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Uncatalyzed Strecker-Type Reaction of *N*,*N*-Dialkylhydrazones in Pure Water

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Aldehyde and ketone *N*,*N*-dialkylhydrazones behave as a stable class of imine surrogates exhibiting a unique reactivity in the Strecker reaction with in situ generated HCN, that proceeds in pure water in the absence of co-solvents, catalysts or promoters. Experimental evidence suggests that the reaction is assisted by an intramolecular activation of HCN by the dialkyl amino lone pair.

Introduction

The development of environment-friendly organic reactions (green chemistry) is a very active field of research, emerged as a response to the increasing regulatory pressure directed to the elimination/reduction of chemical waste.[1] Implementation of methods that avoid the use of organic solvents and/or metal-based catalysts are fundamental strategies in this field. Among the alternative reaction media, reactions that can be performed in pure water are particularly valuable,[2] also for the added economical benefit.

The Strecker reaction is an industrially relevant reaction useful for the synthesis of α-amino nitriles, direct precursors of α-amino acids.[3] Due to the limitations of the original method, this reaction is generally carried out in organic solvents, by the nucleophilic addition of HCN or TMSCN to imines **1** (preformed or not) using different Lewis acid or base catalysts.[4] There are also reports of Strecker reactions performed in aqueous media,[5] including water-containing DMF,[6] polyethylene glycol/water (2:1),[7] and β-cyclodextrin in water/methanol (9:1).[8] The $Sc(OTf)_3$-catalyzed one-pot Strecker reaction from aldehydes and benzhydrylamine takes place in pure water, but toxic tributyltin cyanide is required as the reagent.[9] Strecker-type reactions in ionic liquids have also been recently reported,[10] but this approach has obvious economic disadvantages and ionic liquids are not free of toxicity[11] and biodegradability[12] issues.

One of the limitations of the Strecker reaction is related to the instability, difficult preparation and storage of the imine substrates **1**, in particular in the aliphatic series. Thanks to their higher stability, *N*-acylhydrazones **2** and *N*,*N*-dialkylhydrazones **3** (Figure 1) are privileged substrates that have been used as imine surrogates in reactions with cyanide, HCN, or TMSCN using a variety of catalysts or promoters. For instance, compounds **2** have been activated by phase-transfer catalysts,[13] (PYBOX)lanthanide complexes,[14] or a combination of a Brønsted base and a Lewis acid,[15] whereas compounds **3** react with TMSCN in the presence of $TiCl_4$[16] or concentrated $LiClO_4$ in diethyl ether solution.[17]

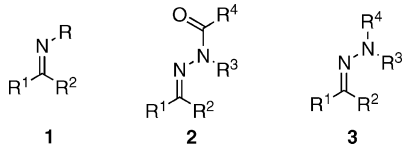

Figure 1. Imines **1**, *N*-acylhydrazones **2** and *N*,*N*-dialkylhydrazones **3**.

Results and Discussion

Recently, we started investigations directed to explore the organocatalytic activation of *N*,*N*-dialkylhydrazones as imine surrogates in the Strecker reaction. Preliminary screenings were performed in CH_2Cl_2 as the solvent, with TMSCN as the cyanide source and hydrazone **3a** as a model substrate. In the background studies, we realized that the addition of MeOH or PhOH as additives proved to be beneficial for the reactivity, leading to partial conversions after relatively short reaction times (Table 1, Entries 2, 3). This is a surprising result because related Strecker-type additions to different imine surrogates require the activation by catalysts of diverse nature,[18] and it suggests that HCN, produced in situ by the reaction of MeOH or PhOH with TMSCN, spontaneously adds to the hydrazone C=N bond.

