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Azabicyclic Amino Acids by Stereoselective Dearomatizing Cyclization of the Enolates of *N*-Nicotinoyl Glycine Derivatives

Gareth Arnott, Jonathan Clayden,* and Stuart D. Hamilton

School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, U.K.

j.p.clayden@man.ac.uk

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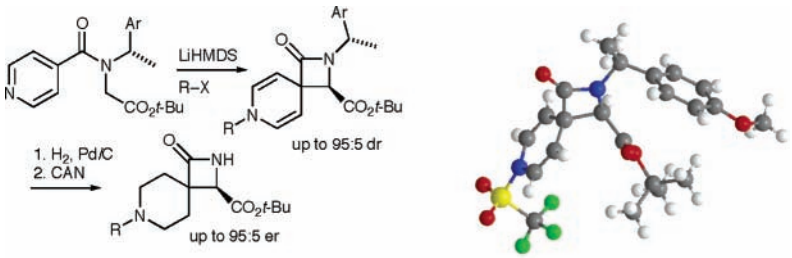
ABSTRACT



On activation by pyridine N-acylation, enolates of *N*-nicotinoyl and *N*-isonicotinoyl glycine and alanine derivatives cyclize to yield 6,5-azabicyclic or 6,4-azaspirocyclic lactams. With an *N*-α-methyl-*p*-methoxybenzyl group the cyclization is diastereoselective; hydrogenation and deprotection yields azabicyclic amino acids in 94:6 er.

Dearomatizing intramolecular nucleophilic addition of anions to aromatic rings has proved a useful strategy for building bicyclic scaffolds carrying synthetically versatile functional groups.[1,2] The cyclization of *N*-benzyl benzamides, for example, provides useful intermediates for the synthesis of the cyclic kainoid amino acids.[3] For dearomatization to be viable, however, the cyclization must be propelled by a considerable driving force and for this reason has been successful only with relatively unstable, basic anions such as benzyllithiums,[4] restricting subsequent synthetic application of the reaction. We now report success in the dearomatizing cyclization of the enolates of amino acid derivatives provided the acceptor is an electron-deficient pyridine ring, which may be activated toward attack by N-acylation *even in the presence of the enolate*.

We had previously observed that *N*-benzyl pyridinecarboxamides, on lithiation, will cyclize to yield fused or spiro

(1) For an overview of recent work in this area, see: (a) Clayden, J., Stravinsky: Total synthesis of kainoids by dearomatizing anionic cyclization. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: 2004; Vol. 4, pp 72−96. (b) Clayden, J.; Kenworthy, M. N. *Synthesis* **2004**, 1721. (c) Clayden, J.; Knowles, F. E.; Menet, C. J. *J. Am. Chem. Soc.* **2004**, *110*, 9278.

(2) For examples of dearomatizing anionic cyclizations from other research groups, see: (a) Fernández, I.; Ortiz, F. L.; Tejerina, B.; Granda, S. G. *Org. Lett.* **2001**, *3*, 1339. (b) Gómez, G. R.; Ortiz, F. L. *Synlett* **2002**, 781. (c) Fernandez, I.; Ortiz, F. L.; Velazquez, A. M.; Granda, S. G. *J. Org. Chem.* **2002**, *67*, 3852. (d) Aggarwal, V. K.; Alonso, E.; Ferrara, M.; Spey, S. E. *J. Org. Chem.* **2002**, *67*, 2335. (e) Breternitz, H.-J.; Schaumann, E.; Adiwidjaja, G. *Tetrahedron Lett.* **1991**, *32*, 1299. (f) Padwa, A.; Filipkowski, M. A.; Kline, D. N.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1993**, *58*, 2061. (g) Crandall, J. K.; Ayers, T. A. *J. Org. Chem.* **1992**, *57*, 2993.

