Notes

An Improved Procedure for Ring Annelation with 3,5-Dimethylisoxazoles

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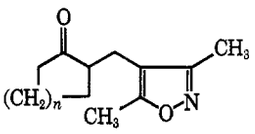
In two accompanying papers[1,2] on steroid total synthesis we have outlined a method for obtaining significantly higher yields in the Stork isoxazole ring annelation reaction.[3] In order to test the generality of this sequence, we have investigated the conversion of 2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclopentanone (**1a**)[4] and 2-[3,5-dimethyl-4-isoxazolyl)methyl]cyclohexanone (**1b**)[3] to 2,3,7,7a-tetrahydroindan-5(6*H*)-one (**5a**)[5] and 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one (**5b**).[5]

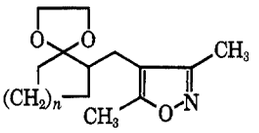
The ketones **1a** and **1b** were ketalized with ethylene glycol in the usual fashion. The desired ketals **2a** and **2b** could be obtained in analytically pure form by distillation in 85 and 86% yield, respectively.[6] The distilled ketals **2a,b** were hydrogenated over palladium on carbon in 3–4% ethanolic potassium hydroxide solution. The uptake of hydrogen proceeded smoothly, stopping after the uptake of 1 equiv in 4–10 hr. The resulting vinylogous amides **3a** and **3b** were not isolated; rather, the hydrogenation solutions, after removal of the catalyst by filtration, were concentrated at reduced pressure. Addition of 20% aqueous potassium hydroxide solution, followed by heating at reflux for 12–16 hr, gave the keto ketals **4a** and **4b**. These materials could be isolated in analytically pure form in 83 and 84% yield, respectively, from the isoxazole ketals **2a** and **2b**.

When the crude keto ketal **4b** was heated with methanolic hydrochloric acid, the octalone **5b**, bp 70–76° (0.25 mm), was obtained in 76% yield from the distilled isoxazole ketal **2b**. The material was, as expected,[5] a mixture containing approximately 20% of the isomeric β,γ-unsaturated ketone **6b**. When the product was isolated as its 2,4-dinitrophenylhydrazone, the yield was 78%. These yields compare favorably with the 50% previously reported[3] for the conversion **1b** → **5b**.

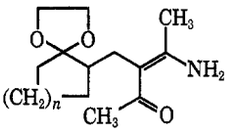
Treatment of the crude keto ketal **4a** with methanolic hydrochloric acid caused deketalization to give 2-(3-oxobutyl)cyclopentanone (**7**),[7] which was not cyclized under these conditions. Heating this dione with methanolic sodium hydroxide gave indenone **5a**, bp 60–68° (0.25 mm), of 95% gc purity[8] in 57% yield from the isoxazole ketal **2a**. Since the lower yield in this second example clearly arose only from difficulties in cyclization of the dione **7**, extensive attempts to raise the yield in this step were not made.[9]



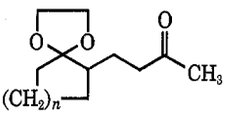
1a, $n = 1$
b, $n = 2$



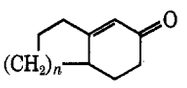
2a, $n = 1$
b, $n = 2$



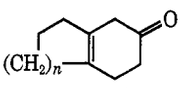
3a, $n = 1$
b, $n = 2$



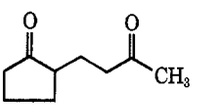
4a, $n = 1$
b, $n = 2$



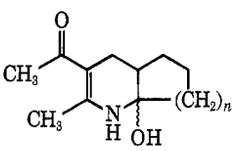
5a, $n = 1$
b, $n = 2$



6a, $n = 1$
b, $n = 2$



7



8, $n = 1, 2$

In our opinion, the improved yields in the procedure here described are traceable to the suppression of formation of the carbinolamines **8**.[10] As noted previously,[2,10] these compounds, upon treatment with base, rapidly dehydrate to dihydropyridines, which are susceptible to oxidation and/or disproportionation to give, for annelation purposes, useless by-products.

Experimental Section[11]

1,1-Ethylenedioxy-2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclopentane (2a).—To a solution of 25.0 g (0.13 mol) of 2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclopentanone[4] in 50 ml of ethylene glycol and 300 ml of benzene was added 3.0 g (16 mmol) of *p*-toluenesulfonic acid monohydrate. The resulting solution was degassed, placed under nitrogen, and heated at reflux, with azeotropic removal of H_2O (water-jacketed Dean–Stark trap),

