Heterocycle Synthesis

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The Cyano Group as a Traceless Activation Group for the Intermolecular [3+2] Cycloaddition of Azomethine Ylides: A Five-Step Synthesis of (±)-Isoretronecanol**

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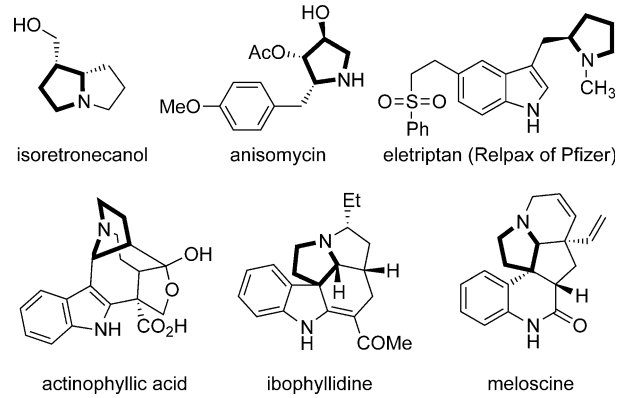
Dedicated to Professor Samuel J. Danishefsky on the occasion of his 79th birthday

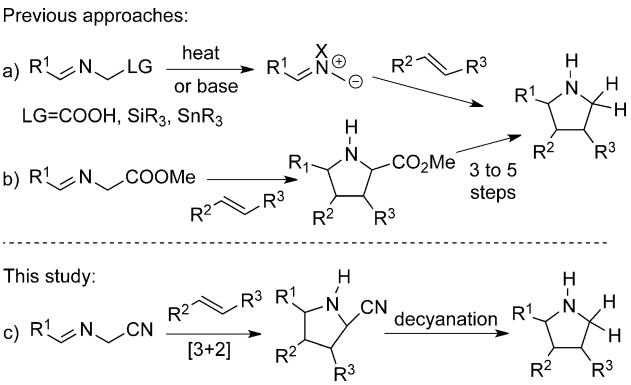
Abstract: *The cyano group was used as a traceless activation group for the [3+2] cycloaddition of azomethine ylides in a two-step process, thereby providing a highly effective approach to 5-unsubstituted pyrrolidines. The transformation includes the silver acetate catalyzed intermolecular 1,3-dipolar cycloaddition of α-iminonitriles and an unprecedented sodium borohydride induced reductive decyanation reaction. A diverse array of substrates is amenable to this transformation. The methodology was further extended to a five-step total synthesis of the pyrrolizidine natural product isoretronecanol.*

Pyrrolidines without a substituent at the 5-position are privileged substructures of numerous biologically active natural products and drugs (Scheme 1).[1] Furthermore, a myriad of proline derivatives bearing this structural feature have found widespread application in organocatalysis.[2] From the perspective of alkaloid biosynthesis, the absence of a C5 substituent on pyrrolidine rings partially stems from a decarboxylation process of amino acids that is catalyzed by the corresponding decarboxylases at an early biosynthetic stage.[3] Despite their importance in natural products and drugs, the synthesis of highly functionalized 5-unsubstituted pyrrolidines is rather underdeveloped.[4]

The 1,3-dipolar cycloaddition of azomethine ylides with alkenes is a powerful method for the syntheses of multisubstituted pyrrolidines.[5] A couple of strategies for the preparation of 5-unsubstituted pyrrolidines through [3+2] cycloaddition with nonstabilized azomethines have been developed (Scheme 2). Nonstabilized dipoles derived from α-imino acids by thermal decarboxylation[5d] or α-trialkylsilyl/α-trialkylstannyl imines by treatment with a base[4,6] undergo [3+2] cycloaddition to afford 5-unsubstituted pyrrolidines (Scheme 2a). However, significant disadvantages of these technologies, such as the requirement of harsh conditions and the utilization of expensive or toxic reagents, have limited their overall scope and application. Moreover, the stereoselectivity (regio- and diastereoselectivity) of these technologies has sometimes been problematic, especially in inter-



Scheme 1. Examples of natural products and drugs containing 5-unsubstituted pyrrolidine rings.



Scheme 2. Background and design of the traceless activation strategy involving [3+2] cycloaddition aided by a CN group for the preparation of 5-unsubstituted pyrrolidines.

