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SYNTHESIS OF 4-OXO-4H-BENZISOXAZOLO[2,3-a]PYRIDINES VIA DIMERIZATION OF 1,2-BENZISOXAZOLE-3-ACETIC ACIDS[1)]

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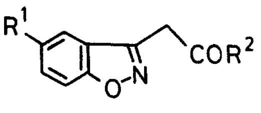
Reactions of 1,2-benzisoxazole-3-acetic acid (1) with tosyl chloride and acyl chlorides in pyridine afforded the corresponding 4-oxo-4H-benzisoxazolo[2,3-a]pyridines (2).

KEYWORDS —— 1,2-benzisoxazole-3-acetic acids; dimerization; mixed anhydrides; tosyl chloride; N-C bond formation; 4-oxo-4H-benzisoxazolo[2,3-a]pyridines

During the course of our studies on the derivatives of 1,2-benzisoxazole-3-acetic acid (1a), we have paid much attention to the abnormally high nucleophilicity of the α-methylene group of 1a.[2)] As an extension of this series, a reaction of mixed anhydrides of 1a was examined, and it was found that treatment of 1a with tosyl chloride in pyridine gave the 4-oxo-4H-benzisoxazolo[2,3-a]-pyridine derivative (2a).[3)] This N-C bond formation is the first example of a reaction concerning the 1,2-benzisoxazole ring. This paper deals with the synthesis of 2 and some of its reactions.

Treatment of 1a with tosyl chloride (4 equiv.), acetyl chloride (1 equiv.), and benzoyl chloride (5 equiv.) in pyridine at room temperature for 0.5 – 1 h afforded 2a, 2b and 2c in 60%, 26% and 50% yield, respectively. In a similar manner, 2d and 2e were obtained from 1b in 65% and 28% yield, respectively. On hydrolysis with NaOH at room temperature, 2a, 2b and 2c gave the same product (3a) in quantitative yield. And similar mild hydrolysis of 2d and 2e gave 3b. Tosylation or acylation of 3 gave the original tosylates (2a, 2d) or acylates (2b, 2c, 2e) in quantitative yield.

A dimeric structure of 2 and 3 was suggested from their ^{1}H-NMR (PMR) and mass (MS) (Table I) spectral data in accordance with the ^{13}C-NMR (CMR) spectral data of 2e.[4)] The PMR spectra (DMSO-d_6) of 2 and 3 showed a characteristic one proton singlet attributable to C_1-H at δ 7.38–7.62 and δ 6.86–6.93, respectively. Of these, the PMR spectrum ($CDCl_3$) of 2e was the most informative, because all its proton signals were assignable.[4)] Moreover, there was an observable NOE of 13% at C_1-H (δ 6.83)[4)] when C_{10}-H at δ 7.27 was irradiated. On the IR spectra (KBr), 2 and 3 exhibited amide carbonyl bands at 1650–1665 cm^{-1} as shown in Table I. The structures for the dimers (2 and 3) were derived from these data. These structures were further confirmed by the following reactions and an alternative synthesis of 3a.



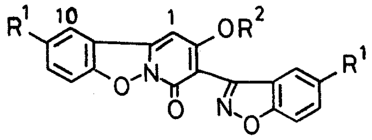
$\underline{1a}$ R^1=H, R^2=OH

$\underline{1b}$ R^1=OCH_3, R^2=OH

$\underline{1c}$ R^1=H, R^2=OCH_3

$\underline{1d}$ R^1=H, R^2=Cl

Ts=p-$CH_3C_6H_4SO_2$
Ac=CH_3CO
Bz=C_6H_5CO



$\underline{2a}$ R^1=H, R^2=Ts

$\underline{2b}$ R^1=H, R^2=Ac

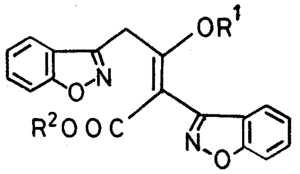
$\underline{2c}$ R^1=H, R^2=Bz

$\underline{2d}$ R^1=OCH_3, R^2=Ts

$\underline{2e}$ R^1=OCH_3, R^2=Ac

$\underline{3a}$ R^1=R^2=H

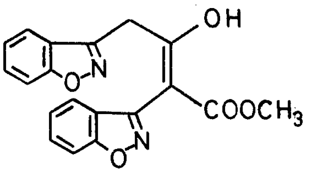
$\underline{3b}$ R^1=OCH_3, R^2=H



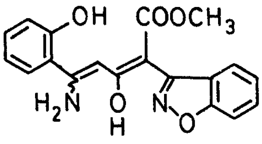
$\underline{4a}$ R^1=R^2=H

$\underline{4b}$ R^1=H, R^2=CH_3

$\underline{4c}$ R^1=Ac, R^2=CH_3



4d



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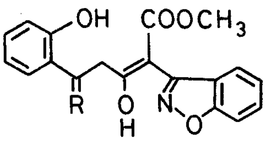

6a R=O

6b R=$<^{H}_{OH}$

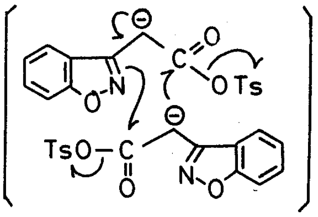

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Table I 4-Oxo-4H-benzisoxazolo[2,3-$\underline{a}$]pyridines

Compound No.	mp °C	IR(KBr) $\nu_{C=O}$ cm^{-1}	MS (m/z) M^+
2a	225-227	1665	472
2b	219-222	1650, 1750	360
2c	223-231	1660, 1730	422
2d	231-233	1660	532
2e	195-197	1650, 1770	420
3a	>280(dec)	1660	318
3b	240-242(dec)	1660	378

