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SYNTHESIS OF 5-ALKYNYLIDENE-OXAZOLIDIN-2-ONES[1a]

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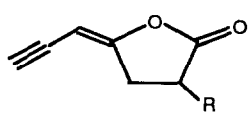
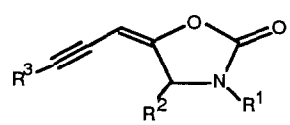
Abstract: N-carboethoxy-N-alkyl-propargylamines react with iodine, silver tetrafluoroborate and 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride to give N-alkyl-5(E)-iodomethylidene-oxazolidin-2-ones which can be converted to the corresponding 5-alkynylidene-oxazolidin-2-ones by palladium chloride catalyzed coupling with alkynes.

The importance of human leukocyte elastase (HLE) as an agent in a variety of disease states has stimulated interest in the design and synthesis of potent synthetic inhibitors of this enzyme[2]. In earlier reports[3], we described the preparation of a series of ynenol-lactones (1) that were shown to be potent, mechanism based inhibitors of HLE. We were therefore interested in assessing the biological activity of a series of 3-aza-analogs of (1), the 5-alkynylidene-oxazolidin-2-ones (2).



(1)

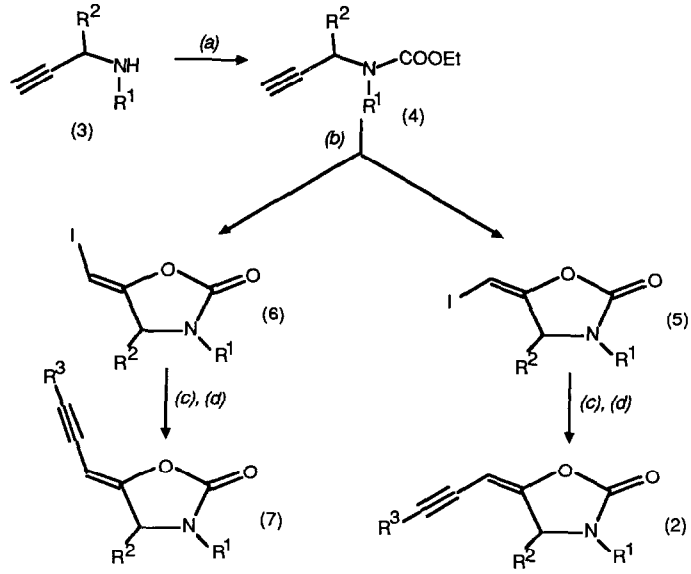


(2)

The synthesis of 5-alkynylidene-oxazolidin-2-one (2) is shown in Scheme I. Reaction of propargylamine (3) with ethyl chloroformate in the presence of sodium bicarbonate in chloroform at 25°C afforded the urethane (4). Compound (4) reacted with iodine, silver tetrafluoroborate and EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride) in methylene chloride at 25°C to give a mixture of two isomers (5) and (6). In all cases studied, the E-isomer (5) was formed as the major product. The Z-isomer accounted for less than 10% of the product. Compound (5) was converted to a mixture of (5) and (6) (approx. 95 : 5) under the conditions employed to effect the cyclization.

To our knowledge, the halo-cyclization of propargyl carbamates is unprecedented[4]. In the $I_2/AgBF_4$/EDCI cyclization of (4) to (5), all three reagents are essential for optimal yields. The $I_2/AgBF_4$ pair alone gave poor yields of (5), along with other decomposition products. The EDCI serves as a water scavenger in this reaction. Other conditions such as I_2, $I_2/AgBF_4$/DCC, I_2/EDCI also effect the halo-cyclization of (4) to (5), but the yield of (5) is slightly lower under these conditions.

Scheme I



(a) EtOCOCl, Na_2CO_3, $CHCl_3$; (b) I_2, $AgBF_4$, EDCI, CH_2Cl_2; (c) $PdCl_2(Ph_3P)_2$, CuI, R^3-C≡CH, Et_3N; (d) AgN KCN/H_2O.

Table I

no.	R^1	R^2	R^3	mp (°C)	% yield [(b), (c), (d)]
(2a)	Me	H	Bu	oil	52, 44
(2b)	Me	H	Ph	105-106	52, 37
(2c)	Me	H	H	110-111	52, 80, 76
(2d)	Me	Me	H	53-54	69, 81, 28
(2e)	i-Bu	H	H	43-44	52, 92, 81
(2f)	$PhCH_2$	H	H	124-125	75, 80, 82
(2g)	Ph	H	H	95-96	52, 88, 77
(2h)	p-NO_2-Ph	H	H	167-168	50, 67, 60
(2i)	p-Cl-Ph	H	H	110-111	57, 87, 31
(7a)	$PhCH_2$	H	H	105-106	5, 83, 63
(7b)	Me	H	H	122-123	5, 71, 52

The oxazolidin-2-ones (2) were obtained by condensing the appropriate terminal alkynes with the requisite iodo-ene derivatives (5) in the presence of $PdCl_2(Ph_3P)_2$/CuI in triethylamine[5]. Desilylation of the 5-alkynylidene-oxazolidin-2-ones (R^3 = trimethylsilyl) to the unsubstituted acetylenes was achieved with silver nitrate and potassium cyanide[6]. The results are summarized in Table 1.

