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Revisiting a Classic Transformation: A Lossen Rearrangement Initiated by Nitriles and "Pseudo-Catalytic" in Isocyanate

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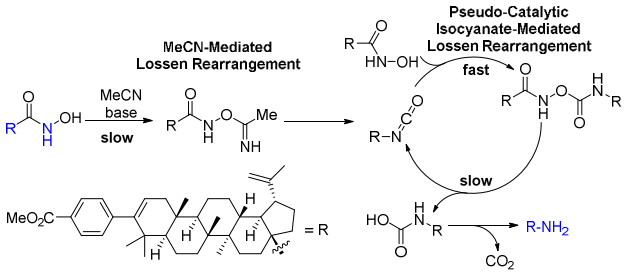
Supporting Information



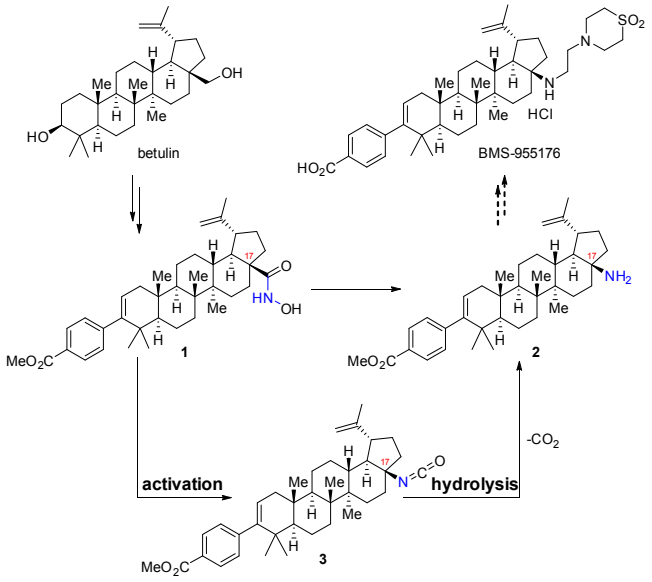
ABSTRACT: The direct conversion of a hydroxamic acid to an amine has been accomplished in a single step in the synthesis of HIV drug candidate BMS-955176. This process utilizes catalytic base and proceeds under mild conditions (CH_3CN, cat. DBU, 60 °C), without the need for strong electrophiles required for typical Lossen rearrangements, and can be applied to aliphatic and aromatic hydroxamic acids. Through investigation of the kinetics of this transformation, a mechanism was revealed involving a novel initiation pathway and a self-propagation cycle. The initiation pathway involves activation of hydroxamic acid by nitriles, and subsequent Lossen rearrangement to generate the corresponding isocyanate. The isocyanate functions as a "pseudo-catalyst" for this system, leading to generation of product through a second Lossen rearrangement and regeneration of a new isocyanate molecule. Thorough mechanistic understanding allowed for this highly efficient process to be implemented on a 55kg scale in 95.5% isolated yield.

INTRODUCTION

The Lossen rearrangement is a method for converting hydroxamic acids to amines via isocyanates, and shares many similarities with the well-known Curtius and Hofmann rearrangements.[1] This process typically involves activation of the hydroxamic acid with acyl or sulfonyl reagents, followed by treatment with base to trigger a carbon migration and departure of a leaving group. Several studies have presented evidence supporting a concerted mechanism for the Lossen rearrangement involving concomitant carbon to nitrogen migration and expulsion of the oxyanion.[2] The resulting isocyanate can be converted to a carbamate in the presence of water, which after decarboxylation gives an efficient route to an amine.

In the course of development of the novel HIV-inhibitor BMS-955176, our team was faced with the challenge of installing an amine functionality at C-17 of a pentacyclic triterpene scaffold (Scheme 1).[3] Conversion of the natural product betulin, readily obtained from birch bark, to the corresponding hydroxamic acid (**1**) allowed for investigation of a Lossen rearrangement as a potential route to the amine **2**.[4] While typical Lossen rearrangement conditions, involving activation of the hydroxamic acid with an electrophile/base, converted **1** to isocyanate **3** *via* migration of C-17 to nitrogen, the subsequent hydrolysis led to significant impurities and was operationally challenging. Moreover, it was undesirable to handle the highly energetic, genotoxic isocyanate species.[5]

Scheme 1. Proposed route from betulin to BMS-955176 via Lossen rearrangement.