(1) J. W. Scott and G. Saucy, *J. Org. Chem.*, **37**, 1652 (1972).
(2) J. W. Scott, R. Borer, and G. Saucy, *ibid.*, **37**, 1659 (1972).
(3) G. Stork, S. Danishefsky, and M. Ohashi, *J. Amer. Chem. Soc.*, **89**, 5459 (1967).
(4) M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *ibid.*, **89**, 5460 (1967).
(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).
(6) The crude ketals, obtained in quantitative yield, had infrared spectra identical with those of the distilled materials. Either sample was suitable for further reaction.
(7) H. O. House, B. M. Trost, R. W. Magin, R. A. Carlson, R. W. Franck, and G. N. Rasmussen, *J. Org. Chem.*, **30**, 2513 (1965).
(8) The impurity presumably[7] was the β,γ-unsaturated ketone **6a**. Spectral measurements were in agreement with this assumption (see Experimental Section).
(9) Cyclization with pyrrolidine, followed by cleavage of the resulting enamine with acetate buffer,[7] gave the indenone **6a** in 49% yield from the ketal **2a**.
(10) G. Stork and J. E. McMurry, *J. Amer. Chem. Soc.*, **89**, 5463 (1967).
(11) Melting points were determined on a Kofler hot stage and are uncorrected. A Varian A-60 spectrometer was used to obtain the nmr spectra and tetramethylsilane was used as the internal standard. Infrared spectra were recorded on a Beckman IR-9 spectrophotometer. The uv spectra were recorded on a Cary Model 14M spectrophotometer.

for 16 hr. The cooled mixture was washed twice with saturated $NaHCO_3$ solution and three times with H_2O and saturated brine and dried ($MgSO_4$). The benzene solutions were concentrated and then distilled through a short Vigreux column to give 26 g (85%) of **2a** as a colorless liquid: bp 125–129° (0.4 mm); uv max (C_2H_5OH) 221 nm (ϵ 4970); ir ($CHCl_3$) 1642 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.24 (s, 3) and 2.34 ppm (s, 3, 2 isoxazole-CH_3) and 3.95 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 66.10; H, 8.42; N, 5.72.

1,1-Ethylenedioxy-2-[(3,5-dimethyl-4-isoxazolyl)methyl]cyclohexane (2b).—This compound, prepared as described in the previous experiment from 2-[(3,5-dimethyl-4-isoxazolyl)methyl]-cyclohexanone,[3] was obtained in 86% yield as a colorless liquid: bp 126–132° (0.25 mm); uv max (C_2H_5OH) 222–223 nm (ϵ 4880); ir ($CHCl_3$) 1645 cm^{-1} (isoxazole); nmr ($CDCl_3$) δ 2.35 (s, 3) and 2.34 (s, 3, 2 isoxazole-CH_3), and 4.04 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.95; H, 8.25; N, 5.58.

1,1-Ethylenedioxy-2-(3-oxobutyl)cyclopentane (4a).—To a solution of 5.0 g (21 mmol) of **2a** in 100 ml of 3.2% ethanolic KOH solution was added 100 mg of 10% palladium on carbon catalyst and the resulting mixture was hydrogenated at atmospheric pressure and room temperature. After 8 hr, the uptake of hydrogen had ceased. The catalyst was removed by filtration and washed with fresh ethanol. The filtrates were concentrated at reduced pressure to approximately 30 ml. To this solution of the vinylogous amide **3a** was added 100 ml of 20% aqueous KOH solution and the resulting mixture was degassed, placed under nitrogen, and heated at reflux overnight. The cooled solution was extracted with benzene. The benzene solutions were washed with saturated brine and dried ($MgSO_4$). Solvent removal, followed by distillation, gave 3.52 g (83%) of **4a** as a colorless liquid: bp 85–90° (0.35 mm); no uv absorption; ir ($CHCl_3$) 1723 cm^{-1} (CH_3CO-); nmr ($CDCl_3$) δ 2.12 (s, 3, CH_3CO-), 2.45 (t, 2, J = 7 Hz, $-CH_2COCH_3$) and 3.90 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.73; H, 8.98.

1,1-Ethylenedioxy-2-(3-oxobutyl)cyclohexane (4b).—This compound, prepared by the method described in the previous experiment, was obtained in 84% yield as a colorless liquid, bp 96–101° (0.3 mm), which solidified upon standing to a white solid: mp 38–40°;[11] no uv absorption; ir ($CHCl_3$) 1710 cm^{-1} (CH_3CO-); nmr, ($CDCl_3$) δ 2.15 (s, 3, CH_3CO-), 2.45 (t, 2, J = 7 Hz, $-CH_2COCH_3$), and 3.96 ppm (s, 4, $-OCH_2CH_2O-$).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.19; H, 9.70.

