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SYNTHESES AND REACTIONS OF 1,2-DIHYDROCYCLOBUTA[c]ISOQUINOLIN-4(3H)-ONES[1]

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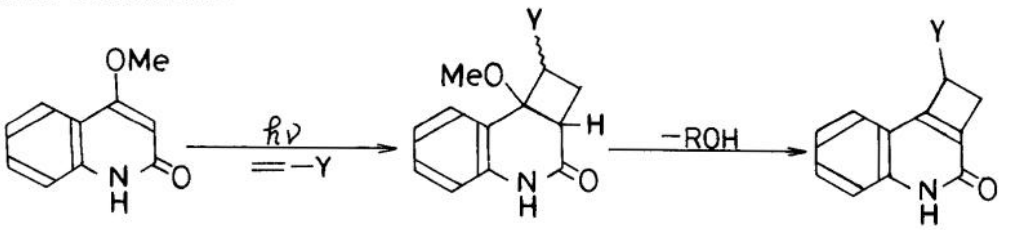
Summary: Two-step synthesis of 1,2-dihydrocyclobuta[c]isoquinolin-4(3H)-ones, novel cyclobutane-fused heterocycles, from 3-methoxy-2-methylisoquinolin-1(2H)-one and their reaction with olefins are described.

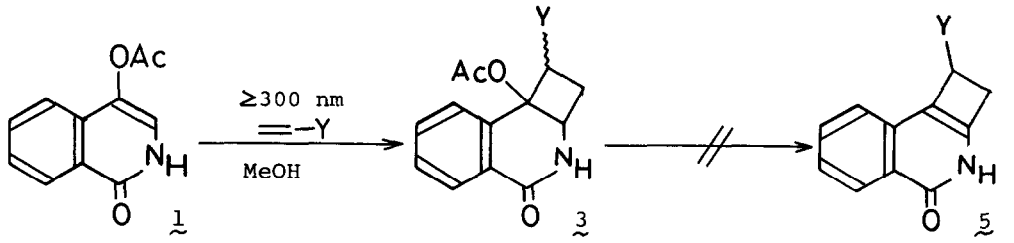
We have recently shown that intermolecular 2+2 cycloaddition of heteroaromatics having a β-alkoxy-enone function in their skeleton to olefins can be effected photochemically and the resultant adducts afforded the corresponding cyclobutane-fused heteroaromatics (e.g., 1,2-dihydrocyclobuta[c]quinolin-3(4H)-ones,[2] -pyridin-3(4H)-ones,[3] and -coumarins[1] by elimination of an alcohol under appropriate conditions.



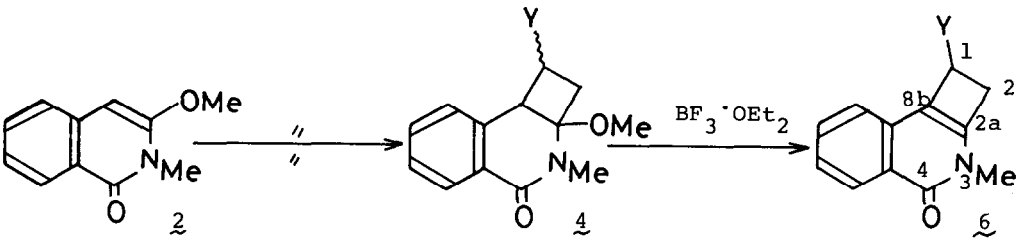
In an extension for our synthetic study of cyclobutane-fused heteroaromatics as well as for enlargement of the scope for the above two-step procedure for the syntheses of this kind of compounds, we have applied the above procedure to the synthesis of title compounds starting either from 4-acetoxy- or 3-methoxy-2-methyl-isoquinolin-1(2H)-one (1 or 2), having a conjugated dienone system oxygenated at γ- or δ-position (Scheme 1 and 2). As expected,[4] both 1-isoquinolones afforded upon irradiation the 2+2 cycloadducts with olefins. Though the adducts from the former did not afford the desired compounds in any conditions examined, the ones from the latter gave the desired compounds by the use of boron trifluoride-etherate in an appropriate aprotic solvent. This paper describes these synthetic studies as well as reactions of the resultant 1,2-dihydrocyclobuta[c]-isoquinolin-4(3H)-ones with olefins.

