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Nucleophilic Addition to Electron-Rich Heteroaromatics: Dearomatizing Anionic Cyclizations of Pyrrolecarboxamides

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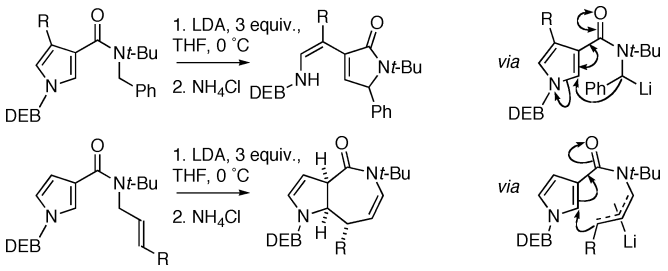
ABSTRACT



Despite its electron-rich nature, a pyrrole ring is susceptible to intramolecular nucleophilic attack by organolithiums. The resulting dearomatizing anionic cyclization yields new 5- or 7-membered heterocyclic rings. Formation of a new 5-membered ring, by cyclization of an *N*-benzylpyrrolecarboxamide, is accompanied by ring opening of the original pyrrole to yield 3-aminovinylpyrrolinones. Formation of a new 7-membered ring, by cyclization of an *N*-allyl pyrrolecarboxamide, yields bicyclic pyrroloazepinones.

Nucleophilic addition to, and substitution at, heteroaromatic rings is well-known for the 6-membered heterocycles such as pyridines, pyrazines, and pyrimidines.[1] Nucleophilic attack on the electron-rich family of 5-membered heterocycles is much less well established.[2] In recent years, we have reported examples of intramolecular nucleophilic attack by organolithiums on a series of aromatic rings, both electron-rich and electron-deficient,[3] and in this paper we report the result of using pyrroles as acceptors for organolithium nucleophiles during anionic cyclization reactions.

The pyrrolecarboxamides **4a**−**f** were made from the acyl chlorides **1a**−**c** by conversion to the acrylamide derivatives **2a**−**c** followed by cycloaddition with toluenesulfonylmethylisocyanide (TosMIC). We chose initially to protect the nitrogen atom of the pyrroles **3a**−**c** with a methyl group and with a range of electron-withdrawing groups (Boc, Adoc, DEB[4]), which we hoped would maximize the chances of success in the cyclization (Scheme 1).

Treatment of **4e** and even **4f** with base (LDA or *t*-BuLi) led only to deprotection of the pyrrole nitrogen, and **3a** was recovered from the product mixture. However, treatment of **4a**, which bears the yet more hindered 2,2-diethylbutanoyl (DEB[4]) protecting group, with 3 equiv of LDA for 3 h at 0 °C, yielded cyclization product **9a** in high yield.

The cyclization has evidently followed the pathway shown in Scheme 2. The expected[3,5] benzylic lithiation gives **5**,

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(1) For a recent example, see: Comins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1611.

(2) For dearomatization by other methods, see: Brooks, B. L.; Gunnoe, T. B.; Harman, W. D. *Coord. Chem. Rev.* **2000**, *206*, 3. Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron: Asymmetry* **1996**, *7*, 317. Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999 and references therein.

(3) Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun.* **1998**, 297. 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.; Tchabanenko, K.; Yasin, S. A.; Turnbull, M. D. *Synlett* **2001**, 302.

(4) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 1010. Fukuda, T.; Mine, Y.; Iwao, M. *Tetrahedron* **2001**, *57*, 975.