(3) (a) Clayden, J.; Read, B.; Hebditch, K. R. *Tetrahedron* **2005**, *61*, 5713. (b) Clayden, J.; Knowles, F. E.; Baldwin, I. R. *J. Am. Chem. Soc.* **2005**, *127*, 2412. (c) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727. (d) Clayden, J.; Tchabanenko, K. *Chem. Commun.* **2000**, 317. (e) Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3397. (f) Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. *Tetrahedron Lett.* **2001**, *42*, 3407.

(4) (a) Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.* **1998**, 297. (b) Ahmed, A.; Clayden, J.; Yasin, S. A. *Chem. Commun.* **1999**, 231. (c) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett.* **2000**, *2*, 4229. (d) Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett* **2003**, 1701. (e) Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.* **2004**, *6*, 609. (f) Clayden, J.; Turnbull, R.; Helliwell, M.; Pinto, I. *Chem. Commun.* **2004**, 2430. (g) Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1049.

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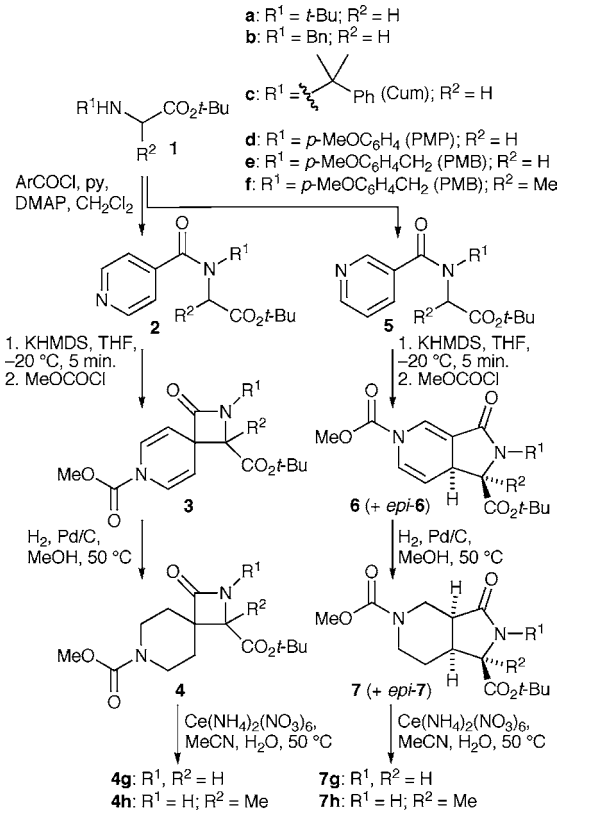
bicyclic dihydropyridines.[5] The reaction's rate was enhanced, its regioselectivity modified, and the products stabilized when the pyridine was activated by N-acylation. Given an acceptor as electrophilic as an *N*-acylpyridine, it seemed reasonable that rather less basic nucleophiles, such as enolates, might also undergo the cyclization. Dearomatizing intermolecular additions to activated pyridines are well-known,[6] and our proposed cyclization would lead directly to structurally interesting bicyclic or spirocyclic amino acids.

Cyclization precursors **2a** and **5a** were made by acylating *N*,*O*-di-*tert*-butyl glycine **1a** with nicotinoyl and isonicotinoyl chloride (Scheme 1). Both esters were treated with KHMDS

Scheme 1



at −20 °C to form the enolate. After 5 min, methyl chloroformate was added. In both cases, a dearomatizing cyclization of the enolate onto the pyridine ring resulted, and dihydropyridines **3a** and **6a** were isolated. Although **3a** was found to be stable at room temperature, **6a** oxidized rapidly in air, and in order to obtain a stable compound for characterization it was immediately hydrogenated in high yield to give the bicyclic γ-lactam **7a** as a 2:1 mixture of diastereoisomers. These were inseparable by chromatography, but on standing the major diastereoisomer crystallized and was isolated and fully characterized. Stereochemistry was assigned by NOE studies and on the basis of the X-ray crystal structures reported below; interestingly the major diastereoisomer of **7a** has relative stereochemistry opposite to that formed in related cyclization of *N*-benzyl nicotinamides.[5] The spirocyclic β-lactam **4a** could also be formed in excellent yield in the same way (Table 1, entries 1 and 7).

