which had a maximum of 0.8 kcal/mol (α = 4.18 in Table I). A comparison of this figure with the *E-Z* energy difference of 2–3 kcal/mol (obtained from the MM calculations)[13] indicate that the stabilization of high-energy conformations may be significant.

The results here reported should be of use in the design of synthetic polymers possessing antibody- or enzyme-like properties.

Acknowledgment. This work was supported by the Swedish Natural Science Research Council and the National Swedish Board for Technical Development.

Supplementary Material Available: The experimental procedure for the synthesis of PheNHPh and PheNMePh and the full characterization of these compounds are available (3 pages). Ordering information is given on any current masthead page.

The Chemistry of Vicinal Tricarbonyls. Preparation and Reactions of Acetylenic Tricarbonyls

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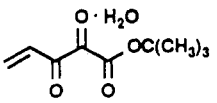
Received October 3, 1989

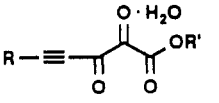
Summary: The acetylenic tricarbonyl **2** serves as a polyelectrophile in addition reactions of primary amines substituted with nucleophilic groups.

Sir: We have previously reported studies on the use of vicinal tricarbonyl derivatives as potent electrophiles. When substituted on β-lactam rings, they have served as acceptor centers for the construction of the fused 4,5-bicyclic systems of carbapenams and penems.[1] In combination with neighboring ester or vinyl groups, they have taken part in cyclization reactions leading to vincamine,[2] erythrina,[3] and phthalideisoquinoline alkaloids.[4] Other applications have been reported in the synthesis of hydroxypyrroles[5] including the bacterial pigment, prodigiosin.[6]

A particularly useful intermediate prepared in this series of investigations has been the vinyl tricarbonyl ester **1**, which has served as a versatile dielectrophile for the tandem addition of primary amines to the α,β-unsaturated ketone as well as to the central carbonyl group.[7] We now report that the related acetylenic derivatives **2a–e** may be used to extend this methodology, providing new polyelectrophiles of unusual potential in organic synthesis.



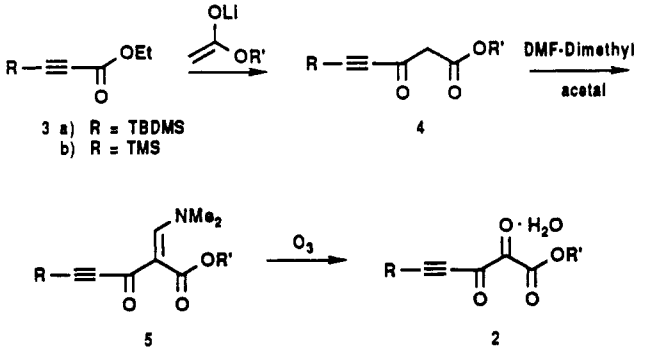
1



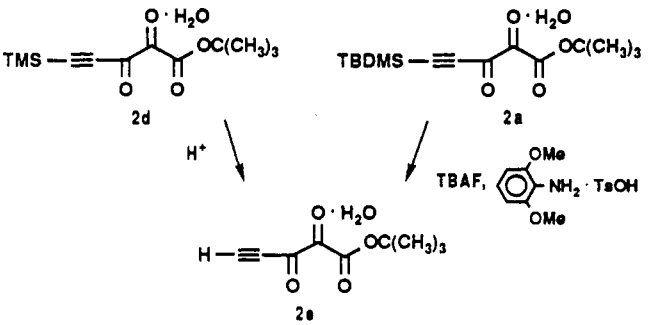
2 a) R = TBDMS, R' = *t*-Bu
b) R = TBDMS, R' = Et
c) R = TBDMS, R' = Me
d) R = TMS, R' = *t*-Bu
e) R = H, R' = *t*-Bu

