Aminocyanation

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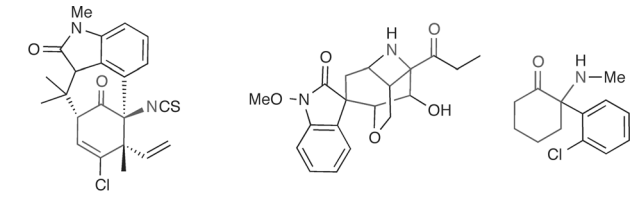
Formal Aminocyanation of α,β-Unsaturated Cyclic Enones for the Efficient Synthesis of α-Amino Ketones**

Chunrui Sun, Matthew J. O'Connor, Daesung Lee, Donald J. Wink, and Robert D. Milligan*

Dedicated to Professor Teruaki Mukaiyama

Abstract: *Installation of amino functionality on organic molecules through direct C–N bond formation is an important research objective. To achieve this goal, a 1,2-aminocyanation reaction was developed. The reaction occurs through the formation of pyrazolines by means of a formal dipolar cycloaddition of cyclic α,β-unsaturated ketones with lithium trimethylsilyldiazomethane followed by novel protonolytic N–N bond cleavage under mild conditions. This two-step process provides a diverse array of structurally complex free and mono-alkylated α-amino ketones in excellent yields.*

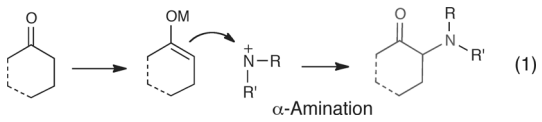
Compounds containing α-amino ketones constitute an important class of biologically active natural products and pharmaceuticals; *N*-methylwelwitindolinone C isothiocyanate,[1] gelsemoxonine,[2] and ketamine[3] are just a few representative examples (Figure 1). Conceptually, one of the most straightforward synthetic approaches to α-amino



N-Methylwelwitindolinone C isothiocyanate | Gelsemoxonine | Ketamine

Figure 1. Important natural products and pharmaceuticals that contain α-amino ketones.

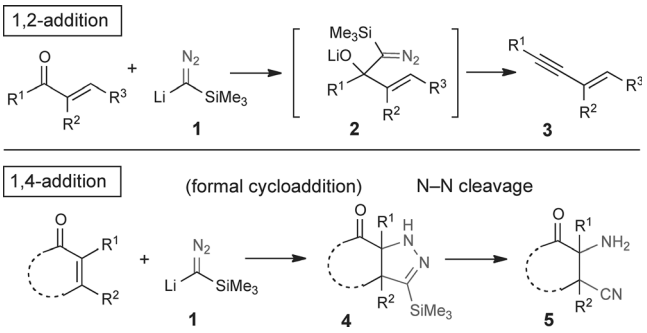
ketones is α-amination, wherein an enol or enolate form of a ketone reacts with an electrophilic nitrogen-containing species [Eq. (1)]. Various α-amination methods have been developed[4] but most of these share a typical shortcoming, namely the tedious manipulation involved in removing the extra functionality on the nitrogen atom after C–N bond



(1)

formation. Therefore, the invention of a new method that can effectively provide free α-amino ketones would be highly desirable.

Herein, we describe an efficient and operationally simple formal aminocyanation that relies on the unprecedented reactivity of lithium trimethylsilyldiazomethane **1**[5,6] toward α,β-unsaturated ketones. In contrast to the 1,2-addition of **1** with acyclic α,β-unsaturated ketones to generate 1,3-enyne **3** via adduct **2**, the reaction of cyclic counterparts proceeds exclusively through 1,4-addition to provide Δ^2-pyrazoline **4**. Facile cleavage of the N–N bond in **4** was realized under mild nonreductive conditions to generate free α-amino ketone **5** (Scheme 1).



Scheme 1. 1,2 addition of acyclic enones and 1,4-addition of cyclic enones.

Considering the extensive investigations of Aoyama and co-workers,[7] it is surprising to note the lack of literature reports on Δ^2-pyrazoline formation from **1** and α,β-unsaturated ketones with the exception of enaminoketone (vinylogous amide).[8] The requirement for selective 1,4-addition–cyclization (formal cycloaddition)[9] between **1** and α,β-unsaturated ketones seems to be a synergistic effect of the steric bulk of the trimethylsilyl group in **1** and the cyclic nature of the α,β-unsaturated ketones.

