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CYCLOADDITION REACTION OF HETEROCUMULENES AND ESTER ENOLATES: A NOVEL SYNTHESIS OF 4-ALKYLIDENE-AZETIDIN-2-ONES.

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Summary: The cycloaddition of ketenimines with ester enolates gives 4-alkylidene-azetidin-2-ones in fairly good yields.

We recently undertook[1] a systematic study on the reaction of ester enolates with different electrophilic partners[2] in order to explore methods for the production of synthetically useful azetidin-2-ones. Within the framework of this project, we studied the synthesis of 4-alkylidene ß-lactams[3] which are endowed with unique structure. Typically, this functional unit is produced by multi-step procedures from penicillin or olefination of thiomalonimides by diazo compounds[3]. In this letter we now describe a methodology which directly provide these synthetically useful compounds by reacting easily available ketenimines with ester enolates (SCHEME 1).

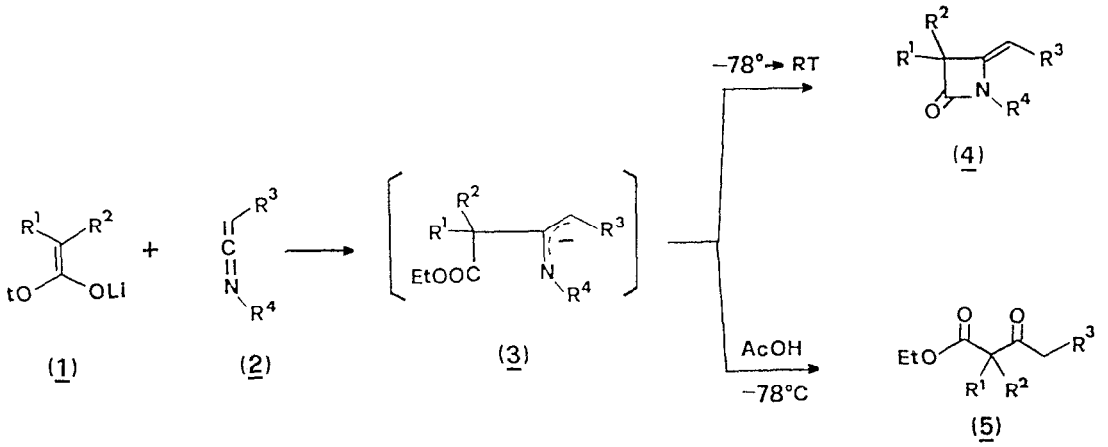
The cycloaddition is performed by treating the lithium ester enolate (1) with an aryl- or cycloalkyl ketenimine[4] (2), in tetrahydrofuran (THF) at -78°C. After hydrolytic work-up, the corresponding 4-alkylidene-azetidin-2-one (4) is obtained in 30-82% yields (Table 1). The reactions were carried on 1-20 mmoles scale and the yields are referred to pure isolated products. The following procedure for the preparation of 3-ethyl-4-ethyliden-azetidin-2-one (4a) is typical: a 250 ml flask was flushed with argon and charged with LDA (4.65 mmol), obtained from n-butyllithium (2.1 ml, 2.2 M solution in hexane) and diisopropylamine (0.47g) in 15 ml of tetrahydrofuran (THF). To this solution, cooled at -78°C, ethyl butyrate (0.54g, 4.65 mmol) in 10 ml of THF, was added and the reaction mixture stirred for 1 hour at -78°C. Ketenimine (2a), (0.5g, 3.1 mmol), dissolved in 40 ml of THF, was added during 15 minutes. The reaction mixture was stirred 2 hours at -78°C and further 1 hour at r.t.. Finally, quenching the reaction mixture at 0°C with solid NH_4Cl, H_2O, and rapidly extracting with ethyl acetate, the target compound was obtained, after flash

chromatography, as pale-yellow oil in 53% yield.

The above reported procedure is general and has been applied to all substrates included in Table 1, unless otherwise stated[5].

Concerning the mechanism of this novel azetidinone synthesis, the first step of the reaction involves the attack of the nucleophilic enolate on the electrophylic sp carbon of the ketenimine. The acyclic intermediate (3) thus formed, spontaneously cyclizes to the ß-lactam ring (4). As matter of fact, the intermediate (3) may be trapped as the corresponding ß-keto ester (5) by quenching the reaction mixture at -78°C with acetic acid (SCHEME I).

SCHEME 1

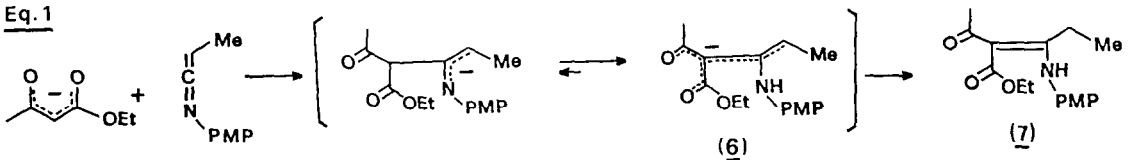


Some remarks, for the entry (12) and entry (13) have to be pointed out. In the first case, the reaction yielded, as single product, in quantitative yield, the compound (7) (Eq. 1). The formation of this product can be explained by assuming the competitive formation of the inert intermediate (6) which gives rise (7) after hydrolytic work-up.