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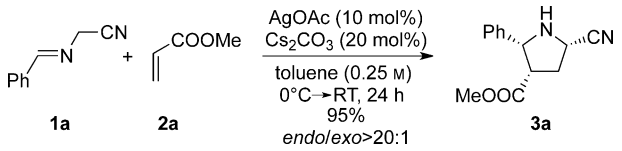
molecular cases.[7] By contrast, the great efficacy of α-imino esters as stabilized azomethine ylide precursors for the synthesis of 2,5-disubstituted pyrrolidines through [3+2] cycloaddition is well-documented.[5] However, it usually takes three to five steps to access 5-unsubstituted pyrrolidines from the cycloadducts (Scheme 2b).[8] Hence, the development of efficient methods for the stereoselective construction of this scaffold is still attractive.

We envisaged a novel strategy involving the 1,3-dipolar cycloaddition of α-iminonitriles and a subsequent reductive decyanation reaction to access the 5-unsubstituted pyrrolidine architecture (Scheme 2c). In this context, the cyano group functions as a "traceless" activation group,[9] which facilitates the [3+2] cycloaddition through the formation of a stabilized azomethine ylide intermediate and can be removed afterwards. However, there are two challenges posed by this design. First, despite sporadic reports about the 1,3-dipolar cycloaddition of α-iminonitriles in the last three decades,[10] a method with high substrate versatility and good stereoselectivity is still in high demand. Second, secondary α-aminonitriles remain challenging substrates for reductive decyanation.[11] Usually, a stoichiometric amount of an activating agent, such as a Brønsted or Lewis acid, is necessary. Herein we describe the successful execution of the above design ideals and outline an efficient route to diverse 5-unsubstituted pyrrolidines. A five-step total synthesis of isoretronecanol with the current method as the key transformation is also reported.

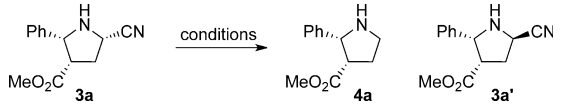
To establish optimal conditions for the intermolecular [3+2] cycloaddition of α-iminonitriles, we chose *N*-benzylideneaminoacetonitrile (**1a**) and methyl acrylate as model substrates and AgOAc as a catalyst. In a survey of a series of bases and solvents, the best results in terms of reactivity and diastereoselectivity were obtained in toluene with AgOAc (10 mol%) and Cs_2CO_3 (20 mol%) as the base (Scheme 3; for details, see the Supporting Information).



Scheme 3. Optimal reaction conditions for the 1,3-dipolar cycloaddition of α-iminonitrile **1a** and methyl acrylate.

We then focused on the decyanation reaction of α-cyanopyrrolidines. A range of reduction conditions were screened with compound **3a** as the substrate (Table 1). To our surprise, when **3a** was treated with $NaBH_4$ (5.0 equiv) in methanol, the 5-epimeric cyanopyrrolidine **3a′** was obtained in moderate yield (40%; Table 1, entry 1) together with a trace amount of the decyanated product **4a**. The reduction with either $NaBH_4$ and $AgBF_4$ in THF (Table 1, entry 3) or $NaBH_3CN$ in an acidic mixed solvent (MeOH/AcOH 3:1; entry 4) delivered **4a** in good yield in 24–48 h. Although decyanation with borane only provided **4a** in moderate yield (40%; Table 1, entry 5) in 24 h, a combination of borane

Table 1: Optimization of the reaction conditions for the reductive decyanation.[a]



Entry	Reductant (equiv)	Solvent	Yield [%][b] (product)	*t* [h]
1	$NaBH_4$ (5.0)	MeOH	40 (**3a′**)	48
2	$NaBH_4$ (5.0)	THF	15 (**4a**)	48
3	$NaBH_4$ (3.0), $AgBF_4$ (1.5)	THF	80 (**4a**)	24
4	$NaBH_3CN$ (2.0)	MeOH/AcOH (3:1)	83 (**4a**)	48
5	BH_3 (3.0)	THF	40 (**4a**)	24
6	BH_3 (1.2), $NaBH_4$ (1.0)	THF	95 (**4a**)	0.5
7	BH_3 (0.2), $NaBH_4$ (1.0)	THF	80 (**4a**)	72
8	**BH_3 (1.2), $NaBH_4$ (0.2)**	**THF**	**95 (4a)**	**0.5**

[a] Reactions were carried out with 0.5 mmol of **3a** in 5 mL of solvent at room temperature. All reactions except those in entries 1 and 4 were quenched with aqueous NaOH (20%), and the crude product was later treated with Pd/C (10 wt%) in methanol. BH_3 refers to BH_3·THF.
[b] Yield of the isolated product.

