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Redox-Neutral α-Cyanation of Amines

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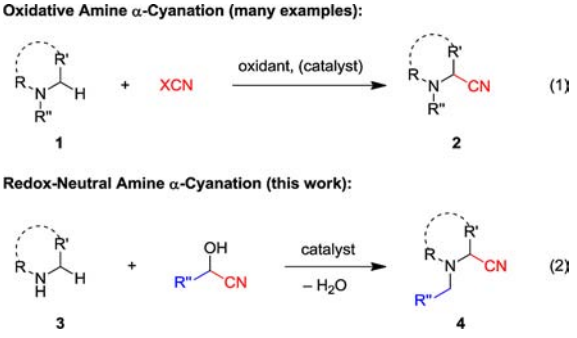
Supporting Information

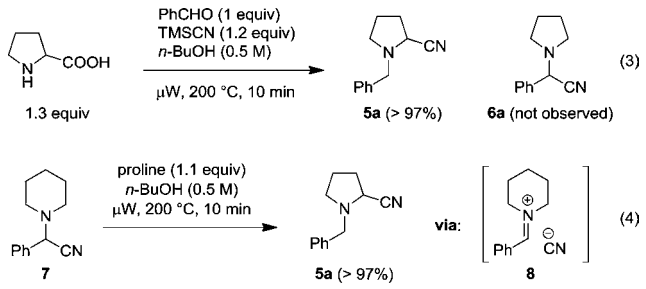
ABSTRACT: α-Aminonitriles inaccessible by traditional Strecker chemistry are obtained in redox-neutral fashion by direct amine α-cyanation/N-alkylation or alternatively, α-aminonitrile isomerization. These unprecedented transformations are catalyzed by simple carboxylic acids.

The exceptional versatility of α-aminonitriles continues to inspire the development of methods that provide access to these valuable building blocks.[1] While the classic Strecker reaction[2,3] remains an important tool in this regard, α-aminonitriles that are part of a ring system cannot easily be prepared by this methodology. A particularly attractive alternative approach to α-aminonitriles such as **2** is the replacement of an amine α-C−H bond with a C−CN bond (**1** → **2**, eq 1). Previous efforts to develop such methods have



relied on oxidative approaches,[4,5] including electrochemical methods.[6] Photoredox catalysis has recently emerged as a promising tool for oxidative amine α-cyanation, although this strategy has largely been limited to *N*-aryl tetrahydroisoquinolines and *N*,*N*-dialkylanilines.[7] Here we report a conceptually new strategy for the α-cyanation of amines (eq 2). In contrast to previous approaches, this method is redox-neutral[8] and does not require metal-based catalysts.

As part of a program to develop novel reactions of amines and amino acids for the rapid buildup of molecular complexity,[9,10] we recently reported a decarboxylative version of the classic Strecker reaction (eq 3).[9g] Specifically, we found that α-amino acids such as proline react with aldehydes and TMSCN to form cyclic α-aminonitriles (e.g., **5a**) rapidly under microwave irradiation. We also discovered that α-aminonitrile **7** reacts with proline to form **5a** (eq 4). This reaction most likely proceeds via reaction of proline with iminium ion pair **8**, which is thought to be present in equilibrium with α-aminonitrile **7**.



The notion that iminium ions such as **8** are accessible from their corresponding α-aminonitriles led us to consider the possibility of a novel α-aminonitrile isomerization (Figure 1).

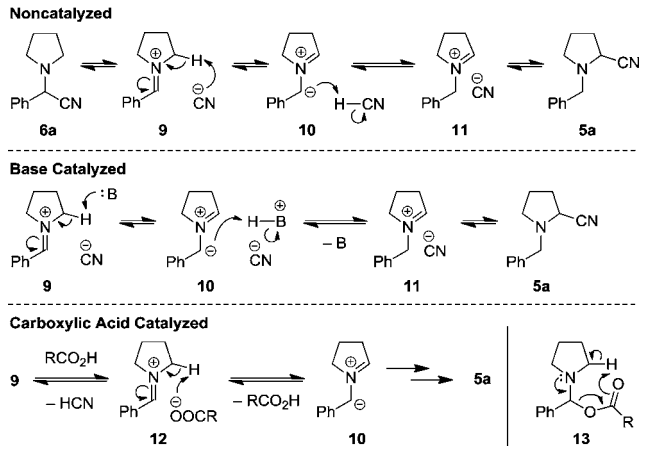


Figure 1. Potential pathways for α-aminonitrile isomerization.

The ability to generate cyclic α-aminonitriles such as **5a** from **6a**, which is readily available by standard Strecker chemistry,[11,12] would represent a significant advance as this would enable the use of simple amines as starting materials in place of amino acids. As outlined in Figure 1, a number of potential pathways can be considered that would result in the desired isomerization process.

