Registry No. **1a**, 71424-66-3; **1b**, 71386-38-4; **2a**, 97315-42-9; **2b**, 97315-43-0; **3**, 97315-44-1; **4**, 97315-45-2; **5**, 97315-46-3; **6**, 82691-87-0; **7**, 97315-47-4; **9**, 55057-45-9; **10**, 97315-48-5; **11**, 97315-49-6; **12**, 97336-04-4; **13**, 97315-50-9; **14**, 97371-82-9; 1-pyrrolidinocyclopentene, 7148-07-4.

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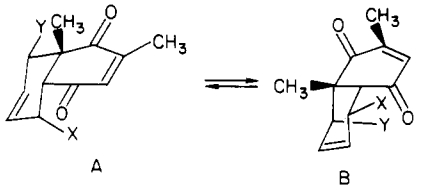
Acetylide Additions to Enediones. Regioselectivity Based on Stereoelectronic Control

Summary: Regiospecific addition of acetylide anions to enediones can be achieved without the need of protecting groups. The selectivity of these additions appears to be the result of a preference for these anions to add in an axial fashion.

Sir: We report the results of our study on acetylide additions to enediones in which the regioselectivity (and stereoselectivity) of the additions depends primarily on stereoelectronic control at the reaction site. The results of our study are listed in Tables I and II.[2] Chronologically, the first reaction studied is entry a in Table I. At the time, we believed that the remarkable regiospecificity of this reaction resulted from direct interaction between the sulfur lone pair electrons and the less-hindered, proximate carbonyl group. Such interaction would effectively preclude any nucleophilic addition to this carbonyl group and, by default, direct the acetylide to the other carbonyl group.

While this direct substituent/carbonyl interaction may actually be operative,[3] interactions of this sort are not a necessary condition for obtaining highly regioselective addition. This is apparent from entries b and c in Table I. In both examples regiospecific acetylide additions are observed, despite the lack of any substituent interactions of the type previously discussed. Indeed, as the results in Table I indicate, *the selectivity of these additions is quite independent of the nature of X, Y, and the attacking acetylide.*[4]

On the basis of our observations, there appeared to be only a few reasonable rationales for explaining this consistent pattern of selectivity. The one that we prefer is based on the following premises: (a) the preferred reaction pathway should involve axial addition of the acetylide ion to the enedione chromophore and (b) the more-accessible conformation B is the only reactive conformation for enediones with cis-ring junctures. If the acetylide addition occurs in an axial fashion (attack at the "more-hindered" carbonyl), then the transition state will be "chair-like" and good overlap can be maintained between the double bond and the other carbonyl group during the entire addition process. Equatorial attack (attack at the "less-hindered" carbonyl) requires a "boat-like" transition state which involves poorer overlap. This should lead to an overall preference for axial attack and result in the production of **2** from **1** and **5** from **4**. The only exceptions to this rule occur when axial addition is hindered by the presence of an axial substituent at C-1 of the A ring (Table II, entries a, b, and e).



We have also considered and rejected a number of other possible rationales for our observations. The first requires that significant electronic differences (e.g., LUMO coefficients, charge densities, etc.) exist between the two carbonyl carbons.[5] These differences can be addressed from both a theoretical[6] and experimental viewpoint. If the observed selectivity has, as its origins, the fundamental electronic characteristics of the 2-methyl enedione chromophore, then epimerization of these adducts to the corresponding trans isomers **4** should represent only a minor electronic perturbation and should not dramatically alter the regioselectivity of these additions. As all of the results in Table II indicate, this is *not* the case, since acetylide additions to trans enediones **4** can produce either **5** or **6**, depending upon the nature of the substitution pattern of ring A.

(1) Recipient of a Camille and Henry Dreyfuss Teacher–Scholar Fellowship, 1981–86.

