Lewis base-catalyzed three-component Strecker reaction on water. An efficient manifold for the direct α-cyanoamination of ketones and aldehydes†

Fabio Cruz-Acosta,[ab] Alicia Santos-Expósito,[a] Pedro de Armas*[ab] and Fernando García-Tellado*[ab]

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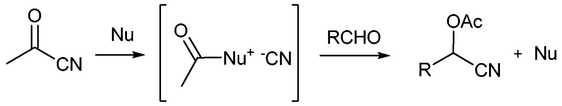
The first three-component organocatalyzed Strecker reaction operating on water has been developed. The manifold utilizes ketones (aldehydes) as the starting carbonyl component, aniline as the primary amine, acetyl cyanide as the cyanide source and *N*,*N*-dimethylcyclohexylamine as the catalyst.

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-aminonitriles, 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 fluorous solvents,[7] solid acid catalysts[8] and high pressures.[9] However, all of them utilize toxic and expensive trimethylsilyl cyanide (TMSCN) as the cyanide source and only three of them display a wide ketone scope (iron,[5b] gallium[6] and solid acid[8] catalyzed reactions). Acyl cyanides[10] have emerged as less toxic and efficient alternatives to TMSCN (eqn (1)).[11] Therefore, its use in the 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.



(1)

A large list of examples in the recent chemical literature shows that organic reactions performed at the organic–water interface (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 approximately 25% of the 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 liphophilic ketones with primary amines and acetyl cyanide could be one such catalyzed reaction 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.

Accordingly, we began our investigation studying the multicomponent reaction of 3-octanone (**2a**) with aniline and acetyl cyanide in the presence of catalytic amounts of liphophilic *N*,*N*-dimethylcyclohexylamine, (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 reactions performed at the water surface, we used brine instead of water as the reaction medium. Thus, 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 5 h 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 became almost quantitative (≥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 pK_a's and lipophobicities (*N*,*N*-diisopropylethylamine, DABCO, pyridine and quinine) were also good catalysts for this reaction (see the ESI for details†).

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[a] *Department of Química Biológica y Biotecnología, Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas, Astrofísico Francisco Sánchez 3, 38206 La Laguna-Tenerife, Spain. E-mail: fgarcia@ipna.csic.es, parmas@ipna.csic.es; Fax: (+34) 922-260135;*
Web: http://www.ipna.csic.es/departamentos/qbb/qb/
[b] *Instituto Canario de Investigación del Cáncer, Spain*
Web: www.icic.es

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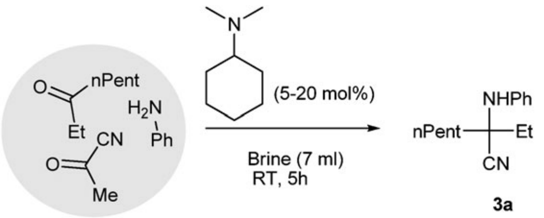
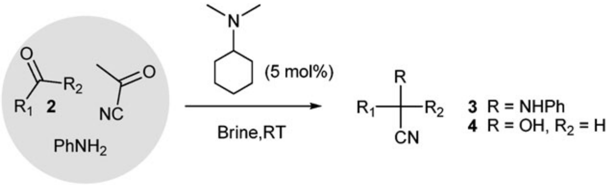
Further experimentation showed that the catalyst charge could be reduced to a more practical 5 mol% without yield erosion. Finally, the efficiency of the manifold was considerably reduced in the absence of catalyst, affording product **3a** in less than 10% yield.



(2)

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, independent 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 poorly 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–3t** in a high overall average yield. Even acetaldehyde (**2k**), a hydrophilic aldehyde, could be transformed into the corresponding aminonitrile **3k** in a modest-to-good yield (entry 12). A chain effect was observed with aldehyde **2p** featuring a linear C_{10} carbon alkyl chain. After 1 h 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 C_6 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 the 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).

