The use of vicinal tricarbonyl derivatives in alkaloid synthesis

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Abstract - We have recently shown that 1,2,3-vicinal tricarbonyl derivatives may serve as potent electrophiles in synthetic operations. When generated as substituents on β-lactam rings, they have served as acceptor centers for the construction of the fused 4,5-bicyclic systems of carbapenams and penems. In combination with neighboring ester, or vinyl groups, they have taken part in cyclization reactions leading to vincamine, erythrina, and phthalideisoquinoline alkaloids. Other applications involve the synthesis of hydroxypyrroles and indolizidines.

A particularly useful intermediate prepared in this series of investigations has been the vinyl tricarbonyl ester 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. In addition, related acetylenic derivatives may be used to extend this methodology, providing polyelectrophiles of unusual potential. Natural products which we have synthesized using tricarbonyl reactivity in key steps include prodigiosin, 3-demethoxy-erythratidinone, vasicine, eburnamonine and the C1-C15 segment of antibiotic FK506. Progress in the synthesis of the tricyclic nucleus of bicyclomycin is also reported.

The powerful electrophilicity of 1,2,3-vicinal tricarbonyls has been known to organic chemists for many decades. These systems are prone to react readily at the central electron-deficient site with donor reagents such as water, alcohols, and amines. It is therefore not surprising that these functional group aggregates exist primarily in the form of adducts such as the hydrates of ninhydrin and oxomalonic ester.1 Despite the potential for exploiting the electrophilic reactivity of tricarbonyls, they have found relatively little use by organic chemists in synthetic operations. Thus a recent review by Rubin1 describes Diels-Alder reactions at the central carbonyl, as well as reactions with water, alcohols, thiols, amines, active methylene compounds, and diazo compounds. However, it is clear from this account that little attention has been given to the use of these aggregates in synthetically-directed bond formation.

We have recently found that these systems, either partially or fully hydrated, may react with nucleophiles in varied molecular settings, and have sought to utilize this reactivity in the synthesis of alkaloids and other natural products. Our present work has been oriented in two directions. One pursuit aims to incorporate the tricarbonyl into a key intermediate such as 1 so that, in a subsequent step attack at the central ketonic residue by a nucleophile would result in bond formation. This is illustrated in the formation of the carbapenem system 2 in our synthesis of the antibiotic PS-5, 3 (Scheme 1).2 Other natural products made in this way have been prodigiosin,3 members of the vincamine,4 and isoquinoline alkaloid families,5 and vasicine.6 Another general pathway involves the use of the vinyl tricarbonyl reagent 57 as a polyelectrophile is illustrated in the synthesis of (±)-3-demethoxyerythratidinone 78 (Scheme 2) and by the formation of the indolizidine derivative 39 from an aminopyrrole (Scheme 7).
The following discussion will outline the use of tricarbonyl chemistry in the formation of cordrastines, eudistomins, and the C₁ to C₁₅ fragment of FK-506. We also describe a novel and efficient method for the formation of indolizidines and carbazoles through this route.

One method for forming the required tricarbonyl unit 10 involves the singlet oxygen cleavage of enamines 9 as shown in Scheme 3. A second method makes use of the condensation of an acid chloride 11 with the ylide 12. In the next step, singlet oxygen or ozone can be used to generate 10 from the derivative 13 (Scheme 3).

Scheme 3

In our synthesis of the cordrastines, we employed the tricarbonyl derivative 16 (Scheme 4). This, in turn, was conveniently prepared by the condensation of the acid chloride 14 with 1-butyl-(triphenylphosphoryl)acetate. Ozonolysis of 15 gave the tricarbonyl compound 16 (67%) as the monohydrate. Reaction of 16 with the phenethylamine derivative 17 afforded the keto-imine 18 (61%). This reaction appeared to take place by initial formation of a Schiff base at the central carbonyl, followed by a Pictet-Spengler cyclization and rapid oxidative decarboxylation of the resulting β-keto-ester. Methylation (80%) and subsequent hydride reduction (72%) led directly to the cordrastines (diastereomeric ratio of 1:2 in favor of 20).

Scheme 4

For our synthesis of the eudistomins, members of a family of marine alkaloids possessing antiviral activity, a similar strategy was employed. As shown in the synthesis of eudistomin T (24) (Scheme 5), the tricarbonyl derivative 22 was mixed with tryptamine in excess trifluoroacetic acid (TFA) to give 23 (76%). Refluxing 23 in CCl₄ for three days produced the natural product 24 in high yield (88%).
The above procedure for forming tricarbonyl derivatives was also applied successfully in the formation of the C1-C15 α,β-diketo amide subunit of FK-506 (Figure 1). Our synthesis began with the condensation of the ylide 25 with the William’s acid chloride 26 in the presence of BSA to yield the keto ylide intermediate 27 (91%). Oxidative cleavage of 27 using ozone (88%) or singlet oxygen (69%) yielded the α,β-diketo amide 28. The tricarbonyl 28 was then readily converted in dilute acid to the hemiketal 29.

To prepare indolizidine derivatives, we exploited the capability of the vinyl tricarbonyl ester 5 to act as a trielectrophile. The aminopyrrole 30 took part in a two-fold addition to the α,β-unsaturated ketone and the central carbonyl group generating a hydroxypyrrolidinone carboxylate 31 (Scheme 7). Under mild acid conditions (silica gel) this intermediate formed an iminium salt which acted as an acceptor for a third stage nucleophilic attack of the pyrrole to form the tricyclic system 33 (90%).

We have recently found that treatment of the indole tricarbonyl 34 with an excess of the Schiff base 35 resulted in a facile transformation to the N-benzylamino-4-hydroxycarbazole carboxylate 36 (Scheme 8).
We picture the transformation of 34 to 36 according to the sequence outlined in Scheme 9. Tautomerization of the imine 35 to the enamine 37 provides the donor species which initiates the addition leading to 38. Intramolecular cyclization to 38 is then followed by dehydration and aromatization to 36.

REFERENCES

1 Rubin, M. B. Chem Rev. 1975, 75, 177.
6 Wasserman, H. H.; Kuo, G.-K., manuscript in preparation.
13 For a recent reference concerning the isolation and properties of these compounds see: Bentley, K. W. Natural Products Reports 1987, 667.