With these considerations in mind, we turned our attention to a 2009 report by Hoshino and coworkers which disclosed a method for the base-catalyzed *direct* conversion of arylhydroxamic acids to amines in DMSO without the observation of an intermediate isocyanate.[6,7,8] The authors proposed an interesting mechanism for this process, although they offered only limited experimental support for it (Figure 1). Reaction initiation was proposed to occur by condensation of two molecules of hydroxamic acid **A** to give *N,O*-diacyl intermediate **B**, followed by a Lossen rearrangement to generate isocyanate **C**. Reaction propagation was proposed to occur by attack of **A** on isocyanate **C** to give intermediate **D**. Intermediate **D** could then undergo a Lossen rearrangement to regenerate **C**, and form amine **E** following decarboxylation. In this way, **A** could be converted to **E** without the buildup and observation of **C**.

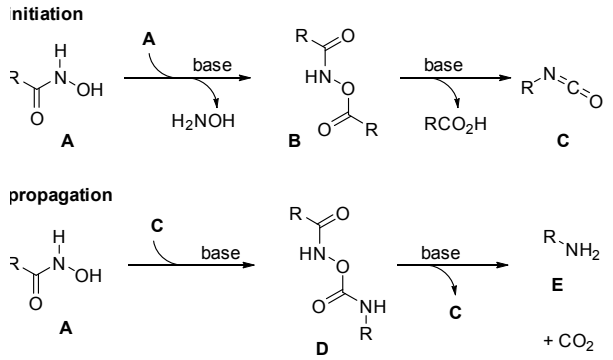


Figure 1. Previously proposed mechanism of isocyanate-mediated conversion of hydroxamic acids to amines.

Inspired by this promising method, we set out to develop facile conditions for direct conversion of **1** to **2**, aided by a thorough mechanistic understanding of this process. Herein we describe the development of a mild base-promoted rearrangement through the discovery of a nitrile-mediated activation process, and the elucidation of a "pseudo-catalytic" cycle involving isocyanate **3**. This process has been successfully implemented on a 55 kg scale.

RESULTS AND DISCUSSION

The conditions described by Hoshino and coworkers were not reactive for our system, likely due to the low solubility of **1** in DMSO, so we began to screen various solvents and bases to develop suitable conditions. In our initial studies in alternative solvents, exposure to moderate bases such as DBU, cleanly converted **1** to amine **2**, albeit at high temperatures (Scheme 1). A study of the kinetics of this reaction in various solvents yielded two surprising observations which led us to investigate this system further. First, while temperatures of >100 °C were necessary for reaction in most solvents (2-methyl-2-butanol, CPME, DMA, etc), the reaction proceeded rapidly at 60 °C in CH_3CN with THF added to achieve homogeneity (Table 1; Figure 2). A clear trend was observed in reaction rate based on solvent polarity, with a moderate increase in rate with dielectric constant (Table 1, entries 1-4; Figure 2). However, the impact of changing from 50% DMA co-solvent to 50% CH_3CN (ε = 37.5) dominated these polarity effects and showed an 18-fold increase in reaction rate, despite no change in dielectric constant (Table 1, entry 3 vs entry 5; Figure 2).

Table 1. Effect of solvent polarity on reaction time.

Entry	Solvent (v/v)	Dielectric constant (ε)	$t_{1/2}$ (min)
1	THF	7.58	1800
2	2-methyl-2-butanol	15.6	1082
3	1:1 DMA:THF	22.68	830
4	DMA	37.78	267
5	1:1 MeCN:THF	22.54	45

Conditions: **1** (0.0825 M), 20 vol solvent, 0.25 equiv DBU, 60 °C.

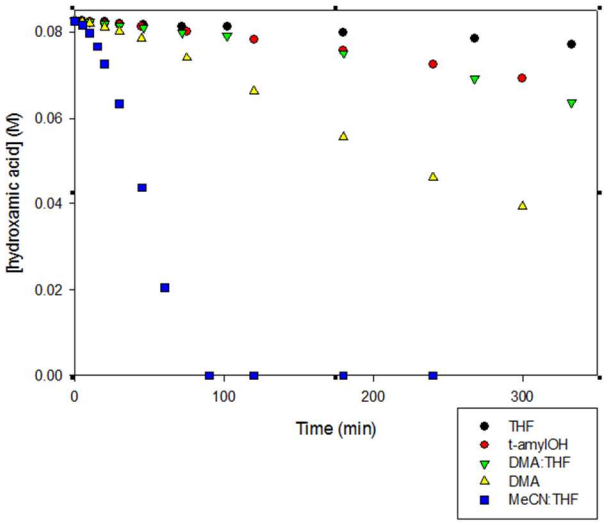


Figure 2. Reaction of **1** in various solvents at 60 °C with 0.25 equiv DBU.

