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Polyoxygenated Coumarins. Oxonium Ylides *en route* to Polyoxa-Macrocyclic Coumarins

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Abstract: The overall sequence of Rh(II)-catalysed carbenoid generation, oxonium ylide formation and subsequent sigmatropic rearrangement utilising 3-diazo-2*H*-1-benzopyran-2,4(3*H*)-dione in cyclic ethers as solvents has been satisfactorily used to achieve the synthesis of several medium- to large-membered polyoxa macrocycles embodying the coumarin subunit.

Keywords: *Coumarins Crown Ethers Diazo Compounds Carbene Ylides*

Since the first report on a metal-induced decomposition of a diazocompound appeared in 1906,[1] α-ketocarbenoids have been pursued as synthetically attractive intermediates, being involved in a great number of reactions (*e.g.*, dimerisation and telomerisation, cyclopropanation, σ-bond insertion, dipolar cycloaddition). The versatility of carbenoids generated from the corresponding α-diazocarbonyl compounds arises through their potential to react as i) electrophiles, ii) nucleophiles (or bases), iii) 1,3-dipoles and iv) *via* radical reactions.[2]

As part of our ongoing program aimed at developing a general method for the preparation of 3,4-dioxygenated coumarins, we recently began to explore the potential of 3-diazo-2*H*-1-benzopyran-2,4(3*H*)-dione **1**[3] as a precursor of polyoxygenated structures. Preparation of **1** was accomplished by a diazo-transfer reaction involving 4-hydroxycoumarin **2**, 4-nitrobenzenesulphonyl azide (PNBSA) (2.0 equiv.) and DBU (2.0 equiv.) in dry CH_2Cl_2.[4] By this procedure, the resulting **1** was typically isolated as colourless crystalline solid in 68% yield and could be stored at room temperature for an extended period of time (> 3 months) without significant decomposition. In prior work, we examined the reaction of **1** with several alcohols (used as both solvent and reagent) and, we found that, under the proper conditions (*e.g.*, transition metal-complex catalysis), the intermediate metal-carbenoid underwent O-H bond

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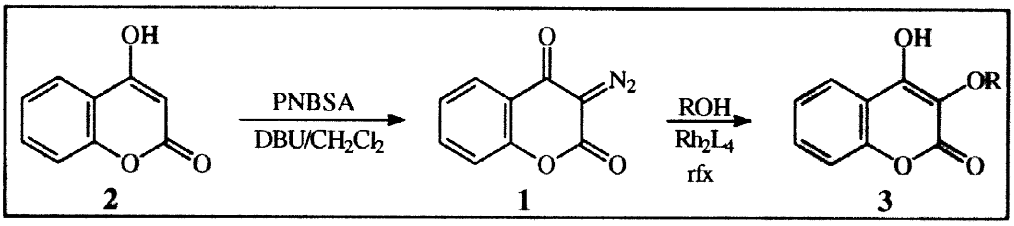
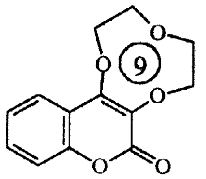
insertion to generate an exceedingly wide range of 3-alkoxy-4-hydroxycoumarins **3**, in good to excellent yields (Eq. 1).[5]

(Eq. 1)



