

Lewis Base-catalyzed Three-Component Strecker Reaction On Water. An Efficient Manifold for the Direct α -Cyanoamination of Ketones and Aldehydes

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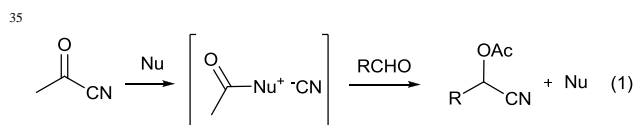
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The first three-component organocatalyzed Strecker reaction operating on water has been developed. The manifold utilizes ketones (aldehydes) as the starting carbonyl component, aniline as the primary amine, acetyl cyanide as the cyanide source and N,N-dimethyl cyclohexylamine as the catalyst.

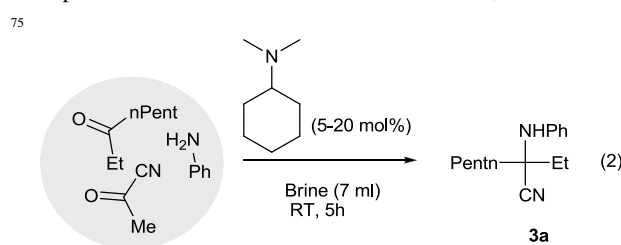
The three-component reaction of an aldehyde or ketone, a primary amine and a cyanide ion, (Strecker reaction, S-3CR),¹ constitutes one of the most efficient manifolds for the synthesis of α -amino nitriles, versatile precursors of α -amino acids.² Since its discovery in 1850, a large survey of modified reaction conditions and different cyanating agents has been described.³ In spite of these advances, the development of simple, efficient and general multicomponent manifolds utilizing ketones remains a challenge.⁴ During the last two years, some interesting advances have been reported including solvent-free systems,⁵ gallium (III) triflate catalyzed reactions,⁶ the use of fluororous solvents,⁷ solid acid catalysts⁸ and high pressures.⁹ However, all of them utilize toxic and expensive trimethyl silyl cyanide (TMSCN) as the cyanide source and only three of them display a wide ketone scope (iron,^{5b} gallium⁶ and solid acid⁸ catalyzed reactions). Acyl cyanides¹⁰ have emerged as less toxic and efficient alternatives to TMSCN (eqn (1)).¹¹ Therefore, its use in catalytic S-3CR involving ketones remains an unsolved challenge.^{11a} Among other possibilities, the development of water-compatible S-3CR manifolds involving this reagent and ketones would be advantageous.



A large list of examples in recent chemical literature shows that organic reactions performed at the interface organic-water (on water)¹² are not only typically faster but also display novel reactivity profiles and selectivity.¹³ A theoretical model based on the unique structure of the water-organic interface has been recently postulated to explain this effect.¹⁴ The model relates these effects with the special structure of water at the oil-water interface, which maintains an approximately 25% of water molecules in the form of tri-coordinated water, with their free OH group protruding into the organic phase.¹⁴ The unmet hydrogen bonding demand of these tri-coordinated water molecules on the surface of the water phase provides an immediate energy

advantage to the reactants capable of generating hydrogen bonding for catalysis. We hypothesized that the S-3CR of lipophilic ketones with primary amines and acetyl cyanide could be one of such catalyzed reactions on water because: 1) ketimines (intermediates) are expected to form stronger and better H-bonds than their parent ketones (reactants) (selective ketimine activation); 2) ketimine formation is catalyzed by H-bond interactions (carbonyl activation); 3) cyanide generation involving Lewis base catalysis is expected to be H-bond favored (increased carbonyl reactivity). As a proof of concept, we report herein the first Lewis base-catalyzed S-3CR of ketones operating on water. The manifold utilizes a tertiary amine as the catalyst, acetyl cyanide as the cyanide source and aniline as the primary amine. To the best of our knowledge, no precedents for this base-catalyzed MCR have been reported to date.

