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Functional desymmetrization of 1,3-dioximes for the obtention of 1,2,3-hetero trisubstituted carbocycles

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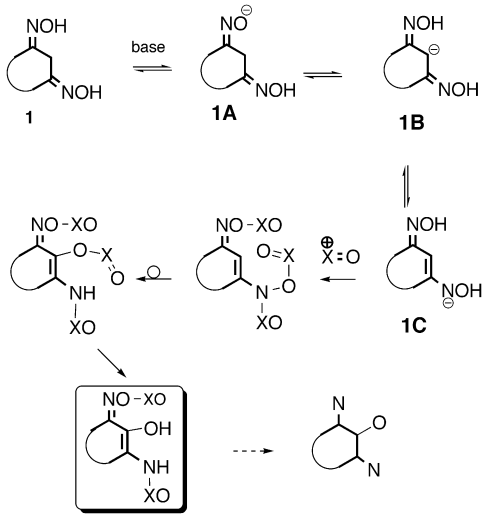
ABSTRACT

Carbocylic 1,3-dioximes react with acyl chlorides giving systems that may, upon heating, suffer [3,3]-sigmatropic rearrangements in high yields in only one of the oximes esters, yielding 1,3-dinitrogen-2-oxygen trisubstituted carbocycles. Use of more reactive electrophiles, such as *p*-toluenesulfonyl chloride and diethyl chlorophosphate, introduces the halogen at position 2, while cleaving the N–O bond of just one of the oxime functions.

1,2,3-Hetero trisubstituted carbocycles are important structural features found in a variety of products of practical importance. Examples are manifold and can bear the 1,2,3-trihydroxy motif, as in the key biosynthetic precursor shikimic acid, or include other heteroatoms, such as nitrogen, as in the 1,2-diamino-3-hydroxy present in the anti-flu drug Tamiflu®.[1] The size of the cycle can also vary, and the 1,2,3-trisubstituted motif can be found embedded in, for example, 5-membered rings, part of more complex structures.[2,3]

We disclose in this work a method to generate precursors of the densely functionalized system of 1,3-diamino-2-hydroxy carbocycles by *functional desymmetrization* of simple symmetrical cyclic 1,3-dioximes **1** (Scheme 1). These are simple compounds which can be easily generated from the corresponding 1,3-dicarbonyl compounds by reaction with hydroxylamine.[4] In basic media, the anionic species derived from **1**, that is, **1A**, **1B**, and **1C**, are amenable to react with electrophiles. Species **1C**, in particular, is a key for the desymmetrization reaction, since it contains one of the oxime functions as the tautomeric ene-hydroxylamine, ideally suited for further transformation.[5–7] For example, cyclohexan-1,3-dioxime (**1a**)[8] (1 equiv), when reacted at 0 °C to rt in the presence of a base (3 equiv), such as Et_3N, DABCO or Hunig's, and a suitable electrophile such as Cl(CO)Ph (3 equiv), gave rise after work-up to compound **2a** which presented the diagnostic olefinic proton (δ 6.63) in position 2. Upon further heating at 110 °C for 22 h in toluene a smooth [3,3]-sigmatropic rearrangement afforded the tribenzoyl **3a** in 75% yield [Scheme 2(a)].[9]

Compound **3a** now displays the 3 contiguous heteroatoms N, O and N, and still retains one oxime function for further transforma-



Scheme 1. 1,3-Dioximes as precursors of 1,3-diamino-2-hydroxy carbocycles.