α-Aminonitrile **6a** may isomerize to **5a** simply by heating in the absence of any additives (noncatalyzed pathway). Iminium ion **9**, which is expected to be present in low equilibrium concentrations, could be transformed into azomethine ylide **10** via iminium α-deprotonation by the relatively basic cyanide counteranion. The thus formed HCN would subsequently

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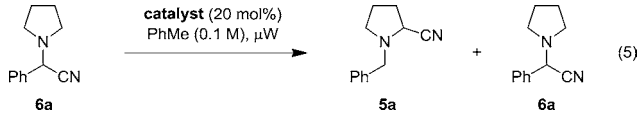
protonate azomethine ylide **10** at the benzylic position, resulting in the formation of the new iminium ion **11**, the direct precursor of α-aminonitrile **5a**.[13,14] A base catalyzed pathway can be envisioned as a variation of this isomerization process. In this case, similar intermediates are accessed with the difference being that the initial deprotonation of iminium ion **9** is achieved by an external base more basic than cyanide.

The perhaps most promising approach for α-aminonitrile isomerization is a carboxylic acid catalyzed pathway (Figure 1). Here, the cyanide anion of **9** is protonated by a carboxylic acid catalyst to form iminium ion **12**. The carboxylate anion could subsequently deprotonate the iminium α-proton to give azomethine ylide **10** which goes on to form α-aminonitrile **5a**. Alternatively, *N*,*O*-acetal **13**, which is expected to exist in equilibrium with **12**, could eliminate carboxylic acid to form azomethine ylide **10** via a concerted pathway. A closely related mechanism was proposed by Yu et al.[15] as part of a computational investigation of Tunge's benzoic acid catalyzed formation of *N*-alkyl pyrroles from 3-pyrroline.[10i] Independently, we have recently shown by means of intramolecular [3 + 2] trapping experiments that azomethine ylides are likely intermediates in this and other carboxylic acid catalyzed redox-isomerization processes.[9d]

Different catalysts were tested in the proposed α-aminonitrile isomerization, using **6a** as a model substrate (Table 1).[16] Interestingly, brief exposure of **6a** to microwave irradiation at 200 °C led to some isomerization in the absence of any additives (entry 1). The addition of triethylamine had no discernible effect on the outcome of the isomerization (entry 2).[17] Gratifyingly, a catalytic amount of benzoic acid (20 mol %) led to almost complete isomerization to the desired α-aminonitrile **5a**. Specifically, **5a** and **6a** were isolated in an 18:1 ratio in 84% combined yield (entry 3).[18] A number of other aliphatic and aromatic carboxylic acid catalysts exhibited a very similar but slightly inferior performance (entries 4−7). Carboxylic acids with increased acidities resulted in less favorable product ratios or led to poor yields. Diphenylphosphate was completely ineffective as a catalyst (entry 11). Shorter reaction times led to lower levels of isomerization (entries 12−13), whereas prolonged exposure to microwave irradiation did not serve to improve product ratios but rather led to slightly reduced yields (entry 14). Exchange of toluene for xylenes as the solvent made virtually no difference (entry 15), whereas the degree of isomerization was substantially lower in acetonitrile (entry 16). Interestingly, very little isomerization was observed in *n*-butanol (entry 17), the solvent that was previously found to be optimal in the decarboxylative Strecker reaction. Lastly, reaction temperatures below 200 °C led to incomplete isomerization and higher temperatures resulted in partial substrate decomposition (entries 18−20). In some cases, 1,3-dibenzylpyrrole was observed as a minor byproduct of the isomerization process.[10c]

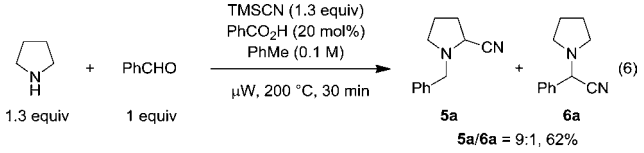
Table 1. Evaluation of Isomerization Conditions[a]



entry	catalyst	temperature [°C]	time [min]	ratio **5a**/**6a**	yield (%)
1	–	200	20	1:5	91
2	NEt_3	200	20	1:4	ND
3	$PhCO_2H$	200	20	18:1	84
4	$MeCO_2H$	200	20	10:1	84
5	2-Ethylhexanoic acid	200	20	16:1	84
6	Pivalic acid	200	20	15:1	70
7	4-MeO-benzoic acid	200	20	12:1	86
8	4-NO_2-benzoic acid	200	20	16:1	43
9	Chloroacetic acid	200	20	7:1	13
10	CF_3CO_2H	200	20	1:2	ND
11	Diphenylphosphate	200	20	<1:20	ND
12	$PhCO_2H$	200	5	11:1	90
13	$PhCO_2H$	200	10	13:1	86
14	$PhCO_2H$	200	30	17:1	77
15[b]	$PhCO_2H$	200	20	18:1	79
16[c]	$PhCO_2H$	200	20	4:1	ND
17[d]	$PhCO_2H$	200	20	1:1	ND
18	$PhCO_2H$	150	20	1:2	ND
19	$PhCO_2H$	180	20	13:1	79
20	$PhCO_2H$	250	20	9:1	41