The acetylenic tricarbonyl compounds **2a–c** were prepared most efficiently by using the procedure shown in Scheme I. Thus, in forming **2a**, Claisen condensation of lithio-*tert*-butyl acetate with ethyl (*tert*-butyldimethylsilyl)propiolate (**3a**)[8] gave the β-keto ester **4** (R = TBDMS, R' = *tert*-butyl), which was then allowed to react with *N,N*-dimethylformamide dimethyl acetal to give the enamine **5** (R = TBDMS, R' = *tert*-butyl). Selective ozonolysis of this product using the indicator dye Sudan III[9]

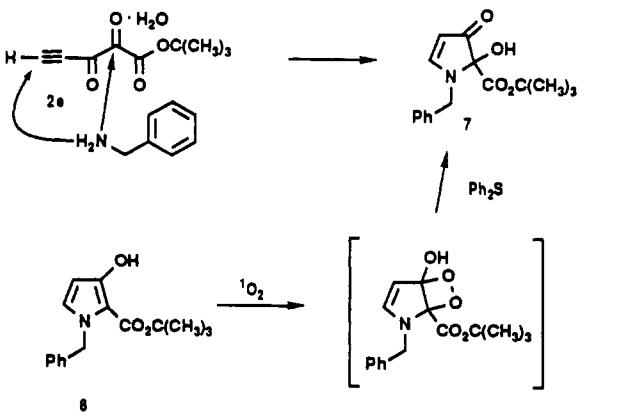
Scheme I



Scheme II



Scheme III

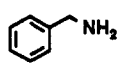
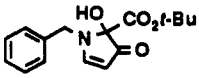
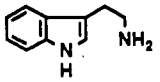
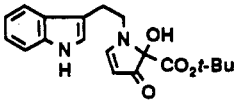
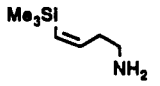
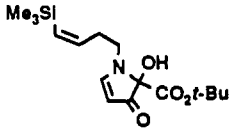
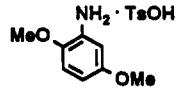
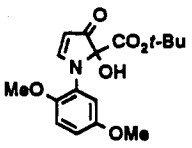
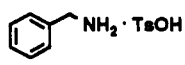
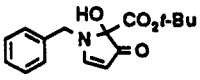
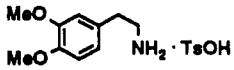
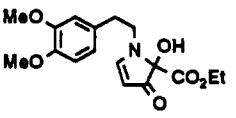
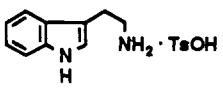
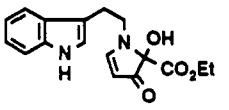


(1) (a) Wasserman, H. H.; Han, W. T. *J. Am. Chem. Soc.* **1985**, *105*, 1444. (b) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743. (c) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3747.
(2) Wasserman, H. H.; Kuo, G.-H. *Tetrahedron Lett.* **1989**, *30*, 873.
(3) Wasserman, H. H.; Amici, R. *J. Org. Chem.* **1989**, *54*, 5843.
(4) Wasserman, H. H.; Amici, R.; Frechette, R.; van Duzer, J. H. *Tetrahedron Lett.* **1989**, *30*, 869.
(5) Wasserman, H. H.; Cook, J. D.; Fukuyama, J. M.; Rotello, V. M. *Tetrahedron Lett.* **1989**, *30*, 1721.
(6) Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725.
(7) (a) Wasserman, H. H.; Fukuyama, J.; Murugesan, N.; van Duzer, J.; Lombardo, L.; Rotello, V.; McCarthy, K. *J. Am. Chem. Soc.* **1989**, *111*, 371.

(8) Compound **3a** was prepared by the reaction of ethyl propiolate with *tert*-butyldimethylsilyl chloride in the presence of sodium hydride.

0022-3263/89/1954-6012$01.50/0

Table I

nucleophile	tricarbonyl	product	yield (%)[a]
	2e		65
	2e		43
	2e		57
	2a		33
	2a		62
	2b		47
	2b		40

[a] Yields are not optimized.

