Communications to the Editor

Chem. Pharm. Bull.
34(10)4429—4431(1986)

SYNTHESIS OF 4-TRIFLUOROMETHYLAZETIDIN-2-ONES BY A NOVEL 2+2 PHOTOCYCLOADDITION OF 3-TRIFLUOROMETHYL-QUINOXALIN-2-ONE OR -1,4-BENZOXAZIN-2-ONE TO KETENE

Nobuya Katagiri,* Kouichi Kasai, and Chikara Kaneko*
Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan

This is a description of the facile synthesis of 4-trifluoromethylazetidin-2-ones from 3-trifluoromethyl derivatives of quinoxalin-2-one and 1,4-benzoxazin-2-one, using a novel 2+2 photocycloaddition of the latter compounds to ketene.

KEYWORDS —— 4-trifluoromethylazetidin-2-one; 2+2 photocycloaddition; 3-trifluoromethylquinoxalin-2-one; 3-trifluoromethyl-1,4-benzoxazin-2-one; ketene; imine; methanolysis

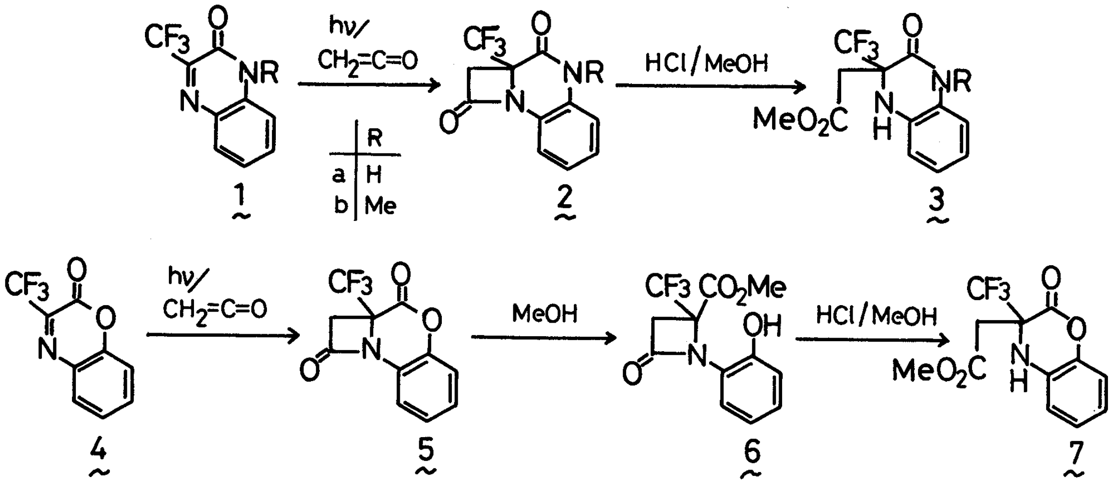
The recent discovery of the biologically potent 4α-methyl-1-sulfoazetidin-2-one derivatives[1] has stimulated considerable interest in the synthesis of azetidin-2-ones having a fluorinated methyl group at the 4-position.[2] This is because the electron-withdrawing property of the fluorinated methyl group increases the chemical reactivity of the β-lactam ring that may be correlated with the biological activity.[3] Recently, we observed that while quinoxalin-2-one[4] or 1,4-benzoxazin-2-one[5] afforded the 2+2 photocycloadducts only with electron-poor olefins, their 3-trifluoromethyl derivatives gave the corresponding azetidines irrespective of the kinds of olefins.[6] In this paper, we describe a facile synthesis of some 4-trifluoromethylazetidin-2-ones from 3-trifluoromethyl derivatives (1a, 1b, and 4) of quinoxalin-2-one and 1,4-benzoxazin-2-one by the 2+2 photocycloaddition reactions with ketene.

