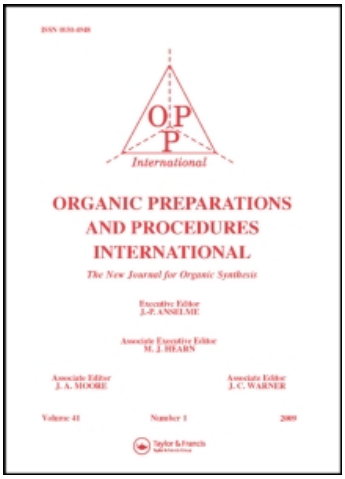

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A CONVENIENT REDUCTION OF UNSATURATED BICYCLIC ANHYDRIDES

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A CONVENIENT REDUCTION OF UNSATURATED BICYCLIC ANHYDRIDES

Submitted by Ferenc Csende*[a] and Géza Stájer[b]

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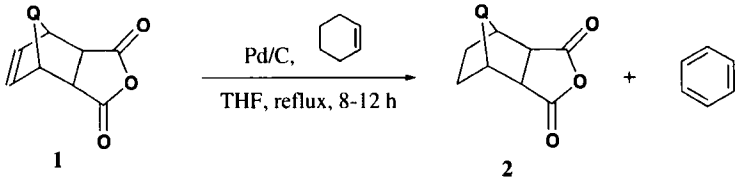
Bicyclic anhydrides **2a-2d** and those related amides, which can be obtained from saturation of Diels-Alder adducts, are valuable intermediates for the synthesis of pharmacologically important componunds.[1-3] Catalytic hydrogenation is a widely used method for the saturation of alkenes. The procedure is carried out under hydrogen atmosphere as the reducing agent in the presence of some catalyst *e.g.* Pd/C, PtO_2, Raney-Ni[4-6] , or with rare-earth alloy containing adsorbed hydrogen.[7] We reinvestigated these method due to flammable property of the hydrogen and catalyst (*e. g.* Raney-Ni) and searched for simpler and safer conditions for the reduction. This paper reports a simple and convenient modification of a method described earlier by Raphael *et al.* [8]

This method employs cyclohexene as hydrogen transfer agent, instead of higlhly flammable hydrogen gas, in the presence of Pd/C catalyst at room temperature in dry THF solvent. We had to modify the reduction temperature from 20-25° to reflux temperature. In this way, **2a-2d** were obtained in good to excellent yield (89-98%). In the course of reduction cyclohexene was converted to benzene nearly quantitatively and only small amount of cyclohexene takes part in a disproportion process as side reaction resulting in cyclohexane.[9]



1 2

a) Q = CH_2, *endo* b) Q = CH_2, *exo* c) Q = O, *endo* d) Q = CH_2-CH_2, *endo*

EXPERIMENTAL SECTION

Melting points were determined using an Electrothermal block and are uncorrected. Infrared spectra were recorded for KBr discs with a Perkin-Elmer 177 instrument. ^{1}H- and ^{13}C-NMR spectra were

measured in $CDCl_3$ solutions on Varian Gemini-200 instrument operating at 200 and 50 MHz with tetramethylsilane as internal standard ($\delta = 0$).

General Procedure.- To a solution of 0.1 mol anhydride in 250 ml dry THF, 16.3 g (0.2 mol) cyclohexene and 0.5 g 5% Pd/C were added. The mixture was refluxed for 8-12 h on a water bath. After cooling and filtration the solution was evaporated and the residue was recrystallized from benzene.

***endo*-Bicyclo[2.2.1]heptane-2,3-dicarboxylic Anhydride (2a)**, mp. 164-166°, lit.[10] 169-171°, 98% yield. IR (KBr): 1850, 1820, 1775cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25-1.92 (m, 6H), 2.85 (m, 2H, H-1, H-4), 3.40 (m, 2H, H-2, H-3). ^{13}C NMR ($CDCl_3$): δ 27.0 (C-5,6), 30.8 (C-1,4), 33.2 (C-7), 39.5 (C-2,3), 171.0 (C=O).