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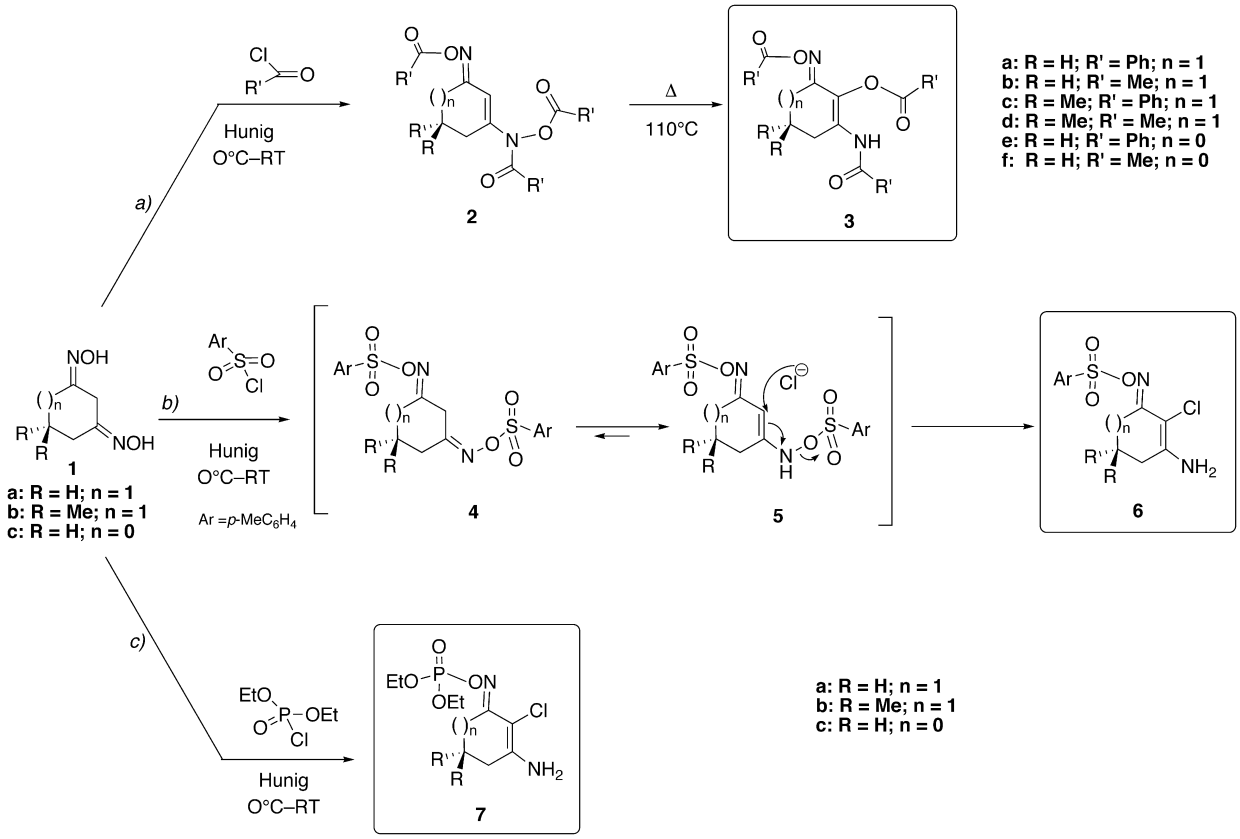

Scheme 2. Reactions of 1,3-dioximes **1** and (a) benzoyl chloride, (b) *p*-toluenesulfonyl chloride, (c) diethyl chlorophosphate.

Table 1
Functional desymmetrization of 1,3-dioximes via [3,3]-sigmatropic rearrangement of their acyl derivatives

Entry	1,3-Dioxime	Electrophile	Temp (°C)	Solvent/time (h)	Products[a]	Yield[b] (%)
1	**1a**	PhC(O)Cl	110	Toluene/22	**3a**	75
2	**1a**	$CH_3C(O)Cl$	110	Toluene/15	**3b**	95
3	**1b**	PhC(O)Cl	110	Toluene/26	**3c**	85
4	**1b**	$CH_3C(O)Cl$	110	Toluene/22	**3d**	92
5	**1c**	PhC(O)Cl	110	Toluene/54	**3e**	60
6	**1c**	$CH_3C(O)Cl$	110	Toluene/42	**3f**	98

[a] All the products characterized by NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography and/or crystallization.

