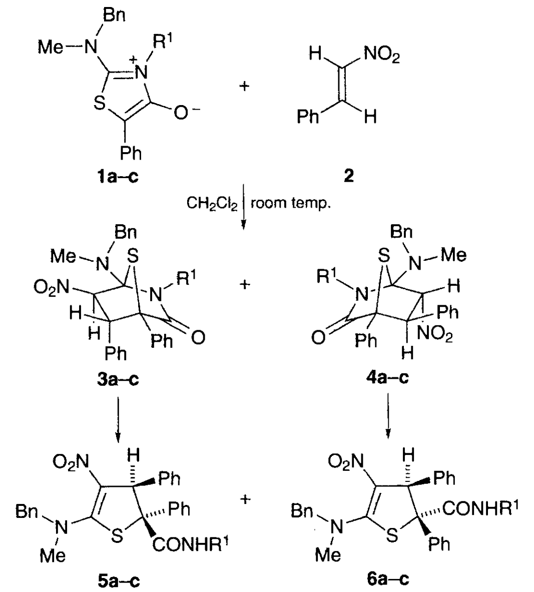
A Novel Highly Diastereoselective Synthesis of Chiral Dihydrothiophenes from Mesoionic Compounds

Martín Avalos,*[a] Reyes Babiano,[a] Andrés Cabanillas,[a] Pedro Cintas,[a] María J. Diánez,[b] María D. Estrada,[b] José L. Jiménez,[a] Amparo López-Castro,[b] Juan C. Palacios[a] and Simeón P. Garrido[b]

[a] *Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain*
[b] *Departamento de Física de la Materia Condensada, Instituto de Ciencias de Materiales, Universidad de Sevilla, E-41080 Seville, Spain*

Thioisomünchnones undergo 1,3-dipolar cycloaddition with chiral nitroalkenes to afford stereoselectively 4,5-dihydrothiophenes by means of an unprecedented fragmentation of cycloadducts; the structures of these products have been established by single crystal X-ray structure analyses.

In recent years, there has been an increasing interest in the synthetic applications of mesoionic ring systems, namely, five-membered heterocycles that cannot be satisfactorily represented by Lewis forms not involving charge separation. Their attractiveness arises from the fact that mesoionics behave as masked 1,3-dipoles and therefore readily participate in cycloadditive processes.[1,2] Isomünchnones and thioisomünchnones are amongst the most widely used mesoionic rings *en route* to a variety of functionalized heterocycles, including natural products.[3] Recently, Padwa has further enhanced their versatility by means of a tandem transition metal-catalysed cyclization–intramolecular dipolar cycloaddition reaction.[2]