Investigation of solvent conditions highlighted an additional and interesting facet of the decomposition pathway of **1** in the absence of proton donors through reactions with ethers (1,4-dioxane, THF, oxane, 1,2-dimethoxyethane).[6] The reaction conditions were screened in detail in the reaction of **1** with 1,4-dioxane. Among the transition-metal catalysts surveyed, $Rh_2(OAc)_4$ was found to be the catalyst of choice, while replacement with typical Lewis acids (such as $TiCl_4$, $SnCl_4$, $MgCl_2$ or $BF_3{\cdot}Et_2O$) or protic acids (TFA, $MeSO_3H$) gave inferior results or was ineffective. Accordingly, the reaction was best conducted by heating at 120°C for 5h in a threated Pyrex® tube with a Teflon® cap a 0.05M solution of **1** in the presence of 2 mol% $Rh_2(OAc)_4$ and oven-dried powdered 4Å-molecular sieves (200 mg/mmol substrate). The crude reaction mixture was chromatographed on silica gel to yield two compounds incorporating either one or two dioxane molecules (*i.e.*, **4** and **5** in 35 % and 42 % yields, respectively). To further test the generality of this behaviour, **1** was subjected to similar reaction conditions in THF (sealed tube, 110°C, 4h), affording an inseparable ~ 1:1 mixture of the 1,4-dioxecine **6** and the 1,4,9-trioxa-cyclotridecane **7** formed by a twofold insertion of THF (65 % overall yield). Similarly, the reaction of **1** in neat oxane (tetrahydropyran) (110°C, sealed tube, 6h) gave the respective 1,4-dioxonine **8** (31%) and 1,4,10-trioxacyclopentadecane **9** (47%). In contrast to above mentioned behaviour, **1** underwent a sluggish reaction in neat DME (110°C, sealed tube, 8h) affording the 1:1 adduct **10** in only 27% yield along with a complex mixture. The presence of molecular sieves was crucial for obtaining satisfactory yields of coumarin-containing oxamacrocycles, whereas higher reaction concentrations of **1** (> 50-80 mM) invariably resulted in the formation of a sparingly soluble deep-orange polymeric material. This behaviour was predictable since thermodynamically controlled oligomerisation should produce only cyclic products below the critical monomer concentration (CMC).[7]



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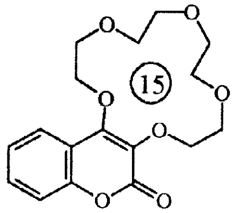

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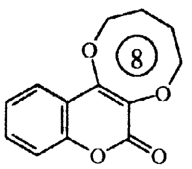

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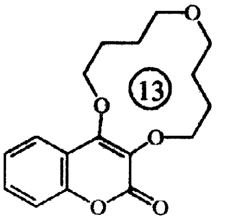

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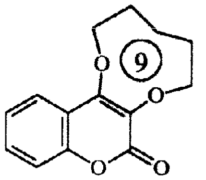

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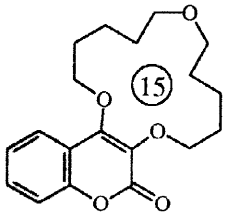

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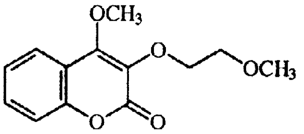

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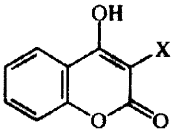
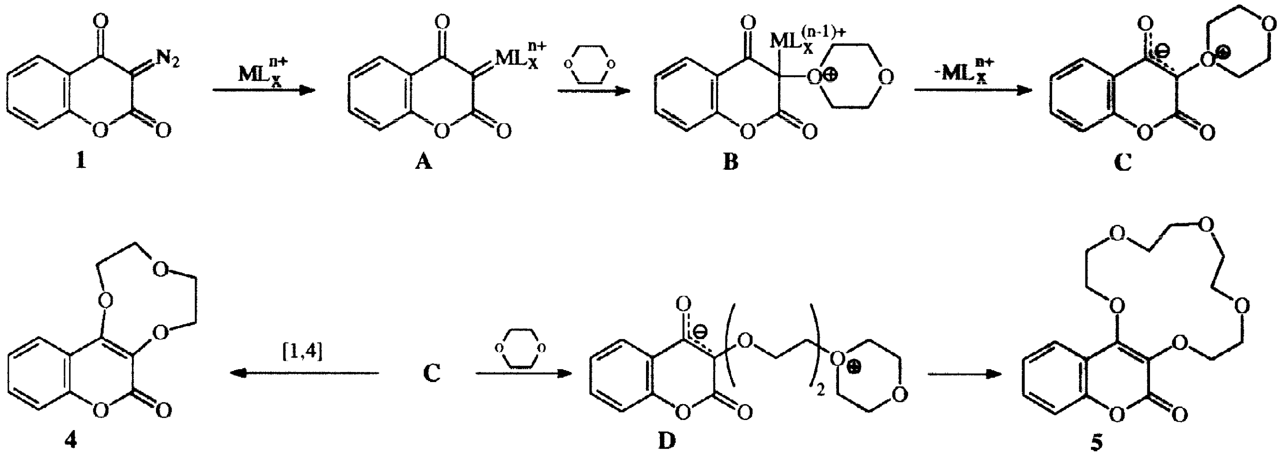