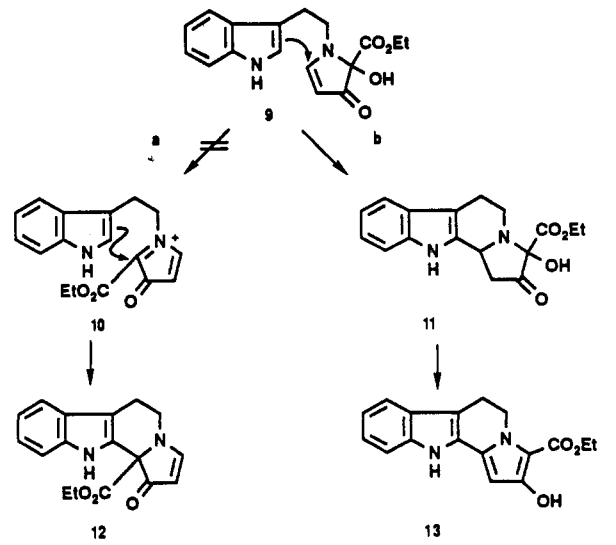
afforded the tricarbonyl **2a**, mp 77–79 °C (71% from **3**). With use of the same two-step process, the lithio derivatives of ethyl and methyl acetate yielded the tricarbonyls **2b** and **2c**, respectively (55% and 40% overall).[10]

The trimethylsilyl-protected acetylenic tricarbonyl derivative **2d** was prepared starting with ethyl (trimethylsilyl)propiolate (**3b**).[11] The labile trimethylsilyl group was removed to form **2e** by exposure to silica gel. Although desilylation is not always necessary for subsequent reaction,[12] the more stable silyl group in **2b** may also be removed by treatment with tetrabutylammonium fluoride in the presence of 2,5-dimethoxyanilinium *p*-toluenesufonate (Scheme II).[13]

The acetylenic tricarbonyl compounds **2** react with primary amines to generate hydroxypyrrolinone carboxylates by a reaction that is analogous to that observed with the vinyl counterpart.[7] Thus, reaction of benzylamine with **2e** produced the derivative **7**, mp 119–120 °C (65%) by a

(9) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.
(10) Efforts to synthesize these compounds by alternative methods involving phosphorus ylides or *p*-aminonitrosobenzene (cf. ref 7) have proven to be less efficient than the enamine route.
(11) Kraihanzel, L. S.; Losee, M. L. *J. Org. Chem.* **1968**, *33*, 1983.
(12) Under carefully defined conditions, the reaction of primary amines with **2** may be carried out without prior removal of the silyl group. Thus, the *p*-toluenesulfonic acid salt of benzylamine reacts with **2a**, in the presence of tetrabutylammonium fluoride, to generate **7** (62%) presumably by in situ desilylation followed by the normal 2-fold nucleophilic attack.
(13) The aniline salt appears to function both as a proton source and protecting group for the central carbonyl. Polycarbonyl functions are particularly prone to rearrangements and polymerization reactions in basic media. See, for example: (a) Rubin, M. B. *Chem. Rev.* **1975**, *75*, 177. (b) Askin, D.; Reamer, R. A.; Jones, T. K.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1989**, *30*, 671.

Scheme IV

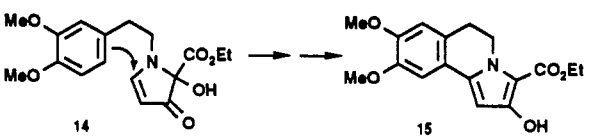


2-fold nucleophilic attack involving conjugate addition to the α,β-ynone function and addition to the central carbonyl group (Scheme III). Table I lists examples of hydroxypyrrolinone carboxylates formed from the reactions of **2** with primary amines or their corresponding salts.

The structure of **7** was confirmed by an independent synthesis from the hydroxypyrrolecarboxylate **8**.[7] Dye-sensitized photooxygenation of **8** in the presence of diphenyl sulfide yielded the pyrrolinone **7** (50%). The formation of **7** in the reaction with singlet oxygen most probably takes place by 2,3-addition to the pyrrole with the formation of a dioxetane, followed by diphenyl sulfide deoxygenation.[14]

As observed with the vinyl tricarbonyl compound **1**,[7] a primary amine substituted with an additional nucleophilic component may undergo a "third stage" reaction with **2**. The indole ring of tryptamine is well suited for such a transformation. The intermediate pyrrolinone **9**, formed by the 2-fold addition of tryptamine to **2b**, could undergo further reaction by two different routes: (a) formation of the imminium ion **10** followed by cyclization to **12** as observed in the reaction with the vinyl analogue **1**; (b) conjugate addition to the α,β-unsaturated ketone group of **9** (Scheme IV).

