Reductive Methylation of Naphthoic Esters

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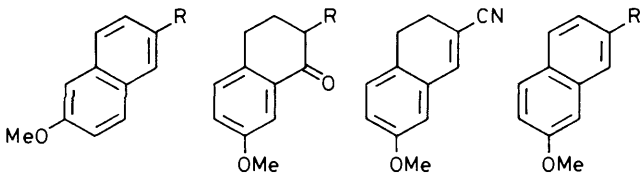
Reductive methylation of the naphthoic esters (**3**), (**9**), (**13**), and (**15**) was carried out in distilled liquid ammonia in the presence of sodium to give the esters (**19**), (**20**), (**21**), and (**22**), respectively.

In connection with our interest in terpenes, we have been seeking convenient methods for the incorporation of geminal methyl–methoxycarbonyl substituents at C-1 and C-2 of the naphthalene nucleus. Although reductive methylation of naphthoic acids is known,[1] the process suffers from two major disadvantages: (i) naphthoic acids in most cases are only sparingly soluble in the organic solvents commonly used in Birch reduction, and (ii) the incorporation of a methyl group is invariably incomplete resulting in mixtures of methylated and unmethylated products which are difficult to separate. Reductive methylation of benzoic acid derivatives in the presence of Bu^{t}OH has recently been reported by Mander *et al.*[2] and Schultz *et al.*[3] However, during Birch reduction of naphthoic acid in the presence of Bu^{t}OH, the other aromatic ring suffers partial reduction.[4] We have observed that reductive methylation of both α- and β-naphthoic esters proceeds cleanly in the absence of Bu^{t}OH and the products are not contaminated with unmethylated materials. Catalytic hydrogenation of the initial neutral products gives the desired saturated esters in fairly good yields. Furthermore, as the substrates are readily soluble in tetrahydrofuran (THF), this reaction is very easy to perform and convenient for practical purposes.

Four different routes were used for the preparation of the naphthoic esters. (1) 2-Bromo-6-methoxynaphthalene (**1**) was converted[5] in 85% yield into 2-cyano-6-methoxynaphthalene (**2**) (m.p. 108—109 °C), which on alkaline hydrolysis and subsequent esterification furnished the ester (**3**) (84%, m.p. 130—131 °C). (2) 7-Methoxy-1-tetralone (**4**) was converted into the corresponding β-ketonitrile (**5**) (82%, m.p. 110—111 °C) using the isoxazole procedure of Johnson *et al.*[6] Reduction of (**5**) with $NaBH_4$ and subsequent dehydration of the crude hydroxy-nitrile with $KHSO_4$ (170 °C, 10 min) furnished the unsaturated nitrile (**6**) (85%, m.p. 72—73 °C). Dehydrogenation of (**6**) with 10% Pd–C in refluxing xylene gave (**7**) (92%, m.p. 85 °C). Base hydrolysis of (**7**) and subsequent esterification of the acid (**8**) gave the ester (**9**) (86%, m.p. 93—94 °C). (3) Vilsmeier formylation of 1,6-dimethoxynaphthalene yielded the aldehyde (**10**) (82%, m.p.

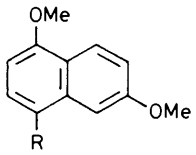


(1) R = Br
(2) R = CN
(3) R = CO_2Me

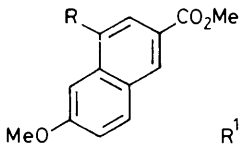
(4) R = H
(5) R = CN

(6)

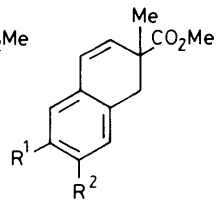
(7) R = CN
(8) R = CO_2H
(9) R = CO_2Me



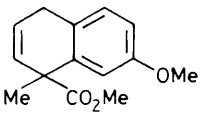
(10) R = CHO
(11) R = CN
(12) R = CO_2H
(13) R = CO_2Me



(14) R = OAc
(15) R = OMe



(16) R^1 = OMe, R^2 = H
(17) R^1 = H, R^2 = OMe



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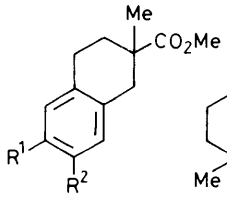
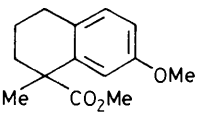