Irradiation of 5~6 x 10^{-3} mol solution of 1 or 2 in methanol containing a large excess of olefin (500-600 mol equiv.) by high pressure mercury lamp (Toshiba-400P, Pyrex filter) until disappearance of the starting isoquinolone[5]

afforded in all cases 1-substituted 1,2,2a,8b-tetrahydrocyclobuta[c]isoquinolin-4(3H)-ones (3 and 4) as a mixture of two diastereoisomers. These two isomers were easily separated by column chromatography over silica gel and the melting points and yields are shown in the Table. Regiochemistries of these adducts can be determined from their nmr spectra.[6,7] Thus in $CDCl_3$ solution, 2a-proton of each of 3a-c appeared at around δ 4.2-4.9 with expected splitting pattern by coupling with 2-protons (J=8-10 Hz) and was further splitted as doublets by N_3-proton (J=4.5-6 Hz and these doublets collapsed to singlets by the addition of D_2O) and 8b-proton in 4 appeared as a doublet centered at around δ 3.8-4.1 indicating the presence of only one proton at the 1-position in each adduct (4).



Scheme 1



Scheme 2

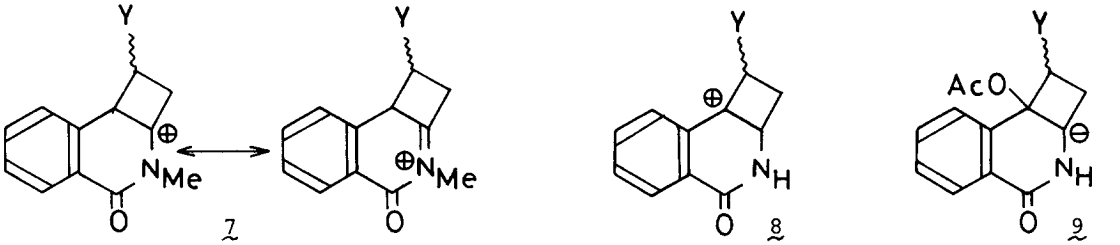
Table. Melting Points and Yields of 1,2,2a,8b-Tetrahydrocyclobuta[c]isoquinolin-4(3H)-ones (3 and 4) and 1,2-Dihydrocyclobuta[c]isoquinolin-4(3H)-ones (6).

comp.	3*		4*			6**	
Y	mp	(%)	Y	mp	(%)	R	mp (%)
a	221-223° dec.	55	e	154-155°	49	e	173-173.5° ca. 90
CN	249-251° dec.	41	CN	168-169°	45	CN	
b C_2 $-(CH_2)_4$	238-239.5°	51	f	oil	70	f	142-143° ca. 90
	223-224.5°	15	COOMe	oil	21	COOMe	
c	226.5-227.5° dec.	43					
OAc	236.5-238° dec.	21					

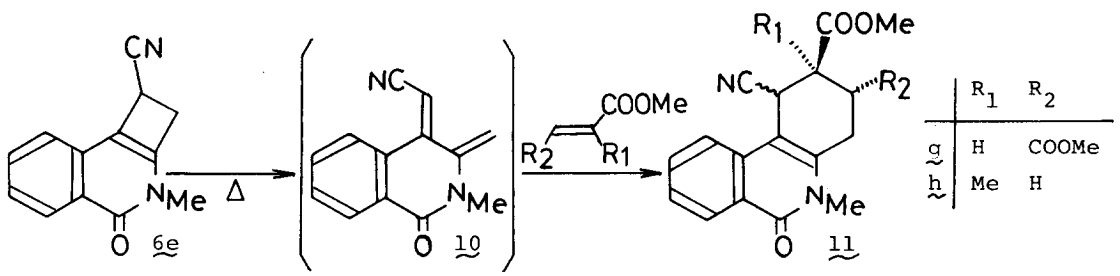
* Stereochemistry of each isomer has not been determined as yet.

** The yields of 6e,f from 4 were almost the same irrespective to their stereochemistries.

All attempts (such as treatment with base or acid, or pyrolysis) to convert the adducts (3) to 5 have failed. However, while the action of base to 4e resulted in the recovery of the starting material, the action of boron trifluoride-etherate to 4 in benzene led, irrespective to their stereostructures, to the corresponding cyclobutenes[8] (6) in high yields. The successful elimination of methanol from 4 by the Lewis acid probably reflects the appreciable stability of the carbonium ion structure at C_{2a} (7) due to the participation of the neighboured NMe group. On the contrary, such a stability can not be expected for the carbonium ion structure at C_{8b} (8) nor the carbanion structure at C_{2a} (9) expected from 3 and this argument may account for the failure in the formation of 5 from 3.