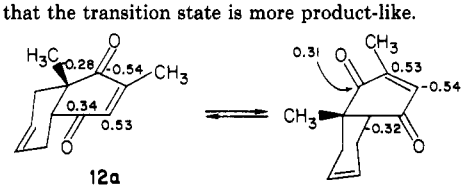
(2) The regioselectivity of these acetylide additions can be determined by using a variety of techniques, the simplest of which is proton NMR. Since the products of these additions are enones, it is quite a straightfoward matter to determine if the material in question possesses an α enone proton (δ = 5.8–6.0 ppm) or a β enone proton (δ = 6.7–7.0 ppm). Stereochemical assignments at quaternary centers were made by using combinations of ^{13}C NMR correlations, X-ray crystal structure determinations, and general literature precedents. All starting materials were prepared by either thermal or Lewis acid catalyzed Diels–Alder reactions of the appropriate diene and quinone. All products were characterized on the basis of their physical and spectral properties, including high-resolution mass spectrometry.

(3) The ultraviolet spectra of **1a** (X = H, Y = SPh) and **1b** (X = H, Y = CH_3) strongly support this sulfur/carbonyl interaction: **1a** λ_{max} (EtOH) 248, 337 nm; **1b** λ_{max} (EtOH) 238, 362 nm.

(4) Since the observed product ratios do not change when these additions are quenched prior to completion of the reaction, these reactions are most probably operating under kinetic control.

(5) Various unsaturated dicarbonyl compounds have been reported to undergo regioselective additions of nucleophiles. Some examples are the following: (a) Liotta, D.; Barnum, C.; Saindane, M. *J. Org. Chem.* **1981**, *46*, 3369. (b) Bloomfield, J. J.; Lee, S. *J. Org. Chem.* **1967**, *32*, 3919. (c) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1978**, *56*, 1524. (d) Kayser, M. M.; Morand, P. *Tetrahedron Lett.* **1979**, 695. (e) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1980**, *58*, 2484.

(6) We have performed a series of MNDO calculations on **12a**, **12b**, and **13**. Each of these structures has been subjected to *complete* geometric optimization, i.e., *all* bond lengths, bond angles, and dihedral angles were varied until a minimum energy structure was achieved. As can be seen from the LUMO coefficients shown with each structure, Frontier Molecular Orbital (FMO) considerations consistently predict nucleophilic attack at the *wrong* carbonyl group. Since FMO theory extrapolates to transition states on the basis of the electronic characteristics of the reactants, the complete inconsistency of these calculations with experimental results lends some additional credence to out hypothesis that the transition state is more product-like.



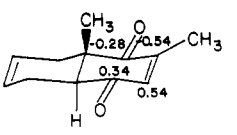
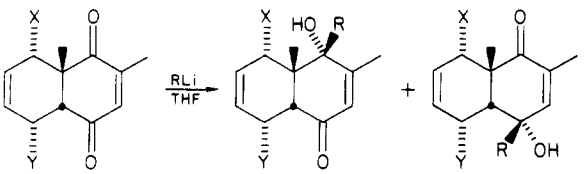


Table I

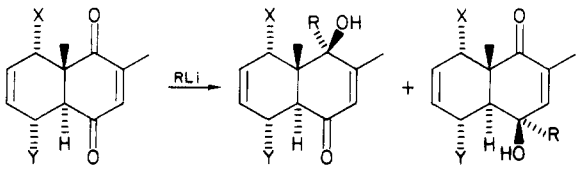


1 2 3

entry	X	Y	RLi	%2	%3	conditns[a]
a	H	SPh	LiC≡CCH$_2$OTHP	79		−78 °C (1 h) 0 °C (30 min) 25 °C (1 h)
b	H	CH_3	LiC≡CCH$_2$OTHP	99		−78 °C (1 h) 0 °C (30 min)
c	H	CH_3	LiC≡CPh	85		−78 °C (1 h) 0 °C (1 h)
d	$(CH_3)_3SiO$	CH_3	LiC≡CCH(OEt)$_2$	94		−78 °C (10 h)
e	t-Bu$(CH_3)_2SiO$	CH_3	LiC≡CCH(OEt)$_2$	92		−78 °C (12 h)
f	H	CH_2OCH_2Ph	LiC≡C-(3-furyl)	85		−78 °C (1 h) 0 °C (1 h) 25 °C (overnight)
g	AcO	CH_3	LiC≡CCH$_2$OTHP	70		−78 °C 0 °C (1 h)

[a] Some acetylide additions to enediones revert upon warming to 0 °C.

