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Chemoselective synthesis of multiple epoxy-bridged tetrahydropyranone ring systems

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Abstract—Bis- as well as tris-tetrahydropyranone ring systems were obtained via multiple tandem cyclization–1,3-dipolar cycloaddition reactions of α-diazo ketones with ketone as well as aldehyde functional groups in a chemoselective manner.

The tandem cyclization–1,3-dipolar cycloaddition methodologies involving α-diazo carbonyl compounds[1] have been shown to be important tools for constructing many bonds with high degrees of regio- and stereocontrol. The 1,3-dipolar cycloaddition reactions of carbonyl ylides generated from α-diazo carbonyl compounds offer a versatile route for the construction of a variety of complex molecules[2] and natural products.[3] As a result, this technique continues to be the subject of considerable interest and intensive investigation in synthetic organic chemistry. Intramolecular carbenoid–carbonyl group cyclizations have been represented as one of the most effective methods for generating carbonyl ylides from α-diazo ketones, their successive cycloaddition reactions with C=C bonds have been documented[2] but not much studied in the presence of hetero-dipolarophiles. A survey of the literature revealed that only a few reports are available on the reactions of carbonyl ylides with carbonyl groups as hetero-dipolarophiles. It is worth mentioning that brevicomins[4] and zaragozic acid A[5] have been inventively approached via tandem cyclization–cycloaddition methodology in the presence of aldehydes such as propionaldehyde and methyl glyoxalate, respectively. However, the chemistry and selectivity observed in these reactions have not been investigated in detail. Further, control of the stereoselectivity in the cycloaddition of carbonyl ylides presents a challenge with the prospect of applications in the synthesis of natural products. Reactions of five- or six-membered-ring carbonyl ylides with *o*-quinones,[6] *p*-benzoquinones[7] and other carbonyl compounds[8] have also been studied to afford 1:1, 2:1 or 3:1 cycloadducts without any selectivity in the presence of copper or rhodium catalysts. Furthermore, the epoxy-bridged tetrahydropyran skeleton is present in a wide range of natural products and exists as a part of polycyclic frameworks, for example, loukacinols,[9] xanthane epoxide,[10] and isogosterones.[11] In continuation of our interest in the synthetic utility of α-diazo carbonyl compounds for the synthesis of highly substituted epoxy-bridged poly- or spirocyclic frameworks,[12] we report herein the multiple tandem cyclization–cycloaddition reactions of rhodium(II)-carbenoids with ketone as well as aldehyde functional groups in a chemoselective manner.

It was envisaged that the reaction of α-diazo ketones such as **1** or **2** with $Rh_2(OAc)_4$ would generate the corresponding metallo-carbenoids, based on our earlier work.[7a] The respective transient five-membered cyclic carbonyl ylides **3** or **4** could successfully be generated in the presence of rhodium(II) acetate as a catalyst (Fig. 1). To investigate the multiple tandem cyclization–cycloaddition reactions of these cyclic carbonyl ylides **3** or **4** with carbonyl groups as heterodipolarophiles, the required starting materials of type **1** or **2** were prepared[7a] (Table 1).

To explore the reaction of cyclic carbonyl ylides **3** and **4** with substrates having several carbonyl groups, we initially planned to study the reaction of alicyclic diazo diketones **1**. Towards this, an excess of diazo ketone **1c** was added to a dichloromethane solution containing

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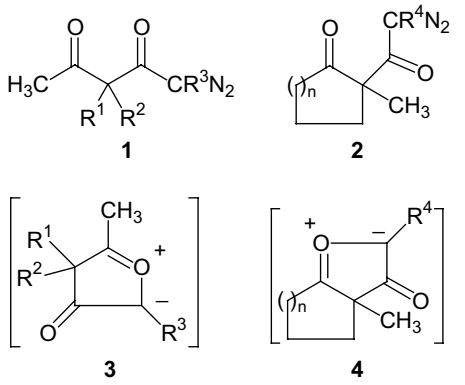

Figure 1. α-Diazo ketones **1** and **2** and five-membered cyclic carbonyl ylides **3** and **4**.

