Synthesis of Fused β-Lactams by Copper-promoted Intramolecular Aromatic Substitution

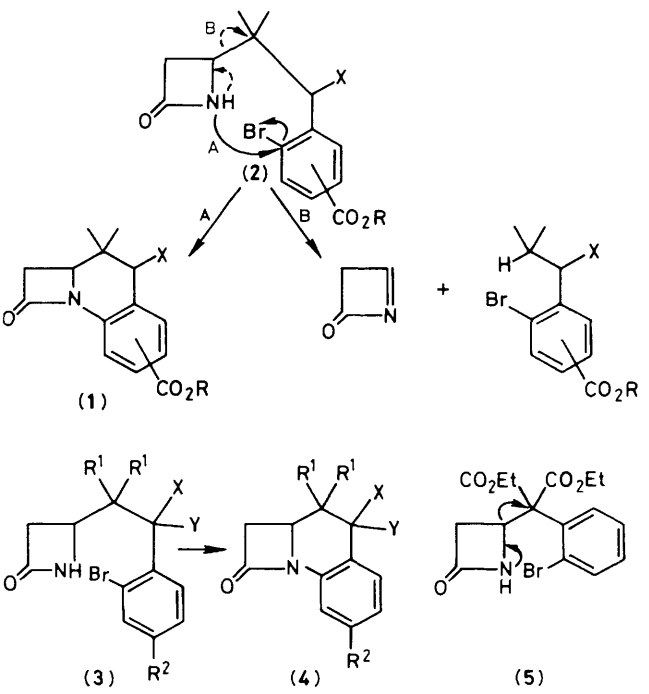
Roger Joyeau, Yann Dugenet, and Michel Wakselman*
C.E.R.C.O.A.-C.N.R.S., 2, rue Henry Dunant, 94320 Thiais, France

Competition between intramolecular aromatic substitution and elimination of the C-4 substituent occurs on heating the monocyclic azetidinones (**3**) in the presence of copper powder; steric hindrance favours the formation of the tricyclic azetidinones (**4**).

Some *N*-aryl azetidinones are good competitive inhibitors of β-lactamases *in vitro*.[1] However their bromomethylated analogues[2] are not enzyme-activated irreversible inhibitors. This is probably because the monocyclic azetidinone ring is too stable for enzymatic ring-opening to occur.[1] Therefore we decided to synthesize the more strained tricyclic β-lactams of type (**1**).

One possible synthesis of (**1**) involves an intramolecular aromatic substitution by a neighbouring β-lactam function (Scheme 1, pathway A). Generally, the intermolecular[3] or efficient intramolecular[4,5] reactions of aromatic halides with acetanilides or amides which lead to *N*-[3,4] or *O*-[5] substituted compounds are carried out in alkaline media and are catalysed by copper salts.† However in the β-lactam field the catalysed annelation of a 4-(bromovinylthio)azetidinone by copper salts[6] does not lead to the expected penem.[7,8]

Several monocyclic β-lactams (**3**) as models of compound (**2**), were prepared from 4-acetoxyazetidinone by extensions of methods described recently; substitution by substituted



Scheme 1

† A recent note described the thermal bimolecular reactions of amides and γ-lactams with aromatic halides in the presence of an excess of copper metal: T. Yamamoto and Y. Kurata, *Chem. Ind. (London)*, 1981, 737.

Table 1. Results of the formation of compounds (**3**) and (**4**).

	(**3**)[a]		(**4**)[a]	
	M.p./ °C	Yield, %	M.p./ °C	Yield, %
a: $R^1 = CO_2Et$; $R^2 = H$; X = Y = H	oil	36[b]	62–63	60
b: $R^1 = R^2 = CO_2Et$; X = Y = H	oil	48[b]	oil	45
c: $R^1 = CO_2CH_2Ph$; $R^2 = H$; X, Y = O	98	23[b]	oil	5
d: $R^1 = R^2 = H$; X, Y = O	oil	93[c]	121	13
e: $R^1 = H$; $R^2 = CO_2Me$; X, Y = O	112	27[c]	164	10

[a] Satisfactory microanalysis, mass, i.r., and n.m.r. data were obtained for all compounds. [b] Substitution by substituted alkyl and aryl malonates. [c] ZnI_2 catalysed condensation of enoxysilanes.

alkyl and aryl malonates[9] and ZnI_2 catalysed condensation of enoxysilanes[10]‡ (Table 1).

The reaction of these substituted bromoaryl-azetidinones (**3**) with CuI in a basic medium often led to the decomposition of the starting material. To avoid the elimination of the substituent at C-4 by alkali we used freshly prepared active copper powder[11] in *N*,*N*-dimethylformamide at 100 °C.† Under these conditions the tricyclic azetidinones (**4**) were obtained (Table 1). The yield from intramolecular aromatic substitution depends on the structure of the monocyclic azetidinone (**3**) and on the ease of the competitive thermal elimination (Scheme 1, pathway B). The elimination of the acidic aryl malonate is the only observed result from the attempted cyclisation of (**5**). The high acidity of the acyl malonates also explains the poor yield of (**4c**). This is the first copper-catalysed arylation of β-lactams and it is assisted by steric hindrance in the starting compound as for (**3a**) and (**3b**). The analogous vinylic substitution which may lead to substituted carbapenems or carbacephems is under study.[12]

‡ The enoxysilanes were prepared from the parent ketone by treatment with Me_3SiCl, Et_3N, and NaI (P. Cazeau, F. Moulines, O. Laporte, and F. Duboudin, *J. Organomet. Chem.*, 1980, **201**, C9) or, better, in the presence of a catalytic amount of 4-dimethylaminopyridine (M. Sekine, T. Kutatsugi, K. Yamada, and T. Hata, *J. Chem. Soc. Perkin Trans.* 1, 1982, 2509; S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99) and NaI.

Received, 19th January 1983; Com. 092

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