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SYNTHETIC STUDIES ON VIRGINIAMYCIN M2: FUNCTIONALIZATION AT THE 2-METHYL GROUP OF 4-*t*-BUTOXYCARBONYL-2-METHYL-1,3-OXAZOLE

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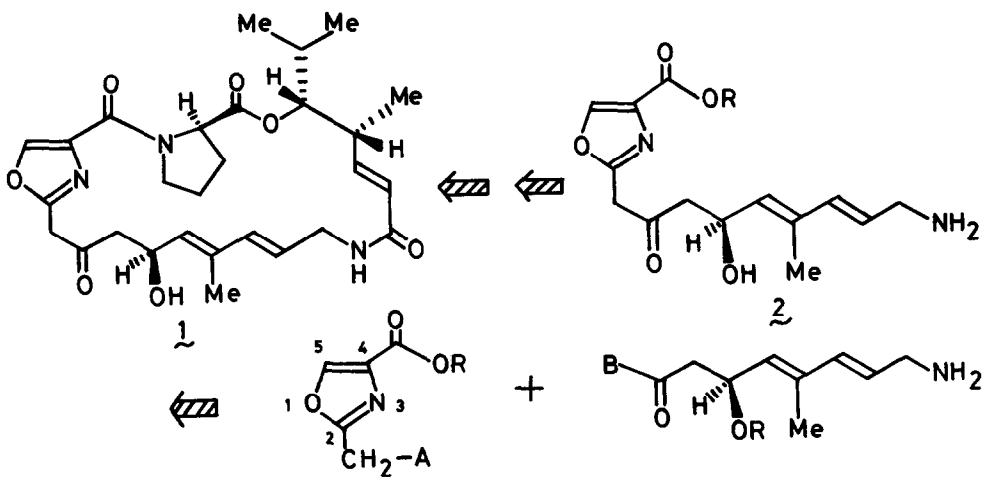
Summary: Substitution reactions of 2-bromomethyl-4-*t*-butoxycarbonyl-1,3-oxazole (6) with several anions (C^-, S^-, O^-, and I^-) were performed to yield the desired products 7a ∿ 7k.

We have been investigating in detail the chemical behavior of 4-alkoxycarbonyl-2-methyl-1,3-oxazoles, important synthons for the total synthesis of virginiamycin M2 (1)[1] and its analogs[1], because their chemical information [2,3] is poor as contrasted with that of 2-methyl-1,3-oxazoles which do not have any carboxyl or alkoxycarbonyl substituents.[4,5]

In the preceding communication,[6] we reported a useful model experiment utilizing 2-benzenesulfonylmethyl-4-*t*-butoxycarbonyl-1,3-oxazole ("BSMBO")(7j) for the construction of a key segment 2 of virginiamycin M2 (1). That report is concerned with the reaction between an anionic synthon 3a and a cationic synthon 4a (see Scheme 1). We also planned another approach to 2 *via* a reaction procedure between the cationic synthon 3b and the anionic synthon 4b (Scheme 1), and designed 2-bromomethyl-4-*t*-butoxycarbonyl-1,3-oxazole ("BMBO")(6) as 3b.

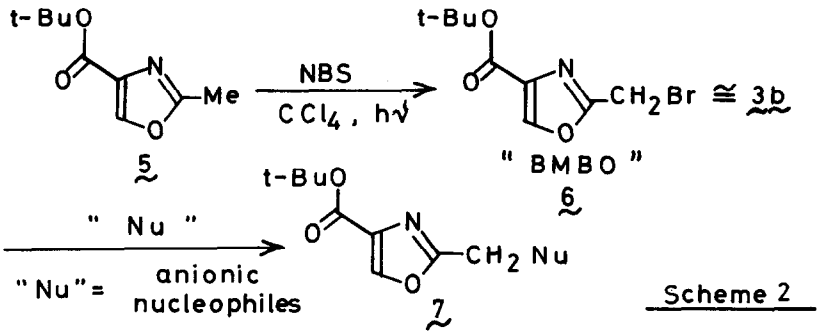


Scheme 1

Thus, we carefully prepared "BMBO" (6)[42% yield; colorless oil; bp 115 ∿ 118°/ 1 mmHg; IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.58 (9H, s), 4.47 (2H, s), 8.14 (1H, s) ppm; M^+ + 2 m/e

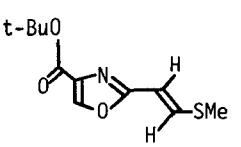
263.000, M^+ 261.003] by refluxing 4-*t*-butoxycarbonyl-2-methyl-1,3-oxazole (5)[7] with N-bromosuccinimide (1.5 mol equiv)-catalytic benzoylperoxide in CCl_4 under irradiation.[8] The process for introduction of carbanion nucleophiles and several functional groups into the methyl group of 5 utilizing the "BMBO"(6) is illustrated in Scheme 2.

We first carried out the substitution reactions of "BMBO"(6) with some carbanions; the results are summarized in Table 1. The desirable products 7a ~ 7d were obtained as crystals in various yields, respectively. The structures of all products were confirmed by their



Scheme 2

Table 1. Reactions of "BMBO"(6) with Carbanions

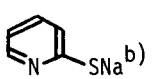
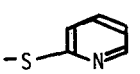
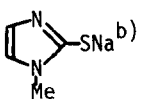
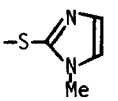
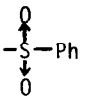
	"Nu"	Reaction Conditions[a]			Product	Yield(%)
		Solvent	Temp	Time(h)		
1)	KCN	MeCN	r.t.	7	7a Nu= -CN mp 82°- 83°	37
2)	$NaCH(CO_2Et)_2$	THF	r.t.	24.3	7b Nu= $-CH(CO_2Et)_2$ mp 31.5°- 32.5°	80
3)		THF	-78°- -20°	5	7c  mp 61°- 62°	54
4)	$(EtO)_2P(O)-CH(Li)-SMe$	THF	-78°	6.5	7d Nu= $-CH(SMe)-P(O)(OEt)_2$ mp 84°- 85°	24

[a] Reactions were carried out under the presence of catalytic 18-crown-6(for entries 1 and 2) or dicyclohexyl-18-crown-6(for entries 3 and 4).

spectroscopic data (IR, ^{1}H-NMR, and Mass) and elemental analyses. Compound 7c should be derived from the original desirable product *via* elimination of the methanesulfenic acid under the basic conditions (Scheme 3).

