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The Decarboxylative Strecker Reaction

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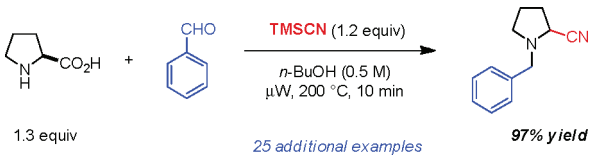
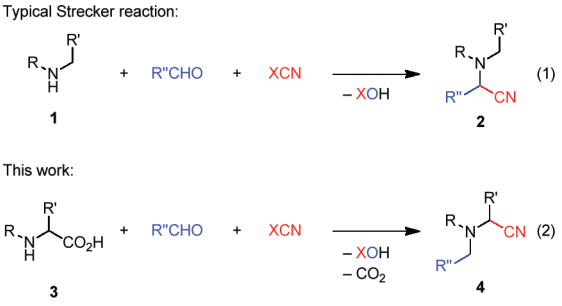
ABSTRACT



α-Amino acids react with aldehydes in the presence of a cyanide source to form α-amino nitriles in what can be considered a decarboxylative variant of the classical Strecker reaction. This unprecedented transformation does not require the use of a metal catalyst and provides facile access to valuable α-amino nitriles that are inaccessible by traditional Strecker chemistry.

First reported in 1850,[1] the Strecker reaction remains of considerable interest as a valuable tool for the construction of α-amino nitriles, exceptionally versatile precursors to amino acids and various other building blocks.[2,3] While the original Strecker reaction used ammonia, a variety of other amines have been employed. In a prototypical Strecker reaction, an amine **1** is condensed with an aldehyde in the presence of a cyanide source to give product **2** (eq 1). Here we report that α-amino acids **3** react with aldehydes and different sources of cyanide to form α-amino nitriles **4** in a remarkably facile fashion (eq 2). This unprecedented decarboxylative variant of the Strecker reaction provides rapid access to valuable α-amino nitriles not accessible via traditional Strecker chemistry.



Transition metal catalyzed decarboxylative C–C bond formations have recently emerged as a valuable synthetic strategy that enables a variety of useful transformations.[4] In the context of metal-free decarboxylative C–C bond formation, the condensation of α-amino acids with various

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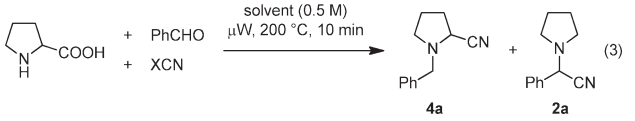
aldehydes or ketones has long been recognized to lead to the formation of azomethine ylides.[5] These reactive dipolar intermediates have seen tremendous use in synthesis. However, despite their utility, the chemistry of azomethine ylides has largely been limited to pericyclic reactions such as inter- and intramolecular [3 + 2] cycloadditions as well as 1,5- and 1,7-electrocyclizations.[6] An early example of a nonpericyclic reaction of azomethine ylides was reported by Cohen et al. in 1979, namely the reaction of proline with sterically congested 2-hydroxyacetophenones to form *N*, *O*-acetals.[7] As part of our efforts to develop redox-neutral[8] reaction cascades for the rapid buildup of molecular complexity,[9] we recently reported decarboxylative three-component coupling reactions of α-amino acids and aldehydes with indoles, naphthols, and nitroalkanes.[9e,10] In addition, we[9e] and the group of Li[11] independently reported a copper catalyzed decarboxylative alkynylation of α-amino acids. In other work, we were able to show that related intramolecular reactions enable a rich azomethine ylide annulation chemistry.[9g,12] These reactions are thought to proceed through protonation of the intermediate azomethine ylide by a pronucleophile (e.g., indole), resulting in the formation of iminium ion pairs that ultimately give rise to the products.