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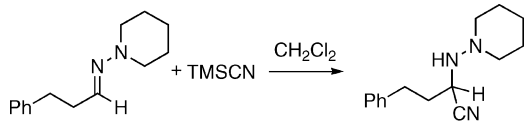
Table 1. Uncatalyzed Strecker reaction of **3a** with TMSCN at room temperature.[a]



3a **4a**

Entry	Solvent	Additive	Time [h]	Conversion [%][b]
1	CH_2Cl_2	–	18	4
2	CH_2Cl_2	MeOH[c]	3	14
3	CH_2Cl_2	PhOH[c]	3	31
4	MeOH	–	3	97
5	H_2O	–	3	>99

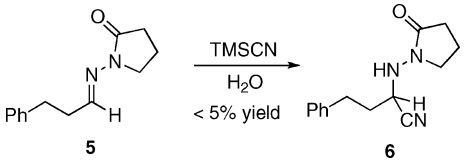
[a] Experimental conditions: TMSCN (0.2 mmol) was added to a solution of hydrazone **3a** (0.1 mmol) in 0.5 mL of solvent. [b] Calculated by ^{1}H NMR analysis of the crude reaction mixtures. [c] 0.2 mmol of additive.

Therefore, the reaction was performed in pure MeOH to afford cleanly the addition product in excellent yield (Entry 4). Disregarding eventual solubility issues, we decided to look at the possibility of performing the uncatalyzed reaction in pure water. Satisfyingly, the reaction also took place smoothly in short reaction times to afford the product **4a** in nearly quantitative yield (Entry 5).

The scope of the reaction was explored by using a variety of aldehyde *N*,*N*-dialkylhydrazones **3a**–**g** of diverse nature, and, interestingly, even ketone derivatives **3h**–**k** could be used with the results collected in Table 2. These data indicate that the reaction is highly efficient for all types of substrates. The more reactive aldehyde derivatives **3a**–**g** react in 5–8 h, requiring only a slight excess of reagent to reach complete conversions and providing adducts **4a**–**g** in excellent yields (Entries 1, 3–8).

More hindered dialkyl (**3h**–**j**) or aryl alkyl ketone hydrazones (**3k**), however, reacted at slower rates but also reached high conversions of products **4h**–**k** in reasonable reaction times when 2–3 equiv. of TMSCN were employed (Entries 9–12). Though piperidine derivatives were initially chosen as substrates for their poorer n–π conjugation with respect to other hydrazones,[19] the simplest dimethylamino aldehyde and ketone derivatives **3a′** and **3k′** showed a similar reactivity (Entries 2 and 13).

The unexpected reactivity of hydrazones was suspected to be related with the presence of the dialkylamino group as a differential structural motif. In order to gain a better insight into the role of the N(sp^3) lone pair in the observed reactivity, *N*-acyl derivative **5** was also used as substrate under the same reaction conditions (Scheme 1). In spite of the similar stability and the higher electrophilicity provided by the carbonyl group, this compound exhibited a very low reactivity with TMSCN in water compared with the *N*-dialkyl analogues, affording a low conversion (< 5%) to product **6**[20] under the above conditions. This result indicates that the availability of the N-lone pair is essential for the reactivity.

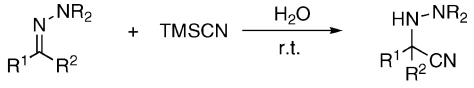


5 **6**

Scheme 1. Reactivity of *N*-acylhydrazone **5**.

Two different mechanisms that explain the unexpected reactivity induced by the dialkylamino group can be postulated. A first possibility considered (mechanism A, Scheme 2) consists of the activation of the TMSCN reagent by attack of the silicon atom by the NR_2 lone pair.[21] This

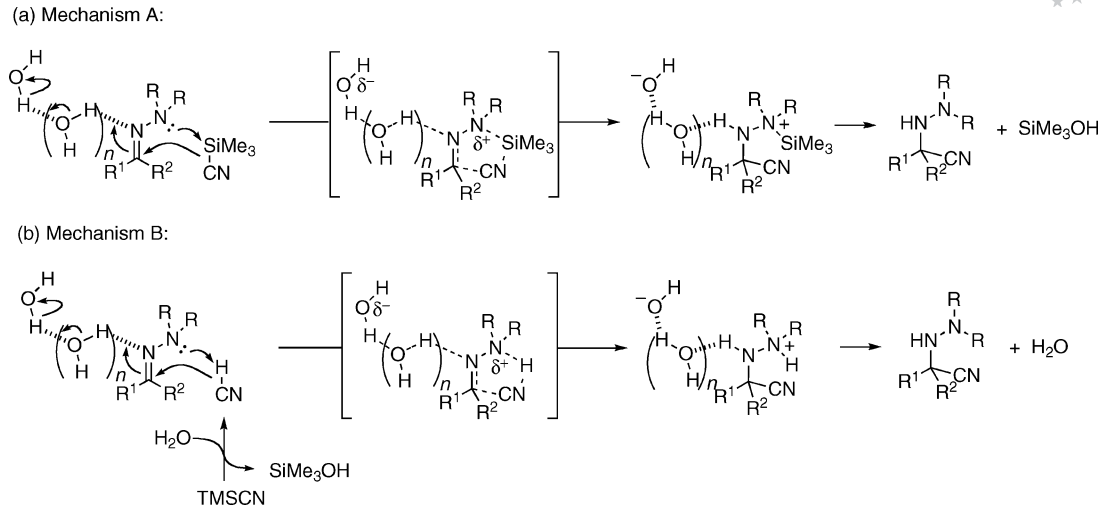
Table 2. Uncatalyzed Strecker reaction of *N*,*N*-dialkylhydrazones with TMSCN in water.[a]



