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Cyclization of Lithiated Pyridine and Quinoline Carboxamides: Synthesis of Partially Saturated Pyrrolopyridines and Spirocyclic β-Lactams

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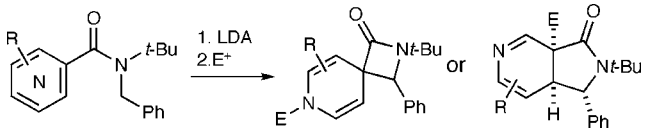
ABSTRACT



Lithiation of *N*-benzyl pyridine and quinoline carboxamides α to nitrogen gives anions that undergo intramolecular attack on the pyridine or quinoline ring, either directly or on activation of the ring by N-acylation. The resulting four-, five-, or six-membered-ring-containing compound may be oxidized, protonated, alkylated, or acylated to give a range of polycyclic heterocycles, including pyrrolopyridines, pyrroloquinolines, benzonaphthyridines, and azaspirocyclic β-lactams.

The addition of nucleophiles to pyridines activated toward nucleophilic attack (for example by N-acylation or N-alkylation) is an important method for the synthesis of functionalized piperidines and has been used in a number of recent syntheses.[1] An intramolecular version of this reaction could provide a valuable route to ring-fused piperidine derivatives. We have shown that *N*-benzyl benzamides, on lithiation and warming, undergo dearomatizing cyclization[2] to yield 6,5-fused ring systems (partially saturated isoindolones)[3] of synthetic value.[4] Amide derivatives of pyrroles[5] and thiophenes[6] undergo comparable dearomatizing cyclizations and rearrangements. In this paper, we report that the analogous pyridine derivatives (nicotinamides, isonicotinamides, picolinamides, and quinoline carboxamides) undergo cyclizations that in some cases mirror the reactivity of the benzamides, giving partially saturated pyrrolopyridines by 5-*endo*/*exo* cyclization, but in others yield isomeric spiro-β-lactam products by 4-*exo* cyclization.

To establish the feasibility of cyclizing a lithiated benzyl group onto a pyridine ring, the isonicotinamide **1** was made

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(1) For leading references, see: Kuethe, J. T.; Comins, D. L. *J. Org. Chem.* **2004**, *69*, 5221. Bennasar, M.-L.; Zulaica, E.; Alonso, Y.; Bosch, J. *Tetrahedron: Asymmetry* **2003**, *14*, 469. Comins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1622. Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829. Rezgui, F.; Mangeney, P.; Alexakis, A. *Tetrahedron Lett.* **1999**, *40*, 6241. Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587.

(2) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002. Clayden, J.; Kenworthy, M. N. *Synthesis* **2004**, 1721.

(3) Ahmed, A.; Clayden, J.; Yasin, S. A. *Chem. Commun.* **1999**, 231. Clayden, J.; Menet, C. J.; Mansfield, D. J. *Org. Lett.* **2000**, *2*, 4229. Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38. Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett* **2003**, 1701.

(4) Clayden, J.; Tchabanenko, K. *Chem. Commun.* **2000**, 317. Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727. Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. *Tetrahedron Lett.* **2001**, *42*, 3407. Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411. Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3397. Clayden, J.; Knowles, F. E.; Menet, C. J. *J. Am. Chem. Soc.* **2004**, *110*, 9278. Clayden, J.; Knowles, F. E.; Baldwin, I. R. *J. Am. Chem. Soc.* **2005**, *127*, 2412. Clayden, J. Total Synthesis of Kainoids by Dearomatizing Anionic Cyclization. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: Academic Press, 2004; Vol. 4.

(5) Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.* **2004**, *6*, 609.

(6) Clayden, J.; Turnbull, R.; Helliwell, M.; Pinto, I. *Chem. Commun.* **2004**, 2430.