Table 1. Evaluation of Reaction Parameters[a]



entry	proline (equiv)	solvent	XCN (equiv)	ratio **4a**:**2a**	yield (%)
1	2.0	PhMe	TMSCN (1.2)	**4a** only	81
2	1.5	PhMe	TMSCN (1.2)	28:1	90
3	1.5	PhMe	TMSCN (1.1)	17:1	89
4	1.3	PhMe	TMSCN (1.2)	5:1	81
5	1.2	PhMe	TMSCN (1.2)	4:1	77
6	1.5	*n*-BuOH	TMSCN (1.2)	**4a** only	>97
7	1.3	*n*-BuOH	TMSCN (1.2)	**4a** only	>97
8	1.2	*n*-BuOH	TMSCN (1.2)	31:1	>97
9	1.5	xylenes	TMSCN (1.2)	17:1	>97
10	1.5	*n*-BuOH	CuCN (1.2)	N/A	Trace
11	1.5	*n*-BuOH	KCN (1.2)	**4a** only	53
12	1.5	*n*-BuOH	$K_3[Fe(CN)_6]$ (1.2)	**4a** only	8
13	1.5	*n*-BuOH	EtOCOCN (1.2)	5:1	55

[a] Reactions were performed on a 1 mmol scale.

We reasoned that azomethine ylides may be converted to valuable Strecker-type products if they were exposed to an appropriate source of cyanide. Consequently, we decided to investigate this possibility by allowing proline and benzaldehyde to react in the presence of various cyanide sources. Conventional thermal reaction conditions were initially evaluated but quickly abandoned in favor of reactions performed under microwave irradiation, as the latter led to vastly accelerated reaction rates. The results of this survey are summarized in Table 1. Gratifyingly, the reaction proceeded as anticipated and the desired regioisomer **4a** was consistently formed as the predominant product, with only small amounts of **2a** being obtained.[13−15] In favorable cases, the formation of **2a** could be suppressed completely. Although various sources of cyanide including simple potassium cyanide enabled product formation, the use of

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trimethylsilyl cyanide (TMSCN) was found to be most convenient. Under optimized microwave conditions, the reaction of benzaldehyde, 1.3 equiv of proline, and 1.2 equiv of TMSCN in *n*-butanol as the solvent gave rise to product **4a** as the only detectable regioisomer in near-quantitative yield (>97%, entry 7). A particularly attractive feature of this reaction is the brief reaction time, requiring only 10 min for completion. In comparison, an otherwise identical reaction conducted under reflux in *n*-butanol for 5 h provided **4a** in 64% yield.

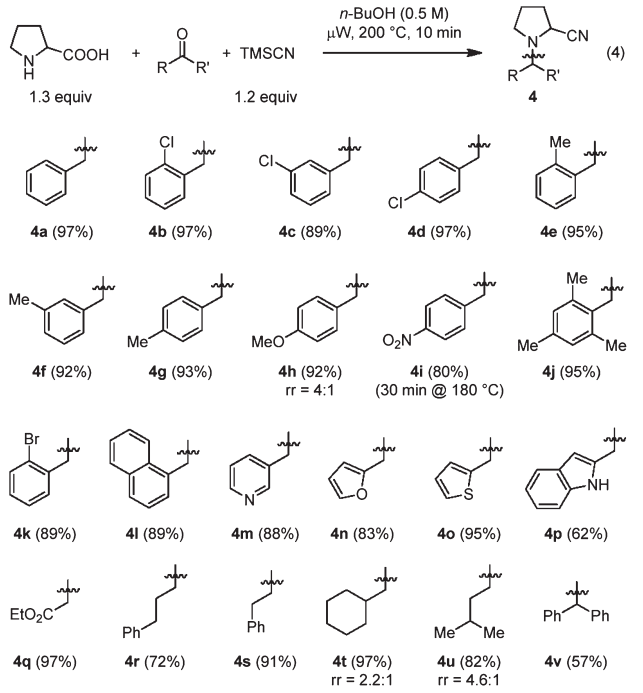
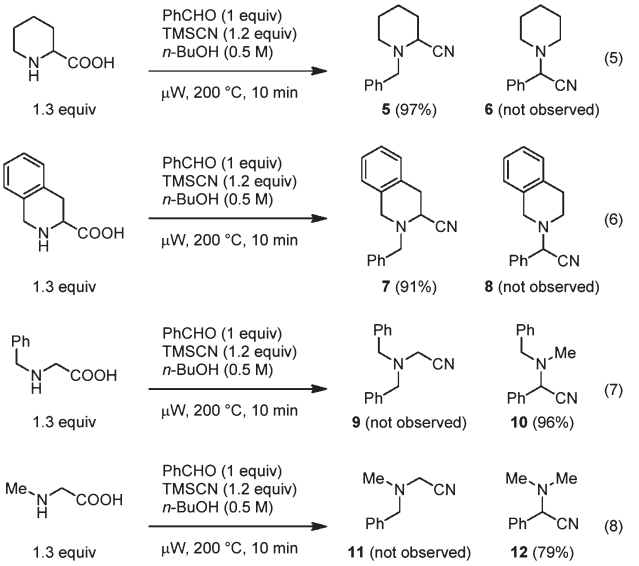