(1.2 equiv) with $NaBH_4$ (1.0 equiv)[12] furnished **4a** in high yield (95%; entry 6) within 0.5 h. To elucidate the respective functions of borane and $NaBH_4$, we carried out two experiments (Table 1, entries 7 and 8). We found that a combination of 1.2 equivalents of borane with 0.2 equivalents of $NaBH_4$ provided the best results with regard to yield and reaction time (Table 1, entry 8). A modified version of the workup procedure described by Couturier et al.[13] was necessary to release the free pyrrolidine product from its borane complexes (see below) when the above conditions were used. As a promoter, a catalytic amount of $NaBH_4$ dramatically accelerated the reductive decyanation reaction with borane. As far as we know, a combination of borane and $NaBH_4$ has not been employed previously in a reductive decyanation reaction.

Having optimized the reaction conditions, we next examined the scope of this two-step transformation with regard to the substituent R on the α-iminonitrile **1** and the use of different electron-deficient olefins **2** (Scheme 4). A wide variety of α-iminonitriles bearing electron-deficient substituted phenyl groups could be smoothly converted into cyanopyrrolidines and the corresponding 5-unsubstituted pyrrolidines in good yield (products **3b–f**, 84–95% yield; **4b–f**, 80–94% yield). The reaction of α-iminonitrile **1g** bearing an electron-rich 4-methoxyphenyl group and methyl acrylate afforded **3g** in only 52% yield in 48 h. However, with the stronger base DBU, the yield was enhanced remarkably to 92% within 4 h. We also found the current protocol to be compatible with a wide variety of heterocycles, including pyridine, furan, thiophene, pyrrole, and indole substrates (products **3i–n**, 74–91% yield; products **4i–n**, 52–90% yield). Interestingly, the double bond of cyanopyrrolidine **3o** survived the reductive decyanation with borane without the occurrence of any evident hydroboration reaction. Dipolarophiles bearing ester, sulfone, or amide groups (including bulky ester groups) also worked well in this sequence (products **3p–t**, 56–90% yield; products **4p–t**, 84–93%

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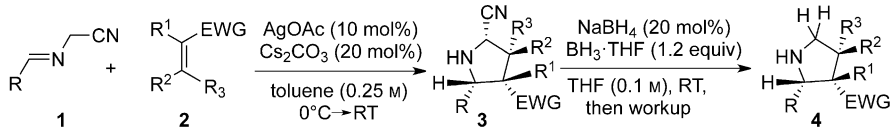
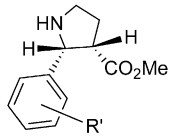
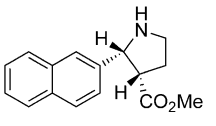


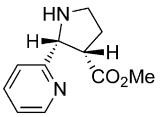


3a R'=H, *endo/exo*>20:1, 95% (92%, gram scale)
3b R'=*p*-Br, *endo/exo*>20:1, 95 %
3c R'=*o*-Br, *endo/exo*>20:1, 85%
3d R'=*m*-Br, *endo/exo* 14:1, 87%
3e R'=*p*-F, *endo/exo*>20:1, 85%
3f R'=*p*-CF_3, *endo/exo*>20:1, 84%
3g R'=*p*-OMe, *endo/exo*>20:1, 52%(92%)[b]

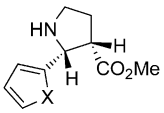
4a[a] R=H, 91% (gram scale)
4b R=*p*-Br, 94%
4c R=*o*-Br, 80%
4d R=*m*-Br, 90%
4e R=*p*-F, 91%
4f R=*p*-CF_3, 93%
4g R=*p*-OMe, 92%