To illustrate the importance of the structural characteristics of both of the reacting counterparts, cyclic and acyclic α,β-unsaturated ketones **6** and **10** were treated with **1** under

[*] C. Sun, M. J. O'Connor, Prof. D. Lee, Prof. D. J. Wink, R. D. Milligan
Department of Chemistry, University of Illinois at Chicago
845 West Taylor Street, Chicago, IL, 60607 (USA)
E-mail: dsunglee@uic.edu

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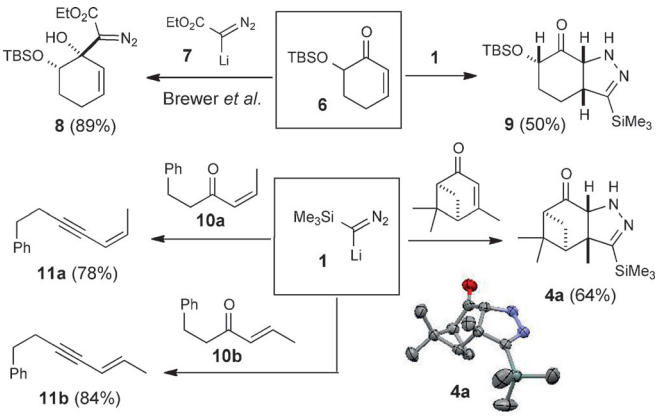


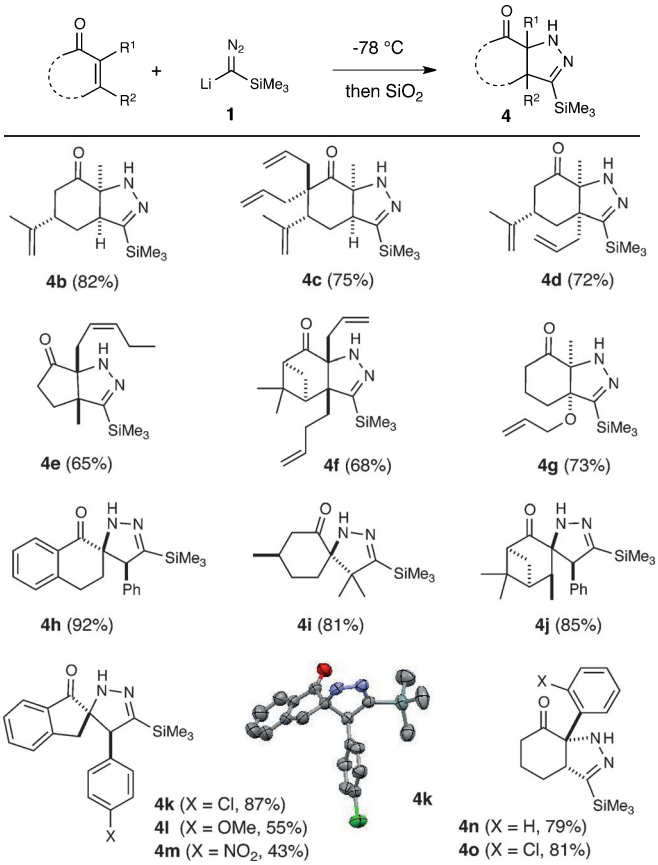
Scheme 2. 1,2- versus 1,4-addition with acyclic and cyclic enones.

identical conditions (Scheme 2). In contrast to the reports by Brewer and co-workers[10] on the 1,2-addition of enone **6** with lithium ethyldiazoacetate **7** to afford **8** (89%), the exclusive 1,4-addition-cyclization of the same enone **6** with **1** provided Δ^2-pyrazoline **9** (50% and 35% pyrazole).[11] While the reaction of acyclic enones **10a** and **10b** with **1** afforded only 1,3-enynes **11a** (78%) and **11b** (84%), respectively, the corresponding reaction of the cyclic enone verbenone provided pyrazoline **4a** (64%) exclusively.[12]

The contrasting reactivity profiles of **7** versus **1** and cyclic enone **6** versus acyclic enones **10** clearly suggest a crucial role for the trimethylsilyl substituent on the diazo compound and the cyclic connectivity of the enone moiety in the formation of pyrazolines. Although the cause of the observed discrepancy between the behaviors of **1** and **7** is yet to be elucidated, we tentatively surmise that an unfavorable steric interaction between the trimethylsilyl group and the C4-methylene moiety of cyclohexenone disfavors the approach of **1** toward the carbonyl group. This hypothesis is further supported by the exclusive 1,2-addition of **1** observed with various acyclic enones.[13]

