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Stereoselective substituted pyrrolidine and cyclic ether synthesis by PhS migration

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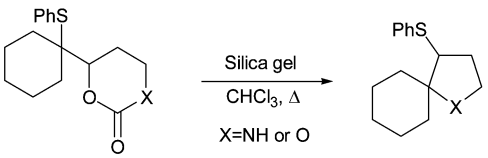
The effect of substitution on heterocycle synthesis by a novel silica gel catalysed decarboxylative ring-closing reaction is shown to be stereospecific and dependent on the nature of the nitrogen substituent.

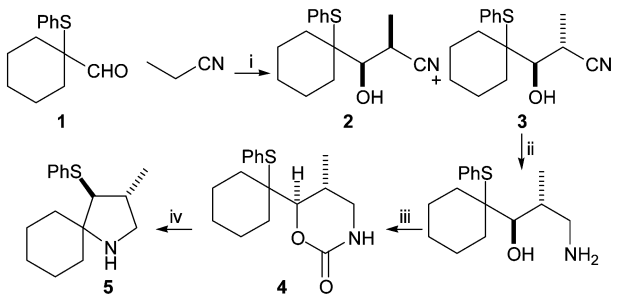
The novel silica gel catalysed ring-closing reaction recently reported allows for the synthesis of nitrogen and oxygen heterocycles by the intramolecular trapping of episulfonium ions in neutral conditions (Scheme 1).[1] We wished to extend this methodology to the stereoselective synthesis of more highly substituted heterocycles with a view to the synthesis of useful compounds and as an aid to the understanding of the scope and mechanism of the reaction. The strong acid catalysed sulfur migration used in cyclic ether synthesis is a stereospecific process,[2] but the novel silica gel catalysed reaction occurs in markedly different reaction conditions, and might not occur *via* a stereochemically stable episulfonium ion. To this end, a pair of complementary diastereoisomers of a cyclic carbamate was synthesised (Schemes 2 and 3).



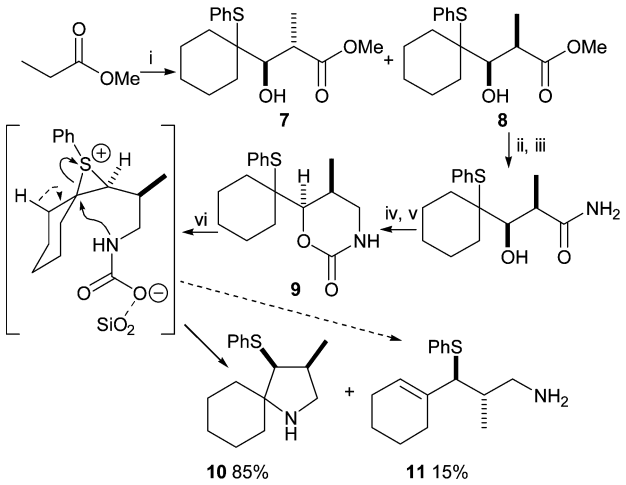
Scheme 1

A nitrile-aldol reaction with aldehyde[3] **1** produced an excess of the *anti*-diastereoisomer **3** (*anti*-**3** : *syn*-**2** 3 : 1) which could be reduced and cyclised with carbonyldiimidazole (CDI) to give the carbamate **4** as a single diastereoisomer (Scheme 2). The stereochemistry was confirmed by X-ray crystallography (Fig. 1).† Treatment of the carbamate **4** with silica gel in refluxing chloroform produced pyrrolidine **5** in excellent yield as a single diastereomer as the only product (Scheme 2), the configuration of which was also confirmed by X-ray crystallography of its 3,5-dinitrobenzamide **6** (Fig. 1).

The *syn*-diastereoisomer of cyclic carbamate **9** was made *via* ester **8**, from a more *syn*-selective ester aldol reaction, followed by amide coupling, reduction and cyclisation. This *syn*-carbamate was also treated with silica gel in refluxing



Scheme 2 *Reagents and conditions*: i, LDA, THF, −78 °C; **1**, 15% (**2**), 56% (**3**); ii, $LiAlH_4$, Et_2O, 89%; iii, CDI, CH_3CN, 63%; iv, SiO_2, $CHCl_3$, Δ, 97%.