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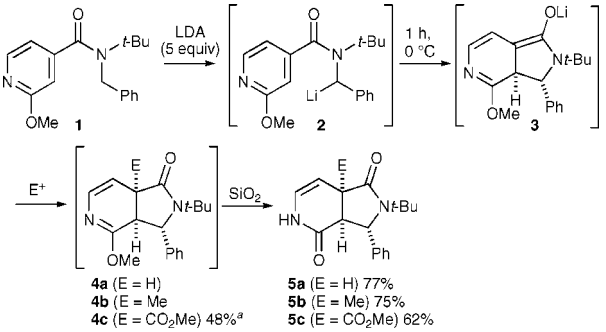
using standard methods and treated with excess LDA[7] at 0 °C. A red-brown organolithium was formed, presumably **2**. Stirring for 1 h at 0 °C and neutral workup yielded a product (**4a**) resulting from dearomatizing cyclization of **2** into the 3-position[8] of the pyridine ring and protonation of the resulting enolate **3**. Hydrolysis of the unstable amidate **4a** on purification by chromatography on silica yielded the stable lactam **5a** as a single diastereoisomer. Alkylating the enolate **3** with methyl iodide or acylating with methyl chloroformate gave, after hydrolysis, lactams **5b** and **5c**, respectively, as single diastereoisomers (Scheme 1).[9]

Scheme 1. Dearomatizing Cyclization of a Lithiated Isonicotinamide

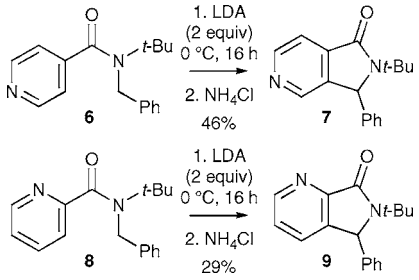


[a] Yield on purification by rapid filtration through silica.

Extending the cyclization to other simple pyridine carboxamides led to some related products, but the expected rapid rearomatization of the dihydropyridines initially made it difficult to isolate dearomatized products. The three pyridine carboxamides, isonicotinamide **6**, picolinamide **8**, and nicotinamide **10**, were made straightforwardly from the appropriate acyl chlorides, and each was treated with an excess of LDA. On lithiation, the isonicotinamide **6** and the picolinamide **8** cyclized only slowly, and after a number of hours, only moderate yields of cyclized and rearomatized (presumably by oxidation of either the cyclized product or the intermediate enolate corresponding to **3** or **4**) pyrrolopyridines **7** and **9** were isolable (Scheme 2).[10]

The nicotinamide **10** cyclized much more rapidly than **1**, **6**, or **8**: even at −40 °C, lithiation with LDA promoted

Scheme 2. Cyclization with Rearomatization of a Lithiated Isonicotinamide and Picolinamide

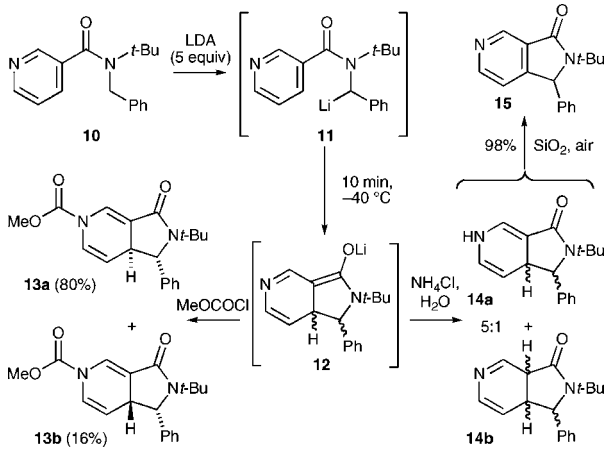


lithiation to give **11** and cyclization to **12** within 10 min. An aqueous quench of the resulting enolate **12** yielded a mixture of regioisomers of the unstable dihydropyridine derivatives **14a** and **14b**. These rearomatized on purification to yield the pyrrolopyridine **15** in 70% yield from **10**. Acylation of the enolate **12** with methyl chloroformate on the other hand led to a 5:1 mixture of diastereoisomers of the unstable dihydropyridine **13** in 96% yield.[11]

The difference in rate and efficiency of cyclization between the three isomers **6**, **8**, and **10** is presumably due to the additional stabilization afforded to the enolate **12** by delocalization of the negative charge onto the nitrogen atom, something not possible in the analogous enolates derived from **6** and **8**. This difference also accounts for the fact that the dearomatized enolate **3** acylates at carbon while enolate **12** acylates at nitrogen.[12]

