Tetrahedron Letters,Vol.27,No.15,pp 1695-1698,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

A SYNTHETIC APPROACH TO AZETIDINONES FROM NITRILES AND LITHIUMTRIETHOXYALUMINIUM HYDRIDE.

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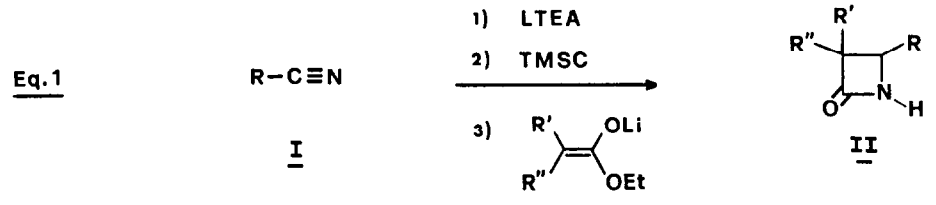
ABSTRACT: A CONVENIENT ONE-POT PROCESS FOR DIRECT CONVERSION OF NITRILES TO 3,4-DISUBSTITUTED AZETIDINONES HAS BEEN DEVELOPED.

Azetidinones such as (II) are useful intermediate for preparing β-lactam antibiotics.[1] In connection with our study on the synthesis of this kind of molecule,[2] we required a convenient synthesis of 3,4-disubstituted azetidin-2-ones. In this Letter we report that azetidinones can be readily prepared from nitrile precursors by a three step one-pot synthesis as is outlined by eq 1. Results of some application of this method are presented in Table I. These reactions were carried out on 10-20 mmol scales and yields are for isolated pure products.



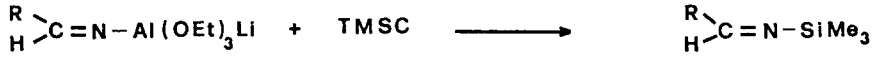
The present method starts with generally readily available nitriles and gives good results with both aliphatic and aromatic nitriles.[3]

The following procedure for the preparation of 3-amino-4-(2'-furanoyl)-2-azetidinone (exp. 1) is typical. A 100 ml flask was flushed with argon and charged with 11 ml of $LiAlH_4$ 1 M solution in ether.[4] To this solution was added freshly distilled anhydrous ethyl acetate (1.61 ml, 16.5 mmol) in ether. After 15 min, to the resulting solution 2-furonitrile (0.88 ml, 10 mmol) in ether (10 ml) was added. The reaction mixture was stirred for 1 h at 0°C. At this point trimethylchlorosilane (1.25 ml, 10 mmol) was added and the mixture allowed to warm to room temperature. After 2 h the enolate of ethyl 2-(2,2,4,4-tetramethyl-2,5-disilylazacyclopentyl)-glycinate[5] (4.84 g, 20 mmol), obtained following standard procedure[6], was added at -78°C and the reaction mixture stirred overnight while the temperature was allowed to reach -30°C. The reaction was quenched at 0°C with solid NH_4Cl and H_2O and rapidily extracted with ethyl acetate. After the solvent was dried ($MgSO_4$) and removed, chromatography of the residue yielded 0.65 g (43%) of the target compound. The above procedure is general and applicable to all nitriles included in Table 1.

Concerning the mechanism of this novel azetidinones synthesis, the first step of the reaction involves the reduction of the nitrile with lithium-triethoxy aluminium hydride (LTEA) (III) to give an addition product (IV)[4].

III IV

Preliminary experiments shown that this aluminium-imine derivative reacts with the lithium ester enolate to give few percent of the expected azetidinone only under rather drastic conditions (reflux) (Exp.8). Addition of trimethylchlorosilane to the heterogeneous mixture of (IV) remarkably improves the azetidinone yield probably through the intermediate formation of the corresponding trimethylsilylimine, which is known to afford azetidinones with ester enolates.[7] As a matter of fact we were able to isolate the intermediate silylimine in the case of N-(trimethylsilyl)benzaldimine[7a] (V) by treatment of the aluminum adduct (IV) with trimethylchlorosilane followed by filtration and removal of the solvent under vacuum.



IV V

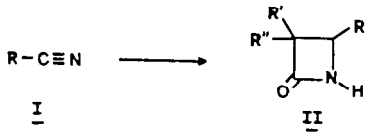
R = Ph

Although the stoichiometry of the reaction requires equimolar amounts of nitrile and organometallic reagent, the use of a 2/1 ratio of enolate anion and nitrile appears to improved the yield (method B).

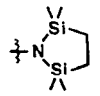
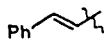
In conclusion, although the yields of several entries are lower than desirable and further work should be done to optimize the yields, it is noteworthy that this is the first time that the synthesis of azetidinones has been achieved starting from enolizable metallo-imine derivatives (Exp.10, 11).

Further studies are currently under active investigation.

Table 1. Conversion of nitrile (I) to azetidinone (II)



I II

Exp	Nitrile	Enolate		Method[§]	% (II) isolated[3]	Cis/trans ratio
	R	R'	R"			
1		H		B	43[a, &]	95/5
2	"	H	Et	A	30[b]	77/23
3	"	H	Et	B	56	70/30
4	"	Me	Me	A	36[c]	--
5		H	Et	B	50	50/50
6	"	H	Et	A	29[d]	44/56
7	pOMe-Ph	H	Et	A	30[e]	66/34
8	Ph	Me	Me	C	12[f]	--
9	"	Me	Me	B	57	--
10	nC_3H_8	H	Et	A	12[g]	50/50
11	"	H	Et	B	40	50/50
12		Me	Me	A	20[h]	--
13	"	H	Et	B	25[i]	86/14

§ Ratio Nitrile/Enolate/TMSC: Method A:1/1/1; Method B: 1/2/1; Method C: 1/1/0

& Isolated as 3-amino-4-(2'-furanoyl)-azetidin-2-one.

