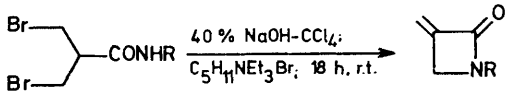
Synthesis of α-Methylene-β-lactams

By Stephen R. Fletcher and I. Trevor Kay*
(*I.C.I. Plant Protection Division, Jealott's Hill, Bracknell, Berkshire* RG12 6EY)

Summary The phase-transfer catalysed cyclisation of 3-bromo-2-bromomethylpropionamides provides a simple synthesis of α-methylene-β-lactams.

The biological activity of natural products containing α-methylenelactone structures[1] is probably dependent upon the addition of nucleophiles to their activated methylene

groups.[2] We wished to obtain for biological screening other heterocycles containing similar activated methylene groups, and amongst the structures we sought were α-methylene-β-lactams. The only reported routes to these compounds are by the cycloaddition of chlorosulphonyl isocyanate and allenes,[3] or by the thermolysis of 3-methyl-3-phenylsulphinyl-β-lactams.[4] The first method suffers the disadvantage that it gives only 1-unsubstituted methylenelactams (in low yield), and the second approach is lengthy and requires vigorous (200 °C) conditions for the final elimination step. We now describe a versatile and simple procedure for the preparation of the α-methylene-β-lactams (**2**).



(1) (2)

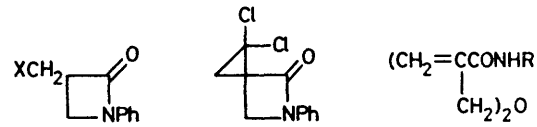
Our approach was based upon the readily obtainable[5] 3-bromo-2-bromomethylpropionic acid. This was converted ($SOCl_2$) into its acid chloride, and thence into the amides (**1**). Cyclisation of the *N*-arylamides (**1**; R = aryl) using an excess of 40% NaOH and CCl_4 with a trace of pentyltriethylammonium bromide under phase-transfer conditions[6] (18 h; room temp.) gave high yields of the stable crystalline 1-aryl-methylenelactams (**2**; R = aryl). The yields given for a variety of aryl substituents (Table) show that the method is not unduly constrained by electronic or steric factors. A typical member of the series (**2**; R=Ph) had $\nu_{C=O}$ (Nujol) 1740 cm^{-1}, τ($CDCl_3$) 2·7 (5H, m), 4·15 (1H, m), 4·7 (1H, m), and 5·9 (2H, m).

TABLE. Preparation of the α-methylene-β-lactams (**2**)[a]

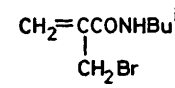
R	M.p. (*t*/°C)	Yield (%)
Ph	61—63	86
p-$MeOC_6H_4$	105—107	96
p-$O_2NC_6H_4$	150—151	83
oo'-$Cl_2C_6H_3$	79—80	78
mp-$Cl_2C_6H_3$	128—129	92
oo'p-$Br_3C_6H_2$	67—68	82
oo'-$Me_2C_6H_3$	62—63	92
p-NCC_6H_4	70—71	76
Et	Oil[b]	18
Bu^i	Oil[c]	56
Cyclohexyl	Oil[d]	40

[a] All products gave satisfactory elemental analyses. [b] n_D^{20} 1·4826. [c] n_D^{20} 1·4757. [d] n_D^{20} 1·5106.

For the amide (**1**; R=Ph), a reduction in the reaction time to 30 min gave (65%) the bromomethyl-lactam (**3**; X=Br, m.p. 102—103 °C), together with a small quantity of the methylenelactam (**2**; R=Ph). The bromomethyl-lactam was readily dehydrobrominated (18 h) to the methylenelactam using the same phase-transfer conditions.



(3) (4) (5)



(6)

The replacement of CCl_4 with CH_2Cl_2 in the phase-transfer reaction caused no change in yield of the products, but the use of $CHCl_3$ as a solvent caused complications. Thus, after a more prolonged reaction time (72 h), the amide (**1**; R=Ph) gave (48%) the spirolactam (**4**; m.p. 150—152 °C) formed by further reaction of the methylenelactam with dichlorocarbene.

The cyclisation of the *N*-alkylamides (**1**; R=alkyl) was more complex. Yields of 1-alkyl-methylenelactams were lower and ethers (**5**) were formed as by-products. In contrast to the *N*-phenylamide, work-up of the reaction using *N*-isobutylamide (**1**; R=Bu^i) after 1 h gave, besides starting material, a mixture of the methylenelactam (**2**; R=Bu^i) and the bromomethylacrylamide (**6**; m.p. 67—68 °C). Further reaction of this acrylamide under the phase-transfer conditions (18 h) showed it to be a precursor of the methylenelactam (**2**; R=Bu^i). The oily 1-alkyl-methylenelactams, on storing at room temperature, slowly (*ca.* 1 week) polymerised as evidenced by an increase in viscosity and a disappearance (^1H n.m.r.) of the methylene protons. The unsubstituted amide (**1**; R=H) failed to give a lactam on attempted cyclisation.

As electrophiles the methylenelactams showed a marked and surprising selectivity. Thus (**2**; R=Ph) rapidly formed adducts (**3**; X=NMe_2, SEt) with dimethylamine and ethanethiol at room temperature, but failed to react with methylamine or ammonia under these conditions.

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