Communications to the Editor

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A NOVEL PHOTOCHEMICAL PRENYLATION REACTION OF HETEROAROMATICS INVOLVING AN ENONE FUNCTION IN THEIR RING SYSTEM[1)]

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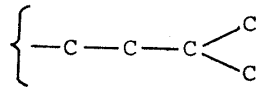
In a novel photochemical prenylation of heteroaromatics involving an enone function in their ring system, the key step is an acid-catalyzed C-C bond fission in the head-to-tail adduct formed by photocycloaddition of these heteroaromatics to 2-methyl-3-buten-2-ol to give the heteroaromatics having a 3-methylbut-2-enyl function (or its equivalent) at the α-position of the enone system. Examples using 2-quinolones, 2-pyridones, and coumarins are reported.

KEYWORDS —— photochemical synthesis; photochemical prenylation; 3,3-dimethylallylation of heteroaromatics; photochemical 2+2 cycloaddition; 3-(3-methylbut-2-enyl)-2-quinolones; 2-methyl-3-buten-2-ol as prenylation reagent; synthesis of khaplofoline

A majority of natural products contain the typical isoprenoid residue (I) whose ultimate source is mevalonic acid.



(I) isoprenoid residue

So far, the 3,3-dimethylallylation of aromatic or heteroaromatic rings has been carried out using 3-methyl-2-buten-1-ol or its equivalents (e.g., its halides) irrespective of the methods employed. However, this alcohol is less available than 2-methyl-3-buten-2-ol which is provided commercially at low cost. Actually, 3-methyl-2-buten-1-ol or its derivatives are all synthesized from the latter alcohol, both in the laboratory and industrially.[2)] We report a novel photochemical prenylation (3,3-dimethylallylation and its equivalent reactions are abbreviated as prenylation) of heteroaromatics involving an enone function using 2-methyl-3-buten-2-ol as the prenylation reagent.

The general chart of this photoprenylation reaction is summarized in chart 1. The enone function involved in a heteroaromatic ring (II) is added photochemically to 2-methyl-3-buten-2-ol to give the 2+2 head-to-tail adduct (III). This addition reaction proceeds in a regioselective manner. Treatment of the adduct with an acid (either protic or Lewis acid) then affords the heteroaromatics prenylated at the α-position of the enone function (IV), irrespective of its stereochemistry.

In a typical experiment, 4-methylquinolin-2(1H)-one (1) was irradiated[3)] at ≥300 nm in methanol in the presence of 50 mol. eq.[4)] of 2-methyl-3-buten-2-ol

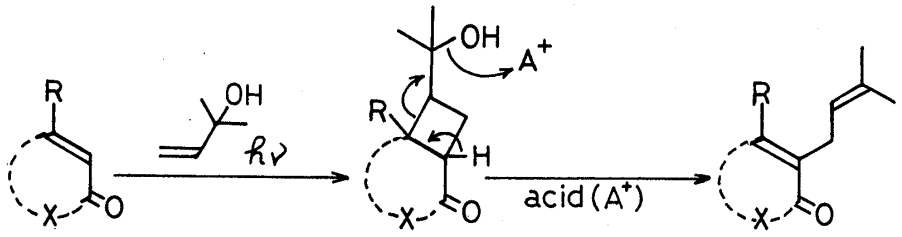
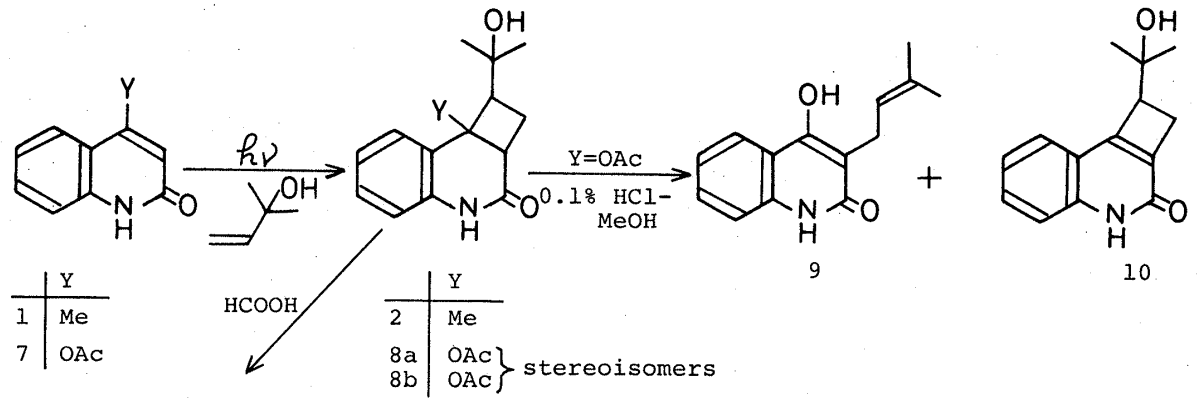
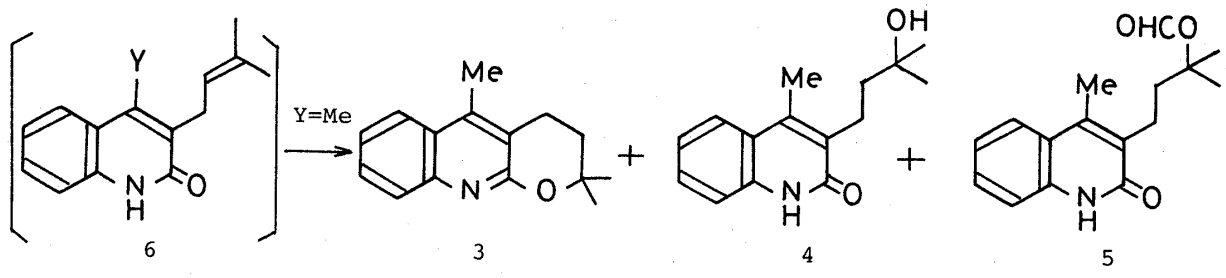