3: NR_2 = piperidin-1-yl, NMe_2 **4**

Entry	Hydrazone	R^1	R^2	NR_2	TMSCN [equiv.]	Product	Time [h]	Yield [%][b]
1	**3a**	$PhCH_2CH_2$	H	piperidin-1-yl	1.5	**4a**	7	90
2	**3a′**	$PhCH_2CH_2$	H	NMe_2	1.5	**4a′**	7	90
3	**3b**	Me	H	piperidin-1-yl	1.2	**4b**	7	90
4	**3c**	*i*Pr	H	piperidin-1-yl	1.2	**4c**	8	89
5	**3d**	*i*Bu	H	piperidin-1-yl	1.2	**4d**	7	95
6	**3e**	*t*Bu	H	piperidin-1-yl	1.2	**4e**	5	92
7	**3f**	cyclohexyl	H	piperidin-1-yl	1.5	**4f**	7	91
8	**3g**	cyclopropyl	H	piperidin-1-yl	1.5	**4g**	7	90
9	**3h**	$-(CH_2)_4-$		piperidin-1-yl	2	**4h**	15	94
10	**3i**	*t*Bu	Me	piperidin-1-yl	2	**4i**	15	90
11	**3j**	cyclopropyl	Me	piperidin-1-yl	2	**4j**	18	93[c]
12	**3k**	Ph	Me	piperidin-1-yl	3	**4k**	17	88[d]
13	**3k′**	Ph	Me	NMe_2	3	**4k′**	72	71

[a] Experimental conditions: TMSCN was added to a mixture of hydrazone **3** (0.2 mmol) and H_2O (0.5 mL). Product **4** was isolated by extraction with AcOEt from the reaction media. [b] Isolated yield. [c] Contains 7% of unreacted ketone hydrazone. [d] Contains 9% of unreacted ketone hydrazone.



Scheme 2. Activation of cyanide for the addition to hydrazones.

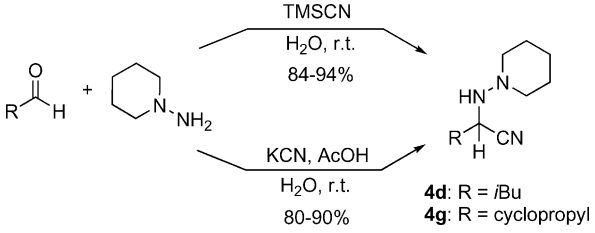
leads to a pentavalent silicon transition state, in which the nucleophilic addition of cyanide to the azomethine carbon atom is intramolecularly assisted by the neighbouring amino group, trough a transition state where the silicon atom shifts to the nitrogen atom. In this scenario, a cooperative activation of the C=N bond by water is postulated to explain the absence of reactivity in other solvents under non-catalyzed conditions. Alternatively, a second situation (mechanism B) can be envisaged, in which a previous hydrolysis of TMSCN takes place to afford HCN that is then "activated" in a similar way.[22]

Therefore, additional experiments were also carried out by using a 1:1 mixture of AcOH/KCN for the in situ generation of HCN in the reaction media. The reaction also proceeds to give the same adducts in similar yields and *with the same reaction rates*. This fact strongly suggests that a previous hydrolysis of TMSCN occurs, thereby enabling the reaction to progress through mechanism B.[23]