Table II



4 5 6

entry	X	Y	RLi	%5	%6	conditns[a]
a	AcO	CH_3	LiC≡CCH$_2$OTHP		60[b]	−78 °C (1 h) 0 °C (1 h) 25 °C (overnight)
b	CH_3OCO	H	LiC≡CCH$_2$OTHP		80[b]	−78 °C (5 h)
c	H	CH_3	LiC≡CCH$_2$OTHP	85		−78 °C (5 h) 0 °C (30 min)
d	H	CH_2OAc	LiC≡CCH$_2$OTHP	90		−78 °C (2 h)
e	CH_3	CH_3	LiC≡CCH$_2$OTHP		80	−78 °C (2 h)

[a] Some acetylide additions to enediones revert upon warming to 0 °C. [b] Yield based on recovered starting material.

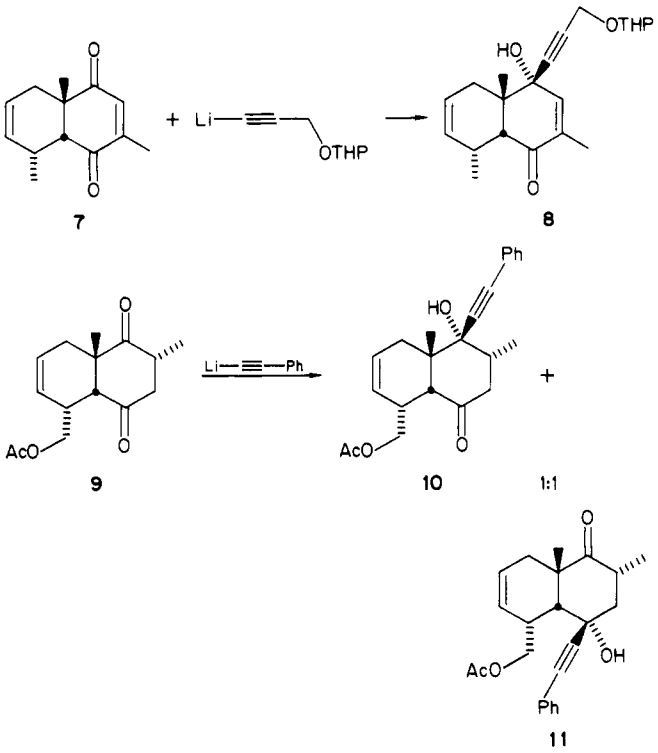
A second plausible explanation for the observed regiospecificity relies on trajectory approach control arguments.[7] Such arguments are based on the elegant work of Burgi and Dunitz,[7g] who showed that the optimum approach vector of a nucleophile with a carbonyl group is 110°. However, for interference by the angular methyl group to be important in systems such as 1, the addition reaction must be occuring exclusively on conformer A *in every case*. This seems quite unlikely for two reasons. First, it is inconsistent with the complete lack of sensitivity which these additions exhibit with respect to the A-ring substitution pattern.[8] Second, and more importantly, conformer B is obviously much more accessible to nucleophilic attack than is its counterpart, A. Thus, neither the electronic characteristics of the methylene dione group nor trajectory approach control factors adequately explain the observations given in Tables I and II.

