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The Chemistry of Vicinal Tricarbonyls. Use of Vinyl and Acetylenic Derivatives in the Synthesis of Substituted Indoles.

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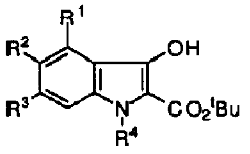
Abstract: Vinyl and acetylenic vicinal tricarbonyl derivatives take part as dienophiles in Diels-Alder reactions leading to substituted indoles as well as to their dihydro and tetrahydro derivatives.

As part of our continuing investigation of the chemistry of vicinal tricarbonyls,[1] we report the results of recent studies on the reaction of the vinyl and acetylenic derivatives **2** and **3**. As outlined below, this work has led to a novel, flexible synthesis of 3-hydroxyindole-2-carboxylate derivatives **1** from the readily available acetylenic ester **3**.



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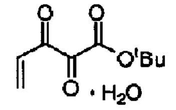

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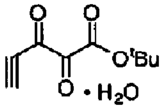
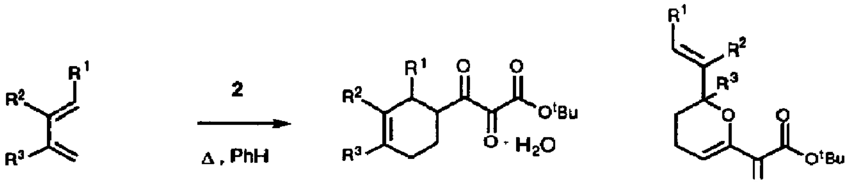


3

Earlier work with reagents **2** and **3** focused primarily on the tandem reactivity of both the electrophilic central carbonyl and the double or triple bond functionalities in reactions with dinucleophiles.[2,3] In the present work, we have explored the use of **2** and **3** as dienophilic components in Diels-Alder reactions. Although the central carbonyl in vicinal tricarbonyl systems lacking α,β-unsaturation has been shown to act as an effective heterodienophile in reactions with dienes,[4] products resulting from addition to the carbon-oxygen double bond were not observed in these studies. In the present work, [4+2] cycloaddition reactions involving the diene and the terminal vinyl or acetylenic group represented the predominant reaction outcome. Thus, when dienes **4a-c** were heated with the vinyl tricarbonyl **2**, good yields of adducts **5** were obtained along with minor amounts of the dihydropyran adducts **6**.[5,6,12]

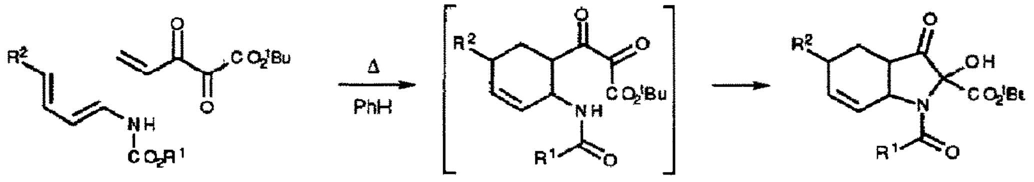


4a $R^1 = R^2 = R^3 = H$
4b $R^1 = CH_3$, $R^2 = R^3 = H$
4c $R^1 = H$, $R^2 = R^3 = CH_3$

5a (78%)
5b (60%)
5c (82%)

6b (8%)
6c (5%)

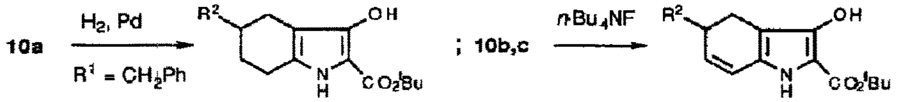
When **2** was heated in benzene with *trans*-1-N-acylamino-1,3-dienes (**8**),[8] the bicyclic pyrrolidinones (**10**) were produced in a single step. Here, the initial Diels-Alder addition product (**9**) underwent a second-stage cyclization, involving attack of the nucleophilic NH of the carbamate residue with the favorably located central carbonyl. Subsequent hydrogenolysis of the Cbz-protected pyrrolidinone **10a** afforded the tetrahydroindole **11a**. Fluoride deprotection of **10b** and **10c** yielded dihydroindoles **11b** and **11c**. Attempts to oxidize these derivatives to the corresponding indoles with DDQ gave only dimeric indole species.[9]



