A Cyclization of Humulene by Means of a Mercuric Salt in Aceto- and Benzonitrile

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Synopsis. Humulene was converted to 3,6-secoprotoilludane derivatives by treatment with mercury(II) trifluoroacetate in aceto- and benzonitrile.

For the purpose of accomplishing a biogenetically patterned chemical cyclization of humulene (**1**)[1] to illudoids and hirsutanoids,[2] mercury(II) salt induced cyclization of humulene had been examined. The key reaction, C(2)–C(9) bond formation, was previously achieved[1b,c] by using mercury(II) acetate in aqueous acetic acid or mercury(II) nitrate in aqueous tetrahydrofuran to give ethereal 3,6-secoprotoilludane derivatives **2**, **3**, and **4** (Fig. 1). The cyclization did not, however, proceed further to form the protoilludane or a hirsutane skeleton. Clearly, the formation of the ethereal products became favourable because of the presence of the cosolvent water. If the reaction was performed in a neat, polar aprotic solvent, further cyclized, tricyclic skeletons could be obtained. We report here the results of mercury induced cyclization of humulene in anhydrous nitriles.

Humulene was treated with more than 2 equivalents of mercury(II) trifluoroacetate in dry acetonitrile at room temperature and a product was demercurated with sodium borohydride and subsequently acetylated. Chromatographic purification gave a crystalline compound **5** in 60% yield. The mercuration-demercuration in benzonitrile was also carried out in the same manner without subsequent acetylation, and a crystalline mass **6** was obtained in 66% yield.

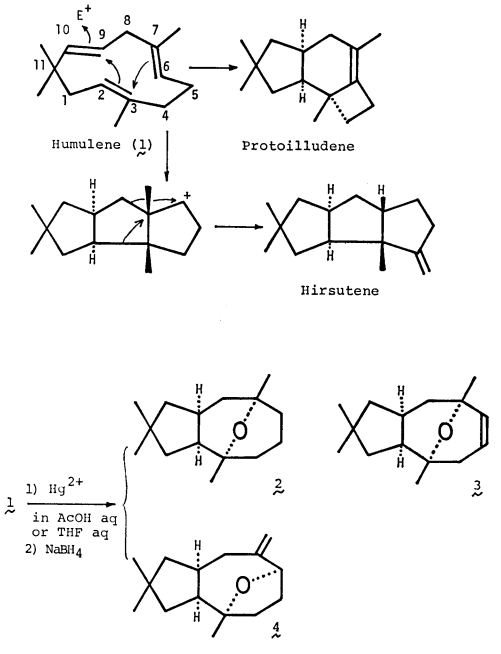

Fig. 1. Biosynthetic and chemical conversions of humulene.

The high resolution mass sepctra of the products showed that a solvent molecule had been added to a molecule of each substrate and in the case of **5** 1 mol of hydrogen was further incorporated in the product. ^{1}H NMR studies on the product **5** including extensive decoupling experiments in the presence of a shift reagent revealed the existence of partial structures depicted in Fig. 2. Taking into consideration the possible combination of these fragments, together with probable reaction courses, we deduced 3,6-secoprotoilludane structure **5** for the product. LIS-values[3] [11(CH_3CO), 11(2-H), 9.9(14-CH_3), 9(10-H), 7(6-H), 5.8(18-CH_3), 1.6(CH_2=)] supported the proposed structure and moreover indicated that 2-H, 6-H, 10-H are placed near the *N*-acetyl group. The conclusive reaction course[4] and stereostructure **7** were shown in Fig. 3.

^{13}C NMR spectrum of the product in benzonitrile was reminiscent of that of a previously obtained 3,6-secoprotoilludane derivative **4**,[1c] except for the peaks due to the phenyl group, in multiplicities and in part in chemical shifts. ^{1}H NMR spectral data were in conformity with the formula **6**. In contrast to the case of acetonitrile, compound **6** was not reduced by $NaBH_4$, probably because of the resonance and steric effects in the conjugated C=N double bond.

In conclusion, it was shown that the reaction of mercuric salt with humulene in anhydrous nitriles is

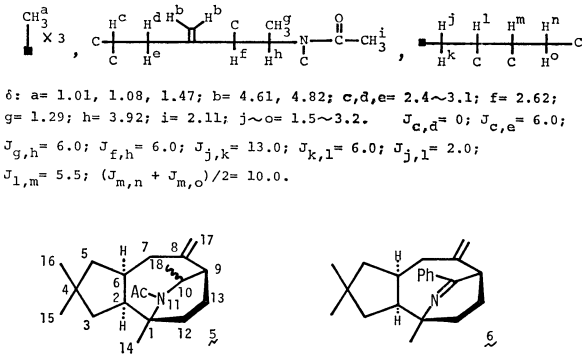

Fig. 2. Partial structures deduced from NMR studies. Chemical shifts (δ) and coupling constants (Hz) were shown.

