Tetrahedron Letters,Vol.26,No.10,pp 1311-1314,1985
Printed in Great Britain

0040-4039/85 \$3.00 + .00

1,4-ADDITION REACTIONS TO METHACRYLAMIDE : A ONE POT SYNTHESIS OF 3,4-DIHYDRO 2(1H)-PYRIDINONES AND 3,5-DISUBSTITUTED GLUTARIMIDES

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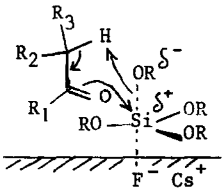
Summary : Ketones and β-cyano or β-keto esters were found to add directly to methacrylamide in a one pot process in the presence of $CsF/Si(OCH_3)_4$ to give 1,4-addition compounds.

In previous papers (1-3), we have described the $CsF/Si(OCH_3)_4$ system as promoting the Michael type reactions (4-6). It reacts selectively and efficiently giving the 1,4-addition of ketones and phenylacetonitriles to α, β-unsaturated ketones, esters and nitriles.

The proposed mechanism involves a nucleophilic activation by fluoride ion giving an extension of coordination at silicon (7,8).



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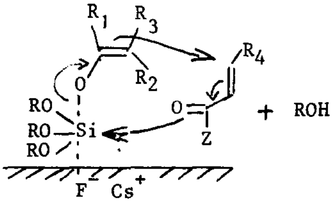

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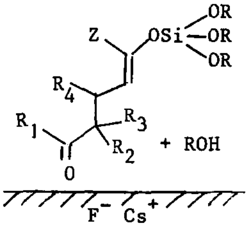

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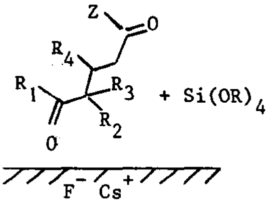

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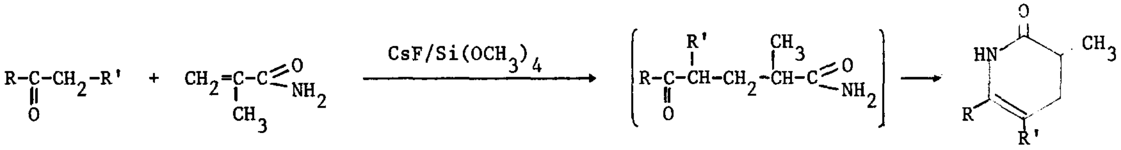
More recently (9), $CsF/Si(OCH_3)_4$ was successfully used for 1,4-addition reactions to α, β-unsaturated tertiary amides. We now report (see Table) the results concerning the 1,4-addition of ketones and β-cyano or β-keto esters to methacrylamide when $CsF/Si(OCH_3)_4$ was used in the same conditions as before. In this case, the Michael type reaction occurs and is followed, *in situ*, by the cyclisation, leading to 3,4-dihydro 2(1H)-pyridinones or 3,5-disubstituted glutarimides.



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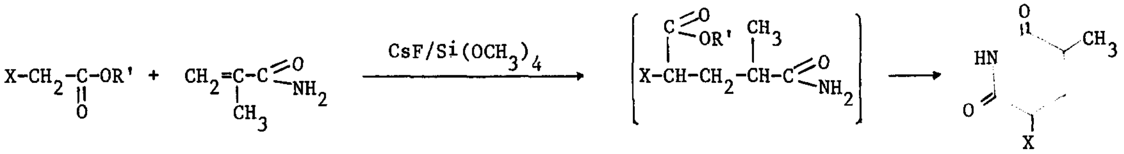


The typical procedure is the following one : synthesis of 3-methyl 5,6-diphenyl 3,4-dihydro 2(1H)-pyridinone.

