## CHEMOSELECTIVITY IN THE CONJUGATE ADDITION OF ALLYLSILANE TO MICHAEL ACCEPTORS[†]

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SUMMARY: The allylic carbanion species generated by treatment of allylsilane with fluoride ion undergoes highly chemoselective conjugate addition to a series of Michael acceptors for which alternative known allylation procedures proved less general.

Conjugate addition of most nucleophilic reagents to an α,β-unsaturated system can be achieved routinely using an organocopper reagent or a copper-catalyzed Grignard reagent.[1] House and Fischer,[2] however, observed that the condensation of allyllithium cuprate with an α,β-enone was highly substrate dependent. Their findings inspired a search for a general means of allylating α,β-unsaturated functions.

Sakurai and Hosomi were the first to demonstrate that treatment of an allylsilane in the presence of an α,β-enone with a Lewis acid effected allylation in high yield.[3,4] Later they reported that the fluoride ion-catalyzed allylation of an enone resulted in only a 75% yield of 1,2 and 1,4 addition products in a 2:1 ratio.[5] Sakurai also reported that nitriles, epoxides and esters all failed to react with the allylic anionic species generated.[6]
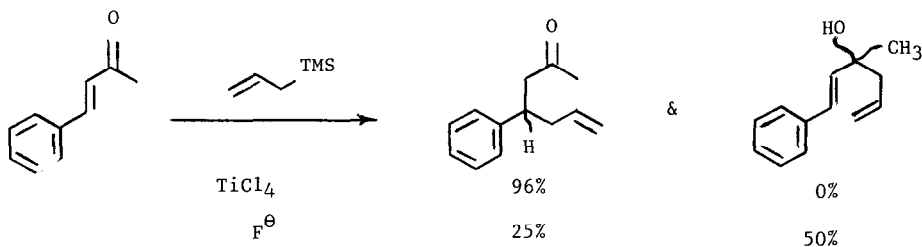
These results suggest that less-electrophilic Michael acceptors might pre-ferentially undergo conjugate addition, rather than 1,2 addition, during the fluoride-induced allylation. Our findings in this area are highlighted in this report. Surprisingly, little information is available concerning allylation of substrates other than α,β-enones. Our findings using known methods and various Michael acceptors are also described.[7]

Since our initial concern was whether the free allylic anion would exhibit high chemoselectivity for Michael addition, we chose to investigate substrates deprived of acidic protons[8]. These experiments showed that the fluoride induced allylation is capable of

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[†]In memory of Dr. Anthony Ames, Ph.D., University of Pittsburgh (1981), N.I.H. Post-doctoral Fellow, (1981-1982).

considerable chemoselectivity.[9] The nature of the solvent used was influential; significantly lower yields were obtained in ether, THF, DMSO, DME, acetonitrile, hexanes, toluene or neat. Optimum results were obtained using a highly basic medium consisting of HMPA and DMF.[11] Tetra-n-butylammonium fluoride (TBAF) proved to be the best source of the fluoride ion, in either catalytic or stoichiometric amounts. Other fluoride salts, such as benzyltrimethylammonium fluoride, catalyzed the reaction only sluggishly, while sodium fluoride and potassium fluoride failed to promote any reaction.

TABLE ONE

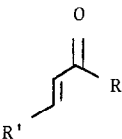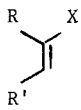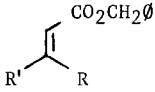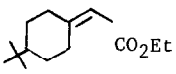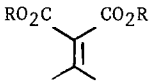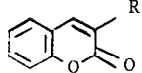| R =		$F^{\ominus}$ / TMS	TiCl4 / TMS	Li(Allyl)$_2$Cu
R = (phenyl)	X=CO$_2$Me	90%	No Reaction	61%
	=CN	65%	No Reaction	52%
	=CONEt$_2$	80%	No Reaction	no 1,4 addition
R = CO$_2$CH$_3$	X=CO$_2$CH$_3$	80%	No Reaction	64%
R = (furyl)	X=CO$_2$Et	83%	No Reaction	26%
	=CN	91%	No Reaction	73%
R = (t-Bu)	X=CO$_2$Et	80%	No Reaction	no 1,4 addition
	=CN	65%	No Reaction	47%
R = H	X=CO$_2$CH$_2\emptyset$	65%	Decomposed	28%
R = (cinnamyl)	X=CO$_2$Et	63%	No Reaction	95%(1,6)[12]
	=CN	27%	No Reaction	80%(1,6)[12]

The synthetic utility of the fluoride-induced allylation would be severely limited should the allylic anion cause enolate formation rather than undergo conjugate addition. To address this issue several examples with acidic protons were examined. Although conjugate addition predominates, yields vary. With di- and tri-substituted Michael acceptors, no unreacted starting material was ever recovered, precluding the possibility of enolate formation. The major side reaction proved to be the intermolecular condensation of the initially allylated Michael acceptor with unallylated material. High dilution of the reagents failed to suppress this process.[13]

Several entries in Table two merit further comment. As expected, steric bulk adjacent to the carbonyl moiety enhances conjugate addition for α,β-enones, and β,β-disubstituted enoates undergo deprotonation only. Our observations that α,β-unsaturated carboxylic acids failed to react and unsaturated anhydrides furnished complex mixtures have not been listed.

Known procedures were compared with the fluoride-induced allylation. Although highly efficient for allylation of enones, the Lewis acid-catalyzed process using either BF_3 etherate[14] or $TiCl_4$[4] failed for enoates and α,β-unsaturated nitriles.[15] In contrast, doubly activated Michael acceptors readily underwent allylation.

