FACILE SYNTHESIS OF ALKOXYOXAZOLINE-CARBOXYLATE FROM 2-(N-BROMOACETYL)AMINO-2-ALKENOATE AND ALCOHOL[1)]

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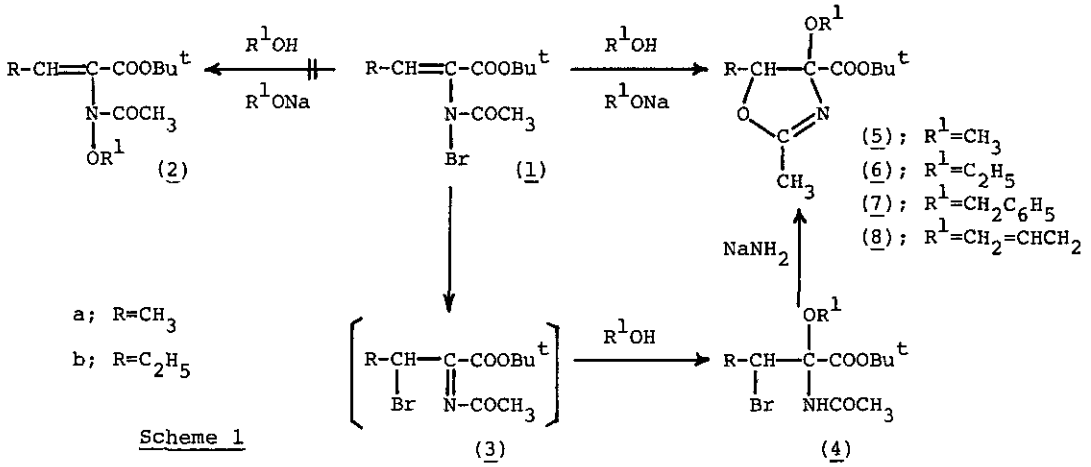
Abstract——The one-pot reaction of 2-(N-bromoacetyl)amino-2-alkenoate with sodium alkoxide in alcohol proceeded to give 4-alkoxyoxazoline-4-carboxylate. The structure and the formation mechanism were elucidated by the independent preparation from 2H-azirine-2-carboxylate in three steps.

Previously, we reported briefly that the reaction of t-butyl 2-(N-bromoacetyl)amino-2-alkenoate (1) with sodium alkoxide (RONa) gave t-butyl 2-(O-alkyl-N-acetylhydroxyl)amino-2-alkenoate (2).[2)] However, the proposed structure was found to be inconsistent with the expected 2 and instead it was supposed to be the unexpected oxazoline derivative. Here, we will report in detail the synthesis and the formation mechanism of 4-alkoxyoxazoline-4-carboxylates by one-pot reaction of 1 with RONa and the independent preparation from 2H-azirine-2-carboxylate in three steps. Moreover, the structural confirmation of the new products are discussed.

Treatment of 1 (a; R=CH_3, b; R=C_2H_5: 15 mmol) with RONa (made from Na 18 mmol) in alcohol (30 ml) at room temperature for 2 h gave a viscous oil, which was purified on a silica gel column using a mixture of benzene-ethyl acetate (50 : 1 v/v) as the eluent to give a colorless syrup or crystals. On the other hand, the reaction of t-butyl 2-alkoxy-3-bromo-2-acetylaminoalkanoate (4: 3.09 mmol), prepared by the addition of alcohol to the corresponding α-imino acid derivative (3) formed by the 1,3-shift of bromine in 1,[3)] with $NaNH_2$ (3.70 mmol) in DMF (30 ml) gave a syrup or crystals, which were found to be in complete agreement with the product obtained directly from 1 and RONa.

