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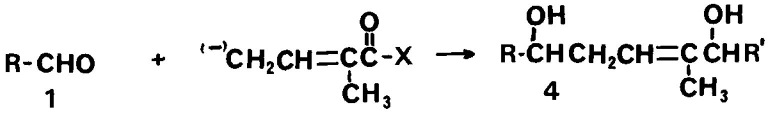
A METHOD FOR γ-FUNCTIONALIZATION OF TIGLALDEHYDE VIA THE LITHIO ALDIMINE

E. Vedejs* and D. M. Gapinski; S. M. McElvain Laboratory of Organic Chemistry,
Chemistry Department, University of Wisconsin, Madison, Wisconsin 53706

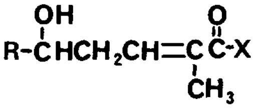
Abstract: $\mathrm{LiCH_2C{=}C(CH_3)CH{=}NC_6H_{11}}$ reacts with carbonyl compounds to give γ capture products (HMPA present) or α capture products (no HMPA).

Anions obtained from tiglic acid or tiglaldehyde derivatives are of interest as functionalized and reactive terpenoid precursors. Ikekawa et al have reported that treatment of the lithium enolate of ethyl tiglate with aldehydes in THF-HMPA affords products of enolate γ-functionalization.[1] In the closely related senecoic acid system, the dianion has been studied in detail. Kinetic α-capture with aldehydes has been observed, and isomerization of the kinetic adducts to the products of γ-capture occurs upon heating in THF.

In the course of a synthetic project, we required a method for the conversion 1→4.



$$\underset{1}{\mathrm{R\text{-}CHO}} + {}^{(-)}\mathrm{CH_2CH{=}\underset{CH_3}{C}\overset{O}{\overset{\|}{C}}\text{-}X} \longrightarrow \underset{4}{\mathrm{R\text{-}\overset{OH}{C}HCH_2CH{=}\underset{CH_3}{C}\overset{OH}{C}HR'}}$$



$$\mathrm{R\text{-}\overset{OH}{C}HCH_2CH{=}\underset{CH_3}{C}\overset{O}{\overset{\|}{C}}\text{-}X}$$

2, X=OLi

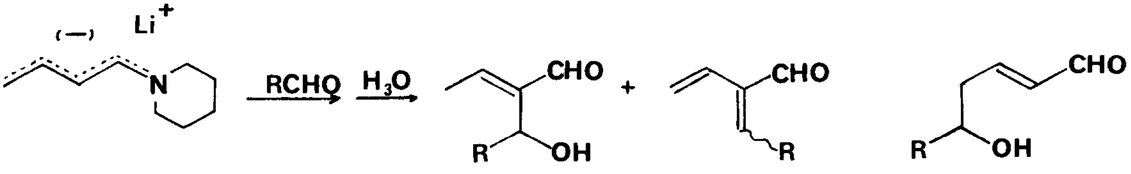
3, X=H

Initial plans assumed that 4 would be obtained from 3 by Grignard addition, and that 3 would be prepared from 2 by standard redox manipulations. As expected from the close precedent with senecoic acid dianion, the conversion of 1 into 2 ($R{=}C_2H_5$) could be effected by condensation of the tiglic acid dianion (from LDA in THF) with propionaldehyde under equilibrating conditions. The product of α-capture predominates strongly if the reaction is quenched at room temperature, but the γ-capture product 2 predominates if the initial adduct is heated at 65° in THF (Table 1). The isomerization is facilitated by HMPA.

In view of the rather harsh conditions required for α to γ isomerization we examined an alternative approach which might lead directly to the desired aldehydes 3. Anions derived from α,β-unsaturated aldimines are known to react at both the α and γ positions with electrophiles,[3] although condensation with carbonyl compounds has not been studied systematically. We have found that the lithium salt of tiglaldehyde cyclohexylimine reacts smoothly with carbonyl compounds. In general, both α and γ products are formed in THF at -78° (acetic anhydride quench; acid hydrolysis of imine). The results in Table 2 suggest an increasing preference for γ capture with increasing steric bulk of the electrophile.

The reaction with $PhCH_2CH_2CHO$ has been studied in detail to define the factors which control the α to γ rearrangement. No change in the product ratio occurs if the adduct is warmed from -78° to 0° in THF prior to quenching. However, addition of HMPA to the adduct at 0° results in rapid conversion to a mixture which favors the γ-adduct by a 3.8:1 ratio. This equilibration by HMPA does not occur at -78° (2.5 hrs). Based on these observations a general procedure has been developed for preparation of adducts 3 which correspond formally to γ-capture of the tiglaldehyde enolate. To a solution of LDA (1.1 eq. diisopropyl amine + 1.1 eq. n-BuLi in 1.5 hexane:THF, ca. 0.2 M) is added the cyclohexyl imine of tiglaldehyde dropwise via syringe at 0° (N_2 atmosphere). A bright yellow color develops. After 20 min., HMPA (1 eq.) is added and the mixture is cooled to -78°. The aldehyde is dissolved in dry hexane (15% solution by volume) and is added dropwise to the stirred anion solution at -78°. After 1 h at -78° and 2 h at 0°, acetic anhydride (4.4 eq.) is added. After 1 h at 0°, the reaction mixture is hydrolized with pH 4.5 buffer (CH_3CO_2H/CH_3CO_2Na), 1 h at 25°. After routine aqueous-organic workup, the products can be isolated by chromatography (see Table 2).

