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γ -Lactams and furan bispyrrolidines via iodine mediated cyclisation of homoallylamines \dagger

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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 nico-

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including a guest Professor at East China University of Science and Technology (ECUST) and enjoys working with others to develop new catalysts and sensors. tine 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 Rigidiuculamide A (4) shows cytotoxic effects against selected cell lines,⁵ and 1,3,5-trisubstituted pyrrolin-2-ones act as CCR4 antagonists.⁶ Katritzky *et al.*⁷ and Sun *et al.*⁶ have also reported on the importance of this calss 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

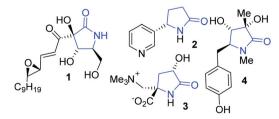


Fig. 1 Representative γ -lactams.

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Scheme 1 Azetidine and pyrrolidine synthesis via iodine mediated cyclisation of homoallylamines ($R^3 = H$).

Scheme 2 When R^3 = Me, γ -lactam 6a is formed as a 1:1 mixture of diastereoisomers.

(35% yield, Scheme 2). Compounds similar to this have been previously accessed by reaction of nitrones, reported in 1968 by Huisgen *et al.*⁹ and elegantly revisited by Yang *et al.* where a chromium catalysed cyclisation of ketoenamides delivered cyclic compounds containing C—C double bonds that could

be converted to y-lactam related to 6.10 Ficarra et al. studied the separation of secondary alcohol analogues of 6 (i.e. 6, R^3 = H). 11 At least three equivalents of iodine were required to form the product (6a), any less and only by-products were observed, this led us to speculate a number of possible mechanistic explanations. In the absence of computational support for a mechanistic hypothesis our current tentative model is that iodine activates the double bond of the homoallyl amine (see ESI† for suggested mechanism). Unlike the case where $R^3 = H$, the present hypothesised intermediate may be too sterically encumbered to cyclise to a 4-membered ring and instead delivers an intermediate iodo-pyrrolidine, a sequence of oxidations¹² and hydrations deliver 6a as a mixture of diastereoisomers. With a route to tertiary alcohol bearing γ -lactams in hand we next looked at optimising the reaction conditions to improve yield and explore the potential for obtaining 6a as a single diastereoisomer. Table 1 details a range of solvents and bases, inspection of crude proton NMR spectrums revealed the ratio of starting material 5a to lactam product 6a and a by-product imine I derived from oxidation of starting material. 12 After an initial purification step cis- and trans-6a were isolated as a mixture and the combined yield and diastereoisomer ratios (proton NMR) are also given in the

In a parallel screen of bases the best conversion to **6a** was achieved using LiOH (47% conversion), but problems purifying **6a** from unreacted stating material and by-product **I** compromised isolated yield (Table 1, entry 8). This trend was observed

Table 1 Base and solvent screening for synthesis of γ -lactams **6a** and **6b**

Entry	Base	Solvent	5a ^a	6a ^a	\mathbf{I}^a	$6a^b cis + trans$	d.r. ^c
1	NaHCO ₃	CH ₃ CN	35	35	_	35	46:54
2	Cs_2CO_3	CH ₃ CN	27	_	73	_	_
3	NaOAc	CH ₃ CN	60	20	_	20	50:50
4	NaOH	CH ₃ CN	75	25	_	18	51:49
5	Na_2CO_3	CH ₃ CN	33	27	_	20	60:40
6	K_2CO_3	CH ₃ CN	33	30	42	25	43:57
7	Li_2CO_3	CH ₃ CN	48	22	30	22	56:44
8	LiOH	CH ₃ CN	34	47	19	17	57:43
9	KOH	CH ₃ CN	53	22	26	21	54:46
10	NaHCO ₃	$CH_3CN: H_2O^d$	48	30	21	21	33:67
11	NaHCO ₃	EtOAc	_	>99	_	89	46:54
12	NaHCO ₃	THF anhydrous	10	60	30	60	38:62
13	NaHCO ₃	MeOH	43	40	17	10	45:55
14	NaHCO ₃	DCM	90	10	_	10	50:50
15	NaHCO ₃	CH ₃ CN anhydrous	60	20	20	20	48:52

^a Determined by inspection of the crude ¹H NMR spectrums reported as a ratio of whole numbers totalling 100 to aid comparison. ¹H NMR dd peaks at 4.16 and 4.53 ppm, corresponding to CH of diastereoisomers **6a** and **6b**, were compared to an apparent singlet at 4.84 ppm or an apparent singlet at 4.88 ppm corresponding to $C=CH_2$ of 5 along with a singlet at 8.10 ppm corresponding to imine CH=N of compound **I.** b Isolated combined yield of **6**-cis + **6b**-trans after initial purification. ^c Determined by inspection of the ¹H NMR spectra of **6**-cis + **6b**-trans. ^d $CH_3CN:H_2O(1:1)$.

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 Cs₂CO₃ served to oxidise starting material under these conditions (Table 1, entry 2), giving by-product I (73% conversion) and unreacted starting material only. Diastereoisomer ratios were not improved across bases employed, Na₂CO₃ (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, NaHCO3 (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 byproduct (Table 1, entry 15). Addition of water to acetonitrile also did not improve the reaction ourtcome (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 R¹ and R² was investigated (Table 2).

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

Entry	R^1	\mathbb{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	t-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	6 l	64	60:40
13	4-NO ₂ -Ph	Bn	6m	55	45:55
14	1-Naph	Bn	6n	72	24:76
15	Ph	Me	60	43	56:44
16	3-Pyr	PMB	6р	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 R¹ 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 R¹ also allowed for lactam products to be formed (67% yield Table 2, entry 6). A range of benzylic groups could be incorporated at R², including 3-picolyl, *para*-methoxybenzyl and *para*-chlorobenzyl (Table 2, entries 2, 8 and 12 respectively) with *para*-chlorobenzyl giving

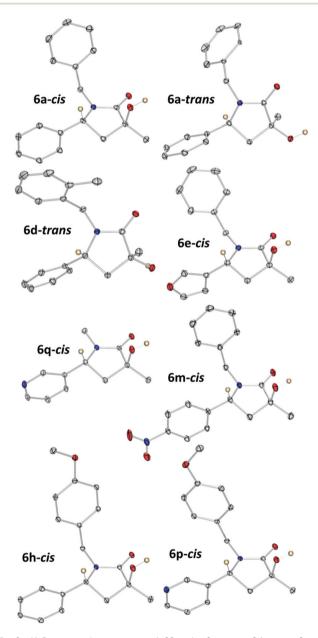


Fig. 2 X-Ray crystal structures of 60a-cis, 6a-trans, 6d-trans, 6e-cis, 6h-cis, 6m-cis, 6p-cis and 6q-cis. One molecule of each plot using Ortep III for windows at 30% probability and PovRay. Certain protons and disorder (in one case) removed for clarity. For full details, collection parameters and analysis 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 diasteromer 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 cisand 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 R^3 substituent might improve diastereoselectivity of the cyclisation to γ -lactams. To test this hypothesis compounds **10a–c** were prepared with phenyl at the R^3 position and benzyl, *para*-methoxybenzyl and methyl at the R^2 positions, respectively, see ESI† for more information.

Changing the R^3 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 C_2 -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 3 Example transformations performed on 6 to give O-derivatives 7 and 8 or pyrrolidine 9.

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 C_2 -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.

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