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The chemistry of vicinal tricarbonyls. Formation of oxomalondiamides

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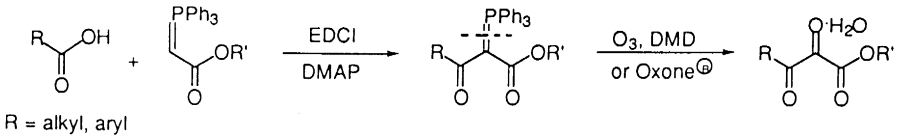
Abstract

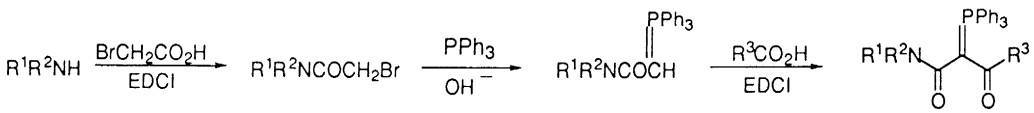
Oxomalondiamides and related systems are readily formed from derivatives of oxalic acid monoamides. The monoamides are converted to labile triacyl nitriles through cyano ylide intermediates for further coupling with amines and other nucleophiles.

In previous studies[1] we outlined procedures for forming vicinal tricarbonyl derivatives from carboxylic acids which are converted to the tricarbonyl system by EDCl coupling with (triphenylphosphoranylidine)acetate followed by oxidation of the carbon–phosphorus double bond (Scheme 1).



Scheme 1.

The ylides were derived from α-halo carboxylic esters, and the tricarbonyl esters were isolated as stable hydrates. In a related approach,[2a] we employed a phosphorane as the coupling agent for forming the tricarbonyl subunit in the depsipeptide antibiotics, YM-47141 and YM-47142. In this procedure (Scheme 2) used earlier in our work related to FK-506, [2b] we treated an amine with bromoacetic acid, converted the halo acyl derivative to the triphenylphosphoranylidene ylide for coupling with a carboxylic acid to form the ylide precursor to the hydrated tricarbonyl.



Scheme 2.

We now report a further method for forming the tricarbonyl array starting from oxalic acid mono amides which are readily available by monoacylation of an amine such as piperidine with dimethyl

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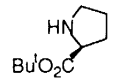
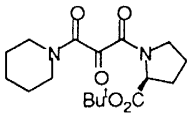
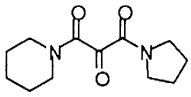
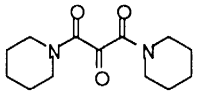
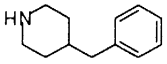
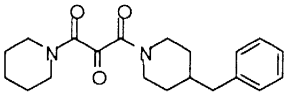
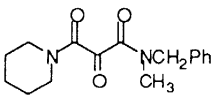
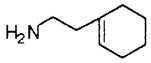
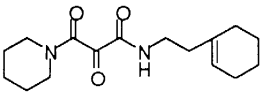
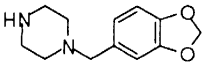
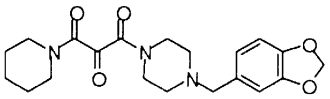
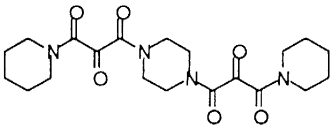
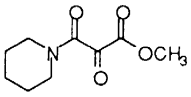
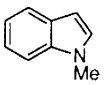
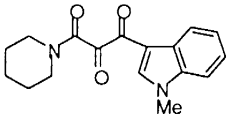
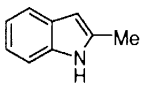
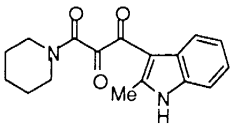
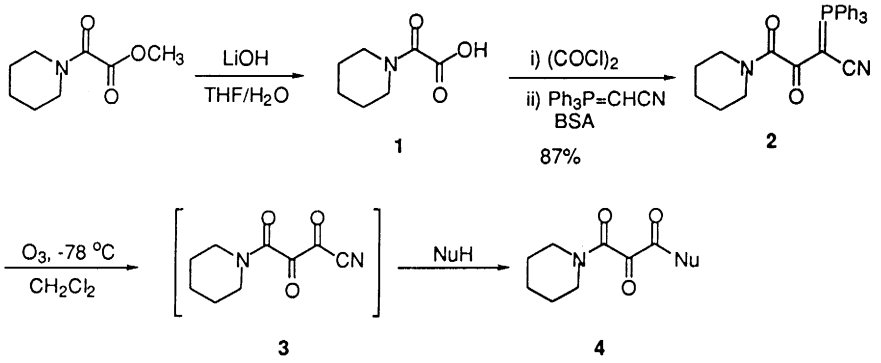
Table 1
Coupling of tricarbonyl intermediate **3** with various nucleophiles[a]

Entry	NuH	Products (**4**)	Yield, %
a			89
b			51
c			64
d			58
e			64
f			37
g			85
h			44
i	CH_3OH		40
j			52
k			66

[a]All the yields were based on nucleophiles used.

