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The first Pummerer cyclisations on solid phase. Convenient construction of oxindoles enabled by a sulfur-link to resin

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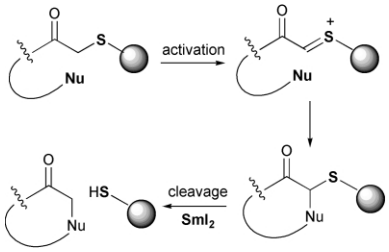
α-Sulfanyl *N*-aryl acetamides, attached to resin *via* the sulfur atom, undergo efficient Pummerer cyclisation upon activation of the sulfur link, to give oxindoles; heterocyclic products can be cleaved from the resin in a traceless manner using samarium(II) iodide.

Linker strategies lie at the heart of solid phase synthesis and combinatorial chemistry.[1] We have recently described a new traceless linking strategy for solid phase organic synthesis where the link to resin is cleaved using the electron-transfer reagent samarium(II) iodide.[2] We refer to this new class of linkers as HASC (α-Hetero-Atom Substituted Carbonyl) linkers. We originally focused on an ether-based HASC linker[2] but now wish to describe the considerable potential of a sulfide-based HASC linker.

The Pummerer reaction of sulfoxides has emerged as a powerful strategy for the efficient synthesis of carbocycles and heterocycles.[3] α-Sulfanyl carbonyl compounds bearing tethered nucleophilic groups undergo cyclisation *via* the formation of reactive sulfonium ions and are of particular synthetic utility.[4] We envisaged that oxidation of sulfur in α-sulfanyl *N*-aryl acetamides, attached to resin *via* the sulfur atom, followed by sulfonium ion[5] formation would trigger cyclisation (Scheme 1).

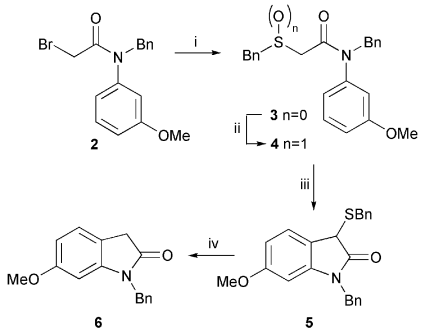


Scheme 1 Pummerer cyclisation on solid phase enabled by a sulfur link to resin.

Crucially, the sulfur link remains intact thus allowing further solid phase steps to be carried out before traceless cleavage of the link using samarium(II) iodide.

We chose to establish the sulfur linkage through the reaction of a thiol resin with α-bromo acetamides. This simple approach would allow access to Pummerer cyclisation substrates in a straight-forward manner. Benzyl thiol resin **1**[6] was prepared from Merrifield resin by two routes (Scheme 2). Routes *via* the thiourea[7] and *via* the thioacetate[6] were found to give similar loadings of *free* 'SH' sites.†

The feasibility of our approach was initially investigated in solution using benzyl thiol as a model for thiol resin **1**. Thus reaction of α-bromoamide **2**, readily accessible from the corresponding secondary amine and bromoacetyl bromide, with benzyl thiol gave sulfide **3**, which was then oxidised selectively to the sulfoxide **4** using H_2O_2 and hexafluoro-2-propanol (HFIP).[8] Pummerer cyclisation of the electronically activated sulfoxide **4** was readily achieved using trifluoroacetic anhydride.[9] After chromatographic removal of the minor oxindole regioisomer (see Table 1, entry 5), cleavage of the benzylsulfanyl group from oxindole **5** was carried out using SmI_2 and DMPU (Scheme 3).[2]

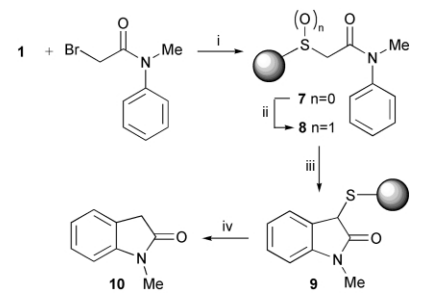


Scheme 2 *Reagents and conditions*: i, $KSC(O)CH_3$, DMF, rt; ii, $LiBH_4$, THF, rt; iii, thiourea, DMF, 60 °C; iv, $^nBuNH_2$, DMF, 60 °C.

Scheme 3 *Reagents and conditions*: i, BnSH, NEt_3, DMF, rt, 47%; ii, HFIP-CH_2Cl_2 (2 : 1), H_2O_2, rt, 92%; iii, TFAA, 1,2-dichloroethane, rt, 63%; iv, SmI_2, DMPU, THF, rt, 48% (unoptimised).