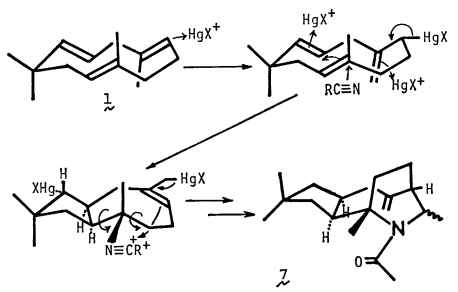

Fig. 3. Reaction course[4,5] in nitriles.

quite similar to that in the aqueous solvents, but the two reactions are different in that in the former solvents a new C–C bond is formed at C-6, and a C–N bond rather than a C–O bond is formed at C-3.

Experimental

All melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a HITACHI R20B (60 MHz) and a JEOL JNM FX-100 (25 MHz) instrument using TMS as an internal standard respectively. High resolution mass spectra were measured on a JEOL JMS D-300 mass spectrometer.

*11-Acetyl-1,4,4,10-tetramethyl-8-methylene-11-azatricyclo[7.2.2.0^{2,6}]tridecane (**5**).* To a stirred solution of $Hg(OCOCF_3)_2$ (1.88 g, 4.4 mmol) in CH_3CN(15 ml) was added 300 mg (1.47 mmol) of humulene at room temperature under argon and the mixture was stirred for 2 h. The solvent was removed *in vacuo* and the residue was dissolved in 10 ml of THF–H_2O (1:1). The solution was made alkaline (3 mol dm^{-3} NaOH) and $NaBH_4$ (300 mg, 7.89 mmol) was added by portions at 0 °C and the mixture was stirred for 3 h at room temperature. After evaporation of the THF *in vacuo*, the solution was extracted with ether three times. The combined extracts were washed with water, dried and concentrated to give a pasty mass which was subjected to acetylation (Ac_2O–pyridine, 20 °C, 12 h). Usual workup followed by chromatographic purification (silica-gel column, 10% AcOEt–C_6H_6) afforded a crystalline product **5** (254 mg, 60%): mp 102—103 °C; ^{1}H NMR ($CDCl_3$) δ=1.01, 1.08 (each 3H, s), 1.29 (3H, d, J=6), 1.47, 2.11 (each 3H, s), 3.92 (1H, quintet, J=6), 4.61, 4.82 (each 1H, t, J=1.5). Found: m/z 289.2408. Calcd for $C_{19}H_{31}NO$: M, 289.2407.

*1,4,4-Trimethyl-8-methylene-10-phenyl-11-azatricyclo[7.2.2.0^{2,6}]tridec-10-ene (**6**).* Humulene (100 mg, 0.44 mmol) was treated with $Hg(OCOCF_3)_2$ (427 mg, 1 mmol) and PhCN (5 ml) in the same manner as above. After evaporation of the polar solvent the residue was dissolved in 3 ml of a mixture of volatile solvent (THF, MeOH, H_2O/1:1:1). The solution was made alkaline (3 mol dm^{-3} NaOH) and $NaBH_4$ (150 mg, 3.9 mmol) was added by portions at 0 °C and the whole was stirred for 2 h at room temperature. The organic solvent was removed *in vacuo* and the residue was extracted with $CHCl_3$ three times. The combined extracts were washed with water, dried and concentrated to give a pasty mass which was throughly made free from PhCN under reduced pressure. The solid obtained was crystallized from hexane to give a pure product **6** (230 mg, 66%): mp 83—85 °C; ^{1}H NMR ($CDCl_3$) δ=1.01, 1.09, 1.39 (each 3H, s), 3.72 (1H, t, J=4), 4.7 (2H, bs), 7.0—8.0 (5H, m); ^{13}C NMR ($CDCl_3$) δ=24.2(t), 24.4(t), 31.7(q), 32.4(q), 35.1(q), 36.8(s), 40.2(t), 40.7(d), 41.3(t), 42.4(d), 50.5(t), 53.6(d), 58.1(s), 113.8(t), 126.6(d×2), 128.1(d×2), 129.0(d), 140.6(s), 144.5(s), 168.2(s). Found: m/z 307.2300. Calcd for $C_{22}H_{29}N$: M, 307.2302.

References

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3) LIS value=$\Delta\delta$/molar ratio of the shift reagent to the substrate.

4) It was figured referring the previous cyclization of humulene to ethers using mercury(II) salts. See Refs. 1b and c. For acylamination of olefins by means of Hg(II) in nitrile, see, for example, H. C. Brown and J. T. Kurek, *J. Am. Chem. Soc.*, **91**, 5647 (1969).

5) About humulene conformations, see H. Shirahama, E. Osawa, and T. Matsumoto, *J. Am. Chem. Soc.*, **102**, 3208 (1980).