Stereospecific Syntheses of (*Z*)- and (*E*)-4-Bromomethylene-5,5-Dimethyl-3-Phenyloxazolidin-2-one

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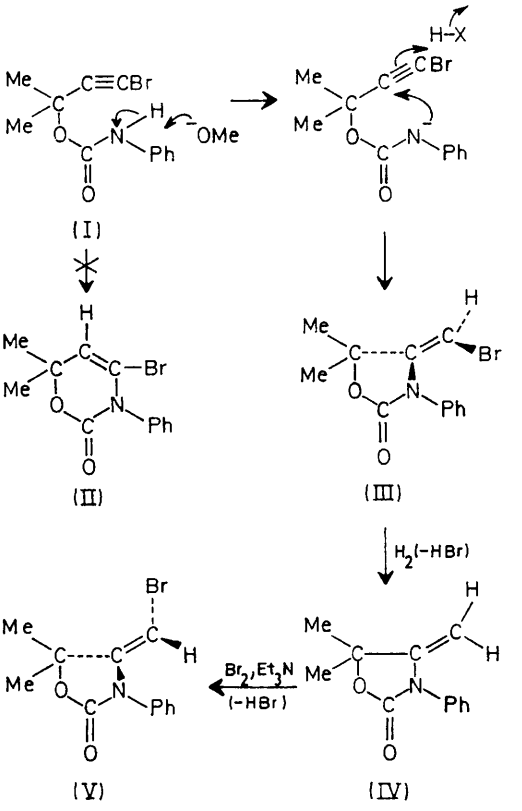
3-Bromo-1,1-dimethylprop-2-ynyl carbanilate undergoes base-catalysed cyclisation to give (*Z*)-4-bromomethylene-5,5-dimethyl-3-phenyloxazolidin-2-one. Bromination of 5,5-dimethyl-4-methylene-3-phenyloxazolidin-2-one, followed by dehydrobromination, gives the *E*-isomer. The stereoisomers have been characterised by n.m.r. spectroscopy. The stereospecificity of each reaction is rationalised in mechanistic terms.

THE base-catalysed cyclisation of prop-2-ynyl carbanilates to 4-methyleneoxazolidin-2-ones is well established.[1-5] We now report stereospecific syntheses of (*Z*)- and (*E*)-4-bromomethylene-5,5-dimethyl-3-phenyloxazolidin-2-one.

Halogenoacetylenes normally react with secondary amine nucleophiles at the terminal acetylenic carbon atom bearing the halogen atom. For instance, 1-bromo-2-phenylacetylene reacts with diethylamine to give 1,1-bisdiethylamino-2-phenylethylene.[6] Similarly alk-1-ynamines have been prepared from 1-chloroacetylenes and secondary amines.[7] Thus, intramolecular cyclisation of 3-bromo-1,1-dimethylprop-2-ynyl carbanilate (I) might be expected to give the oxazin-2-one (II). However, this would be unlikely on stereochemical grounds in view of the linearity of the acetylene function. The reaction of compound (I) (or alternatively of 4-bromo-2-methylbut-3-yn-2-ol [8] with phenyl isocyanate) in the presence of a catalytic amount of sodium methoxide, in fact, gives a crystalline product showing ν_{CO} 1 770 cm^{-1}, indicating the oxazolidin-2-one structure (III) rather than the oxazin-2-one structure (II) which would be expected to show ν_{CO} *ca.* 1 690 cm^{-1}.[9,10] Hydrogenolysis of the product over Adams catalyst gave the 4-methylene derivative (IV), identical with a sample prepared by an alternative method.[2]

Bromination of compound (IV), followed by dehydrobromination with triethylamine, gave the stereoisomeric bromo-derivative (V) which was a crystalline solid, lower melting than (III), showing ν_{CO} 1 775 cm^{-1}. Each stereoisomer gave an n.m.r. signal for =CHBr at τ 4.9.

The geometry of the C=C bond in the stereoisomers (III) and (V) was assigned by n.m.r. spectra. Irradiation at the frequencies corresponding to the 2- and 6-protons of the phenyl group and to the methyl protons of (III) and (V) caused appropriate nuclear Overhauser enhancements of the =CHBr signal. In the case of (III), no enhancement was observed on irradiation at the phenyl 2- and 6-proton frequency, whereas (V) showed an enhancement of 26% under the same conditions. However, irradiation at the methyl frequency of (III) gave an enhancement of 42% as compared with only 5% for (V). These results agree with the assigned stereochemistry.



Addition of tris-(1,1,1,2,2,3,3-heptafluoro-7,7-di[$^2H_3$]-methyloctane-4,6-dionato)europium [Eu(fod)$_3$] resulted in the shifts listed in Table 1. The results suggest that the position of association in (III) and (V) is the same and similar to that in (IV) (in which the smaller shifts are probably due to reduced steric hindrance). Thus it can be inferred that the site of association is close to the carbonyl group and that the exocyclic methylene proton in (III) is closer to the *gem*-dimethyl group than the phenyl group, whereas in (V) the reverse is true.