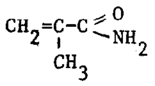
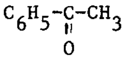
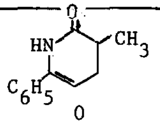
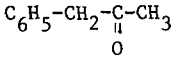
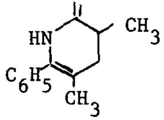
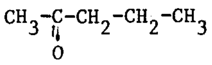
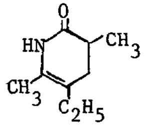
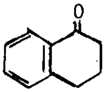
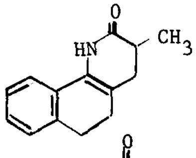
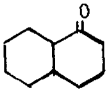
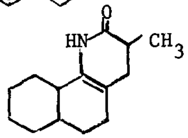
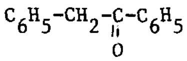
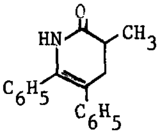
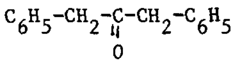
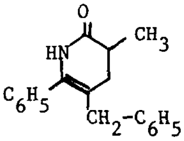
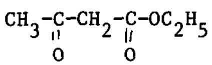
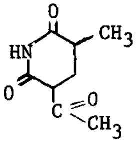
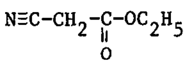
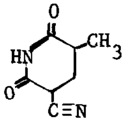
25 mmol of methacrylamide $CH_2=C(CH_3)-C(=O)NH_2$, 25 mmol of phenylacetophenone are added to 15 mmol of $Si(OCH_3)_4$ and 20 mmol of CsF under nitrogen atmosphere.

The mixture was stirred and heated at 80°C for 5 hours. Hydrolysis was not necessary and the mixture was extracted with CH_2Cl_2 and the crude product was recrystallized from ethyl acetate (m p : 157°C).

Even, if some ketones (cyclohexanone, methyl isopropyl ketone, 2,4-pentanedione) give mixtures, in many cases this method allows the formation of the pure cyclic compound in a one pot process, without hydrolysis and in good yields while stepwise reactions are usually necessary (10).

The mechanism we propose is the one previously indicated : nucleophilic activation of $Si(OCH_3)_4$ by the fluoride ion giving a basic species which promotes enolate formation. The fast silylation of this enolate gives the silyl enol ether which promotes the 1,4 adduct on the α,β-unsaturated primary amide. This compound reacts in situ with the alcohol present in the mixture to give the 1,5-difunctionnal compound. This primary amide undergoes a fast cyclisation in situ and the final product is isolated by recrystallisation.

Michael additions on methacrylamide in the presence of $CsF/Si(OCH_3)_4$

Electrophile	Michael donor	Reaction conditions		Isolated product		Yield(%)
		t(h)	T°C			
 $CH_2=\underset{\underset{CH_3}{\vert}}{C}-C{\scriptstyle\begin{matrix}\nearrow O\\ \searrow NH_2\end{matrix}}$	 $C_6H_5-\underset{\overset{\Vert}{O}}{C}-CH_3$	2	80		(a)	55
″	 $C_6H_5-CH_2-\underset{\overset{\Vert}{O}}{C}-CH_3$	12	80		(a)	46
″	 $CH_3-\underset{\overset{\Vert}{O}}{C}-CH_2-CH_2-CH_3$	12	80			33
″		12	100			94
″		12	100			90
″	 $C_6H_5-CH_2-\underset{\overset{\Vert}{O}}{C}-C_6H_5$	5	80			76
″	 $C_6H_5-CH_2-\underset{\overset{\Vert}{O}}{C}-CH_2-C_6H_5$	6	80			70
″	 $CH_3-\underset{\overset{\Vert}{O}}{C}-CH_2-\underset{\overset{\Vert}{O}}{C}-OC_2H_5$	2	80		(b)	83
″	 $N\equiv C-CH_2-\underset{\overset{\Vert}{O}}{C}-OC_2H_5$	12	80		(c)	84

(a) see ref. 13 (b) see ref. 12 (c) see ref. 11.

Elemental analysis and spectral data (IR and NMR) are consistent with the structures of the products.

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(Received in France 28 December 1984)