***exo*-Bicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride (2b)**, mp. 81-83°, 96% yield. IR (KBr): 1870, 1833, 1780cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27-1.90 (m, 6H), 2.75-2.97(m, 4H). ^{13}C NMR ($CDCl_3$): δ 27.0 (C-5,6), 30.8 (C-1,4), 33.2 (C-7), 39.5 (C-2,3), 171.0 (C=O).

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.26; H, 6.15

***exo*-Oxabicyclo[2.2.1]heptane-2,3-dicarboxylic Anhydride (2c)**, mp. 110-112°, 95% yield. IR (KBr): 1878, 1850, 1782cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.48-2.05 (m, 4H, H-5, H-6), 3.15 (s, 2H, H-2, H-3), 4.95 (m, 2H, H-1, H-4). ^{13}C NMR ($CDCl_3$): δ 28.1 (C-5,6), 40.6 (C-2,3), 75.2 (C-1,4), 182.7 (C=O).

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H,4.80. Found: C, 57.35; H, 4.92

***endo*-Bicyclo[2.2.2]octane-2,3-dicarboxylic anhydride (2d)**, mp. 139-140°, 89% yield. IR (KBr): 1869, 1835, 1770cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25-2.07 (m, 8H),2.80-3.35(m,4H). ^{13}C NMR ($CDCl_3$): δ 18.6 (C-1,4), 23.3 (C-5,6,7,8), 37.4 (C-2,3), 165.3 (C=O).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H,6.71. Found: C, 66.80; H, 6.83

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A SIMPLE PROCEDURE FOR THE ALKYLATION OF 4-HYDROXYCOUMARINS AT C-3 POSITION

Submitted by (10/22/98)

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A number of pharmacologically interesting compounds contain the coumarin skeleton[1] and 4-hydroxycoumarins bearing a substituent at C-3 are particularly important compounds. The most significant biological activities are anticoagulation effect[1] and HIV protease inhibition.[2] The alkylation[3] of 4-hydroxycoumarin at C-3 position with alkyl halides is not selective, with O-alkylation being a competing reaction.[4] This explains why efforts have been devoted to produce 3-substituted 4-hydroxycoumarins from 4-hydroxycoumarins (**1**) and aldehydes, a reaction which, however, leads[5] to the Michael adducts **5** as the final products.[6] Treatment of these adducts **5** with 2 molar equivalent sodium cyanoborohydride at reflux in methanol for 42 h gave the desired 3-alkyl-4-hydroxycoumarins **4** and an equivalent amount of the 4-hydroxycoumarin. The method[6] requires two steps however, with long reaction times and the separation of **4** from **1** is tedious in some cases. The yields for 3-methyl- and 3-benzyl-4-hydroxycoumarin were 60 and 79%, respectively. Another recent two-step method[7] involves the reaction of an aldehyde, 4-hydroxycoumarin and thiophenol in the presence of catalytic amounts of pyridine and acetic acid in ethanol at reflux for 48 h. The isolated [4-hydroxy-3-coumarinyl]phenylmercaptomethane intermediates were hydrogenated over Raney-Ni catalyst in ethanol at room temperature for 2 hours. Details for both steps were given only for two compounds. The overall yield of 3-benzyl- and 3-methyl-4-hydroxycoumarin was 55%.

We now report a simple method for the production of 3-alkyl-4-hydroxycoumarins **4** in 60-83% yield. The coumarin **1** and aldehyde **2** were heated in a mixture of triethylamine and formic acid (2:5 molar ratio). The reaction was complete at 140-150° within 2 hours. This route is based on the reported reduction of 2-benzylidene-1,3-diketones (at 140-150°),[8] benzylidenebarbiturates (at 60-125°)[9]