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Catalytic High Pressure Synthesis of Hindered β -Aminoesters.

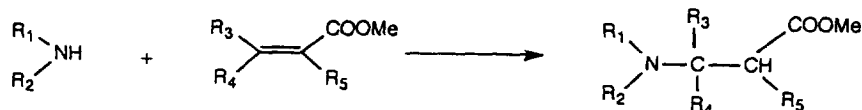
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Abstract : Hindered β -aminoesters are obtained in fair to high yields by the conjugate addition of amines to α,β -unsaturated esters, both substrates harbouring bulky groups, under high pressure in the presence of catalytic amounts of ytterbium triflate.

β -Lactams are widely used *inter alia* as antibiotics.¹ A simple potential route involves in a first step the conjugate addition of primary amines to α,β -ethylenic esters yielding β -aminoesters which can be subsequently converted into β -lactams by known procedures.^{2,3} However, the limits of the method are rapidly reached as the reaction is extremely sensitive to steric hindrance.^{4,5} In fact, only acrylic esters and simple unsubstituted primary amines enter smooth addition under moderate temperature conditions.⁶ Two notable improvements in the field were recently reported : the use of appropriate catalysts such as lanthanide triflates⁷ and high pressure.⁸ Ytterbium triflate was shown to be an effective catalyst in the addition of ethyl crotonate to benzylamine⁷ whereas crotonates were reacted with chiral amines under 5-15 kb pressure to yield enantioselectively β -aminoesters.⁸

Our laboratory has initiated a kinetic study in order to quantify the pressure effect in a series of reactions involving amines and α,β -ethylenic esters of increasing bulkiness.⁹ Remarkably, it could be observed that the reactions were very sensitive to pressure and characterized by high negative values for the volume of activation (-50 to -60 cm³.mol⁻¹), meaning acceleration factors of about $2 \cdot 10^4$ to $1.5 \cdot 10^5$ at 10 kb and 25° C. Quite obviously, such significant increases in reaction rates make pressure as a parameter of choice for the synthesis of sterically congested β -aminoesters. In addition, we felt that the combination of physical (high pressure) and chemical (catalysis) activation could emerge as an exceptional powerful synthetic method in the preparation of hindered β -aminoesters which, otherwise, could not be synthesized by traditional procedures.

Table 1. : Effect of catalyst^a :

Catalyst	Yields (%)			
	A ^b	B ^b	C ^b	D ^b
none	26 (8)	62	1.5	30
Eu(fod) ₃	-	59	1.5	29
Yb(OTf) ₃	100 (42)	95	8	63
ZrCl ₄	-	100	6	88
LiClO ₄ ^c	-	34	-	-
LiClO ₄	-	14	-	-
Bu ₄ NF	-	-	traces	-
PBu ₃	-	52	-	19
DABCO	-	-	0	0

^a (5 % in moles), solvent (acetonitrile), t (24 h), amine:ester (2:1)

^b Reaction A (PhCH₂NH₂ + ethyl crotonate, 1 bar, 30° C) (in parentheses, yields obtained under conditions of ref. 7 : 20° C, solvent (CH₂Cl₂), t (15 h)

Reaction B (iPrNH₂ + methyl crotonate, 1 bar, 30° C)

Reaction C (iPrNH₂ + methyl methacrylate, 1 bar, 30° C)

Reaction D (tBuNH₂ + methyl crotonate, 3 kbar, 36° C)

^c 5M in diethyl ether. No acetonitrile was added

In a first stage, the results of ref. 7 are checked under two different conditions (Table 1). At 20° C, 1 bar, 15 h in CH₂Cl₂, the yield of ester is 8 % (0 % according to ref. 7) and 42 % (vs 92 % in ref. 7) without and in the presence of the ytterbium catalyst respectively. In CH₃CN, a temperature increase of 10° C raises these values to 26 % and 100 % respectively, indicating a relatively facile reaction compared to the reactions studied below (Table 2). Then, we screen some catalysts including strong and mild Lewis acids as well as organic bases.¹⁰ Clearly, organic bases are not suitable. The strong Lewis acid ZrCl₄ is a potent catalyst, however, the results are puzzling as ZrCl₄ can undergo complexation with amines and act as polymerization catalyst (for example in reactions involving methyl acrylate). LiClO₄ in diethyl ether is much less efficient. Among the two lanthanide compounds, only ytterbium triflate improves the yield, in harmony with the former study⁷ though not to the same extent. Accordingly, the high pressure experiments are carried out in the presence of Yb(OTf)₃. The results are listed in Table 2.

Table 2. : High pressure synthesis of β -aminoesters^a :

Entry	Methyl ester	Amine	T (°C)	P(bar)	Yield (%) ^b	
					no catalyst	with Yb(OTf) ₃
1	acrylate	iPr ₂ NH	50	1	0	17
			50	3000	13	80
2	methacrylate	tBuNH ₂	30	1	0	4
			30	3000	11	47
3	methacrylate	Ph ₂ CHNH ₂	50	1	0	0
			50	3000	0	--
			50	9500	34	100
4	methacrylate	iPr(Me)NH	50	1	0	10
			50	3000	28	50
5	crotonate	iPr(Me)NH	50	1	2	6
			50	3000	55	61
6	crotonate	iBu ₂ NH	50	1	0	7
			50	3000	20	47
7	crotonate	iPr ₂ NH	50	1	0	0
			50	3000	0	0
			50	9500	0	10
8	DMA ^c	iPrNH ₂	50	1	0	0
			50	3000	1	7
			50	9500	45	78
9	DMA ^c	tBuNH ₂	50	1	0	0
			50	3000	0	0
			50	9500	5	13

^a Solvent (acetonitrile), 24 h, catalyst (5 % mole).