References and notes.

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3. Yields are reported for isolate chromatographically pure products and have been not optimized. ^{1}H NMR (90 MHz, $CDCl_3$), MS, IR ($CHCl_3$, cm^{-1}) spectra were enterely consistent with assigned structure and satisfactory combustion analyses were obtained. Selected spectroscopic data as follow: a: (cis isomer): I.R. (film) 3450, 1760. ^{1}H NMR 2.4 (bs, 2 H); 4.5 (d J_{cis}=6 Hz 1 H, C_3H); 4.8 (d J=6Hz 1H, C_4H); 6.3 (m 2H); 7.1 (bs 1H N-H); 7.4 (m 1H); b: (cis isomer): I.R. 3400, 1750 . ^{1}H NMR 0.80 (t, 3H); 1.1-1.9 (complex pattern 2H); 3.35 (dq 1 H J_{cis}=6Hz C_3H); 4.8 (d J=6Hz 1H; C_4H); 6.4 (m 2H); 6.8 (bs 1H N-H); 7.4 (m 1H). (trans isomer): I.R. 3400, 1750. ^{1}H NMR 1.05 (t 3H); 1.4-2.1 (complex pattern 2H); 3.35 (td J_{trans}=3 Hz 1H, C_3H); 4.4 (d J_{trans}=3Hz 1H, C_4H), 6.4 (m 3H 2 Ar and N-H); 7.4 (m 1H). c: I.R. 3410, 1765. ^{31}H NMR 0.95 (s 3H); 1.4 (s 3H); 4.45 (s 1H); 6.35 (m 2H); 6.5 (bs 1H N-H); 7.4 (m 1H). d: (cis isomer): I.R. 3400, 1750. ^{1}H NMR 0.85 (t 3H); 1.1-1.8 (complex pattern 2H); 3.35 (dt J_{cis}=6Hz 1H C_3H); 5.1 (d J=6Hz 1H, C_4H); 6.5 (bs 1H N-H); 7.0 (m 2H); 7.2 (m 1H). (trans isomer): I.R. 3400, 1750. ^{1}H NMR 1.1 (t 3H); 1.80 (m 2H); 3.2 (dt J_{trans}=3Hz 1H, C_3H); 4.65 (d J=3Hz 1H, C_4H); 7.07 (m 3H, 2 Ar and N-H); 7.25 (m 1H). e: (cis isomer): I.R. 3395; 1745. ^{1}H NMR 0.75 (t, 3H); 0.9-1.6 (complex pattern 2H); 3.3 (dq J_{cis}=6Hz 1H C_3H); 3.8 (s 3H OCH_3); 4.8 (d J=6Hz 1H C_4H); 6.8-7.4 (m 5H 4Ar and N-H). (trans isomer): I.R. 3395, 1745. ^{1}H NMR 1.05 (t 3H); 1.7 (m 2H); 2.85 (dt J_{trans}=3Hz 1H C_3H); 3.8 (s 3H OCH_3); 4.3 (d J=3Hz C_4H); 6.8-7.4 (m 5H 4Ar and N-H). f: I.R. 3410, 1760. ^{31}H NMR 0.75 (s 3H); ^{1}1.42 (s 3H); 4.5 (s 1H); 6.75 (bs 1H N-H) 7.3 (m 5H). g: (cis isomer) I.R. 3400, 1750. ^{1}H NMR 0.85 (t 3H); 1.25-1.85 (m 6H); 3.1 (m 1H C_3H); 3.7 (m 1H C_4H); 6.9 (bs 1H N-H). (trans isomer): I.R. 3400, 1750. ^{1}H NMR 1.25 (t 3H); 1.3-1.9 (m 6H); 3.1 (m 1H C_4H); 3.7 (m 1H C_3H); 6.9 (bs 1H N-H). h: I.R. 3410, 1760. ^{1}H NMR 1.15 (s 3H); 1.3 (s 3H); 3.9 (d J=6Hz, 1H); 6.20 (dd J_1=6Hz J_2=16Hz 1H); 6.65 (d J_2=16Hz 1H); 6.85 (bs 1H N-H); 7.3 (5H Ar). i: cis isomer: I.R. 3410, 1755. ^{1}H NMR 0.95 (t 3H); 1.1-1.9 (complex pattern 2H); 3.22 (dq J_{cis}=6Hz, 1H, C_3H); 4.3 (t J=6Hz, 1H, C_4H); 6.20 (dd J_1=6Hz, J_2=16Hz, 1H); 6.6 (d J=16Hz, 1H); 6.9 (bs 1H, N-H); 7.3 (5H Ar). trans isomer: I.R. 3410, 1755. ^{1}H NMR 1.05 (t 3H); 1.8 (m 2H); 2.9 (dt J_{trans}=3Hz, 1H, C_3H); 4.0 (dd J_{trans}=3Hz 1H, C_4H); 6.25 (dd J_1=6Hz, J_2=16Hz 1H); 6.6 (d J=16Hz 1H); 7.0 (bs 1H, N-H).
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Acknowledgements: This work has been supported by a grant from "Progetto Finalizzato Chimica Fine e Secondaria. C.N.R. Rome".

(Received in UK 17 February 1986)