Some Novel Reactions of Benzoxazole Derivatives with Dimethyl Acetylenedicarboxylate II [1]

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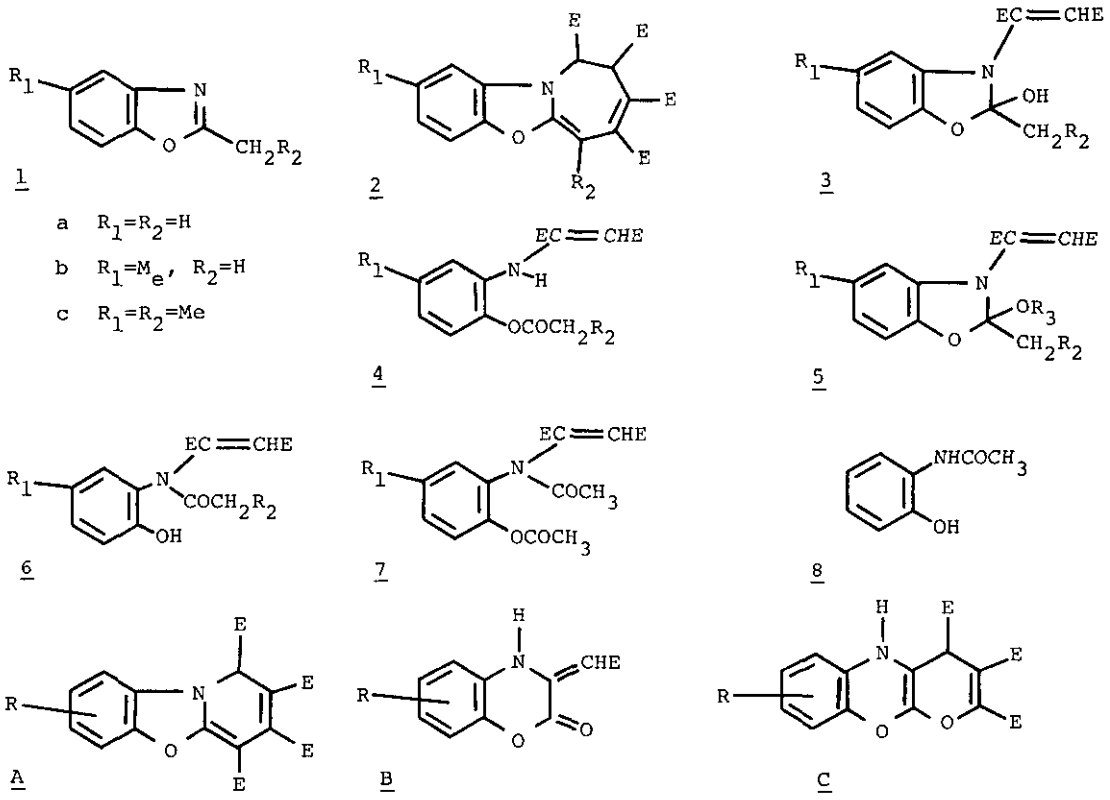
Abstract— 2-Alkylbenzoxazole derivatives (1) reacted with dimethyl acetylenedicarboxylate (DMAD) in alcoholic solvents at room temperature to afford tricyclic compound (2), hydration product (3), solvent adduct (5) and ring-opened compounds (4 and 6). And the ring-opened compound (6) is a main product of photocycloaddition reaction of 1 with DMAD.

During our continuous experiments on the synthesis of heterocyclic compounds from acetylenic esters [2] we have recently found some novel addition reactions of benzoxazole derivatives with dimethyl acetylenedicarboxylate (DMAD) in alcoholic solvents, and formulated plausible mechanisms for the reactions. This paper describes other novel reactions of 2-alkylbenzoxazoles with DMAD. 2,5-Dimethylbenzoxazole (1b) was treated with DMAD (3 equiv.) in EtOH for 2 weeks at r.t. in the dark. Separation of the reaction mixture by preparative TLC (Wakogel 13-5F, EtOAc : benzene = 1.5 :8.5) gave three products [2b (mp 222°, 24.2%), 3b (oil, 15.4%) and 4b (oil, 4.6%)]. Their spectral data were consistent with the corresponding structures (Table 1) [3]. It can be presumed from the next experiments that ring-opened compound (4) should be formed via hydration product (3). When 2-methylbenzoxazole (1a) was treated with DMAD in t-BuOH containing a small amount of H_2O for 3 weeks at r.t., 3a (oil, 33%) and 6a (mp 147-149°, 8.67%) were isolated from the reaction mixture by column chromatography on silica gel. Whereas 3a was gradually converted to 6a when allowed to stand at r.t. in CH_2Cl_2, it immediately