The second surprising observation was that the reaction routinely exhibited an induction period followed by linear kinetics (Figure 3). These observations prompted us to probe the mechanism of this transformation further.

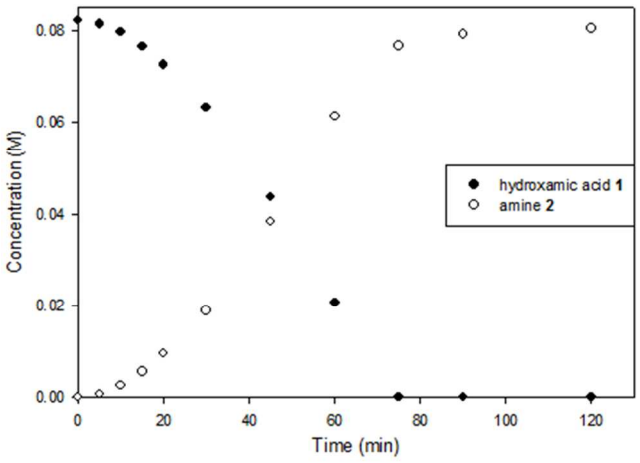


Figure 3. Reaction kinetics for conversion of **1** to **2**.

We began by examining the role of base by screening various amines and alkoxides. Moderately strong bases like DBU [p*K*a(DMSO) ~12], DBN, and TMG showed 50% conversion in 1-2 h, while a strong base like potassium tert-pentoxide [pKa(DMSO) ~ 29.4] showed 50% conversion in 15 min. Triethylamine, a weaker base [pKa(DMSO) ~ 9], gave a much slower reaction which reached only 2% conversion in 24h. Interestingly, all bases exhibited an induction period, regardless of reaction rate (Supporting information, Figure S1).

We hypothesized that a possible cause of this induction period could be autocatalysis by amine product **2** or byproduct (CO_2), and would result in an increased rate as the reaction proceeded. When equal concentrations of **1** and **2** were aged in the absence of DBU, no reaction was observed after 24h, consistent with the expected weak basicity of **2**.[9] Similarly, addition of CO_2 at atmospheric pressure to a standard reaction showed no impact on rate. The induction period clearly could not be explained by autocatalysis by **2** or CO_2.

In addition to the identity of the base, the concentration of DBU was explored from 0.1 to 4 equiv relative to **1** (Table 2, entries 1-5). This reaction shows a positive-order dependence on DBU (up to 1 equiv), but beyond this point exhibited no additional increase in rate (Supporting information, Figure S2). This result is consistent with fast, quantitative deprotonation of hydroxamic acid by DBU, and disqualifies rate limiting deprotonation as a possible explanation for the induction period.

Table 2. Effect of base concentration on reaction rate.

Entry[a]	[**1**] (M)	[DBU] (M)	DBU (equiv)	Rate at 50% conv. (M/min)
1	0.0825	0.00825	0.10	0.00082
2[b]	0.0825	0.0206	0.25	0.00134
3	0.0825	0.0825	1	0.00224
4	0.0825	0.165	2	0.00245
5	0.0825	0.330	4	0.00235
6	0.0402	0.0206	0.50	0.00065

a) Conditions: 60 °C, 1:1 MeCN:THF; b) Standard Conditions

An alternative hypothesis for Hoshino's findings was proposed by Roithová and coworkers based on spectroscopic and computational results.[10] To account for the reactivity observed with K_2CO_3/DMSO, they invoked a mechanism involving a metal-assisted (K, Zn) Lossen rearrangement of free hydroxamic acids to carbamic acids, without the need for additional electrophiles or dehydrating agents. While our results cannot entirely preclude such a mechanism, the observation that DBU also mediates the Lossen rearrangement of a free hydroxamic acid suggests that another pathway must be accessible. Moreover, the induction period observed with DBU or potassium *tert*-pentoxide cannot be explained by Roithová's proposed mechanism.

To further characterize our process, we next studied the effect of [**1**] on the reaction rate and observed an approximate first-order rate dependence.[11] By holding [DBU] constant (0.0206M), but doubling [**1**], the rate increased by a factor of 2.06 (Table 2, entry 2 vs entry 6). Although the shape of a single kinetic curve pointed towards zero-order kinetics following an induction period (Figure 3), the rate impact when [**1**] is varied clearly supports a significant positive order dependence on [**1**].

