A Trimethylsilylamine-Acyl Fluoride Amide Bond Forming Protocol for Weakly Nucleophilic Amines that is Amenable to the Parallel Synthesis of Di(hetero)arylamides

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Abstract The reaction of a 2-pyridinone-based acid fluoride with the *N*-TMS derivatives of different weakly nucleophilic heteroaryl/aryl amines in acetonitrile containing catalytic fluoride ion provides a clean, efficient and simple means to access a diverse range of polar di(hetero)arylamide structures. This amide bond forming protocol is readily amenable to the parallel synthesis of compound libraries.

Key words amide coupling, di(hetero)arylamide, acid fluoride, heteroarylamine, *N*-TMS activation, parallel synthesis

The screening of compound libraries has repeatedly demonstrated its effectiveness as a research tool in drug discovery. In particular, when mechanistic and/or structural details for the therapeutic target are lacking, compound library screening is one of very few options possible to identify new and/or groundbreaking avenues for drug development. In our laboratory, parallel synthesis is used to connect and functionalize novel scaffolds into libraries of bioactive molecules containing different architectures. In particular, amide bond formation was used to generate molecules that possess a di(hetero)arylamide (DHA) substructure. The screening of a 256-membered library containing 119 DHA compounds identified four novel and related molecules **1–4** (Figure 1) that block HIV-1 replication by a mechanism involving perturbation of the alternative splicing events leading to production of key HIV regulatory proteins.^{1a,b}

For the construction of the amide bond, a wide range of peptide (amide) bond forming reagents and conditions are available.² However, in our library project, where electron-deficient (weakly nucleophilic) heterocyclic amines were engaged,³ the yield of the DHA product in reactions using

the acid chloride method and different peptide coupling reagents rarely exceeded 10–30%. In fact, the formation of complex mixtures of polar compounds was generally observed, complicating workup and isolation/purification of the desired product. To advance the anti-HIV project, and other applications for the DHA library, it became important to develop a new amide synthesis protocol.

In this report, we describe the development of such a protocol for amide bond construction that is efficient and amenable to the parallel synthesis of novel di(hetero)aryl-amides. The procedure is based on the reaction of readily available *N*-trimethylsilylamines with acid fluorides in the presence of catalytic fluoride ion. Formally, the fluoride ion reacts with the silylated amine to form a 'hypervalent' silicon species,⁴ which readily decomposes to produce volatile TMSF and an amine anion intermediate, which is higher in energy and more nucleophilic/reactive than the corresponding free amine. Although often stable to water, and less reactive than acid chlorides toward alcohols, acid fluorides react efficiently with amines to give the expected amide products.^{5,6} An additional attractive feature of the use of acid fluorides and silylated amines as the coupling partners is that these heterocyclic components are nonpolar relative to their amine/acid precursors and to the amide products that are generated. Consequently, by choosing a reaction solvent in which the polar di(hetero)arylamide product selectively precipitates, its isolation is reduced to a simple filtration. For development of the protocol, the acid fluoride derivative of 2-pyridinone-5-carboxylic acid (**6**) was used as the acid component, as beyond the discovery of compound **4**¹ (Figure 1) relatively little development of this scaffold in amide synthesis has been described.⁷

Carboxylic acid **6** was prepared (Scheme 1) by O4-alkylation of 2-pyridinone ester **5**^{1,7} with 1-bromo-2-methoxyethane (DMF, Cs₂CO₃) and subsequent hydrolysis of the ester group using LiOH in THF–H₂O (2:1). Conversion of **6** to acid fluoride **7** was best achieved through reaction with fluoro-*N,N,N',N'*-tetramethylformamidinium hexafluorophosphate (TFFH)⁸ and cesium fluoride (CsF) in anhydrous MeCN at room temperature for 5 hours. The presence of added fluoride ion was mandatory in order to avoid com-

peting formation of the symmetrical anhydride **8**.⁹ Compound **7** was isolated pure as a colorless solid (90%) by washing the crude product mixture with hexane to remove the tetramethylurea formed, and then taking the solid material up in dichloromethane, filtering to remove the excess CsF, and concentrating to dryness. The structure of **7** was confirmed by the presence of a peak at 25.43 ppm in the ¹⁹F NMR spectrum, and by the up-field shift ($\Delta\delta$ 0.14 ppm) from δ = 8.34 for the peak for H-6 in the ¹H NMR spectrum. As expected, acid fluoride **7** was much more stable than the corresponding (and corrosive) acid chloride derivative, and could be conveniently stored for periods exceeding one month in an airtight container at 4 °C. In fact, when dissolved in dichloromethane and washed with ice water, it was recovered in greater than 90% yield (purity check by ¹H NMR spectroscopy).