Scheme 3 *Reagents and conditions*: i, LDA, THF, −78 °C; **1**, 15% (**7**), 57% (**8**); ii, KOH, H_2O, THF; iii, DCC, NHS, THF; NH_3, 72% (2 steps); iv, BH_3, THF, Δ, 83%; v, CDI, CH_3CN, Δ, 73%; vi, SiO_2, $CHCl_3$, Δ.

chloroform to produce the *syn*-pyrrolidine **10** in good yield, along with a small quantity of allylic sulfide **11** (Scheme 3).

In this case the ring-closing transition state is destabilised by a 1,3-diaxial relationship between the methyl and the cyclohexane ring, therefore the competing elimination is more significant than in the *anti*-diastereomer. The conformational lock in the cyclohexane ring tends to maximise this elimination, compared to related compounds.[2] The formation of allylic sulfide does not occur in the reaction of the *gem*-dimethyl carbamate **12a**, where the ring closure is favoured by the *gem*-dialkyl effect[4] although a *syn*-relationship of substituents on the ring is also produced (Scheme 4). A similar cyclisation *via* an

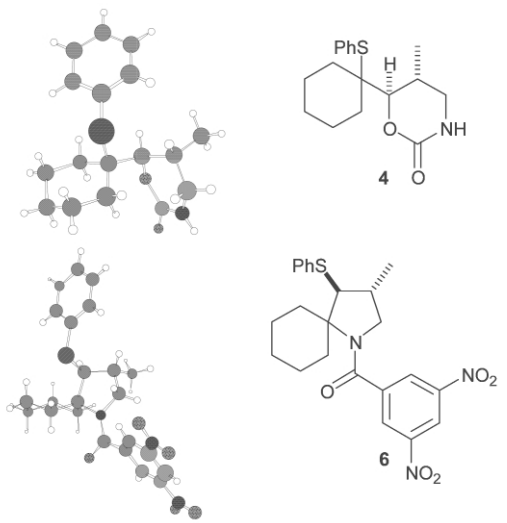


Fig. 1 Molecular structure of *anti*-carbamate **4** and the 3,5-dinitrobenzamide (**6**) of *anti*-pyrrolidine **5** determined by X-ray analysis.

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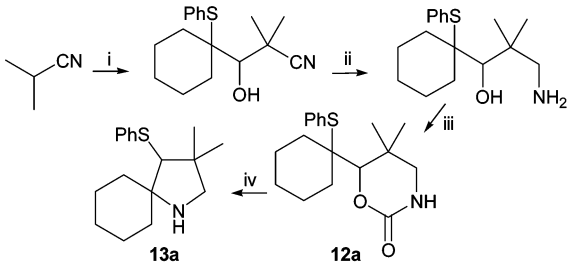


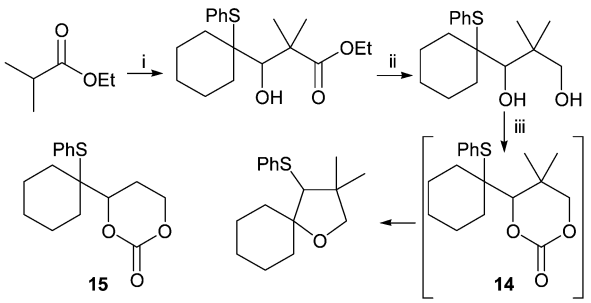
Scheme 4 *Reagents and conditions*: i, LDA, THF, −78 °C, **1**; 78%; ii, $LiAlH_4$, Et_2O, 98%; iii, CDI, CH_3CN, 89%; iv, SiO_2, $CHCl_3$, Δ, 95%.

iodonium ion also favours 3,4-*anti*-substitution, resulting in the formation of a single diastereoisomer.[5]

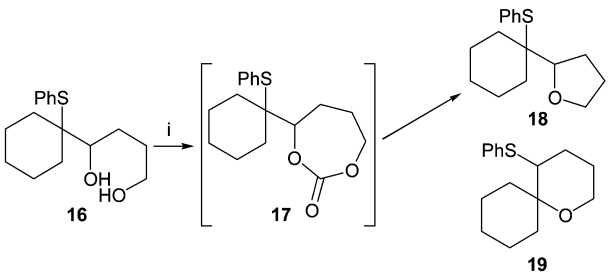
Cyclic carbonates also react in the presence of silica gel with loss of carbon dioxide to form cyclic ethers.[1] The *gem*-dimethyl substituted cyclic carbonate **14** (Scheme 5) was much more labile than carbonate **15** and the decarboxylation and cyclisation were initiated by silica gel at ambient temperature during purification. It is not clear why this substitution should increase the reactivity of the carbonate intermediates.