If the mechanism proposed by Hoshino were involved in our system: 1) carboxylic acid **4** (Figure 4) would be produced as a byproduct of reaction initiation and, 2) the rate would be accelerated by addition of isocyanate **3**. We found that under our standard conditions (Table 1, Entry 2), only ~0.2 mol% of carboxylic acid **4** was produced, and nearly all of it in the first 5 min of reaction, inconsistent with the proposed initiation mechanism.[12] The small amount of isocyanate (<0.2%) that could be generated from this proposed initiation pathway based on the levels of **4**, could not explain the observed reaction kinetics.[13]

On the other hand, the addition of 3 mol% isocyanate **3** to a reaction under standard conditions successfully produced a shorter induction period, consistent with the proposed propagation mechanism (Supporting information, Figure S3).[14] Together these results support the intermediacy of the isocyanate as previously proposed, but suggest that a different initiation mechanism is at work in our system.

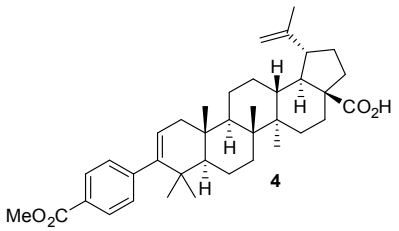


Figure 4. Carboxylic acid **4**.

Since a variety of electrophiles have been previously used to facilitate Lossen rearrangements, we wondered if the CH_3CN (**5a**) solvent could be activating **1** in a similar fashion through an unseen intermediate **6a** (Scheme 2).[15] A series of kinetic experiments were performed under standard conditions (Scheme 2) with a solvent mixture that was 50% THF and 50% (CH_3CN+DMA mixture) to maintain a constant solvent polarity (Table 3). A positive order of ~1.3 in [CH_3CN] was found, which is consistent with a mechanism involving generation of **3** and initiation through **6a**.[16,17] This activation by acetonitrile represents a novel method of facilitating Lossen rearrangements without the need for strong electrophiles.

Scheme 2. Nitrile-mediated activation of hydroxamic acid **1** and Lossen rearrangement. Standard Conditions: 1 (0.0825 M), 0.25

eq DBU, 1:1 THF/CH_3CN (**5a**) (20 vol), 60 °C. Arylnitrile Conditions: 0.25 eq DBU, THF (20 vol), 2.0 eq **5b-g**, 60 °C.

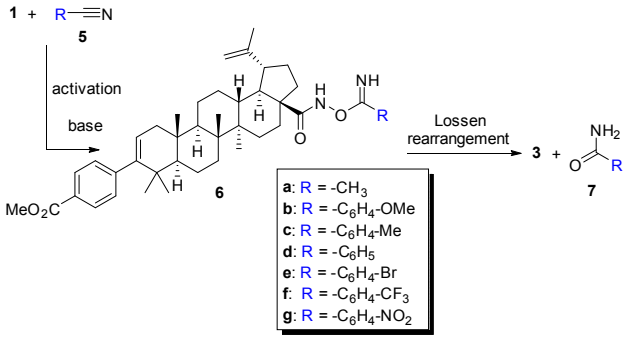


Table 3. Effect of [CH_3CN] on reaction rate.

Entry	THF:**MeCN**:DMA (v:v:v)	[MeCN] (M)	Rate to 10% conv (x 10^{-5}, M/min)
1	50:**50**:0	9.0	47.0
2	50:**35**:15	6.3	25.3
3	50:**20**:30	3.6	12.2
4	50:**10**:40	1.8	8.12
5	50:**5**:45	0.90	6.07
6	50:**0**:50	0	4.23
7	100:**0**:0	0	2.06

Conditions: **1** (0.0825 M), 20 vol solvent, 0.25 eq DBU, 60 °C.

To further support this CH_3CN mediated mechanism, **1** was subjected to standard conditions, except that the CH_3CN co-solvent was replaced with THF and 2 equiv of various benzonitrile derivatives were added (Scheme 2). All of the arylnitriles (**5b-g**) mediated the desired reaction (Supporting information, Figure S5). Interestingly, *p*-NO_2-benzonitrile (**5g**) demonstrated a rate comparable to that obtained under standard conditions (1:1 THF/CH_3CN, Table 2, entry 2), despite being present in a concentration of only 1/50th of that of CH_3CN in a typical reaction.