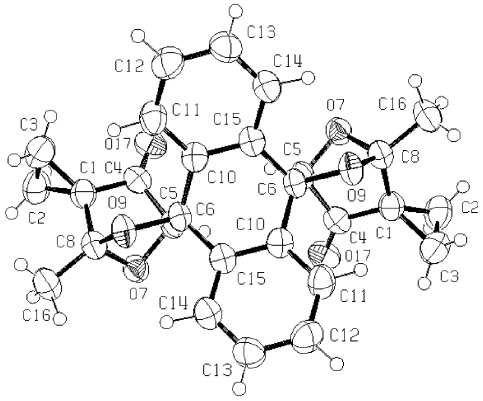

Figure 3. ORTEP diagram of compound **5a**.

Table 1.

Entry	*n*	R^1	R^2	R^3	R^4
1a or **3a**	—	CH_3	CH_3	H	—
1b or **3b**	—	CH_3	CH_3	COOEt	—
1c or **3c**	—	$-(CH_2)_2-$		H	—
2a or **4a**	2	—	—	—	H
2b or **4b**	2	—	—	—	COOEt
2c or **4c**	1	—	—	—	H

Table 2.

Entry	R	X	Y	Z	Yield (%)[a]
5a	H	CH_3	$-(CH_2)_2-$		75
5b	H	CH_3	CH_3	CH_3	70
5c	H	$-(CH_2)_4-$		CH_3	60

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds.

anthraquinone and a catalytic amount of $Rh_2(OAc)_4$ under an argon atmosphere. The reaction was monitored by TLC and column chromatographic purification of the crude reaction mixture afforded the interesting symmetric bis-cycloadduct **5a** in 75% yield (Fig. 2). The formation of the bis-spiro epoxy-bridged tetrahydropyranone ring system **5a** was confirmed[13] based on the characteristic singlet resonance signal around 4.63 ppm for the bridgehead proton (R = H) in the ^1H NMR spectrum. Further, the structure was unequivocally confirmed by single-crystal X-ray analysis[14] (Fig. 3). This reaction revealed that the cyclopropyl substituted carbonyl ylide **3c** generated from diazo ketone **1c** undergoes cycloaddition *syn*-facially in a head-to-tail fashion with the carbonyl groups in the rigid six-membered ring system of anthraquinone in a chemospecific and diastereoselective manner. Similarly, reaction of diazo ketone **1a** and cyclohexane fused diazo ketone **2a** with anthraquinone afforded the respective symmetric bis-cycloadducts **5b**,**c** in good yields (Fig. 2, Table 2). Interestingly, no cycloadduct arising from the carbonyl group present in the oxa-norboranane ring system was observed.

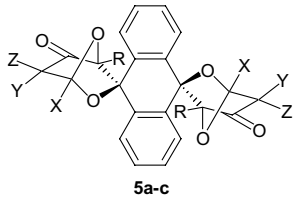

Figure 2. Reaction of carbonyl ylides with anthraquinone.

Next, we aimed to explore the multiple tandem reactions of diazo ketones **1** and **2** with substrates possessing several aldehyde functionalities. Thus, the tandem cyclization–cycloaddition reaction of α-diazo ketone **1b** with phthalaldehyde in the presence of rhodium(II) acetate catalyst under reflux afforded[13] bis-cycloadduct **6a** in 76% yield. The spectral data showed that this product existed as a bis-dioxabridged compound symmetric in nature (Fig. 4, Table 3). A similar result was obtained when diazo ketone **2b** was used affording **6b** as the product. Further, the Rh(II)-catalyzed double 1,3-dipolar cycloaddition reactions of the transient cyclic carbonyl

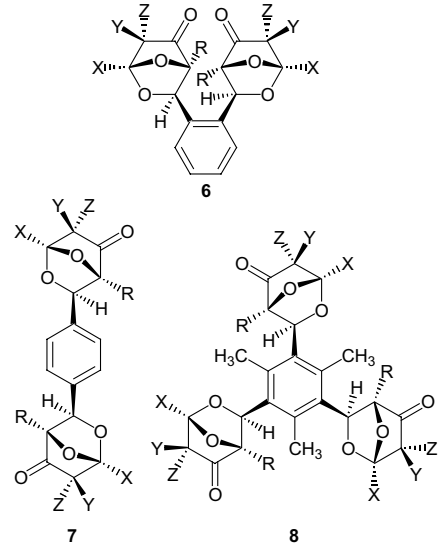

Figure 4. Reaction of carbonyl ylides with various aromatic di- and tri-aldehydes.

