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SYNTHESIS OF UNSYMMETRICAL, *gem*-DISUBSTITUTED BISAMIDES

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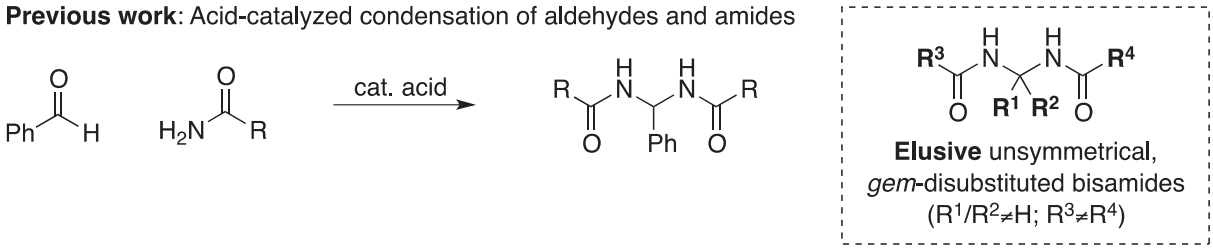
Dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday

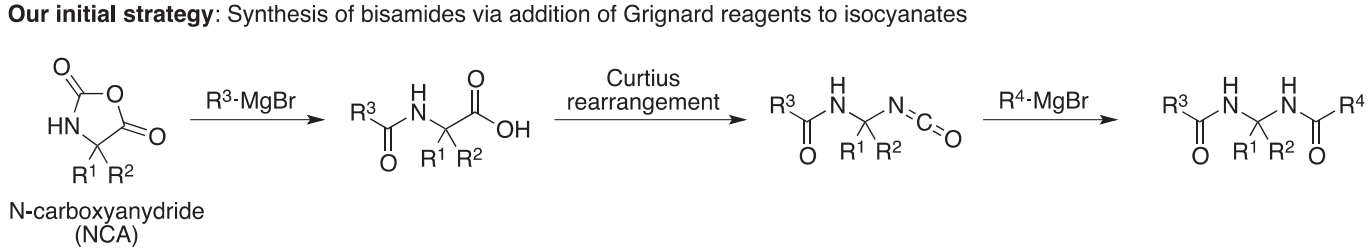
Abstract – The addition of Grignard reagents to isocyanates allowed for the first successful synthesis of ketone-derived unsymmetrical, *gem*-disubstituted bisamides. The key to success was the *in situ* generation of the isocyanates under mild reaction conditions via Lossen rearrangement from the corresponding hydroxamic acids.

Bisamides, which consist of two amide functionalities that are interconnected to each other via a single methylene bridge, are a powerful but rare class of compounds. They have been used as key fragments in retro-inverso pseudopeptide derivatives, where they have proven to be exceptionally stable moieties despite their relationship to notoriously labile aminals.[1] The novelty of bisamides makes them particularly interesting for medicinal chemistry, as they would allow the exploration of previously unknown chemical space and the circumvention of existing intellectual property (IP) restrictions. From a synthetic point of view bisamides are highly challenging targets. Even though several research groups have independently reported the preparation of bisamides via the acid-catalyzed condensation of aldehydes with primary amides (Scheme 1),[2] all these approaches suffer from two major limitations: 1) only symmetrical bisamides can be obtained and 2) the use of ketones is not possible. For these reasons, the synthesis of unsymmetrical, *gem*-disubstituted bisamides remains elusive.



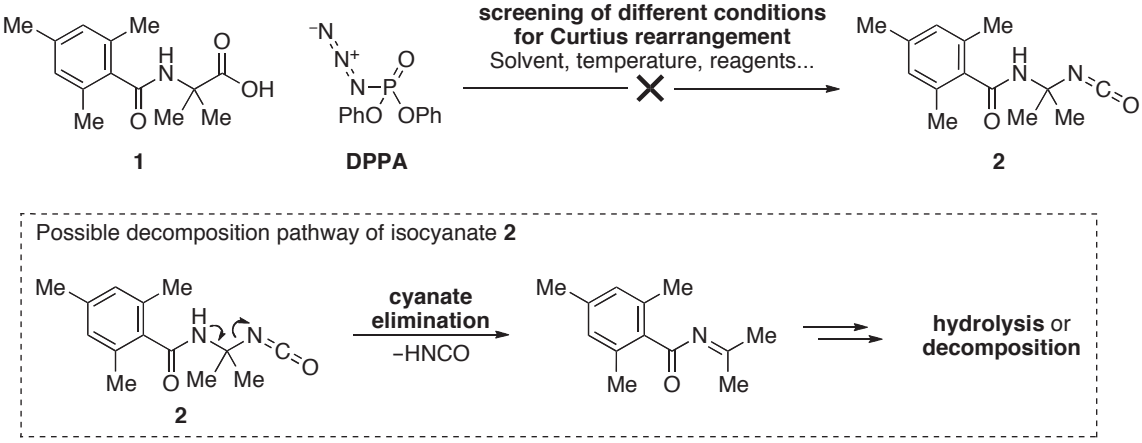
Scheme 1. Synthesis of bisamides via acid-catalyzed condensation of aldehydes and primary amides

Our initial strategy towards the synthesis of unsymmetrical, *gem*-disubstituted bisamides was to use our recently reported protocol for the synthesis of amides by the addition of Grignard reagents to isocyanates.[3,4] We envisioned starting from *N*-acylated amino acids, which can be prepared in one step with our procedure for the addition of organometallic reagents to *N*-carboxyanhydrides (NCAs),[5] and converting them into the corresponding isocyanates via Curtius rearrangement. These crucial isocyanate building blocks could undergo a reaction with Grignard reagents to form the desired bisamides (Scheme 2).



