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High Pressure and Lanthanide Catalyzed Synthesis of Enamino Compounds

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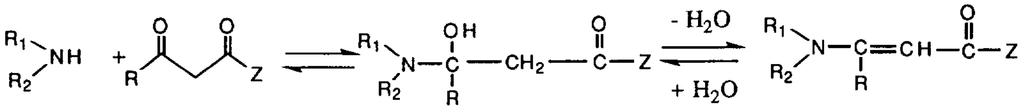
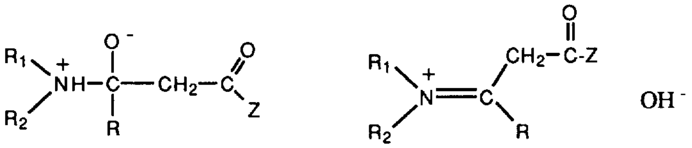
Abstract : The synthesis of enaminoketones from the condensation of bulky amines with ethyl acetoacetate or 2,4-pentanedione is described. The reaction can be activated either by high pressure or catalysis by ytterbium triflate. However, the pressure route is of wider applicability. The method is limited by the kinetic competition between the formation of the intermediate aminoalcohol and the dehydration step. Copyright © 1996 Elsevier Science Ltd

Enamino ketones and esters are gaining increased interest, particularly cyclic β-enaminoesters which are known as important intermediates for the synthesis of natural products[1]. The most direct route for the synthesis of enamino compounds is the condensation of a primary amine and a 1,3-diketone or 3-ketoester[2,3]. The reaction is usually facile when uncrowded primary amines are involved. Aromatic or hindered amines react more sluggishly and necessitate azeotropic removal of the water formed[4]. In recent years, chemical and physical activation methods have been proposed in order to improve the chemical yield: BF_3 catalysis[5], heterogeneous clay catalysis[6,7], microwave irradiation[8,9]. The reaction can simply be depicted as a sequence of an addition reaction followed by elimination of a molecule of water. However, depending on the basicity of the amine and the steric environment of both the keto compound and the amine, an equilibrium can exist[3] in such way that it may become necessary to trap the water formed in order to shift the equilibrium towards the enamine :



The step precluding to the formation of the enamine involves ionic forms[10] :



The formation of the zwitterion is reminiscent of the mechanism of the addition of an amine to α,β-unsaturated compounds[11]. We have recently shown that such addition is a highly pressure dependent reaction involving considerable electrostriction within the transition state[12]. In addition, we also demonstrated that combination of high pressure (300-1000 MPa) and lanthanide catalysis was remarkably beneficial in the synthesis of hindered β-aminoesters[13]. These results prompted us to contemplate both the pressure effect as well as the catalytic effect of ytterbium triflate on the condensation reaction yielding enamino compounds.

Table 1. Condensation of 1,3-keto compounds with amines $(R_1)(R_2)NH$.Yields (%)[a,b].

Entry	R_1	R_2	Product	T (°C) (1 day)	0.1 MPa		300 MPa	
					nc	Yb	nc	Yb
Ethyl acetoacetate **1**								
1	n-Pr	H	**3**	30	100	-	-	-
2	Ph_2CH	H	**4**	20	40	-	99	-
3	PH	H	**5**	20	4	64	23	92
4	$PhCH_2$	Me	**6**	30	100	-	-	-
5	i-Pr	Me	**7**	30	1	63	62	81
6	n-Pr	n-Pr	**8**	20	8	6	16 [c]	70
	n-Pr	n-Pr		30	-	37 [c]	49 [c]	-
7	$PhCH_2$	PhCH2	**9**	20	0	10	15	-
	$PhCH_2$	PhCH2		30	6	61	-	64
8	$-(CH_2)_5-$		**10**	20	8	36	67	82
9	i-Bu	i-Bu	**11**	30	~ 0	14	22	39
10	i-Pr	i-Pr		30	0	0	0	0
11	Ph	Me		30	0	0	0	-
12	Ph	Ph		30	0	0	0	-
2,4-Pentanedione **2**								
13	n-Pr	H	**12**	30	100	-	-	-
14	Ph_2CH	H	**13**	20	100	-	-	-
15	Ph	H	**14**	20	9	100	85	-
16	i-Pr	Me	**15**	20	0	-	12	3 [c]
17	n-Bu	n-Bu	**16**	30	0	0 [c]	23	-
18	i-Bu	i-Bu	**17**	20	0	0 [c]	3	0 [c]
				30	0	0 [c]	17	-
				50	-	0 [c]	32	-
19	$-(CH_2)_5-$		**18**	30	6	-	63	-

[a] : Yields are based on NMR data (see experimetal part).
[b] : nc (no catalyst added) - Yb (with 2 % ytterbium triflate).
[c] : Other products are also formed.