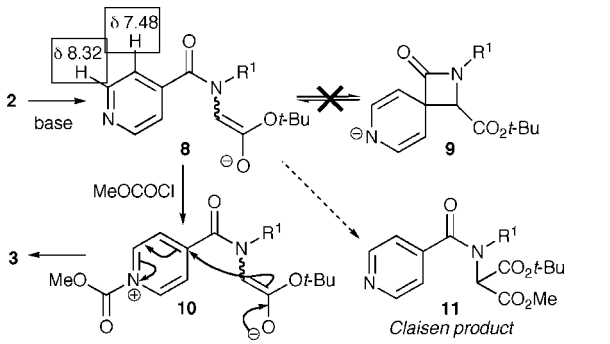
Table 1. Cyclization, Hydrogenation, and Deprotection with Various N-Protecting Groups

entry	S.M.	R^1	R^2	**3** (yield %)	**4** or **7** (yield %)	**4g,h** or **7g,h**[a] (yield %)
1	**2a**	*t*-Bu	H	**3a** (94)	**4a** (97)	
2	**2b**	Bn	H	**3b** (39)	**4b** (89)	
3	**2c**	Cum	H	**3c** (98)	**4c** (94)	
4	**2d**	PMP	H	**3d** (47)	**4d** (96)	
5	**2e**	PMB	H	**3e** (68)	**4e** (85)	**4g** (70)[b]
6	**2f**	PMB	Me	**3f** (55)	**4f** (79)	**4h** (44)[b]
7	**5a**	*t*-Bu	H	*c*	**7a** (60)[d,e]	
8	**5c**	Cum	H	*c*	**7c** (54)[d,f]	
9	**5e**	PMB	H	*c*	**7e** (64)[d,e,f]	**7g** (74)[b]
10	**5f**	PMB	Me	*c*	**7f** (43)[d,g]	**7h** (33)[b]

[a] Deprotection yield. [b] Accompanied by 20−50% of **4**or **7** (R = COC_6H_4OMe). [c] Compound **6** not isolated. [d] Yield from **5**. [e] 2:1 mixture of diastereoisomers. [f] 1:1 mixture of diastereoisomers. [g] 6:1 mixture of diastereoisomers. Stereochemistry assigned by analogy.

In order to establish whether cyclization takes place immediately on formation of the enolate or after activation of the pyridine ring by addition of the acylating agent, **2a** was cyclized in an NMR tube. On addition of KHMDS to **2a** in d_8-THF, only two 2H doublets were observed, at 7.48 and 8.32 ppm, consistent with the formation of **8** but not **9** prior to addition of the chloroformate (Scheme 2). We

Scheme 2



conclude, remarkable though it is, that the chloroformate reacts preferentially with the pyridine nitrogen atom faster than it can undergo Claisen condensation (to give **11**) with the enolate. The varying stereoselectivity of reactions presented below (Table 2) is also consistent with a mechanism in which electrophilic quench is not preceded by an irreversible cyclization step.