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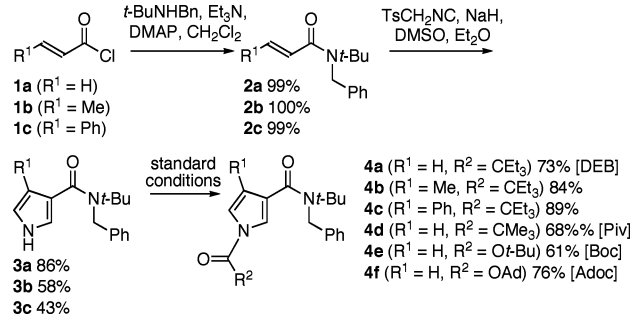
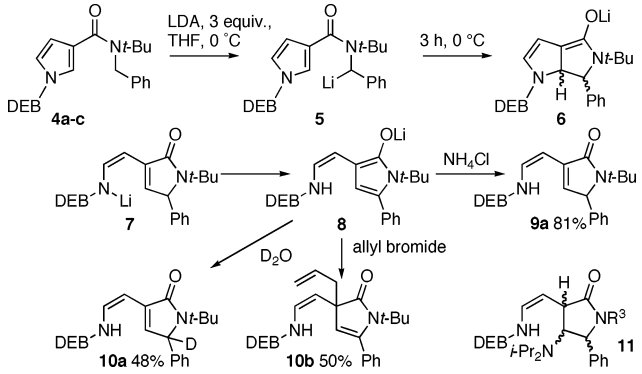
Scheme 1. Synthesis of the Pyrrole-3-carboxamides



Scheme 2. Cyclization−Ring Opening of Lithiated Pyrrolecarboxamides



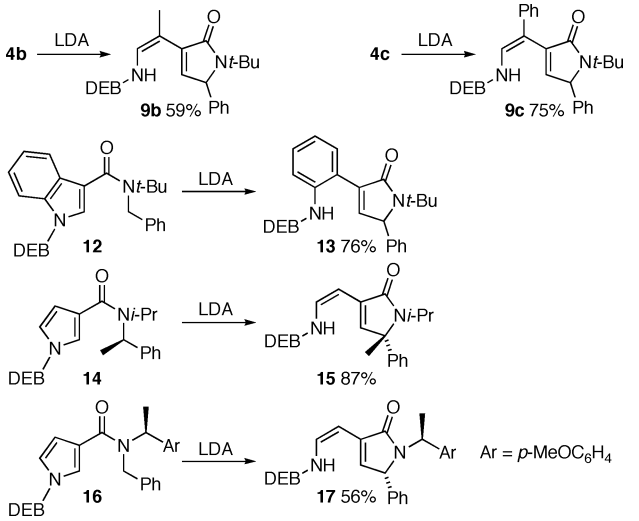
which cyclizes by nucleophilic attack on the 2-position of the pyrrole. The product, the extended enolate **6**, is unstable due to the extensive unsaturation in the 5,5-fused ring system. A decomposition pathway, which can be rationalized either as a 5-*endo*-*trig* or an electrocyclic ring opening, relieves the strain and generates **7**. This product must undergo an intramolecular proton transfer to yield a new extended enolate **8**, which is finally protonated to yield **9**. The intermediacy of the extended enolate **8** could be demonstrated by γ-deuteration, which gave **10a**, or α-allylation, which gave **10b**. It was important to avoid a greater excess of LDA in the cyclization, or byproducts **11** were generated arising from conjugate addition of LDA to the pyrrolinone ring of **7** or **9** (with 6 equiv of LDA, **11** was formed in 20% yield).

The cyclization (effectively a conjugate substitution of the pyrrole nitrogen by the benzyllithium) was repeated using the substituted pyrroles **4b** and **4c** and again good yields of the products **9b** and **9c** were obtained. Changing the protecting group to the more readily available Piv (**4d**) gave poorer yields (14%). Incorporating the pyrrole into an indole ring system **12** produced an aminophenyl-substituted product **13** in high yield (Scheme 3).

Although the cyclizations generate chiral products, an attempt to promote asymmetric cyclizations of **4** by using a chiral lithium amide base in the place of LDA (a strategy

(5) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, 2002.