8a $R^1 = CH_2Ph$, $R^2 = CH_3$
8b $R^1 = CH_2CH_2Si(CH_3)_3$, $R^2 = H$
8c $R^1 = CH_2CH_2Si(CH_3)_3$, $R^2 = CH_3$

9

10a (77%)
10b (75%)
10c (87%)



11a (51%)

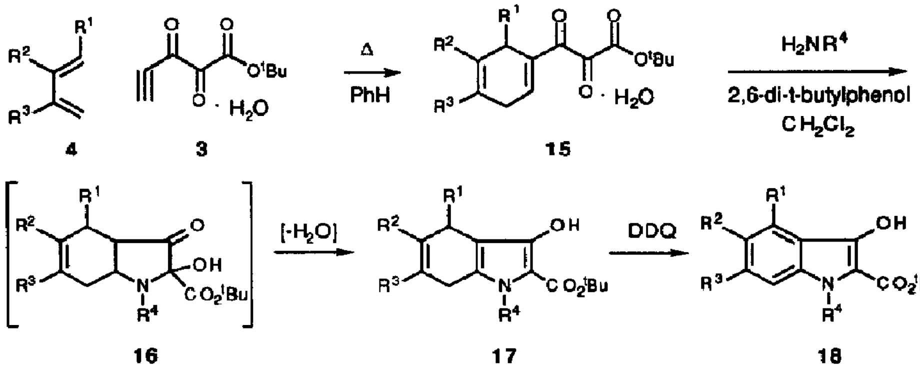
11b (62%)
11c (47%)

In order to adapt the above findings to the synthesis of indoles, we used the acetylenic tricarbonyl **3** as the dienophilic component for reaction with dienes **4a-d**. In this process, good yields of the 1,4-cyclohexadiene adducts (**15**) were obtained (Table 1).[12] Compounds **15** could be chromatographed, and stored at 0° for short periods without significant oxidation. However, when no precautions were taken to avoid prolonged exposure to air, aromatization took place.[10]

Table 1. Reactions of Dienes with Acetylenic Tricarbonyl[a]

Diene	R^1	R^2	R^3	% Yield of **15**[12]
4a	H	H	H	79
4b	Me	H	H	86
4c	H	Me	Me	quant.
4d	CH_2CO_2Et	H	H	57

[a] Reaction conditions: The tricarbonyl, diene (1.1-2 equiv) and hydroquinone (1-5 mol %) were thermolyzed in degassed benzene (sealed tube) for 3-5.5 h.



Reactions of intermediates **15** with primary amines yielded dihydroindoles **17** (Table 2),[12] as expected in view of earlier findings on the pyrrole-forming reactions of amines with vinyl and alkenyl tricarbonyls.[11] Compounds **17** could be cleanly aromatized to the corresponding indole derivatives **18** by the action of DDQ (Table 3).[12]

Table 2. Reactions of Cyclohexadiene-tricarbonyls with Amines[a]

Diene	R^1	R^2	R^3	R^4	% Yield of **17**[12]
15a	H	H	H	*n*-Bu	72
15b	Me	H	H	*n*-Bu	42
15c	H	Me	Me	*n*-Bu	58
15d	CH_2CO_2Et	H	H	*n*-Bu	57[b]
15e	H	H	H	CH_2Ph	32

[a] Reaction conditions: The tricarbonyl, diene (1-1.1 equiv) and 2,6-di-tert-butylphenol (1-5 mol %) were stirred in degassed CH_2Cl_2 at room temperature overnight under an Ar atmosphere. [b] Based on recovered tricarbonyl, **15d** (9%).