It was found that, in the presence of $BF_3{\cdot}OEt_2$, the pyrrolinone **9** underwent cyclization exclusively by pathway b. Under these conditions, the product of conjugate addition **11** readily aromatized to the hydroxypyrrole **13** (93%). The alternative pathway (a) observed with the vinyl counterpart **1** would require the formation of the disfavored iminium ion **10**, an antiaromatic type of intermediate, resembling cyclopentadienone. An analogous result was observed in the reaction of **2b** with 3,4-dimethoxyphenethylamine to form **14**, which then leads to the corresponding tricyclic product **15** (60%).



In summary, we have shown that the cluster of functional groups incorporated in the acetylenic tricarbonyl derivatives **2** represents a readily available, reactive polyelectrophilic system. Applications of these findings to the

(14) Wasserman, H. H.; Saito, I. *J. Am. Chem. Soc.* **1975**, *97*, 905.

synthesis of alkaloids is under investigation.

Acknowledgment. This research was supported by grants from the National Institutes of Health (GM-07874 and GM-31350). A PHS postdoctoral fellowship to R. Frechette is gratefully acknowledged. We also thank Ms. Jan Cook for providing valuable assistance with the desilylation reactions.

Supplementary Material Available: Spectroscopic data for all new compounds (6 pages). Ordering information is given on any current masthead page.

Stereoselective Synthesis of Exocyclic Alkenes via Zirconium-Promoted Alkyl–Diene Coupling[1]

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Received September 5, 1989

Summary: The reaction of 1-vinyl-1-cycloalkenes with 1 equiv of $(RCH_2CH_2)_2ZrCp_2$, where R is H or alkyl, followed by treatment with electrophiles, e.g., proton donors, I_2, and ketones, can provide the corresponding exocyclic alkenes in good yields, the stereoselectivity being ≥95%.

Sir: We have recently reported the reactions of "$ZrCp_2$", such as *n*-Bu_2ZrCp_2,[2,3] with nonconjugated enynes,[3,4] diynes,[2,3,5] and dienes.[1] With *n*-Bu_2ZrCp_2 the actual "$ZrCp_2$" reagent has been shown to be (η^2-1-butene)$ZrCp_2$ (**1a**), in which 1-butene serves as a $ZrCp_2$-protecting but "nonparticipating" ligand.[3,6] On the other hand, the reaction of alkene–$ZrCp_2$ complexes (1) with monoalkenes incorporates the alkene moiety in the products.[7]

$(RCH_2CH_2)_2ZrCp_2 \longrightarrow$

a: R = Et. b: R = H.

(1)

We now report that the reaction of 1 with conjugated dienes (**2**) gives zirconacycles represented by **3**, which can be converted to a variety of organic products, such as **4–6** shown in Scheme I. Particularly noteworthy is that 1-vinyl-1-cycloalkenes can be readily converted to stereodefined exocyclic alkenes.[8,9] Although zirconacycles represented by **3** have been previously prepared by the reaction of alkenes with conjugated diene–$ZrCp_2$ complexes obtained by either the enediylmagnesium–Cl_2ZrCp_2 reaction[10a] or the diene–Ar_2ZrCp_2 reaction,[10b] the conversion of **2** to **3** as shown in Scheme I represents a novel route. Furthermore, the conversion of 1-vinyl-1-cycloalkenes to stereodefined exocyclic alkenes has not been previously reported.