From the above results and the facts,[4,5)] the products from the above two routes were assumed to be either the corresponding N-acetylaziridine or oxazoline



Scheme 1

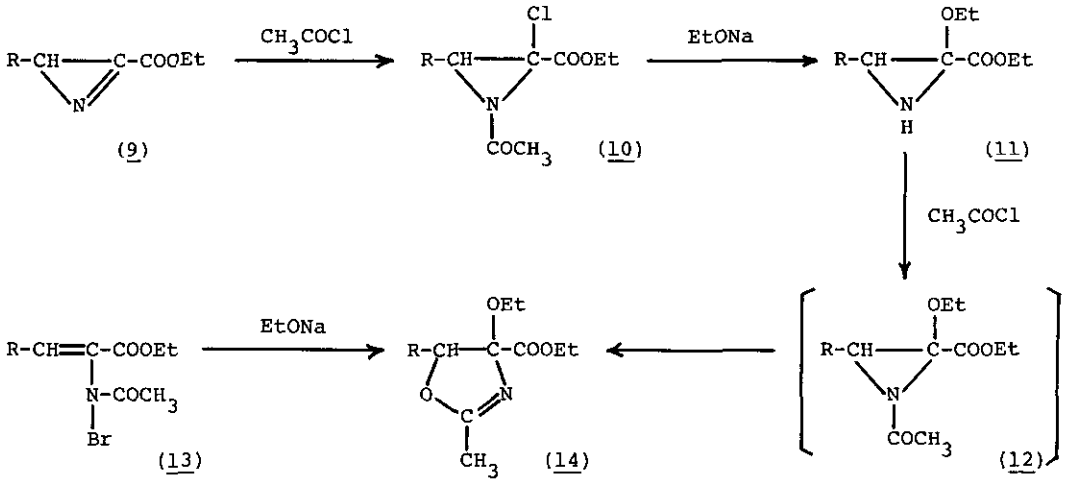
derivative. In order to determine the presumed structure, 2-alkyl-2-ethoxycarbonyl-2H-azirine (9)[6] was subjected to the independent preparation of the alkoxyaziridine and/or the alkoxyoxazoline derivative.

Treatment of 9 (20 mmol) with CH_3COCl (40 mmol) in benzene (30 ml) by the usual way gave the desired 1-acetyl-3-alkyl-2-ethoxycarbonyl-2-chloroaziridine (10). Subsequently, for example, deacetylation of 3-isopropyl derivative (10d: 10 mmol) with an equimolar EtONa in EtOH (10 ml) at room temperature gave the expected 2-ethoxy-2-ethoxycarbonyl-3-isopropylaziridine [11: yield 91%, colorless syrup. IR (KBr): 3260 (NH), 1740 (COOEt) cm^{-1}. NMR ($CDCl_3$): δ 1.70 (1H, br s, NH), 2.13 (1H, d, J=9.0Hz, ring proton)]. Reacetylation of 11 (10 mmol) with CH_3COCl (12 mmol) in ethyl ether (200 ml) gave a colorless syrup, which was in complete agreement with the product (14) derived directly from ethyl 2-(N-bromoacetyl)amino-4-methyl-2-pentenoate (13)[7] and EtONa.

In the IR spectra of 10 and 11, the disappearance of C=N absorption band at 1755 cm^{-1} in 9 and the appearance of acetyl carbonyl band at 1730 cm^{-1} in 10 suggest the formation of addition product. Furthermore, the appearance of NH band at 3260 cm^{-1} in 11 also indicates the deacetylated structure. In the NMR spectrum, because the ring proton signals appeared at considerably higher magnetic field (at δ 2.67 and δ 2.13), the aziridine ring of 10 and 11 was found to be retained during the addition and the subsequent deacetylation reactions.

On the other hand, in the IR and NMR spectra of 14, the appearance of C=N band at 1695 cm^{-1} and that of the ring proton resonating at comparatively lower (at δ 3.85) are consistent with the structure of the large-membered compound such as the oxazoline derivative. Therefore, the syrup (14) obtained from the two

routes could be determined as 4-ethoxy-4-ethoxycarbonyl-5-isopropyl-2-methyl-oxazoline [Yield 52% from 11 and 78% from 13. IR (KBr): 1760 (COOEt), 1695 (C=N) cm^{-1}. NMR ($CDCl_3$): δ 3.85 (1H, double d, J=2.0Hz, ring proton)].



