New Synthesis of β-Lactams

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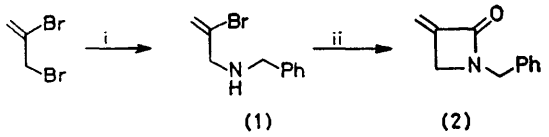
Summary The insertion of carbon monoxide into various 2-bromo-3-aminopropene derivatives, (**1**) and (**7**—**11**) in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 gave the corresponding α-methylene-β-lactams (**2**) and (**12**—**16**) in fairly good yields.

THE development of β-lactam antibiotics prompted various methods for synthesising β-lactams, including [2+2] cycloadditions, intramolecular cyclization, ring contraction of five-membered rings, and ring expansion of three-membered rings.[1] However, a synthesis which can be represented as [N–C–C + C=O] has not been described.[2] We now report a new synthesis of β-lactams according to this scheme as an extension of lactam synthesis by the use of organometallic complexes.[3]

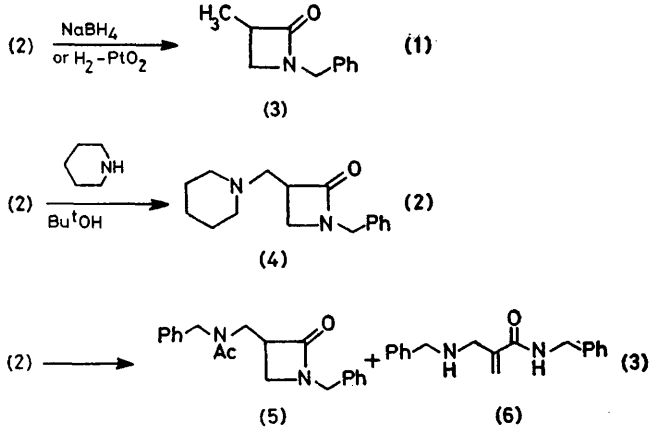
A typical procedure is as follows. 2-Bromo-3-(*N*-benzyl)-aminopropene (**1**, 5·16 mmol) (which was prepared from 2,3-dibromopropene, benzylamine, and potassium carbonate) and Bu^n_3N (6·45 mmol) in hexamethylphosphoramide (HMPA) were stirred at 100 °C under CO (1 atm) with a catalytic amount of $Pd(OAc)_2$ (0·1 mmol) and PPh_3 (0·4 mmol) for 5 h to afford the *N*-benzyl-α-methylene-β-lactam (**2**) [m.p. 32 °C (from ether), 66·9% yield] (Scheme). The spectral data [$\nu_{C=O}(CHCl_3)$ 1740 cm^{-1}; δ ($CDCl_3$) 3·65 (2H, t, *J* 1 Hz, $-CH_2-N-CH_2Ph$), 4·54 (2H, s, $-N-CH_2-Ph$), and 5·17 and 5·75 (both 1H, dd, *J* 1 and 3 Hz, vinyl H); *m/e* 173 (M^+) and 133] and elemental analysis



SCHEME. i, $PhCH_2NH_2$, K_2CO_3; ii, CO, Pd catalyst, PPh_3, Bu^n_3N–HMPA.

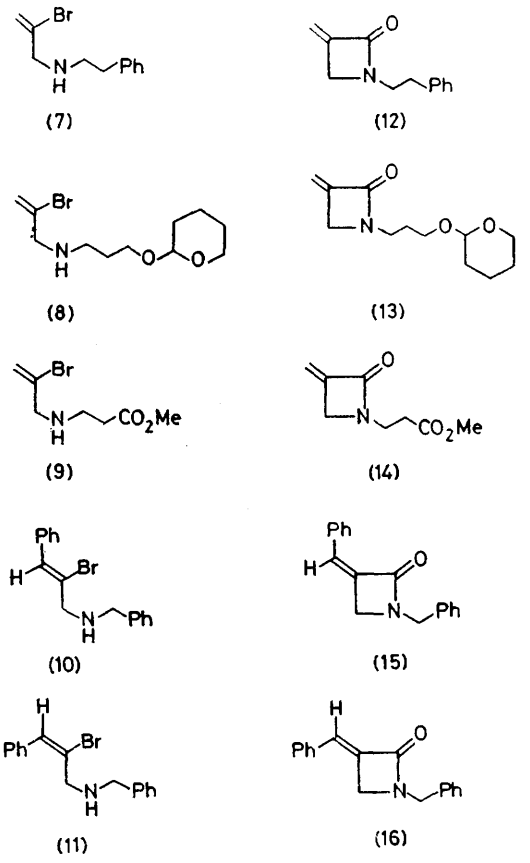
supported this assignment. The use of 0·5 mol% of $Pd(OAc)_2$ as catalyst gives (**2**) in 53·3% yield. $Pd(acac)_2$ may be used instead of $Pd(OAc)_2$ with similar results.

