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ß-LACTAMS FROM ESTERS AND SILYLIMINES: A REVALUATION. SYNTHESIS OF N-UNSUBSTITUTED 4-ALKYL-ß-LACTAMS.

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Summary: The first preparation of enolizable silylimines is reported. The "in situ" trapping of these species with lithium enolates of esters gives rise in fairly good yields to N-unsubstituted 4-alkyl-ß-lactams.

Ester-imine cycloaddition has been known, for several years, to be a good method for the synthesis of the ß-lactam ring.[1] One goal of our continuing studies on this route to ß-lactams has been the search for azomethines which provide rapid access to N-unsubstituted ß-lactams.[2]

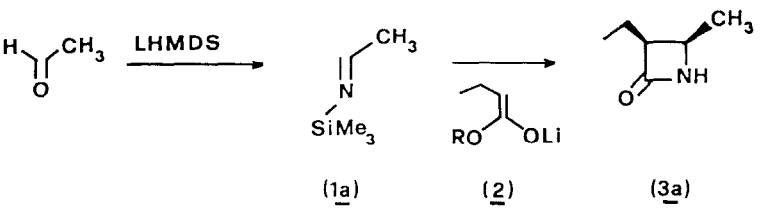
N-trimethylsilylimines have been found [3] excellent in this regard as they directly afford the desidered substitution pattern. However, the main drawback of this method relies on the difficulty to use enolizable aldehydes as starting imine precursors. This limitation has been claimed to be due to the competitive enolization of the aldehyde during the preparation of silylimine[3a], and/or competitive isomerization of the imine to the corresponding enamine[4]. In two recent reports[5], we have proposed, to overcome this problem, the use of aluminum-imines, obtained from aliphathic and aromatic nitriles by reduction with several aluminum hydrides.

We have now found that, despite what is reported by other authors, silylimines of enolizable aliphatic aldehydes, including acetaldehyde, can be prepared and used as starting material for the preparation of azetidin-2-ones upon reaction with ester enolates. (**SCHEME 1**)

Treatment of acetaldehyde with lithium hexamethyldisilylamide (LHMDS) in dry THF at -30°, produces the trimethylsilylimine (**1a**)[9]. Analysis of the I.R. and ^{1}H NMR spectra shows the caracteristic -C=N- absorption at 1680 cm^{-1}, and the signal of the vinylic proton -CH=N- at 8.50 ppm (d_8 THF). All attempts to isolate pure silylimine failed. The trapping, in situ, at -78°C, of this

electrophilic species with the lithium ester enolate of t-butyl butyrate, prepared according standard procedure with lithium diisopropylamide, followed by stirring overnight while the temperature was allowed to reach room temperature, work-up with solid NH_4Cl, H_2O, extraction with ethyl acetate and finally flash column chromatography on silica gel afforded the ß-lactam (3) in 46% yield. This standard methodology has been applied to all experiments reported in Table 1. All the reactions were carried out on 1-100 mmoles scale and the yields reported are for pure isolated products[6].

SCHEME 1



(1a) (2) (3a)

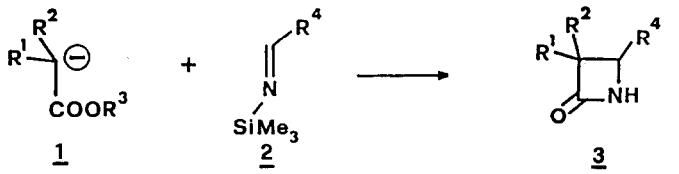
Some aspects of this chemistry warrant comments: the reaction between (1) and (2) is one of the few examples of ß-lactam formation in a reaction involving lithium enolates and enolizable imines. In fact, although enolizable N-aryl and N-alkylaldimines react with Reformatsky reagents under certain conditions[7], no successul examples have been reported, for ß-lactam formation, with lithium ester enolates[8]. Finally, the reaction presents high cis-stereoselectivity[9] which parallels the results obtained with simple lithium enolates and non-enolizable N-trimethylsilyl or N-arylaldimines[3].

An interesting application of the enolizable silylimines (SCHEME 2) to the azetidinone ring is given by the preparation of a range of 3-amino-4-alkyl-ß-lactams[10] or the corresponding carbobenzoyloxy derivatives.

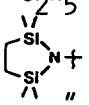
Typical procedure: The lithium enolate of silylglycine derivative (STABASE)[11] (1m) (50 mmol) in THF (30 ml) was added to the silylimine (2m) (50 mmol), obtained in THF as above reported. After 1 hour at -78°C, the reaction mixture was allowed to reach room temperature during 8 hours. The pH of the crude reaction mixture was adjusted to 7 with solid NH_4Cl and 1 N HCl. Solid $NaHCO_3$ (112 mmol, 9.45 g) and carbobenzoxychloride (75 mmol), in acetone (20 ml) were added at 0°C. After 1 h, extraction with ethyl acetate, removal of the solvent and precipitation with ethyl ether yielded azetidinone (3m) in 57%[12].

Additional studies, including applications to the total synthesis of non traditional ß-lactams antibiotics are underway.