We investigated ways to trap dearomatized products from isonicotinamide **6** in the manner of those derived from **1** via **3**, and during these studies we discovered that the cyclization of the isonicotinamide **6** could be both redirected and dramatically accelerated by addition of an acylating agent directly after lithiation of the amide (Scheme 4). Thus, treatment of **6** with LDA at −40 °C and addition of methyl chloroformate led to the formation of a dearomatized product

Scheme 3. Dearomatizing Cyclization of a Lithiated Nicotinamide



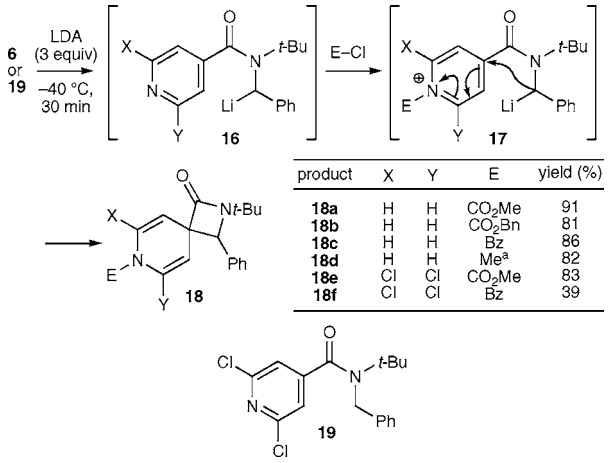
(7) As with most of the reactions described in this paper, use of fewer equivalents of LDA led to incomplete reaction.

(8) Regioselectivity of the cyclization is in accordance with previous observations in the field (see: Clayden, J.; Tchabanenko, K.; Yasin, S. A.; Turnbull, M. D. *Synlett* **2001**, 302. Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett* **2003**, 1701). It seems that the organolithium always prefers to attack ortho rather than para to a π donating group such as OMe, presumably because at the ortho position inductive σ electron withdrawal at least partially counterbalances the increased π electron density.

(9) We have proposed that related cyclizations are electrocyclic ring closures (see: Clayden, J.; Purewal, S.; Helliwell, M.; Mantell, S. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1049) rather than Baldwin-disfavored (Baldwin, J. E. *Chem. Commun.* **1976**, 734) intramolecular *5-endo trig* conjugate additions. Calculations suggest that both interpretations of the mechanism are valid, depending on the starting material structure; see: Ramallal, A. M.; López-Ortiz, F.; González, J. *Org. Lett.* **2004**, *6*, 2141. The stereochemistry of **5a**−**c** was assigned by analogy with ref 3.

(10) A similar ring system has been made by cyclization with substitution, see: Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudaon, P. *J. Org. Chem.* **2001**, *66*, 8064.

Scheme 4. Dearomatizing Cyclization to Form β-Lactams



product	X	Y	E	yield (%)
18a	H	H	CO_2Me	91
18b	H	H	CO_2Bn	81
18c	H	H	Bz	86
18d	H	H	Me[a]	82
18e	Cl	Cl	CO_2Me	83
18f	Cl	Cl	Bz	39

[a] MeOTf.

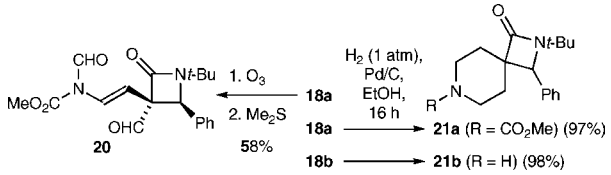
18a in 91% yield. Instead of the 6,5-fused bicycle formed from **1**, however, **18a** was a 2,7-diazaspiro[3,5]nonane, a spiro-linked β-lactam-dihydropyridine.[13] Other acylating agents, namely, benzyl chloroformate and benzoyl chloride, were equally effective at promoting this new type of cyclization (giving **18b**,**c**), as was methyl triflate (which gave **18d**). Methyl iodide gave significantly lower yields, and no dearomatized product was obtained on quenching with ammonium chloride, a good indication that electrophilic attack at the pyridine nitrogen is needed to promote the cyclization.