We accordingly begun our investigation studying the multicomponent reaction of 3-octanone (**2a**) with aniline and acetyl cyanide in the presence of catalytic amounts of lipophilic N,N-dimethyl cyclohexylamine, (a common structural component of many Lewis base-based organocatalysts), under on water conditions (eqn (2)). Because hydrophobic effects are known to play an important role in the reactions performed at the water surface, we directly used brine instead of water as the reaction medium. Thus, the vigorous stirring of a salt-saturated aqueous suspension of stoichiometric mixtures of ketone, aniline and



acetyl cyanide and 20 mol% of the tertiary amine, afforded, after 5h at room temperature, the corresponding α -aminonitrile derivative **3a** in 49% yield. Because acetyl cyanide is known to afford base-catalyzed homo-O-acylation with release of one unit of cyanide anion,^{10b} we increased the amount of this reactant to two equivalents. Under these new conditions, the multicomponent reaction turned almost quantitative ($\geq 95\%$ yield). Remarkably, the reaction did not produce N-acylated α -aminonitriles which indeed constitute the main products in organic media using this cyanide source.¹¹ Other tertiary amines spanning different pKa's and lipophobicities (N,N-diisopropyl

ethylamine, DABCO, pyridine and quinine) were also good catalysts for this reaction (see ESI for details). Further experimentation showed that the catalyst charge could be reduced to a more practical 5 mol% without yield erosion. Finally, the efficiency of the manifold was considerably reduced in the absence of catalyst, affording product **3a** in less than 10% yield.

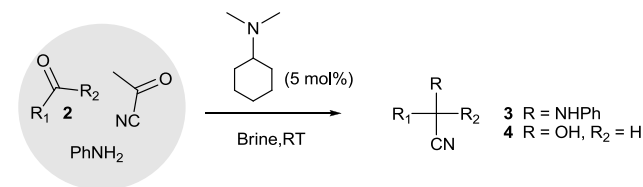
Once the experimental conditions were standardized, we next studied the scope of this S-3CR with regard to the ketone (Table 1). Both aromatic and aliphatic cyclic or acyclic ketones were good substrates for this reaction. Acyclic ketones were conveniently transformed into the α -aminonitrile derivatives with independence of the chain length (entries 1-7). Branched aliphatic ketone **2d** afforded the corresponding α -aminonitrile **3d** in good yield (entry 5). Ketone **2h** featuring a cyclohexane ring and a phenyl ring showed a diminished reactivity affording compound **3h** in low yield and under a prolonged reaction time (entry 9). Even acetophenone (**2g**), a scarcely reactive ketone, gave the corresponding cyanoamination product **3g** in good yield (entry 8). Most reactive cyclic ketones proved to be excellent substrates for this manifold (entries 10-11). Remarkably, products coming from the C-acylation of the enamine tautomer of the ketimine intermediate were not detected under these standardized conditions. Finally, the manifold could be performed at a 25 mmol scale without a severe erosion of yield (entry 2).

Encouraged by these results we extended our findings to the S-3CR with aldehydes. Although a large array of methodologies are available for this reaction,³ water-compatible multicomponent manifolds remain significantly less explored.¹⁵ Under the same experimental conditions, a wide set of aldehydes could be transformed into the corresponding α -aminonitrile derivatives by the three-component manifold (Table 1, entries 12-21). Both aliphatic and aromatic aldehydes **2k-t** were efficiently transformed into the corresponding α -aminonitriles **3k-t** in a high overall average yield. Even acetaldehyde (**2k**), a hydrophilic aldehyde, could be transformed into the corresponding aminonitrile **3k** in a modest-good yield (entry 12). A chain effect was observed with aldehyde **2p** featuring a linear C₁₀ carbon alkyl chain. After 1h of reaction, only 30% of the corresponding cyanoamination compound **3p** could be obtained (entry 17). This chain length seems to be large enough to induce hydrophobic associations affording reduced aldehyde reactivity. On the other hand, heptanal (**2o**), featuring a linear C₆ carbon alkyl chain, generated compound **3o** in very good yield (entry 16). Aromatic aldehydes **2s-t** were fully transformed into the corresponding products **3s-t** practically in quantitative yield (entries 20-21). Remarkably, we could not detect the formation of cyanohydrins **4** coming from a competitive addition of cyanide on the starting aldehydes (see ESI for details). This observed chemoselectivity reinforces our previous hypothesis that the imines would form stronger and better H-bonds than aldehydes or ketones with the H-bond network of the tri-coordinated structural water molecules at the interface, and therefore, they would be more reactive than their parent carbonyl compounds (selective imine activation).