Since chemists are by nature skeptical of rationalizations, we felt compelled to do two additional sets of experiments to further test our hypothesis. The first involved studying acetylide additions to 7. If electronic factors are not important in determining the regioselectivity of these additions, then switching the position of the methyl group on the enedione chromophore should not significantly alter the selectivity of these additions. As indicated below, the experimental results are in complete accord with this prediction. Second, if maintenance of overlap in the transition state between the unreacted carbonyl and double bond is important, then removal of the double bond between the two carbonyl groups should dramatically alter the selectivity of these additions. Indeed, this is the case (e.g. **9** → **10** + **11**)!

In summary, we have described a useful and selective method for preparing highly functionalized synthetic intermediates without the use of protecting groups.[9] Application of the methodology to the synthesis of a variety of natural products will be the subject of additional reports in the near future.

(7) (a) Burgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974** *30*, 1563. (b) Burgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956. (c) Suess, R. *Helv. Chim. Acta* **1977**, *60*, 1656. (d) Rosenfield, R. E.; Dunitz, J. D. *Helv. Chim. Acta* **1978**, *61*, 2176. (e) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 738. (f) See also ref 3d. (g) Burgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.

(8) We have performed over 120 MM2 calculations on a variety of systems related to 1 and 4. Not surprisingly, the relative energies of both conformers are reasonably sensitive to the A-rng substitution pattern, i.e., in many cases conformer A is *not* favored over conformer B. Thus, trajectory approach control cannot be important in determining regioselectivity in these cases. The complete details of this study will be the subject of a future report.



Acknowledgment. This work was supported by the National Institutes of Health and, in part, by Schering-Plough Corporation. We also thank the National Science Foundation for providing funds for the purchase of a Nicolet 360-MHz NMR spectrometer.

(9) A typical experimental procedure follows. To a solution of 1.17 g (8.35 mmol, 2 equiv of propargyl alcohol and tetrahydropyranyl ether in 20 mL of dry THF at ~78 °C under argon was added 7.11 mL (7.52 mmol, 1.8 equiv) of a 1.06 M solution of *n*-BuLi. The mixture was allowed to stir at ~78 °C for $^1/_2$ h and at 0 °C for an additional $^1/_2$ h. At this point it was cooled to ~78 °C again and added via syringe to a solution of 1.25 g (4.18 mmol, 1 equiv) of 1 (X = H, Y = SPh) in 20 mL of THF at ~78 °C under argon. The mixture was allowed to stir at ~78 °C for 2 h and at 0 °C for $^1/_2$ h. The reaction mixture was then quenched with a saturated NH_4Cl solution and the solvent was removed under vacuum. The residue was diluted with water and extracted with ether (3 × 50 mL). The combined extracts were washed successively with 5% HCl solution, saturated brine, and water. The ether was removed under reduced pressure and the residue was purified by MPLC (silica gel) to give 2 (X = H, Y = SPh, R = C≡CCH_2OTHP) (1.73 g, 97% yield): 90-MHz ^1H NMR ($CDCl_3$) 7.15-7.61 (m, 5 H), 5.88-6.12 (m, 1 H), 5.84 (brs, 1 H), 5.48-5.72 (m, 1 H), 4.78-4.93 (m, 1 H), 4.32 (s, 2 H), 3.58-4.05 (m, 2 H), 3.25 (d, J = 3 Hz, 1 H), 2.25-2.61 (m, 1 H), 2.03 (d, J = 1 Hz, 3 H), 1.39-1.98 (m, 8 H), 1.35 (s, 3 H); mass spectrum, m/e, 438.