4,4a,5,6,7,8-Hexahydronaphthalen-2(3*H*)-one (5b).—To a solution of crude keto ketal **4b**, prepared as described above from 6.00 g of isoxazole ketal **2b**, in 60 ml of methanol was added 6 ml of 4 *N* HCl and the resulting mixture was heated at reflux under nitrogen for 3 hr. The solution was cooled, poured into H_2O, and extracted with benzene. The benzene solutions were washed with saturated $NaHCO_3$ solution and saturated brine and dried ($MgSO_4$). Solvent removal followed by distillation gave 2.73 g (76%) of colorless liquid: bp 70–76° (0.25 mm) [lit.[5] bp 135–138° (15 mm)]; uv max (C_2H_5OH) 237 nm (ϵ 14,100) and 308–310 (60); ir ($CHCl_3$) 1719, 1675 (~1:4, $-CH_2CO-$ and C=CHCO–) and 1625 cm^{-1} (C=C); nmr ($CDCl_3$) δ 5.85 ppm (s, 0.8, =CHCO–).

In a separate preparation, the crude octalone mixture was treated with 2,4-dinitrophenylhydrazine to give 4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one 2,4-dinitrophenylhydrazone, mp 170–172° (lit.[5] mp 168–170°), in 78% yield after crystallization from ethyl acetate.

2,3,7,7a-Tetrahydroindan-5(6*H*)-one (5a).—Crude 1,1-ethylenedioxy-2-(3-oxobutyl)cyclopentane (**4a**), prepared from 5.0 g of isoxazole ketal **2a**, was treated with HCl in ethanol as described in the preceding experiment. The resulting colorless oil [2-(3-oxobutyl)cyclopentanone (**7**), ir ($CHCl_3$) 1748 (cyclopentanoe C=O) and 1710 cm^{-1} (CH_3CO-)] was dissolved in 50 ml of 2% methanolic NaOH. The resulting solution was heated at reflux under nitrogen for 3 hr, cooled, diluted with H_2O, and extracted with benzene. The benzene extracts were washed with saturated brine and dried ($MgSO_4$). Solvent removal and distillation gave 1.64 g (57%) of **5a** as a colorless liquid: bp 60–68° (0.25 mm) [lit.[5] bp 80–81° (0.4 mm)]; uv max (C_2H_5OH) 237 nm (ϵ 13,090) and 310 (60); ir ($CHCl_3$) 1750 (weak, cyclopentanone C=O) and 1670 cm^{-1} (C=CHO–); nmr ($CDCl_3$) δ 3.20 (q, ~0.1, J = 14 Hz, $CH_2C=O$) and 5.88 ppm (q, ~0.95, J = 1 Hz, =CHC=O); semicarbazone mp 217–219° (1-butanol) (lit.[5] mp 214–219°).

Registry No.—**2a**, 34803-84-4; **2b**, 34769-83-0; **4a**, 34803-85-5; **4b**, 34769-84-1; **5a**, 1489-28-7; **5b**, 1196-55-0.

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Compounds Affecting the Central Nervous System. I. Tropane-2β,3β-diol Derivatives. A Reverse Ester of Cocaine

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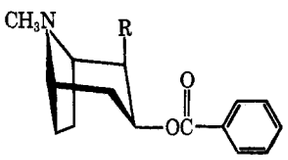
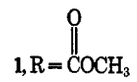
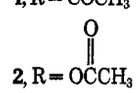
Investigation of all possible modifications of a known drug has been one of the approaches used to find better therapeutic agents. A drug having an ester group can typically be modified by formation of a "reverse ester." It appeared to us that the reverse ester **2** of cocaine (**1**)





1, R = $COCH_3$



2, R = $OCCH_3$

might have an activity profile more interesting than that of cocaine.

The most convenient intermediate for the preparation of **2** was tropane-2β,3β-diol (**7**), a compound first prepared by Einhorn and Fischer[1] and later characterized fully by Davies, Jones, and Pinder.[2] Large-scale preparation of **7** has now been achieved by permanganate oxidation of ethyl nortrop-2-ene-8-carboxylate (**5**) followed by reduction with $LiAlH_4$.

A method for the preparation of precursor **5** (see Experimental Section) involved dehydration of alcohol **3**. This alcohol, with its hydroxyl group in the axial position, was formed along with the equatorial epimer **4** (3:1 ratio) when ethyl 3-oxonortropane-8-carboxylate[3] was reduced catalytically (Pt in EtOH or HOAc) or by hydrides [$NaBH_4$ in MeOH or LiAl (*tert*-OBu)$_3$H in THF]. The role of the basic nitrogen in steric control of catalytic hydrogenation was illustrated here when tropan-3-one (basic N) was reduced catalytically (Pt in

(1) A. Einhorn and L. Fischer, *Chem. Ber.*, **26**, 2008 (1893).
(2) W. A. M. Davies, J. B. Jones, and A. R. Pinder, *J. Chem. Soc.*, 3504 (1960).
(3) B. J. Calvert and J. D. Hobson, *ibid.*, 2723 (1965).