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A SYNTHETIC APPROACH TO 4-OXO AND 4-THIOXO AZETIDINONES FROM HETEROCUMULENES AND ESTER ENOLATES. A NOVEL SYNTHESIS OF 4-THIO-ACETOXY AZETIDIN-2-ONES.

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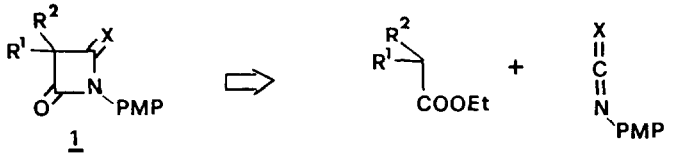
Summary: The addition of the ester enolates (3) to the heterocumulenes (4), yields acyclic derivatives (5), which can be cyclized to the thio or to the oxo malonimmides (1). A further elaboration of thiomalonimides (5a) and (5c) led to 4-thio-acetoxy azetidinones (10a) and (10c).

Malonimide[1] or thiomalonimides[2] such as (1) are interesting building blocks for preparing ß-lactam antibiotics[3].

Within the framework of a project on the synthesis of non-classical ß-lactam antibiotics[4], we were interested in the convenient generation of (1). The avalaible methodology for the synthesis of these compounds involves a multi-step procedure[5]. Nevertheless, retrosynthetic analysis of the target, suggests that readily available heterocumulenes (X = O or = S), could be used for the synthesis of (1).



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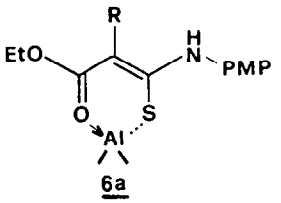
In this Letter we report that 4-oxo and 4-thioxo azetidinones can be, in fact, readily prepared from isocyanates and isothiocyanates by a two step procedure: addition of the nucleophilic enolate of the ester to the electrophilic heterocumulene and cyclization of the acyclic adduct thus obtained. Results of some applications of this method are presented in Table I. The reactions were carried out on 10 - 20 mmoles scale and the yields are reported for isolated pure products.

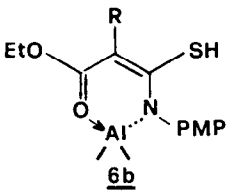
Treatment of the esters (2) with 1 eq. of lithium diisopropylamide (LDA) or lithium triphenyl methane (LTPM)[6] in dry tetrahydrofuran at -78°C, produces the lithium enolate (3). Subsequent treatment of (3) with 1 eq. of the isothiocyanate (4a) or isocyanate (4b) at -78°C, leads to the thiomalonamic and malonamic esters (5a) and (5b) respectively[7] in the range of 40-90% yield[8] after work-up and purification of the crude reaction mixture by flash chromatography (**TABLE** 1). In a subsequent elaboration, the acyclic intermediates (5a) and (5b), could be converted to the corresponding azetidinone derivatives (1a) and (1b) by cyclization with triethyl aluminum in refluxing toluene[9] in 25-80% yield. (SCHEME 1 and TABLE 1).

From the data presented in TABLE I, it can readily be discerned that the substituents on the C_2 carbon atom of the acyclic intermediates (5a) and (5b) play a crucial role in determining the yields of the cyclization reaction.

The presence of an enolizable proton at the position 2 of the starting material (entries 3, 6, 7), is responsible for the low yield of the cyclization products. As a matter of fact, starting material is the only by-product recovered after hydrolytic work-up. This behaviour can be explained by assuming the competitive formation of an inert cyclic aluminum complex (6a or 6b).



6a

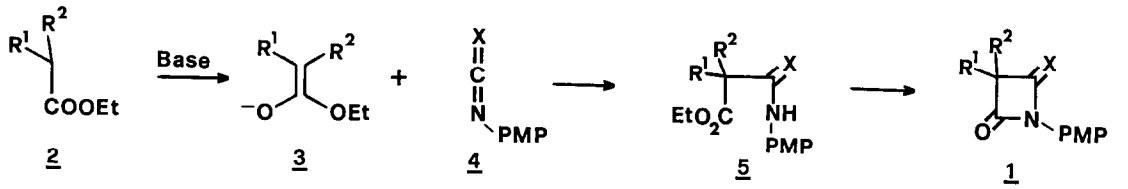


6b

The utility of this approach is illustrated in the preparation of 4-thioacetoxy azetidinones (10a) and (10c). The syntheses were performed by reduction of thiomaloimmides (1a) and (1c) by means of tributyltin hydride (But_3SnH) (ether, room temperature, 1 eq, 2 h) in the presence of catalytic amount of azobisisobutyronitrile (AIBN) to give tin-mercaptides (7a) and (7c) (1/1 cis-trans mixture) in 98 and 60% yield respectively. The tin derivatives thus obtained were converted to the corresponding thioacetoxy derivatives (9a and 9c) by sequential treatment with butyllithium (1 eq, 0°C, ether) and acetyl chloride (1 eq, 0°C,). Final deblocking involves the oxidative cleavage of the p-methoxy-phenyl group (PMP) by means of ceric ammonium nitrate (CAN) in acetonitrile[11] to give the target azetidinones (10a) and (10c) in 92% and 60% yield respectively, starting from (7a) and (7c). (SCHEME 2).