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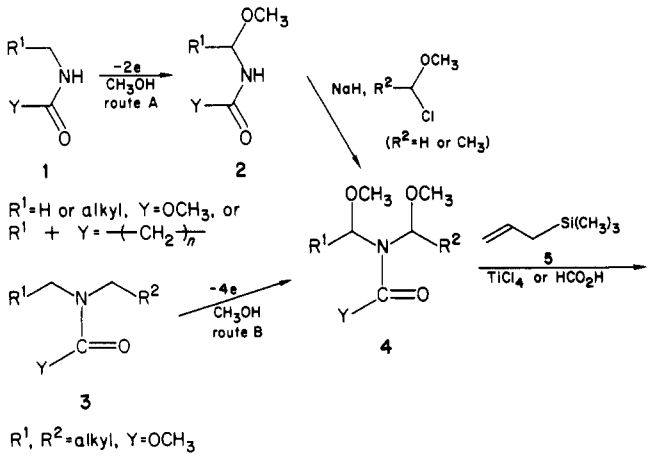
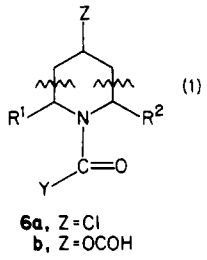
A New [3+3]-Type Annelation Useful for the Formation of Piperidine Skeletons[1]

Summary: A [3 + 3]-type annelation between α,α'-dimethoxylated amides **4** and allyltrimethylsilane (**5**) gave piperidine derivatives **6**. It was applied to the synthesis of piperidine, indolizidine, quinolizidine, 1-azabicyclo[5.4.0]undecane, 1-aza-8-oxabicyclo[4.3.0]nonane, 8-azabicyclo[3.2.1]octane, and 9-azabicyclo[3.3.1]nonane derivatives.

Sir: Ring formation through [m + n]-type annelation[2] is highly useful to the synthesis of new cyclic compounds. We wish to report a convenient method for the formation of piperidine skeletons by utilizing a new [3 + 3]-type annelation between allyltrimethylsilane (**5**) and α,α'-dimethoxylated amides **4** easily prepared either by anodic α-monomethoxylation[3] of *N*-monoalkylamides **1** followed by methoxyalkylation of the α-methoxylated products **2** (route A) or by anodic α,α'-dimethoxylation[4] of *N,N*-dialkylamides **3** (route B) (eq 1).





(1)

6a, Z=Cl
b, Z=OCOH

A typical procedure is exemplified by the synthesis of a piperidine derivative **10** from α,α'-dimethoxylated carbamate **9**. Thus, the anodic oxidation[3] of **7** followed by methoxymethylation of the product **8** gave **9** (route A).[5] A solution of **9** (2 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a solution of $TiCl_4$ (4 mmol) in CH_2Cl_2 (5 mL) at room temperature, and then a solution of **5** (3.3 mmol) in CH_2Cl_2 (2 mL) was added to the mixture. After the solution was stirred overnight it was treated with water, and the isolation by column chromatography gave **10** in 65% yield (eq 2). $SnCl_4$ gave a similar result (yield 60%) to $TiCl_4$, and using (2-bromoallyl)trimethylsilane (**11**) instead of **5** yielded **12** (eq 2). The annelation between **9** and **5** also took place in formic acid to give **6b** ($R^1 = R^2 = H$; $Y = OCH_3$) in 73% yield.[6]

One of the advantages of our method consists in the wide applicability as exemplified by the facile synthesis of bi-

(1) Electroorganic Chemistry. 89.
(2) (a) Pine, S. H.; Hendrickson, J. B.; Cram, D. J.; Hammond, G. S. "Organic Chemistry"; 4th ed.; McGraw-Hill: New York, 1981; p 710. (b) For examples of the recent studies on the synthesis of nitrogen heterocycles, see the following. [3 + 2] annelation: Vedejs, E.; West, F. G. *J. Org. Chem.* **1983**, *48*, 4773. Livinghouse, T.; Smith, R. *J. Chem. Soc., Chem. Commun.* **1983**, 210. [4 + 2] annelation: Bailey, T. R.; Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 3240 and references cited therein.
(3) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264.
(4) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Aoki, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697.
(5) Synthesis of **9** was also achievable by the anodic α,α'-dimethoxylation of *N*-carbomethoxydimethylamine in methanol (route B).
(6) The annelation of **15** or **20** with **5** in formic acid resulted in low yields.

0022-3263/85/1950-3243$01.50/0