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NOVEL METHODS FOR INTRODUCING A TWO-CARBON UNIT AT EITHER THE 3- OR 4-POSITION OF THE ISOQUINOLONE RING BY MEANS OF PHOTO[2+2]CYCLOADDITION REACTION[1)]

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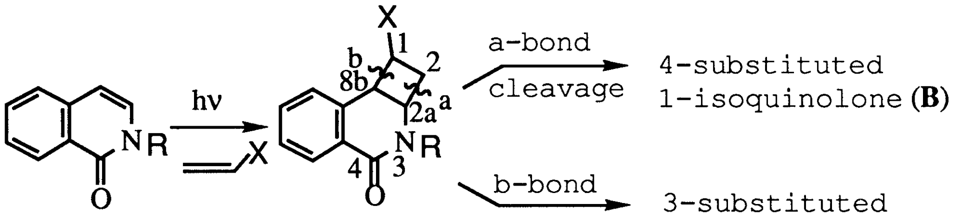
A novel method is described for introducing a two-carbon unit at either the 3- or 4-position of the 1-isoquinolone ring. The method for the synthesis of the 4-vinyl or 4-ethynyl derivative of isoquinolone consists of 1) photoaddition of the isoquinolone to chloroethylenes and 2) base treatment of the major (head-to-tail) adduct giving the 4-substituted isoquinolones. Similarly, by using 3-methoxyisoquinolone and vinyl acetate in step 1) and an acidic condition in step 2), a formylmethyl group is introduced into the 3-position of the isoquinolone ring.

KEYWORDS photo[2+2]cycloaddition; 1,1-dichloroethylene; 4-vinyl-1-isoquinolone; 4-ethynyl-1-isoquinolone; 3-formylmethyl-1-isoquinolone; photochemical cyclobutanation; l-isoquinolone

Photochemical cyclobutanation of a cyclic enone system, coupled with subsequent C-C bond fission in the strained four-membered ring, provides a useful method for the construction of a variety of complex carbon frameworks.[3-6)] Our continuing studies concerning the application of this method to heteroaromatic compounds[6-8)] have led us to examine the chemical behaviour of the adducts (**A**) obtained from 1-isoquinolones (**1a**, **1b** and their 3-methoxy derivatives) and an appropriate olefin, with an expectation that the cyclobutanes thus formed would undergo C-C bond fission between 2- and 2a- (a-bond cleavage) or 1- and 8b-positions (b-bond cleavage) to give isoquinolones having a two-carbon unit at either the 4- or 3-position.



1 **A**

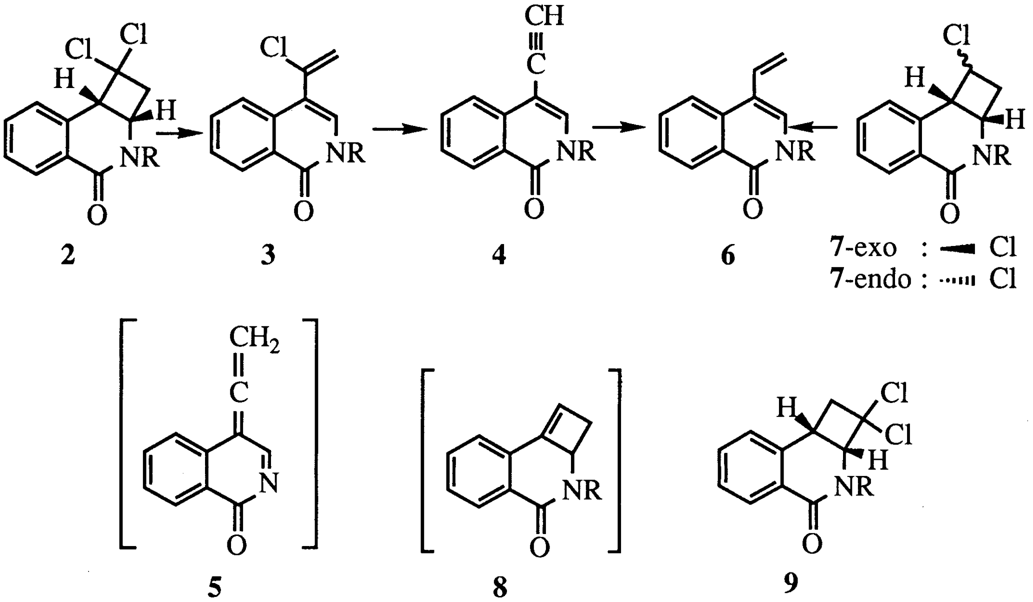
a: R=H, b: R=Me

Here, we report that, while treatment of the adduct (**A**) obtained by photoaddition of 1-isoquinolones (**1**) to chloroethylenes with a base afforded the 4-substituted 1-isoquinolones (**B**), treating the adduct, derived by photoaddition of 1-isoquinolone having an alkoxyl group at 3-position to vinyl acetate, with an acid gave the 3-substituted derivative (**C**).