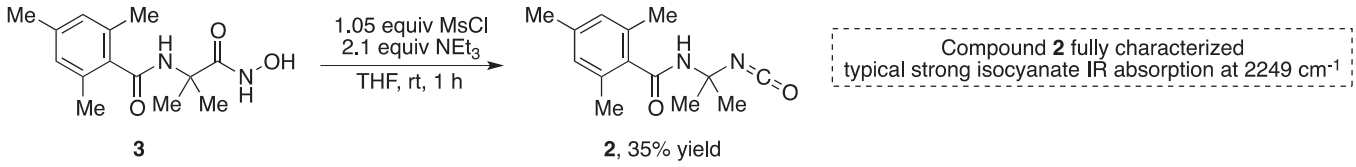
Scheme 2. Synthesis of unsymmetrical, *gem*-disubstituted bisamides via addition of Grignard reagents to isocyanates

We chose 2-methyl-2-(2,4,6-trimethylbenzamido)propanoic acid (**1**) as a model substrate and investigated its transformation into the corresponding isocyanate **2** via Curtius rearrangements with diphenylphosphoryl azide (DPPA). Despite a long period of screening of different reaction conditions and parameters (temperature, solvent, base, reagents and additives), we were never able to observe any formation of desired isocyanate **2**. Nevertheless, in some cases it was possible to observe vigorous gas evolution, which would be in accordance with the formation of nitrogen during a Curtius rearrangement. We concluded that isocyanate **2** could exist, but that this compound is sensitive towards cyanate elimination and therefore not stable at higher temperature.



Scheme 3. Attempted synthesis of isocyanate **2** via Curtius rearrangement

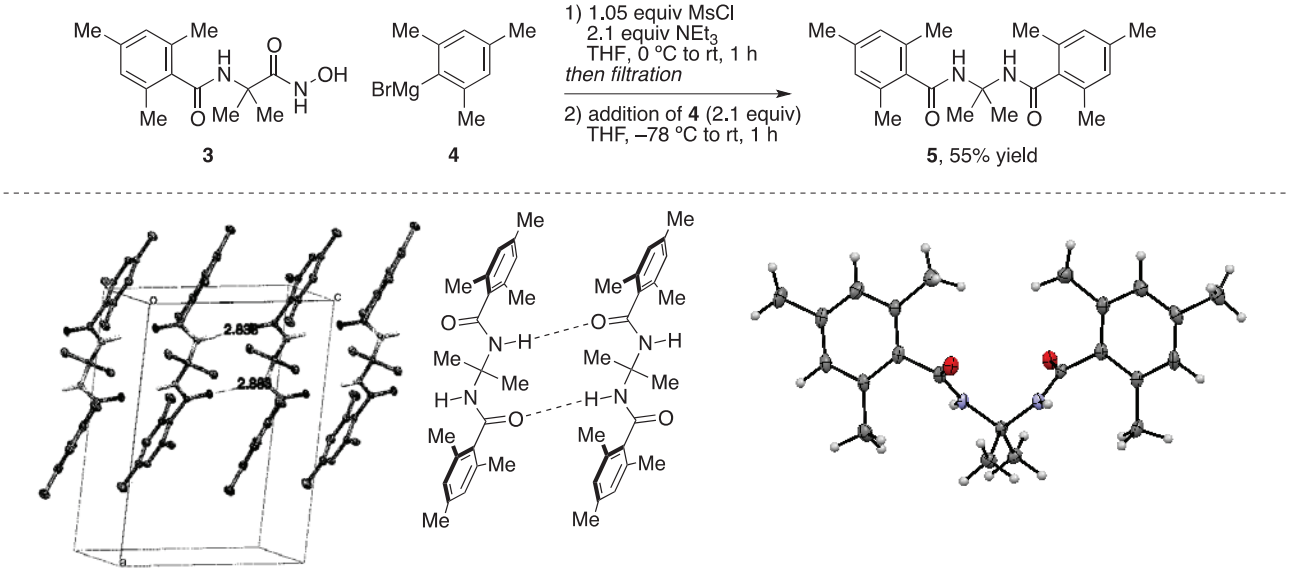
We focused our attention on the investigation of milder isocyanate-forming reactions. The Lossen rearrangement is the conversion of a hydroxamic acid to an isocyanate via the formation of an *O*-acyl, -sulfonyl or -phosphoryl intermediate.[6] This reaction normally takes place under mild reaction conditions and in non-aqueous solvents, which prevents the hydrolysis of the isocyanate to the amine. We examined different bases and activating reagents and found that hydroxamic acid **3**, which was prepared in one step from amino acid **1**, could be successfully converted into the desired isocyanate **2** by using methanesulfonyl chloride (MsCl) and triethylamine (Scheme 4). However, the purification of the isocyanate was cumbersome and partial decomposition of the relatively unstable product occurred on silica gel, leading to a low isolated yield.