Using the rate to 10% conversion as a measure, a Hammett plot was constructed for the six benzonitrile derivatives (**5b-g**) showing a positive ρ-value of +1.07 (Figure 5). This positive value is consistent with faster nucleophilic attack of **1** on more electron-deficient nitriles leading to faster initiation. In all cases, formation of substituted benzamide (**7b-g**) was observed by LC at level of 2% to 14% of benzonitrile input. Interestingly, high levels of isocyanate **3** were observed with more electron-deficient benzonitriles as well. While in a typical CH_3CN-mediated reaction **3** was observed at a peak level of 1-2%, peak levels of 3.8%, 8.5%, and 13.7% were observed for **5e**, **5f**, and **5g**, respectively.[18] In all cases, **3** was fully consumed by adventitious water to yield **2** within 20h.[19] Interestingly, even with highly electrophilic nitrile additives, the majority of reaction did not proceed through direct activation through **6**, as evidenced by the low proportions of benzamides (**7**) formed, and instead proceed through the self-propagation cycle.

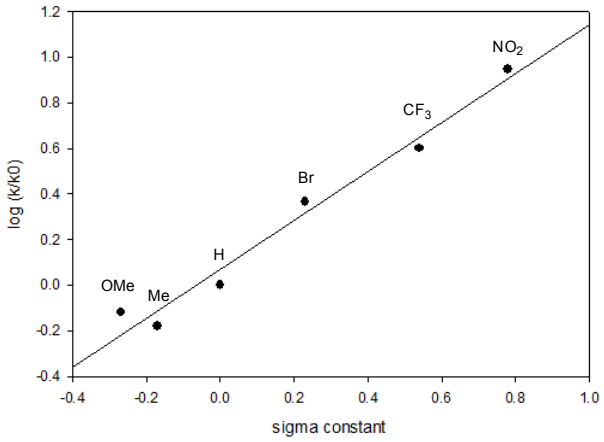


Figure 5. Hammett plot for reaction promotion by *p*-substituted benzonitriles.

Since conversion of **1** to **2** was still observed in various solvents in the absence of nitriles, we sought to understand what secondary activation pathway was responsible for initiation.[20] Careful analysis by HPLC showed that carboxylic acid **4** gradually formed both in DMA (1.7%) and THF (1.3%) over 20h (Supporting information, Figures S6 and S7). This finding suggests that a self-condensation pathway for **1**, as previously proposed, is active in the absence of a faster CH_3CN-mediated activation pathway.

In THF where this activation pathway is very slow, the initiation step can be effectively ignored, and the impact of isocyanate **3** on the kinetics of the propagation step can be readily studied. When **3** (2-8 mol%) was added under standard conditions in THF, the reaction was accelerated proportionally to the concentration of **3** employed (Figure 6, Table 4, entries 2-4). Moreover, these plots of [**1**] vs time were linear, consistent with a zero-order dependence on **1**. This is further supported by experiments where the initial [**1**] can be changed without an impact on rate (Table 4, entry 6 vs entry 3). Moreover, [DBU] appears to show no impact on the reaction rate in this THF system (Table 4, entry 5 vs entry 3). The kinetics are greatly simplified in THF and reactions follow the rate law $-d[\mathbf{1}]/dt = k[\mathbf{3}]$, where $k = 0.073$ min^{-1} (60 °C, THF). This is in contrast to the results in CH_3CN, where the initiation and propagation kinetics were mixed, and a positive order in both **1** and DBU was observed. These results lend further support to Hoshino's self-propagation mechanism.

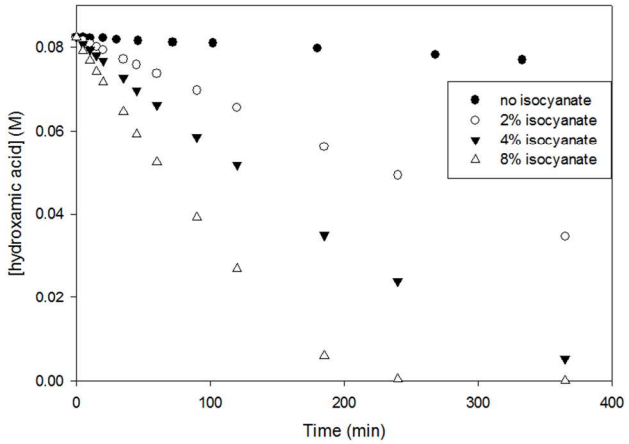


Figure 6. Effect of isocyanate (**3**) concentration on reaction kinetics. Conditions: **1** (0.0825 M), 20 vol THF, 0.25 equiv DBU, 0-8% isocyanate **3**, 60 °C.

Table 4. Effect of DBU and isocyanate (**3**) concentration on reaction rate in THF.