(19) R^1 = OMe, R^2 = H
(20) R^1 = H, R^2 = OMe



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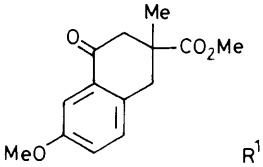

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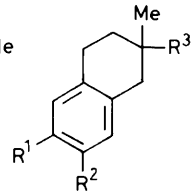
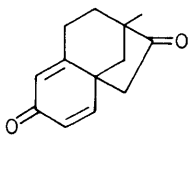


(23) R^1 = OMe, R^2 = H, R^3 = CO_2H
(24) R^1 = H, R^2 = OMe, R^3 = CO_2H
(25) R^1 = OMe, R^2 = H, R^3 = $COCHN_2$
(26) R^1 = H, R^2 = OMe, R^3 = $COCHN_2$



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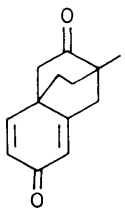
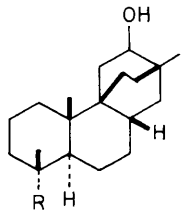


(28)



(29) R = Me
(30) R = CO_2Me

78—79 °C). The nitrile (**11**) (m.p. 110—111 °C), prepared[7] from (**10**) in 88% yield, was converted into the methyl ester (**13**) (m.p. 65—67 °C), *via* the acid (**12**), in 85% overall yield. (4) Stobbe condensation[8] of anisaldehyde with dimethyl succinate afforded a half-ester (60%) which cyclised with Ac_2O to give the acetate (**14**) (85%, m.p. 124—125 °C); deacetylation (MeOH, *p*-$MeC_6H_4SO_3H$) followed by methylation (MeI, K_2CO_3, dimethoxyethane) furnished the ester (**15**) (74%, m.p. 104 °C). Although House *et al.*[9] have expressed doubts about the structure of (**14**), our results confirm that the structure shown is correct.

For the reductive methylation of the esters (**3**), (**9**), and (**15**), a solution of the ester in THF was stirred with 2.5 equiv. Na in distilled liquid ammonia for 3 min and then excess of MeI was added; for the ester (**13**), 5 equiv. of Na was used. Although the initial unsaturated products (**16**) and (**17**) from the reductive methylation of (**3**) and (**9**) could be isolated in a pure condition, complete loss of the *p*-methoxy group was observed in the reductive methylation of (**13**) and the initial product (**18**) was converted into a mixture of double bond isomers during purification. Catalytic hydrogenation of the crude products (**16**), (**17**), and (**18**) with 10% Pd–C furnished the saturated esters (**19**), (**20**), and (**21**) respectively in 70%, 72%, and 69% overall yields. The initial product from the reductive methylation of (**15**) was converted into the keto-ester (**22**) (70%, m.p. 78—79 °C) during attempted purification.

The application of this method to the synthesis of diterpenoid resin acids appears promising. In order to extend the scope of these studies, the esters (**19**) and (**20**) were converted into the bridged-ring dienones (**27**) and (**28**) incorporating bicyclo[3.2.1]octanone and bicyclo[2.2.2]octanone ring systems, respectively. Base hydrolysis of (**19**) and (**20**) furnished the corresponding acids (**23**) (90%, m.p. 132—133 °C) and (**24**) (90%, m.p. 130—131 °C) which were converted[10] into the respective diazomethyl ketones (**25**) and (**26**). Acid-induced intramolecular cyclisation[11] (trifluoroacetic acid, CH_2Cl_2, −20 °C) of (**25**) and (**26**) afforded the dienones (**27**) (65%, m.p. 119—120 °C) and (**28**) (60%, m.p. 160 °C), respectively. The sequence of reactions leading to (**27**) provides a convenient route to the B/C/D rings of the tetracyclic diterpene hibaene.[12] Bridged tetracyclic compounds (**29**) and (**30**) incorporating 1-methyl-2-hydroxybicyclo[2.2.2]octanes as C/D rings have recently been utilised[13] as key intermediates in the synthesis of the stemodane group of diterpenoids. For entry into the ring systems of these compounds, the Diels–Alder reaction of the dienone (**28**) is currently being investigated.

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