Table 3. Dehydrogenation of Dihydroindoles using DDQ[a]

Diene	R^1	R^2	R^3	R^4	% Yield of **18**[12]
17a	H	H	H	*n*-Bu	42
17b	Me	H	H	*n*-Bu	90[b]
17c	H	Me	Me	*n*-Bu	53[c]
17d	CH_2CO_2Et	H	H	*n*-Bu	77[d]
17e	H	H	H	CH_2Ph	50

[a] Reaction conditions: A solution of DDQ (1-1.5 equiv) in PhH was added slowly to a solution of the dihydroindole in PhH at 5-10°C. The reaction was continued at room temperature for 0.1-1.5 h and monitored by TLC. [b] Based on recovered **17b** (10%). [c] Reaction performed with tetrachloro-1,4-benzoquinone. [d] Based on recovered **17d** (26%).

The attractiveness of the above indole-forming sequence lies in the ease with which substituents can be placed on the target products by varying the diene and the primary amine components. Considering the reactivity of 3-hydroxyindoles as (ketonic) acceptors in nucleophilic reactions, this method could have useful application in alkaloid synthesis.

Acknowledgments: This work was supported by Grants from the National Institutes of Health.

References and Notes.

1. For recent work, see Wasserman, H.H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364, and references cited therein.
2. Wasserman, H. H.; Cook, J. D.; Vu, C. B. *J. Org. Chem.* **1990**, *55*, 1701 and references cited therein.
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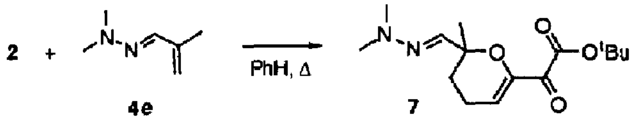
4. (a) Schmidt, R. R.; Vogt, K. *Synthesis*, **1983**, 799. (b) Schmidt, R. R.; Wagner, A. *Ibid.* **1981**, 273. (c) Abele, W.; Schmidt, R. R.; Bonjouklian, R. *J. Am. Chem. Soc.* **1975**, *97*, 6892. (d) Schönberg, A.; Singer, E. *Chem. Ber.* **1971**, *104*, 160.
5. Electron rich alkenes, for example alkyl and silyl enol ethers, gave good yields of the inverse electron demand Diels-Alder product in reactions with **2**. These results parallel those obtained by other workers using similar heterodiene systems: Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 5793.
6. When the diene contained an electron-rich double bond as with 1-aza-1,3-diene (**4e**),[7] the dihydropyran **7** was the only product.



4e **7**

7. Tamura, Y.; Tsugoshi, T.; Nakajima, Y.; Kita, Y. *Synthesis*, **1984**, 930.
8. Compounds **8a-c** were prepared by Curtius rearrangement of the appropriate carboxylic acids (**8b**, trans-2,4-pentadienoic acid; **8a** & **8c**, sorbic acid) followed by trapping of the formed isocyanates with the appropriate alcohol (**8a**, benzyl alcohol; **8b-c**, 2-(trimethylsilyl)ethanol). The preferred method for carrying out this transformation was that reported by Shioiri et al.: *J. Am. Chem. Soc.* **1972**, *94*, 6203.
9. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970; p 364 and references cited therein.
10. Boeckman, R. K., Jr.; Ramaiah, H.; Medwid, J. B. *Tetrahedron Lett.* **1977**, 4485. The conversion of **15a** to the known phenyl tricarbonyl ester in refluxing methylene chloride in the presence of air, was dramatically accelerated upon addition of 1.2 equiv of Hünig's base.
11. Wasserman, H. H.; Lombardo, L. J. *Tetrahedron Lett.* **1989**, *30*, 1725, and references cited therein.
12. Satisfactory spectroscopic data (^{1}H NMR, IR and HRMS) and/or C and H analyses were obtained for all new compounds.

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