The formation of the *Z*-isomer (III) may be rationalised in terms of deprotonation of the carbanilate nitrogen atom by sodium methoxide, followed by addition of the

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nitrogen nucleophile to the internal acetylenic carbon atom with concomitant abstraction of a proton from the medium. The *E*-isomer may be formed as a result of β-elimination of hydrogen bromide from the conformer which leads to the least hindered and thermodynamically more favoured isomer.

TABLE 1

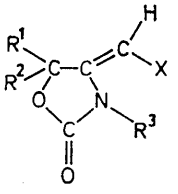
Lanthanide-induced shifts * for compounds (III)—(V)

Compd.	Phenyl 2- and 6-H	CMe_2	=CH
(III)	5.75	8.2	8.2
(IV)	4.9	7.85	7.85 and 7.3
(V)	5.8	8.2	7.15

* Values in p.p.m. obtained by extrapolating the tangent to the chemical shift *vs.* $Eu(fod)_3$ molar ratio curve at zero $[Eu(fod)_3]$ to a 1 : 1 molar ratio.

TABLE 2

(*Z*)-5,5-Dialkyl-3-aryl-4-halogenomethyleneoxazolidin-2-ones

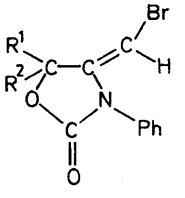


(VI)

R^1	R^2	R^3	X	Yield (%)	M.p. (°C)
Me	Me	Ph	Br	88	155
Me	Me	*m*-ClC_6H_4	Br	80	158
Me	Et	Ph	Br	85	134
Me	Et	*m*-ClC_6H_4	Br	75	143
Me	Et	Ph	Cl	59	138
Me	Et	3,4-$Cl_2C_6H_3$	Cl	86	142
Me	Bu^t	Ph	Br	80	85
$[CH_2]_5$		Ph	Cl	78	188
$[CH_2]_5$		Ph	Br	72	158
$[CH_2]_5$		Ph	I	70	179

TABLE 3

(*E*)-5,5-Dialkyl-4-bromomethylene-3-phenyloxazolidin-2-ones



(VII)

R^1	R^2	Yield (%)	M.p. (°C)
Me	Me	74	121
Me	Et	70	72
$[CH_2]_5$		68	124

The foregoing stereospecific reactions are quite general, and have been used to obtain several (*Z*)- or (*E*)-5,5-dialkyl-4-bromomethylene-3-phenyloxazolidin-2-ones (see Tables 2 and 3). Furthermore, (*Z*)-5,5-dialkyl-3-aryl-4-halogenomethyleneoxazolidin-2-ones have been prepared from 3-chloro-, 3-bromo-, and 3-iodo-1,1-dialkylprop-2-yn-1-ols and aryl isocyanates (see Table 2). This is apparently the first reported example of a base-catalysed cyclisation involving addition of a nitrogen nucleophile to a halogenoacetylene at the carbon atom β to the halogen atom.

EXPERIMENTAL

Unless otherwise stated, cyclohexane was used as solvent and sodium methoxide as catalyst. I.r. spectra were determined for Nujol mulls with a Perkin-Elmer Infracord spectrometer, and n.m.r. spectra for solutions in carbon tetrachloride with tetramethylsilane as internal standard, with a JEOL MH100 spectrometer. M.p.s were determined with a Kofler hot-stage apparatus. The following preparations of compounds (III) and (V) illustrate the general methods used. Details of the products listed in Tables 2 and 3 are available as Supplementary Publication No. SUP 21392 (5 pp.).†

(Z)-4-*Bromomethylene-5,5-dimethyl-3-phenyloxazolidin-2-one* (III).—(*a*) To 3-bromo-1,1-dimethylprop-2-ynyl carbanilate (14.0 g, 0.05 mol) in cyclohexane (75 ml) was added sodium methoxide (0.03 g). The mixture was stirred at 45—55 °C for 1 h and then allowed to cool to room temperature. The precipitate was filtered off and recrystallised from ethanol to give a product (12.3 g, 88%) identical (m.p., mixed m.p., and i.r. and n.m.r. spectra) with that obtained by method (*b*).