Table I. Preparation of N-unsubstituted azetidinones (3a) - (3p)

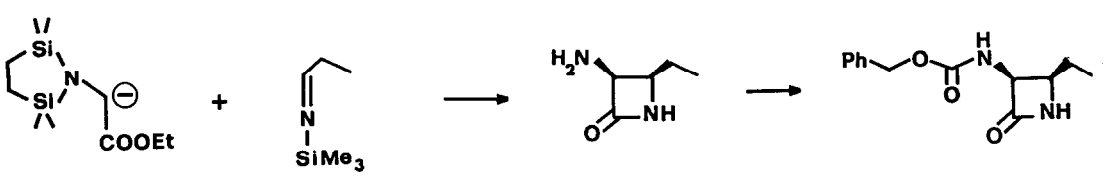


1 2 3

Entry	R_1	R_2	R_3	R_4	(Product) Yield%	cis/trans ratio*
a	C_2H_5	H	t-C_4H_9	CH_3	(3a) 46	78/22
b	"	H	C_2H_5	"	(3a) 38	86/14
c	"	H	"	C_9H_{19}	(3c) 44	92/8
d	"	H	t-C_4H_9	i-C_3H_7	(3d) 29	8/92
e	CH_3	CH_3	C_2H_5	i-C_3H_7	(3e) 60	----
f	CH_3	CH_3	C_2H_5	C_2H_5	(3f) 40	----
g	CH_3	CH_3	C_2H_5		(3g) 33	----
h	C_2H_5	H	C_2H_5	"	(3h) 20	77/23
i	C_2H_5	H	C_2H_5	n-C_3H_7	(3i) 28	72/28
l		H	C_2H_5	CH_3	(3l) 40[&]	90/10
m	"	H	C_2H_5	C_2H_5	(3m) 57[&]	90/10
n	"	H	C_2H_5	i-C_3H_7	(3n) 28[&]	8/92
o		H	C_2H_5	CH_3	(3o) 36	95/5

* Determined by ^1H NMR integration of the characteristic protons.
& Identified as carbobenzoxy derivatives.

SCHEME 2



(1m) (2m) (3m)

References and notes.

1. **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.
2. For other methods for the synthesis of N-unsubstituted azetidin-2-one see:**.a.** D. J. Hart, K. Kanai, D. G. Thomas, and T.-K. Yang, **J. Org. Chem.,**1983, **48,** 289; **b.** G.I. Georg, J. Kant, H.S. Gill, **J.Am.Chem.Soc.,** 1987, **109,** 1129. **c.** G. Cainelli, M. Panunzio, T. Basile, A. Bongini, D. Giacomini, G. Martelli, **J.Chem.Soc. Perkin 1 ,** in press. **d.** K. Ikeda, Y. Yoshinaga, K. Achiwa, M. Sekiya, **Chem. Lett.** 1984, 369. **e. D.**A. Burnett, D.J. Hart, J. Liu, **J.Org.Chem.,** 1986, **51,** 1930.
3. **a.** D.J. Hart, K. Kanai, D.G. Thomas, T.-K. Yang, **J.Org.Chem.** 1983, **48,** 289. **b.** G. Cainelli, M. Contento, G. Giacomini, M. Panunzio, **Tetrahedron Lett.,** 1985, **27,** 937. **c.** E. W. Coçlvin and D. G. McGarry, **J. Chem. Soc., Chem. Commun.,** 1985, 539. **d..** -C. Ha, D. J. Hart, and T.-Yang, **J. Am. Chem. Soc.,** 1984, **106,** 4819; **e.** T.Chiba, M. Nagatsuma, T. Nakai, Chem.**Lett. 1984, 1927. f.** T.Chiba, T. Nakai, **Chem. Lett.** 1985, 651.
4. **D.L. Comins, J.D. Brown, Tetrahedron Lett. 1981, 22,** 4213.
5. **a.** P. Andreoli, G. Cainelli, M. Contento, D. Giacomini, G. Martelli, M. Panunzio, **Tetrahedron Lett.** 1986, **27,** 1695. **b.** P. Andreoli, G. Cainelli, M. Contento, D. Giacomini, G. Martelli, M. Panunzio, **J.Chem.Soc. Perkin 1,** in press.
6. All new compounds reported herein gave ^{1}H NMR, IR, and MS or combustion analytical data consistent with the assigned structures. Stereochemical assignements were based on J_{3-4} values of 1.5-3.0 Hz (trans) and 5-6 Hz (cis).
7. F. Dardoize, J.-L. Moreau, M. Gandemar, **Bull.Soc.Chim.Fr.,** 1972, 3841.
8. C. Gluchowski, L. Cooper, D.E. Bergbreiter, M. Newcomb, **J.Org.Chem.,** 1980, **45,** 3413.
9. In the case of the entries **d** and **n** (Table I), a high trans stereoselectivity is observed. This behaviour is currently under investigation.
10. C. M. Cimarusti and R.B. Sykes, **Chem. Br.,** 1983, 302.
11. S.Djaric, J.Vernit, P.Magnus, **Tetrahedron Lett.** 1981, 1787.
12. Alternatively the 3-amino-4-alkyl-azetidin-2-ones have been isolated from crude reaction mixture, adjusting the pH at 4 with 1 N HCl at 0°C, stirring at room temperature for 1 hour and purifying the target by short column chromatography.

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