Tetrahedron Letters, Vol. 34, No. 13, pp. 2123-2126, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Synthesis in Dry Media Coupled with Microwave Irradiation : Application to the Preparation of β-Aminoesters and β-Lactams via Silyl Ketene Acetals and Aldimines.

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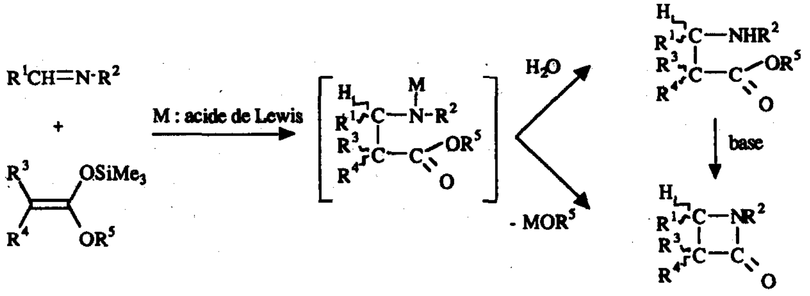
Key words : *silyl ketene acetals ; β-aminoesters ; β-lactams ; microwave irradiation ; dry media.*

Abstract : According to the reaction conditions, silyl ketene acetals react with aldimines to give β-aminoesters (montmorillonite clay K_{10}, or para-toluenesulfonic acid) or β-lactams (KF/18 crown-6) in a few minutes under microwave irradiation.

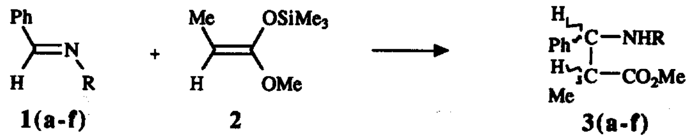
The β-lactam skeleton is present in a wide variety of biologically active compounds, the synthesis of which has been extensively reviewed[1-3]. In the literature, it is known that β-lactams can be prepared from silyl ketene acetals and imines either by hydrolysis of a preformed metalated intermediate[4-6] or by treatment of a β-aminoester with LDA[4,7,8-13] (scheme 1)



Scheme 1

β-Aminoesters are prepared in the presence of various catalysts such as $TiCl_4$, TMS OTf, metallic solids, phosphonium triflate, trityl hexachloroantimonate[4-16].

Organic reactions in a dry medium, eventually under microwave irradiation, are at present under extensive examination[17-22]. As part of our program related to the study of the reactivity of organosilicon compounds in heterogeneous medium[23], we report now a new procedure for the synthesis of β-aminoesters and β-lactams starting from imines and silyl ketene acetals. As a model for the β-aminoester synthesis, we studied the reaction of benzylidene aniline **1a** (R=Ph) with the silyl ketene acetal **2** over dried montmorillonite K_{10} as acidic inorganic support.



Scheme 2

The experimental procedure is particularly simple : **1a** (1.25 mmol) and **2** (1.25 mmol) are mixed together without solvent in a 10 ml erlenmeyer flask and then 1.5 g of K_{10} montmorillonite clay (previously dried in a domestic microwave oven during 5 mn at 400 watts) is added by small amounts. After standing at room temperature or microwave irradiation (under nitrogen), the mixture is washed with 2 times 25 ml of CH_2Cl_2. Filtration of the solid and removal of the solvent afford the crude β-aminoester **3a**. At room temperature, a kinetic study shows that the yield is quantitative after 24 hrs (evaluated by ^1H NMR) and **3a** is isolated in 90% yield after short path distillation. Under microwave irradiation (400 W), the kinetic study shows that the best yield is 65% after 5 mn (for longer time, some benzaldehyde resulting from the imine degradation appears). The reaction at room temperature was extended to various imines and the results are given in table 1. In all the cases, a mixture of two diastereoisomers anti and syn characterized by $^3J_{HH}$[16] is formed.

