (s, 1H, C_4–H). Found: C, 62·16; H, 4·18. $C_{10}H_8ClNO$ requires: C, 62·04; H, 4·16%.

Likewise 8-chloro-3-methyl-carbostyril (10*e*) was obtained from 2g of the anilide 9*e* and aluminum chloride (5 g) in chlorobenzene (30 ml) at 120° for 4 hr. Yield: 1·215 g, 84%; mp 151–2°. IR (KBr): 1640–55 cm^{-1}. NMR (CF_3CO_2H): δ 2·17 (s, 3H, CH_3), 7·2–7·7 (m, 3H, aromatic) and 8·03 (s, 1H, C_4–H).

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