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STUDIES ON 1-CARBADETHIACEPHEMS, PART II: REACTION OF 4-ACETOXY-2-AZETIDINONE WITH ALUMINIUM ENOLATES

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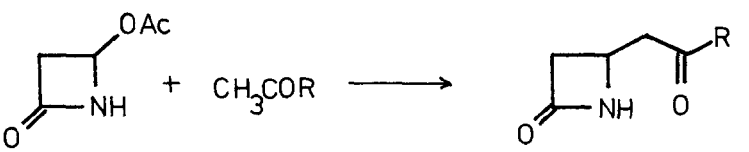
ABSTRACT. A procedure for the novel reaction of αβ-unsaturated ketones (as zinc-free aluminium enolates) with 4-acetoxy-2-azetidinone, giving products 2, is reported. A 1-carbadethia-2-oxocephem derivative 5 has been prepared from compound 2b.

Our synthesis of 1-carbadethiacephem derivatives described in the preceding communication[1] relies on the generation of a reactive α-ketoaldehyde by ozonolysis of a suitable αβ-unsaturated ketone. A recent publication[2] from the Sankyo group suggested that a suitable intermediate for our synthesis might be prepared by the reaction of an αβ-unsaturated aluminium enolate with 4-acetoxy-2-azetidinone, 1. However, we have shown that success with this method when applied to αβ-unsaturated ketones requires several significant modifications as described below.

We confirm the published yield (33%) of 2a obtained from the reaction of 4-acetoxy-2-azetidinone with bromoacetophenone in the presence of zinc and diethylaluminium chloride. However, when bromomethyl ketone 3 was used, no β-lactam product was obtained. Alternative methods of generating suitable aluminium enolates were tried and we report that enolates generated from αβ-unsaturated methyl ketones using diethylaluminium 2,2,6,6-piperidide[3] react with 4-acetoxy-2-azetidinone to give the required C-alkylated products 2[4] (see table). Moreover, inverse addition (aluminium enolate added to 1) at low temperature results in a dramatic yield improvement. Addition of cuprous cyanide (10 mole %) gave a further enhancement of yield. This procedure was also successful with acetophenone and gave a better yield of 2a than the bromomethyl ketone method. Interestingly, addition of Zn (II) ($ZnCl_2$, 10 mole %), which would be present using the Sankyo procedure, resulted in the formation of a very low



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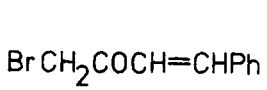
yield of 2b (13% by inverse addition method).

Table. Yields of 4-substituted azetidinones

	R	Direct Addition %	Inverse Addition CuCN added %
2a	Ph	14	42
2b	-CH=CH-Ph	16	43
2c	$-CH=C(CH_3)_2$	6	15

The most promising intermediate for our synthesis was 2b which was converted to 4 (58%) and 5[1] (55%) in analogy to Part I. Thus the preparation of 5 is essentially a three step process from 4-acetoxy-2-azetidinone.



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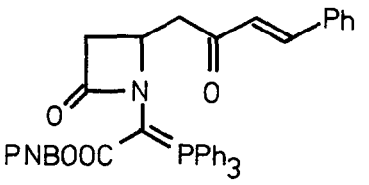

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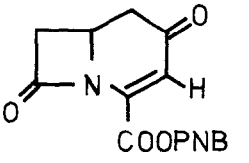

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Typical Procedure for Aluminium Enolate Reaction

To a solution of 2,2,6,6-tetramethylpiperidine (5.38 g, 39 mmole) in THF (140 ml) at 0°C under N_2 was added nBuLi (1.0 equiv.). After 30 minutes, Et_2AlCl (1.0 equiv. 25% solution in hexane) was added dropwise and stirring was continued for a further 30 minutes before cooling to -78°C. To this was added over 10 minutes a THF (25 ml) solution of 4-phenyl-3-buten-2-one (1.0 equiv.). After stirring at -78°C for 1 hour, the resulting solution was added dropwise over 45 minutes to 4-acetoxy-2-azetidinone (3.3 g, 26 mmole) and CuCN (225 mg, 2.6 mmole) in THF (100 ml) at -78°C. Stirring was continued at -78°C for 2 hours before slowly warming to 0°C (2 hours). 0.5N HCl was added, then EtOAc (800 ml) and the organic phase separated. Column chromatography (SiO_2, EtOAc) gave 2b in 43% yield (2.36 gms, mp 112-114°C from EtOAc).

References

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2. S. Oida, A. Yoshida and E. Ohki, Chem. Pharm. Bull., 28, 3494 (1980).
3. H. Nozaki, K. Oshima, K. Takai and S. Ozawa, Chemistry Letters, 379 (1979).
4. All new compounds had spectral properties in accord with their assigned structures.

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