Table 3.

Entry	R	X	Y	Z	Yield (%)[a]
6a	COOEt	CH_3	CH_3	CH_3	76
6b	COOEt	$-(CH_2)_4-$		CH_3	65
7a	H	CH_3	CH_3	CH_3	82
7b	COOEt	CH_3	CH_3	CH_3	64
7c	H	$-(CH_2)_4-$		CH_3	63
7d	COOEt	$-(CH_2)_4-$		CH_3	58
7e	H	$-(CH_2)_4-$		CH_3	55
8a	H	CH_3	CH_3	CH_3	70
8b	H	$-(CH_2)_4-$		CH_3	65

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds.

ylides **3** and **4** with terephthalaldehyde afforded[13] the corresponding bis-cycloadducts **7** in a chemoselective manner. Interestingly, the reaction was extended to 2,4,6-trimethylbenzene-1,3,5-tricarbaldehyde to afford[13] the respective tris-cycloadducts **8** in good yields. Based on earlier work[12a] and the singlet resonance of the proton (when R = H), we confirmed the *exo*-addition of aldehydes to carbonyl ylide intermediates. The formation of a single product indicates the complete diastereoselectivity involved in these multiple tandem cyclization–cycloaddition reactions similar to our work on aromatic aldehydes.[12a] Representatively, the structure and stereochemistry of compound **8a** was unequivocally characterized by single-crystal X-ray analysis[15] (Fig. 5). Several isomers of products **5**–**8** are possible in these reactions. Based on the literature reports,[8] isomers **9** and **10** (Fig. 6) are mainly apparent from the reaction of anthraquinone and 2,4,6-trimethylbenzene-1,3,5-tricarbaldehyde with an excess amount of α-diazo ketones, respectively. Essentially, in all the above reactions, there was no formation of such 2:1 or 3:1 cycloadducts as shown in Figure 6 observed even in the presence of an excess amount of diazo ketone. Interestingly, these reactions furnished the stereochemically favourable cycloadducts **5** and **6**–**8** with chemospecificity and chemoselectivity, respectively.

In conclusion, the transient five-membered ring carbonyl ylides generated from α-diazo ketones undergo multiple 1,3-dipolar cycloaddition reactions with heterodipolarophiles such as ketone or aldehyde functional groups, which are the fundamental building blocks in synthetic organic chemistry, to afford the bis- or tris-epoxy-bridged tetrahydropyranone ring systems in a chemo and diastereoselective manner. In turn, these multiple tandem cyclization–cycloaddition processes, from simple starting materials, provide up to nine new bonds with many stereocentres and with stereoselectivity in a single synthetic operation. We are in the process of applying this interesting tandem methodology in the area of dendrimers.

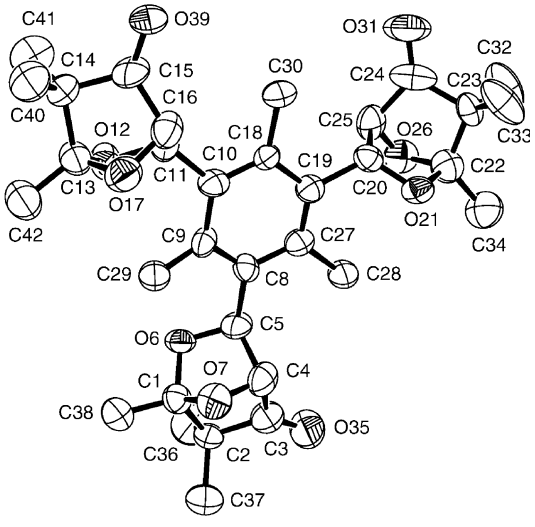

Figure 5. ORTEP representation of compound **8a**.

