Exploring a new, connective Pummerer reaction: formation of oxindoles by the reaction of thiols with glyoxamides†

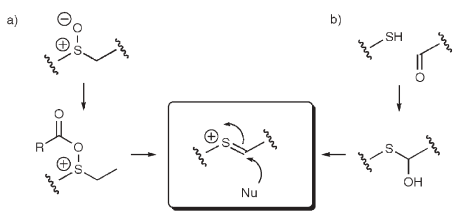
Marc Miller,[a] William Tsang,[a] Andrew Merritt[b] and David J. Procter*[a]

Received (in Cambridge, UK) 19th September 2006, Accepted 16th October 2006
First published as an Advance Article on the web 31st October 2006
DOI: 10.1039/b613591a

The reaction of a range of thiols with mono- and bis-glyoxamides derived from secondary anilines, triggers a new, connective Pummerer cyclisation process and leads to the formation of oxindoles.

The Pummerer reaction[1] has evolved into a useful tool for synthesis.[2] We have recently developed a fluorous synthesis of *N*-heterocycles that utilises a Pummerer process to introduce the fluorous tag and construct the heterocyclic scaffold in a single step.[3] The pivotal cyclisation step involves the reaction of a fluorous thiol with glyoxamide substrates in the first example of a 'connective' Pummerer reaction.[3] The classical Pummerer reaction of sulfoxides and the connective Pummerer reaction are compared in Scheme 1.

In the classical Pummerer reaction, sulfoxides are activated by acylation of the sulfoxide oxygen. Elimination then generates a thionium ion that is trapped by an external or internal nucleophile. In the connective variant, thiol addition to an aldehyde generates a hemithioacetal that upon activation generates a thionium ion. The connective variant has several advantages over its traditional counterpart: the process utilises widely-available thiol and aldehyde starting materials, negating the need to prepare sulfoxide or sulfide starting materials (sulfides are essentially prepared *in situ*). In addition, the properties or structural features of the thiol and aldehyde substituents are united in a single synthetic operation, with concomitant addition of a nucleophile. Reactive aldehydes such as glyoxylates[4] and glyoxamides[3] are ideal substrates and the use of an internal nucleophile allows heterocycles to be constructed.[3] Attractively, the organosulfanyl group can impart specific properties to the Pummerer adducts or can be used as a synthetic handle for further manipulation.

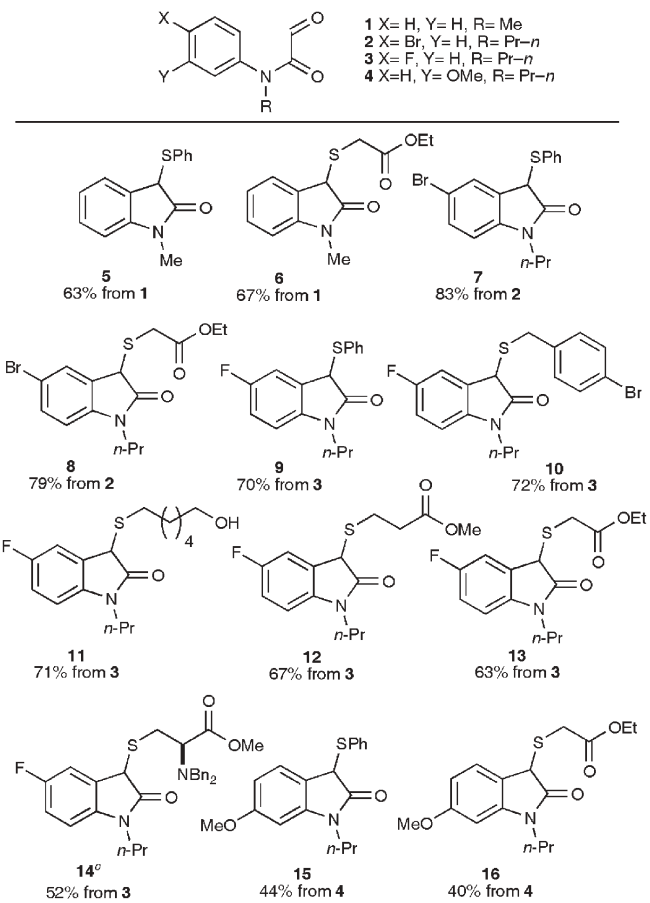


Scheme 1 (a) Pummerer reaction of sulfoxides; (b) the connective Pummerer reaction.

In this communication, we explore the scope of this new Pummerer process. Concentrating on the reactions of glyoxamides derived from aniline derivatives has allowed us to look at the role of the thiol component, the Lewis acid, and to pursue the idea of two-directional Pummerer reactions. In addition, the products of this Pummerer process possess a substituted oxindole structure and are amenable for the synthesis of natural product and pharmaceutically interesting target molecules.