For wider applicability in synthesis it seemed appropriate to replace the *N*-*tert*-butyl group[7] of **2a** with an alternative

(5) Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673.

group more readily removable during a deprotection step. A range of base-stable N-protecting groups−Bn, Cum,[8] PMP, and PMB−were surveyed (Table 1). Glycine derivatives **2b**−**e** and **5c,e** were made by acylation of the parent amines **1b**−**e** and cyclized under the same conditions as for **2a** and **5a** (Scheme 1 and Table 1). β-Lactam cyclization product **3c** was obtained in excellent yield, but in contrast with **2a** and **2c** the cyclizations of less hindered isonicotinamides **2b**, **2d**, and **2e** were accompanied by competing Claisen acylation yielding **11** (tentatively identified in the crude reaction product mixture). Bulky protecting groups assist the cyclization by slowing the competing Claisen reaction and perhaps also favoring adoption of the reactive conformation. Hydrogenation of the cyclized products was successful in all cases, but only with the PMB protecting group was it possible to achieve clean deprotection. β-Lactam **4g** (R = H) was formed on treatment of **4e** with ceric ammonium nitrate. Even then, yields of up to 70% were obtained only with excess CAN, and a significant byproduct was amide **4** (R^1 = COC_6H_4OMe). Nicotinamides **5c** and **5e** gave, after hydrogenation, the bicyclic products **7c** and **7e** in moderate yield with competing oxidation of the dihydropyridine. Two diastereoisomers were formed in each case, and the relative stereochemistry of the more polar and more crystalline one was confirmed by X-ray crystallography of **7c** (Figure 1a).

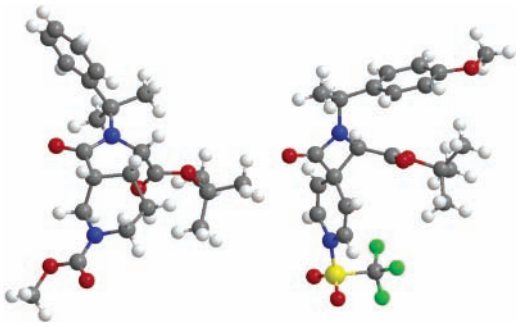
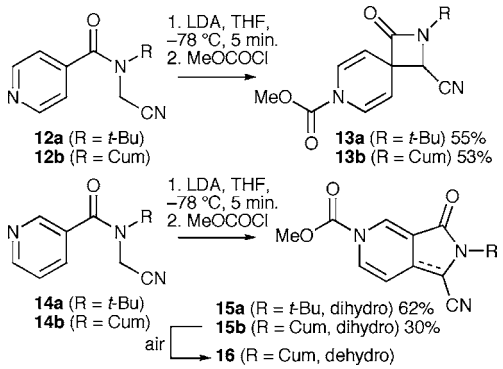


Figure 1. (a) X-ray crystal structure of **7c**; (b) X-ray crystal structure of *anti*-**19d**.

Alanine derivatives **2f** and **5f** also cyclized cleanly to β- and γ-lactams **3f** and **6f**, and the products were stabilized by hydrogenation to **4f** and **7f** (Scheme 1 and Table 1). Compounds **6f** and **7f** were formed as an inseparable 6:1 mixture of diastereoisomers. Deprotection of the lactams was achieved by treatment with CAN, but again competing overoxidation to an amide **4** or **7** (R^1 = COC_6H_4OMe) compromised the yield of the products **4g** and **4h** or **7g** and **7h**.

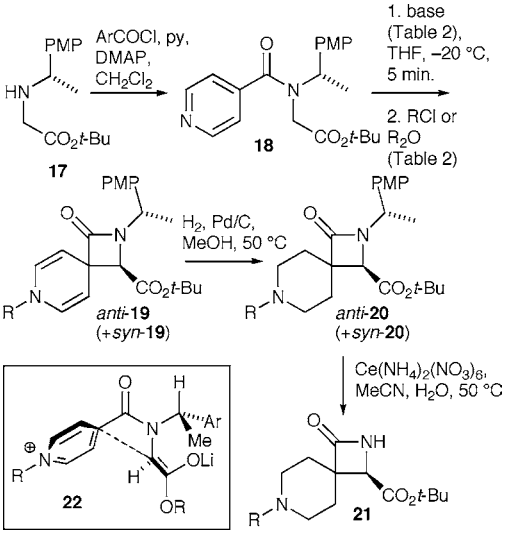
The "enolates" of nitriles **12** and **14** cyclized in moderate yield under similar conditions (though with LDA as base) (Scheme 3). Isonicotinamides **12a** and **12b** gave the β-lactams **13**, and nicotinamides **14a** and **14b** gave the γ-lactams **15** as single diastereoisomers (by ^{1}H NMR, relative stereochemistry unknown); **15b** was unstable toward oxidation to the unusual aromatic azaisoindolone **16**.