The diversity set of 18 trimethylsilylated heteroaryl/arylamines **9a–r** (Table 1) used in this study was prepared by reacting 0.5 mmol of the requisite amine in neat trimethylsilyl cyanide (TMSCN) (0.5 mL) at 70 °C (30 to 180 min) (Table 1).¹⁰ The advancement of each reaction was monitored by ¹H NMR spectroscopy (CDCl₃). Interestingly, the time required to observe complete dissolution of the amine, that is, an indicator of complete *N*-silylation, appeared to be a function of both the reactivity of the amine and its solubility. Indeed, the duration of reaction required did not follow a clear linear relationship to the electron density on the exocyclic amine nitrogen (as calculated using Spartan software¹¹) (see calculated *e*[−]-density values in Table 1). With the exception of TMS-amines **9m** and **9p**, the polar amine substrates dissolved in TMSCN as the reaction progressed. As the only by-product of the reaction was volatile HCN, it and the residual TMSCN were removed under vacuum.

Scheme 1 Preparation of acyl fluoride **7** and its reaction with TMS-**9a–r**

Table 1 Synthesis of Di(hetero)arylamides **4** and **10** from TMS-Amines **9a–r**

	TMS-amine 9 ^a	Electron density	N-Silylation time	Amide ^{a,b} (yield, %)
TMS- 9a		140.1	7 (91%) ^c	10a (78)
TMS- 9b ¹²		132.2	30	10b (7)
TMS- 9c		120	30	10c (27)
TMS- 9d		119.5	15	10d (34)
TMS- 9e		115	30	10e (53)
TMS- 9f ^{13a–d}		112.8	30	10f (55)
TMS- 9g ¹⁴		105.9	180	10g (89)
TMS- 9h ^{13a}		100.5	90	10h (42)
TMS- 9i		98	120	10i (62)
TMS- 9j		97.8	30	10j (71)
TMS- 9k		96	180 (96%) ^c	10k (85)
TMS- 9l ¹⁵		92.9	30	10l (87)
TMS- 9m ^{1b}		88.8	30	4 (60) ^{1a,b}
TMS- 9n		88.7	30	10n (92)
TMS- 9o ^{13a}		80.4	180	10o (81)

Table 1 (continued)

	TMS-amine 9 ^a	Electron density	N-Silylation time	Amide ^{a,b} (yield, %)
TMS- 9p		77.3	60	10p (63)
TMS- 9q		74.7	30	10q (44)
TMS- 9r		58.4	360 (85%) ^c	10r (67)

^a All known compounds are cited by literature references.^b Amide formation: TMS-amine (0.5 mmol) + acid fluoride (0.89 mmol) in MeCN (5 mL), 50 °C, overnight, (isolated yield).^c Percent conversion to TMS-amine.

