

Facile C–N Cleavage in a Series of Bridged Lactams

Yao Lei, Aaron D. Wroblewski, Jennifer E. Golden, Douglas R. Powell, and Jeffrey Aubé*

Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, Room 4070, Malott Hall,
University of Kansas, Lawrence, Kansas 66045-7582

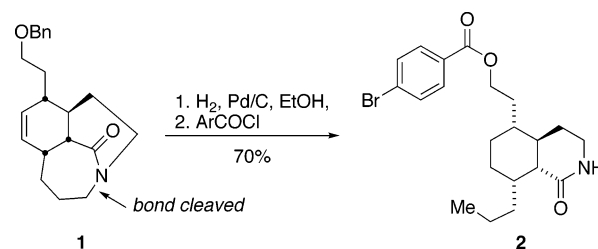
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Twisted amides, in which the amide bond deviates significantly from the planar conformation usually associated with this functional group, are of interest from both a structural and reactivity perspective.¹ Such amides are markedly sensitive to hydrolysis of the amide bond, they are subject to reactions that are more commonly associated with ketones than amides, and they undergo N- rather than O-protonation.² These features have been ascribed to loss of conjugation between the amide nitrogen and the C=O π bond, although this interpretation is subject to continuing investigation from a theoretical perspective.³ Nonplanar amides are also interesting because they are encountered midway in the cis/trans isomerization of peptide bonds.⁴ We wish to report a class of twisted amides whose non-carbonyl, C–N σ bond is remarkably susceptible to cleavage, even exhibiting a highly unusual sensitivity to catalytic hydrogenolysis.

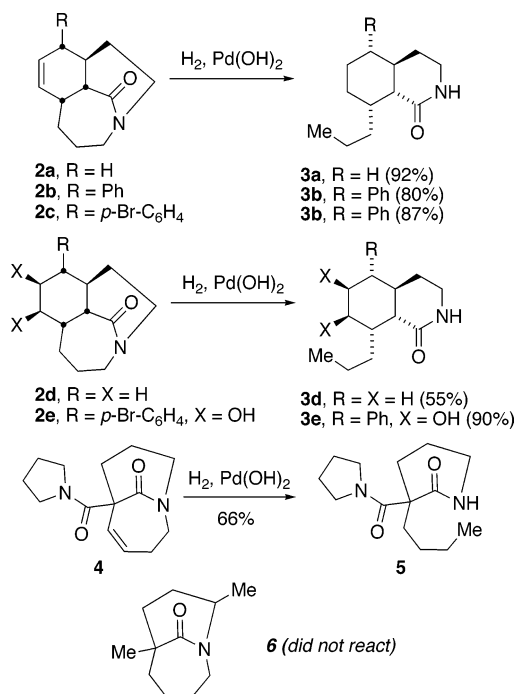
Twisted amides most commonly arise by the incorporation of the amide bond into a ring system that prohibits the amide from attaining its usual planar geometry.^{5,6} Recently, we encountered lactam **1** as the minor component of a tandem intramolecular Diels–Alder/Schmidt reaction sequence carried out in the context of a total synthesis of stenine (Scheme 1).⁷ Wishing to verify the structure of this byproduct, we sought to prepare a crystalline derivative by removing the benzyl group by catalytic hydrogenation (an act that also reduced the olefinic group in the compound) and then making the *p*-bromobenzoyl ester of the resulting alcohol. Although the product was indeed crystalline, it was not the tricyclic amide that we had expected. Strikingly, the sole product resulted from the regioselective, reductive cleavage of the C–N bond within the seven-membered ring. None of the product resulting from reaction at the C–N bond in the six-membered ring was observed.^{7,8}

Although heightened reactivity of a twisted amide linkage is well-known, the breaking of an otherwise unactivated C–N σ bond has been reported in only a single specialized example.⁹ A series of analogues of **1** was subjected to similar conditions, demonstrating that this unusual reduction was not peculiar to **1** (Scheme 2; see Supporting Information for substrate preparations). The successful hydrogenolysis of two examples lacking an olefin demonstrated that an alkene was not necessary for hydrogenolysis (e.g., by migrating into an allylic position). In addition, two bicyclic analogues were made and similarly challenged; one of these underwent hydrogenolysis and one did not. Since compound **6** appears to have a similar extent of strain as **4**, its lack of reactivity is possibly due to increased steric hindrance, although this point will require additional study. Although a number of conditions afforded product, the yields of all of these reactions were dependent on catalyst and solvent. The best results were obtained in ethanol using Pearlman's catalyst (Pd(OH)₂), although reactions in non-protic solvents also succeeded to a lesser extent (e.g., reaction of **1** in THF gave a 16–27% yield of the alcohol corresponding to **2**).