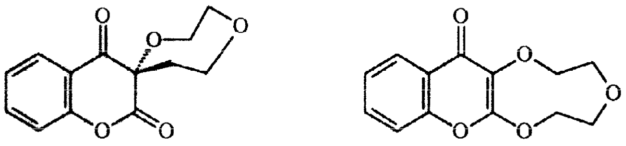
11 X: OH
12 X: $CHCl_2$

Mixed solvents containing cyclic ethers were not conducive to the formation of the above mentioned products; the major product (**11**)[8] was then derived from formal O-H insertion into adventitious water, while C-H insertion analogous (*e.g.*, **12**) to that observed by Pirrung[9] was seen with CH_2Cl_2 as the solvent.

The proposed structures of these adducts were consistent with data provided by their NMR (^{13}C and ^1H) and combustion analysis.



Our ring expansion process is believed to proceed mechanistically as illustrated in the above Scheme using dioxane as an example. Addition of a non-bonded electron pair of dioxane to the electrophilic metal-carbenoid **A** initially produces a stabilised oxonium ylide **C** (or its enolate-like structure). Surprisingly, **C** did not give any products (*e.g.*, the strained spiro-compound **13**) derived from the well-precedented Stevens-type [1,2]-rearrangement.[10] Although defined as a stereoelectronically unappealing transformation,[11] the Stevens rearrangement has been used in several systems to provide ring expansion products with high levels of regio- and stereocontrol.[12] Product **4** likely arises from an overall [1,4]-sigmatropic shift in preference to the other possible isomeric [1,4]-shift (→ **14**). In all the reactions examined, the cyclisation was completely regioselective, the sole product being formed by intramolecular attack of ketone carbonyl to oxonium ylide **C**. The high regioselectivity is somewhat surprising because in our previous work the annulation of 4-hydroxycoumarin did not prove very regioselective.[13] The intermolecular interception of zwitterion **C** can account for formation of **5** arising from 15-membered ring closure.



13 **14**

Accordingly, the inability of **4** to insert dioxane (→ **5**) under Rh(II)-catalysis supported this mechanistic pathway. This mechanism is similar to that recently proposed by Lin, Chow and co-workers[14] for the photolysis of azulenoquinone diazides wherein the key reaction step is the formation of oxonium azulenolate by interaction of photogenerated ketocarbenes with cyclic ethers as solvents.[15] The oxonium ylides (such as **C**) invoked in our mechanism were also shown to be intermediates in the reactions of strained lactones with diazocarbonyl compounds under Rh(II)-catalysis.[16]

It is worth noting that compounds **4** and **5** would be expected to accommodate various guests in their cavity thereby providing a new class of crown ethers. Their complexing ability, coupled to the well-known fluorophoric properties exhibited by some 7-substituted coumarins, might rende these molecules as new efficient fluorescent probes for monitoring trace amounts of essential metal cations in biological materials.[17]

In conclusion, we have shown that the overall sequence of Rh(II)-catalysed carbenoid generation, oxonium ylide formation and subsequent sigmatropic rearrangement utilising the diazo-compound **1** in *n*-membered cyclic ethers can be used to achieve in satisfactory yields the synthesis of several medium- to large-membered oxamacrocycles possessing a coumarin subunit. Further applications of this (*n*+3)- and (2*n*+3)-ring expansion method are now being explored.

Acknowledgement

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Experimental

THF, DME, dioxane and tetrahydropyran were freshly distilled from benzophenone ketyl prior to use. Powdered 4Å molecular sieves were dried at 300°C/0.1 mmHg for 24h before use. Silica gel (230-400 Mesh) was used for column chromatography and silica gel glass-backed analytical plates (0.2 mm) were used for TLC with UV detection. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 MHz and 75.3 MHz, respectively, by using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were registered in electron impact ionisation mode with direct inlet system.