As alluded to already, reactions where the acid chloride derivative of carboxylic acid **6** (and the related compound containing a 4-OMe substituent¹) was coupled to amines **9** using different solvents (DMF, CH₂Cl₂, THF) and bases (Et₃N, pyridine, K₂CO₃) at room temperature, or with heating, resulted in incomplete conversion to the desired amide products. Under these conditions, the product mixture contained unreacted amine/acid, as well as copious amounts of unidentified polar material. This, plus the fact that the product mixtures were poorly soluble, complicated purification and limited applicability to synthesis or parallel synthesis. In contrast, the reaction of the four (nonsilylated) amines **9c**, **9g**, **9l**, and **9n** with excess of acid fluoride **7** in acetonitrile at 50 °C was remarkably efficient. Under these conditions the product precipitated from the medium as the reaction progressed, and was contaminated with much smaller quantities (up to 15%) of residual amine. Encouraged by this result, the reaction of TMS-**9n** with an excess (1.8 equiv) of acid fluoride **7** was evaluated. It was observed that any residual amine that may not have reacted remained in solution, as amide **10n** was isolated pure after filtration and drying in 47% yield. Further, a significant improvement in product yield (47% to 92%) was achieved by addition of a catalytic amount of TBAF (2 mol%) at the outset, to initiate reaction of fluoride ion with silicon and formation of the putative amine anion. The protocol that was subsequently employed for the synthesis of the new DHA molecules involved adding acid fluoride **7** (0.89 mmol) in acetonitrile (5 mL) to the requisite TMS-amine TMS-**9a–r** (0.5 mmol) (prepared immediately before the reaction). TBAF was then added, and the resulting mixture was heated at 50 °C overnight. After cooling, the precipitated material was collected by suction filtration and dried. As product purity, and not quantity, was the principle criterion for these reactions, efforts were generally not made to improve the amide product yields beyond those indicated in Table 1. In this context, it was interesting to observe that the yield

for the preparation of amide **10a** from the electron-rich amine TMS-**9a** was comparable to that for the preparation of **10r** from the electron-deficient amine TMS-**9r**. In fact, the initial yield for **10a** was 38%, but could be brought up to 78% by washing with a mixture of MeCN/Et₂O. This reflected the fact that amide **10a** is more soluble in MeCN than amide **10r**. The relatively lower yields for the isolation of amides **10b–d** also reflects their significant solubility in MeCN. For our purposes, ¹H NMR spectroscopy was used to determine product purity. In the large majority of cases, no impurities were detected, and in the few cases where the presence of the amine component persisted, only trace amounts were detectable (purity >95%) (see Supporting Information for copies of the ¹H NMR spectra for amides **10a–l**, **4**, and **10n–r**, isolated by filtration).

The results obtained with the test set of 18 different N-trimethylsilylated heteroaryl/arylamines in acetonitrile demonstrate the simplicity of the protocol and suggests its general applicability to a wide range of amines expressing weak nucleophilic character. Further, as extractive workup can be avoided and minimum waste is produced. This 'green' chemistry method¹⁶ can be readily adapted to rapid parallel synthesis of libraries of di(hetero)arylamide-based compounds.

All chemicals were purchased from Sigma Aldrich or Oakwood Chemicals and were used without purification, unless otherwise mentioned. All solvents were dried and kept under N₂. ¹H and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker AC 400 Ultrashield 10 spectrometer. Chemical shifts are expressed in ppm (δ scale). Standard abbreviations are used to report peak multiplicities. Coupling constants are reported in hertz (Hz). High-resolution mass spectra was recorded on a Thermo Scientific Q Exactive Orbitrap High Resolution Mass Spectrometer. IR spectra (cm⁻¹) were recorded on a Agilent Technologies (Cary 600 series) FT-IR spectrometer, using a PIKE MIRacle ATR accessory for sampling. Melting points were obtained using a Mel-Temp II apparatus.

4-(2-Methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carbonyl Fluoride (7)

A mixture of **6**^{1a,b} (1.0 g, 4.40 mmol), TFFH (1.18 g, 4.40 mmol), and CsF (1.57 g, 10.3 mmol) in MeCN (22 mL) was stirred for 12 h at r.t. The mixture was then concentrated under reduced pressure and washed with hexanes to remove the tetramethylurea formed. The product mixture was then dissolved in CH₂Cl₂ and filtered to remove the excess CsF. The filtrate was concentrated and dried under high vacuum for 2 days to afford **7** as a beige solid (0.91 g, 90%).

IR (ATR): 1814, 1778, 1678, 1617, 1530 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 8.20 (s, 1 H), 5.91 (s, 1 H), 4.13 (t, *J* = 4.3 Hz, 2 H), 3.81 (t, *J* = 4.3 Hz, 2 H), 3.57 (s, 3 H), 3.46 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 165.6, 163.5, 154.1, 150.8, 148.1, 97.3, 70.1, 69.0, 59.6, 37.8.