With this encouraging initial result in hand, we examined the reaction profiles of other α,β-unsaturated cyclic ketones with various substituent patterns on or near the double bond (Table 1). (*S*)-Carvone, a trisubstituted enone with a α-methyl group, afforded pyrazoline **4b** in 82% yield. An α′,α′-diallyl substituted carvone derivative afforded pyrazoline **4c** with similar efficiency (75%). Surprisingly, even a tetrasubstituted carvone-derived enone and jasmone provided vicinal quaternary-center-containing pyrazolines **4d** and **4e** in 72% and 65% yields, respectively. The verbenone-derived[14] pyrazoline **4f** was also obtained in 68% yield despite the extreme steric hindrance. An alkoxy substituent at the β-position of the enone was not deleterious to 1,4-addition–cyclization and thus pyrazoline **4g** was obtained in good yield (73%). The spiro-bicyclic pyrazolines **4h–m** were generated as single diastereomers in a similar manner irrespective of substituent pattern and steric hindrance on or around the enone systems.[12] Considering the fact that substituents at the β-position of enones significantly retard 1,4-additon, the efficient formation of adducts **4d–g**, even from tetrasubstituted enones, is noteworthy. These unexpected outcomes may

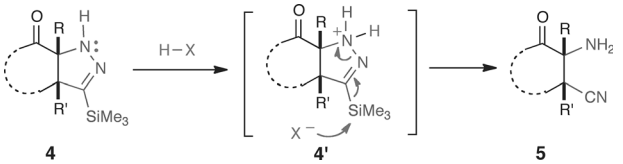
Table 1: The reaction of **1** and cyclic enones to give pyrazolines (**4**).



suggest that direct cycloaddition[15] by the anionically activated dipole is a preferred reaction pathway compared to 1,4-addition–cyclization, although more rigorous study is necessary to confirm this. Finally, enones containing α-aryl groups reacted cleanly with **1** to afford pyrazolines **4n** and **4o**.

Next, we investigated the N–N bond cleavage of pyrazolines **4**. The cleavage of N–N bonds has typically been achieved under hydrogenolytic conditions[16] or by using single-electron reduction,[17] but these known reductive conditions are not suitable owing to the presence of carbonyl functionality.

In search of alternative protocols,[18] we envisioned that the trimethylsilyl group on the pyrazolines **4** would facilitate the protonolytic cleavage of the N–N bond in the presence of a suitable Brønsted acid (Scheme 3). We hypothesized that under acidic conditions, the transfer of a proton to the α-nitrogen would generate an ammonium intermediate **4′**, which will then undergo nucleophilic attack by the conjugate base X on the silicon atom of the trimethylsilyl group to

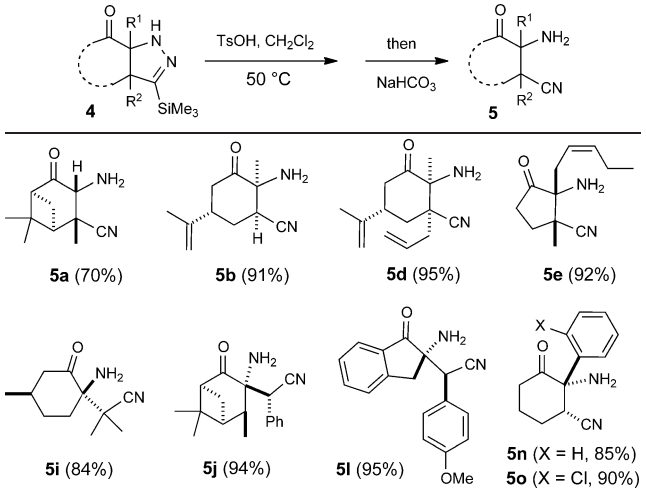


Scheme 3. Proposed mechanism of N–N bond cleavage induced by a Brønsted acid.

induce simultaneous C–$SiMe_3$ and N–N bond cleavage,[19] thereby providing α-amino ketone **5**.[20]

A brief screening of mineral and organic acids showed that most of the pyrazolines **4** underwent smooth and efficient cleavage of the N–N bond. Out of the acids tested, *p*-toluenesulfonic acid was found to be the most convenient and effective reagent, delivering α-amino-β-cyano ketones **5** in excellent yields (Table 2; TsOH (2.0 equiv), CH_2Cl_2, 50 °C then neutralization with aq. $NaHCO_3$).

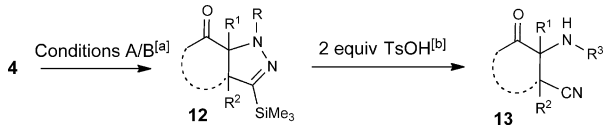
Table 2: Ring opening of pyrazolines under acidic conditions.