Scheme 2 a; R=CH_3, b; R=C_2H_5, c; R=n-C_3H_7, d; R=i-C_3H_7

Table 1. 1-Acetyl-3-alkyl-2-ethoxycarbonyl-2-chloroaziridine (10)

Compound[a] No.	Yield/%	IR, cm^{-1} (KBr)		NMR, δ ($CDCl_3$)	
		COOEt	$COCH_3$	3-H (J_{Hz})	$COCH_3$
10a	79	1755,	1730	3.02 (q, 6.0),	2.27
10b	83	1758,	1730	2.92 (t, 7.0),	2.27
10c	82	1760,	1730	2.95 (t, 7.5),	2.27
10d	72	1760,	1730	2.67 (d, 9.0),	2.23

a) Colorless syrup.

Consequently, from the spectroscopic data (see Table 2) and the satisfactory results in elemental analysis, the products obtained from both 1 and 4 could be confirmed unambiguously as 5-alkyl-4-alkoxy-4-t-butoxycarbonyl-2-methyloxazoline (5-8). The compounds were found to be a mixture of cis and trans isomers, but the geometry of each isomer could not be assigned.

It is interesting that the oxazoline derivative introduced an alkoxy or hydroxyl group to the same carbon atom attaching an alkoxycarbonyl group is able to prepare readily from 1 and alcohol in one-pot. Moreover, surprizingly, 10 and 11 could be isolated stably, since the activated aziridine (N-acetylated) is further labilized in the presence of base or by heating. In fact, attempt to

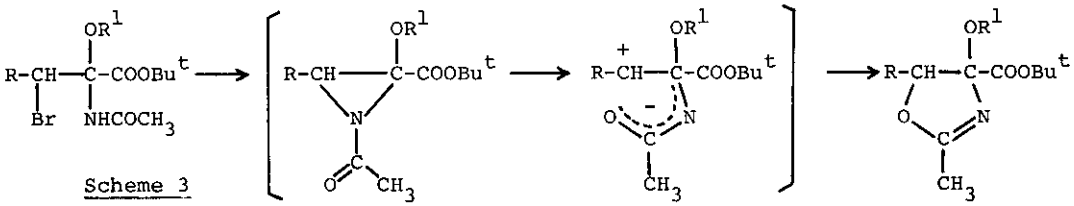
Table 2. 5-Alkyl-4-alkoxy-4-t-butoxycarbonyl-2-methyloxazoline (5-8)

Compound No.	Yield/% A[a]	Yield/% B[b]	Bp °C/mmHg (Mp °C)	IR, cm^{-1} (KBr) C=N	NMR, δ ($CDCl_3$) 5-H (J_{Hz})
5a	96	81	67-68/2	1670	4.53 (q, 7.0), 4.45 (7.0)
5b	66	91	72-73/1	1665	4.24 (dd, 6.0,7.0), 4.23 (5.0,9.0)
6a	63	84	69-70/1	1665	4.53 (q, 7.0), 4.47 (7.0)
6b	48	95	78-79/1	1670	4.25 (dd, 6.0,8.0), 4.23 (4.5,9.5)
7a	72	85	(58-59)[c]	1670	4.64 (q, 6.5), 4.58 (6.5)
7b	60	71	(67-68)[c]	1670	4.36 (dd, 6.0,7.5), 4.31 (5.0,8.5)
8a	52	91	78-80/1	1660	4.56 (q, 6.5), 4.50 (6.5)
8b	74	83	81-83/1	1665	d)

a) Yield from 1 and RONa. b) Yield from 4 and $NaNH_2$. c) Colorless prisms from petroleum ether. d) Overlapped with allyl protons.

isolate 12 by the reacetylation of 11 was unsuccessful and only 14 was obtained.

In conclusion, the formation mechanism of 14 from 11 was supposed that 11 was acetylated, followed by the ring cleavage of the resulting 12 and immediate re-cyclization. From the result, the transformation of 4 to 5-8 was also supposed that activated aziridine formed initially by the dehydrobromination of 4, followed by the ring expansion, as is illustrated in Scheme 3.



Scheme 3

References

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