¹⁹F NMR (400 MHz, CDCl₃): δ = 25.43.

N-Trimethylsilylated Heteroaryl/arylamines TMS-9a–r; General Procedure

The starting amines were dried under high vacuum for 12 h. Then, a solution/mixture of the requisite amine (0.5 mmol) in Me₃SiCN (0.5 mL) was heated at 70 °C for the required time (Table 1). Without removing the hot oil bath, the resulting solution was flushed with N₂ for 15 min and then concentrated under high vacuum. The percent conversion of each amine to its N-silylated derivative was determined by ¹H NMR analysis in CDCl₃ (passed through a basic alumina column prior to use).

N-[(6-Chloropyridin-3-yl)methyl]-1,1,1-trimethylsilanamine (TMS-9a)

Heated for 7 min; yellow oil; 91% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 8.22 (s, 1 H), 7.54 (d, *J* = 8.1 Hz, 1 H), 7.18 (d, *J* = 8.1 Hz, 1 H), 3.85 (d, *J* = 8.2 Hz, 2 H), 0.00 (s, 9 H).

5-Methyl-N-(trimethylsilyl)isoxazol-3-amine (TMS-9b)¹²

Heated for 30 min; yellow solid; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 5.46 (s, 1 H), 3.75 (s, 1 H), 2.24 (s, 3 H), 0.23 (s, 9 H).

N-(Trimethylsilyl)isoquinolin-4-amine (TMS-9c)

Heated for 30 min; yellow solid; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 8.62 (s, 1 H), 8.03 (s, 1 H), 7.79 (d, *J* = 7.8 Hz, 1 H), 7.73 (d, *J* = 8.4 Hz, 1 H), 7.55 (t, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 3.88 (s, 1 H), 0.30 (s, 9 H).

4-Methyl-N-(trimethylsilyl)thiazol-2-amine (TMS-9d)

Heated for 15 min; yellow oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 5.95 (s, 1 H), 4.84 (s, 1 H), 2.14 (s, 3 H), 0.23 (s, 9 H).

3-Methyl-N-(trimethylsilyl)isoxazol-5-amine (TMS-9e)

Heated for 30 min; orange solid; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 4.78 (s, 1 H), 4.30 (s, 1 H), 2.08 (s, 3 H), 0.21 (s, 9 H).

N-(Trimethylsilyl)thiazol-2-amine (TMS-9f)^{13a–d}

Heated for 30 min; orange oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.02 (s, 1 H), 6.40 (s, 1 H), 5.20 (s, 1 H), 0.25 (s, 9 H).

Methyl 4-[(Trimethylsilyl)amino]benzoate (TMS-9g)¹⁴

Heated for 180 min; yellow oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.68 (d, *J* = 7.8 Hz, 2 H), 6.48 (d, *J* = 7.9 Hz, 2 H), 3.69 (s, 4 H), 0.14 (s, 9 H).

N-(Trimethylsilyl)pyrazin-2-amine (TMS-9h)^{13a}

Heated for 90 min; yellow oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.83 (t, *J* = 1.2 Hz, 3 H), 4.23 (s, 1 H), 0.24 (s, 9 H).

6-Chloro-N-(trimethylsilyl)pyridin-3-amine (TMS-9i)

Heated for 120 min; purple solid; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.73 (s, 1 H), 6.97 (d, *J* = 8.7 Hz, 1 H), 6.85 (d, *J* = 8.7 Hz, 1 H), 3.44 (s, 1 H), 0.20 (s, 9 H).

N-(Trimethylsilyl)benzo[d]thiazol-2-amine (TMS-9j)

Heated for 30 min; yellow oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.41 (s, 2 H), 7.13 (s, 1 H), 6.93 (s, 1 H), 4.91 (s, 1 H), 0.21 (s, 9 H).

3-[(Trimethylsilyl)amino]benzonitrile (TMS-9k)

Heated for 180 min; yellow oil; 96% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.03 (t, *J* = 7.8 Hz, 1 H), 6.81 (d, *J* = 7.5 Hz, 1 H), 6.69 (m, 2 H), 3.51 (s, 1 H), 0.13 (s, 9 H).