We began by examining the reaction of functionalised alkyl and aryl thiols with glyoxamides[5] **1–4** derived from secondary anilines containing neutral, electron-withdrawing and electron-releasing

Table 1 Reaction of thiols with glyoxamides derived from anilines[a,b]



[a] RSH (1 eq.), TFAA (9 eq.), $BF_3{\cdot}OEt_2$ (4 eq.). [b] Yields are for 2 steps as glyoxamides are not purified. [c] 1 : 1 mixture of diastereoisomers.

[a]*School of Chemistry, University of Manchester, Oxford Rd., Manchester, UK M13 9PL. E-mail: david.j.procter@manchester.ac.uk*
[b]*GlaxoSmithKline, Gunnelswood Rd., Stevenage, UK SG1 2NY*
† Electronic supplementary information (ESI) available: Experimental details, selected ^1H and ^{13}C NMR spectra. See DOI: 10.1039/b613591a

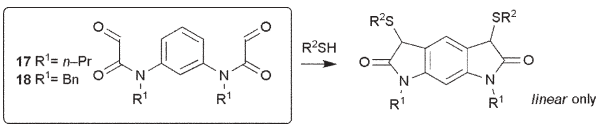
substituents (Table 1). The cyclisations were carried out by stirring thiol with glyoxamide, followed by addition of trifluoroacetic anhydride (TFAA), then $BF_3{\cdot}OEt_2$. Omitting TFAA or the Lewis acid led to the isolation of the hemithioacetal or trifluoroacetylated hemithioacetal intermediates. We have found that at least two equivalents of $BF_3{\cdot}OEt_2$ and four equivalents of TFAA are required before a significant degree of cyclisation is seen. A preliminary survey of other Lewis acids showed that $Sc(OTf)_3$ gave comparable results to $BF_3{\cdot}OEt_2$ when used in the cyclisation, while $Yb(OTf)_3$ also promoted the Pummerer reaction but gave lower yields.

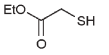
In all cases, the connective Pummerer cyclisation occurred to give the corresponding oxindole products in moderate to good isolated yields (over two steps) indicating that the process is compatible with thiols bearing a range of functional groups (aryl rings, ester, bromide, amino and hydroxyl groups). The reaction of **3** with a thiol derived from cysteine proceeded to give the expected product **14** (Table 1). This preliminary result suggests that the connective Pummerer reaction could form the basis of a method for chemical ligation:[6] hemithioacetal formation through the reaction of a carbonyl compound, or a masked derivative, with a cysteine residue could be followed by cyclisation to make the attachment permanent.

We have also examined the reaction of readily accessible bis-1,3-glyoxamides and bis-1,4-glyoxamides with thiols. To the best of our knowledge these represent the first examples of two-directional Pummerer cyclisations (Tables 2 and 3). Although, the overall yields are somewhat lower than those obtained with simple glyoxamides, the expected bis-oxindoles are obtained in acceptable yields and good purity. In the case of bis-1,3-glyoxamides, the oxindole products were obtained as single, *linear* regioisomers and inseparable ~1 : 1 mixtures of *cis* and *trans* diastereoisomers.

The corresponding reaction of bis-1,4-glyoxamides proceeded to give oxindoles with the *linear* regioisomers predominating (approximately 2 : 1 to >5 : 1) (*vide infra*). The use of bulkier thiols such as thiophenol and *para*-bromobenzylthiol gave more *linear* isomer presumably due to unfavourable steric interactions involved in the formation of the *bent* isomers. Both the *linear* and *bent* regioisomers were obtained as ~1 : 1 mixtures of *cis* and *trans* diastereoisomers. In most cases regioisomeric bis-oxindole products could be separated by chromatography (*e.g.* **30**) or recrystallisation (*e.g.* **27**).

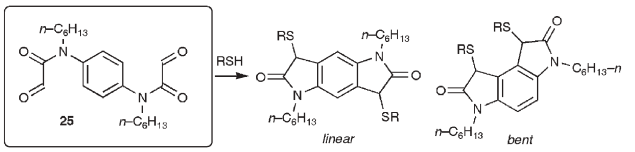
Table 2 Connective Pummerer cyclisation of bis-1,3-glyoxamides[a,b]

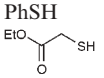
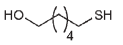
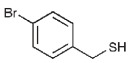


R^2SH	R^1	Isolated yield[b]	Product
BnSH	*n*-Pr	51%	**19**[c]
PhSH	*n*-Pr	47%	**20**[c]
	*n*-Pr	45%	**21**[c]
	*n*-Pr	56%	**22**[c]
BnSH	Bn	62%	**23**[c]
PhSH	Bn	45%	**24**[c]

[a] See Table 1 for reaction conditions. [b] Yields are for 2 steps as glyoxamides are not purified. [c] 1 : 1 mixture of diastereoisomers.

