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Conjugate Addition of Amides to α,β-Unsaturated Esters by CsF-Si(OEt)$_4$ System

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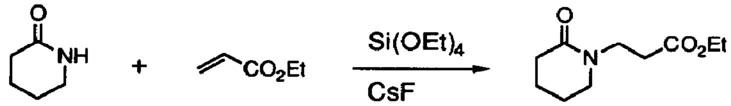
Abstract: *The conjugate addition of amides to α,β-unsaturated esters proceeds efficiently with an equimolar amount of Si(OEt)$_4$ and a catalytic amount of CsF to afford the corresponding N-substituted amides.*

The conjugate addition of stabilized carbanions to α,β-unsaturated carbonyl systems (the Michael addition) has been a fundamental method of carbon-carbon bond formations.[1] The undesired side reactions such as retro-additions, auto-condensations, bis-additions, and polymerizations that frequently follow under the conventional base-catalyzed processes have been circumvented by a variety of mild reaction conditions. Use of phase-transfer catalysts,[2] solid-supported catalysts,[3] transition-metal complexes,[4] surface-mediated solid phase reactions,[5] LiI in refluxing DME,[6] and CsF-Si(OR)$_4$ system[7] have been reported.[8] In the course of our synthetic study of xestospongin A,[9] the conjugate addition of a substituted δ-valerolactam to an acrylate to get the corresponding N-substituted lactam was needed.

In contrast to the various Michael addition methods, there are few examples of the conjugate addition of heteronucleophiles such as lactams or their analogs (N-conjugate addition).[10] In the conventional Michael addition, the nucleophile is usually a stabilized (the pK$_a$ value of its conjugate acid is in the range of 9-13) and soft carbanion, whereas the pK$_a$ value of the lactam NH proton is much larger[11] and its anion is a hard species. Considering these unfavorable factors, most of the aforementioned Michael reaction conditions may not be suitable for the N-conjugate addition of lactams and their analogs. Indeed, under the conventional conjugate addition condition that employs a strong base such as NaOMe or NaOH,[12] the desired N-substituted δ-valerolactam was formed only in less than 5% yield. Other mild systems such as Cs_2CO_3-$CHCl_3$[13] and n-$Bu_4N^+Cl^-$-KF·2H_2O-CH_3CN[2b] did not give the product.[14] We surmised that a probable obstacle of the reaction might be the retro-additions. Desirable is the conjugate addition method that generates a strong base which can deprotonate the lactam NH proton and most importantly can interrupt the retro-addition from the adduct. The CsF-Si(OR)$_4$ system of Corriu and co-workers[7] was expected to fulfill these requirements. Indeed, under the Corriu condition (equimolar amounts of CsF and Si(OEt)$_4$ without solvent) the conjugate addition of δ-valerolactam to ethyl acrylate proceeded instantly at ambient temperature to afford the corresponding N-substituted lactam in 98% yield.



We have found that an equimolar amount of CsF is not a mandatory requirement and 10 mol % is enough for the conjugate addition, although for some less reactive amides a longer reaction time is needed. Considering the mechanism, $Si(OEt)_4$ is believed to play two roles: (1) the generation of EtO^- that is promoted by the coordination of fluoride ion to the silicon compound,[15] and (2) the trapping of the enolate adduct to give the corresponding silyl enol ether.[7] In the absence of $Si(OEt)_4$ a lower yield was obtained for the above reaction (19% after 4 days at room temperature).[16]

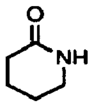
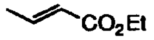
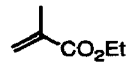
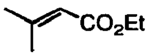
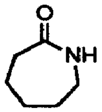
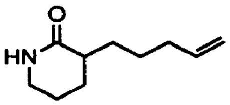
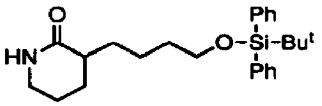
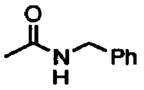
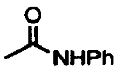
Table 1 illustrates the results. As is often the case with the Michael addition,[4b,7a] the substitution pattern of conjugate addition acceptors has great influence on the reactivity. Thus, ethyl β,β-dimethylacrylate does not undergo the conjugate addition at all. Interestingly ethyl methacrylate, an α-substituted ester, reacted sluggishly under the modified reaction condition; however, with an equimolar amount of CsF it reacted rapidly to afford the corresponding adduct in high yield. In the case of acyclic amides the conjugate addition did not proceed to completion even with an equimolar amount of CsF. Thus, the treatment of N-phenylacetamide and ethyl acrylate with equimolar amounts of CsF and $Si(OEt)_4$ afforded the corresponding adduct in 76% yield and 19% of the recovered starting material. It is notable that a *tert*-butyldiphenylsilyl ether survives under the condition. When methyl vinyl ketone or N,N-diethylacrylamide was used as conjugate acceptor, the desired adduct was not formed: polymerization of the acceptor was observed in the former case.