Scheme 3. Cyclizations of Substituted Pyrrolecarboxamides



which works well in the benzamide series)[6] was frustrated by the unavoidable formation of achiral enolate **8**. However, with the chiral and enantiomerically pure amide **14**, the cyclization product **15** cannot re-form an enolate, and indeed **15** is formed fully stereospecifically from **14**: a fully substituted stereogenic center is incorporated into the ring with >99% ee. In agreement with previous reports of similar cyclizations,[7] both the lithiation and cyclization of **14** are stereospecific, and the intermediate organolithium must be configurationally stable on the time scale of the cyclization.

Remarkably, it was also possible to cyclize **16** diastereoselectively, despite the late deprotonation/reprotonation of the benzylic center. The amide **17** is formed as a single diastereoisomer. The "auxiliary" α-methyl-*p*-methoxybenzyl substituent of **16** must be exerting an effect by controlling the facial selectivity of the final protonation step, and we are currently investigating more widely the ability of similar auxiliaries to govern the selectivity of protonation of related pyrrolinones.

The ring-opening of the pyrrole prevents us forming the 5,5-fused systems we had envisaged from these compounds. However, we had noted previously that the cyclization of an *N*-allyl substituted naphthamide was able to generate a 7-membered ring,[8] and it seemed reasonable to suppose that a 7,5-fused ring system might be much less strained than the 5,5-fused systems **6**. *N*-Allyl pyrrolecarboxamides **19a**−**c** were made by cycloaddition of the acrylamides **18** with TosMIC and protection with DEBCl (Scheme 4).

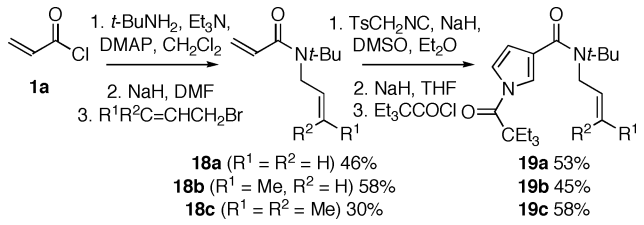
Treatment of the *N*-allyl pyrrolecarboxamides **19** with LDA gave colored allyllithiums **20** which, with the exception of **20c**, cyclized over a period of 3 h at 0 °C to yield the enolates **23**. As we had hoped, these enolates turned out to

(6) Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38.

(7) Clayden, J.; Knowles, F. E.; Menet, C. J. *Tetrahedron Lett.* **2003**, *44*, 3397. Clayden, J.; Knowles, F. E.; Menet, C. J. *Synlett* **2003**, 1701. The absolute stereochemistry of **15** is assumed according to this precedent.

(8) Ahmed, A.; Clayden, J.; Rowley, M. *Synlett* **1999**, 1954.

Scheme 4. Synthesis of *N*-Allyl, Crotyl, and Prenyl Pyrrolecarboxamides



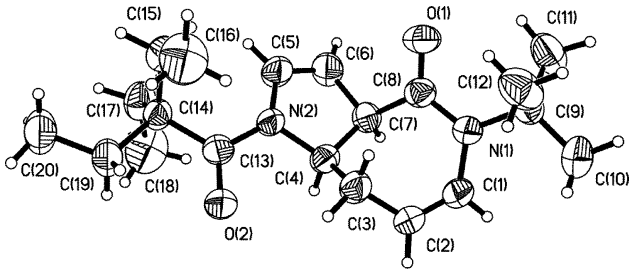


Figure 1. X-ray crystal structure of *cis*-**24a**.

be stable, and stereoselective alkylation yielded in every case essentially a single diastereoisomer of the 7,5-fused pyrroloazepinones **24**. The cis stereochemistry at the ring junction of *cis*-**24d** was proved by X-ray crystal structure (Figure 2).