Vigorous hydrolysis of $\underline{3a}$ with NaOH at 100°C in dioxane-H_2O gave an enol-acid ($\underline{4a}$) (mp 249-252°C, $\nu_{C=O}^{KBr}$ 1705 cm^{-1}) in 10% yield,[5] whose PMR spectrum (DMSO-d_6) exhibited eight aromatic protons of two benzisoxazole rings and methylene protons at δ 4.92 as a singlet. A methyl ester ($\underline{4b}$) (mp 167-168°C, $\nu_{C=O}^{KBr}$ 1705 cm^{-1}) and its acetate ($\underline{4c}$) (mp 158-159°C, $\nu_{C=O}^{KBr}$ 1710, 1760 cm^{-1}) were derived from $\underline{4a}$. Catalytic reduction of $\underline{4b}$ on 5% Pd-C in dioxane-EtOH was stopped when one molar equivalent of hydrogen was absorbed. The main product of this reduction was $\underline{5}$ (mp 250-260°C, 45% yield) in which the N-O bond of the non-conjugated benzisoxazole ring of $\underline{4b}$ was cloven. The PMR spectrum (DMSO-d_6) of $\underline{5}$ showing two singlets of vinyl proton at δ 5.80 and 6.18 in a ratio of 3:1 indicated that $\underline{5}$ was a mixture of ($\underline{E}$)- and ($\underline{Z}$)-isomers. On acidic hydrolysis, 5 gave a ketone (6a) (mp 160-162°C, ν^{KBr} 1705, 1640, 1625 cm^{-1}). Reduction of 6a with $NaBH_4$ in MeOH afforded an alcohol (6b) (mp 161-162°C, ν_{OH}^{KBr} 3550, 3320 cm^{-1}, ν^{KBr} 1705, 1625 cm^{-1}) whose PMR spectrum showed an A_2X system consistent with a partial structure of $-CH(OH)CH_2-$. These results substantiated the structure of 4a.

On the other hand, an alternative synthesis of 4b was attempted by condensation of a methyl ester (1c) with an acid chloride (1d)$^{6)}$ in the presence of NaH in DMF. From the reaction mixture, 1c, 3a and 4d (oil, ν^{neat} 3050, 1720, 1660 cm^{-1}) were isolated in 80%, 5% and 5% yield, respectively, although 4b was not obtained. Alkaline hydrolysis of 4d gave 4a in 70% yield accompanied by isomerization. In consideration of the anisotropic effect of the benzisoxazole ring, the stereo-structures of (E)-4b and (Z)-4d were deduced from a comparison of their PMR ($CDCl_3$) spectra in which a singlet methylene signal of 4d appeared at higher field (δ 4.09) than that of 4b at δ 4.87 indicating that 4d is a (Z)-isomer. From the fact that treatment of 4a with tosyl chloride-pyridine and reaction of 4b with NaH in DMF did not give any 4-oxo-4H-benzisoxazolo[2,3-a]pyridines, it is tentatively assumed that the dimerization of mixed anhydrides of 1 proceeds by the mechanism as shown in 7.

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REFERENCES AND NOTES

1) Part IX of "Studies on 3-Substituted 1,2-Benzisoxazole Derivatives". Part VIII; S. Naruto, H. Mizuta, T. Sawayama, T. Yoshida, H. Uno, K. Kawashima, Y. Sohji, T. Kadokawa, and H. Nishimura, J. Med. Chem., accepted for publication.
2) a) H. Uno, M. Kurokawa, K. Natsuka, Y. Yamato, and H. Nishimura, Chem. Pharm. Bull., 24, 632 (1976). b) H. Uno and M. Kurokawa, ibid., 26, 312 (1978). c) Idem., ibid., 26, 3498 (1978). d) T. Yoshida, S. Naruto, H. Uno, and H. Nishimura, J. Chem. Soc. Chem. Commun., 1982, 106.
3) All new compounds described in this paper gave satisfactory spectral (PMR, IR, and MS) and analytical data.
4) 2e: PMR (δ in $CDCl_3$); C_1-H 6.83(s) (δ 7.38 in DMSO-d_6), C_7-H 7.52 (dd, J=9.0, 1.2 Hz), C_8-H 7.33 (dd, J=9.0, 2.5 Hz), C_{10}-H 7.27 (dd, J=2.5, 1.2 Hz), $C_{4'}$-H 7.17 (d, J=2.5 Hz), $C_{6'}$-H 7.17 (dd, J=9.0, 2.5 Hz), $C_{7'}$-H 7.50 (d, J=9.0 Hz), C_9-OCH_3 3.82 (3H, s), $C_{5'}$-OCH_3 3.90 (3H, s), $COCH_3$ 2.20 (3H, s). CMR (δ in $CDCl_3$); 20.86(q), 55.98(q), 56.20(q), 92.55(d), 103.47(d), 103.56(d), 107.12 (s), 110.35(d), 110.79(d), 118.25(s), 121.04(d), 122.11(s), 122.83(d), 139.69 (s), 150.83(s), 151.26(s), 153.01(s), 156.39(s), 157.66(s), 157.73(s), 159.07 (s), 168.16(s). An assignment of CMR data is in progress.
5) In this reaction, 3a was recovered unchanged in 80% yield.
6) 1d: oil, IR $\nu_{C=O}^{neal}$ 1780 cm^{-1}, PMR (δ in $CDCl_3$) 4.59 (2H, s), 7.2-7.9 (4H, m). 1d was obtained by treatment of 1a with PCl_5 at 30-40°C for 1 h.

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