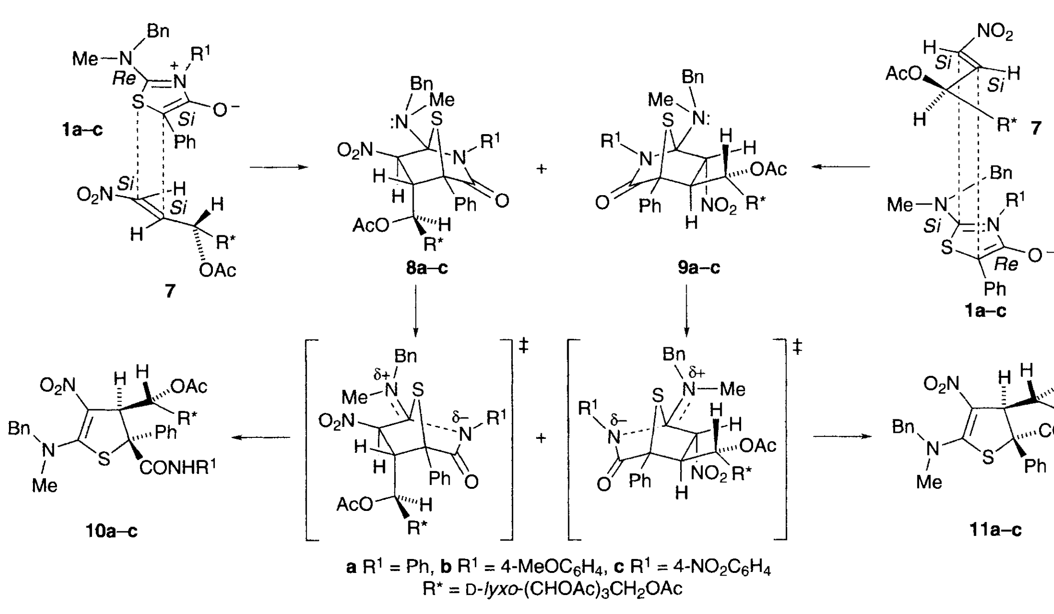


a R^1 = Ph, b R^1 = 4-$MeOC_6H_4$, c R^1 = 4-$NO_2C_6H_4$

Scheme 1

In general, thioisomünchnones (1,3-thiazolium-4-olates) are known to undergo dipolar cycloadditions with alkenes to provide stable bridged cycloadducts,[4] which eventually fragment into α-pyridones by extrusion of hydrogen sulfide.[5] Remarkably, the reaction of thioisomünchnones **1a–c** with *trans*-β-nitrostyrene **2** in dichloromethane solution at room temperature afforded a mixture of two transient cycloadducts **3** and **4**, that converted into the corresponding 4,5-dihydrothiophenes **5** and **6** in 90–98% overall yield (**5a**:**6a**, 3:1; **5b**:**6b**, 4:1; **5c**:**6c**, 1:2) (Scheme 1). As far as we know, this opening represents a novel type of cycloadduct fragmentation in the reactions of mesoionic compounds with alkenes.

In order to ascertain the scope of this useful tandem cycloaddition–fragmentation reaction and as a part of our current research on asymmetric transformations with mesoionic systems for the construction of optically active heterocycles,[6] we investigated the reaction of heterocycles **1a–c** with a carbohydrate-based nitroalkene **7**, having a side chain with the D-*galacto* configuration, under the aforementioned conditions. NMR monitoring of crude samples at 0 °C detected the formation of cycloadducts **8–9** and their conversion into dihydrothiophenes **10–11** in *ca.* 80% combined yield (**10a**:**11a**, 1:1; **10b**:**11b**, 1:1; **10c**:**11c**, 1:6) (Scheme 2). The transformation is fast with electron-withdrawing groups on the heterocycle, **1c**, for which cycloadducts could be detected at a lower temperature (−10 °C), whereas it was slow from the 4-meth-



a R^1 = Ph, b R^1 = 4-$MeOC_6H_4$, c R^1 = 4-$NO_2C_6H_4$
R^* = D-*lyxo*-$(CHOAc)_3CH_2OAc$

Scheme 2

oxyphenyl-substituted heterocycle **1b**. Notably, cycloadduct **8** fragments more rapidly than **9**, and exceptionally the intermediate **9b** could be isolated (40%), which under the reaction conditions led to dihydrothiophene **11b**.

Compounds **10** and **11** were separated by flash chromatography and fully characterized by spectroscopic methods and elemental analyses.† Moreover, the molecular structures of compounds **10a** and **11a** were determined by X-ray crystallographic analyses.‡

Based on these unequivocal configurational assignments, the structures of the diastereoisomeric series of compounds **10** and **11** could be established, as they showed the same NMR pattern in terms of chemical shifts and coupling constants, evidence for a high diastereofacial control of the process. Both cycloadducts **8** and **9** were obtained with the same regiochemistry and only one diastereoisomer is observed for each. Some conclusions should be noted. Firstly, the cycloaddition reactions proceed with complete facial diastereoselectivity with respect to the starting nitroalkene, as the *Si*(C1)–*Si*(C2) face is exclusively involved. This can most likely be attributed to the chiral environment provided by the sugar side chain. Inspection of a simple CPK model reveals acetate groups largely disfavour the attack at the *Re* face. Secondly no facial selectivity is observed with respect to the mesoionic heterocycle. Thirdly regarding the *endo–exo* selectivity, the approach of the nitroalkene towards the *Re*(C2)–*Si*(C5) face of thioisomünchnone leads to cycloadduct **9** having the nitro group with an *endo* orientation, while the attack on the *Si*(C2)–*Re*(C5) face affords the *exo* cycloadduct **8**. Further semiempirical studies are currently under way to corroborate these selectivity features. Finally, the presence of the *N*,*N*-dialkylamino group appears to be largely responsible for the heterolytic breaking of cycloadducts. Replacement of the *N*-benzyl-*N*-methylamino group with phenyl gave no reaction at 0 °C, and only after refluxing in toluene for 48 h was the cycloadduct (like **8**) exclusively isolated (40%).