Table 1 *N*,*N*-dimethylcyclohexylamine-catalyzed S-3CR on brine



Entry	R^1	R^2		Product	Time/h	Yield (%)[a]
1	Et	*n*Pent	**2a**	**3a**	5	≥ 95
2	Et	*n*Pent	**2a**	**3a**	48	62[b]
3	Me	Me	**2b**	**3b**	5	≥ 95
4	Me	Et	**2c**	**3c**	5	90
5	Me	*i*Pr	**2d**	**3d**	5	78
6	Et	Et	**2e**	**3e**	5	85
7	*n*Pr	*n*Pr	**2f**	**3f**	5	≥ 95
8	Me	Ph	**2g**	**3g**	24	71
9	*c*Hex	Ph	**2h**	**3h**	24	13
10	$-(CH_2)_4-$		**2i**	**3i**	5	89
11	$-(CH_2)_5-$		**2j**	**3j**	5	≥ 95
12	Me	H	**2k**	**3k**	1	65
13	Et	H	**2l**	**3l**	1	≥ 95
14	*n*Pr	H	**2m**	**2m**	1	83
15	*i*Pr	H	**2n**	**3n**	1	92
16	*n*Hex	H	**2o**	**3o**	1	82
17	*n*Dec	H	**2p**	**3p**	1	30
18	3-Ph-propanal		**2q**	**3q**	1	70
19	*c*Hex	H	**2r**	**3r**	1	86
20	Ph	H	**2s**	**3s**	1	≥ 95
21	*p*-anisaldehyde		**2t**	**3t**	1	≥ 95

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

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).

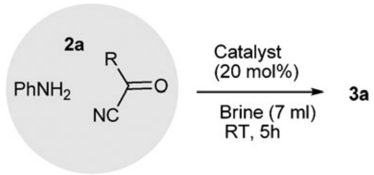
The basic character of this catalyzed S-3CR was confirmed by the following experimental facts:

(1) The 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*-diisopropylethylamine catalyzes the reaction of **2a** with aniline, generating the cyanoamination compound **3a** in 85% yield (Table 2, entry 1).

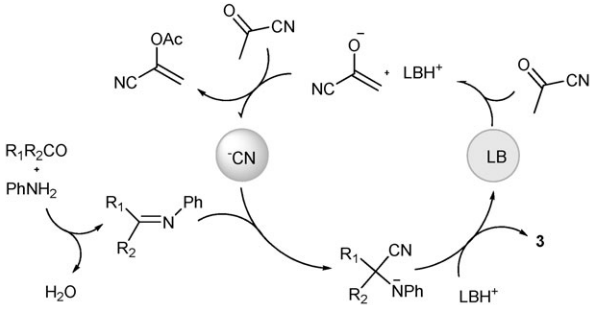
(3) Substitution of acetyl cyanide by the less α-CH acidic butyryl cyanide raises the pK_a's threshold for the

Table 2 Basic character of the S-3CR manifold



Entry	R	Catalyst	Yield (%)[a]
1	Me	*N*,*N*-diisopropylethylamine	85
2	*n*Pr	*N*,*N*-dimethylcyclohexylamine	69
3	*n*Pr	Pyridine	12
4	Me	None	≤ 10
5	Ph	*N*,*N*-dimethylcyclohexylamine	≤ 10

[a] Yields of analytically pure products.



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

catalyst: while pyridine roughly catalyzes the reaction (12%), the more basic *N*,*N*-dimethylcyclohexylamine 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** ($\leq$10%) (entry 4). If we compare the yields in the absence of catalyst (acetyl cyanide) and that obtained with pyridine (butyryl cyanide), both are in the same range; that is, they represent the background yield for the non-catalyzed S-3CR. Finally, benzoyl cyanide, lacking α-protons, drastically reduces the efficiency of the manifold to the background level ($\leq$10%) (entry 5).

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 towards 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.

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Notes and references

‡ General procedure. To a stirred (250 rpm) salt-saturated aqueous solution (brine) (7 ml) is sequentially added acetyl cyanide (1.4 mmol), *N*,*N*-dimethylcylclohexylamine (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 (1 h 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, ^{1}H NMR (400 MHz, CDCl$_3$): 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); ^{13}C NMR (100 MHz, CDCl$_3$) δ = 8.0, 13.9, 22.4, 23.6, 30, 31.6, 36.6, 57.3, 117.1, 120.3, 121.1, 129.3 (×3C), 143.8; IR (CHCl$_3$, cm^{-1}): 3431 (NH), 2230,5 (CN); Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.02; H, 9.79; N, 12.06.

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