N-(Trimethylsilyl)-1,3,4-thiadiazol-2-amine (TMS-9l)¹⁵

Heated for 30 min; yellow solid; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 8.35 (s, 1 H), 6.01 (s, 1 H), 0.32 (s, 9 H).

5-Nitro-N-(trimethylsilyl)benzo[d]isothiazol-3-amine (TMS-9m)^{1b}

Heated for 30 min; red/orange solid; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 8.70 (s, 1 H), 7.99 (s, 1 H), 7.40 (s, 1 H), 5.96 (s, 1 H), 0.43 (s, 9 H).

4-Chloro-N-(trimethylsilyl)benzo[d]thiazol-2-amine (TMS-9n)

Heated for 30 min; yellow oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.37 (d, *J* = 7.7 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 6.92 (t, *J* = 7.7 Hz, 1 H), 5.22 (s, 1 H), 0.30 (s, 9 H).

4-[(Trimethylsilyl)amino]benzonitrile (TMS-9o)^{13a}

Heated for 180 min; yellow oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.23 (d, *J* = 8.0 Hz, 2 H), 6.49 (d, *J* = 8.0 Hz, 2 H), 3.79 (s, 1 H), 0.14 (s, 9 H).

5-(2-Chlorophenyl)-N-(trimethylsilyl)-1,3,4-oxadiazol-2-amine (TMS-9p)

Heated for 60 min; white solid; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.85 (d, *J* = 7.3 Hz, 1 H), 7.43 (d, *J* = 7.5 Hz, 1 H), 7.30 (m, 2 H), 5.45 (s, 1 H), 0.32 (s, 9 H).

2-Chloro-N-(trimethylsilyl)pyridin-4-amine (TMS-9q)

Heated for 30 min; orange oil; 100% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, J = 5.7 Hz, 1 H), 6.47 (s, 1 H), 6.38 (d, J = 5.6 Hz, 1 H), 4.09 (s, 1 H), 0.24 (s, 9 H).

5-[(Trimethylsilyl)amino]picolinonitrile (TMS-9r)

Heated for 6 h; orange solid; 85% conversion.

¹H NMR (400 MHz, CDCl₃): δ = 8.01 (s, 1 H), 7.37 (d, J = 8.6 Hz, 1 H), 6.88 (d, J = 8.6 Hz, 1 H), 3.99 (s, 1 H), 0.26 (s, 9 H).

Di(hetero)arylamides 10a–r; General Procedure

Acid fluoride **7** (200 mg, 0.89 mmol) in MeCN (5 mL) was added in one portion to the silylated amine **9a–r** (0.50 mmol) at r.t. This was quickly followed by addition of 1 M TBAF in THF (10 μ L, 0.01 mmol). The reaction mixture/solution was stirred at 50 °C for 12 h. The precipitated product was collected with suction filtration and washed with MeCN or the specified solvent (Table 1).

N-[(6-Chloropyridin-3-yl)methyl]-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10a)

From TMS-amine **9a**. The precipitated product was washed with MeCN/Et₂O (1:1) to afford **10a** as a white solid; yield: 274 mg (78%); mp 187–188 °C.

IR (ATR): 3393, 1675, 1632, 1528 cm^{−1}.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 8.37 (d, J = 2.4 Hz, 1 H), 8.28 (m, 2 H), 7.78 (dd, J = 2.5, 8.2 Hz, 1 H), 7.50 (d, J = 8.2 Hz, 1 H), 5.92 (s, 1 H), 4.49 (d, J = 5.9 Hz, 2 H), 4.19 (m, 2 H), 3.67 (m, 2 H), 3.42 (s, 3 H), 3.19 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.7, 162.7, 162.5, 148.9, 148.8, 144.5, 138.9, 134.5, 124.0, 105.7, 96.3, 69.3, 68.0, 58.1, 36.3.

HRMS (HESI): m/z [M – H][−] calcd for C₁₆H₁₇ClN₃O₄: 350.0913; found: 350.0916.