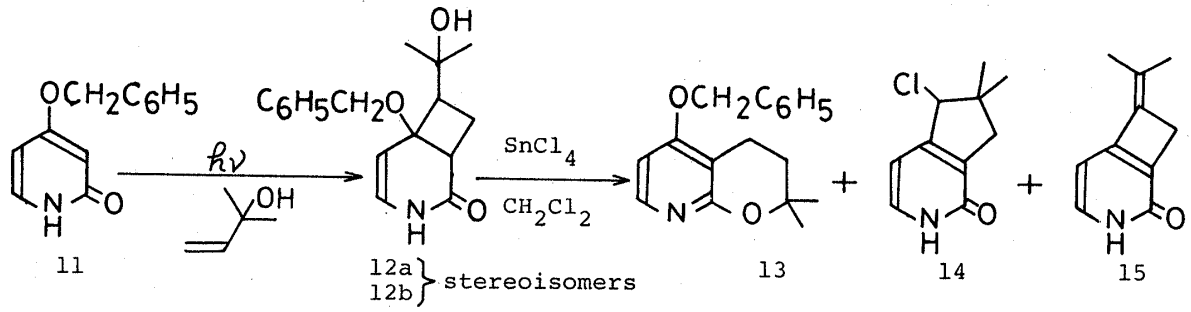
Chart 1. Two-step Prenylation Method of Heteroaromatics involving an Enone Function in Their Ring System (II)

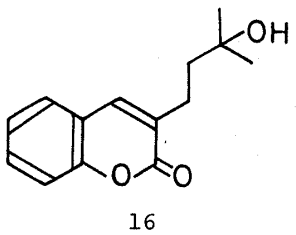
until complete consumption of 1. One kind of 2+2 adduct[5,6] [2, mp 185.5-187.5°C, ν_{max} cm^{-1}: 3450, 1662, δ: 1.10 (3H, s), 1.27 (3H, s), 1.68 (3H, s), 1.53 (OH, s), 2.1-3.1 (4H, m), 6.55-7.3 (4H, m), and 9.16 (NH, bs), λ_{max} nm: 212, 255 with shoulder peaks at 283 and 293] was obtained in 98% yield. Treatment of the adduct (2) in formic acid at 50°C for 1 h followed by the usual work-up gave 3,4-dihydro-2,2,5-trimethyl-2H-pyrano[2,3-b]quinoline [3, mp 91-92°C, δ: 1.43 (6H, s), 1.92 (2H, t, J=6.5 Hz), 2.53 (3H, s), 2.88 (2H, t, J=6.5 Hz)] in 56% yield, together with two 4-methyl-2-quinolones [4, mp 228-229°C (25%) and 5, mp 160-162°C (8%)]. All of these may be formed from 3-(3-methylbut-2-enyl)-4-methylquinolin-2(1H)-one (6), initially formed from 1 by the route as shown in chart 1. In a similar manner, 4-acetoxyquinolin-2(1H)-one (7) afforded the cycloadducts [8a, mp 189-190°C (75%) and 8b, mp 232-233°C (9%)]. In this case, the photodimer of 7 was obtained in a small amount (13%).[7] Though the adducts gave, irrespective of their stereochemistry, the cyclobuta[c]quinolin-3(4H)-one[8] (10, mp 218-219°C) as the major product (73%) upon treatment with formic acid, refluxing of 8a in 0.1% HCl-methanol for 2 h resulted in the formation of 3-(3-methylbut-2-enyl)-4-hydroxyquinolin-2(1H)-one[9] [9, mp 183.5-184.5°C, δ(pyridine-d_5): 1.63 (3H, s), 1.80 (3H, s), 3.81 (2H, bd, J=7.0 Hz), 5.57 (1H, bt, J=7.0 Hz)] and the cyclobutaquinolone (10) in the respective yields of 32 and 28%. 2-Pyridone derivatives were also prenylated at the 3-position. Thus, for example, irradiation of 4-benzyloxypyridin-2(1H)-one (11) in acetone in the presence of an excess of the olefin afforded 92% of the cycloadducts (12a, mp 136-137.5°C and 12b, mp 148-150°C in a ratio of ca. 5.5:1). Treatment of the major adduct (12a) with stannic chloride in dichloromethane at room temperature resulted in the formation of 5-benzyloxy-3,4-dihydro-2,2-dimethyl-2H-pyrano[2,3-b]-pyridine [13, oil, δ: 1.37 (6H, s), 1.78 (2H, t, J=6.8 Hz), 2.69 (2H, t, J=6.8 Hz), 5.07 (2H, s), 7.29 (5H, bs), 6.47 (1H, d, J=6.0 Hz), 7.94 (1H, d, J=6.0 Hz)], together with two α-pyridones [15, mp 239-242°C (dec.) and 14,[10] mp 180-183°C)] in the respective yields of 24, 32, and 25%. 3-(3-Hydroxy-3-methylbutyl)coumarin [16, mp 73-74.5°C, δ: 1.32 (6H, s), an A_2B_2 pattern centered at 1.80 and 2.69 (total 4H), 7.1-7.5 (4H, m), 7.54 (1H, s), λ_{max} nm: 275, 282 (sh.), 308] was obtained as the major product from coumarin by the above two-step prenylation procedure.