Table I. Synthesis of Exocyclic Alkenes by the Reaction of Conjugated Dienes with Dialkylzirconocenes

conjugated diene	R of R_2ZrCp_2	exocyclic alkene	yield, % GLC	yield, % isolated
2a	Et	**4a**	91	56
2a	Et	**7**	–	55
2a	Et	**8**	–	66
2a	Et	**5a**	55	48
2a	*n*-Bu	**4b**	90	80
2b	Et	**4c**	82	67
2b	*n*-Bu	**4d**	89	72
2c	Et	**4e**	67	64
2c	*n*-Bu	**4f**	–	70
2d	*n*-Bu	**4g**	83	68

Typically, ethyllithium in Et_2O (1.0 M, 6.0 mL, 6.0 mmol) was added to a solution of Cp_2ZrCl_2 (0.88 g, 3.0 mmol) in 10 mL of THF at −78 °C. After having been stirred for 1 h at −78 °C, the mixture was treated with 1-ethenyl-1-cyclohexene (0.325 g, 3.0 mmol), and warmed to 25 °C over a few hours. Examination of the reaction mixture by ^1H NMR spectroscopy using benzene as an internal standard indicated the formation of a $ZrCp_2$ derivative exhibiting two singlets for the Cp groups at δ 5.50 and 5.65 in >90% yield. The compound has been tentatively identified as **3a** on the basis of the following. The reaction mixture obtained above was quenched with a mixture of 2 N HCl and Et_2O, extracted with Et_2O, washed with aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Distillative workup gave 0.23 g (56%) of butylidenecyclohexane: IR (neat) 3030 (w), 1675 (w), 1450 (s), 1370 (m) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.88 (t, J = 7 Hz, 3 H), 1.25–1.4 (m, 2 H), 1.4–1.7 (m, 6 H), 1.9–2.0 (m, 2 H), 2.0–2.2 (m, 4 H), 5.07 (t, J = 7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, Me_4Si) δ 13.75, 27.89, 28.11, 28.17, 28.77, 29.18, 37.24, 121.27, 139.56. Treatment of **3a** with D_2O (1 mL/3 mmol of diene, 25 °C, 2 H) followed by workup with 2 N HCl produced a >95% pure monodeuterio derivative of **4a**, i.e., **7**, in 55% isolated yield. The use of 2 N DCl in place of HCl cleanly produced the dideuterio derivative **8** in 66% yield, the extents of deuterium incorporation on the ring

(1) Metal-Promoted Cyclization. 31. Part 30. Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5105.
(2) Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.
(3) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A.; Cederbaum, F. E.; Swanson, D. R.; Takahashi, T. *J. Am. Chem. Soc.* **1989**, *111*, 3336.
(4) (a) Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568. (b) Negishi, E.; Swanson, D. R.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1987**, *28*, 917. (c) See also: Rajan Babu, T. V.; Nugent, W. A.; Taber, D. F.; Fagan, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 7128.
(5) For a related study by other workers, see Nugent, W. A.; Thorn, D. L.; Harlow, R. L. *J. Am. Chem. Soc.* **1987**, *109*, 2788.
(6) 1-Butene is not incorporated in the product and recovered as such.
(7) Swanson, D. R.; Rousset, C. J.; Negishi, E.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521.
(8) For a review, see Negishi, E. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1988; Vol. 1, p 177.
(9) For our previous papers on the synthesis of exocyclic alkenes other than refs 2–4, see: (a) Luo, F. T.; Negishi, E. *J. Org. Chem.* **1983**, *48*, 5144. (b) Miller, J. A.; Negishi, E. *Isr. J. Chem.* **1984**, *24*, 76. (c) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080. (d) Negishi, E.; Zhang, Y.; Bagheri, V. *Tetrahedron Lett.* **1987**, *28*, 5793. (e) O'Connor, B.; Zhang, Y.; Negishi, E. *Tetrahedron Lett.* **1988**, *29*, 3903. (f) Zhang, Y.; Negishi, E. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (g) Zhang, Y.; Miller, J. A.; Negishi, E. *J. Org. Chem.* **1989**, *54*, 2043.
(10) (a) Yasuda, H.; Kajihara, Y.; Nagasuna, K.; Mashima, K.; Nakamura, A. *Chem. Lett.* **1981**, 719. (b) Erker, G.; Engel, K.; Dorf, U.; Atwood, J. L.; Hunter, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 914.

0022-3263/89/1954-6014$01.50/0