The N-conjugate addition of amides to acrylates can be carried out under our modified condition (with 10 mol % of CsF) in the presence of solvent such as THF or toluene, but not in CH_2Cl_2. With solvent the addition requires longer reaction time (In 0.3 M THF, 92% conversion after 24 h; in 0.3 M toluene, 96% conversion after 12 h).

A typical experimental procedure: To a suspension of δ-valerolactam (1.30 g, 13.1 mmol), CsF (0.20 g, 1.31 mmol), and $Si(OEt)_4$ (2.92 mL, 13.1 mmol) at 25 °C under argon atmosphere, was added ethyl acrylate (1.56 mL, 14.4 mmol) dropwise. After being stirred for 20 min, the reaction mixture was directly subjected to flash column chromatography on silica gel (eluent: ethyl acetate/petroleum ether=1:1 by volume) to afford the corresponding adduct in 98% yield (2.56 g) as a colorless oil.

In conclusion, the N-conjugate addition of amides to α,β-unsaturated esters, which is rather difficult under several conditions that have been used for the Michael addition, now can be carried out efficiently by CsF-$Si(OEt)_4$ system. Under our modified condition only 10 mol % of CsF is enough, and solvents such as toluene and THF can be employed when necessary.

Table 1. Conjugate Addition of Amides to α,β-Unsaturated Esters by CsF-$Si(OEt)_4$[a]

				N-Substituted adduct[c]	
Amides	α,β-Unsaturated esters[b]	CsF (equiv)	Reaction time	Yield[d] (%)	bp,°C (mmHg)
		0.1	10 min	98	143-144 (1.6)
		0.1	10 min	96	160-161 (2.2)
		0.1	24 h	50	
		1.0	20 min	95	
		1.0	48 h	0[e]	
		0.1	1 h	89	158-159 (2.2)
		0.1	15 min	92	212-213 (1.8)
		0.1	20 min	93	
		0.1	48 h	83 (15)[f]	
		0.1	48 h	77 (23)[g]	
		1.0	12 h	76 (19)[f,h]	

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[a] At 25 °C without solvent; with 1.0~1.1 molar equiv of $Si(OEt)_4$. [b] 1.1 molar equiv was used. [c] All products were characterized by nmr (^1H, ^{13}C), ir and mass data. [d] Yields after purification by SiO_2 column chromatography. [e] Starting material remained. [f] Those in parenthesis are recovered starting materials. [g] Determined by ^1H nmr spectrum analysis. [h] 1.5 molar equiv of $Si(OEt)_4$ was used.

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8. The conjugate addition of enol silyl ethers to α,β-unsaturated carbonyl systems, a Mukaiyama-type addition, is distinguished from the mentioned direct conjugate addition reactions: for recent examples of this type of reactions, see: Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1990**, *33*, 1581; Kobayashi, S.; Hachiya, I.; Takahori, T; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815; de Weghe, P. V.; Collin, J. *Tetrahedron Lett.* **1993**, *34*, 3881 and references therein.
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14. The N-conjugate addition of an urea to methyl acrylate has been reported with K_2CO_3-$BnEt_3N^+Cl^-$-DMF system (Kumar, S.; Saini, R.; Singh, H. *Tetrahedron Lett.* **1992**, *33*, 7937). Under this condition we found that the reaction of δ-valerolactam with ethyl acrylate gave the N-substituted conjugate adduct but a considerable amount of unidentified side product was also formed.
15. In case $Si(OMe)_4$ was used, transesterification was accompanied to afford the adduct in a mixture of the ethyl and methyl esters. Transesterification with CsF-$Si(OMe)_4$ system is under study.
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