Finally, we examined the 4+2 cycloaddition of 1,2-dihydrocyclobuta[c]isoquinolones (6e) to olefins via the aza-o-quinodimethane intermediate (10) derived from the formers.[9] Thus, refluxing of 6e with dimethyl fumarate (15 mol equiv.) in xylene for 60 min. resulted in the formation of a mixture (11g, oil: ca. 2:1 ratio) in a quantitative yield. Though these two isomers could not be separated, their ratio was determined from nmr spectrum, which showed COOMe signals at δ 3.58, 3.72, and 3.76 for the major product, and at δ 3.52, 3.79, and 3.84 for the minor one. In a similar manner, a mixture (11h, oil) composed of two diastereoisomers was again obtained in a quantitative yield by the cycloaddition of 6e to methyl methacrylate. In this case, the proportion of the two isomers was ca. 1:1 and each showed the methine proton signal (CHCN) as a singlet (δ 4.17 and 4.60). This fact demonstrated that cycloaddition of 6e to the



acrylate proceeded regioselectively to give the head-to-head adducts (11h).

The present study not only indicates that our two-step procedure for the synthesis of cyclobutane-fused heteroaromatics can be applicable to heteroaromatics having δ-alkoxy-dienone system in them as starting materials, but also demonstrated that newly synthesized 1,2-dihydrocyclobuta[c]isoquinolin-4(3H)-ones can serve as synthons for 1,2,3,4-tetrahydrophenanthridin-6(5H)-ones (11).

REFERENCES AND NOTES

1. Part VII of "Cycloadditions in Syntheses." For part VI, see: T. Naito, N. Nakayama, and C. Kaneko, Chemistry Lett., 1981, 423.
2. C. Kaneko and T. Naito, Chem. Pharm. Bull., 27, 2254 (1979).
3. H. Fujii, K. Shiba, and C. Kaneko, J. Chem. Soc. Chem. Comm., 1980, 537.
4. 3,4-Unsubstituted 1-isoquinolones added to olefins to form diastereomeric mixture of products having 1-substituted 1,2,2a,8b-tetrahydrocycobuta[c]isoquinolin-4(3H)-one structure. The reactions competed with photo-dimerization of these isoquinolones. See, G.R. Evanega and D.L. Fabiny, Tetrahedron Lett., 1971, 1749.
5. The reactions were monitored either by gas chromatography or tlc.
6. Regioselectivity of the photoaddition of 1 to olefins was further demonstrated by the regioselective formation of 8b-acetoxy-1,1-dimethyl-1,2,2a,8b-tetrahydrocyclobuta[c]isoquinolin-4(3H)-one [3d: mp 210-213°, nmr δ of 2a-H in $CDCl_3$: 4.22 dt, J=5 and 8 Hz and the signal collapsed to triplet (J=8 Hz) after addition of D_2O]. The poor yield (ca. 20%) of 3d reflects an intrinsic instability of 1 (and 2) for irradiation at ≥300 nm and a low solubility of isobutene in methanol. As noted in the text, in order to prevent the photodecomposition of 1 or 2 and to attain the high yields of the adducts (3 or 4) a large amount of olefin must be present in the irradiation solution of these isoquinolones.
7. Satisfactory analyses and mass spectra were obtained for all new crystalline compounds. Satisfactory mass data were obtained for all oily products.
8. The structure of the products (6) was supported by acceptable spectral data. For example, 6e showed a typical 1-isoquinolone absorption in UV spectrum [λ_{max}^{MeOH} nm: 205, 230, 282, 291, and 336] and nmr [δ in $CDCl_3$: 3.33 s (N-Me), 3.41 dd (H_2), 3.66 dd ($H_{2'}$), 4.00 dd (H_1) with $J_{2-2'}$=13.5, $J_{1-2'}$=3.5, and J_{1-2}=2.5 Hz].
9. Upon pyrolyses, benzocyclobutene and its analogues afforded highly reactive o-quinodimethanes, which reacted in situ with dienophiles to give the 4+2 adducts. T. Kametani and K. Fukumoto, Heterocycles, 3, 29 (1975); W. Oppolzer, Synthesis, 1978, 793; C. Kaneko, T. Naito, and M. Ito, Tetrahedron Lett., 1980, 1645.

(Received in Japan 3 April 1981)