Further studies on the extension and the application of the present method are currently underway.

SCHEME 1

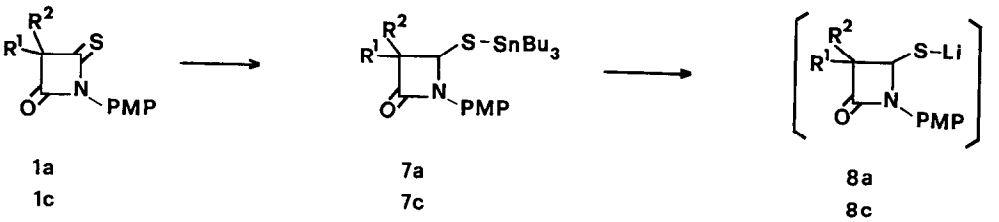


2 3 4 5 1

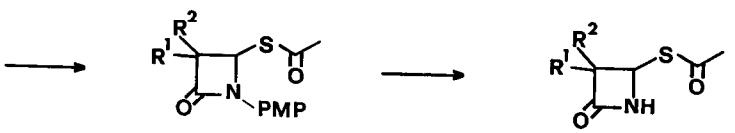
Table I. Preparation of 4-oxo and 4-thioxo-azetidin-2-ones.

Entry	R_1	R_2	X	Base	Acyclic (Product) Yield %	Cyclic (Product) Yield %
1	CH_3	CH_3	S	LDA	(5a) 94	(1a) 85
2	CH_3	CH_3	O	LTPM	(5b) 40	(1b) 24
3	H	CH_3CH_2	S	LTPM	(5c) 56	(1c) 18
4	CH_3	CH_3CH_2	S	LDA	(5d) 64	(1d) 72
5	$HC=(CH_3)_2$		S	LDA	(5e) 68	(1e) 25
6	H	$COOCH_3$	S	NaH	(5f) 70	-----
7	H	$CO-CH_3$	S	NaH	(5g) 78	-----
8	$HC=C(CH_3)_2$		O	LDA	(5h) 41	-----

SCHEME 2



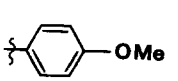
1a 1c 7a 7c 8a 8c



9a 9c 10a 10c

a: $R^1 = R^2 =$ Me

c: $R^1 = H$; $R^2 = CH_2CH_3$

PMP = 

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6. The use of LDA, NaH, or LTPM is strictly related to the ester. In the case of disubstituted esters the best metallating agent results LDA whereas in the case of n-butyric ethyl ester LTPM is the metallating agent of choice. See also Ref 7.
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8. All new compounds gave satisfactory spectral ^{1}H NMR, ^{13}C NMR, IR, MS, UV) and analytical data. Selected data as fellow:(1a) I.R. 1810. ^{1}H NMR 1.4 (s, 6H); 3.8 (s 3 H); 6.9 (d, J 8 Hz, 2 H); 8.0 (d, J 8 Hz, 2 H). (1c): I.R. 1810. ^{1}H NMR: 1.1 (t, 3H); 1.9 (q 2 H); 3.8 (s 3 H); 6.9 (d, 2 H) 8.0 (d 2 H). (1e) I.R. 1805. ^{1}HNMR: 2.15 (s 3 H); 2.4 (s 3 H); 3.8 (s 3 H); 6.9 (d, J 8 Hz, 2 H); 8.1 (d, J 8 Hz, 2 H). (10a): I.R. 1770. ^{1}H NMR: 1.2 (s, 3 H); 1.4 (s 3 H); 2.4 (s 3 H); 5.1 (s 1 H); 6.25 (bs N-H). (10c): cis isomer: I.R. 1870. ^{1}H NMR 1.1 (t 3 H); 1.7 (m 2 H); 2.35 (s 3 H); 3.5 (m 1 H); 5.45 (d, J 7 Hz, 1H); 6.2 (bs N-H). trans isomer: ^{1}H NMR: 1.15 (t 3 H); 1.7 (m 2 H); 2.3 (s 3 H); 3.15 (m, 1 H); 5.0 (d, J 3 Hz, 1H); 6.2 (bs N-H).
9. At our knowledge this is the first example that the Woodward's cyclization reaction[10] has been used in cyclizing 2-monosubstituted as well as 2,2'-disubstituted malonamic and thiomalonamic esters.
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