We next adapted the sequence to solid-phase whilst also assessing the feasibility of carrying out solid-phase Pummerer cyclisations on *unactivated* aromatic substrates. Immobilisation of *N*-methyl-*N*-phenyl α-bromoacetamide was achieved by stirring the amide with resin **1** in DMF. The sulfur link in immobilised amide **7** was then oxidised to give sulfoxide **8**. In this electronically unactivated substrate, Pummerer cyclisation was found to be most efficiently carried out using stronger activation with TFAA and $BF_3{\cdot}Et_2O$.[9] Cleavage of the sulfur link to resin was then carried out using SmI_2 and DMPU according to our previously reported conditions.[2] Pleasingly, oxindole **10** was isolated in high purity, *vide infra*, in 47% yield after four steps (Scheme 4).

By varying the α-bromoamide used in the sequence, a range of oxindoles has been prepared (Table 1). As can be seen from the table, neutral, electron rich and electron-deficient aromatic amide substrates have been employed in the sequence. Interestingly, in the solid-phase synthesis of 5-iodo-1-propyl-



Scheme 4 *Reagents and conditions*: i, NEt_3, DMF, rt; ii, HFIP–CH_2Cl_2 (2 : 1), H_2O_2, rt; iii, TFAA, $BF_3{\cdot}OEt_2$, 1,2-dichloroethane, rt; iv, SmI_2, DMPU, THF, rt, 47% isolated yield after four steps on resin.

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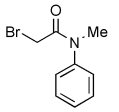
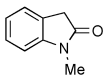
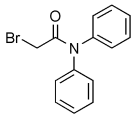
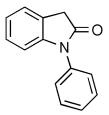
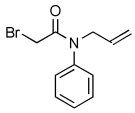
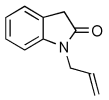
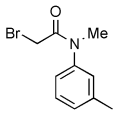
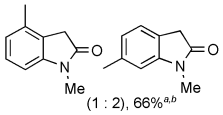
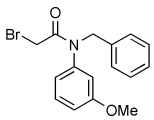
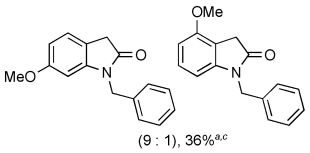
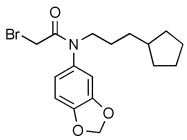
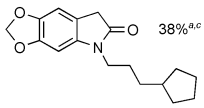
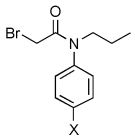
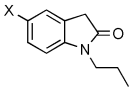
Table 1 Oxindoles prepared by Pummerer cyclisation on solid phase

Entry	Amide	Oxindole(s)
1		 47%[a,b]
2		 39%[a,b]
3		 29%[a,b]
4		 (1 : 2), 66%[a,b]
5		 (9 : 1), 36%[a,c]
6		 38%[a,c]
7		 X= I, 22%[a,b] X= Cl, 41%[a,b]

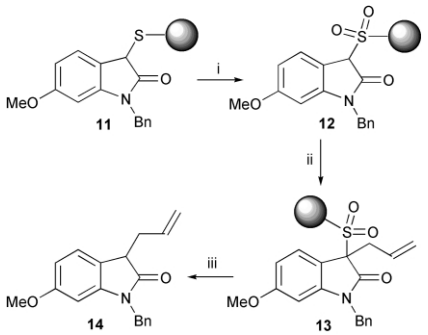
[a] Isolated, overall yields after four steps. [b] Cyclised using TFAA and $BF_3{\cdot}OEt_2$. [c] Cyclised using TFAA.

1,3-dihydro-indol-2-one (entry 7, X = I), cleavage of the sulfur-link to resin can be achieved chemoselectively in the presence of the aryl iodide.[10]

Crucially, no aqueous work up is needed after cleavage of the product from resin. In the majority of cases, the products could be separated from DMPU and inorganic by-products by simple filtration through a short pad of silica after which they were found to give satisfactory ^{1}H and ^{13}C NMR spectra.[11]

As the sulfur link to resin remains intact after the Pummerer cyclisation to form oxindoles, further synthetic steps on resin allow access to elaborated oxindole frameworks. By way of illustration we have oxidised resin-bound oxindole **11** to sulfone **12**. Efficient alkylation was then carried out to give the allylated sulfone **13**. *Thus our approach proceeds with assistance from the sulfur link in two different oxidation states.* Cleavage of the link with SmI_2 and DMPU gave the expected product **14** as a 9 : 1 mixture of regioisomers in 30% overall yield (six steps) (Scheme 5).

In conclusion, we have described the first Pummerer cyclisations on solid-phase. The cyclisation reactions are enabled by a sulfur atom linking the substrate to the resin. Crucially, the sulfur link remains intact during the cyclisation allowing further solid-phase modification of the basic heterocyclic scaffold. We have investigated the generality of the approach by preparing a range of oxindoles. Finally, by utilising the linking sulfur atom a second time but in a different oxidation state, we have illustrated how Pummerer products can be readily manipulated on resin. The application of our Pummerer approach to the synthesis of other heterocyclic systems is currently under investigation.