3h *endo/exo*>20:1, 83%
4h 97%

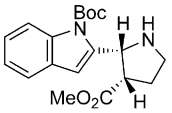


3i *endo/exo* 10:1, 79%
4i 52%

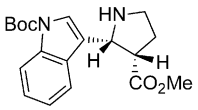


3j X=O, *endo/exo*>20:1, 74%
3k X=S, *endo/exo*>20:1, 91%
3l X=NBoc, *endo/exo*>20:1, 88%

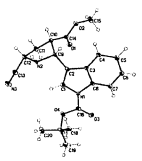
4j X=O, 65%
4k X=S, 80%
4l X=NBoc, 87%



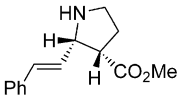
3m *endo/exo*>20:1, 90%
4m 77%



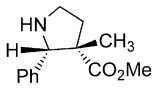
3n[c] only *endo*, 76% (gram scale)
4n[a] 94%, (gram scale)



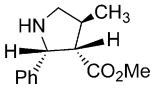
X-ray structure of **3n**



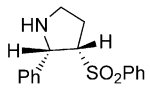
3o *endo/exo*>20:1, 64% (gram scale)
4o 76%



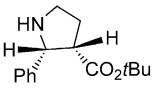
3p[d] *endo/exo*>20:1, 56%
4p 93%



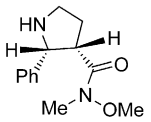
3q[d] *endo/exo*>20:1, 57%
4q 91%



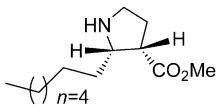
3r[d] *endo/exo*>20:1, 68%
4r 87%



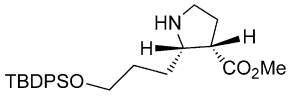
3s *endo/exo*>20:1, 86%
4s 91%



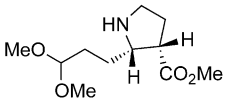
3t *endo/exo*>20:1, 90%
4t 84%



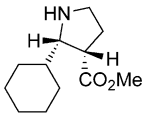
3u[b] *endo/exo*>20:1, 81%
4u 88%



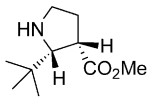
3v[b] *endo/exo*>20:1, 77% (gram scale)
4v 72%



3w[b] *endo/exo*>20:1, 83%,
4w 69%



3x[b] *endo/exo*>20:1, 96%
4x 83%



3y[b] *endo/exo*>20:1, 88%
4y 79%

Scheme 4. Two-step synthesis of 5-unsubstituted pyrrolidines. The ratios of *endo*/*exo* diastereomers were determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Yields of the isolated *endo* products are given. [a] The reaction was performed with 10 mol% of $NaBH_4$. [b] DBU (20 mol%) was used as the base. [c] The reaction was performed at −10°C with AgOAc (1.1 equiv) and DBU (1.0 equiv). [d] Another portion of AgOAc (10 mol%) was added after 12 h. Boc = *tert*-butoxycarbonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, EWG = electron-withdrawing group, TBDPS = *tert*-butyldiphenylsilyl.

yield). The relative configuration of **3n** was confirmed by X-ray crystallographic analysis,[14] and that of other cyanopyrrolidines was assigned by analogy and also reexamined by NOE NMR spectroscopic studies.

At this point, we turned our attention to more challenging aliphatic α-iminonitrile substrates.[10b] To our delight, the AgOAc-catalyzed [3+2] cycloaddition of aliphatic α-iminonitriles proceeded smoothly with DBU as the base, although it was ineffective with Cs_2CO_3. The 1,3-dipolar cycloaddition of methyl acrylate and a series of aliphatic α-iminonitriles gave consistently good results (products **3u**–**y**, 77–96% yield), thereby leading to 5-unsubstituted pyrrolidines with aliphatic substituents at C2 (products **4u**–**y**, 69–88% yield). Notably, the labile dimethyl acetal group (in products **3w** and **4w**) tolerated the two-step manipulation.