Scheme 3



Hoping both to solve our protecting group problems and lay the foundation of a new asymmetric method, we modified the PMB group of **2e** by adding a methyl group, making **18** from **17** (Scheme 4). Increased steric bulk meant that competition from Claisen acylation during the cyclization of **18** to **19** was minimal. Furthermore, cyclization of the

Scheme 4



(6) For leading references, see: (a) Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5221. (b) Bennasar, M.-L.; Zulaica, E.; Alonso, Y.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 469. (c) Comins, D.; King, L.; Smith, E.; Fevrier, F. *Org. Lett.* **2005**, *7*, 5059. (d) Comins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1622. (e) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829. (f) Rezgui, F.; Mangeney, P.; Alexakis, A. *Tetrahedron Lett.* **1999**, *40*, 6241. (g) Bennasar, M. L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **2001**, *42*, 585. (h) Bennasar, M.; Ljimenez, J-M.; Vidal, B.; Sufi, A.; Bosch, J. *J. Org. Chem.* **1999**, *64*, 9605. (i) Bennasar, M. L.; Juan, C.; Bosch, J. *Tetrahedron Lett.* **1998**, *39*, 9275. (j) Lavilla, R.; Gotsens, G.; Güero, M.; Masdeu, C.; Santano, C.; Minguillon, C.; Bosch., J. *Tetrahedron* **1997**, *53*, 13959. (k) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587. (l) Wang, X.; Kauppi, A.; Olsson R.; Almqvist, F. *Eur. J. Org. Chem.* **2003**, 4586. (m) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184. (n) Pabel, J.; Hösl, C.; Maurus, M.,; Ege, M.; Wanner, K. *J. Org Chem.* **2002**, *65*, 9272. (o) Hösl, C.; Maurus, M.; Pabel, J.; Polborn, K.; Wanner, K. *Tetrahedron* **2002**, *58*, 6757.

chiral *N*-α-methyl-*p*-methoxybenzyl amide **18** was highly diastereoselective,[9] with stereoselectivity increasing to 94:6 when LiHMDS was used as a base (Table 2, entries 1−3).

Table 2. Diastereoselective Cyclization

entry	base	R	**19** (yield %, dr)	**20** (yield %)	**21** (yield %)
1	KHMDS	MeOCO[a]	**19a** (94, 83/17)		
2	NaHMDS	MeOCO[a]	**19a** (79, 89/11)		
3	LiHMDS	MeOCO[a]	**19a** (99, 94/6)	**20a** (98)	**21a** (97)
4	LiHMDS	BnOCO[a]	**19b** (97, 95/5)		
5	LiHMDS	Fmoc[a]	**19c** (91, 93/7)		
6	LiHMDS	CF_3SO_2[b]	**19d** (35, 96/4)		
7	LiHMDS	menthyl[c]	**19e** (88, 94/6)	**20e** (92)	**21e** (83)[d]
8	LiHMDS	PhOCO[a]	**19f** (82, 94/6)	**20f** (96)	**21f** (80)[e]