4-(2-Methoxyethoxy)-1-methyl-N-(5-methylisoxazol-3-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (10b)

From TMS-amine **9b**. The precipitated product was washed with MeCN to afford **10b** as a pale yellow solid; yield: 21 mg (7%); mp 179–181 °C.

IR (ATR): 3337, 1685, 1660, 1612, 1548 cm^{−1}.

¹H NMR (400 MHz, CDCl₃): δ = 9.98 (s, 1 H), 8.36 (s, 1 H), 6.71 (s, 1 H), 5.94 (s, 1 H), 4.24 (t, J = 3.8 Hz, 2 H), 3.85 (t, J = 3.7 Hz, 2 H), 3.58 (s, 3 H), 3.54 (s, 3 H), 2.41 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 169.8, 163.9, 163.8, 160.8, 158.2, 145.9, 105.6, 97.3, 97.1, 69.6, 68.7, 59.6, 37.7, 12.8.

HRMS (HESI): m/z [M – H]⁺ calcd for C₁₄H₁₆N₃O₅: 306.1095; found: 306.1102.

N-(Isoquinolin-4-yl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10c)

From TMS-amine **9c**. The precipitated product was washed with Et₂O to afford **10c** as a white solid; yield: 95 mg (27%); mp 213–214 °C.

IR (ATR): 3286, 1664, 1627, 1543 cm^{−1}.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.88 (s, 1 H), 9.20 (s, 1 H), 8.85 (s, 1 H), 8.48 (s, 1 H), 8.20 (d, J = 8.5 Hz, 1 H), 8.06 (d, J = 8.5 Hz, 1 H), 7.87 (d, J = 15.2 Hz, 1 H), 7.75 (d, J = 15.2 Hz, 1 H), 6.07 (s, 1 H), 4.36 (m, 2 H), 3.80 (m, 2 H), 3.50 (s, 3 H), 3.19 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.6, 162.8, 161.8, 149.5, 145.3, 138.4, 130.7, 130.0, 128.4, 128.3, 127.9, 127.7, 121.3, 105.8, 96.5, 69.4, 68.5, 58.2, 36.4.

HRMS (HESI): m/z [M + H]⁺ calcd for C₁₉H₂₀N₃O₄: 354.1448; found: 354.1449.

4-(2-Methoxyethoxy)-1-methyl-N-(4-methylthiazol-2-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (10d)

From TMS-amine **9d**. The precipitated product was washed with Et₂O to afford **10d** as a yellow solid; yield: 110 mg (34%); mp 189–190 °C.

IR (ATR): 3308, 1680, 1635, 1530 cm^{−1}.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.07 (s, 1 H), 8.48 (s, 1 H), 6.81 (s, 1 H), 6.00 (s, 1 H), 4.27 (m, 2 H), 3.75 (m, 2 H), 3.47 (s, 3 H), 3.40 (s, 3 H), 2.27 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.3, 162.7, 160.3, 156.5, 147.0, 145.8, 108.4, 104.0, 96.4, 69.4, 68.5, 58.5, 36.5, 16.9.

HRMS (HESI): m/z [M + H]⁺ calcd for C₁₄H₁₈N₃O₄S: 324.1013; found: 324.1015.

4-(2-Methoxyethoxy)-1-methyl-N-(3-methylisoxazol-5-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (10e)

From TMS-amine **9e**. The precipitated product was washed with Et₂O to afford **10e** as a white solid; yield: 163 mg (53%); mp 211–213 °C.

IR (ATR): 3306, 1694, 1656, 1610, 1528 cm^{−1}.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.72 (s, 1 H), 8.42 (s, 1 H), 6.24 (s, 1 H), 5.99 (s, 1 H), 4.25 (m, 2 H), 3.74 (m, 2 H), 3.46 (s, 3 H), 3.36 (s, 3 H), 2.21 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 162.7, 160.8, 160.4, 159.1, 145.7, 104.6, 96.4, 89.3, 69.4, 68.3, 58.3, 36.5, 11.4.

HRMS (HESI): m/z [M – H][−] calcd for C₁₄H₁₆N₃O₅: 306.1095; found: 306.1102.