Scheme 1



Scheme 2



The C–N bond also underwent cleavage by treatment with methyl iodide (Scheme 3). This reaction, which is mechanistically related to the dealkylation of tertiary amines with haloformates,¹⁰ was also completely regioselective. The C–N bond also proved susceptible to oxidative cleavage using DDQ. This reaction, which presumably involves initial single-electron transfer, afforded a ca. 5:1 mixture of aldehydes from the unsubstituted ring system **2a** but exclusively **7c** from **2c**.

We obtained an X-ray structure of bridged lactam **2c** (Figure 1). As expected, the nitrogen atom is nearly pyramidal, with bond angles ranging from 110 to 119°. It is also evident that the labile C10–N bond is further from the carbonyl plane than the C11–N bond. However likely that this feature is related to the observed regiochemistry, it is unclear whether the underlying reason is related only to strain or if improved overlap of the labile bond with the carbonyl π system is also a factor.

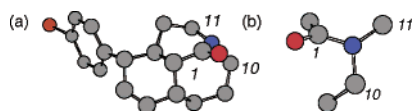
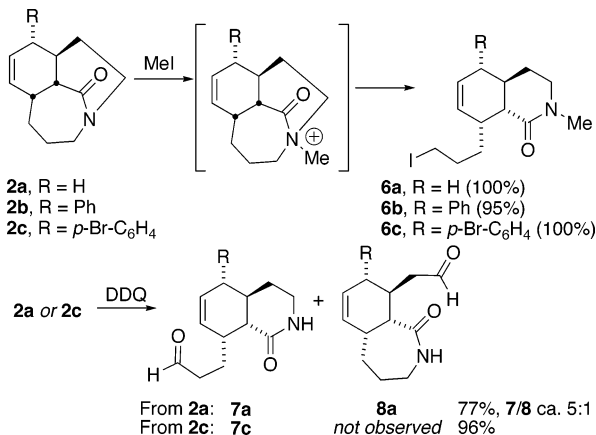
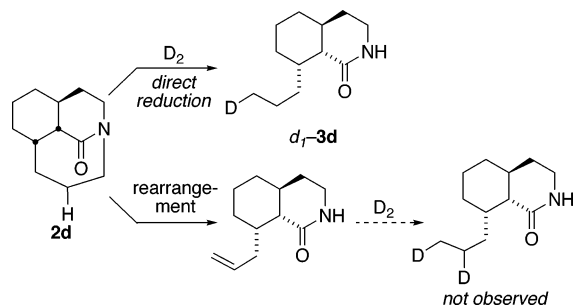


Figure 1. (a) Ball-and-stick depiction of the X-ray-derived structure of compound **2c**. (b) Close-up of the amide region, showing dihedral angles of $\angle\text{C10-N-C1-O} = 62.9^\circ$ and $\angle\text{C11-N-C1-O} = -152.9^\circ$ (which corresponds to a 27.1° deviation from planarity).

Scheme 3



Scheme 4



While the mechanism of the MeI-mediated cleavage reaction almost certainly involves initial formation of the amidinium species followed by S_N2 displacement by iodide, we considered the possibility that the hydrogenolysis reaction might instead involve a McClafferty-type rearrangement (possibly Pd-promoted) to afford an olefin that was subsequently reduced (Scheme 4). This idea lost favor when it was shown that no change occurred when the twisted amides were subjected to Pd(OH)₂/EtOH treatment under a non-hydrogen atmosphere. In addition, carrying out the reaction using D₂/EtOD¹¹ resulted in the incorporation of a single D atom at the end of the propyl chain, which is consistent with a direct displacement either by Pd-activated hydride or by metal insertion followed by reductive elimination. In either case, the NH proton undergoes exchange when the compound is isolated. The preference for a protic solvent in the hydrogenolysis likely indicates a role for hydrogen bonding to nitrogen in the cleavage reaction.

Finally, we note that, in contrast to many other examples of twisted amides, none of these lactams readily form the corresponding seco acid. Thus, incubation in aqueous THF with pH ranging

from 4 to 11 afforded only recovered starting material. We think that hydration or hydrolysis does occur but the amide re-forms due to the transannular relationship of the amine and ketone groups in the ring-opened analogue.

This work shows that the C–N bond adjacent to a twisted amide can undergo interesting strain-activated chemistry. Future work will systematically address the effect of amide structure on reactivity in this class of lactams.

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Supporting Information Available: Experimental procedures and compound characterizations (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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