The adduct (**2b**) obtained by the photoaddition of 2-methyl-1-isoquinolone (**1b**) to 1,1-dichloroethylene[9)] was treated with a base (t-BuOK-THF/reflux) to give 4-(1-chlorovinyl)-2-methyl-1-isoquinolone (**3b**: mp 89-90 °C)[10)] in a quantitative yield. When the adduct (**2a**) derived from **1a** was used in this reaction, 4-ethynylisoquinolone [**4a**: mp 231-232 °C,

ν^{KBr}, 2110, 1650 cm^{-1}, ^{1}H-NMR δ; 4.33 (s, ≡C-H)] was formed in 71% yield as a sole product. The formation of the latter product probably proceeds via the allene species (**5**) as the intermediate from 3a. Catalytic hydrogenation of the **4a** over Lindlar's catalyst afforded in an almost quantitative yield the corresponding 4-vinyl derivative (**6a**: mp 167-169 °C)). The same type of transformation was also carried out using the adduct (**7**: either endo- or exo-isomer) of 1-isoquinolones and vinyl chloride to give directly the vinylisoquinolones (**6a** and **6b**: oil) in yields of 92 and 98%, respectively. The ease of the desired C-C bond fission depends upon the stereochemistry of the adduct and the endo-adduct (**7-endo**) was found to be cleaved even by NaOH-MeOH/reflux, while the exo-adduct (**7-exo**) was stable under the same condition. Since only the minor adduct (**7-endo**) has a trans relationship between 8b-H and 1-Cl atoms, the cleavage probably proceeds in two steps via the cyclobutene (**8**) as the intermediate.

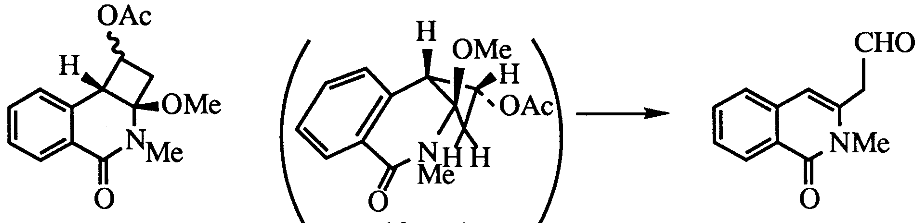
a-bond cleavage reaction



Since this type of reaction proceeded smoothly even by using the adduct derived from 1-isoquinolones and tetrachloroethylene, the method seems to have wide applicability for the introduction of a variety of a two-carbon unit at the 4-position of the isoquinolone ring. Obviously from the data shown above, this type of reaction (a-bond cleavage) would proceed in the [2+2]-adducts having a suitable leaving group at the 1-position. Actually when the 2-chloro derivatives (**9**) were employed in the above reaction, only the starting material was recovered unchanged.

Obvious extention of the above a-bond cleavage reaction then suggested that treatment of the cyclobut[c]isoquinolones having a hydroxyl group at the 1-position under suitable condition would give 3-formylmethylisoquinolones (b-bond cleavage products). This expectation was realized by the following experiment. The adduct (**10**: a ca. 5:2 mixture of endo- and exo isomers[11]) obtained from 3-methoxy-2-methyl-1-isoquinolone and vinyl acetate[12]) was treated with an acid (BF_3-Et_2O/CH_3CN, at room temperature) to give the expected isoquinolone (**11**) in 40% yield. Contrary to the a-bond cleavage reactions, the methoxyl group at 2a-position in the adduct (**10**) acts as the leaving group.

b-bond cleavage reaction



10 (**10**-endo) **11**

The scope of the two types of bond cleavage reactions (a and b) used to synthesize isoquinolones having a functionalized C-2 unit at the 3- or 4-position is now under investigation, together with the use of a 4-vinyl derivative as the diene in the Diels-Alder reaction.[13]

REFERENCES AND NOTES

1) This paper forms Part 53 of "Cycloadditions in Syntheses." For part 52, see reference 9.

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5) M. Demuth and G. Mikhail, *Synthesis*, **1989**, 145.

6) C. Kaneko and T. Naito, *Heterocycles*, **19**, 2183 (1982).

7) T. Naito and C. Kaneko, *Yuki Gosei Kagaku Kyokai Shi*, **42**, 51 (1984).

8) N. Katagiri, *Yakugaku Kenkyu no Shinpo* (*Advances in Pharmaceutical Sciences: The Research Foundation for Pharmaceutical Sciences*), **6**, 24 (1990).

9) The photoaddition of 1-isoquinolones to chloroethylenes was reported recently from this laboratory and all of their structures (including conformations) were determined unequivocally by X-ray analyses and 500 MHz ^{1}H-NMR spectra: T. Chiba, Y. Takada, C. Kaneko, F. Kiuchi, and Y. Tsuda, *Chem. Pharm. Bull.*, in press.

10) All new compounds were identified either by elemental analysis or by high-resolution mass spectra and the structures were supported by acceptable spectral data.

11) Two isomers could be separated into the major (mp 80-81 °C) and minor adducts (oil), in which the former could be assigned as the endo isomer due to ca. 1 Hz long-range coupling (W-conformation, cf. the puckered conformation shown by formula **10-*endo***) between 2-endo- and 8b-protons.

12) The two-step synthesis of 1,2-dihydrocyclobut[*c*]isoquinolin-4(3*H*)-ones from 3-methoxy-2-methyl-1-isoquinolone and their reaction with some olefins were reported previously: T. Naito and C. Kaneko, *Tetrahedron Lett.*, **22**, 2671 (1981); idem, *Chem. Pharm. Bull.*, **33**, 5328 (1985).

13) Several 7-azasteroid derivatives were previously synthesized by Diels-Alder reaction of 4-vinylisoquinolines with appropriate cyclopentenes. However, none of the vinylisoquinoline used in those studies was isolated nor characterized: S. F. Dyke, M. Sainsbury, D. W. Brown, and D. J. Clipperton, *Tetrahedron*, **26**, 5959 (1970); S. F. Dyke, P. A. Bather, A. B. Garry, and D. W. Wiggins, *ibid*., **29**, 3881 (1973).

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