Ethyl acetoacetate **1** and 2,4-pentanedione **2** were reacted with primary and secondary amines involving more or less congested alkyl and aryl groups (Table 1)[14]. Temperature was kept as low as possible (20-30°C) since for less reactive amines, the low rate favours inverse or subsequent reactions (vide infra).

The following observations are in order :

* Primary amines with unbulky alkyl groups readily entered condensation with both keto compounds at ambient pressure (entries 1,13,14), in line with the results reported in the literature with other simple primary amines.

* Aniline (entries 3,15) reacted with difficulty. However, the yield was increased by an appreciable factor (6 to 9) when pressure was raised to 300 MPa. The yield was also improved in the presence of ytterbium triflate (64 % and 100 % respectively). A 92 % yield was obtained in the condensation involving **1** by carrying out the reaction under pressure with the lanthanide catalyst (literature values are respectively 50 % and 77 % of products **5** and **14**, obtained under heterogeneous catalysis [7]).

* Generally, combination of pressure and lanthanide catalysis gave good yields even with dialkylamines. This comment is true as long as condensations of **1** with amines are considered (entries 5-9). In reactions involving **2**, the ytterbium catalyst diverted the reaction along other pathways (with the notable exception of reaction shown in entry 15). Omitting the lanthanide compound and using 300 MPa pressure promoted the formation of the enaminoketone (entries 16-19).

* Secondary amines with two bulky groups could not be brought to reactivity despite the conjugate action of pressure and catalysis (entries 10-12), even under very high pressure (1000 MPa).
Such high pressure (950 MPa) was also tried to improve the yields in entries 9 (with Yb catalyst) and 17 (no catalyst added). The corresponding yields of enaminocompounds were 48 % and 13 % respectively together with formation of other products. This means that very high pressures (compared to 300 MPa) either improve only slightly the yield of the enamino compound (entry 9) or depress it (entry 17). These experiments reveal the limits of the generalisation of the present method like all other methods cited [5-9].

In some reactions, other products are generated additionally or, in most cases, exclusively (entries 9, 16 and 6 -at 950 MPa-). They were isolated as solid compounds and shown to be amides, probably originating from hydrolysis of the initial formed aminoalcohol (mechanism of Stork)[15]. These results may suggest that the water released can be troublesome for a good yield of the enaminoketone. In fact, pressure may also accelerate hydrolysis reactions as exemplified in other works[16-19]. This could explain the low increase in yield when pressure was raised from 300 to 950 MPa (in entry 9). In order to obviate to this problem, we examined the effect of drying agents on two condensations involving **1**. Table 2 lists also additional results comparing physical (high pressure) and chemical (acid catalysis) activation methods. The results show that desiccants do not improve the yields, the presence of molecular sieves even exert a detrimental effect contrary to expectation. Inorganic solid catalysts which were previously used in such reactions[7] were much less active than lanthanide catalysts.

Table 2. Effect of desiccants and catalysts on the condensation of **1** with secondary amines at 30° C.

Conditions	$(i\text{-}Bu)_2NH$	$(i\text{-}Pr)(Me)NH$
no catalyst[a]	0	1
$Yb(OTf)_3$[a]	14	63
$Sc(OTf)_3$	39	29
Al_2O_3[a]	2	4
Na_2SO_4[a]	1	0
Mont(Fe)[a,c]	4	3
no catalyst[b]	24	62
MS (4Å)[b,d]	6	no run
MS (crusched)[b,d]	8	no run

[a] : At atmospheric pressure.
[b] : Under 300 MPa.
[c] : Mont(Fe) : montmorillonite doped with Fe^{+++}.
[d] : MS : molecular sieves.

Conclusion :

High pressure (≤ 300 MPa) is a valuable activation method in the formation of enaminoketones from the condensation of bulky amines with **1** and **2**. Lanthanide catalysis operates only in reactions involving **1**. The present methods are at least as efficient as those previously reported[5-9]. In particular, the pressure route appears of more general applicability. However, the final yield of enaminoketone is connected with the rate of formation of the intermediate aminoalcohol (which depends on the basicity and the steric environment of the amine, as stated in the introduction) and the rate of the dehydration step, both processes being influenced by pressure.

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14. Experimental. A $CHCl_3$ solution of 0.8 mmol ethyl acetoacetate (or 1.0 mmol acetylacetone), the appropriate amine (1-1.5 eq.) and 0.10-0.15 mmol of 1,2,3-trimethoxybenzene (internal standard) was placed in a flexible PTFE tube and submitted to atmospheric or high pressure for one day. After release of pressure, $CHCl_3$ and the volatile compounds were removed in vacuo. The crude mixture was submitted to ^1H NMR (Brucker AC 200, 200 MHz, $CDCl_3$). The yield of product was determined from the relative intensities of the olefinic proton (~ 4.5 ppm in the case of products from **1**, ~ 5 ppm in the case of products from **2**) vs methoxy groups of the internal standard (~ 3.85 ppm). Pure enamino compounds were obtained either by simple crystallization from pentane or by flash column chromatography.
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