4-(2-Methoxyethoxy)-1-methyl-6-oxo-N-(thiazol-2-yl)-1,6-dihydropyridine-3-carboxamide (10f)

From TMS-amine **9f**. The precipitated product was washed with Et₂O to afford **10f** as a pale yellow solid; yield: 170 mg (55%); mp 185–186 °C.

IR (ATR): 3311, 1678, 1632, 1612, 1530 cm^{−1}.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.14 (s, 1 H), 8.50 (s, 1 H), 7.50 (d, J = 3.5 Hz, 1 H), 7.27 (d, J = 3.5 Hz, 1 H), 6.01 (s, 1 H), 4.28 (m, 2 H), 3.76 (m, 2 H), 3.47 (s, 3 H), 3.38 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.3, 162.7, 160.4, 157.3, 145.8, 138.0, 114.2, 104.0, 96.4, 69.4, 68.5, 58.5, 36.5.

HRMS (HESI): m/z [M – H][−] calcd for C₁₃H₁₄N₃O₄S: 308.0711; found: 308.0696.

Methyl 4-[4-(2-Methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamido]benzoate (10g)

From TMS-amine **9g**. The precipitated product was washed with MeCN to afford **10g** as a white solid; yield: 321 mg (89%); mp 213–215 °C.

IR (ATR): 3348, 1688, 1656, 1592, 1527 cm^{−1}.

¹H NMR (400 MHz, CDCl₃): δ = 9.76 (s, 1 H), 8.41 (s, 1 H), 8.03 (d, J = 8.6 Hz, 2 H), 7.73 (d, J = 8.6 Hz, 2 H), 6.04 (s, 1 H), 4.28 (t, J = 3.9 Hz, 2 H), 3.90 (m, 5 H), 3.61 (s, 3 H), 3.53 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 166.8, 163.9, 163.7, 161.1, 145.7, 142.7, 130.9, 125.6, 119.5, 106.3, 97.3, 69.8, 68.0, 59.1, 52.2, 37.7.

HRMS (HESI): m/z [M – H][−] calcd for C₁₈H₁₉N₂O₆: 359.1249; found: 359.1251.

4-(2-Methoxyethoxy)-1-methyl-6-oxo-N-(pyrazin-2-yl)-1,6-dihydropyridine-3-carboxamide (10h)

From TMS-amine **9h**. The precipitated product was washed with Et₂O to afford **10h** as a white solid; yield: 128 mg (42%); mp 191–193 °C.

IR (ATR): 3331, 1693, 1645, 1528 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.20 (s, 1 H), 9.44 (d, *J* = 1.5 Hz, 1 H), 8.53 (s, 1 H), 8.43 (m, 2 H), 6.01 (s, 1 H), 4.29 (m, 2 H), 3.76 (m, 2 H), 3.49 (s, 3 H), 3.36 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.3, 162.7, 161.1, 148.3, 146.2, 142.9, 140.2, 136.3, 104.5, 96.4, 69.5, 68.8, 58.4, 36.6.

HRMS (HESI): *m/z* [M + Na]⁺ calcd for C₁₄H₁₆N₄O₄Na: 327.1064; found: 327.1062.

N-(6-Chloropyridin-3-yl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10i)

From TMS-amine **9i**. The precipitated product was washed with MeCN to afford **10i** as a white solid; yield: 209 mg (62%); mp 195–196 °C.

IR (ATR): 3329, 1694, 1649, 1596, 1529 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.96 (s, 1 H), 8.63 (d, *J* = 2.5 Hz, 1 H), 8.41 (s, 1 H), 8.16 (dd, *J* = 2.8, 8.7 Hz, 1 H), 7.54 (d, *J* = 8.8 Hz, 1 H), 6.00 (s, 1 H), 4.27 (m, 2 H), 3.79 (m, 2 H), 3.47 (s, 3 H), 3.33 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.3, 162.7, 161.4, 145.2, 143.9, 140.8, 134.9, 130.2, 124.3, 105.6, 96.3, 69.4, 67.9, 58.1, 36.5.

