

ORGANIC CHEMISTRY

FRONTIERS



RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2015, 2, 1445

Received 9th June 2015,
Accepted 10th August 2015

DOI: 10.1039/c5qo00183h

rsc.li/frontiers-organic

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 nico-

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 Rigidiculamide 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 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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† Electronic supplementary information (ESI) available: Experimental details and corresponding spectra. CCDC 1028121–1028130 and 1038737. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5qo00183h

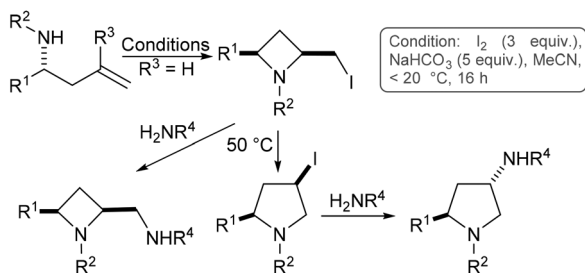


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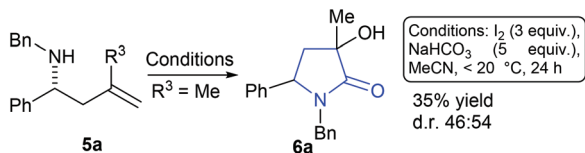
Dr John S. Fossey, University of Birmingham, UK. Obtained an MChem degree from Cardiff University of Wales in 2000, and a PhD, in early 2004, from Queen Mary University of London. After a JSPS postdoctoral position with Professor S. Kobayashi at the University of Tokyo and time as a temporary faculty member at the University of Bath he took up his present post at the University of Birmingham. He holds a number of visiting positions

including a guest Professor at East China University of Science and Technology (ECUST) and enjoys working with others to develop new catalysts and sensors.

Fig. 1 Representative γ -lactams.



Scheme 1 Azetidine and pyrrolidine synthesis *via* iodine mediated cyclisation of homoallylamines (R³ = H).



Scheme 2 When R³ = 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 γ -lactam related to **6**.¹⁰ Ficarra *et al.* studied the separation of secondary alcohol analogues of **6** (*i.e.* **6**, R³ = 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 R³ = 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 table.

In a parallel screen of bases the best conversion to **6a** was achieved using LiOH (47% conversion), but problems purifying **6a** from unreacted starting 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	I ^a	6a ^b <i>cis</i> + <i>trans</i>	d.r. ^c
1	NaHCO ₃	CH ₃ CN	35	35	—	35	46 : 54
2	Cs ₂ CO 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 ₂ CO ₃	CH ₃ CN	33	27	—	20	60 : 40
6	K ₂ CO ₃	CH ₃ CN	33	30	42	25	43 : 57
7	Li ₂ CO 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 ₃ CN : H ₂ O ^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=CH₂ of **5** along with a singlet at 8.10 ppm corresponding to imine CH=N of compound **I**.

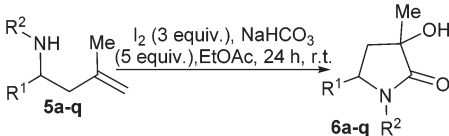
^b Isolated combined yield of *6-cis* + *6b-trans* after initial purification. ^c Determined by inspection of the ¹H NMR spectra of *6-cis* + *6b-trans*.

^d CH₃CN : H₂O (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 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. Diastereomer 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 diastereomer was formed in preference was noticed, but no solvent (of those tried) gave one diastereomer 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