The effect of the hydrophobicity associated with the primary amine was studied using the reaction of acetophenone (**2g**) and aniline, 4-n-butoxyaniline and 4-n-heptylaniline as the amine sources. Under the standardized conditions, the more lipophilic 4-n-butoxy and 4-n-heptylanilines showed a higher efficiency

than aniline, affording the corresponding α -cyanoamination compounds in practically quantitative yields (71% yield using aniline).

Table 1. N,N-dimethyl cyclohexylamine catalyzed S-3CR on brine.



Entry	R ¹	R ²	Product	Time	Yield (%) ^a	
1	Et	<i>n</i> Pent	2a	3a	5h	≥95
2	„	„	„	„	48h	62 ^b
3	Me	Me	2b	3b	5h	≥95
4	Me	Et	2c	3c	„	90
5	Me	<i>i</i> Pr	2d	3d	„	78
6	Et	Et	2e	3e	„	85
7	<i>n</i> Pr	<i>n</i> Pr	2f	3f	„	≥95
8	Me	Ph	2g	3g	24h	71
9	<i>c</i> Hex	Ph	2h	3h	„	13
10		-(CH ₂) ₄ -	2i	3i	5h	89
11		-(CH ₂) ₅ -	2j	3j	„	≥95
12	Me	H	2k	3k	1h	65
13	Et	H	2l	3l	„	≥95
14	<i>n</i> Pr	H	2m	2m	„	83
15	<i>i</i> Pr	H	2n	3n	„	92
16	<i>n</i> Hex	H	2o	3o	„	82
17	<i>n</i> Dec	H	2p	3p	„	30
18	3-Ph-propanal		2q	3q	„	70
19	<i>c</i> Hex	H	2r	3r	„	86
20	Ph	H	2s	3s	„	≥95
21	<i>p</i> -anisaldehyde		2t	3t	„	≥95

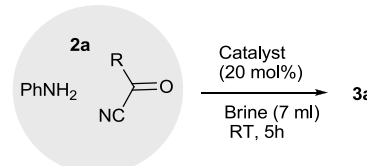
^a Yields of analytically pure products. ^b Ketone (25 mmol), aniline (25 mmol), acetyl cyanide (50 mmol), N,N-dimethyl cyclohexylamine (5 mol%), brine (250 ml), RT. Non optimized yield

The basic character of this catalyzed S-3CR was confirmed by the following experimental facts:

- 1) Manifold requires two equivalents of acyl cyanide to be effective, which is coherent with a cyanide anion release launched by a Lewis base-catalyzed dimerization process,¹⁰ and it rules out a direct cyanide anion release by nucleophilic attack of the Lewis base on the acyl center of the reagent (eqn (1)) or through an alternative base-catalyzed ketene formation.
- 2) The highly basic and non-nucleophilic N,N-diisopropyl ethylamine catalyzes the reaction of **2a** with aniline, generating the cyanoamination compound **3a** in 85% yield (Table 2, entry 1).
- 3) Substitution of acetyl cyanide by the less α -CH acidic butyryl cyanide raises the pK_a's threshold for the catalyst: while pyridine roughly catalyzes the reaction (12%), the more basic N,N-dimethyl cyclohexylamine affords product **3a** with moderate-to-good efficiency (69%) (Table 2, entries 2 and 3). Observe that in the absence of catalyst, the manifold still generates a background amount of α -amino nitrile **3a** (≤10%) (entry 4). If we compare the yields in the absence of catalyst (acetyl cyanide) and that obtained with pyridine (butyryl cyanide), both are in the same range; that is, they represent the background yield for the non-catalyzed S-3CR. Finally, benzoyl cyanide, lacking α -protons,

drastically reduces the efficiency of the manifold to the background level ($\leq 10\%$) (entry 5).