Scheme 4. Preparation of isocyanate **2** via Lossen rearrangement

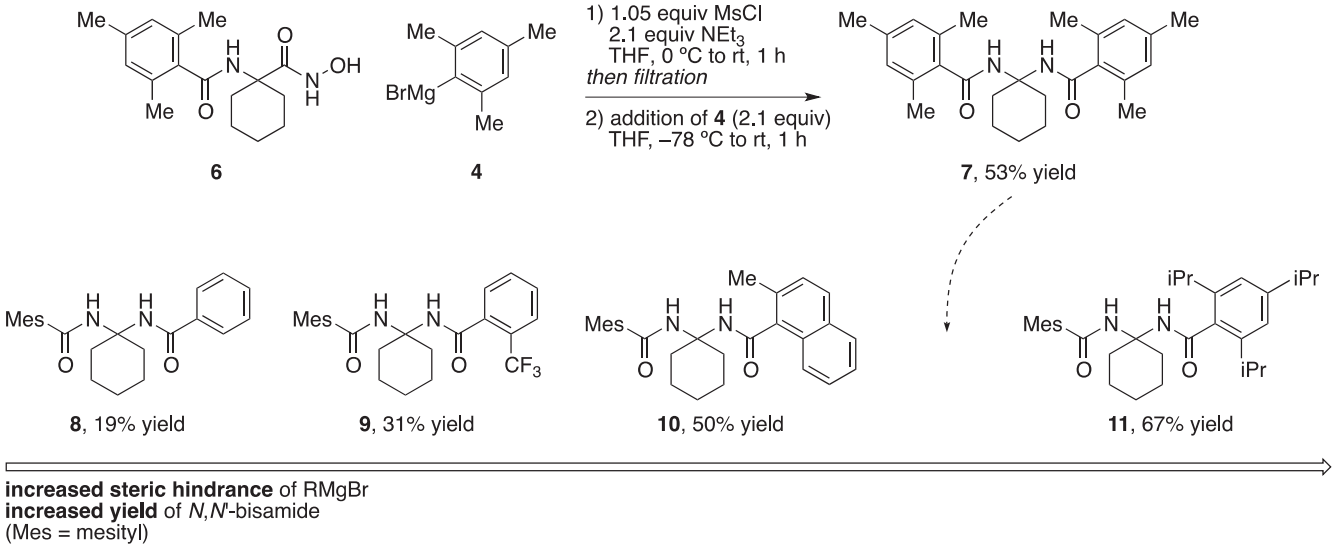
In order to circumvent the isolation of the isocyanate, a semi one-pot approach was envisioned: after completion of the Lossen rearrangement a simple filtration of the reaction mixture was used to remove the precipitated triethylammonium chloride and resulted in a salt-free THF solution containing isocyanate **2**, which could be directly treated with a Grignard reagent to form the desired bisamide. When the reaction mixture was filtered into a new round-bottom flask after complete rearrangement and this isocyanate solution was cooled to –78 ºC and 2.1 equivalents of mesitylmagnesium bromide (**4**) were added, it was possible to isolate *gem*-dimethyl bisamide **5** in 55% yield (Scheme 5). The product proved to be a bench-stable colorless solid and its structure was confirmed by X-ray crystallography. According

to the crystal structure bisamide **5** adapts a sheet-like orientation with intermolecular hydrogen-bonding interactions between the individual amide functionalities.



Scheme 5. Successful synthesis and characterization of bisamide **5**

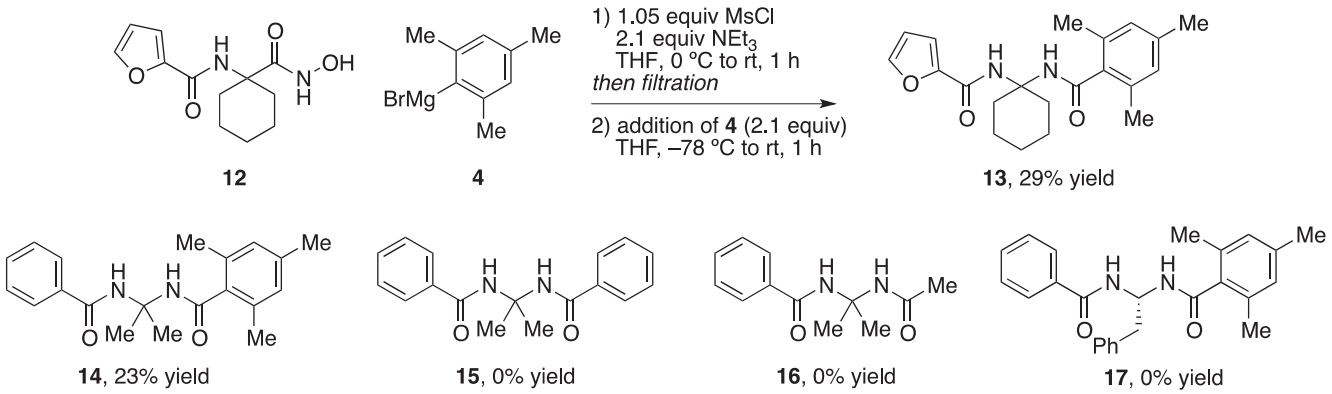
Driven by the success of this filtration/addition protocol, the synthesis of other bisamides was investigated. The more sterically hindered cyclohexyl derivative **6** could be successfully converted into the symmetrical bisamide **7**. By simply changing the Grignard reagent, the synthesis of the previously elusive unsymmetrical, *gem*-disubstituted bisamides was also feasible. Interestingly, the reaction with sterically unbiased organomagnesium reagents provided the bisamide in significantly lower yield than with the sterically hindered counterparts (Scheme 6).