In the case of entry (13) the low nucleophilicity of the intermediate nitrogen anion, due to the presence of an additional phenyl group directly linked to the double-bond in position 4 of the ß-lactam ring, lowers the yield in cyclized product, whereas 80% of the product (8) has been isolated (Eq 2).

Regarding the stereochemistry of the reaction, exclusively Z-isomer has been obtained, unless in the case of entry 1, where a ratio of 95/5 Z/E isomer has been observed[6] . This high stereoselectivity may be explained by a preferred attack of the nucleophilic enolate from the less hindered face of diastereotopic plane of azomethyne bond of (2). (Fig 1)

Eq. 1



PMP = p-methoxyphenyl-

Eq. 2

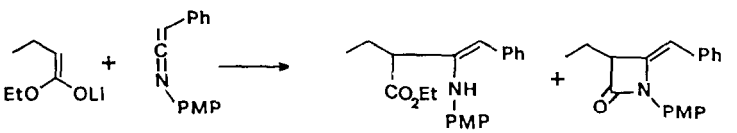
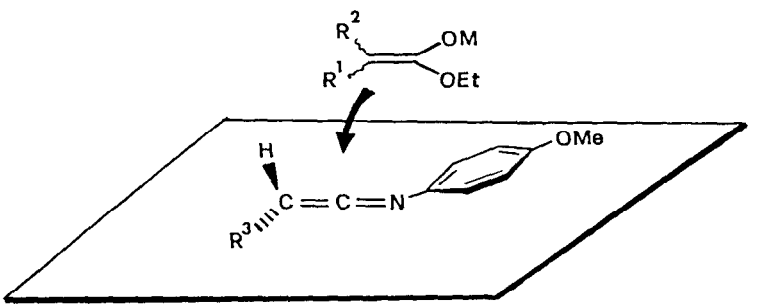


Fig. 1



Further studies on this aspect of the reaction, as well as on the application of 4-alkyliden-ß-lactams to the synthesis of useful ß-lactam antibiotics are currently in progress.

References and notes.

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2. **a.** H. Gilman, M.J. Speeter, **J.Am.Chem.Soc.**, 1943, 65, 2255. **b.** H.B. Kagan, J.J. Basselier, J.L. Luche, **Tetrahedron Lett.**, 1964, 941. **c.** D. J. Hart, K. Kanai, D. G. Thomas, and T.-K. Yang, **J. Org. Chem.**,1983, **48**, 289; **d.** G.I. Georg, H.S. Gill, C. Gerhardt, **Tetrahedron Lett.** 1985, 26, 3903. **e.** G.I. Georg, J. Kant, H.S. Gill, **J.Am.Chem.Soc.**, 1987, **109**, 1129.

TABLE 1

Entry	ESTER (1) R_1	ESTER (1) R_2	KETENIMINE (2) R_3	KETENIMINE (2) R_4	(PRODUCT) Yield %	IR cm^{-1} C=O ß-lact and $C=C_4$
1	H	CH_3CH_2	CH_3	PMP	53 (4a)	1 790 1 700
2	CH_3	CH_3	CH_3	PMP	82 (4b)	1 790 1 700
3	H		CH_3	PMP	34 (4c)	1 790 1 695
4	H	"	CH_3	PMP	49 (4d)	1 790 1 695
5	H		CH_3	PMP	32 (4e)	1 780 1 690
6	CH_3	CH_3CH_2	CH_3	PMP	61 (4f)	1 800 1 700
7	CH_3		CH_3	PMP	56 (4g)	1 800 1 705
8	CH_3	CH_3	C_6H_5	Cyclohexyl	98 (4h)	1 790 1 680
9	H	CH_3CH_2	C_6H_5	Cyclohexyl	54 (4i)	1 790 1 675
10	H		C_6H_5	Cyclohexyl	45 (4l)	1 790 1 670
11	H	"	C_6H_5	PMP	41 (4m)	1 790 1 670
12	H	CH_3COCH_2	CH_3	PMP	------	
13	H	CH_3CH_2	C_6H_5	PMP	16 (4n)	1 790 1 685

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4. The ketenimines used were prepared, unless otherwise stated, according standard procedure: C.L. Stevens and J.C. French, **J.Amer.Chem.Soc.**, 1954, **76**, 4398.
5. All new compounds reported herein gave ^1H NMR, IR, and MS or combustion analytical data consistent with the assigned structures. For the entry 7 metallation of the ester has been performed with LDA in the presence of tetramethylethylenediamine (TMEDA) (1 eq).
   The products (4d) (10d) (11d) were isolated as carbobenzoxy derivatives following the procedure published in the Ref. 1c.
6. The Z and E stereochemistry has been determined from ^1H NMR data. Details wil be published shortly elsewere.

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