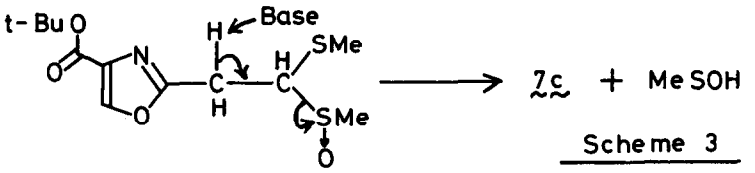
Subsequently we investigated several substitution reactions of "BMBO"(6) with sulfide, oxide, and iodide anions. The desirable products 7e ∿ 7k were obtained in good yield, respectively (see Table 2). Among these products, sulfone 7j is especially a notable compound

Table 2. Reactions of "BMBO"(6) with Sulfide, Oxide, and Iodide Anions

	"Nu"	Reaction Conditions[a] Solvent	Temp	Time(h)	Product		Yield(%)
1)	$MeCO_2K$	MeCN	r.t.	5	7e	Nu= -OCMe (O) oil	82
2)	DMSO	DMSO ($AgBF_4$- Et_3N)	r.t.	4.3	7f	Nu= -OH[11] mp 54°- 55°	32
3)	PhSNa[b]	THF	0°	1.6	7g	Nu= -SPh mp 64.5°- 65.5°	81
4)		THF	0°	3	7h	Nu=  mp 76°- 77°	78
5)		THF	0°	3	7i	Nu=  mp 79.5°- 80.5°	69
6)	$PhSO_2Na \cdot 2H_2O$	MeCN	r.t.	8	7j	Nu=  mp 180°- 182°	76
7)	KI	MeCN	r.t.	8	7k	Nu= -I oil	80

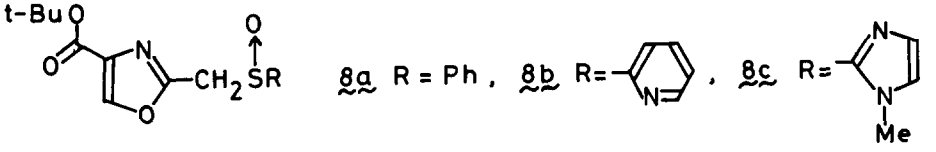
a) In all cases except entry 2, a catalytic amount of 18-crown-6 was used to make the reactions smooth.

b) A reagent solution prepared from the corrsponding thiol and NaH(1.1 mol equiv) in dry THF was used.



Scheme 3

for construction of segment 2. Sulfides 7g ∿ 7i are also interesting in the same sense. Thus, compounds 7g ∿ 7i were oxidized with *m*-chloroperbenzoic acid (1.05 mol equiv) in CH_2Cl_2 under ice-cooling to give the corresponding sulfoxides 8a [83% yield; colorless plates (from ether-petr. ether); mp 129 ∿ 130°; IR ($CHCl_3$) 1727 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.57 (9H, s), 4.20, 4.28 (each 1H, AB, *J*=13 Hz), 7.55 (5H, s), 8.05 (1H, s) ppm; M^+ m/e 307], 8b[57% yield; colorless fine plates (from EtOH); mp 116 ∿ 117°; IR ($CHCl_3$) 1728 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.56 (9H, s), 4.36, 4.61 (each 1H, AB, *J*=13.6 Hz), 7.37 ∿ 7.53 (1H, m), 7.88 ∿ 8.00 (2H, m), 8.07 (1H, s), 8.64 ∿ 8.74 (1H, m) ppm; M^+ m/e 308], and 8c[61% yield; colorless fine plates (from EtOH); mp 125 ∿ 126°; IR ($CHCl_3$) 1729 cm^{-1}; ^{1}H-NMR($CDCl_3$) δ 1.56 (9H, s), 3.92 (3H, s), 4.80, 4.88 (each 1H, AB, *J*= 14 Hz), 7.10 (1H, d, *J*=15 Hz), 7.12 (1H, d, *J*=15 Hz), 8.09 (1H, s) ppm; M^+ m/e 311], respectively. These sulfoxides will be similarly useful for the synthesis of segment 2 according to the reaction manner between the anionic synthon 3a and the cationic synthon 4a.



Thus, we established the general utility of "BMBO"(6) as the cationic synthon 3b. This achievement seems to rank as a milestone in the chemistry of the 1,3-oxazoles having an alkoxycarbonyl group.

References and Notes

1) C. Cocito, *Microbiol. Rev.*, 43, 145 (1979) and references cited therein.
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7) In the 4-alkoxycabonyl compounds other than *t*-butoxycarbonyl compound 5 the products brominated at C-5 were contaminated.
8) Besides "BMBO"(6), the starting compound 5 (22% recovery) and 4-*t*-butoxycarbonyl-2-dibromomethyl-1,3-oxazole (8% yield) were obtained.
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11) Formation of the aldehyde product was not recognized at all. Cf. B. Ganem and R. K. Boeckman Jr., *Tetrahedron Lett.*, 917 (1974).

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