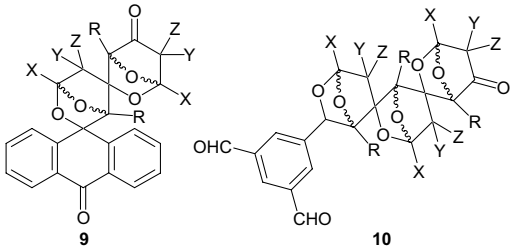

Figure 6. Possible 2:1 and 3:1 adducts with anthraquinone and a trialdehyde.

Acknowledgements

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13. Typical procedure, *Method A*: To an oven-dried flask, a solution containing the appropriate carbonyl compound (1 mmol) and 0.5 mol% of rhodium(II) acetate dimer in 15 mL of dry dichloromethane (dried over phosphorous pentoxide) was degassed using argon. To this reaction mixture, a solution of appropriate α-diazo ketone **1** (R^3 = H) or **2** (R^4 = H) (3 mmol) in dry dichloromethane was added very slowly over a period of 1 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using silica gel column chromatography (hexane/EtOAc) to afford the respective bis-cycloadducts **5**–**7**. For the synthesis of tris-cycloadducts **8**, 5 mmol of the appropriate α-diazo ketone **1** or **2** was used. *Method B*: Reactions utilizing α-diazo ketones **1b** and **2b** were performed in dry benzene (dried over sodium) at reflux. The procedure was further followed as described above. All new compounds exhibited spectral data consistent with their structures. Selected spectral data: Compound **5a**: colourless solid; mp 192–194 °C (chloroform/hexane); IR (KBr): 1760, 1452, 1406, 1334, 1143, 999, 833, 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, J = 7.0 Hz, 2H), 7.66 (d, J = 7.0 Hz, 2H), 7.37–7.31 (m, 4H), 4.63 (s, 2H, OCH), 1.78 (s, 6H, CH_3), 1.41–1.15 (m, 8H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 207 (C=O), 139.2 (*quat*-C), 134.0 (*quat*-C), 128.6 (CH), 128.2 (CH), 126.6 (CH), 126.0 (CH), 113.3 (*quat*-C), 89.7 (O*C*H), 82.0 (*quat*-C), 40.2 (*quat*-C), 15.5 (*C*H_3), 15.4 (*C*H_2), 13.3 (*C*H_2); MS (EI) *m*/*z* (%): 456 (M^+, 2), 333 (5), 248 (7), 124 (100), 67 (22); Anal. Calcd for $C_{28}H_{24}O_6$:C, 73.67; H, 5.30. Found: C, 73.81; 5.36%. Compound **6b**: colourless solid; mp 175–177 °C (chloroform/hexane); IR (KBr): 1781, 1755, 1462, 1380, 1306, 1137, 1019, 760 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.54 (dd, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 2H, arom-*H*), 7.30 (dd, J_1 = 7.5 Hz, J_2 = 2.0 Hz, 2H, arom-*H*), 5.42 (s, 2H, O*CH*), 4.20–3.88 (m, 4H, O*C*H_2), 2.30–1.60 (m, 16H), 1.31 (s, 6H, *C*H_3), 1.01 (t, J = 7.0 Hz, 6H, *C*H_3); ^{13}C NMR (50.3 MHz, $CDCl_3$); δ 206.5 (C=O), 162.8 (COO), 134.6 (*quat*-C), 129.4 (=*C*H), 128.4 (=*C*H), 112.6 (*quat*-C), 92.9 (*quat*-C), 74.5 (O*C*H), 62.7 (O*C*H_2), 52.7 (*quat*-C), 31.9 (*C*H_2), 27.1 (*C*H_2), 23.4 (*C*H_2), 20.5 (*C*H_2), 16.8 (*C*H_3), 14.3 (*C*H_3); MS(EI) *m*/*z* (%): 582 (M^+, 1), 391 (10), 297 (11), 139 (79), 123 (100), 29 (58); Anal. Calcd for $C_{32}H_{38}O_{10}$: requires C, 65.97; H, 6.57. Found: C, 66.15; H, 6.49%. Compound **7d**: colourless solid; mp 192–194 °C (chloroform/hexane); IR (KBr): 2942, 1778, 1732, 1381, 1329, 1133, 1015, 964 