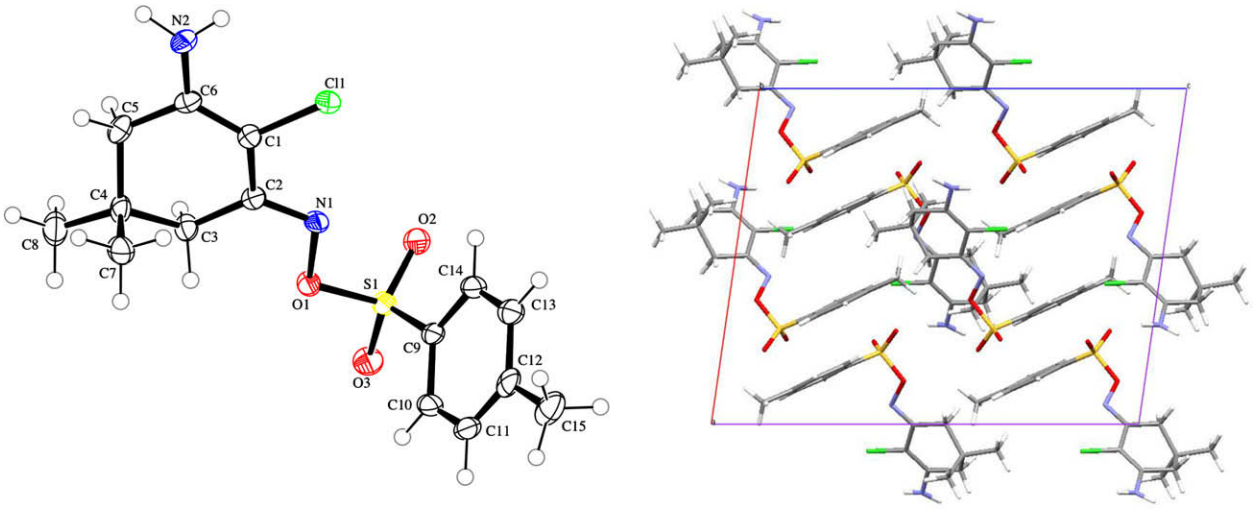

Figure 1. X-ray analysis of **6b** (left) and packing in the unit cell (right).

Table 2
Functional desymmetrization of 1,3-dioximes derivatives using strong electrophiles

Entry	1,3-Dioxime	Electrophile	Temp (°C)	Solvent/time (h)	Products[a]	Yield[b] (%)
1	**1a**	p-$CH_3C_6H_4SO_2Cl$	0 to rt	THF/12	**6a**	98
2	**1a**	$(EtO)_2P(O)Cl$	0 to rt	THF/6.5	**7a**	60
3	**1b**	p-$CH_3C_6H_4SO_2Cl$	0 to rt	THF/12	**6b**	74
4	**1b**	$(EtO)_2P(O)Cl$	0 to rt	THF/5	**7b**	70
5	**1c**	p-$CH_3C_6H_4SO_2Cl$	0 to rt	THF/12	**6c**	73
6	**1c**	$(EtO)_2P(O)Cl$	0 to rt	THF/6	**7c**	81

[a] All the products characterized by NMR, IR, and mass spectrometry.
[b] Yield refers to pure products after chromatography and/or crystallization.

tion. Other 1,3-dioximes, such as the substituted **1b**,[10] (Table 1, entries 3 and 4) as well as five-membered ring oximes, such as **1c**,[11] (entries 5 and 6) reacted in a similar fashion.

With more reactive electrophiles, such as *p*-toluenesulfonyl chloride, reaction with **1b** gave instead compound **6b** most probably via the intermediates **4b** and **5b** [Scheme 2(b)]. Introduction of the halogen at position 2 occurs now with simultaneous cleavage of the N–O bond of one the oximes derivatives.

The X-ray structure of **6b**, shown in the Figure 1, confirms the structure attributed and reveals an interesting crystal packing with strong interactions among the aromatic rings (π–π) as well as in between the sulfonyl group of one molecule and the amino group of another, leading to a ladder-type structure.[12] Other similar results **7a–c**, obtained with $ClP(O)(OEt)_2$, are collected in Table 2 (entries 2, 4 and 6) [cf. Scheme 2(c)]. In conclusion the yields of the compounds obtained range from good to excellent and the ease of the reaction makes it suitable for application to a wide variety of carbocycles, intermediates in the synthesis of more complex materials.