Entry[a]	[**1**] (M)	[DBU] (M)	[**3**] (M)	**3** (mol %)	Initial Rate (x 10^{-5}, M/min)
1	0.0825	0.0206	0	0	1.81
2	0.0825	0.0206	0.0017	2	15.1
3	0.0825	0.0206	0.0033	4	27.7
4	0.0825	0.0206	0.0066	8	51.1
5	0.0825	0.0410	0.0033	4	28.7
6	0.0420	0.0206	0.0033	8	23.5

[a] Conditions: THF, 60 °C

To test the generality of this MeCN-mediated method, the standard conditions were applied to benzohydroxamic acid (**8a**) and hydrocinnamyl hydroxamic acid (**8b**). Full conversion to the corresponding amines, aniline and 2-phenethylamine, respectively, was observed within a few hours. Identical reactions were performed in 1:1 DMA:THF and were found to proceed 20-25 times slower in the absence of MeCN mediation (Figure 7), similar to observations with **1**.

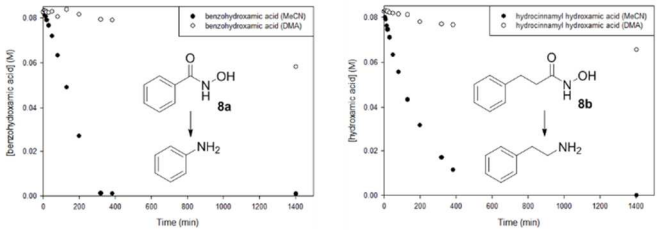
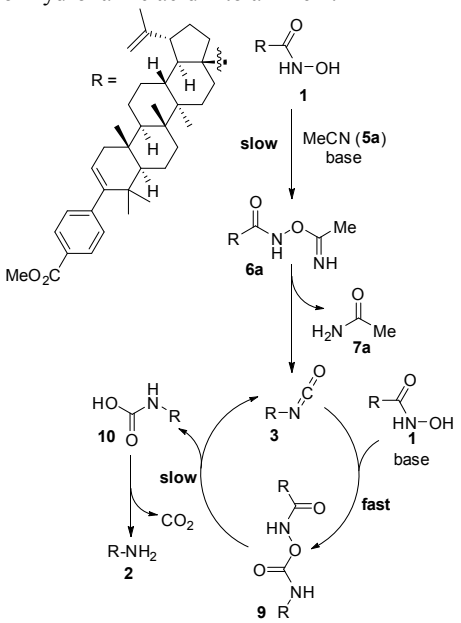


Figure 7. Rate acceleration of conversion of hydroxamic acids to amines in the presence of MeCN for **8a** and **8b**. Conditions: hydroxamic acid (0.0825 M), 0.25 eq DBU, 1:1 THF/CH_3CN (20 vol), 60 °C.

Based on all of these findings, a coherent mechanistic scheme can be constructed, analogous to a system involving a catalyst activation step and a catalytic cycle (Scheme 3). During the initiation phase, deprotonation of **1** by DBU is fast and quantitative based on results with >1 equiv DBU.[21] However, nucleophilic attack of the hydroxamate of **1** on CH_3CN to generate activated hydroxamic acid **6a** is slow, and accordingly shows a positive order dependence on both **1** and CH_3CN. Intermediate **6a** rearranges to generate isocyanate **3**, which enters the propagation cycle as a "pseudo-catalyst". Based on the zero-order dependence on **1** observed when the propagation step was effectively isolated by running in THF, reaction of the hydroxamate of **1** with isocyanate must be rapid. Moreover, **3** is not detectable under standard reaction conditions until near reaction completion, also consistent with rapid conversion to **9** and the short lifetime of **3**.[22] The Lossen rearrangement of **9**, on the other hand, must be slow in accordance with linear kinetics for the propagation cycle observed in THF. It is interesting to note that for each cycle, when **9** undergoes a Lossen rearrangement, the fragment derived from **3** is converted to unseen carbamic acid intermediate **10** (and **2** after decarboxylation), while the fragment derived from **1** is converted to **3**, and must re-enter the cycle to generate **9**. While isocyanate **3** promotes formation of **2** from **1**, with each cycle a *different* molecule of **3** is both consumed and regenerated, making **3** a "pseudo-catalyst" for this process.

Scheme 3. Mechanism for CH_3CN-mediated direct conversion of hydroxamic acid **1** to amine **2**.



