

## EFFICIENT SYNTHESIS OF SUBSTITUTED $\delta$ -OXO ACIDS

Nicole Langlois\* and Nathalie Dahuron<sup>1</sup>

Institut de Chimie des Substances Naturelles, C.N.R.S.,  
91198 Gif-sur-Yvette, France

**Summary :** Activated  $\alpha,\beta$ -unsaturated oxazolines are reactive Michael acceptors in the addition of silyl enol ethers, leading to  $\delta$ -oxo acids after acidic hydrolysis.

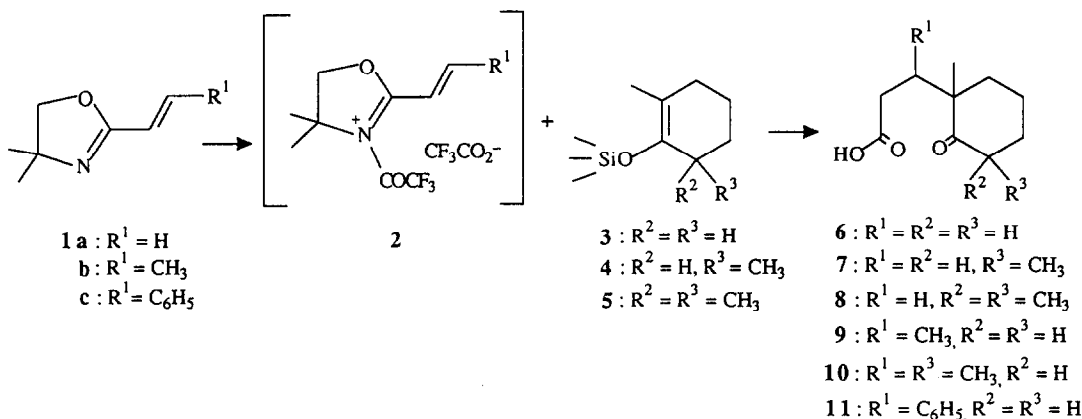
The conjugated addition of organolithium reagents to chiral  $\alpha,\beta$ -unsaturated oxazolines was extensively developed by A.I. Meyers and coworkers.<sup>2</sup>

Previous work demonstrated recently that oxazolines **1**, after activation through *N*-trifluoroacetylation to **2**, are also powerful dienophiles in the Diels-Alder reactions, compared with alkyl acrylates and crotonates<sup>3</sup>. This method of activation is now extended to Michael-type reactions with nucleophiles other than organometallic reagents and we report here the efficient addition of silyl enol ethers of cyclohexanones by this process, without Lewis acid as catalyst.

The Michael additions of  $\alpha$ -substituted monoketone derivatives to electron deficient alkenes are known to be sensitive to steric hindrance.<sup>4</sup> A few examples are described with both donor and acceptor substituted at the reactive carbon atoms,<sup>5</sup> especially in the addition of silyl enol ethers<sup>6</sup> and the method of P. Duhamel constitutes a good improvement in this area.<sup>7</sup>

In the case of the reactive trifluoroacyloxazolinium ions **2**, formed at  $-55^\circ\text{C}$  by treatment of the corresponding oxazolines **1**<sup>8</sup> with trifluoroacetic anhydride in anhydrous dichloromethane, the addition of silyl enol ethers of 2-methylcyclohexanones **3** - **5**<sup>9</sup> at low temperature gave rise to a mixture of compounds after usual workup. These intermediates were directly hydrolyzed by aqueous 3N hydrochloric acid ( $100^\circ\text{C}$ , 4 h) to afford the  $\delta$ -oxo acids **6** - **11**.

The main results are outlined in the Table.

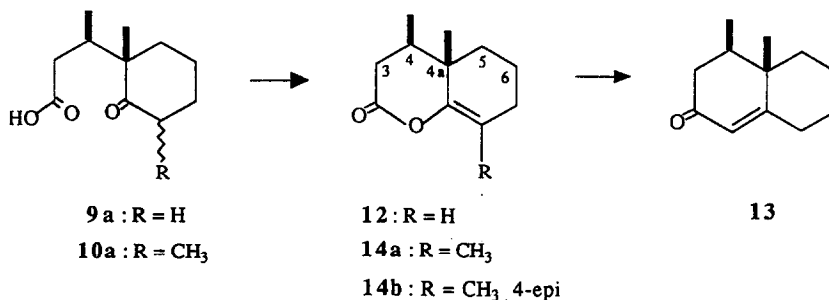
Table : Additions of silyl enol ethers to **1a**

Entry	Starting oxazoline <b>1</b>	Silyl enol ether <sup>b</sup>	t °C	Time (h)	δ-oxoacids (Yields % <sup>c</sup> )
1	<b>1a</b>	<b>3</b>	-55	0.5	<b>6</b> (93) <sup>10</sup>
2	<b>1a</b>	<b>4</b>	-45	0.5	<b>7</b> (91) <sup>11</sup>
3	<b>1a</b>	<b>5</b>	-50	0.5	
			-30	6	<b>8</b> (51) <sup>4a</sup>
4	<b>1b</b>	<b>3</b>	-35	20	<b>9</b> (76 <sup>d</sup> )
5	<b>1b</b>	<b>4</b>	-35	20	<b>10</b> (70 <sup>e</sup> )
6	<b>1c</b>	<b>3</b>	-30	24	<b>11</b> (65)

- a) The reactions were performed by adding trifluoroacetic anhydride (1 eq) to a mixture of oxazoline **1** and CaCO<sub>3</sub> (1 eq) in CH<sub>2</sub>Cl<sub>2</sub> at -55 °C; the silyl enol ether was added at the indicated temperatures. b) 1.2 eq. for all experiments except 4 and 5 which were carried out with 3 eq. c) Not optimized isolated yields. d) As a mixture of diastereomers **9a** (R\*, S\*) and **9b** (S\*, S\*), **9a:9b** = 60:40. e) The crude acidic products were obtained with 85% yield and converted to **14**.