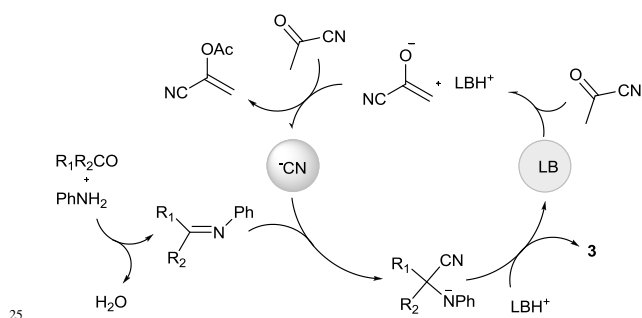
Table 2. Basic character of the S-3CR manifold.



Entry	R	Catalyst	Yield (%) ^a
1	Me	N,N-diisopropyl ethylamine	85
2	nPr	N,N-dimethyl cyclohexylamine	69
3	nPr	Pyridine	12
4	Me	None	≤ 10
5	Ph	N,N-dimethyl cyclohexylamine	≤ 10

^a Yields of analytically pure products.

A mechanistic proposal accounting for the experimental results is outlined in Scheme 1. The ketone (aldehyde) reacts with the primary amine to give the corresponding ketimine (aldimine). To be chemically efficient, this reaction requires a dehydrating agent to shift the equilibrium toward the imine product. Herein, the own manifold realizes this task removing the water generated in the condensation from the organic phase (drop) to the bulk water, shifting the ketone-imine equilibrium toward the imine side. This counterintuitive physicochemical behaviour is very remarkable and it offers a powerful manner to perform “dry” organic chemistry in water. Next, the imine reacts with the cyanide anion generated in the Lewis base-catalyzed dimerization of acetyl cyanide to give the corresponding amide intermediate, which in turn is neutralized by the Lewis base conjugated acid to give the α -amino nitrile derivative **3** with regeneration of the Lewis base to reinitiate the cycle.



Scheme 1. A mechanistic proposal. (LB = Lewis base)

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Notes and references

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- † Electronic Supplementary Information (ESI) available: experimental section and physical data for compounds **3h**. See DOI: 10.1039/b000000x/
⁵⁰ ‡ General procedure. To a stirred (250 rpm) salt-saturated aqueous solution (brine) (7ml) is sequentially added acetyl cyanide (1.4 mmol), N,N-dimethyl cyclohexylamine (0.035 mmol), carbonyl compound **2a** (0.70 mmol) and aniline (0.70 mmol)(dropwise) to form a biphasic system. The stirring rate is increased to 1200 rpm and after a few minutes, the biphasic system breaks into small drops. After 5 h (1h for aldehydes) the reaction is quenched by addition of dichloromethane and the organic materials are recovered in dichloromethane. Concentration and flash chromatography (ethyl acetate-hexanes: 20/80) yields pure compound **3a**: oil, ¹H NMR (400 MHz, CDCl₃): δ = 0.91 (t, ³J(H,H)=7 Hz, 3H), 1.07 (t, ³J(H,H)=7.5 Hz, 3H), 1.29-1.39 (m, 4H), 1.45-1.58 (m, 2H), 1.82-2.08 (m, 2H), 3.5 (bs, NH), 6.86-6.95 (m, 3H), 7.21-7.28 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ = 8.0, 13.9, 22.4, 23.6, 30, 31.6, 36.6, 57.3, 117.1, 120.3, 121.1, 129.3 (x3C), 143.8; IR (CHCl₃, cm⁻¹): 3431 (NH), 2230,5 (CN); Anal. Calcd. for C₁₅H₂₂N₂: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.02; H, 9.79; N, 12.06.
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