The chlorinated isonicotinamide **19** gave comparable β-lactams **18e** and **18f**, and Figure 1 shows the X-ray crystal structure of **18e**.

Scheme 4 outlines the mechanism we propose to account for this cyclization. Remarkably, the electrophile attacks the lithiated amide **16** at the pyridine nitrogen rather than the considerably more basic organolithium center, presumably for steric reasons. The resulting pyridinium system is activated toward attack at C4, and the β-lactam results.[14]

Ozonolysis of **18a** gave a single diastereoisomer of the monocyclic β-lactam **20**, while hydrogenation of **18a** and **18b** yielded saturated 2,7-diazaspiro[3.5]nonan-2-ones **21a** and **21b** (Scheme 5).[15]

Scheme 5. Transformations of β-Lactam **18**[a]



[a] Stereochemistry of **20** was confirmed by NOE.

Similar reactivity is exhibited by the quinolines **22** and **26**, analogues of **10** and **6**, and with **29**: with all three quinolines, cyclization occurs even without the addition of an electrophile (Scheme 6). Thus, lithiation and cyclization of the quinoline-3-carboxamide **22** was rapid at −40 °C, and the product enolate **23** could be protonated to yield, after air oxidation of the unstable intermediate dihydroquinoline, the pyrroloquinoline **24**. Trapping with methyl chloroformate yielded, by acylation at nitrogen, the dihydroquinoline **25**. The quinoline-4-carboxamide **26** cyclized diastereoselectively at 0 °C and yielded, before addition of an electrophile, a spirocyclic lithium azaenolate **27**.[16] Alkylation or acylation at nitrogen gave spirocyclic dihydroquinolines **28a** and **28b**. In confirmation that cyclization does not require the presence of an electrophile, in contrast with the analogous isonicotinamides, protonation of **27** yielded a dihydropyridine (**28c**), though one unstable to chromatography. Cyclization of

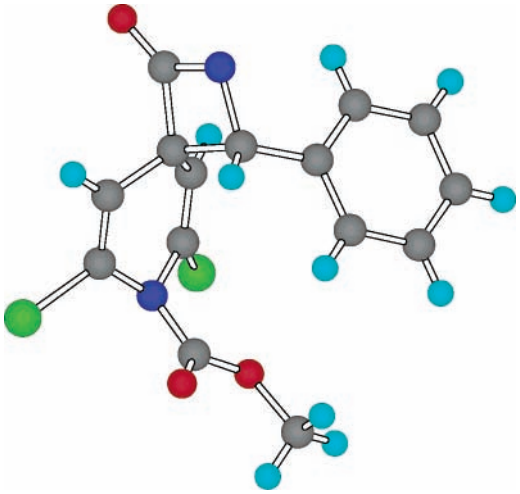


Figure 1. X-ray crystal structure of **18e**. The (disordered) *t*-Bu group has been omitted for clarity.

(11) Lack of stereoselectivity in the formation of **13** suggests that **12** is formed with lower diastereoselectivity than **3**. The two regioisomers **14** each appeared to be a single diastereoisomer, however, suggesting that the regioselectivity of protonation may be dependent on stereochemistry. Stereochemistries of **13** were not determined unequivocally and are assigned by analogy with ref 3.

(12) For a related discussion, see: Donohoe, T. J.; McRiner, A. J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1435.