In accord with the comparatively low reactivity of the carbonyl group in compounds (2) and (7), these compounds are 40,000 times more stable to alkaline hydrolysis than are the ynenol-lactones (1). The biochemical study of these compounds will be reported separately.

The following procedure is illustrative for the halo-cyclization of propargyl carbamate (3) to oxazolidin-2-ones (5) and (6): A solution of N-carboethoxy-N-benzyl-propargylamine (2.01 g, 9.2 mmol) in methylene chloride (35 ml) was added to a suspension of iodine (3.6 g, 28.3 mmol), EDCI (1.8 g, 9.42 mmol) and silver tetrafluoroborate (1.83 g, 9.86 mmol) in methylene chloride at 0°C under argon. The reaction mixture was stirred at 0°C for 6 h and then at room temperature for 16 h. The suspension was worked up by washing with 5% sodium thiosulphate solution (3 x 50 ml), saturated brine solution (50 ml) and water (50 ml). The organic extract was dried over magnesium sulphate and evaporated to give a yellow solid (3.3 gm) which was chromatographed on silica gel (2-5% ethyl acetate : pet. ether) to give N-benzyl-5(E)-iodomethylidene-oxazolidin-2-one (5f) (1.5 g, 75%) and N-benzyl-5(Z)-iodomethylidene-oxazolidin-2-one (6f) (0.5 g, 5%).

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7. All compounds have been characterized by nuclear magnetic resonance (80 MHz), infra-red and mass spectral data or elemental analysis. Selective physical data are as follows: (2a) N-methyl-5(E)-(2-propynylidene)-oxazolidin-2-one, H-NMR ($CDCl_3$): 2.98 (s, 3H, NMe); 3.11 (dt, 1 H, CCH); 4.32 (dd, 2 H, H4, $J_{CCH,H4}$ = 0.86, $J_{C=CH,H4}$ = 2.77); 5.27 (dt [apparent q], 1 H, C=CH, $J_{C=CH,CCH}$ = 2.77). Anal. calc. for $C_7H_7NO_2$: C, 61.13; H, 5.15; N, 10.21. Found: C, 61.23; H, 5.31; N, 10.26. (2f) N-benzyl-5(E)-(2-propynylidene)-oxazolidin-2-one, H-NMR ($CDCl_3$): 3.03 (dt, 1 H, CCH); 4.17 (dd, 2 H, H4, $J_{CCH,H4}$ = 0.8, $J_{C=CH,H4}$ = 2.76); 4.50 (s, 2 H, $PhCH_2$); 5.28 (dt [apparent q], 1 H, C=CH, $J_{C=CH,CCH}$ = 2.76); 7.4 (m, 5 H, ArH). IR: 3278, 1778, 1665 cm^{-1}. Anal. calc. for $C_{13}H_{11}NO_2$: C, 72.23; H, 5.20; N, 6.57. Found: C, 73.26; H, 5.00; N, 6.36. (2g) N-phenyl-5(E)-(2-propynylidene)-oxazolidin-2-one, H-NMR ($CDCl_3$): 3.18 (dt, 1H, CCH); 4.79 (dd, 2 H, H4, $J_{CCH,H4}$ = 0.8, $J_{C=CH,H4}$ = 2.7); 5.38 (dt [apparent q], 1 H, C=CH, $J_{C=CH,CCH}$ = 2.7); 7.40 (m, 5 H, ArH). Anal. calc. for $C_{12}H_9NO_2$: C, 72.35; H, 4.55; N, 7.03. Found: C, 71.77; H, 4.59; N, 6.96. IR: 3302, 2102, 1770 cm^{-1}. (7f) N-methyl-5(Z)-(2-propynylidene)-oxazolidin-2-one, H-NMR ($CDCl_3$): 2.96 (s, 3 H, NMe); 3.14 (dt, 1 H, CCH), 4.24 (dd, 2 H, H4, $J_{CCH,H4}$ = 0.97, $J_{C=CH,H4}$ = 2.25); 4.80 (dt [apparent q], 1 H, C=CH, $J_{C=CH,CCH}$ = 2.25). Anal. calc. for $C_7H_7NO_2$: C, 61.13; H, 5.15; N, 10.21. Found: C, 61.38; H, 5.17; N, 10.46.

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