^b Isolated yields.

^c 3,3-dimethyl acrylate.

At atmospheric pressure, no or very little reaction takes place in the absence of the ytterbium compound. Carrying out the reactions with Yb(OTf)₃ as the catalyst leads to low yields of aminoester, except in entry 1 where a 17 % yield is observed. Increasing the pressure promotes the formation of β -aminoesters. Combination of pressure and lanthanide catalysis is particularly efficient in most cases. The presence of the catalyst increases the yield by a factor varying between 1.1 and 7, indicating a catalyst effect depending on the substrates involved. An interesting result is provided by entry 7 showing a 10 % yield of the corresponding aminoester vs 0 % without catalyst. The reaction with diisobutylamine (entry 6) occurs easier, since the product is formed at lower pressure in substantial yield. However, it is clear that high pressure is the determining parameter (compare the yields in the uncatalyzed vs catalyzed reactions when pressure is increased from atmospheric to 3 kb).

In the last years, it was shown that some reactions, including Michael additions,¹¹ could be promoted in water.¹² In order to compare pressure and hydrophobic effects, the experiments listed in entries 1 and 4

(atmospheric pressure) are carried out in water.¹³ No reaction is observed at all even, surprisingly, when the water soluble Yb(OTf)₃-catalyst is added.

In conclusion, pressure associated with catalysis by ytterbium triflate¹⁴ is a remarkable tool in the synthesis of hindered β -aminoesters which may give access to interesting crowded biological systems as the bioactivity is dependent not only on their chemical, but also structural (steric) properties.¹⁵ In addition, the present syntheses demonstrate the uniqueness of the pressure procedure versus novel activation methods such as use of water or LiClO₄-diethyl ether¹⁶ as reaction medium which are unable to lead to the hindered structures described here. The present results stay in agreement with earlier reports on the beneficial effect of pressure on the synthesis of crowded molecules.¹⁷

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References and Notes :

1. Komiya, T. Recent Advances in the Chemistry of β -Lactam Antibiotics, *Chemical Society*, Cambridge, **1976**, 287-294.
2. Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *J. Am. Chem. Soc.*, **1981**, *103*, 2406-2408.
3. Vorbrüggen, H.; Woodward, R.B. *Tetrahedron*, **1933**, *49*, 1625-1634
4. Pfau, M. *Bull. Soc. Chim. France*, **1967**, 1117-1125.
5. Kinast, R.; Pankiewicz, K.; Stec, W.J.; Farmer, P.B.; Forster, A.B.; Jarman, M. *J. Org. Chem.*, **1977**, *42*, 1650-1652.
6. Temperature should be kept as low as possible. Temperatures above 50° C may divert the reaction along other pathways.
7. Matsubara, S.; Yoshioka, M.; Utimoto, K. *Chem. Lett.*, **1994**, 827-830.
8. D'Angelo, J.; Maddaluno, J. *J. Am. Chem. Soc.*, **1986**, *108*, 8112-8114.
9. Jenner, G. in preparation.
10. Experimental. In a 2.5 mL flexible (runs up to 3 kb) or 1 mL rigid (experiments at 9.5 kb) PTFE tube are introduced successively the catalyst, a first portion of acetonitrile, the unsaturated ester and the amine. The final volume is adjusted with acetonitrile. The tube is placed in a high pressure vessel (4 kb) or cell (10 kb, uniaxial compression). The pressure is released after 24 h. The volatile components of the reaction mixture are removed under vacuum. Diethyl ether is added in order to precipitate Yb(OTf)₃. The filtrate is evaporated, leaving in most cases the aminoester as sole product. With higher boiling amines and esters or when polymers are formed, the residue is placed on a silicagel column and eluted with hexane-ethyl acetate (2:1). The structure of the adducts is determined unambiguously by ¹H NMR.
11. Lubineau, A.; Augé, J. *Tetrahedron Lett.*, **1992**, *33*, 8073-8074.
12. Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis*, **1994**, 741-759.
13. The experiments are carried out with water (5 mL), CH₂Cl₂ (0.1 mL), amine (1.2 mmol), ester (1.0 mmol) and eventually Yb(OTf)₃ (0.05 mmol) for the catalytic runs in water.
14. We have just learned on the ytterbium triflate-catalyzed ring opening of epoxides under pressure. Meguro, M.; Asao, N.; Yamamoto, Y. *J. Chem. Soc. Perkin Trans. 1*, **1994**, 2597-2601.
15. Charton, M. *Top. Curr. Chem.*, **1983**, *114*, 107-118
16. Fujita, T.; Iwamura, H. *Top. Curr. Chem.*, **1983**, *114*, 119-161.
17. Grieco, P.A.; Nunes, J.J.; Gaul, M.D. *J. Am. Chem. Soc.*, **1990**, *112*, 4595-4596
- Jenner, G. *High Press. Res.*, **1993**, *11*, 257-262.
- Jenner, G. *High Press. Res.*, **1992**, *11*, 21-32.

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