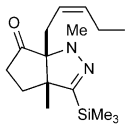
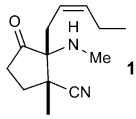
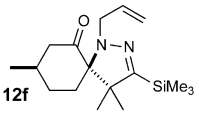
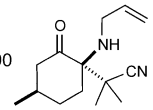
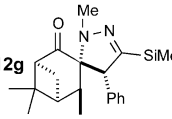
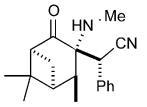
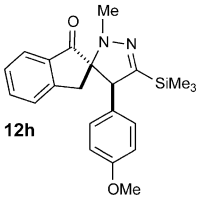
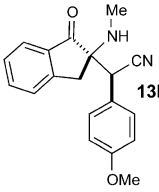
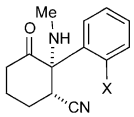
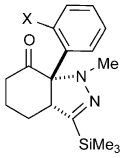


Encouraged by this facile N–N bond cleavage, we extended the acid-mediated N–N bond cleavage to N-alkylated pyrazoline derivatives because many biologically active amino ketones and amino alcohols, such as those in ketamine and epinephrine, contain mono-N-alkylated amino groups. For the preparation of mono-N-alkylated α-amino ketone derivatives, we envisioned that alkylation at the stage of the pyrazoline (**4**) should be most convenient. Under either reductive amination with aldehydes (Conditions A) or direct alkylation with alkyl halides and base (Conditions B), the alkylated pyrazolines **12a–j** were obtained efficiently from the corresponding pyrazolines **4** (Table 3). As expected, when reacted under the same conditions as before (see Table 2), the N-alkylated pyrazolines **12a–j** underwent smooth N–N bond cleavage to deliver the α-alkylamino-β-cyano ketones **13a–j** in excellent yields.

In conclusion, we developed a formal dipolar cycloaddition of α,β-unsaturated cyclic ketones with lithium trimethylsilyldiazomethane **1** to generate a structurally diverse array of pyrazolines. Based on the structural characteristics of the silyl-containing pyrazolines, we also developed a Brønsted-acid-mediated method for nonreductive N–N bond cleavage to generate either free or mono-N-alkylated α-amino ketones. The two-step process, which involves initial pyrazoline formation followed by N–N bond cleavage, constitutes a formal 1,2-aminocyanation of α,β-unsaturated cyclic ketones. The utility of our current aminocyanation reaction for the construction of pharmaceutically relevant α-amino

Table 3: Ring opening of N-alkylated pyrazolines.



Entry	4	Conditions	12	Yield of 12 [%]	13	Yield of 13 [%]
1	**4b**	A	**12a**, R = Me	85	**13a**	91
2	**4b**	B	**12b**, R = 	83	**13b**	95
3	**4b**	B	**12c**, R = 	80	**13c**	93
4	**4b**	A	**12d**, R = 	89	**13d**	90
5	**4e**	A	**12e** 	75	**13e** 	92
6	**4i**	B	**12f** 	90		91
7	**4j**	A	**12g** 	83		90
8	**4l**	A	**12h** 	52		95
9	**4n**, X= H	A	**12i**	90		90
10	**4o**, X = Cl	A	**12j** 	90	**13j**	90

[a] Conditions A: CH_2O (1.5 equiv) or cinnamaldehyde (1.5 equiv), $NaBH(OAc)_3$ (1.5 equiv), $ClCH_2CH_2Cl$, RT. Conditions B: allyl bromide or benzyl bromide (2 equiv), $NaHCO_3$ (2 equiv), EtOH/CH_2Cl_2 (1:1, *v*/*v*), 50 °C. [b] 2.0 equiv TsOH, CH_2Cl_2, 50 °C then neutralization with aq. $NaHCO_3$.

ketone moieties was demonstrated by targeting the ketamine analogues **13i** and **13j**. Further investigations into expanding the scope of this useful 1,2-aminocyanation to other electron-deficient alkenes and its application to natural product synthesis are in progress.

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[11] Facile air oxidation of **9** led to the corresponding pyrazole (35%).

[12] CCDC 968271 (**4a**) and CCDC 968272 (**4k**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] A reviewer suggests that for cyclic enones, the 1,4-addition is fast but reversible, and the subsequent C–N bond formation occurs faster due to conformational rigidity than that of acyclic enones. Although probable, this hypothesis cannot explain the formation of 1,2-adduct **8** by more stabilized reagent **7**, the addition of which should be more reversible than that of **1**. We thank the reviewer for this mechanistic suggestion.

[14] The substrate was prepared by treating the mixture of verbenone and allyl bromide (2.5 equiv) with NaH in *N*,*N*-dimethylformamide.

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