In confirmation of these results, (**2**) was reduced with sodium borohydride in EtOH–tetrahydrofuran (THF) to afford the *N*-benzyl-α-methyl-β-lactam (**3**), [61·3% yield, $\nu_{C=O}$ (neat) 1740 cm^{-1}], which was also obtained by hydrogenation of (**2**) with PtO_2 in THF–EtOH in 86·3% yield (equation 1). The Michael addition of piperidine to the



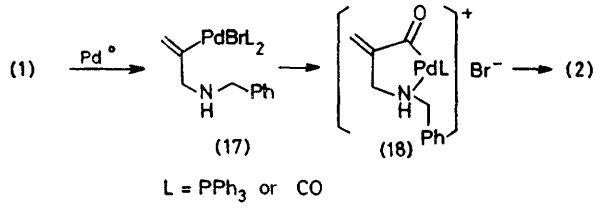
β-lactam (**2**) in Bu^tOH proceeded slowly at room temperature to afford compound (**4**) [46·6% yield, $\nu_{C=O}$ (neat) 1740 cm^{-1}] (equation 2). On addition of benzylamine and after standing at room temperature for one week, followed by acetylation, (**2**) gave only a small amount of the desired product (**5**) (6·8% yield) and the cleaved compound (**6**) (12·6% yield) (equation 3).

This method has been further extended to syntheses of *N*-substituted α-methylene-β-lactams (**12**)—(**14**) from the corresponding 2-bromo-3-aminopropenes (**7**)—(**9**) in 61·9, 62·9, and 37·6% yields, respectively to confirm its broad applicability. Substrates (**10**) and (**11**) were synthesized from styrene in five steps.† The insertion of carbon monoxide into the *Z*-isomer (**10**) was successfully carried out as before to afford *Z*-α-benzylidene-*N*-benzyl-β-lactam (**15**) [75·9%; m.p. 67—67·5 °C (from hexane–ether); $\nu_{C=O}$ (Nujol) 1730 cm^{-1}; δ ($CDCl_3$) 6·19 (1H, s, vinyl H); *m/e* 249(M^+)]. The *E*-isomer (**11**) afforded the *E*-α-benzylidene-β-lactam (**16**) [89·5%; m.p. 140·5—141 °C (from ether); $\nu_{C=O}$ (Nujol) 1730 cm^{-1}; δ ($CDCl_3$) 6·99 (1H, s, vinyl H); *m/e* 249(M^+)]. These results demonstrate that



an olefinic compound like styrene can be easily converted into a vinyl halide bearing an aminomethyl group at the halogeno position, which should be a useful precursor for the synthesis of substituted α-methylene-β-lactams by the present method.

The key intermediate of this reaction is assumed to be an acylpalladium complex (**18**), which may be generated from the vinylpalladium complex (**17**) co-ordinated to carbon



monoxide. α-Methylene-β-lactams should be important in the search for biologically active substances in this series,[4] and an extension of this method is being investigated.

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† The details of the synthesis of the compounds (**10**) and (**11**) from styrene will be described in full papers.

[1] A. K. Mukerjee and R. C. Srivastava, *Synthesis*, 1973, 327; A. K. Mukerjee and A. K. Singh, *Tetrahedron*, 1978, 1731.

[2] A new synthetic method for β-lactams using $Fe(CO)_5$ has been reported in which the carbon monoxide of $Fe(CO)_5$ reacted with the internal amino group of the ammonium salt: P. K. Wong, M. Madhavarao, D. F. Marten, and M. Rosenblum, *J. Amer. Chem. Soc.*, 1977, **99**, 2823.

[3] M. Mori, K. Chiba, and Y. Ban, *J. Org. Chem.*, 1978, **43**, 1684.

[4] Syntheses of α-methylene-β-lactams by other methods have been reported recently: S. R. Fletcher and I. T. Kay, *J.C.S. Chem. Comm.*, 1978, 903; T. Minami, M. Ishida, and T. Agawa, *ibid.*, p. 12; E. J. Moriconi and J. F. Kelly, *J. Amer. Chem. Soc.*, 1966, **88**, 3657.