Scheme 6. Synthesis of different bisamides

We believe that the diminished yield with phenylmagnesium bromide and other small Grignard reagents can be attributed to a rapid abstraction of the amide N-H proton, which leads to elimination of cyanate and results in the decomposition of the intermediate isocyanate. This deprotonation/elimination pathway is much slower for bulky Grignard reagents, which is reflected in a cleaner reaction and easier isolation of the bisamide products compared to the use of sterically unhindered reagents.

By changing the *N*-acyl group, the interesting heterocyclic bisamide **13** could be prepared, albeit in low yield. The use of benzoylated hydroxamic acid in combination with sterically hindered mesitylmagnesium bromide (**4**) led to the successful isolation of **14**. The major limitation of our approach is the restriction to sterically hindered starting materials or Grignard reagents. When two completely unbiased reaction partners are employed, a multitude of side products are generated and the isolation of the bisamide is not possible (Scheme 7).



Scheme 7. Scope and limitations of the methodology

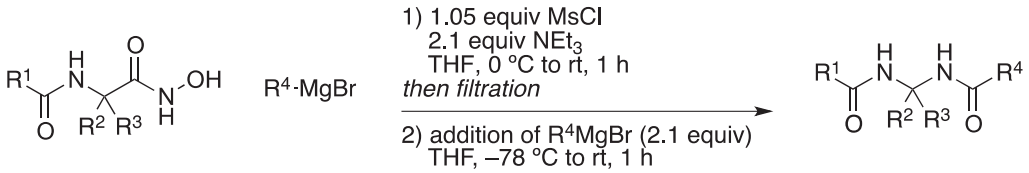
In summary, we have identified an approach to the synthesis of unsymmetrical, *gem*-disubstituted bisamides by the addition of Grignard reagents to *N*-acyl isocyanates. These relatively unstable isocyanates were generated *in situ* via Lossen rearrangement and their isolation could be circumvented by the use of a novel filtration/addition protocol. We believe that these *gem*-disubstituted bisamides could serve as promising building blocks in medicinal chemistry, and that this one-pot Lossen rearrangement/Grignard addition sequence could also be interesting for the generation of other challenging structures.

EXPERIMENTAL

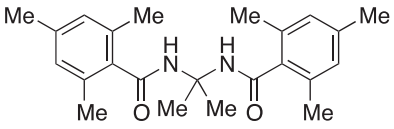
General Methods. All reactions were carried out in oven-dried glassware under dry N_2 atmosphere. Tetrahydrofuran (THF) was distilled from Na with benzophenone. Triethylamine (NEt_3) was distilled over CaH_2 and stored in a Schlenk-flask under N_2 atmosphere. *N*-Acylated amino acids were synthesized

according to our previously published method.[5] All other chemicals were used without further purification. Thin layer chromatography (TLC) was performed on Merck TLC plates pre-coated with silica gel 60 F254. Developed plates were visualized under a UV lamp (254 nm), or stained with potassium permanganate. Column chromatography was performed on Silicycle SiliaFlash F60 (230–400 Mesh) using a forced flow of air at 0.5–1.0 bar. ^{1}H NMR and ^{13}C NMR were measured on VARIAN Mercury 300 MHz, 75 MHz or Bruker Avance 400 MHz, 101 MHz. ^{19}F NMR spectra were recorded with ^{1}H decoupling in $CDCl_3$ referenced to TFA (-76.53 ppm). Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in Hertz (Hz). Splitting patterns are indicated as follows: app, apparent; br, broad; s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; sept, septet; m, multiplet. High-resolution mass spectrometric measurements were performed by the mass spectrometry service of the ETH Zürich on a Waters/Micromass AutoSpec Ultima (EI), a Varian IonSpec FT-ICR (ESI) or a Bruker maXis (ESI) spectrometer. IR spectra were obtained on a Varian 800 FT-IR (ATR) spectrometer. The wavenumbers of the bands are reported in cm^{-1}; the relative intensity of the bands is indicated by w (weak), m (medium), s (strong) and br (broad).

