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γ -Lactams and furan bispyrrolidines *via* iodine mediated cyclisation of homoallylamines†

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1,3,5-Substituted pyrrolidin-2-ones were synthesised *via* an iodine mediated cyclisation of 3-methyl substituted homoallylamines in good to excellent yield, as mixtures of diastereoisomers. These were separable and their identity confirmed by techniques including single crystal X-ray diffraction. When 3-phenyl substituted homoallylamines were cyclised intriguing fused tricyclic motifs were obtained as C_2 -symmetric racemates, whose structures were also confirmed by techniques including single crystal X-ray diffraction analysis.

Introduction

Pyrrolidin-2-ones are an important class of compounds, the lactam core is found in many natural products such as antimicrobial agent pramanicin **1**.¹ Cotinine **2** is a metabolite of nicotine and is found in tobacco,² it can cross the blood brain barrier and has interesting medicinal properties (Fig. 1).³

γ -Lactams with quaternary stereogenic centres at C5, such as dysibetaine **3**, displays neuroexcitotoxine activity.⁴ Rigidulculamide A (**4**) shows cytotoxic effects against selected cell lines,⁵ and 1,3,5-trisubstituted pyrrolidin-2-ones act as CCR4 antagonists.⁶ Katritzky *et al.*⁷ and Sun *et al.*⁶ have also reported on the importance of this class of compound.

Herein, an expeditious route to 1,3,5-trisubstituted γ -lactams bearing a tertiary alcohol at the 3-position is reported. Divergent behaviour of homoallyl starting materials is explored and a new class of furan bispyrrolidines is revealed.

We have previously shown that homoallylamine derivatives may be transformed into 2,4-*cis*-azetidines, which may in turn be thermally isomerised to 4-*cis*-pyrrolidines (Scheme 1, $R^3 = H$).⁸ Following directly on from that work we next chose to investigate substitution at the R^3 position, since we envisaged this may provide a convenient route to substituted azetidines and pyrrolidines.

Compound **5a** ($R^3 = Me$) was prepared as a racemate and exposed to conditions derived from our previous work that we expected to deliver an azetidine product. To our surprise a 1:1 mixture of diastereoisomers of γ -lactam **6a** was formed

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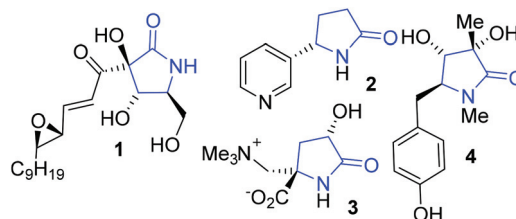


Fig. 1 Representative γ -lactams.





in other reactions, where by-product and unreacted starting material remain, isolated yields of **6a** often suffered from multiple purification steps required and loss of material as a result. As expected Cs_2CO_3 served to oxidise starting material under these conditions (Table 1, entry 2), giving by-product **1** (73% conversion) and unreacted starting material only. Diastereoisomer ratios were not improved across bases employed, Na_2CO_3 (Table 1, entry 5) gave the best ratio of only 1.5 : 1 and isolated yield was low (20%). As judged by isolated yield of a mixture of *cis*- and *trans*-**6a**, NaHCO_3 (Table 1, entry 1) remained the base of choice for further investigation of various solvents. Some divergence (albeit small) in which diastereoisomer was formed in preference was noticed, but no solvent (of those tried) gave one diastereoisomer as a significant major product. The use of anhydrous acetonitrile gave a lower conversion to the desired product, and this was accompanied by an increased prevalence of the unwanted by-product (Table 1, entry 15). Addition of water to acetonitrile also did not improve the reaction outcome (Table 1, entry 10). Methanol and dichloromethane (Table 1, entries 13 and 14 respectively) also did not improve reaction outcomes. Tetrahydrofuran (Table 1, entry 12) gave a jump in isolate yield to 60%. To our surprise the use of ethyl acetate as reaction solvent gave quantitative conversion to desired product (Table 1, entry 11), 89% isolated yield in an approximate 1 : 1 ratio of diastereoisomers. Next scope of functionality at R^1 and R^2 was investigated (Table 2).

Table 2 Substrate scope in the cyclisation of **5** to form **6**

Entry	R^1	R^2	Product	Yield ^a /%	d.r. ^b
1	Ph	Bn	6a	89	46 : 54
2	Ph	3-Picolyl	6b	91	57 : 43
3	Ph	<i>n</i> -Pr	6c	34	56 : 44
4	Ph	2-Me-benzyl	6d	43	60 : 40
5	3-Furyl	Bn	6e	72	54 : 46
6	<i>t</i> -Bu	Bn	6f	67	55 : 45
7	3,4-Di-MeO-Ph	Bn	6g	65	56 : 44
8	Ph	PMB	6h	78	61 : 39
9	Ph	Admantyl	6i	57	30 : 70
10	2-Thio	Bn	6j	73	36 : 64
11	2-Br-Ph	Bn	6k	55	67 : 33
12	Ph	4-Cl-benzyl	6l	64	60 : 40
13	4-NO ₂ -Ph	Bn	6m	55	45 : 55
14	1-Naph	Bn	6n	72	24 : 76
15	Ph	Me	6o	43	56 : 44
16	3-Pyr	PMB	6p	99	52 : 48
17	3-Pyr	Me	6q	68	53 : 47

^a Isolated yield. ^b Determined by inspection of the corresponding ^1H NMR spectrums, reported as a ratio of whole numbers totalling 100 to aid comparison, after initial purification to a mixture of *cis* and *trans* products, see ESI for details.

