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APPLICATIONS OF CHARGE-DIRECTED CONJUGATE ADDITION REACTIONS TO THE FORMATION OF 5- AND 6-MEMBERED RINGS

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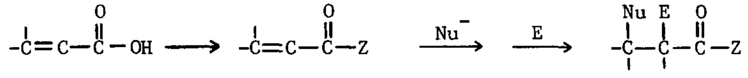
Abstract: Ring constructions through intramolecular trapping of anions generated in charge-directed conjugate addition reactions are reported. Intramolecular reactions of internal nucleophiles including Grignard reagents are also described.

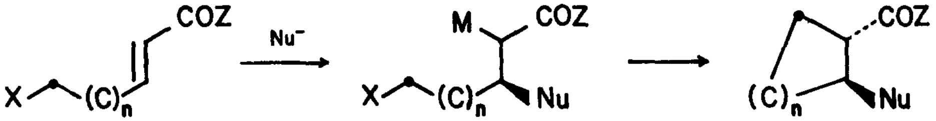
We recently reported that certain readily prepared ylide derivatives (**1**) of α,β-unsaturated acids undergo charge-directed conjugate addition reactions with a variety of nucleophiles to give intermediate anions which further react with electrophiles (eq. 1).[1] We now wish to report applications of this approach to the formation of 5- and 6-membered rings.



$$-\overset{|}{C}=C-\overset{\overset{O}{\|}}{C}-OH \longrightarrow -\overset{|}{C}=C-\overset{\overset{O}{\|}}{C}-Z \xrightarrow{Nu^-} \xrightarrow{E} -\underset{|}{\overset{\overset{Nu}{|}}{C}}-\underset{|}{\overset{\overset{E}{|}}{C}}-\overset{\overset{O}{\|}}{C}-Z \qquad (1)$$

1, Z = $-C(PPh_3)COOEt$

While a cycloalkylation reaction involving the intramolecular trapping of an enolate generated by the addition of an organocopper reagent to an α,β-unsaturated cyclohexenone derivative has been recently reported,[2] the poor yield, owing in part to the low reactivity of such enolates,[3] and the narrow range of nucleophiles which undergo conjugate addition reactions as Gilman reagents[4] severely limit this approach. We find that the anionic intermediates **4** (M = Li) which result from the addition of nucleophiles to ω-halo unsaturated ylides **3**[5] cyclize to give carbocyclic ylides **5**[6] as shown in eq. 2. Results using a variety of nucleophiles to initiate these ring closures are shown in Table 1.



(2)

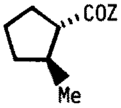
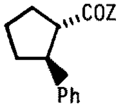
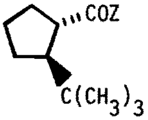
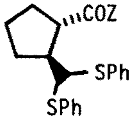
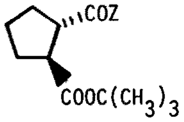
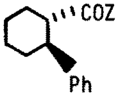
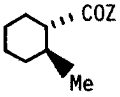
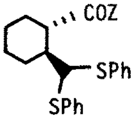
3a (n=2)
b (n=3)

4

5

The use of nucleophiles not ordinarily useful in conjugate addition reactions via organocuprates is especially noteworthy (entries 4, 5 and 9). Reactions are conducted in general by the addition of a slight excess of the nucleophile to solutions of **3** in THF at -78° followed by warming to induce cyclization. In cases leading to 5-membered ring formation, cyclization of **4a** is complete in several minutes at 0° even when X = Cl. The intermediate anion **4a** (X = Cl)

Table 1. Cycloalkylation Reactions of **3** and Nucleophiles (equation 2)

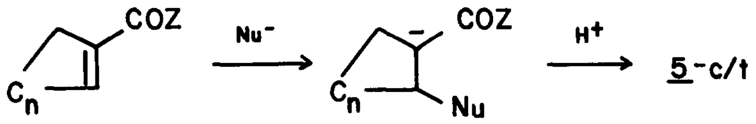
Entry	Ylide	Nucleophile	Product **5**[6]	Yield (%)
1	**3a**, X = Cl	MeLi		82
2		PhLi		90
3		$(CH_3)_3CLi$		72
4		$(PhS)_2CHLi$		95
5		$LiCH_2COOC(CH_3)_3$		90
6	**3b**, X = Cl	PhLi		70
7	**3b**, X = I			79
8	**3b**, X = Cl	MeLi		60
9		$(PhS)_2CHLi$		84

may be intercepted, however, at low temperatures. Treatment of 3a (X = Cl) with MeLi at -78° followed by the addition of water gives the saturated uncyclized ylide 4a (M = H) in 68% yield. Cyclizations of 4b (X = Cl) leading to cyclohexyl derivatives are much slower, however, requiring in general 2 hr at 55° for completion. Cyclizations are substantially faster when the leaving group is iodide (4b, X = I) with ring closures being essentially complete in 15 min at 25° (entry 7).