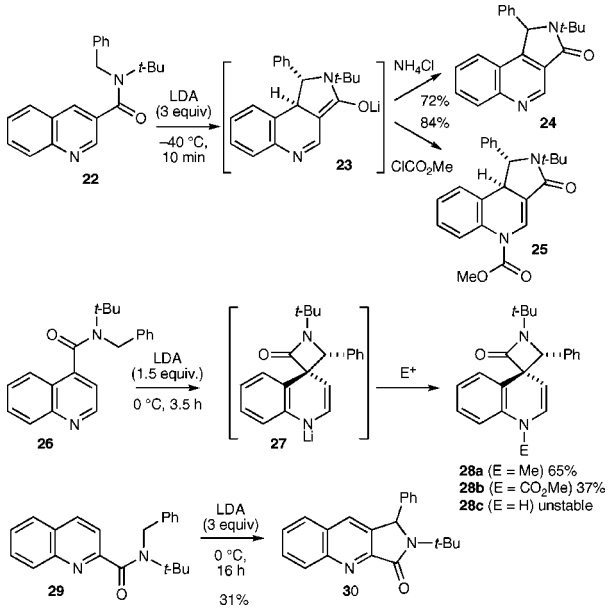
(13) Related spirocyclizations are known, see: Fraenkel, G.; Ho, C. C.; Liang, Y.; Yu, S. *J. Am. Chem. Soc.* **1972**, *94*, 4732 and references therein. See also: Foos, J.; Steel, F.; Rizvi, S. Q. A.; Fraenkel, G. *J. Org. Chem.* **1979**, *44*, 2522.

(14) With MeI as an electrophile, mixtures of products resulting from N- and C-alkylation are obtained, a result that confirms our proposed order of events. We have previously observed β-lactam formation on lithiation and cyclization of an *N*-benzyl maleamide, see: Clayden, J.; Watson, D. W.; Helliwell, M.; Chambers, M. *Chem. Commun.* **2003**, 2582.

(15) For discussions of biological interest in spiro- and other α,α-disubstituted β-lactams, see: Khasanov, A. B.; Ramirez-Whitehouse, M. M.; Webb, T. R.; Thiruvazhi, M. *J. Org. Chem.* **2004**, *69*, 5766. Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S,; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, R. E.; Salisbury, B.; Davis, H. R. *J. Med. Chem.* **1996**, *39*, 3684. Hagmann, W. K.; Kissinger, A. L.; Shah, S. K.; Finke, P. E.; Dorn, C. P.; Brause, K. A.; Ahe, B. M.; Weston, H.; Maycock, A. L.; Knight, W. B.; Dellea, P. S.; Fletcher, D. S.; Hand, K. M.; Osinga, D.; Davies, P.; Doherty, J. B. *J. Med. Chem.* **1993**, *36*, 771.

(16) Single isomer of **25** obtained was assigned stereochemistry by analogy with ref 3. The stereochemistry of **28** is assigned arbitrarily.

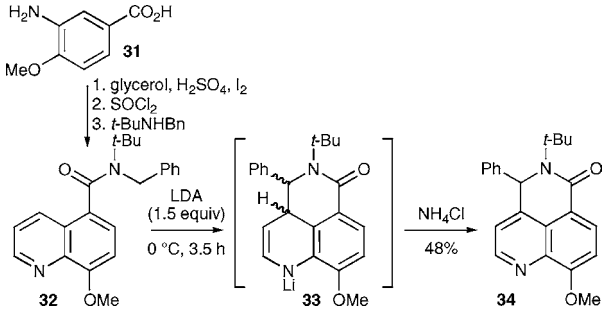
Scheme 6. Cyclization onto Quinolines



quinoline-2-carboxamide **29** gave an enolate which rearomatized to yield quinolopyrrolone **30**.

With the aim of exploring a potential route to kainoid amino acids in the acromelic acid family,[17] we made (by Skraup reaction of 3-amino-4-methoxybenzoic acid **31**[18]) and cyclized the quinoline-5-carboxamide **32** (Scheme 7). We had hoped for cyclization into the C6-position, but lithiation of **32** led instead to attack on the more electron-deficient pyridine ring, generating the lithium azaenolate **33**. Protonation was followed by oxidation to the quinoline **34**.

Scheme 7. Cyclization of a Quinoline-5-carboxamide



According to substitution pattern, then, it is possible to annelate, with or without dearomatization, four-, five-, or six-membered lactams to pyridine or quinoline carboxamides. We are currently aiming to expand this methodology for use in the synthesis of polycyclic alkaloid ring systems.

Acknowledgment. We are grateful to Madeleine Helliwell for determining the X-ray crystal structure of **18e** and to the EPSRC and to AstraZeneca for funding.

Supporting Information Available: Sample experimental procedure; X-ray crystallographic data for **18f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1998**, *54*, 7645.

(18) European Patent EP-A-0498722.