At the R^1 position of compound **5** aromatic and heteroaromatic groups can be accommodated (Table 2, entries 1, 5 10, 14 and 16). Electron donating and withdrawing groups (Table 2, entries 7 and 13 respectively) were employed and yield was slightly compromised for the *para*-nitro substituted variant (55% yield). *tert*-Butyl at R^1 also allowed for lactam products to be formed (67% yield Table 2, entry 6). A range of benzylic groups could be incorporated at R^2 , including 3-picolyl, *para*-methoxybenzyl and *para*-chlorobenzyl (Table 2, entries 2, 8 and 12 respectively) with *para*-chlorobenzyl giving

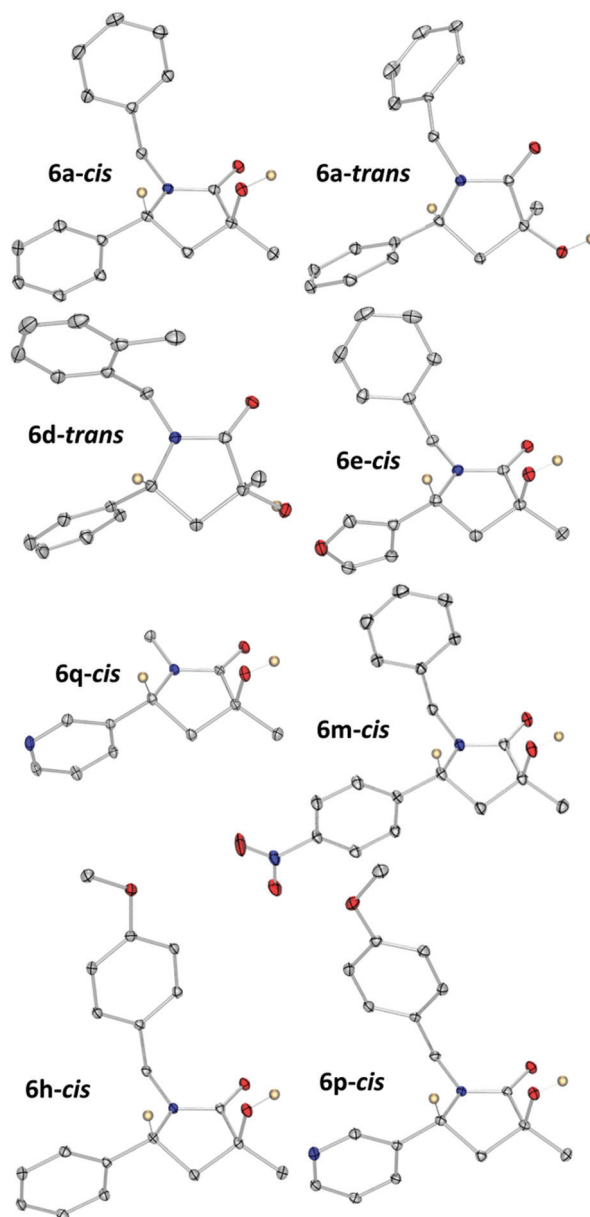


Fig. 2 X-Ray crystal structures of **60a-cis**, **6a-trans**, **6d-trans**, **6e-cis**, **6h-cis**, **6m-cis**, **6p-cis** and **6q-cis**. One molecule of each plot using Ortep III for windows at 30% probability and PovRay. Certain protons and disorder (in one case) removed for clarity. For full details, collection parameters and analysis see ESI.†



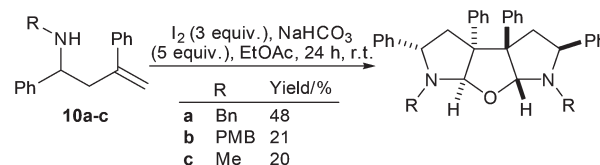
the lowest yield amongst them (64%). *ortho*-Tolylbenzyl at R² led to a much reduced yield (43%, Table 2, entry 4). Whilst alkyl groups could be incorporated at R² yields were generally lower than their benzylic congeners (Table 2, entries 3, 9 and 17). Once again diastereomer ratios were not improved greatly, the best diastereomer ratio came at the expense of yield (Table 2, entry 11) where R¹ was 2-bromophenyl (55% yield, 67:33 d.r.).