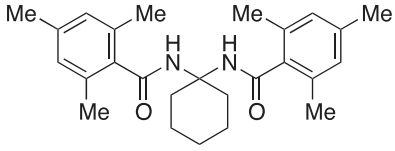
General Procedure for Synthesis of Bisamides via Lossen Rearrangement



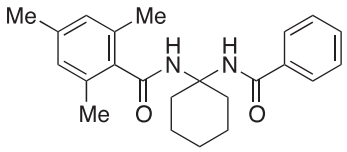
In a flame-dried round-bottom flask under N_2 the hydroxamic acid (0.50 mmol, 1.0 equiv) was dissolved in dry THF (5.0 mL) and NEt_3 (0.15 mL, 1.05 mmol, 2.1 equiv) was added. The solution was cooled to 0 ºC and methanesulfonyl chloride (41 μL, 0.53 mmol, 1.05 equiv) was added slowly. The reaction mixture was warmed to rt and stirred for 1 h. The reaction mixture was quickly filtered through a glass filter (medium porosity) into a second, flame-dried round-bottom flask and the filter cake rinsed with dry THF (1.0 mL). The second round-bottom flask was placed under N_2 and cooled to –78 ºC. The Grignard solution (1.05 mmol, 2.1 equiv) was added dropwise over 2–3 min directly into the solution. The reaction mixture was stirred at –78 ºC for 15 min, before the flask was removed from the cooling bath and the reaction mixture stirred at rt for 1 h. The reaction mixture was quenched with 1 M aq HCl (10 mL) and stirred for 1 min. EtOAc (15 mL) was added and the layers were separated. The aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was purified by washing with 2 x 5 mL of dry Et_2O or via flash column chromatography (slow gradient of cyclohexane:EtOAc) and the bisamide isolated as a bench-stable, colorless solid.



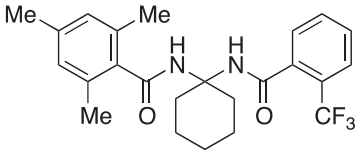
***N*,*N*'-(Propane-2,2-diyl)bis(2,4,6-trimethylbenzamide) (5)**: Prepared according to the general procedure from *N*-(2-isocyanatopropan-2-yl)-2,4,6-trimethylbenzamide (0.13 g, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol). The crude material was washed with Et_2O (2 x 5 mL) and the product isolated as a colorless solid (0.10 g, 0.27 mmol, 55%). **mp** > 225 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.83 (s, 4H), 6.45 (s, 2H), 2.35 (s, 12H), 2.28 (s, 6H), 1.91 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.3, 138.6, 135.1, 134.3, 128.4, 66.7, 60.5, 27.5, 21.2, 21.2, 19.3, 14.3; **IR** (ATR) ν 3273 (m), 2920 (w), 1645 (s), 1543 (s), 1308 (m), 1215 (m), 844 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{23}H_{31}N_2O_2$ ($[M+H]^+$): 367.2380. Found: 367.2387.



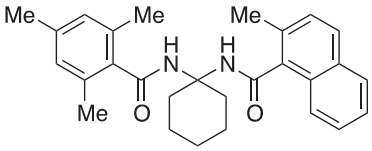
***N*,*N*'-(Cyclohexane-1,1-diyl)bis(2,4,6-trimethylbenzamide) (7)**: Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol). The crude material was washed with Et_2O (2 x 5 mL) and the product isolated as a colorless solid (0.11 g, 0.27 mmol, 53%). **mp** 221 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.84 (s, 4H), 6.25 (s, 2H), 2.38 (br s, 16H), 2.27 (s, 6H), 1.67 – 1.57 (m, 4H), 1.55 – 1.47 (m, 2H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.3, 138.6, 135.2, 134.5, 128.5, 68.5, 35.0, 35.0, 25.3, 22.2, 21.2, 19.7; **IR** (ATR) ν 3287 (m), 2922 (w), 2854 (w), 1643 (s), 1531 (s), 1301 (m), 845 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{26}H_{35}N_2O_2$ ($[M+H]^+$): 407.2693. Found: 407.2693.



***N*-(1-Benzamidocyclohexyl)-2,4,6-trimethylbenzamide (8)**: Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and phenylmagnesium bromide (0.35 mL of a 3.0 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 9:1 to 5:1) and the product isolated as a colorless solid (32 mg, 0.088 mmol, 18%). **mp** 197 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.80 – 7.75 (m, 2H), 7.53 – 7.47 (m, 1H), 7.46 – 7.39 (m, 2H), 6.90 (s, 1H), 6.81 (s, 2H), 6.32 (s, 1H), 2.56 – 2.32 (m, 4H), 2.27 (s, 6H), 2.25 (s, 3H), 1.71 – 1.49 (m, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 171.0, 168.1, 138.5, 135.7, 135.2, 134.3, 131.6, 128.8, 128.3, 127.1, 68.9, 35.3, 25.5, 22.4, 21.2, 19.2; **IR** (ATR) ν 3279 (br), 2929 (w), 1642 (s), 1538 (s), 1451 (m), 850 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{23}H_{29}N_2O_2$ ($[M+H]^+$): 365.2224. Found: 365.2225.