A solution of 1a[7] in benzene was irradiated at ≥ 300 nm[8] under bubbling of ketene[9] for 30 min to give the azetidin-2-one 2a (mp 152-153.5 °C)[10] in 82% yield. In the same manner, the azetidinone 2b (mp 160-162 °C) was obtained in 61% yield from 1b.[11] Complete recovery of 1b when the reaction was carried out in the dark indicates that the addition reactions proceed <u>via</u> the excited species (T_1)[12] of 1. The IR spectra of 2a and 2b showed absorption bands at <u>ca</u>. 1795 cm^{-1} attributable to a β-lactam. Facile ring cleavage reactions of these adducts to esters (3a: mp 136-138 °C and 3b: mp 85-85.5 °C) by methanolysis further confirmed the β-lactam structure of 2.

This remarkable photo-assisted cycloaddition reaction also proceeded smoothly when 4 was irradiated under the same conditions. Again, the β-lactam 5 [mp 118.5-119 °C; IRν_{max} ($CHCl_3$): 1812 sh, 1800, and 1783 cm^{-1}] was obtained in 61% yield. The lactone ring in 5 is more prone to solvolysis than the lactam ring. Thus, merely heating in methanol gave 6 [oil; IRν_{max} ($CHCl_3$): 1790 and 1760 cm^{-1}] which on treatment with HCl in methanol afforded the ester 7 [mp 96.5-97.5 °C; IRν_{max}

($CHCl_3$): 1770 and 1745 cm^{-1}]. The sequential reactions proceeded with almost quantitative yields.

Though thermal 2+2 cycloaddition reactions of imines with ketenes are known,[13)] it is remarkable that the reactions proceed only under irradiation[14)] and that the imine function involved in the heteroaromatic ring participates in this type of cycloaddition reaction. The present method not only provides a new route for the synthesis of azetidin-2-ones having a trifluoromethyl group at the 4-position but also appears to be applicable to related systems (mono- or difluoromethyl derivatives and other heteroaromatic compounds).



REFERENCES AND NOTES

1) H. Breuer, C.M. Cimarusti, Th. Denzel, W.H. Koster, W.A. Slusarchyk, and U.D. Treuner, Antimicrob. Agents Chemother., 8, 1 (1981).

2) P.F. Bevilacqua, D.D. Keith, and J.L. Roberts, J. Org. Chem., 49, 1430 (1984); K. Yoshioka, T. Miyawaki, S. Kishimoto, T. Matsuo, and M. Ochiai, ibid., 49, 1427 (1984); G. Teutsch and A. Bonnet, Tetrahedron Lett., 25, 1561 (1984); J.S. Skotnicki, T.J. Commons, R.W. Rees, and J.L. Speth, J. Antibiot., 36, 1201 (1983); G. Guanti, L. Banfi, E. Narisano, C. Scolastico, and E. Bosone, Synthesis, 1985, 609.

3) H.R. Pfaendler, J. Gosteli, R.B. Woodward, and G. Rihs, J. Am. Chem. Soc., 103, 4526 (1981).

4) T. Nishio, J. Org. Chem., 49, 827 (1984).

5) T. Nishio and Y. Omote, J. Org. Chem., 50, 1370 (1985).

6) C. Kaneko, K. Kasai, H. Watanabe, and N. Katagiri, Chem. Pharm. Bull., in press.

7) N. Ishikawa and S. Sasaki, Bull. Chem. Soc. Jpn., 50, 2164 (1977).

8) The solution was irradiated with a high-pressure mercury lamp with a Pyrex filter at room temperature.

9) Ketene was generated by pyrolysis of acetone: W.E. Hauford, Org. React., 3, 132 (1946).

10) All new compounds were identified by either elemental analysis or by high-

resolution mass spectra showing acceptable spectral data.

11) 1b (mp 136-137 °C) was prepared from 1a by the usual methylation (MeI/K_2CO_3/acetone).

12) The same reactions proceed smoothly in acetone, showing that the excited species of 1 and 4 are T_1. See also reference 6.

13) J.C. Sheehan and E.J. Corey, Org. React., 9, 388 (1957); R. Pfleger and A. Jager, Chem. Ber., 90, 2460 (1957); N. Katagiri, Y. Miura, R. Niwa, and T. Kato, Chem. Pharm. Bull., 31, 538 (1983).

14) To our knowledge, diazetidinone formation from azobenzene and ketene is the only example of this reaction: G.O. Schenck and N. Engelhard, Angew. Chem., 68, 71 (1956).

(Received August 4, 1986)