Figure 1. Scope of the decarboxylative Strecker reaction with proline.

With the optimized reaction conditions in hand, a series of different aldehydes was evaluated (Figure 1). Only one regioisomer was detected in all cases in which no regioisomeric ratio (rr) is given. Electron-rich and electron-poor aromatic aldehydes with different substitution patterns provided products in generally excellent yields. Heteroaromatic aldehydes derived from pyridine, furan, thiophene, and indole were also viable substrates. Ethyl glyoxylate and enolizable aliphatic aldehydes also engaged in reactions with proline and TMSCN to give the desired α-amino nitriles. Benzophenone, although apparently less reactive under these conditions, provided the corresponding product in moderate yield.

Next, we sought to expand the substrate scope to α-amino acids other than proline. Gratifyingly, the analogous reaction with pipecolic acid as outlined in eq 5 provided the desired product **5** as the only detectable regioisomer in near-quantitative yield. The corresponding reaction of tetrahydroisoquinoline-3-carboxylic acid provided the expected product **7** in 91% yield (eq 6). As shown



in eqs 7 and 8, single regioisomeric products were also obtained in reactions of *N*-benzyl glycine and *N*-methyl glycine (sarcosine). Interestingly, products **10** and **12** represent the opposite regioisomers to those obtained with cyclic amino acids. This finding most likely reflects the different reactivity of the corresponding azomethine ylides and their individually preferred protonation sites.

Further analysis of the results displayed in Table 1, in particular a comparison of entries 1, 2, 4, and 5, revealed the striking observation that the regioisomeric ratios of **4a** and **2a** are apparently dependent on the amount of proline used. An increase of the equivalents of proline resulted in a gradual increase of the regioisomeric ratio favoring the desired product **4a**, up to the point where **2a** could no longer be detected. An attempt to rationalize this finding is provided in Figure 2. Under the reaction conditions, regioisomer **2a** may be in equilibrium with small amounts of the ion pair **2a′**. Interception of **2a′** by proline and the associated formation of pyrrolidine could thus be a pathway for regioisomeric enrichment. A sufficient amount of proline could thus lead to complete consumption of undesired **2a**.