After further column chromatography purification steps and recrystallization, of crystals of single diastereoisomers suitable for study by single crystal X-ray diffraction study were obtained, in eight cases (Fig. 2), permitting unambiguous relative stereochemical assignment for **6a-cis**, **6a-trans**, **6d-trans**, **6e-cis**, **6h-cis**, **6m-cis**, **6p-cis** and **6q-cis**. We chose to name *cis*- and *trans*- to describe the relationship of the group at R¹ relative to the methyl group at C3 (Scheme 3). Combination of crystallography data and nOe studies allowed most compounds to be assigned (see ESI†).

With single diastereoisomers of some examples of **6** in hand some test transformations were attempted. *O*-Methylation (of **6a-cis**) and acylation (of **6p-cis**) proceed quantitatively without erosion of stereochemical integrity. Reduction (of **6q-cis**) with LiAlH₄ gave the desired product (4-hydroxypyrrolidine **9-cis**) in 89% isolated yield as a single diastereoisomer.¹³

We envisaged that increasing the steric bulk of the R³ substituent might improve diastereoselectivity of the cyclisation to γ -lactams. To test this hypothesis compounds **10a-c** were prepared with phenyl at the R³ position and benzyl, *para*-methoxybenzyl and methyl at the R² positions, respectively, see ESI† for more information.

Changing the R³ group to Ph certainly solved the diastereomer ratio problem; single diastereoisomer products were isolated from relatively low conversion reactions (Scheme 4). However, NMR spectra and mass spectrometry data did not match the expected products. Fortunately, XRD studies rapidly identified all three products as intriguing C₂-symmetric furan bispyrrolidines (Fig. 3). To the best of our knowledge saturated fused pyrrolidine-furan-pyrrolidine systems like this have not been reported, although we may understand the steps towards



Scheme 4 For phenyl substituted homoallyl amines **10a-c** exposure to oxidative cyclisation conditions delivers tricyclic compounds **11a-c** in 20 to 48% yield.

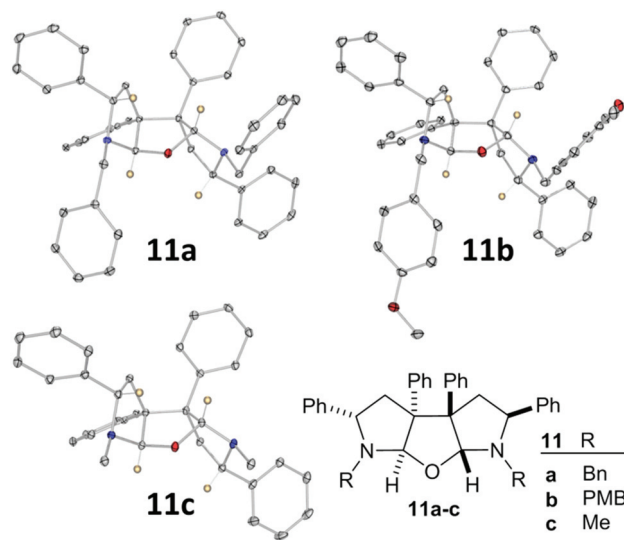
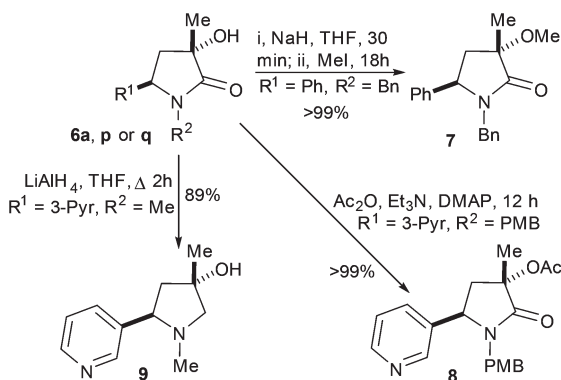


Fig. 3 X-Ray crystal structures of **11a**, **11b** and **11c**. Plot using Ortep III for windows at 30% probability and PovRay. Certain protons removed for clarity. For full details, collection parameters and analysis see ESI.†

formation of our products by contrasting observations made in an authoritative report by Ling *et al.* relating to oxidative indole coupling.¹⁴

Conclusions

We have shown that changing functionality along the ally group at the β -position of a homoallyl amine, from H to Me and Ph, elicits dramatic structural divergence on reaction outcomes. A versatile route to 1,3,5-trisubstituted γ -lactams with tertiary alcohol functionality at the 3-position was demonstrated, when the homoallyl amine derivative has a methyl group at the β -position. Additionally, a unique reaction manifold to deliver C₂-symmetric fused tricyclic pyrrolidine-furan-pyrrolidine systems was accessible, when the starting homoallyl amine bears a phenyl group at the β -position. X-Ray crystallography unambiguously confirmed the identity and relative stereochemistry of each class of product and screening of biological activity of these compounds is on going.



Scheme 3 Example transformations performed on **6** to give *O*-derivatives **7** and **8** or pyrrolidine **9**.



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