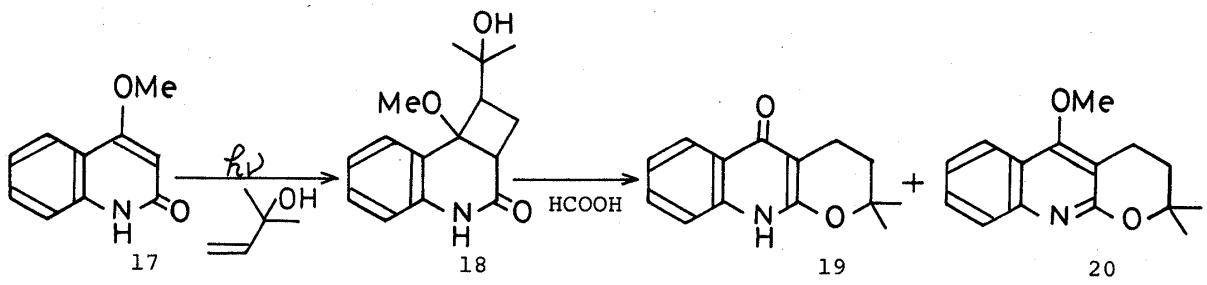
The utility of this two-step prenylation procedure in the synthesis of prenylated 2-quinolone alkaloids[11] was demonstrated by the synthesis of khaplofoline[9,12] (19). Thus, the cycloadduct (18, mp 209.5-210.5°C) obtained in 87% yield from 4-methoxy-2-quinolone (17) was treated by formic acid (50°C, 2 h) to











afford khaplofoline [19, mp 271-273°C (dec.)] in 50% yield. The compounds, 20 (mp 217-218°C) and the corresponding cyclobuta[c]-3-quinolone derivatives, were obtained as minor products.

The scope of this novel prenylation reaction and its application in the synthesis of natural products are being investigated. A possible extension of the present method to the prenylation of a simple enone system is also being pursued.

REFERENCES AND NOTES

1) Part X of "Cycloadditions in Syntheses." For part IX, see: C. Kaneko, H. Fujii, and K. Kato, Heterocycles, 17, 395 (1982).
2) J. H. Babler and D. O. Olsen, Tetrahedron Lett., 1974, 351 and references cited therein.
3) All irradiation was carried out under argon with a Toshiba 400P high-pressure mercury lamp using a Pyrex filter ($\lambda = \geq 300$ nm).
4) Cycloaddition of heteroaromatics to 2-methyl-3-buten-2-ol can be carried out effectively using ca. 10 mM solution of the former in an appropriate solvent containing 20-50 mol equivalent of the olefin.
5) Cycloadditions of heteroaromatics to 2-methyl-3-buten-2-ol proceeded regioselectively to give the head-to-tail adduct (i.e. III) for 2-quinolones,[a] 2-pyridones,[b] and coumarins.[c] a) C. Kaneko and T. Naito, Chem. Pharm. Bull., 27, 2254 (1979); b) H. Fujii, K. Shiba, and C. Kaneko, J. Chem. Soc., Chem. Comm., 1980, 537; c) T. Naito, N. Nakayama, and C. Kaneko, Chemistry Lett., 1981, 423.
6) Satisfactory analyses were obtained for all crystalline compounds. All new compounds were supported by the presence of a molecular ion in their mass spectra and other spectral data (IR, UV, and NMR). Unless otherwise noted, NMR spectra (60 MHz) were recorded in $CDCl_3$, UV in MeOH, and IR in KBr pellet.
7) The dimer was characterized by its molecular weight (m/e: 406) as well as its reversion to 4-acetoxy-2-quinolone (7) by irradiation at 254 nm in a dilute methanol solution.
8) Formation of 1,2-dihydrocyclobuta[c]quinolin-3(4H)-ones from the 2+2 adducts formed from 4-oxygenated 2-quinolone and an olefin has ample precedents. For leading reference, see: C. Kaneko, T. Naito, Y. Momose, H. Fujii, N. Nakayama, and I. Koizumi, Chem. Pharm. Bull., 30, 519 (1982).
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