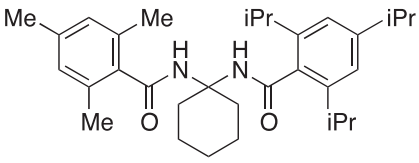


2,4,6-Trimethyl-*N*-(1-(2-(trifluoromethyl)benzamido)cyclohexyl)-benzamide (9): Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and (2-(trifluoromethyl)phenyl)magnesium bromide (1.2 mL of a 0.9 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 9:1 to 3:1) and the product isolated as a colorless solid (67 mg, 0.15 mmol, 31%). **mp** > 225 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.71 (br d, *J* = 7.2 Hz, 1H), 7.66 (br d, *J* = 7.2 Hz, 1H), 7.63 – 7.49 (m, 2H), 6.84 (s, 2H), 6.51 (s, 1H), 6.23 (s, 1H), 2.53 – 2.39 (m, 2H), 2.35 (s, 6H), 2.27 (s, 3H), 2.26 – 2.22 (m, 2H), 1.72 – 1.59 (m, 4H); **^{13}C NMR** (101 MHz, d^6-DMSO) 168.8, 166.3, 137.2 (d, *J* = 1.8 Hz), 136.5 (d, *J* = 47.4 Hz), 134.0, 133.6, 132.1, 129.2 (d, *J* = 38.4 Hz), 127.7, 127.5, 126.0 (d, *J* = 4.7 Hz), 125.7 (d, *J* = 31.3 Hz), 123.9 (d, *J* = 274 Hz), 68.1, 34.0, 25.0, 21.5, 20.6, 19.1; **^{19}F NMR** (376 MHz, $CDCl_3$) –58.7; **IR** (ATR) ν 3417 (br), 2858 (w), 1644 (s), 1536 (m), 1315 (m), 1172 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{24}H_{27}F_3N_2O_2$ ([M+H]$^+$): 432.2025. Found: 432.2027.

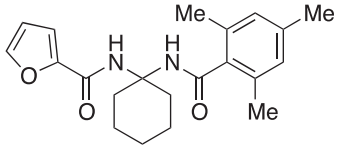


2-Methyl-*N*-(1-(2,4,6-trimethylbenzamido)cyclohexyl)-1-naphthamide (10): *Grignard reagent*: To a flame-dried Schlenk-flask were added Mg turnings (107 mg, 4.4 mmol) and THF (2.0 mL). A few drops of 1,2-dibromoethane were added, followed by dropwise addition of a solution of 1-bromo-2-methylnaphthalene (0.49 g, 2.0 mmol) in toluene (2.0 mL) over 5 min at rt. The reaction mixture was heated to 50 ºC and stirred for 1 h. LC/MS showed complete consumption of 1-bromo-2-methylnaphthalene. The concentration was determined by titration: 0.40 M in THF/toluene 1:1.

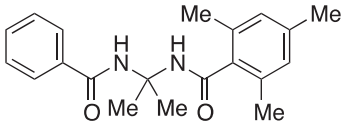
The product was prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and (2-methylnaphthalen-1-yl)magnesium bromide (2.3 mL of a 0.45 M solution in THF/toluene 1:1, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 9:1 to 5:1) and the product isolated as a colorless solid (0.11 g, 0.26 mmol, 53%). **mp** 220 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 8.13 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.52 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.44 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 6.86 (s, 2H), 6.47 (s, 1H), 6.38 (s, 1H), 2.60 (s, 3H), 2.54 – 2.46 (m, 3H), 2.42 (s, 6H), 2.29 (s, 3H), 1.73 – 1.48 (m, 7H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.6, 169.6, 138.7, 135.3, 134.5, 134.0, 132.6, 131.9, 130.3, 129.1, 128.7, 128.5, 128.1, 127.1, 125.6, 125.0, 68.7, 35.1, 25.4, 22.3, 21.2, 20.1, 19.8; **IR** (ATR) ν 3282 (m), 2927 (w), 1641 (s), 1532 (s), 1451 (w), 1258 (m), 808 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{28}H_{33}N_2O_2$ ([M+H]$^+$): 429.2537. Found: 429.2540.



2,4,6-Triisopropyl-*N*-(1-(2,4,6-trimethylbenzamido)cyclo-hexyl)-benzamide (11): Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (0.15 g, 0.50 mmol) and 2,4,6-triisopropylphenylmagnesium bromide (2.1 mL of a 0.5 M solution in THF, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 10:1 to 7:1) and the product isolated as a colorless solid (0.17 g, 0.34 mmol, 67%). **mp** 165 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 7.01 (s, 2H), 6.84 (s, 2H), 6.25 (s, 1H), 6.23 (s, 1H), 3.16 (hept, *J* = 6.7 Hz, 1H), 2.88 (hept, *J* = 6.7 Hz, 1H), 2.51 – 2.41 (m, 2H), 2.38 (s, 6H), 2.35 – 2.29 (m, 2H), 2.28 (s, 3H), 1.66 – 1.47 (m, 6H), 1.30 (d, *J* = 6.4 Hz, 6H), 1.25 (d, *J* = 6.9 Hz, 12H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.5, 170.2, 149.9, 145.2, 138.5, 135.5, 134.4, 133.7, 128.4, 121.3, 68.7, 35.0, 34.5, 30.9, 27.1, 25.3, 24.9, 24.8, 24.1, 22.2, 21.2, 19.6; **IR** (ATR) ν 3280 (br), 2958 (m), 2931 (m), 2866 (w), 1634 (s), 1530 (s), 1454 (m), 1298 (m), 873 (w), 850 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{32}H_{47}N_2O_2$ ($[M+H]^+$): 491.3632. Found: 491.3628.