While in all cases observed to date nucleophilic additions to the double bond of 3 have been faster than any competing process involving the terminal electrophile, in cases where subsequent cyclization is slow (4b) alkylation of any excess nucleophile may occur thereby precluding cyclization. For example, treatment of 3b (X = Cl) with 2 equivalents of bis(phenylthio)methyllithium (25°, 1 hr) gives, after protonation, a mixture of bis-thioacetal 4b [X = Nu = (PhS)$_2$CH-, M = H] and uncyclized adduct 4b [Nu = (PhS)$_2$CH-, X = Cl, M = H] in 44 and 38% yield, respectively. No difficulties are encountered in the absence of excess nucleophile (entry 9).

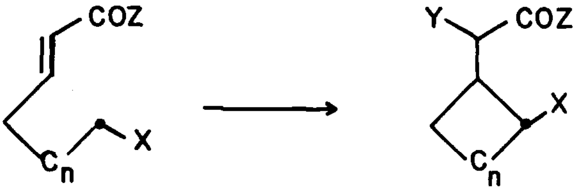
In all cases nearly exclusive formation of the *trans* isomer of 5 is observed suggesting a high preference for closure of 4 in a manner involving attack of the internal electrophile from the face of the nucleophilic α-carbon least encumbered by the β-substituent, Nu. Authentic *cis* isomers (*vide infra*) were not isomerized to *trans*-5 under the reaction conditions.

In nearly all cases 5 could also be obtained by the addition of the same nucleophiles to the corresponding cyclic unsaturated ylide 6 (eq. 3). Protonation of the anions 7 generated in this manner under non-equilibrating conditions invariably gave rise to 5 as a separable mixture of *cis* and *trans* isomers.[7]



6 (n=2,3) 7 (3)

Finally, we have investigated annelations resulting from the intramolecular conjugate addition reactions of internally generated nucleophilic centers (eq. 4). Treatment of 8a and 8b (X = I) with magnesium in THF at 25° gives after protonation cyclic ylides 9a and 9b (X = Y = H) in 60% and 59% yield, respectively. These reactions presumably proceed through the formation of an intermediate Grignard reagent 8 (X = MgI) which cyclizes to 9 (X = H, Y = MgI).[8] These



8a (n=2); 8b (n=3) 9 (4)

reactions are to our knowledge the first examples of uncatalyzed intramolecular conjugate addition reactions of internally generated Grignard reagents. Ring formation through the intramolecular addition of a stabilized carbanionic center has also been demonstrated. Treatment of **3b** (X = CN) with lithium tetramethylpiperidide gives after protonation **9b** (X = CN, Y = H) in 67% yield as a variable mixture of separable *cis-trans* isomers. It is as yet unclear whether isomer formation is inherent in the cyclization process or occurs as a result of an equilibration or other proton transfer process involving the cyano-substituted center. In any event, treatment of either *cis*-**9** or a *cis-trans* mixture with NaOMe-MeOH results in the formation of predominately *trans*-**8**.

Other novel ring-forming processes made possible by conjugate addition reactions to carbonyl-deactivated systems are presently under study.

References and Notes

(1) M. P. Cooke, Jr. and R. Goswami, *J. Am. Chem. Soc.*, **99**, 642 (1977).

(2) G. H. Posner, J. J. Sterling, C. E. Whitten, C. M. Lentz and D. J. Brunelle, *J. Am. Chem. Soc.*, **97**, 107 (1975).

(3) R. D. Boeckman, Jr., *J. Org. Chem.*, **38**, 4450 (1973).

(4) G. H. Posner, *Org. React.*, **19**, 1 (1972).

(5) Unsaturated ylides **3** were prepared by olefination of the appropriate ω-chloroaldehyde [$(EtO)_2P(O)CH_2CO_2Et$, NaH], hydrolysis of the resulting α,β-unsaturated ester (KOH-EtOH), conversion of the unsaturated acid to the acid chloride (oxalyl chloride) followed by treatment with $Ph_3P = CHCO_2Et$ to give **3**.[1] Iodides (**3**, X = I) were prepared from the corresponding chlorides with NaI-acetone.

(6) In all cases product structures were supported by spectral data and elemental analyses. Structures and stereochemistry of the products from entries 1, 6 and 8 were also verified by independent synthesis from the authentic carboxylic acid. In addition, desulfurization of the thioacetal (entry 4) gave the product obtained in entry 1.

(7) Similar results are often obtained upon protonation of substituted exocyclic enolates : H. E. Zimmerman and P. S. Mariano, *J. Am. Chem. Soc.*, **90**, 6091 (1968).

(8) These reactions could also occur through the cyclization of a radical species which has been implicated in Grignard reagent formation.[9a,b] Only a small amount of cyclization is observed in the formation of the Grignard reagent from 6-bromohexene, however, and 6-membered ring formation in this manner should be even less favorable.[9a,10] This along with the observation that performed Grignard reagents readily undergo conjugate addition reactions with these ylide make the Grignard cyclization path seem more likely.

(9) (a) H. W. H. J. Bodowitz, C. Blomberg and F. Bickelhaupt, *Tetrahedron*, **31**, 1053 (1975); (b) H. M. Walborsky and M. S. Aronoff, *J. Organometal. Chem.*, **51**, 31 (1973).

(10) A. I. Meyers, R. Gabel and E. D. Mihelich, *J. Org. Chem.*, **43**, 1372 (1978).

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