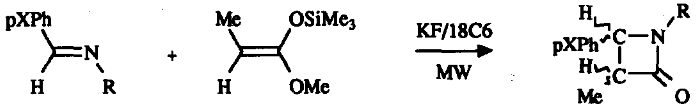
Table 1 : β-Aminoesters 3 (a-f) over montmorillonite K_{10} at room temperature[24].

1	R	Time (h)	Yield (%)^a	isolated Yield (%)^b	% anti/syn
a	Ph	24	95	90^c	78 / 22
b	Me	24	95	90	66 / 34
c	$-CH_2CO_2Me$	72	88	81	61 / 39
d	$-(CH_2)_3CO_2Me$	72	72	67	75 / 25
e	$-CH_2Ph$	24	52	43	75 / 25
f	iso Pr	72	44	-	77 / 23

a. estimated by ^1H NMR on the crude mixture ; b. isolated by short path distillation
c. cristallized m.p = 110°C.

When R is benzyl or isopropyl, the yields are lower but this may be overcome by using catalytic amounts of PTSA (para-toluenesulfonic acid) instead of K_{10}. The optimal amount of PTSA was determined to be 0.1 g for 1.25 mmol of **1** and 1.5 mmol of **2**. In these conditions, **3e** and **3f** are isolated with 72% and 83% yield respectively after short path distillation. The extension of this procedure to some other silyl ketene acetals and silyl enol ethers is actually under progress. It is noteworthy that this technique represents an interesting simplification with respect to the previously reported procedures which required anhydrous solvents and hygroscopic Lewis acids.

With the β-aminoesters **3** in hands, we thought that it would be interesting to cyclize them in β lactams by a similar procedure using a solid base with or without activation by microwaves. All our attempts were unsuccessful (KF, KF/18 crown-6, CsF, powdered KOH, DABCO), so we decided to try this cyclization directly from the starting materials (imine **1** and silyl ketene acetals **2**) over basic solids. KF or KF/Al_2O_3 were not efficient but in the presence of CsF (at room temperature or under microwaves) we got a mixture of β-aminoester **3** and β-lactam **4** though in low yields (30% conversion). Finally, we found that in the presence of KF/18 crown-6 under microwave irradiation it was possible to get exclusively the desired β-lactam.



% anti / syn

1a (X = H, R = Ph) **2** **4a** : 65 / 35

1b (X = H, R = Me) **4b** : 67 / 33

1g (X = Cl, R = Me) **4g** : 86 / 14

Scheme 3

A careful examination of the various parameters showed that the best conditions for the synthesis of β-lactams **4** were the following : to a mixture of 3.75 mmol of KF and 0.25 mmol of 18 crown-6 (dried 20 mn at 400 W) 1.25 mmol of imine **1** and 1.5 mmol of acetal **2** are added in a closed Teflon vessel. The irradiation power is 300 W and the irradiation time is 7 mn. In these conditions, the lactams are obtained in the following isolated yields (**4a** : 93% ; **4b** : 50% ; and **4g** : 47%)[25]. The irradiation time is critical, the best yield is reached after 7 mn and for a longer time the yield decreases and the amount of imine increases.

References and Notes.

