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Notes

A New Practical Synthesis of 5-Hydroxy-3,4-dihydrocarbostyril and 5-Hydroxycarbostyril

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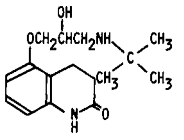
Although compound 1 has been known to show a strong β-blocking activity,[1] a simple synthesis of the key intermediate, 5-hydroxy-3,4-dihydrocarbostyril (2) is lacking. The typical synthetic method hitherto known involves the reaction of 1,3-cyclohexanedione with acrylonitrile as the key step, though the yield is far from satisfactory.[2] We now describe a new and practical synthesis of 2 and 5-hydroxycarbostyril (3) from 3-amino-2-cyclohexenone (4), which is easily obtainable from 1,3-cyclohexanedione in a 95% yield.[3]



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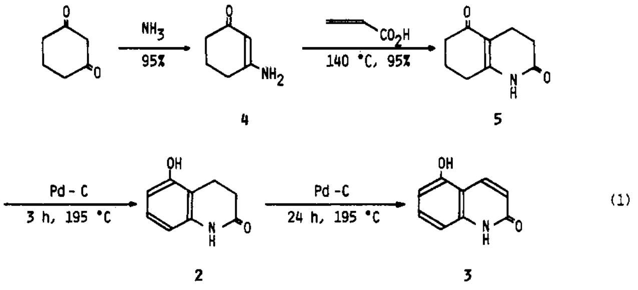
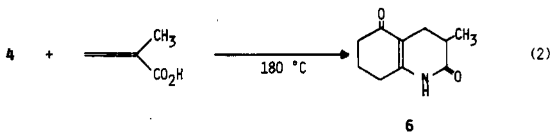
Thus, heating a mixture of 4 and acrylic acid for 3 h at 140 °C gave compound 5 in 95% yield. Dehydrogenation of 5 to 2 was accomplished by refluxing a mixture of 5 and 10% Pd–charcoal in decalin for 3 h. On the other hand, refluxing the same mixture for 24 h gave predominantly 3. Isolation of 2 or 3 was easily achieved by recrystallization. Accordingly, both products 2 and 3 could be prepared in good yields through highly simple procedures (eq 1).



The use of methacrylic acid instead of acrylic acid gave a similar result, although the reaction required a higher temperature than that in the synthesis of 2. Crotonic acid, cinnamic acid, and ethyl acrylate did not react with 4.



Experimental Section

Synthesis of 5. A mixture of 4[3] (33.3 g, 0.30 mol) and acrylic acid (26.0 g, 0.36 mol) was heated at 140 °C for 3 h to afford 5[2a] as a precipitate, which could be recrystallized from methanol: yield 95% (47.0 g); mp 194–195 °C; IR (KBr) 3200, 3100, 1685, 1625, 820 cm^{-1}; NMR (Me$_2$SO-d_6) δ 1.60–2.95 (m, 10 H), 9.90 (m, 1 H). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.15; H, 6.71; N, 8.44.

Synthesis of 2 and 3. A solution of 5 (1.65 g, 0.01 mol) in decalin (20 mL) containing 10% Pd–C (0.5 g) was refluxed for 3 h and extracted with methanol after it was cooled to room temperature. The extracts contained 2, 3, and 5 in the ratio of 8:1:1. Concentration of the methanolic solution gave 2 as a precipitate. When the product is contaminated by a small amount of 3 or 5, the contaminants can be removed by TLC (silica gel, CH_2Cl_2/CH_3OH 10:1). The yield of 2 was 74% (1.21 g). The spectroscopic data and melting point of 2 were identical with those reported in the literature;[4] NMR (Me$_2$SO-d_6) δ 2.23–3.16 (m, 4 H), 6.23–7.45 (m, 3 H), 9.95 (br s, 1 H).

Prolonged heating (24 h) of a mixture of 5 and 10% Pd–C in decalin predominantly yielded 3, which could be purified by recrystallization from methanol. The IR spectrum and melting point of the product were identical with those of an authentic sample:[5] 1.30 g (81%); NMR (Me$_2$SO-d_6) δ 6.35 (d, J = 10 Hz, 1 H), 6.63 (dd, J = 7.5, 7.5 Hz, 2 H), 7.24 (dd, J = 7.5, 7.5 Hz, 1 H), 8.10 (d, J = 10 Hz, 1 H).

Synthesis of 6. A mixture of 4 (1.11 g, 0.01 mol) and methacrylic acid (1.3 g, 0.015 mol) was heated at 180 °C for 3 h. The isolation of the product 6 was carried out in a similar way to that of 2: 1.28 g (72%); mp 197–198 °C; IR 3450, 3250, 1700, 1600, 1480, 1390, 1240, 1220, 1190 cm^{-1}; NMR (Me$_2$SO-d_6) δ 9.50 (br s, 1 H), 1.60–3.0 (m, 9 H), 1.33 (d, J = 6 Hz, 3 H). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.80. Found: C, 66.96; H, 7.51; N, 7.77.

Registry No. 2, 30389-33-4; **3**, 31570-97-5; **4**, 5220-49-5; **5**, 5057-12-5; **6**, 77903-18-5; acrylic acid, 79-10-7; methacrylic acid, 79-41-4.

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Synthesis of (+)-Methyl Vouacapenate from Podocarpic Acid. An Improved Route

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(+)-Methyl vouacapenate (1), an abundant constituent of South American hardwood, was isolated by King et al.[1] who also established its structure as a furanoid diterpene with the cassane skeleton. Later, Spencer et al.[2] completed

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