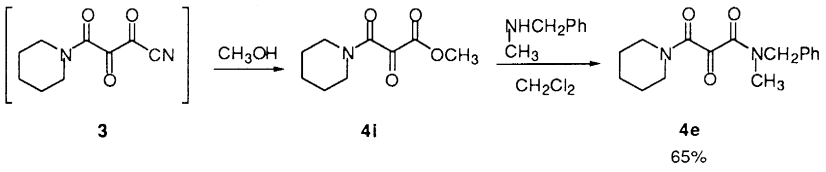
oxalate or by treatment of the amine with the acid chloride of oxalic acid monomethyl ester. Hydrolysis of the ester with LiOH yields the corresponding carboxylic acid **1** (~98%).

To form the oxomalondiamides, the monoamide **1** was transformed to the acid chloride and then coupled with the cyano ylide in the presence of BSA to form the diacyl cyano ylide **2**.[3] Oxidation of **2** yielded a labile triacyl nitrile **3** which was trapped by nucleophiles to give products **4**[4] (Table 1).[5] The tricarbonyl derivatives (Scheme 3) were formed in yields varying from 37–89%. It is noteworthy that in these cases, the central carbonyl is unhydrated. The lack of hydration may be attributed to the weakened electrophilic activity of the central carbonyl which is flanked by two amide groupings. The formation of the tricarbonyl derivatives was most effective in reactions with secondary amines. With primary amines, mixtures of products were formed, and the yield of oxomalondiamide was low as in **4f**.

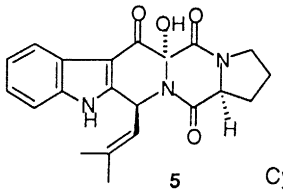


Scheme 3.

Oxygen and carbon nucleophiles were also employed in conversions of **3** to **4**. Reaction with methanol gave methyl 2,3-dioxo-3-piperidinopropanoate **4i** which was treated with *N*-methyl benzylamine to form oxomalondiamide **4e** (Scheme 4). The reactions between **3** and indole derivatives yielded tricarbonyl addition products **4j** and **4k** which are of interest in connection with synthetic approaches to members of the fumitremorgin family such as cyclotryprostatin D (**5**).[6]



Scheme 4.

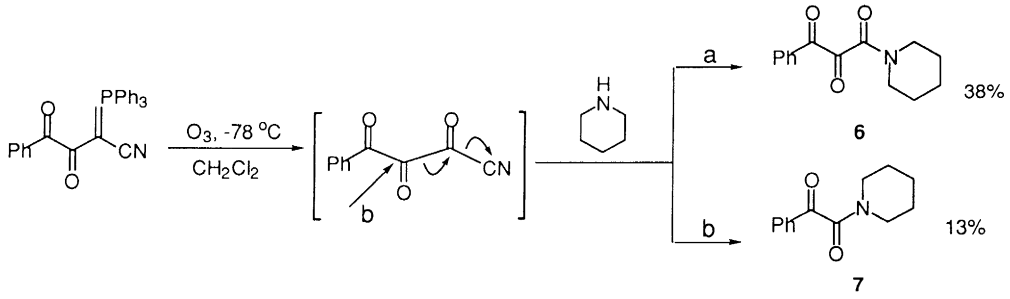


5 Cyclotryprostatin D

Using phenyl glyoxylic acid as a starting component, we were able to form the piperidino tricarbonyl derivative **6** (38%). A major byproduct in this case was the α-keto amide **7** formed most probably by the decarbonylation reaction (Scheme 5).

Acknowledgements

This work was supported by grants from the NIH and NSF.



Scheme 5.