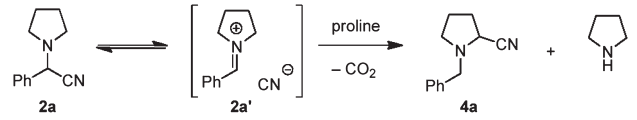
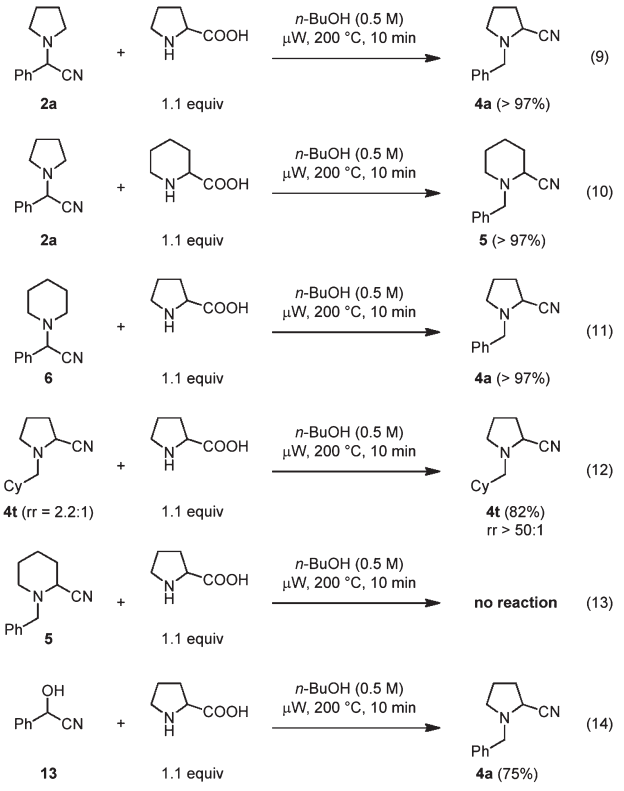


Figure 2. Proposed pathway for regioisomeric enrichment.

To establish whether the mechanism depicted in Figure 2 is indeed operative, a number of control experiments were performed (eqs 9–13). Compound **2a** was exposed to a slight excess of proline (1.1 equiv) under the previously established reaction conditions (eq 9). In line with the

above considerations, amino nitrile **4a** was obtained as the only product in near-quantitative yield.



Replacement of proline for pipecolic acid in an otherwise identical experiment led to the exclusive formation of **5** (eq 10), establishing the role of the amino acid in this process. Likewise, starting from **6** and proline, **4a** was obtained exclusively (eq 11). As implied above, this strategy can be applied to the adjustment of product distribution in reactions that are intrinsically less regioselective. For instance, a 2.2:1 mixture of the cyclohexanecarbaldehyde derived product **4t** and its corresponding regioisomer provides regioisomerically pure **4t** upon treatment with proline (eq 12). As may have been anticipated, a control experiment in which **5** was exposed to an excess of proline led to no reaction (eq 13). As an interesting and related side note, the reaction of cyanohydrin **13** and proline also yielded product **4a** in 75% yield (eq 14). This unoptimized process should provide an intriguing avenue for future inquiry.

As alluded to earlier, α-amino nitriles are extremely versatile compounds and their use extends beyond the synthesis of amino acids.[3] For instance, compound **4a** was recently used by Rychnovsky et al. as a precursor in an intriguing reductive lithiation/intramolecular carbolithiation process.[16] Another particularly useful transformation specific to α-amino nitriles is the Bruylants reaction, which offers the opportunity to replace the cyano group for aryl or alkyl groups.[17,18] Accordingly, α-amino nitrile **4a**, which to our knowledge had not previously been used in Bruylants reactions, readily engaged in reactions with phenyl magnesium bromide or *n*-butyl magnesium bromide to form products **14** and **15** in good yields (Figure 3).

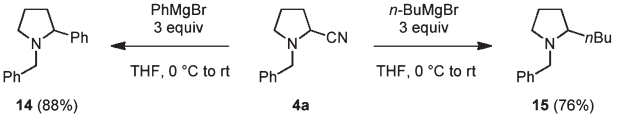


Figure 3. Product modification via the Bruylants reaction.

In summary, we have introduced a decarboxylative variant of the classical Strecker reaction. Due to the versatility of the resulting α-amino nitriles, compounds whose accessibility has now been markedly improved, this new method is expected to find widespread use in synthesis.

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

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