Table 3 Connective Pummerer cyclisation of bis-1,4-glyoxamides[a,b]

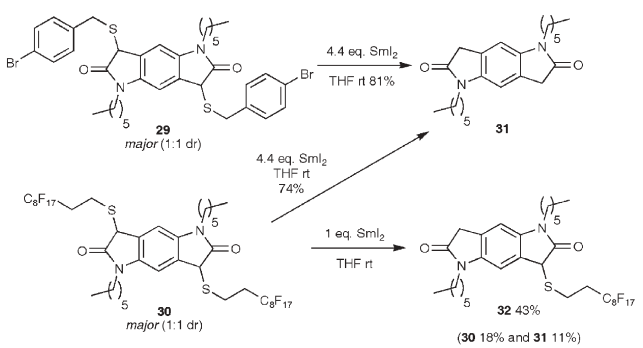


RSH	Isolated yield[b]	Product	*Linear* : *bent*[c,d]
PhSH	55%	**26**	>5 : 1
	54%	**27**	5 : 1
	61%	**28**	~3 : 1
	56%	**29**	5 : 1
	50%	**30**	2 : 1

[a] See Table 1 for reaction conditions. [b] Yields are for 2 steps as glyoxamides are not purified. [c] Regioisomer ratios are estimated from ^1H NMR. [d] Each regioisomer is a 1 : 1 mixture of diastereoisomers.

Due to the symmetry present in the *linear* and *bent* isomers of **26–30**, NMR did not allow the isomers to be distinguished. The nature of the isomers obtained from the cyclisation of bis-1,4-glyoxamides was determined by the following experiments: after the isolation of the major pair of isomers from the reactions to form **29** and **30**, independent treatment of each mixture with SmI_2[7] gave a single product **31** in good yield after reductive removal of the sulfanyl groups[8] (Scheme 2). Thus, the major isomer pair from each reaction are diastereoisomers and the major isomer pairs for **29** and **30** belong to the same regioisomeric family. The structure of the major regioisomers was confirmed by partial SmI_2 reduction to break the symmetry and provide **32**. The presence of two singlets in the ^1H NMR for the aromatic protons in **32** confirmed the major products of cyclisation to be *linear* isomers.

In summary, we have assessed the scope of a new, connective Pummerer process and have carried out the first, two-directional Pummerer cyclisations. We are currently exploring the utility of the connective Pummerer process in several areas including the synthesis of linear, fused-ring organic materials.



Scheme 2 Investigating the selectivity of the Pummerer cyclisations of bis-1,4-glyoxamides.

Notes and references

1 R. Pummerer, *Ber. Dtsch. Chem. Ges.*, 1909, **42**, 2282.

2 For recent reviews on the Pummerer reaction; see: (*a*) K. S. Feldman, *Tetrahedron*, 2006, **62**, 5003; (*b*) S. K. Bur and A. Padwa, *Chem. Rev.*, 2004, **104**, 2401.

3 L. A. McAllister, R. A. McCormick, S. Brand and D. J. Procter, *Angew. Chem., Int. Ed.*, 2005, **44**, 452.

4 For thiol addition to glyoxalates, see: J. Milton, S. Brand, M. F. Jones and C. M. Rayner, *Tetrahedron Lett.*, 1995, **36**, 6961.

5 M. A. Marx, A.-L. Grillot, C. T. Louer, K. A. Beaver and P. A. Bartlett, *J. Am. Chem. Soc.*, 1997, **119**, 6153.

6 P. F. van Swieten, M. A. Leeuwenburgh, B. M. Kessler and H. S. Overkleeft, *Org. Biomol. Chem.*, 2005, **3**, 20.

7 (*a*) D. J. Edmonds, D. Johnston and D. J. Procter, *Chem. Rev.*, 2004, **104**, 3371; (*b*) H. B. Kagan, *Tetrahedron*, 2003, **59**, 10351; (*c*) P. G. Steel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2727.

8 (*a*) L. A. McAllister, S. Brand, R. de Gentile and D. J. Procter, *Chem. Commun.*, 2003, 2380; (*b*) K. L. Turner, T. M. Baker, S. Islam, D. J. Procter and M. Stefaniak, *Org. Lett.*, 2006, **8**, 329; (*c*) L. A. McAllister, K. L. Turner, S. Brand, M. Stefaniak and D. J. Procter, *J. Org. Chem.*, 2006, **71**, 6497.