We next conducted preliminary studies on the novel $NaBH_4$-promoted decyanation reaction and propose a novel mechanism involving an anionic chain reaction[15] (Scheme 5). The exposure of a 5-cyanopyrrolidine **3a** to BH_3 generates a borane–amine complex **I**.[16] Usually, the collapse of **I** to an imine–borane complex **II**[17] is relatively slow; however, basic $NaBH_4$ could promote such fragmentation[11c,e] by deprotonation of the acidic N–H atom ($\delta = 6.7$ ppm in [D_8]THF). With the aid of the cyanoborohydride anion, the imine is reduced by borane[18] to generate amide anion **III**, which then abstracts a proton from complex **I**, thereby regenerating the

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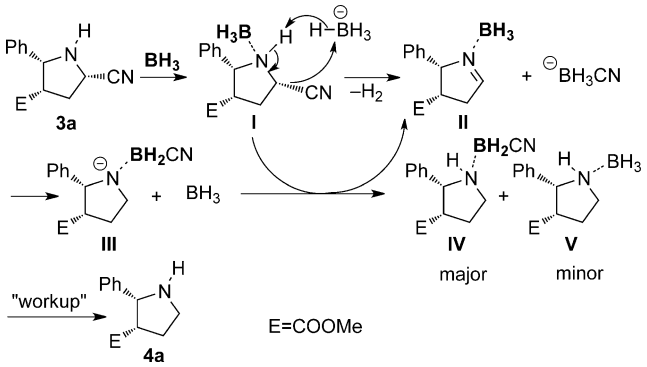
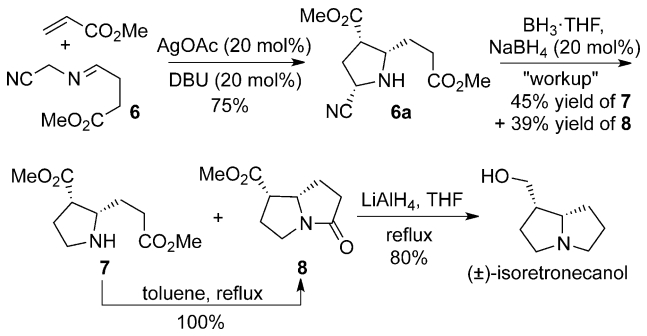


Scheme 5. Proposed mechanism and model study with **3a** (E = CO_2Me) for the $NaBH_4$-induced decyanation reaction (BH_3 = BH_3·THF).

imine–borane complex **II** and BH_3CN^-. These two steps constitute a cyclic process for chain propagation to produce complexes **IV** and **V**. *Notably, amide anion **III** derived from the reaction of compound **IV** and NaH was also effective for this chain reaction* (see the Supporting information). Finally, the resulting complexes **IV** and **V** are converted into a free pyrrolidine **4a** by the previously mentioned workup. In this process, $NaBH_4$ induces a reductive anionic chain reaction, and borane acts not only as a Lewis acid activator for imine formation but also as a reducing agent. A series of deuteration experiments and NMR spectroscopic studies (including ^1H and ^{11}B NMR spectroscopy) supported this proposal (see the Supporting Information). Although the conversion of the imine species into the amide anion **III** is not fully defined, these preliminary results are in favor of the current mechanistic proposal.

To further demonstrate the value of this new two-step protocol for the synthesis of 5-unsubstituted pyrrolidines, we present a five-step synthesis of isoretronecanol,[19] a pyrrolizidine alkaloid. Exposure of the aliphatic α-iminonitrile **6** and methyl acrylate to our two-step protocol, followed by lactamization in toluene at reflux, provided lactam **8** in good yield (63% over 3 steps; Scheme 6). Subsequent one-pot reduction of the ester and lactam groups afforded racemic isoretronecanol in only five steps and 50% overall yield.

In summary, we have demonstrated the utility of the CN group as a traceless activation group for the synthesis of 5-unsubstituted pyrrolidines through a sequence of 1,3-dipolar cycloaddition and reductive decyanation. The two-step protocol offers a highly efficient strategy to rapidly access diverse 5-unsubstituted pyrrolidines. As a proof of concept, the method was successfully applied to a five-step synthesis of isoretronecanol. We also investigated the mechanism of the novel $NaBH_4$-induced reductive decyanation reaction. Further studies on an asymmetric version of this strategy and applications in organic synthesis are under way in our laboratory.



Scheme 6. Five-step total synthesis of (±)-isoretronecanol.

Keywords: cycloaddition · pyrrolidines · reductive decyanation · total synthesis · traceless activation

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