General Procedure for Rh-Catalysed Heterocyclization Reactions

Into a screw-capped vial, equipped with a Teflon®-lined cap and magnetic stirring bar, were placed $Rh_2(OAc)_4$ (2 mol%), **1** (1 mmol), powdered activated 4Å molecular sieves (200 mg/mmol substrate) in 20 ml of dry solvent. The vial was then capped and suspended in an oil bath at the desired reaction temperature for the appropriate period of time. When the reaction was considered complete as checked by TLC, the mixture was allowed to cool to room temperature. After complete removal of solvent *in vacuo*, the residue was purified by silica gel column chromatography, with methylene chloride/methanol mixtures as eluent. The following compounds have been prepared using this general procedure:

2,3,5,6-Tetrahydro-[1,4,7]trioxacyclononino[2,3-*c*]benzopyran-8-one (4)

Colourless needles, m.p. 164-165 °C (CH_2Cl_2-hexane); ν_{max} (CH_2Cl_2) 1721, 1623, 1612, 1574, 1491, 1456 cm^{-1}; δ_H 7.83 (1H, d, *J* 7.3), 7.48 (1H, t, *J* 7.2), 7.29 (1H, d, *J* 7.0), 7.27 (1H, t, *J* 7.2), 5.11 (2H, t, *J* 4.2), 4.09 (2H, t, *J* 4.5), 4.00 (2H, t, *J* 4.2), 3.90 (2H, t, *J* 4.4); δ_C 161.6 (s), 153.2 (s), 150.0 (s), 130.9 (d), 127.4 (s), 124.1 (d), 123.8 (d), 117.5 (s), 116.3 (d), 73.3 (t), 72.9 (t), 71.2 (t), 70.0 (t); *m/z* (EI-MS) 249 (26, M$^+$), 204 (29), 167 (41), 149 (100), 129 (97), 120 (72), 112 (57), 83 (54), 71 (98%). Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90%; H, 4.87%. Found: C, 62.75%; H, 5.02%.

2,3,5,6,8,9,11,12-Octahydro-[1,4,7,10,13]pentaoxacyclopentadecino[2,3-*c*]benzopyran-14-one (5)

Colourless needles, m.p. 127-128 °C (CH_2Cl_2-hexane); ν_{max} (CH_2Cl_2) 1723, 1621, 1612, 1570, 1590, 1470 cm^{-1}; δ_H 7.84 (1H, d, *J* 7.7), 7.46 (1H , t, *J* 7.5), 7.28 (1H, d, *J* 7.7), 7.26 (1H, t, *J* 7.1), 4.99 (2H, t, *J* 5.6), 4.36 (2H, t, *J* 3.8), 3.99 (2H, t, *J* 5.6), 3.82 (2H, t, *J* 3.8), 3.77 (2H, t, *J* 3.8), 3.72-3.64 (6H ,m) ; δ_C 161.7 (s), 154.0 (s), 150.6 (s), 131.3 (d), 127.5 (s), 124.8 (d), 124.4 (d), 118.4 (s), 116.8 (d), 74.2 (t), 72.8 (t), 72.7 (t), 72.0 (t), 71.9 (t), 70.9 (t), 70.8 (t), 70.5 (t). Anal. Calcd. for $C_{17}H_{20}O_7$: C, 60.71%; H, 5.99%. Found: C, 60.48%; H, 5.22%.

5,6,7,8-Tetrahydro-[1,4]dioxocino-[2,3-*c*]benzopyran-7-one (6) and 2,3,4,5,7,8,9,10-octahydro[1,4,9]trioxacyclotridecino-[2,3-*c*] benzopyran-12-one (7)