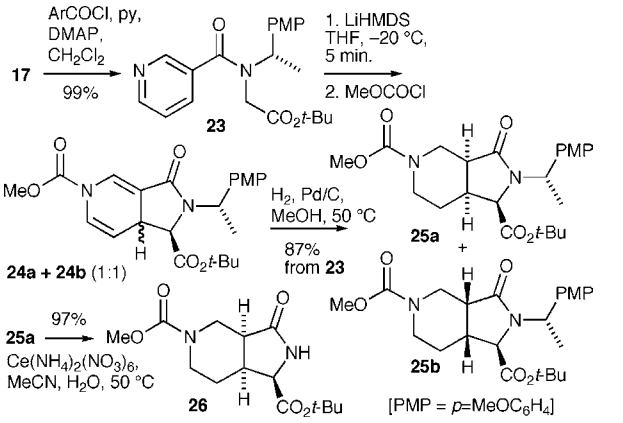
[a] Electrophile = RCl. [b] Electrophile = R_2O. [c] Electrophile = menthylchloroformate. [d] 94:6 ratio of diastereoisomers. [e] 94:6 er.

The diastereoisomers of **19** were inseparable, and both hydrogenation and deprotection of the β-lactams **19** to yield **20** and hence **21** proceeded in excellent yield.

The reaction was repeated with the electrophiles shown in Table 2, entries 4−8. In the case of **19d** the major product was crystalline: Figure 1b shows its X-ray crystal structure. We assume that *anti*-**19** is the major diastereoisomer in the other cyclizations shown in Table 2. We presume stereoselectivity arises because of the way the bulky *p*-$MeOC_6H_4$ group controls the approach of the ester enolate to the pyridinium ring in a conformation approximating that shown as **22**. The ratio of enantiomers of the final product **21** was determined by formation of menthylcarbamates **21e** and by HPLC of **21f** using a chiral stationary phase (Whelk-O1) and was identical with the diastereoselectivity of the cyclization.

Cyclization of *N*-α-methyl-*p*-methoxybenzyl nicotinamide **23** gave only two out of the four possible diastereoisomers of **24** but disappointingly lacked diastereoselectivity at the new ring junction. Hydrogenation and crystallization nonetheless allowed the isolation of **25a** (stereochemistry assigned by NOE studies), which was deprotected to yield a single isomer of pyrrolidinopiperidine **26**.

Scheme 5



In conclusion, intramolecular attack of an enolate anion on pyridinecarboxamides has proved to be a valuable way of making a range of new diazabicyclic and diazaspirocyclic amino acid derivatives, some in enantiomerically enriched form.

Acknowledgment. We are grateful to Dr. Madeleine Helliwell (University of Manchester) for determining the X-ray crystal structures of **7c** and *anti*-**19d** and to Dr. Rukhsana Mohammed (AstraZeneca) for valuable discussions. We thank the EPSRC, AstraZeneca, and the National Science Foundation (South Africa) for support.

Supporting Information Available: Experimental procedures and characterization data for all new compounds and crystallographic data for **7c** and *anti*-**19d** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) In early studies of the cyclization of *N*-benzyl benzamides (refs 4a−c and 1a) we found that bulky, base-stable N-protecting groups gave the highest yields and diastereoselectivities.

(8) Our group (ref 4c) and that of Snieckus (see Metallinos, C. *Synlett* **2002**, 1556) independently introduced the cumyl (-$CPhMe_2$) group for N-protection of amides during lithiation reactions.

(9) We used this stereocontrolling protecting group in our synthesis of α-methylkainic acid (ref 3e). We [(a) Bragg, R. A.; Clayden, J.; Menet, C. J. *Tetrahedron Lett.* **2002**, *43*, 1955. (b) Bragg, R. A.; Clayden, J. *Tetrahedron Lett.* **1999**, *40*, 8323. (c) Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411] and others [(d) Jullian, V.; Quirion, J. C.; Husson, H. P. *Synthesis* **1997**, 1091. (e) Myers, A. G.; Yang, B. H. *Org. Synth.* **2000**, *77*, 22. (f) Myers, A. G.; Yang, B. H.; Chen, H. *Org. Synth.* **2000**, *77*, 29] have used chiral N-substituents to control diastereoselectivity in the reactions of anionic derivatives of amides.