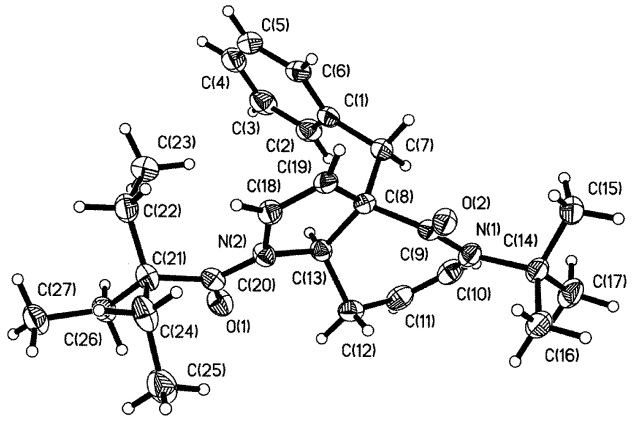
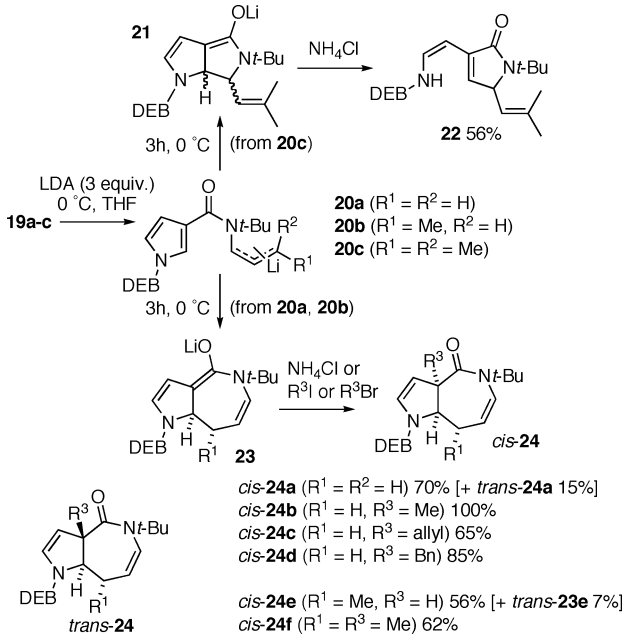


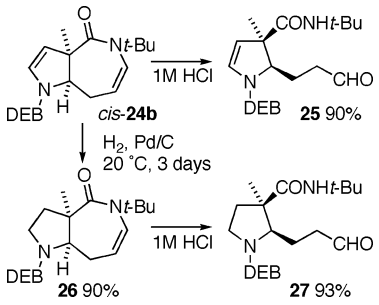
Figure 2. X-ray crystal structure of *cis*-**24d**.

Protonation of **23** also gave mainly the *cis*-fused 7,5-ring system (Figure 1 shows an X-ray crystal structure of *cis*-**24a**), accompanied by a small amount of a *trans*-fused by-product *trans*-**24**. Cyclization of *N*-prenyl-substituted amide **19c** gave no 7,5-fused products, presumably because of steric hindrance at the far end of the allylic system. The only product isolated was the pyrrolinone **22** analogous to the products **9** formed from *N*-benzyl amides **4** (Scheme 5).

Scheme 5. Pyrroloazepinones by Dearomatizing Cyclization



Scheme 6. Transformations of the Products



Products **24** are bisacylenamines, and treatment of *cis*-**24b** with aqueous acid hydrolyzed just one of the enamides to the amide aldehyde, yielding **25** (Scheme 6). Hydrogenation by contrast was selective for the double bond in the 5-membered ring, giving **26**. Hydrolysis of **26** gave pyrrolidine **27**. The ring system of **24** is new, but is related to the pyrroloazepinone present in the natural product hinckdentine A.[9]

Acknowledgment. We are grateful to the EPSRC for a studentship (to R.T.) and to Dr. James Raftery for determining the X-ray crystal structures of *cis*-**24a** and *cis*-**24d**.

Supporting Information Available: Experimental procedures and characterization data for all new compounds; crystallographic data for *cis*-**24a** and *cis*-**24d**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0364071

(9) Liu, Y.; McWhorter, W. W. *J. Am. Chem. Soc.* **2003**, *125*, 4240.