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Footnotes

† *Spectral data* for **10a**: mp 185 °C; $[\alpha]_D$ −183 (*c* 0.5, $CHCl_3$); δ_H (400 MHz; $CDCl_3$): 7.44–7.08 (16 H, m, NH and aryl), 5.93 (1 H, d, $J_{1',4}$ 7.7, $J_{1',2'}$ 0 Hz, 1′-H), 5.35 (3 H, m, 2′-H, 3′-H, 4′-H), 4.90 (1 H, d, 4-H), 4.64 (1 H, d, *J* 15.3 Hz, CH_2), 4.39 (1 H, d, CH_2), 4.21 (1 H, dd, $J_{4',5'}$ 4.7, $J_{5',5''}$ 11.7 Hz, 5′-H), 3.76 (1 H, dd, $J_{4',5''}$ 7.9 Hz, 5″-H), 2.92 (3 H, s, CH_3), 2.42, 2.34, 2.05, 1.97, 1.24 (15 H, 5s, $COCH_3$); δ_C (100 MHz; $CDCl_3$) 173.17, 170.19, 170.06, 169.86, 169.49, 168.14, 165.16 (C-2), 140.13, 136.35, 133.72 (C aryl), 129.49, 128.92, 128.22, 127.67, 126.28, 125.17, 120.27 (CH aryl), 115.93 (C-3), 73.76 (C-5), 70.11 (C-2′), 67.84 (C-3′), 67.44 (C-4′), 65.91 (C-1′), 62.05 (C-5′), 61.90 (N-CH_2), 49.80 (C-4), 43.16 (CH_3), 20.90, 20.76, 20.50, 20.45, 19.32 ($COCH_3$). For **11a**: mp 222 °C; $[\alpha]_D$ −120 (*c* 0.5, $CHCl_3$); δ_H 7.80–7.06 (16 H, m, NH and aryl), 5.19 (1 H, dd, $J_{1',4}$ 7.5, $J_{1',2'}$ 1.0 Hz, 1′-H), 5.13 (2 H, m, 3′-H, 4′-H), 5.01 (1 H, d, 4-H), 4.69 (1 H, d, *J* 15.8 Hz, CH_2), 4.58 (1 H, d, CH_2), 4.41 (1 H, dd, $J_{2',3'}$ 10.0 Hz, 2′-H), 4.03 (1 H, dd, $J_{4',5'}$ 5.0 $J_{5',5''}$ 11.4 Hz, 5′-H), 3.70 (1 H, dd, $J_{4',5''}$ 7.2 Hz, 5″-H), 3.04 (3 H, s, CH_3), 2.26, 2.01, 2.00, 1.99, 1.97 (15 H, 5s,$COCH_3$); δ_C 170.88, 170.23, 170.06, 169.82, 169.32, 168.09, 163.65 (C-2), 137.19, 134.17, 131.83 (C aryl), 129.70, 128.98, 128.88, 128.69, 128.39, 128.18, 127.15, 124.53, 119.71 (CH aryl), 117.38 (C-3), 68.81 (C-5), 68.81 (C-2′), 67.45 (C-3′), 67.31 (C-4′), 66.57 (C-1′), 61.74 (N-CH_2), 61.64 (C-5′), 51.47 (C-4), 43.62 (CH_3), 20.77, 20.62, 20.45 ($COCH_3$).