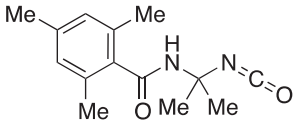


***N*-(1-(2,4,6-Trimethylbenzamido)cyclohexyl)furan-2-carboxamide (13)**: Prepared according to the general procedure from *N*-(1-(hydroxycarbamoyl)cyclohexyl)furan-2-carboxamide (0.13 g, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 4:1 to 1:1) and the product isolated as a colorless solid (51 mg, 0.14 mmol, 29%). **mp** 180 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 8.45 (s, 1H), 7.83 (s, 1H), 7.81 (s, 1H), 7.18 (s, 1H), 6.78 (s, 2H), 6.61 (s, 1H), 2.39 – 2.23 (m, 4H), 2.21 (s, 3H), 2.13 (s, 6H), 1.68 – 1.31 (m, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 169.1, 157.2, 148.0, 144.9, 136.7, 136.2, 133.5, 127.5, 113.4, 111.7, 68.1, 34.3, 24.9, 21.8, 20.6, 18.8; **IR** (ATR) ν 3297 (br), 2923 (w), 1648 (s), 1590 (w), 1516 (m), 1300 (m), 1177 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{21}H_{27}N_2O_3$ ($[M+H]^+$): 355.2016. Found: 355.2014.



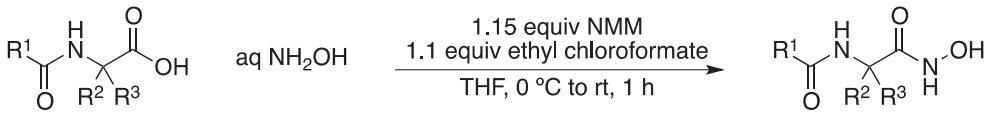
***N*-(2-Benzamidopropan-2-yl)-2,4,6-trimethylbenzamide (14)**: Prepared according to the general procedure from *N*-(1-(hydroxyamino)-2-methyl-1-oxopropan-2-yl)benzamide (0.11 g, 0.50 mmol) and mesitylmagnesium bromide (1.05 mL of a 1.0 M solution in Et_2O, 1.05 mmol). The crude material was purified by flash column chromatography (gradient cyclohexane:EtOAc 5:1 to 1:1) and the product isolated as a colorless solid (37 mg, 0.11 mmol, 23%). **mp** 205 ºC; **^{1}H NMR** (400 MHz, d^6-DMSO) 8.53

(s, 1H), 8.44 (s, 1H), 7.79 (d, *J* = 6.9 Hz, 2H), 7.51 (ddd, *J* = 6.3, 3.7, 1.4 Hz, 1H), 7.48 – 7.41 (m, 2H), 6.80 (s, 2H), 2.21 (s, 3H), 2.16 (s, 6H), 1.77 (s, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 168.6, 166.3, 136.7, 136.2, 135.7, 133.5, 130.9, 128.0, 127.5, 127.4, 66.0, 27.1, 20.6, 18.6; **IR** (ATR) ν 3432 (br), 2982 (w), 1645 (s), 1546 (m), 1313 (m), 1213 (w), 847 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{20}H_{25}N_2O_2$ ([M+H]$^+$): 325.1911. Found: 325.1911.

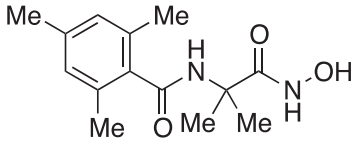


***N*-(2-Isocyanatopropan-2-yl)-2,4,6-trimethylbenzamide (2)**: The isocyanate was prepared according to the general procedure from *N*-(2-isocyanatopropan-2-yl)-2,4,6-trimethylbenzamide (0.13 g, 0.50 mmol), but after filtration the reaction mixture was concentrated under reduced pressure at 25 ºC. The obtained crude material was purified by flash column chromatography (pentane:EtOAc 4:1) and the product isolated as a colorless solid (43 mg, 0.17 mmol, 35%). **mp** 84 ºC; **^{1}H NMR** (400 MHz, $CDCl_3$) 6.84 (s, 2H), 6.00 (s, 1H), 2.31 (s, 6H), 2.28 (s, 3H), 1.80 (s, 6H); **^{13}C NMR** (101 MHz, $CDCl_3$) 170.5, 139.0, 136.1, 134.3, 128.4, 69.2, 30.5, 21.2, 19.1; **IR** (ATR) ν 3260 (br), 2919 (w), 2249 (s), 1635 (m), 1539 (s), 1211 (m), 1151 (s), 844 (m) cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{14}H_{18}N_2O_2$ (M^+): 246.1368. Found: 246.1366.

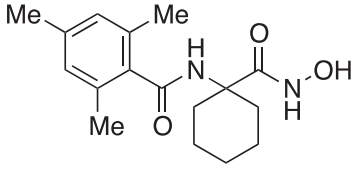
General Procedure for Synthesis of Hydroxamic Acids



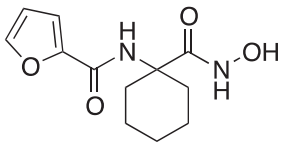
In a flame-dried round-bottom flask under N_2 the *N*-acyl amino acid (1.0 mmol, 1.0 equiv) was dissolved in dry THF (5.0 mL) and *N*-methylmorpholine (NMM, 0.13 mL, 1.15 mmol) was added. The solution was cooled to –5 ºC (if not otherwise noted) and ethyl chloroformate (0.10 mL, 1.1 mmol) was added slowly via micro syringe. The reaction mixture was stirred at –5 ºC for 15 min and a 50% aq hydroxylamine solution (0.5 mL, ca. 10 mmol) was added in one portion. The reaction mixture was warmed to rt and stirred for 30 min. The reaction mixture was quenched with H_2O (10 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The obtained crude material was washed with Et_2O (2 x 5 mL) and the hydroxamic acid isolated as a colorless solid.