Scheme 5 *Reagents and conditions*: i, oxone, DMF–H_2O (4 : 1), rt; ii, K_2CO_3, KI, allyl bromide, DMF, 60 °C; iii, SmI_2, DMPU, THF, rt, 30% overall yield for six steps on resin.

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Notes and references

† The loading of *free* SH sites was determined by the immobilisation of *N*-methyl-*N*-phenyl α-bromoacetamide, followed by SmI_2 cleavage and isolation/quantification of *N*-methyl-*N*-phenyl acetamide. The discrepancy between the loading obtained by this method and that obtained by sulfur microanalysis (~ 1 mmol g^{-1}) is presumably due to oxidative cross-linking of the thiol functional groups.

Typical experimental procedure: Sulfoxide resin **8** (0.172 mmol) was swollen in 1,2-dichloroethane and TFAA (0.243 ml, 1.72 mmol) was added at room temperature. After 2 h, $BF_3{\cdot}OEt_2$ (0.327 ml, 2.58 mmol) was added and the reaction stirred at room temperature for 18 h. The suspension was then filtered and the resin washed with H_2O, THF, THF–H_2O (3 : 1, 1 : 1, 1 : 3), THF, (MeOH, CH_2Cl_2) × 3 and THF. The resin was then dried under high vacuum (ν_{max} C=O stretch 1714 cm^{-1}). To a pre-swollen solution of oxindole resin **9** (0.158 mmol) in THF (4 ml) was added DMPU (0.153 ml, 1.26 mmol), and SmI_2 (4.74 ml of a 0.1 M soln. in THF, 0.474 mmol). The reaction was stirred at room temperature for 18 h. After filtration, the solution phase was collected and concentrated *in vacuo*. Filtration through a short pad of silica gel, washing with 30% EtOAc in hexane, and concentration *in vacuo*, gave oxindole **10** (11 mg, 0.074 mmol, 47%).

1 For recent reviews on linkers and cleavage strategies for solid phase organic synthesis, see: (*a*) I. W. James, *Tetrahedron*, 1999, **55**, 4855; (*b*) F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, 2000, **100**, 2091.
2 F. McKerlie, D. J. Procter and G. Wynne, *Chem. Commun.*, 2002, 584.
3 For reviews of the area, see: (*a*) A. Padwa, D. E. Gunn Jr. and M. H. Osterhout, *Synthesis*, 1997, 1353; (*b*) A. Padwa, D. M. Danca, J. D. Ginn and S. M. Lynch, *J. Braz. Chem. Soc.*, 2001, **12**, 571.
4 See ref. 3*a* and references cited therein.
5 Sulfonium ions have recently begun to find application in solid-phase chemistry: (*a*) in Pd-catalysed cross-coupling reactions, C. Vanier, F. Lorgé, A. Wagner and C. Mioskowski, *Angew. Chem., Int. Ed.*, 2000, **39**, 1679; (*b*) in cyclopropanations and epoxidations, E. La Porta, U. Piarulli, F. Cardullo, A. Paio, S. Provera, P. Seneci and C. Gennari, *Tetrahedron Lett.*, 2002, **43**, 761; (*c*) in the Pummerer cleavage of a sulfoxide linker, C. Rolland, G. Hanquet, J.-B. Ducep and G. Solladié, *Tetrahedron Lett.*, 2001, **42**, 7563.
6 S. Kobayashi, I. Hachiya, S. Suzuki and M. Moriwaki, *Tetrahedron Lett.*, 1996, **37**, 2809.
7 For the preparation of a different thiol resin *via* a thiourea see ref. 5*a*.
8 (*a*) K. S. Ravikumar, J.-P. Bégué and D. Bonnet-Delpon, *Tetrahedron Lett.*, 1998, **39**, 3141; (*b*) H. E. Russell, R. W. A. Luke and M. Bradley, *Tetrahedron Lett.*, 2000, **41**, 5287.
9 It has been noted that $BF_3{\cdot}OEt_2$ is not required for electronically activated systems. (*a*) T. Shinohara, A. Takeda, J. Toda, Y. Ueda, M. Kohno and T. Sano, *Chem. Pharm. Bull.*, 1998, **46**(6), 918; (*b*) T. Saitoh, T. Ichikawa, Y. Horiguchi, J. Toda and T. Sano, *Chem. Pharm. Bull.*, 2001, **49**(8), 979.
10 Aryl and alkyl halides can be readily reduced using SmI_2 with additives such as HMPA: J. Inanaga, M. Ishikawa and M. Yamaguchi, *Chem. Lett.*, 1987, 1485.
11 Routine chromatography was used for the few examples where minor uncharacterised by-products were obtained.