References

1. (a) Wasserman, H. H.; Ennis, D. S.; Blum, C. A.; Rotello, V. M. *Tetrahedron Lett*. **1992**, *33*, 6003; (b) Wasserman, H. H.; Baldino, C. M.; Coats, S. J. *J. Org. Chem*. **1995**, *60*, 8231.
2. (a) Wasserman, H. H.; Chen, J.-H.; Xia, M. *J. Am. Chem. Soc*. **1999**, *121*, 1401; (b) Wasserman, H. H.; Rotello, V. M.; Williams, D. R.; Benbow, J. W. *J. Org. Chem*. **1989**, *54*, 2785.
3. **3,4-Dioxo-4-piperidino-2-(1,1,1-triphenyl-λ^5-phosphanylidene)butanenitrile (2)**. (i) To a stirred, precooled (0°C) solution of 2-oxo-2-piperidinoacetic acid (1.95 g, 12.4 mmol) in 50 mL of dry CH_2Cl_2 was added dry DMF (50 μl) and oxalyl chloride (1.62 mL, 1.5 equiv.) by syringe and the resulting solution was stirred for 1 h at 0°C, then for 2 h at room temperature under N_2. Evaporation of the solvent and excess oxalyl chloride in vacuo and further drying of the residue under high vacuum gave the crude acid chloride as a yellow solid, which was used directly in the next step. (ii) A precooled (0°C) solution of crude acid chloride in dry CH_2Cl_2 (50 mL) was transferred to a precooled (0°C) solution of triphenylphosphoranylideneacetonitrile (4.30 g, 1.15 equiv.) and BSA (3.68 mL, 1.2 equiv.) in 50 mL of dry CH_2Cl_2 via cannula and the resulting reaction mixture was stirred for 1 h at 0°C, then overnight at room temperature under N_2. The reaction mixture was diluted with 60 mL of H_2O and the two layers were separated. The aqueous layer was extracted further with 20 mL of CH_2Cl_2 (×3), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated. Flash chromatography of the crude product on SiO_2 (hexanes/EtOAc, 1/4.5 to 1/5) gave 4.75 g (87%) of pure compound **2** as an off-white solid: mp 247.0–248.5°C (dec); R_f 0.21 (hexanes/EtOAc, 1/5); IR ($CHCl_3$) 3014, 2947, 2869, 2184, 1636, 1579, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.61 (m, 6H), 3.37 (m, 2H), 3.57 (m, 2H), 7.49–7.68 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 25.4, 26.4, 42.2, 47.0, 49.1 (d, J=120.9 Hz), 120.1 (d, J=14.5 Hz), 122.3 (d, J=9.3 Hz), 129.4 (d, J=12.9 Hz), 133.6 (d, J=2.9 Hz), 133.7 (d, J=10.4 Hz), 166.0 (d, J=11.5 Hz), 188.1 (d, J=3.6 Hz); HRMS FAB (*m*-NBA): calcd for $C_{27}H_{26}N_2O_2P$ $(MH)^+$: 441.1732, found: 441.1733. Anal. calcd for $C_{27}H_{25}N_2O_2P$: C, 73.62; H, 5.72; N, 6.36. Found: C, 73.88; H, 5.82; N, 6.14.
4. A typical procedure for preparation of oxomalondiamide: ***tert*-Butyl (2*S*)-1-(2,3-dioxo-3-piperidinopropanoyl)tetrahydro-1*H*-2-pyrrolecarboxylate (4a)**. 3,4-Dioxo-4-piperidino-2-(1,1,1-tripheyl-λ^5-phosphanylidene)butanenitrile (**2**) (653.0 mg, 1.48 mmol, 1.5 equiv.) in 35 mL of dry CH_2Cl_2 containing a small amount of activated molecular sieves (4 Å) was treated with O_3 for 10–15 min at −78°C and the resulting deep green solution was purged with N_2 for 20 min at −78°C. To this yellow solution was transfered a precooled (−78°C) solution of L-proline *t*-butyl ester (169.2 mg, 1.0 equiv) in 10 mL of dry CH_2Cl_2 via cannula and the mixture was stirred for 30 min at −78°C, then for 1 h at 0°C under N_2. The reaction mixture was filtered, concentrated in vacuo, and flash chromatographed on SiO_2 (hexanes/EtOAc, 1.5/1 to 1/1) to give 296.6 mg (89%) of pure compound **4a** as a pale yellow solid, shown to be a mixture of two rotamers (ratio=ca. 3:2) by ^{1}H and ^{13}C NMR: R_f 0.40 (hexanes/EtOAc, 1/1); mp 75.0–77.0°C; $[\alpha]_D^{22}$ −65.1 (c 0.57, $CHCl_3$); IR ($CHCl_3$) 2983, 2962, 1738, 1646 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H×2/5), 1.44 (s, 9H×3/5), 1.63 (m, 6H), 1.85–2.03 (m, 4H×3/5), 2.08–2.26 (m, 4H×2/5), 3.28–3.44 (m, 2H), 3.46–3.87 (m, 4H), 4.40 (dd, 1H×2/5, J=8.1, 3.6 Hz), 4.70 (dd, 1H×3/5, J=8.5, 2.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 24.40, 24.43, 24.8, 25.17, 25.22, 25.9, 26.1, 27.94, 27.97, 28.9, 31.6, 42.4, 42.5, 46.8, 47.0, 47.5, 60.0, 60.5, 81.8, 82.1, 160.5, 162.0, 164.5, 164.6, 170.0, 170.9, 184.5, 185.5; HRMS FAB (*m*-NBA): calcd for $C_{17}H_{27}N_2O_5$ $(MH)^+$: 339.1920, found: 339.1920. Anal. calcd for $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.30; H, 7.69; N, 8.33.
5. All new compounds gave satisfactory spectroscopic and analytical data.
6. Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59.