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27 (s, 4H), 4.86 (s, 2H, O*CH*), 4.07–3.87 (m, 4H, O*C*H_2), 2.20–1.30 (m, 16H), 1.19 (s, 6H), 0.99 (t, J = 7.0 Hz, 6H, *C*H_3); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 206.5 (C=O) 162.8 (COO), 134.6 (*quat*-C), 129.4 (*C*H), 128.4 (*C*H), 112.6 (*quat*-C), 92.9 (*quat*-C), 74.5 (O*C*H), 62.7 (O*C*H_2), 52.7 (*quat*-C), 31.9 (*C*H_2), 27.1 (*C*H_2), 23.4 (*C*H_2), 20.5 (*C*H_2), 16.8 (*C*H_3), 14.7 (*C*H_3); MS (FAB) *m*/*z* (%): 605 [M^+, Na] (20), 487 (5), 391 (7), 247 (45), 225 (100), 149 (40), 123 (70); Anal. Calcd for $C_{32}H_{38}O_{10}$:C, 65.97; H, 6.57. Found: C, 65.81; H, 6.64%. Compound **8a**: colourless solid; mp 228–230 °C (chloroform/hexane); IR (KBr): 2930, 1766, 1396, 1136, 997, 850 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.02 (s, 3H, O*CH*), 4.44 (s, 3H, O*CH*), 2.37 (s, 9H C*H*$_3$), 1.63 (s, 9H, C*H*$_3$), 1.08 (s, 9H, C*H*$_3$), 1.03 (s, 9H, C*H*$_3$); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 212.9 (C=O), 135.6 (*quat*-C), 134.5 (*quat*-C), 115.6 (*quat*-C), 86.1 (OCH), 77.2 (OCH), 52.4 (*quat*-C), 21.3 (*C*H_3), 20.2 (*C*H_3), 18.2 (*C*H_3), 15.0 (*C*H_3); MS (FD^+): *m*/*z* = 582 [M^+]. Anal. Calcd for $C_{33}H_{42}O_9$:C, 68.02; H, 7.27. Found: C, 68.16; H, 7.19%.
14. Crystal data for compound **5a**: colourless rectangular crystal. $C_{28}H_{24}O_6$, M = 456.47, 0.43×0.12×0.07 mm^3, orthorhombic, space group *C*2221 with a = 12.066(8) Å, b = 13.340(9) Å, C = 14.094(9) Å, V = 2269(3) $Å^3$, T = 293(2) K, R_1 = 0.0436, wR_2 = 0.0949 on observed data, z = 4, D_{calcd} = 1.336 g cm^{-3}, F(000) = 960, Absorption coefficient = 0.094 mm^{-1}, λ = 0.71073 Å, 2366 reflections were collected on a smart apex ccd single crystal CCD diffractometer, 2151 observed reflections ($I \geqslant 2\sigma$ (I)). The largest difference peak and hole = 0.176 and −0.156 e $Å^{-3}$, respectively.
15. Crystal data for compound **8a**: colourless plates. $C_{33}H_{42}O_9$, M = 582.67, 0.10×0.06×0.04 mm^3, monoclinic, space group *Cc* with a = 25.550(8) Å, b = 6.2558(19) Å, C = 21.107(6) Å, V = 3049.6(16) $Å^3$, T = 273(2) K, R_1 = 0.0978, wR_2 = 0.2569 on observed data, z = 4, D_{calcd} = 1.269 g cm^{-3}, F(000) = 1248, Absorption coefficient = 0.092 mm^{-1}, λ = 0.71073 Å, 5592 reflections were collected on a smart apex ccd single crystal CCD diffractometer, 2959 observed reflections ($I \geqslant 2\sigma I$). The largest difference peak and hole = 0.626 and −0.338 e $Å^{-3}$, respectively. The structure was solved by direct methods and refined by full-matrix least squares on F^2 using SHELXL-97 software. Crystallographic data for **5a** and **8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC-226282 and 237187, respectively. Copies of the data can be obtained free of charge on application to 12, Union Road, Cambridge CB2 1EZ, UK, (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).