Attempts to use this method to functionalize crotonaldehyde via the lithioaldimine have been largely unsuccessful.[4] A 33% yield of the α-capture product 5 is obtained using cyclohexane carboxaldehyde as the electrophile. However, a dehydration product 6 (21%) is also isolated after imine hydrolysis, a reaction pathway which is unavailable to the analogous tiglaldimine adducts. When the crotonaldimine adduct is subjected to equilibrating conditions (heating in THF, or THF + HMPA, 0°) which might cause α to γ migration, the product mixture obtained after imine hydrolysis at pH 4.5 is extremely complex. We have been unable to isolate the γ-capture product 7.



R = C_6H_{11} 5 6 7

Table 1. Condensation of Tiglic Acid Dianion with Aldehydes in THF

Aldehyde RCHO	Temp[a] (time)	HMPA (eq.)	(% yield)	α:γ[b]
R = C_2H_5	25°(14h)	0	81	2· 1
R = C_2H_5	25°(14h),65°(2h)	0	80	1: 3
R = C_2H_5	25°(14h),65°(2h)	2.8 eq	75[d]	$\leq$1:20[c]
R = C_6H_5	25°(12h)	0	82	2: 1
R = $(CH_2)_5CO_2Et$	25°(14h)	2.8 eq	87	2: 1
R = $(CH_2)_5CO_2Et$	25°(1h),65°(2h)	2.8 eq	85	1: 2.5

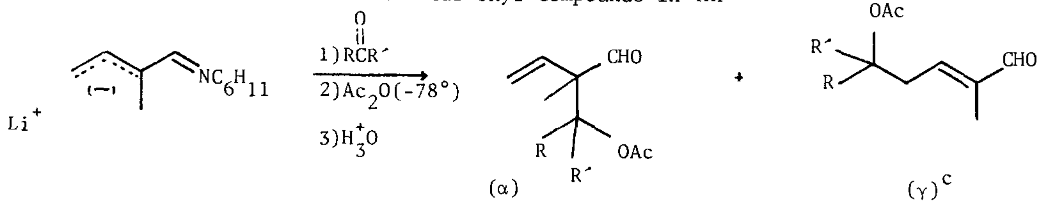
a. The aldehyde was added to the dianion at -78° over several minutes, and the cold bath was then removed.

b. α:γ ratios determined by integration, downfield proton of γ adduct relative to upfield (vinyl) protons of α adduct

c. no α product could be detected by nmr

d. estimated yield, NMR integration: product retains HMPA

Table 2. Condensation of LiCH$_2$C=C(CH$_3$)CH=NC$_6$H$_{11}$ with Carbonyl Compounds in THF



R,R'	Temp (time)	HMPA (eq.)	%α	%γ
$C_6H_5CH_2CH_2$,H	-78°(2h)	0	54%	3%
$C_6H_5CH_2CH_2$,H	-78°(1h),0°(2h)	1 eq.	15%	66%
n-C_3H_7,H	-78°(2h)	0	71%	11%
nC_3H_7,H	-78°(1h),0°(2h)	1 eq.	a	70%
cyclo-C_6H_{11},H	-78°(2h)	0	36%	24%
cyclo-C_6H_{11},H	-78°(1h),0°(2h)	1 eq.	6%	73%
(C_5H_{10})[b]	-78°(2h)	0 eq.	a	70%[b]
C_6H_5,H	-78°(1h),0°(2H)	1 eq.	a	60%
C_6H_5,H	-78°(2h)	0 eq.	71	a

a. less than 3%

b. adduct isolated as free alcohol (no acylation at -78°)

c. γ-adducts are at least 95% E isomers

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References

1) A. Kajikawa, M. Morisaki, and N. Ikekawa, Tetrahedron Lett. 4135 (1975); see also E. J. Corey and G. Schmidt, ibid. 2317 (1979).

2) G. Cainelli, G. Cardillo, M. Contento, G. Trapani, and A. Umani-Ronchi, J. Chem. Soc. Perkin Trans. I. 400 (1973); G. Cardillo, M. Orena, and S. Sandri, Tetrahedron 32, 107 (1976); C. A. Henrick, W. E. Willy, D. R. McKean, E. Baggiolini, and J. B. Siddall, J. Org. Chem. 40, 8 (1975); see also R. W. Dugger and C. H. Heathcock, ibid. 45, 1181 (1980 for related studies with the ester enolate.

3) K. Takabe, H. Fujiwara, T. Katagiri, and J. Tanaka, Tetrahedron Lett. 1237 (1975); G. R. Kieczykowski, R. H. Schlessinger, and R. B. Subsky, ibid. 597 (1976).

4) Crotonic acid dianion gives α and γ products with carbonyl compounds and equilibration is possible: P. E. Pfeffer, L. S. Silbert, E. Kinsel, Tetrahedron Lett. 1163 (1973); T. Fujita, S. Watanabe, K. Suga, and T. Nagase, Isr. J. Chem. 12, 971 (1974; pub. 1975); I. Casinos and R. Mestres, J. Chem. Soc. Perkin Trans. 1, 1651 (1978).

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