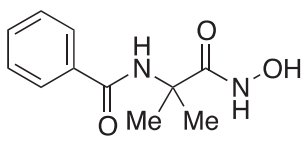
***N*-(1-(Hydroxyamino)-2-methyl-1-oxopropan-2-yl)-2,4,6-trimethylbenzamide (3)**: Prepared according to the general procedure from 2-methyl-2-(2,4,6-trimethylbenzamido)propanoic acid (0.25 g, 1.0 mmol) and the product isolated as a colorless solid (0.23 g, 0.91 mmol, 91%). **^{1}H NMR** (400 MHz, d^6-DMSO) 10.29 (s, 1H), 8.69 (s, 1H), 8.15 (s, 1H), 6.81 (s, 2H), 2.20 (s, 9H), 1.42 (s, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 171.4, 168.7, 136.9, 135.6, 133.9, 127.5, 55.1, 26.8, 25.0, 20.6, 18.7; **IR** (ATR) ν 3253 (br), 1637 (s), 1530 (s), 1454 (m), 1314 (m), 1220 (m), 896 (w) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{14}H_{20}N_2NaO_3$ ([M+Na]$^+$): 287.1366. Found: 287.1372.



***N*-(1-(Hydroxycarbamoyl)cyclohexyl)-2,4,6-trimethylbenzamide (6)**: Prepared according to the general procedure from 1-(2,4,6-trimethylbenzamido)cyclohexanecarboxylic acid (0.29 g, 1.0 mmol) and the product isolated as a colorless solid (0.26 g, 0.87 mmol, 87%). **^{1}H NMR** (400 MHz, d^6-DMSO) 10.19 (s, 1H), 8.63 (s, 1H), 7.99 (s, 1H), 6.81 (s, 2H), 2.25 (s, 6H), 2.22 (s, 3H), 2.17 (d, *J* = 13.1 Hz, 2H), 1.74 – 1.59 (m, 2H), 1.59 – 1.40 (m, 5H), 1.32 – 1.09 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 171.7, 169.6, 136.8, 135.9, 134.0, 127.6, 58.6, 31.9, 25.1, 21.3, 20.6, 19.2; **IR** (ATR) ν 3255 (br), 1638 (s), 1531 (s), 1453 (m), 1311 (m), 848 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{17}H_{24}N_2NaO_3$ ([M+Na]$^+$): 327.1679. Found: 327.1683.



***N*-(1-(Hydroxycarbamoyl)cyclohexyl)furan-2-carboxamide (12)**: Prepared according to the general procedure from 1-(furan-2-carboxamido)-cyclohexanecarboxylic acid (0.24 g, 1.0 mmol) and the product isolated as a colorless solid (0.19 g, 0.74 mmol, 74%). **^{1}H NMR** (400 MHz, d^6-DMSO) 10.38 (s, 1H), 8.59 (s, 1H), 7.83 (d, *J* = 0.9 Hz, 1H), 7.44 (s, 1H), 7.16 (d, *J* = 2.9 Hz, 1H), 6.62 (dd, *J* = 3.4, 1.7 Hz, 1H), 2.17 (d, *J* = 13.1 Hz, 2H), 1.70 (td, *J* = 13.1, 3.4 Hz, 2H), 1.60 – 1.31 (m, 5H), 1.32 – 1.10 (m, 1H); **^{13}C NMR** (101 MHz, d^6-DMSO) 171.1, 157.4, 147.9, 144.9, 113.6, 111.7, 58.4, 31.7, 24.9, 21.0; **IR** (ATR) ν 3216 (br), 2929 (w), 2857 (w), 1643 (s), 1591 (s), 1517 (m), 1298 (w), 1016 (m) cm^{-1}; **HRMS** (ESI) *m/z* calcd for $C_{12}H_{16}N_2NaO_4$ ([M+Na]$^+$): 275.1002. Found: 275.1003.



***N*-(1-(Hydroxyamino)-2-methyl-1-oxopropan-2-yl)benzamide**: Prepared according to the general procedure from 2-benzamido-2-methylpropanoic acid (0.21 g, 1.0 mmol) and the product isolated as a colorless solid (0.14 g, 0.65

mmol, 65%). *Reaction performed at −20 ºC before addition of aq hydroxylamine solution*. **^{1}H NMR** (400 MHz, d^6-DMSO) 10.43 (s, 1H), 8.60 (s, 1H), 8.15 (s, 1H), 7.92 – 7.79 (m, 2H), 7.57 – 7.50 (m, 1H), 7.48 – 7.37 (m, 2H), 1.45 (s, 6H); **^{13}C NMR** (101 MHz, d^6-DMSO) 171.3, 165.8, 134.8, 131.0, 128.0, 127.6, 55.4, 25.4; **HRMS** (ESI) *m/z* calcd for $C_{11}H_{14}N_2NaO_3$ ([M+Na]$^+$): 245.0897. Found: 245.0896.

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