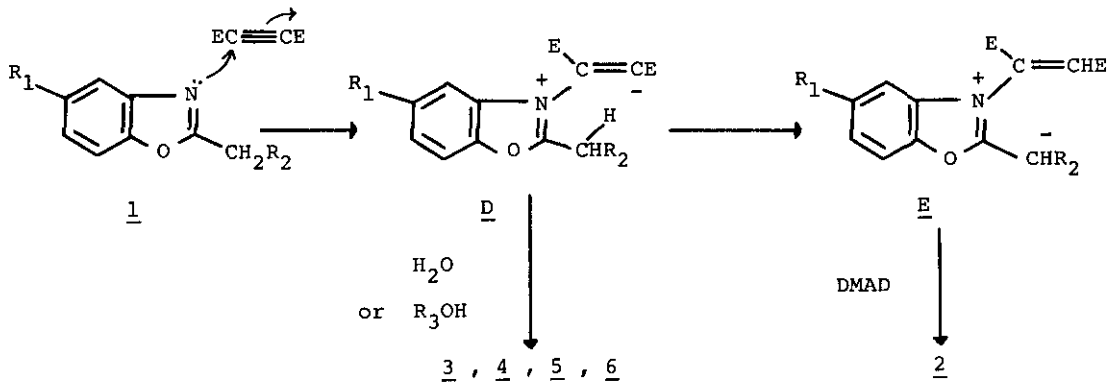
scheme 1

changed on treatment with Et_3N at r.t. to 4a and 6a in a ratio of ca. 1 : 1. Acetylation of 6a with Ac_2O in pyridine gave a diacetate (7a, mp 103-106°), whose structure was assigned from close similarity of its IR and ^{1}H-nmr spectra with those of the acetate of 4b (7b). Further, 1a and 1b were treated with DMAD in other alcoholic solvents (EtOH, iso-PrOH, t-BuOH) to give similar results, and the solvent adducts (5a,b, R_3 = t-Bu) were obtained only in t-BuOH but in poor yield. In order to study the steric effect on this addition reaction, 2-ethyl-5-methylbenzoxazole (1c) was treated with DMAD in similar conditions, to give products 2c, 3c, 4c and 5c, no significant difference of reactivity between 2-Me and 2-Et substituents being recognized. Cycloadducts such as A was not obtained in previous reactions at all [1], however this time, cycloadducts (2a,b,c) were invariably prepared under the same reaction conditions. Another interesting result is that any recyclic compound (B) or tricyclic compound (C) is not obtained at all, in contrast with the case of the reaction of 2-nonsubstituted

Table I. Spectral data of the representative products

products	MS (M^+)	PMR ($CDCl_3$) δ (ppm)
2b	431	2.41(s, 3H, CH_3); 3.60,3.71,3.76,3.83(s, 12H, 4xOMe); 4.95(s, 1H, vinylic); 5.46(d, 1H, J=5Hz); 5.71(d, 1H, J=5Hz); 6.70-7.30(m, 3H, aromatic)
3b	307	1.98(s, 3H, CH_3); 2.27(s,3H, CH_3); 3.83(s, 6H, 2xOMe); 6.87(s, 1H, vinylic); 6.70-7.50(m, 3H, aromatic); 8.17 (s, 1H, OH)
4b	307	2.17(s, 3H, CH_3); 2.30(s, 3H, CH_3);3.73,3.82(s, 6H, 2xOMe); 5.44(s, 1H, vinylic); 6.50-7.20(m, 3H, aromatic); 9.50(broad, 1H, NH)
5b	363	1.27(s, 12H, t-Bu); 2.25,2.30(s, 6H, 2xCH_3); 3.72,3.97 (s, 6H, 2xOMe); 5.92(s, 1H, vinylic); 6.20-7.20(m, 3H, aromatic)
6a	293	1.90(s, 3H, CH_3); 3.64,3.95(s, 6H, 2xOMe); 5.49(s, 1H, vinylic); 6.70-7.50(m, 4H, aromatic); 7.73(broad, 1H, OH)
7a	335	1.95(s, 3H, CH_3); 2.35(s, 3H, CH_3); 3.64,3.91(s, 6H, 2xOMe); 5.01(s, 1H, vinylic); 7.32(m, 4H, aromatic)

benzoxazole with DMAD [1]. A mixture of 1a and DMAD in dry acetone or dry acetonitrile was irradiated for 16 hr under N_2 at 25° (300W high pressure mercury arc lamp in a pyrex cell). Ring-opened compounds 6a (23.5%) and N-acetyl aminophenol (8, mp 205-206°, 8.28%) were isolated by colomn chromatography on silica gel. In this reaction, the seven membered ring compound (2a) was not obtained [4]. The structure of 8 was established by comparison of its IR spectrum with that of an authentic sample. Benzoxazole gave a crystalline compound (B, R = H) as the only isolable product in same photoaddition reaction conditions. The above-mentioned results apparently suggest that 2-alkyl substituents in benzoxazole ring play essential roles in the cycloaddition of 1 with DMAD. In view of its reaction mechanism proposed by R. M. Acheson et al [5], it may be assumed that C_2-CH_2R_2 group and a carbanion in an intermediate (D) can keep a sterically close proximity to cause readily a proton transfer prior to attack of DMAD or R_3OH and afford a following intermediate (E), which reacts with the second molecule of DMAD to give 2 as indicated. However in the presence of H_2O,



scheme 2

H_2O may preferentially react with the intermediate (D) to afford ring-opened compounds (4 and 6) and a hydroxy compound (3). The formation of solvent adducts (5) implies that alcoholes usually react with the intermediate (D).

References and Notes

1 Part I : N.Kawahara, M. Katsuyama, T. Itoh and H. Ogura, Heterocycles., 1980, 14, 15.
presented in part at 100th Annual meeting of the Pharmaceutical Society of Japan, Tokyo, April 2-5, 1980.

2 N. Kawahara, T. Itoh, H. Ogura and K. A. Watanabe, Heterocycles., 1980, 14, 619, and references cited therein.

3 The structure assignments of the products are based on the satisfactory elemental analyses, and MS, IR and NMR spectra.

4 *Similar compounds (2, O → S) are main products of photocycloaddition reaction* of 2-alkylbenzothiazole derivatives with DMAD which results will appear in the following paper.

5 R. M. Acheson, M. W. Foxton and G. R. Miller, J. Chem. Soc., 1965, 3200.

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