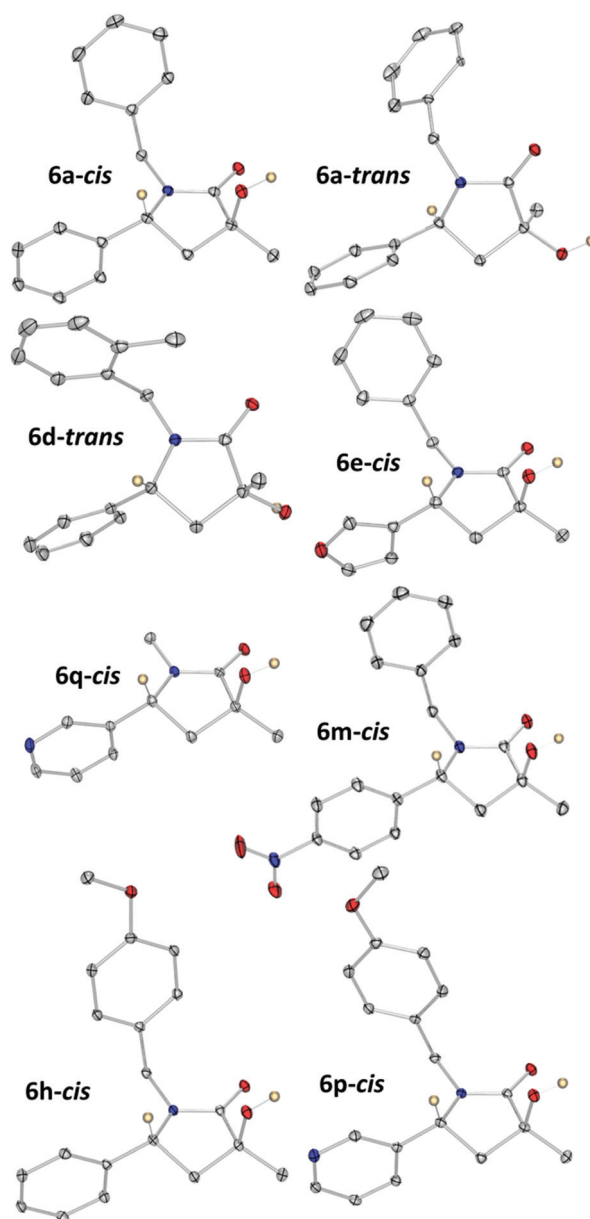


Fig. 2 X-Ray crystal structures of **60a-cis**, **6a-trans**, **6d-trans**, **6e-cis**, **6h-cis**, **6m-cis**, **6p-cis** and **6q-cis**. One molecule of each plot using Ortep III for windows at 30% probability and PovRay. Certain protons and disorder (in one case) removed for clarity. For full details,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



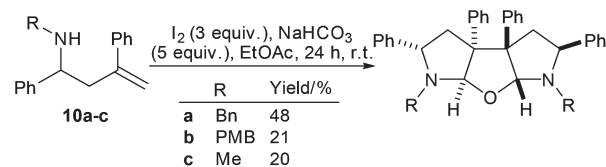
the lowest yield amongst them (64%). *ortho*-Tolylbenzyl at R² led to a much reduced yield (43%, Table 2, entry 4). Whilst alkyl groups could be incorporated at R² yields were generally lower than their benzylic congeners (Table 2, entries 3, 9 and 17). Once again diastereomer ratios were not improved 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.

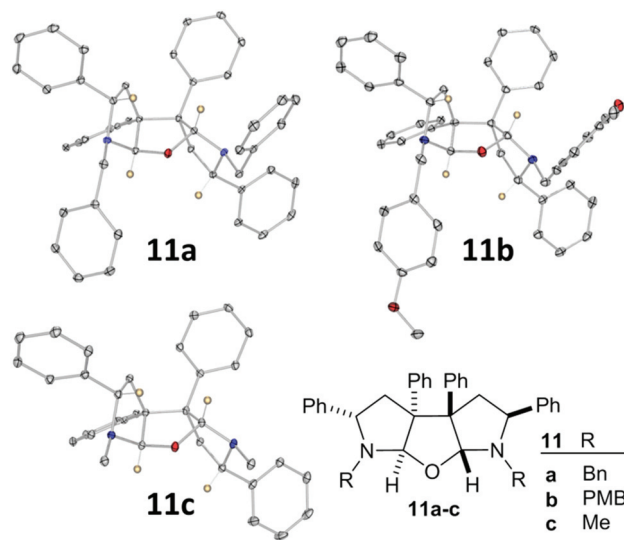
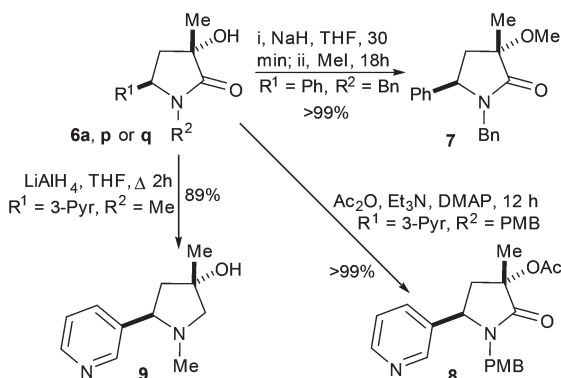


Fig. 3 X-Ray crystal structures of **11a**, **11b** and **11c**. Plot using Ortep III for windows at 30% probability and PovRay. Certain protons removed for clarity. For full details, collection parameters and analysis see ESI.†

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 allyl 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**.



Acknowledgements

The authors thank the University of Birmingham and ERDF AWM II for support. JSF is extremely grateful to the Royal Society Industry Fellowship scheme (2012/R1) for on-going support. MHS thanks the HCDP-Kurdistan government for financial support.

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