With a firm mechanistic understanding of this rearrangement in place, our team began to investigate the scale up and application of this process towards the preparation of BMS-955176. By employing more concentrated reaction conditions and reducing the volume from 20 vol to 4 vol [THF:MeCN (1:1)], the reaction could be accelerated. Furthermore, the upfront addition of H_2O (2-3 eq) enabled a higher yield of **2** by facilitating the hydrolysis of the residual isocyanate (**3**) at the end of the reaction. Interestingly, this reaction of water with isocyanate is significantly slower than the desired pathway (**3**+**1**), leading to a highly efficient process. Under these optimized conditions (10 mol% DBU, 65 °C, 3 eq H_2O, THF/CH_3CN), **1** (55 kg) achieved 99.8% conversion within 1.5 h. The subsequent addition of CH_3CN and cooling to ambient temperature resulted in a direct crystallization of **2** in 95.5% isolated yield.

CONCLUSIONS

In conclusion, we have discovered a general and mild method for direct conversion of primary, tertiary, and aryl hydroxamic acids to amines mediated by base and CH_3CN, and without the need for strong electrophiles. Kinetic studies have demonstrated that this reaction proceeds primarily through an initiation phase involving activation of hydroxamic acid by CH_3CN to generate an isocyanate through a Lossen rearrangement. Furthermore, these studies lend support to a previously proposed propagation mechanism involving the activation of a hydroxamic acid by an isocyanate as a "pseudo-catalyst", and are inconsistent with a mechanism involving metal-assisted rearrangement of free hydroxamic acids. Knowledge of this reaction mechanism enabled facile pilot plant scale up this process to deliver **2** with excellent yield and purity.

EXPERIMENTAL SECTION

General:
The synthesis of compounds 1, **2**, **3**, and **4** was previously reported.[3,4]

*General procedure for kinetics of conversion of **1** to **2** under standard conditions*
In an 8 mL vial, **1** (58.2 mg, 0.0990 mmol), THF (600 uL), and MeCN (600 uL) were combined to make a 0.0825 M solution. This vial was sealed and heated to 60 °C. DBU (3.8 uL, 0.025 mmol) was added by syringe, which started the reaction. Samples were taken periodically by uncapping the vial, sampling and diluting 12 uL of reaction mixture into 900 uL 3% TFA in THF, and then recapping vial. HPLC analysis showed >96% mass balance based on wt% analysis. HPLC, Ascentis Express C18, 2.7 µm, 4.6x50 mm, 210 nm, 25 °C, solvent A: TFA(0.05%) in water:MeCN (95:5); solvent B: TFA(0.05%) in water:MeCN (5:95). t = 0 min, 10% B; t = 3 min, 100% B; t = 8 min, 100% B. **2** (rt = 2.09 min), **1** (rt = 5.58 min), **4** (rt = 7.05 min), **3** (rt = 12.36 min)

*General procedure for kinetics of conversion of **1** to **2** in the presence of arylnitriles*
In an 8 mL vial, **1** (58.2 mg, 0.0990 mmol), THF (1200 uL), and benzonitrile (20.5 mL, 20.6 mg, 0.198 mmol) were combined to make a 0.0825 M solution. This vial was sealed and heated to 60 °C. DBU (3.8 uL, 0.025 mmol) was added by syringe, which started the reaction. Samples were taken periodically by uncapping the vial, sampling and diluting 12 uL of reaction mixture into 900 uL 3% TFA in THF, and then recapping vial. Formation of byproduct benzamide **7d** was observed by HPLC and was quantified based on comparison to an authentic sample of **7d**.

*Conversion of benzohydroxamic acid (**8a**) to aniline in MeCN or DMA*
In an 8 mL vial, **8a** (13.7 mg, 0.0990 mmol), and MeCN or DMA (1200 uL) were combined to make a 0.0825 M solution. This vial was sealed and heated to 60 °C. DBU (3.8 uL, 0.025 mmol) was added by syringe, which started the reaction. Samples were taken periodically by uncapping the vial, sampling and diluting 12 uL of reaction mixture into 900 uL 3% TFA in THF, and then recapping vial. The product was identified by LC-MS comparison to an authentic sample of aniline.

*Conversion of hydrocinnamyl hydroxamic acid (**8b**) to 2-phenethylamine in MeCN or DMA*
In an 8 mL vial, **8b** (16.4 mg, 0.0990 mmol), and MeCN or DMA (1200 uL) were combined to make a 0.0825 M solution. This vial was sealed and heated to 60 °C. DBU (3.8 uL, 0.025 mmol) was added by syringe, which started the reaction. Samples were taken periodically by uncapping the vial, sampling and diluting 12 uL of reaction mixture into 900 uL 3% TFA in THF, and then recapping vial. The product was identified by LC-MS comparison to an authentic sample of 2-phenethylamine.