It is noteworthy that the reactions between the activated oxazoline **1a** and silyl enol ethers of hindered ketones such as 2,6-dimethyl and 2,2,6-trimethylcyclohexanones **4** and **5** gave rise to the corresponding δ-oxo acids **7** and **8** in 91% and 51% overall yield respectively.

The relative configurations of the diastereomeric δ-oxo acids **9** were determined by PMR after a chemical correlation. Thus the diastereomer **9a** led, through the enol lactone **12**, to the well known *cis* 4,4a,5,6,7,8-hexahydro-2(3H) naphthalenone **13**<sup>6c,d,13</sup> by a Robinson annelation.



The steric course of the Michael addition of 2,6-dimethyl-1-(trimethylsiloxy)cyclohexene **4** on the oxazoline **1b** (entry 5) was easier to study on the enol lactones **14** which have only two asymmetric centers. These derivatives were obtained with 82% yield in the ratio **14a**:**14b** = 9:1 by heating the crude acidic fraction in acetic anhydride in the presence of sodium acetate. The relative configurations were proposed on the basis of PMR. Thus, in the major diastereomer **14a**, the coupling constants between the vicinal protons at C-3 and C-4 are the same as those observed in the enol lactone **12** ( $J_{3a,4} = 12.5$  Hz and  $J_{3b,4} = 6.0$  Hz), indicating a *cis* relationship between the two methyl groups.

This original activation of Michael acceptors could be applied to the synthesis of several natural products, particularly in the sesqui- and diterpenes field.

The extension of these results to asymmetric conjugated additions of various nucleophiles is now being investigated with several chiral  $\alpha,\beta$ -unsaturated oxazolines available in our laboratory.

#### Acknowledgements

We wish to thank Professor Y. Langlois and Dr. E. Guittet for helpful discussions.

#### References and Notes

1. Student of the IUT of Chemistry (Orsay) in training period. Preliminary communication : Third Belgian Organic Synthesis Symposium (BOSS-3), Louvain-La-Neuve, 16-20 July 1990.
2. Lutomski, K.A.; Meyers, A.I., *Asymmetric Synthesis*, 1984, 3, 213 and references therein.
3. a) Pouilhès, A.; Kouklovsky, C.; Langlois, N.; Langlois, Y. *Tetrahedron Letters*, 1987, 28, 6183.  
 b) Pouilhès, A.; Uriarte, E.; Kouklovsky, C.; Langlois, N.; Langlois, Y.; Chiaroni, A.; Riche, C. *Tetrahedron letters*, 1989, 30, 1395.  
 c) Kouklovsky, C., Thèse de Doctorat en Sciences, Université de Paris Sud, Orsay, 14th November 1989.

4. a) Meyer, W.L.; Clemans, G.V., Manning, R.A., *J. Org. Chem.*, **1975**, *40*, 3686 and references therein.  
b) d'Angelo, J., Guingant, A., *Tetrahedron Letters*, **1988**, *29*, 2667.
5. Duhamel, P., Hennequin, L.; Poirier, J.M.; Tavel, G.; Vottero, C. *Tetrahedron*, **1986**, *42*, 4777.
6. a) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Chemistry Letters*, **1974**, 1223.  
b) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.*, **1976**, *49*, 779.  
c) Kikuchi, M.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.*, **1981**, *54*, 3420.  
d) Huffman, J.W.; Potnis, S.M.; Satish, A.V., *J. Org. Chem.*, **1985**, *50*, 4266.
7. Duhamel, P.; Hennequin, L.; Poirier, N.; Poirier, J.M. *Tetrahedron Letters*, **1985**, *26*, 6201.
8. The oxazolines 1a and 1b were prepared according to ref. 3c. The oxazoline 1c was obtained as previously described : Luteri, G.F.; Ford, W.T.; *J. Org. Chem.*, **1977**, *42*, 820, according to Meyers, A.I.; Temple, D.L.; Haidukewych, D.; Mihelich, E.D.; *J. org. Chem.*, **1974**, *39*, 2787.
9. a) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron*, **1987**, *43*, 2075.  
b) Rubottom, G.M.; June H.D. Jr.; *J. Org. Chem.*, **1983**, *48*, 422.
10. Pfau, M.; Revial, G.; Guingant, A., d'Angelo, J. *J. Amer. Chem. Soc.*, **1985**, *107*, 273.
11. Martin, J., Parker, W.; Raphael, R.A. *J. Chem. Soc.*, **1964**, 289.
12. a) Fujimoto, G. *J. Amer. Chem. Soc.*, **1951**, *73*, 1856.  
b) Heard, R.D.H.; Ziegler, P. *J. Amer. Chem. Soc.*, **1951**, *73*, 4036.
13. Sims, J.J.; Selman, L.H. *Tetrahedron Letters*, **1969**, 561.

(Received in France 31 August 1990)