TABLE TWO

			TMS/F$^{\ominus}$	TMS/TiCl$_4$	Li(Allyl)$_2$Cu
O‖ R'(C=O)-CH=... R	R'=Phenyl	R=H	86%(1,2)	No Reaction[16]	86%(1,2)
		=CH$_3$	50%(1,2) 25%(1,4)	89%(1,4)	47%(1,4) 26%(1,2)
		=sec-butyl	20%(1,2) 57%(1,4)	8%(1,2) 74%(1,4)	17%(1,2)
		=t-butyl	26%(1,2) 58%(1,4)	92%(1,4)	45%(1,4) 43%(1,2)
	R'=CH$_3$	R=OEt	19%(1,4)	No Reaction	31%(1,2)
	R'=$\curlyvee$	R=OEt	21%(1,4)	No Reaction	61%(1,6)
R X / R'	X=CO$_2$CH$_2\emptyset$	R'=phenyl R=CH$_3$	76%(1,4)	No Reaction	no 1,4 addition
		R',R= $\vdash$(CH$_2$)$_3$$\dashv$	50%(1,4)	No Reaction	15%(1,4)
	X=CN	R',R= $\vdash$(CH$_2$)$_3$$\dashv$	44%(1,4)	No Reaction	23%(1,4)
CO$_2$CH$_2\emptyset$ / R' R	R'=phenyl	R=CH$_3$	47%(1,4)	No Reaction	64%(1,2)
	R'=R=CH$_3$		deprotonation only	Decomposed	27%(1,4)
(cyclohexylidene)=CH-CO$_2$Et	–	–	deprotonation only	No Reaction	31%(1,2)
RO$_2$C CO$_2$R /	R=Et	–	52%	35%(1,4)	86%(1,4)
(coumarin) R / O=...=O	R=COCH$_3$	–	22%(1,4)	79%(1,4)	decomposed
	=CO$_2$Et		49%(1,4)	83%(1,4)	91%

As expected, organocopper allylation proved highly substrate dependent.[17] In general, β-mono-substituted enoates and their analogous nitriles experienced conjugate addition. Highly substituted ethylenic esters resulted in the corresponding tertiary allylic alcohols, in varying yields.

In summary we have found that the fluoride-induced allylation is far more general than either cuprate addition or Lewis acid-catalyzed allylation for a wide variety of Michael acceptors.

References

1. G. H. Posner, Organic Reactions, 19, 1 (1972).
2. H. O. House and W. F. Fischer, Jr., J. Org. Chem., 34, 3615 (1969).
3. For a comprehensive review of allylsilanes in organic synthesis see: H. Sakurai, Pure and Appl. Chem., 54, 1 (1982).
4. A. Hosomi and H. Sakura, J. Am. Chem. Soc. 99, 1673 (1977).
5. A. Hosomi, A. Shirhata, and H. Sakurai, Tetrahedron Lett., 3043 (1978).
6. Sakurai's experiments could be interpreted as the consumption of the allylic anions by reaction with solvent before reaction with nitriles, esters, or epoxides could occur.
7. Satisfactory spectral data were obtained for all products.
8. The pKa of propene, the conjugate acid of the allylic anion, is 36.5.
9. The following experimental procedure is typical. A reaction vessel containing 100 mg of 4A molecular sieves was flame-dried under vacuum (5 minutes) and placed under nitrogen. A solution of 20 mg of TBAF dissolved in 1 ml of DMF (freshly distilled over CaH_2) was then added. Methyl cinnamate (100 mg, 0.617 mmol) dissolved in 1 ml of DMF was then added. A solution of 331.5 of HMPA (1.851 mmol) and 212 mg of freshly distilled allylsilane (1.851 mmol) in 2 ml of dry DMF was then added dropwise to the reaction vessel at room temperature. Coloration occurred immediately. After 10 min., TLC analysis revealed that reaction was complete[10] After methanolysis of the reaction mixture using 1 ml of a MeOH-HCl solution (9:1, volume ratios), the reaction mixture was diluted with 20 ml of water. Workup afforded 170 mg of residue which was homogeneous on TLC. Column chromatography afforded 101 mg (79%) of methyl 3-phenyl-5-hexenoate.
10. On occasion, additional allylsilane was necessary to achieve total conversion; this material was added 1 eq. at a time. At no time was greater than 6 eq. (total) of silane necessary to achieve complete condensation.
11. For an example of the effect of HMPA on 1,4-addition see H. O. House, and T. U. Lee, J. Org. Chem., 43, 4369 (1978).
12. The 1,4 addition observed contrasts with the report that ethyl sorbate undergoes 1,6 addition exclusively upon treatment with allyllithium cuprate: G. Daviaud and P. Miginiac, Tetrahedron Lett., 3345 (1973).
13. This side reaction can be minimized by adding three equivalents of trimethylsilyl fluoride to the reaction mixture. This experimental modification is undergoing further testing.
14. T. K. Sarkar and N. H. Andersen, Tetrahedron Lett., 3513 (1978).
15. The experimental procedures of references 4 and 14 were followed. In all cases, substrate failed to react. This conclusion is based on: 1) warming to RT over several hours, 2) cooling the reaction to -78°C, 3) adding trans-4-phenyl-3-buten-2-one. In all cases, only the 1,4-adduct of the added butenone (and unreacted substrate) were obtained.
16. The cinnamaldehyde is consumed by the $TiCl_4$ catalyzed 1,2 addition of chloride. This adduct, upon hydrolysis, regenerates the cinnamaldehyde.
17. The experimental procedures of references 12 and G. M. Whitesides, W. F. Fischer, Jr., J. S. Filippo, Jr., R. W. Bashe and H. O. House, J. Am. Chem. Soc., 91, 4871 (1969) were used. Only 1.5 eq. of organocuprate were employed. Additional amounts of cuprate or longer reaction times at elevated temperatures gave increased yields of the tertiary alcohols.