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9. *Experimental procedure*: Table 1, entry 1—to a solution of dioxime **1a** (142 mg, 1 equiv) in dry distilled THF, under inert atmosphere, was added at rt with stirring *i*-Pr_2NEt (3 equiv). The mixture was then cooled in an ice-bath and benzoyl chloride (3 equiv) carefully added. The reaction was allowed to reach room temperature and showed the full consumption of the starting dioxime after 2 h. The amine salt was removed by filtration and the resulting solution was evaporated under vacuum, the residue of **2a** redissolved in CH_2Cl_2, washed with brine, dried and heated in toluene t 110 °C for 22 h to afford after work-up and purification by preparative TLC (SiO_2, CH_2Cl_2/*n*-hexane, 1:1) a white crystalline solid (yield 75%) of **3a**: mp 164–165 °C (CH_2Cl_2:*n*-hexane); IR (KBr) υ: 3419, 3067, 1750, 1689, 1645, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.99 (2H, m), 2.92 (2H, t, J = 6.4 Hz), 3.26 (2H, t, J = 6.0 Hz), 7.39–7.68 (9H, m, ArH), 7.71 (2H, d, J = 7.3 Hz), 8.02 (2H, d, J = 7.2 Hz), 8.11 (1H, br s), 8.24 (2H, d, J = 8.4 Hz, ArH) ppm; ^{13}C NMR ($CDCl_3$) selected δ_C: 163.23, 164.42, 165.04 ppm. Calcd $C_{27}H_{22}N_2O_5$: C, 71.35; H, 4.88; N, 6.16. Found: C, 71.29; H, 4.97; N, 6.10. Table 2, entry 4—to a solution of dioxime **1b** (170 mg, 1 equiv) in dry destilled THF (5 ml), under inert atmosphere, was added at rt with stirring *i*-Pr_2NEt (3 equiv). The mixture was then cooled in an ice-bath and diethyl chlorophosphate (3 equiv) carefully added. The reaction was allowed to reach room temperature and showed the full consumption of the starting dioxime after 5 h. The amine salt was removed by filtration and the resulting solution was evaporated under vacuum, the residue dissolved in CH_2Cl_2, washed with brine, dried and the product purified by preparative TLC (SiO_2, AcOEt) to give a clear light-yellow oil (214 mg, yield 70%) of **7b**: IR (KBr) ν: 3326, 3208, 2961, 1633, 1600, 1557, 1470, 1386, 1367, 1258, 1165, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 1.04 (6H, s), 1.36 (6H, t, J = 7.0 Hz), 2.21 (2H, s), 2.59 (2H, s), 4.21–4.29 (4H, m), 4.56 (2H, br s) ppm; ^{13}C NMR ($CDCl_3$) δ_C: 14.21 (2C), 19.70, 27.41, 27,56, 37.12, 46.51, 59.84 (2C), 124.65, 129.8, 166.75 ppm; ^{31}P NMR ($CDCl_3$) δ_P: −0.137 ppm; EI–MS *m/z*: 324 (8) $[M]^+$), 289 (3), 188 (3), 174 (14), 172 (48), 137 (53), 116 (62), 99 (100). Calcd. $C_{12}H_{22}ClN_2O_4P$: C, 44.38; H, 6.83; N, 8.63. Found: C, 44.56; H, 6.69; N, 8.39. Table 2, entry 3—a similar protocol but using instead *p*-toluenesulfonyl chloride afforded after 12 h a white crystalline solid (yield 74%) of **6b**: mp 148–150 °C (CH_2Cl_2/*n*-hexane); IR (KBr) ν: 3472, 3371, 3203, 2960, 1633, 1595, 1469, 1359, 1278, 1190, 1176, 1122 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H: 0.99 (6H, s), 2.16 (2H, s), 2.42 (3H, s), 2.51 (2H, s), 4.64 (2H, br s), 7.31 (2H, d, J = 8.2 Hz), 7.91 (2H, J = 8.2 Hz). Calcd. $C_{15}H_{19}ClN_2O_3$: C, 52.55; H, 5.59; N, 8.17. Found: C, 52.67; H, 5.39; N, 8.32.
All new compounds gave correct microanalyses and/or HRMS. Spectral data for selected compounds: δ_H ($CDCl_3$), **7a**: 1.38 (6H, t, J = 7.12 Hz), 2.24 (2H, t, J = 6.3 Hz), 2.51 (2H, t, J = 6.9 Hz), 2.76 (2H, quint, J = 6.4 Hz), 4.19–4.25 (4H, m), 4.68 (2H, br s); **6a**: 1.75–1.81 (2H, quint, J = 6.3 Hz), 2.31–2.35 (2H, t, J = 6.2 Hz), 2.43 (3H, s), 2.68–2.71 (2H, t, J = 6.5 Hz), 7.32 (2H, d, J = 8.1 Hz), 7.93 (2H, d, J = 8.2 Hz); 8.02 (2H, d, J = 7.2 Hz), 8.11 (1H, br s), 8.24 (2H, d, J = 8.4 Hz); **3b**: 1.92 (2H, m), 2.14 (3H, s), 2.16 (3H, s), 2.27 (3H, s), 2.51 (2H, t, J = 6.3 Hz), 2.72 (2H, t, J = 5.8 Hz) 8.05 (1H, br s); **3f**: 2.12 (3H, s), 2.16 (3H, s), 2.29 (3H, s), 3.10 (2H, m), 3.52 (2H, m), 8.90 (1H, br s).
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12. CCDC 756960 contains the crystallographic data which can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request @ccdc.cam.ac.uk, or by contacting CCDC, UK; fax: +44 1223 336033.