*Pilot plant scale procedure for conversion of **1** to **2***
To an 1800 L glass-lined vessel were charged **1** (55.0 kg, 93,6 mol), THF (110 L), MeCN (110 L), water (5.5 kg, 3.5 equiv), and DBU (3.50 L, 3.55 kg, 23.3 mol). The reaction mixture was heated and aged at 65 °C for 1.5 h to reach reaction completion. To crystallize **2**, MeCN (330 L) was added over 3 h at 65 °C and then cooled to 0 °C over 3 h. The product was isolated from the liquor on a filter drier at 0 °C and the resulting cake was washed with 9:1 MeCN/THF (165 L) followed by MeCN (165 L). The solids were dried at 55 °C to remove residual solvent and afford crystalline **2** (46.5 kg, 95.5% yield). HPLC analysis showed 99.67 area % purity and 99.4 weight % potency. ^{1}H NMR (600 MHz, 1:0.7 DMSO-d_6:$CDCl_3$): δ 7.84 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 5.22 (dd, J = 6.2, 1.3 Hz, 1H), 4.66 (d, J = 2.1 Hz, 1H), 4.52 (br s, 1H), 3.83 (s, 1H), 2.52 (td, J = 11.0, 5.9 Hz, 1H), 2.06 (dd, J = 17.2, 6.4 Hz, 1H), 1.96 (m, 1H), 1.73 (m, 1H), 1.72 (m, 1H), 1.65, (m, 1H), 1.64 (m, 1H), 1.63 (s, 1H), 1.50 (m, 1H), 1.49 (m, 1H), 1.46 (m, 1H), 1.43 (m, 1H), 1.42 (m, 2H), 1.40 (m, 1H), 1.39 (m, 1H), 1.37 (m, 1H), 1.35 (m, 1H), 1.33 (m, 1H), 1.28 (m, 1H), 1.24 (m, 1H), 1.18 (m, 1H), 1.05 (s, 1H), 1.03 (m, 1H), 1.03 (m, 1H), 0.94 (s, 1H), 0.93 (s, 1H), 0.88 (s, 1H), 0.87 (s, 1H). ^{13}C{^{1}H} NMR (150 MHz, 1:0.7 DMSO-d_6:$CDCl_3$): δ 166.0, 149.7, 148.0, 145.5, 129.6, 127.9, 127.3, 123.5, 109.2, 59.2, 52.1, 51.5, 48.7, 47.9, 47.1, 41.6, 41.0, 40.0, 39.3, 37.1, 36.8, 35.6, 34.5, 32.9, 28.9, 28.9, 26.3, 24.6, 20.8, 20.6, 19.1, 18.9, 16.0, 15.3, 13.6. HRMS (ESI-Orbitrap) Calcd for $[C_{37}H_{53}NO_2+H]^+$ 544.4149, Found 544.4133 (2.9 ppm error).

Supporting Information

Additional kinetic plots and NMR spectra of **2**.

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11. The rate at 50% conversion, which was the maximum rate for each experiment, was used for comparison.
12. Experiments where carboxylic acid **4** (2.5% or 10%) was spiked into a reaction mixture showed that it was stable, and does not decrease throughout the reaction.
13. We hypothesize that **4** could also be generated through hydrolysis of **1** by trace water.
14. Isocyanate **3** was only visible under standard reaction conditions once >95% of **1** was consumed. It typically reached levels of 1-2% and was consumed rapidly (<30 min) by adventitious water, leading to **2** via carbamic acid.
15. The formation of acetamide over the course of the reaction can be observed by GC analysis
16. The order in MeCN was obtained from a plot of log(rate - background rate in DMA:THF) vs log[MeCN] (Supporting information, Figure S4)
17. Proposed intermediates **6a-j** have not been detected in process, which is consistent with the expected short lifetime of these species and the positive order in MeCN.
18. Mole equiv relative to **1.**
19. The reaction of **3** (0.0165 M) with water (0.245 M) and DBU (0.206 M) under standard conditions showed 50% conversion of **3** to **2** in 30 min.
20. We considered an activation pathway involving acylation of **1** with DMA, but found identical reaction rates in DMA and DMF, suggesting that acylation was unlikely
21. The nature of the hydroxamate of **1** (K^+ vs DBU-H^+) could impact the rate of nucleophilic attack on MeCN, which could explain why potassium tert-pentoxide leads to a higher reaction rate than DBU, even though adding excess DBU offers no rate acceleration.
22. An intermediate is observed by LC-MS at early time points which is believed to be **9**. LC-MS (ESI) m/z: $[M+H]^+$ calcd for for $C_{76}H_{105}N_2O_7$: 1157.8, found: 1157.6