As mentioned above, stronger electrophiles containing more polarized carbon–heteroatom bonds do not react with TMSCN or HCN in the absence of catalysts. This circumstance makes it possible to perform the reaction in a one-pot fashion starting from the aldehyde (not reactive), the hydrazine and TMSCN in water (Scheme 3). By using these conditions, hydrazones **3d** and **3g** afforded exclusively products **4d** and **4g** in 94 and 84% yield, respectively. The alternative in situ generation of HCN from AcOH and KCN is also a suitable strategy for the one-pot synthesis of adducts **4d** and **4g**, obtained in similar 90 and 80% yield, respectively.

Conclusions

The *N*-(dialkylamino) group in hydrazones plays a dual role in that it allows their use as substrates for the uncatalyzed hydrocyanation in pure water: (a) stabilization of the substrate related with the n→π conjugation that minimizes the tendency to tautomerization, and (b) high reactivity



Scheme 3. One-pot, direct synthesis of hydrazino nitriles **4** from aldehydes.

provided by the intramolecular activation of HCN, driving the addition of cyanide to the neighbour azomethine carbon atom and making the use of external catalysts unnecessary.

Experimental Section

General Procedure for the Synthesis of Hydrazino Nitriles 4a–k, 4a′, and 4k′ from Hydrazones 3: TMSCN (1.2–3.0 equiv.) was added to a solution of hydrazone **3a**–**k**, **3a′**, or **3k′** (0.2 mmol) in H_2O (0.5 mL, 0.4 M), and the mixture was stirred until total consumption of starting material (5–72 h), diluted with satd. $NaHCO_3$ (2 mL), extracted with AcOEt (3 × 1 mL), dried (Na_2SO_4), filtered, and concentrated to yield compounds **4** in pure form.

Direct Three-Component Reactions with TMSCN as the Cyanide Source: A mixture of hydrazine (130 μL, 1.2 mmol) and isovaleraldehyde or cyclopropanecarbaldehyde (1 mmol) was stirred for 10 min. H_2O (2.5 mL) and TMSCN (268 μL, 2 mmol) were then added.[24] The mixture was stirred until total consumption of the starting material (8 h), then satd. $NaHCO_3$ (2 mL) was added, and the mixture was extracted with AcOEt (3 × 1 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated to afford compounds **4** in pure form.

Direct Three-Component Reactions with KCN as the Cyanide Source: Hydrazine (130 μL, 1.2 mmol) and isovaleraldehyde or cyclopropanecarbaldehyde (1 mmol) were stirred for 10 min. H_2O (2.5 mL, 0.4 M), KCN (1.4 mmol or 2 mmol) and AcOH (1.4 mmol or 2 mmol) were consecutively added.[23] The mixture was stirred

until total consumption of the starting material (18 h), then satd. $NaHCO_3$ (2 mL) was added, and the mixture was extracted with AcOEt (3 × 1 mL). The combined organic phases were dried with Na_2SO_4, filtered, and concentrated to afford compounds **4**.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data for compounds **3** and **4**. ^1H and ^{13}C NMR spectra for new compounds.

Acknowledgments

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[19] The planar conformations required for the n→π conjugation in the N–N=C system are efficiently inhibited in this case by the strain associated with the loss of the preferred chair-like conformation of the six-membered piperidine ring. This particularity increases the electrophilic character of the azomethine carbon atom in these derivatives with respect to other *N*,*N*-dialkylhydrazones.
[20] After 7 h at room temp., the starting material remained essentially unchanged. Only traces of product **6** were detected by ^1H NMR analysis {300 MHz, [D_6]acetone: δ = 4.11 (dd, J = 6.9, 13.2 Hz, 1 H)} and MS-FAB (m/z = 266) of the crude reaction mixture.
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[23] As expected, no reaction takes place when KCN alone is added to the hydrazone in water.
[24] Reactions performed without a preliminary stirring of the aldehyde and the hydrazine also afforded products **4d** or **4g**, and no cyanohydrin resulting from the hydrocyanation of the aldehyde could be detected. The reactions, however, were not so clean under these conditions and the yields were lower. This can be attributed to a partial silylation or protonation of the hydrazine.

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