Colourless glass for 1:1 mixture of (6) and (7). ν_{max} (CH_2Cl_2) 1718 cm^{-1}. Data for (6) δ_H 7.77 (1H, d, *J* 7.9), 7.43 (1H, t, *J* 7.1), 7.26-7.22 (2H , m), 4.92 (2H, t, *J* 6.0), 4.24 (2H, t, *J* 5.6), 2.12 (2H, quint *J* 6.1), 1.80 (2H, quint , *J* 5.8); δ_C 161.2 (s), 152.8 (s), 150.1 (s), 130.8 (d), 128.5 (s), 123.9 (d), 123.3 (d), 118.3 (s), 116.3 (d), 73.8 (t), 70.4 (t), 29.4 (t), 22.4 (t). Data for (7): δ_H 7.77 (1H, d, *J* 7.9), 7.41, (1H, t, *J* 7.1), 7.26-7.22 (2H, m), 4.78 (2H, t, *J* 7.8), 4.15 (2H, t, *J* 5.8), 3.57 (2H, t, *J* 5.2), 3.52 (2H, t, *J* 5.2), 2.02-1.95 (4H, m), 1.77 (2H, m), 1.70 (2H, quint, *J* 5.5); δ_C 161.2 (s), 152.8 (s), 149.9 (s), 130.3 (d), 128.5 (s), 123.9 (d), 123.5 (d), 118.3 (s), 116.0 (d), 72.8 (t), 72.2 (t), 70.6 (t), 70.4 (t), 28.5 (t), 28.1 (t), 24.7 (t), 24.4 (t).

4,5,6,7,8,9-Hexahydro-[1,4]dioxonino[2,3-*c*]benzopyran-8-one (8)

Colourless foam; ν_{max} (CH_2Cl_2) 1722, 1620, 1613, 1571, 1590, 1471 cm^{-1}; δ_H 7.81 (1H, d, *J* 7.5), 7.56 (1H, t, *J* 7.7), 7.29-7.22 (2H, m), 5.07 (2H, t, *J* 5.2), 4.08 (2H, t, *J* 4.8), 1.96 (2H, quint, *J* 5.3), 1.87-1.74 (4H, m); δ_C 161.4 (s), 153.6 (s), 149.9 (s), 130.6 (d), 126.8 (s), 123.9 (d), 123.6 (d), 117.5 (s), 116.1 (d), 76.0 (t), 71.0 (t), 31.6 (t), 29.0 (t), 23.1 (t). Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28%; H, 5.73%. Found: C, 68.21%; H, 5.91%.

2,3,5,6,8,9,11,12-Octahydro-[1,4,10]trioxacyclopentadecino[2,3-*c*]benzopyran-14-one (9)

Colourless foam ; ν_{max} (CH_2Cl_2) 1724, 1625, 1611, 1570, 1590, 1471 cm^{-1}; δ_H 7.78 (1H, d, *J* 7.8), 7.45 (1H, t, *J* 7.7), 7.31-7.22 (2H, m), 4.50 (2H, t, *J* 7.7), 4.19 (2H, t, *J* 5.4), 3.53 (2H, t, *J* 5.4), 3.50 (2H, t, *J* 5.4), 1.98 (2H, quint, *J* 7.1), 1.85 (2H, m), 1.80-1.61 (m, 8H); δ_C 160.8 (s), 153.4 (s), 150.0 (s), 130.3 (d), 129.7 (s), 124.0 (d), 123.4 (d), 118.3 (s), 116.2 (d), 74.5 (t), 73.1 (t), 70.3 (t), 69.1 (t), 29.2 (t), 29.0 (t), 28.7 (t), 28.5 (t), 23.5 (t), 21.3 (t). Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.66%; H, 7.28%. Found: C, 68.49%; H, 7.41%.

4-Methoxy-3-(2-methoxyethoxy)-benzopyran-2-one (10)

Colourless foam; ν_{max} (CH_2Cl_2) 1718, 1621, 1614, 1573, 1592, 1475 cm^{-1}. δ_H 7.78 (1H, dd, J_1 8.1, J_2 1.4), 7.46 (1H, td, J_1 7.6, J_2 2.0), 7.30-7.22 (2H, m), 4.38 (3H, s), 4.25 (2H, t, *J* 4.4), 3.72 (2H, t, *J* 4.4), 3.41 (3H, s); δ_C 160.9 (s), 154.0 (s), 150.1 (s), 130.7 (d), 127.3 (s), 124.2 (d), 123.6 (d), 117.8 (s), 116.3 (d), 72.1 (t), 71.6 (t), 61.4 (q), 59.0 (q). Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39%; H, 5.64%. Found: C, 62.39%; H, 5.80%.

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