‡ *Crystal data* for **10a**: $C_{40}H_{43}N_3O_{13}S$, M = 805.9, trigonal, space group $P3_2$, $a = b = 10.303(1)$, $c = 33.750(2)$ Å, $\gamma = 120°$, $V = 3102.6(5)$ Å^3, $Z = 4$, $D_c = 1.29$ g cm^{-3}, D_m (measured by flotation in ClC_6H_5–Cl_4C) = 1.290 g cm^{-3}, $\mu = 0.137$ mm^{-1}, $2\theta_{max} = 50°$, index range: $0 \leqslant h \leqslant 12$, $-10 \leqslant k \leqslant 0$, $-40 \leqslant l \leqslant 40$, 10920 measured reflections, 3665 independent reflections, $R = 0.048$, $R_w = 0.048$ for 2930 observed reflections [$I > 3\sigma(I)$]. Maximum peak on the final ΔF map was 0.3 e Å^{-3}, minimum −0.4 e Å^{-3}. The unit-cell parameters were determined by a least-squares refinement on diffractometer angles for 25 automatically centred reflections with $6 < \theta < 15°$. For **11a**: $C_{40}H_{43}N_3O_{13}S$, M = 805.9, orthorhombic, space group $P2_12_12_1$, $a = 8.986(1)$, $b = 12.598(7)$, $c = 36.669(4)$ Å, $V = 4151(2)$ Å^3, $Z = 4$, $D_c = 1.29$ g cm^{-3}, D_m (in ClC_6H_5–Cl_4C) = 1.28 g cm^{-3}, $\mu = 0.137$ mm^{-1}, $2\theta_{max} = 50°$, index range: $0 \leqslant h \leqslant 10$, $0 \leqslant k \leqslant 14$, $0 \leqslant l \leqslant 434150$ measured reflections, all independent reflections, $R = 0.051$, $wR = 0.053$ for 3096 observed reflections [$I > 3\sigma(I)$]. Maximum peak on the final ΔF map was 0.3 e Å^{-3}, minimum −0.3 e Å^{-3}. The unit-cell parameters were determined by a least-squares refinement on diffractometer angles for 25 automatically centred reflections with $3 < \theta < 12°$. For both crystals an Enraf-Nonius CAD-4 diffractometer was used with monochromated Mo-Kα radiation (0.71069 Å) and an $\omega/2\theta$ scan technique at room temperature. Correction was made for Lorentz-polarization. Empirical absorption correction following the DIFABS[7] procedure was applied. Structures were solved by direct methods using SIR92,[8] and refined by full-matrix least-squares methods. The hydrogen atom positions were calculated geometrically and assigned isotropic temperature factors in fixed positions with U_{iso} values (corresponding to those of the carrier atoms). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

References

1 K. T. Potts in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, vol. 2 p. 1; A. M. Schoffstall and A. Padwa in *Advances in Cycloaddition*, ed. D. P. Curran, JAI Press, Greenwich, 1990, vol. 2, p. 1.

2 M. H. Osterhaut, W. R. Nadler and A. Padwa, *Synthesis*, 1994, 123; A. Padwa and D. J. Austin, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1797.

3 J. P. Marino, Jr., M. H. Osterhout and A. Padwa, *J. Org. Chem.*, 1995, **60**, 2704.

4 K. T. Potts, E. Houghton and U. P. Singh, *J. Org. Chem.*, 1974, **39**, 3627; K. T. Potts, J. Baum and E. Houghton, *J. Org. Chem.*, 1974, **39**, 3631; K. T. Potts, J. Baum, S. K. Datta and E. Houghton, *J. Org. Chem.*, 1976, **41**, 813; K. T. Potts, J. Baum and E. Houghton, *J. Org. Chem.*, 1976, **41**, 818; C. G. Newton and C. A. Ramsden, *Tetrahedron*, 1982, **38**, 2965, and references therein.

5 K. T. Potts and D. R. Choudhury, *J. Org. Chem.*, 1978, **43**, 2697; K. T. Potts and D. R. Choudhury, *J. Org. Chem.*, 1978, **43**, 2700; D. L. Hertzog, W. R. Nadler, Z. J. Zhang and A. Padwa, *Tetrahedron Lett.*, 1992, **33**, 5877.

6 P. Areces, M. Avalos, R. Babiano, L. González, J. L. Jiménez, M. M. Méndez and J. C. Palacios, *Tetrahedron Lett.*, 1993, **34**, 2999.

7 N. Walker and D. Stuart, *Acta Crystallogr., Sect. A*, 1983, **39**, 158.

8 A. Altomare, C. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Crystallogr.*, 1994, **27**, 435.