[a]Reactions were performed on a 0.25 mmol scale. Product ratios were determined by ^{1}H NMR analysis of the crude reaction mixture. Yield corresponds to combined, isolated yields of both regioisomers. ND: not determined. [b]In xylenes. [c]In acetonitrile. [d]In *n*-butanol.

Having identified convenient conditions for α-aminonitrile isomerization, we next sought to develop a one-pot approach to the synthesis of **5a**. Upon exposing a mixture of pyrrolidine, benzaldehyde, TMSCN and benzoic acid (20 mol %) in toluene to microwave irradiation at 200 °C for 30 min, **5a** and **6a** were obtained in a 9:1 ratio and 62% combined yield (eq 6).



Upon further experimentation, we found that it is advantageous to perform the direct α-cyanation of pyrrolidine as a two- rather than three-component reaction, using readily available cyanohydrins as starting materials (eq 7). In this instance, 2-ethylhexanoic acid (2-EHA) slightly outperformed benzoic acid as the catalyst. The scope of this reaction with regard to the cyanohydrin is summarized in Table 2.

Cyanohydrins derived from aromatic aldehydes with various substitution patterns provided α-aminonitriles **5** with favorable regioselectivities and in good yields. A number of hetero-aromatic substituents were also well tolerated. Cyanohydrins derived from aliphatic aldehydes provided less favorable product ratios. This is perhaps due to a lower ionization propensity of the regular Strecker products. Interestingly, benzophenone-derived cyanohydrin provided α-aminonitrile **5p** in essentially regioisomerically pure form.

Importantly, the redox-neutral α-cyanation is applicable to amines other than pyrrolidine. For instance, piperidine readily underwent N-alkylation/α-cyanation when exposed to benzaldehyde cyanohydrin in the presence of 2-ethylhexanoic acid (eq 8). Products **14** and **15** were obtained in a favorable 15:1 ratio in 61% overall yield. An increased temperature was required in this case as a reaction performed at 200 °C provided compound **15** as the major product. Azepane underwent the corresponding reaction at 220 °C to give products **16** and **17** in an 11:1 ratio and 79% combined yield (eq 9).[19]

A reaction of tetrahydroisoquinoline with benzaldehyde cyanohydrin gave rise to predominantly one of the three

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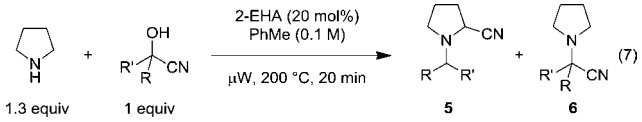
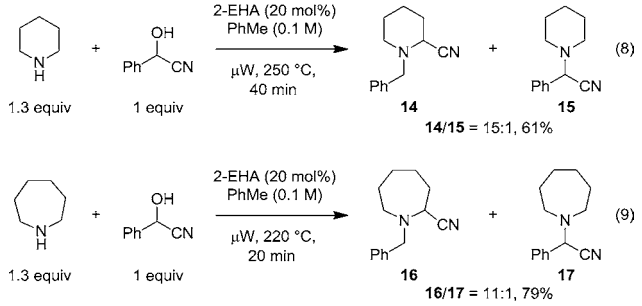
Table 2. Scope of the Direct α-Cyanation of Pyrrolidine[a]