(*b*) To 4-bromo-2-methylbut-3-yn-2-ol [8] (16.3 g, 0.1 mol) in cyclohexane (125 ml) was added sodium methoxide (0.05 g). Phenyl isocyanate (12.0 g, 0.1 mol) was then added dropwise with stirring at such a rate as to maintain the reaction temperature at 45—55 °C. The mixture was allowed to cool to room temperature and stirred for 1 h. The precipitate was filtered off and recrystallised from ethanol to yield *prisms* (21.0 g, 75%), m.p. 155° (Found: C, 50.9; H, 4.3; Br, 28.1; N, 5.0. $C_{12}H_{12}BrNO_2$ requires C, 51.05; H, 4.3; Br, 28.3; N, 4.95%); $\nu_{max.}$ 3 080, 1 770, 1 650, and 1 590 cm^{-1}; τ 2.64 (5 H, s), 4.94 (1 H, s), and 8.42 (6 H, s). The product (1.4 g, 0.05 mol) in methanol (100 ml) with Adams platinum catalyst (0.05 g) absorbed 105.8 ml of hydrogen at 20 °C and 758 mmHg in 45 min to give, after filtration and evaporation, a solid (0.8 g) identical (i.r. spectrum, m.p., and mixed m.p.) with authentic 5,5-dimethyl-4-methylene-3-phenyloxazolidin-2-one.[2]

(E)-4-*Bromomethylene-5,5-dimethyl-3-phenyloxazolidin-2-one* (V).—To a solution of 5,5-dimethyl-4-methylene-3-phenyloxazolidin-2-one [2] (18.9 g, 0.1 mol) in carbon tetrachloride (200 ml) was added a solution of bromine (16.0 g, 0.1 mol) in carbon tetrachloride (50 ml) dropwise with stirring during 1.25 h at 0—10 °C. The solution was then stirred for a further 2 h at room temperature. Triethylamine (25.0 g) was then added during 10 min and stirring was continued for another 2 h at 25—35 °C. The precipitated triethylammonium bromide was filtered off and the filtrate evaporated *in vacuo*. Recrystallisation of the residue from aqueous ethanol yielded *plates* (21.70 g, 74%), m.p. 121° (Found: C, 51.1; H, 4.35; Br, 28.5; N, 5.0%); $\nu_{max.}$ 3 080, 1 755, 1 660, and 1 598 cm^{-1}; τ 2.60 (5 H, m), 4.88 (1 H, s), and 8.20 (6 H, s).

The product (1.4 g, 0.05 mol) in methanol (100 ml) with Adams platinum catalyst (0.05 g) absorbed 107.2 ml of hydrogen at 20 °C and 758 mmHg in 45 min to give, after filtration and evaporation, a solid (0.7 g) identical (i.r.

† For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1974, Index issue.

spectrum, m.p., and mixed m.p.) with authentic 5,5-dimethyl-4-methylene-3-phenyloxazolidin-2-one.[2]

3-Bromo-1,1-dimethylprop-2-ynyl Carbanilate (I).—To 4-bromo-2-methylbut-3-yn-2-ol (16.3 g, 0.1 mol) in cyclohexane (125 ml) was added phenyl isocyanate (12.0 g, 0.1 mol) followed by 3 drops of triethylamine, and the mixture was left at room temperature for 6 h. Evaporation under reduced pressure and recrystallisation of the residue from light petroleum (b.p. 60—80°) gave a crystalline *solid* (26.5 g, 94%), m.p. 95° (Found: C, 51.1; H, 4.4; Br, 28.05; N, 4.4. $C_{12}H_{12}BrNO_2$ requires C, 51.05; H, 4.3; Br, 28.3; N, 4.95%); $\nu_{max.}$ 3 370, 1 730, 1 620, and 1 540 cm^{-1}.

Nuclear Overhauser Effect Measurements.—A solution of the compound (5×10^{-4} mol) in carbon disulphide (0.5 ml) containing 2% v/v dimethylformamide and 1% tetramethylsilane was degassed by freezing in liquid nitrogen, evacuating the tube to 0.1 mmHg, isolating the tube from the vacuum pump, and allowing the sample to thaw to room temperature. This cycle was repeated four times and the sample finally sealed under vacuum. The dimethylformamide served to aid dissolution of the compound and to act as measure of the suitability of the solution for n.O.e. measurements by comparison of the enhancement obtained for the formyl proton signal in each sample when the low field methyl signal was irradiated. In all cases the enhancement was taken as the percentage increase of the average of seven integral traces obtained with irradiation at τ 10. For both compounds (III) and (V) the integral of the =CHBr signal was measured while irradiating first at τ 10, then at the CMe_2 singlet frequency, and finally at the frequency corresponding to the centre of the double doublet assigned to the phenyl 2- and 6-protons. The enhancement found for the formyl proton of dimethylformamide in the solutions of (III) and (V) was 25% in each case.

Use of the Paramagnetic Shift Reagents.—To a solution of the compound (5×10^{-4} mol) in carbon tetrachloride (0.5 ml), weighed amounts of $Eu(fod)_3$ were added, and after each addition the n.m.r. spectrum was recorded. Ten such additions were made up to 1 : 1 molar ratio of shift reagent to compound. Chemical shifts were plotted against the molar ratio of shift reagent to compound. For each curve the tangent at zero concentration of shift reagent was extrapolated to a 1 : 1 molar ratio to give an induced shift value.

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