1. Mukerjee, A.K. ; Srivastava, R.C. ; *Synthesis*, **1973**, 327-346 et références citées.
2. Hart, D.J. ; Ha, D.C. ; Chem. Rev., **1989**, *89*, 1447-1465 et références citées.
3. Palomo, C. ; Recent Progress in the chemical Synthesis of antibiotics ; Springer Verlag Berlin Heidelberg, **1990**, 565-612.
4. Ojima, I. ; Inaba, S. ; Yoshida, K. ; *Tetrahedron Lett.*, **1977**, 3643-3646.
5. Ojima, I. ; Inaba, S. ; *Tetrahedron Lett.*, **1980**, *21*, 2077-2080 ; **1980**, *21*, 2081-2084.
6. Dubois, J.E. ; Axiotis, G. ; *Tetrahedron Lett.*, **1984**, *25*, 2143-2146.
7. Ojima, I. ; Inaba, S. ; Nagai, M. ; *Synthesis*, **1981**, 545-547.
8. Ikeda, K. ; Achiwa K. ; Sekiya, M. ; *Tetrahedron Lett.*, **1983**, *24*, 4707-4710.
9. Okano, K. ; Morimoto, T. ; Sekiya, M. ; J. Chem. Soc., *Chem. Comm.*, **1984**, 883-884.
10. Shono, T. ; Tsubata, K. ; Okinaga, N. ; J. Org. Chem., **1984**, *49*, 1056-1059.
11. Cainelli, G. ; Contento, M. ; Drusiani, A. ; Panunzio, M. ; Plessi, L. ; J. Chem. Soc., Chem. Comm., **1985**, 240.
12. Guanti, G. ; Narisano, E. ; Banfi, L. ; *Tetrahedron Lett.*, **1987**, *28*, 4331-4334 and 4335-4338.
13. Gennari, C. ; Venturini, I. ; Gislon ,G. ; Schimperna, G. ; *Tetrahedron Lett.*, **1987**, *28*, 227-230.
14. Colvin, E.W. ; Mc Garry, D.G. ; J. Chem. Soc., Chem. Comm., **1985**, 539-540.
15. Mukaiyama, T. ; Kashiwagi, R. ; Matsui, S. ; *Chem. Lett.*, **1989**, 1397-1400.
16. Mukaiyama, T. ; Akamatsu, H. ; Han, J.S. ; *Chem. Lett.*, **1990**, 889-892.

17. Gutterriez, E. ; Loupy, A. ; Bram, G. ; Ruiz-Hitzky, E. ; *Tetrahedron Lett.*, **1989**, *30*, 945-948.

18. Bram, G. ; Loupy, A. ; Majdoub, M. ; Synthetic Comm., **1990**, *20*, 125-129.

19. Bram, G. ; Loupy, A. ; Majdoub, M. ; Gutterriez, E. ; Ruiz-Hitzky, E. ; *Tetrahedron* , **1990**, *46*, 5167-5176, et références citées.

20. Loupy, A. ; Bram, G. ; Sansoulet, J. ; *New J. Chem.*, **1992**, *16*, 233-242.

21. Ben Alloum, A. ; Labiad, B. ; Villemin, D. ; J.Chem. Soc., Chem Comm., **1989**, 386-387.

22. Pilard, J.F. ; Klein, B. ; Texier-Boullet, F. ; Hamelin, J. ; *Synlett*, **1992**, 219-220.

23. Latouche, R. ; Texier-Boullet, F. ; Hamelin, J. ; *Tetrahedron Lett.* **1991**, *32*, 1179-1182.

24. **3a** anti : 1.16 (d, 3H, MeCH, $^3J_{HH}$ = 7.1 Hz) ; 2.85 (dq, 1H, CH-Me) ; 3.60 (s, 3H, OMe) ; 4.50 (d, 1H, CH-NHPh, $^3J_{HH}$ = 7.4 Hz). **3a** syn : 1.15 (d, 3H, MeCH,$^3J_{HH}$ = 7.0 Hz) ; 2.95 (dq, 1H, CH-Me) ; 3.59 (s, 3H, OMe) ; 4.72 (d, 1H, CH-NHPh, $^3J_{HH}$ = 5.1 Hz). Mass spectrometry ; calculated for $C_{17}H_{19}NO_2$: 269.140 ; found : 269.140.

25. **4a** anti : 0.87 (d, 3H, MeCH, $^3J_{HH}$ = 7.6 Hz) ; 3.11(dq, 1H, MeCH) ; 5.17 (d, 1H, CH-NPh, $^3J_{HH}$ = 5.9 Hz). **4a** syn : 1.46 (d, 3H, MeCH, J_{HH} = 7.4 Hz) ; 3.66 (dq, 1H, CH-Me) ; 4.57 (d, 1H, CHNPh, $^3J_{HH}$ = 2.4 Hz). Mass spectrometry : $C_{16}H_{15}NO$: calculated : 237.115 found 237.116.

(Received in France 5 December 1992; accepted 26 January 1993)