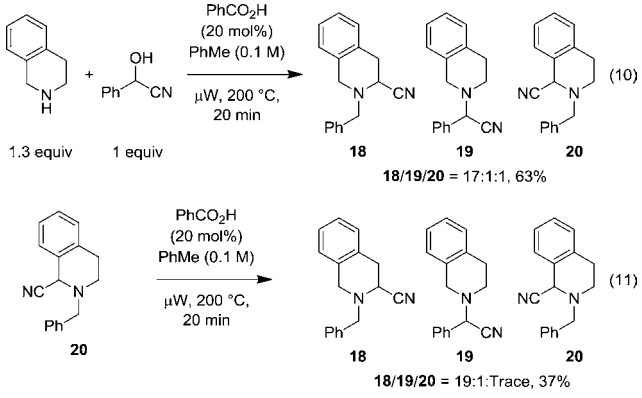


entry	R	R′	product 5/6	ratio 5/6	yield (%)
1[b]	Ph	H	**a**	18:1	86
2	4-Me-C_6H_4	H	**b**	16:1	80
3	4-MeO-C_6H_4	H	**c**	11:1	67
4	4−Cl-C_6H_4	H	**d**	>20:1	94
5[c]	4-NO_2−C_6H_4	H	**e**	1.4:1	41
6	3−Cl-C_6H_4	H	**f**	>20:1	87
7	3-Me-C_6H_4	H	**g**	19:1	79
8	2−Br-C_6H_4	H	**h**	>20:1	85
9	mesityl	H	**i**	>20:1	89
10	1-naphthyl	H	**j**	18:1	85
11	3-pyridyl	H	**k**	>20:1	60
12	2-furyl	H	**l**	20:1	64
13	2-thienyl	H	**m**	>20:1	82
14	CO_2Et	H	**n**	1:1.4	62
15	CH_2CH_2Ph	H	**o**	1:3	74
16	cyclohexyl	H	**p**	1:5	78
17[d]	Ph	Ph	**q**	>20:1	40

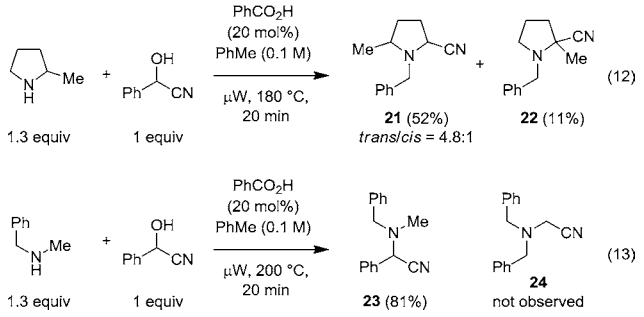
[a]See footnote (a) in Table 1. [b]Reaction time was 30 min. [c]Performed as a three-component reaction according to eq 6. No heating element was used. [d]Benzoic acid was used as the catalyst.



possible regioisomeric products (eq 10). Interestingly, **18** was isolated as the major product, resulting from the functionalization of the nonbenzylic position of the tetrahydroisoquinoline ring. This regioselectivity is complementary to what is observed in oxidative functionalizations of *N*-aryl tetrahydroiso-quinolines.[4−7] In addition to the expected products, 4-benzylisoquinoline[20] was isolated in 14% yield. To establish whether α-aminonitrile **20** could isomerize to **18** or **19**, an independently prepared sample of **20** was exposed to the previously optimized isomerization conditions (eq 11). Indeed, α-aminonitrile **18** was again obtained as the major product.[21] However, the efficiency of this process was rather poor, and 4-benzylisoquinoline was obtained as a byproduct in 17% yield.



As shown in eq 12, a reaction of 2-methyl-pyrrolidine provided a mixture of products **21** (52%, dr = 4.8:1)[22] and **22** (11%). Only trace amounts of the regular Strecker product were observed. Although acyclic α-aminonitriles are readily obtained by standard Strecker chemistry, we conducted a reaction with *N*-benzylmethylamine to probe the reactivity of this substrate class (eq 13). In this instance, **23** was obtained as the sole product in 81% yield.



In summary, we have introduced a conceptually new strategy for the direct α-cyanation of amines, a reaction that provides rapid access to synthetically valuable α-aminonitriles not accessible by traditional Strecker chemistry. The overall transformation was rendered redox-neutral via the combination of a reductive N-alkylation with an oxidative α-functionalization. Further applications of this uncommon mode of azomethine ylide reactivity are the subject of ongoing investigations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(15) Xue, X. S.; Yu, A.; Cai, Y.; Cheng, J. P. *Org. Lett.* **2011**, *13*, 6054.

(16) Microwave reactions were conducted in the presence of a silicon carbide heating element. See the Supporting Information for details.

(17) Yields were not determined in most instances where poor selectivities were observed.

(18) This reaction appears to be under thermodynamic control as the same ratio of product isomers was obtained when **5a** was exposed to identical reaction conditions.

(19) Preliminary experiments with morpholine and *N*-Ph-piperazine have provided mostly regular Strecker products.

(20) Dannhardt, G.; Roelcke, J. *Arch. Pharm.* **1992**, *325*, 671.

(21) Preliminary computational studies indicate that **18** is the thermodynamically most stable of the three regioisomers. See the Supporting Information for details.

(22) Analysis of the crude reaction mixture indicated that product **21** was initially obtained as a 1.8:1 mixture of *trans*- and *cis*-diastereomers. Apparently, partial isomerization to the major *trans*-isomer occurred during chromatographic purification.