The seven-membered carbonate **17**, made from diol[6] **16**, also gave an ether (Scheme 6), but the higher temperature required for seven-membered-ring carbonate formation provided harsh enough conditions to initiate ether-ring closure and decarboxylation. The only cyclic ether isolated from the reaction was however the kinetically favoured unrearranged THF **18**, not the more stable rearranged THP **19**. This route provides a complementary method of forming THFs from 1,4-diols, compared to the strong acid catalysed route that produces the more thermodynamically stable THP.[2,7] The similar iodonium ion mediated reaction produces a kinetically controlled mixture of the five-membered (13%) and six-membered (87%) cyclic ethers.[8]

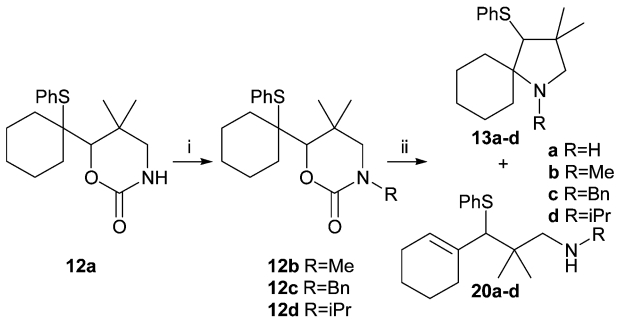
Substitution at the nitrogen in the pyrrolidine synthesis was also investigated, and a range of *N*-alkyl carbamates **12b–d** was made by alkylation of the parent carbamate **12a** (Scheme 7).[1] Treatment of the carbamates with silica gel in refluxing chloroform produced a range of results in which an increase in the steric requirement of the *N*-alkyl substituent led to a decrease in the amount of pyrrolidine **13a–d** produced and an increase in the proportion of allylic sulfide **20a–d** formed by loss of a proton from the episulfonium ion intermediate (Table 1). When the alkyl group is isopropyl the ring closure is disfavoured enough that no cyclic amine is isolated.



Scheme 5 *Reagents and conditions*: i, LDA, THF, −78 °C; **1**, 92%; ii, $LiAlH_4$, Et_2O, 93%; iii, CDI, CH_3CN, then SiO_2 chromatography, 80%.



Scheme 6 *Reagents and conditions*: i, CDI, DMF, 100 °C, 32% (**18**).



Scheme 7 *Reagents and conditions*: i, NaH, MeI or BnBr or iPrI, DMF; ii, SiO_2, $CHCl_3$, Δ, see Table 1.

Table 1 Yields for the alkylation of **12a** and silica catalysed reaction

Carbamate	R	Yield (%) from **12a**	Pyrrolidine yield (%)	Allylic sulfide yield (%)
12a	H	—	> 95	< 5
12b	CH_3	94	77	14
12c	CH_2Ph	96	54	30
12d	$CH(CH_3)_2$	91	< 1	88

Overall, this method is in contrast to other nitrogen heterocycle syntheses involving the attack of iodine[9] or selenium[10,11] reagents where stereochemical control is supplied by other substituents or by reagents.

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Notes and references

† *Crystal data* for **4**: $C_{17}H_{23}NO_2S$, M = 305.42, monoclinic, space group $P2_1/n$ (no. 14), a = 8.5716(4), b = 6.5783(2), c = 28.464(2) Å, β = 92.190(2)°, U = 1603.8(2) Å^3, Z = 4, μ(Mo-Kα) = 0.206 mm^{-1}, 9478 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 3642 unique (R_{int} = 0.044); R_1 = 0.042, wR_2 = 0.098. The structure was solved with SHELXS-97[12] and refined with SHELXL-97.[12] CCDC 207753.

For **6**: $C_{23}H_{25}N_3O_5S$, M = 455.52, monoclinic, space group $P2_1/c$ (no. 14), a = 12.2145(5), b = 7.8483(2), c = 23.4165(11) Å, β = 102.054(2)°, U = 2195.3(2) Å^3, Z = 4, μ(Mo-Kα) = 0.188 mm^{-1}, 11499 reflections measured at 180(2) K using an Oxford Cryosystems Cryostream cooling apparatus, 3763 unique (R_{int} = 0.040); R_1 = 0.039, wR_2 = 0.090. The structure was solved with SHELXS-97[12] and refined with SHELXL-97.[12] CCDC 207754. See http://www.rsc.org/suppdata/cc/b3/b303790h/ for crystallographic data in CIF or other electronic format.

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