HRMS (HESI): *m/z* [M – H][–] calcd for C₁₅H₁₅ClN₃O₄: 336.0757; found: 336.0765.

N-(Benzo[d]thiazol-2-yl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10j)

From TMS-amine **9j**. The precipitated product was washed with MeCN to afford **10j** as a white solid; yield: 255 mg (71%); mp 209–211 °C.

IR (ATR): 3302, 1684, 1640, 1600, 1530 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 11.01 (s, 1 H), 8.45 (s, 1 H), 7.81 (dd, *J* = 7.9, 19.0 Hz, 2 H), 7.44 (t, *J* = 7.5 Hz, 1 H), 7.30 (t, *J* = 7.5 Hz, 1 H), 5.99 (s, 1 H), 4.34 (s, 2 H), 3.94 (s, 2 H), 3.64 (s, 3 H), 3.60 (s, 3 H).

¹³C NMR (100 MHz, CDCl₃): δ = 163.7, 161.1, 157.8, 148.4, 146.3, 132.4, 126.3, 124.1, 121.5, 121.1, 104.4, 97.5, 69.8, 68.9, 59.7, 37.8.

HRMS (HESI): *m/z* [M – H][–] calcd for C₁₇H₁₆N₃O₄S: 358.0867; found: 358.0849.

N-(3-Cyanophenyl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10k)

From TMS-amine **9k**. The precipitated product was washed with MeCN and MeOH to afford **10k** as a white solid; yield: 278 mg (85%); mp 236–238 °C.

IR (ATR): 3356, 2227, 1690, 1649, 1591, 1555 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 9.98 (s, 1 H), 8.40 (s, 1 H), 8.09 (s, 1 H), 7.90 (td, *J* = 1.9, 7.6 Hz, 1 H), 7.58 (m, 2 H), 5.99 (s, 1 H), 4.27 (m, 2 H), 3.80 (m, 2 H), 3.47 (s, 3 H), 3.35 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.3, 162.7, 161.3, 145.2, 139.4, 130.4, 127.2, 124.1, 122.3, 118.6, 111.7, 105.7, 96.3, 69.4, 68.0, 58.0, 36.5.

HRMS (HESI): *m/z* [M – H][–] calcd for C₁₇H₁₆N₃O₄: 326.1146; found: 326.1152.

4-(2-Methoxyethoxy)-1-methyl-6-oxo-N-(1,3,4-thiadiazol-2-yl)-1,6-dihydropyridine-3-carboxamide (10l)

From TMS-amine **9l**. The precipitated product was washed with MeCN to afford **10l** as a white solid; yield: 270 mg (87%); mp 234–236 °C.

IR (ATR): 3308, 1686, 1636, 1611, 1528 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.51 (s, 1 H), 9.20 (s, 1 H), 8.51 (s, 1 H), 6.01 (s, 1 H), 4.28 (m, 2 H), 3.76 (m, 2 H), 3.47 (s, 3 H), 3.39 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.4, 162.7, 160.9, 158.2, 149.2, 146.0, 103.8, 96.4, 69.4, 68.5, 58.5, 36.5.

HRMS (HESI): *m/z* [M – H][–] calcd for C₁₂H₁₃N₄O₄S: 309.0663; found: 309.0647.

4-(2-Methoxyethoxy)-1-methyl-N-(5-nitrobenzo[d]isothiazol-3-yl)-6-oxo-1,6-dihydropyridine-3-carboxamide (4)^{1a,b}

From TMS-amine **9m**. The precipitated product was washed with MeCN and acetone to afford **4** as a yellow solid; yield: 242 mg (60%); mp 296–298 °C.

IR (ATR): 3297, 1692, 1638, 1610, 1511 cm⁻¹.

¹H/¹³C NMR: See references 1a,b.

HRMS (HESI): *m/z* [M – H][–] calcd for C₁₇H₁₅N₄O₆S: 403.0718; found: 403.0695.

N-(4-Chlorobenzo[d]thiazol-2-yl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10n)

From TMS-amine **9n**. The precipitated product was washed with MeCN to afford **10n** as a white solid; yield: 362 mg (92%); mp 266–267 °C.

IR (ATR): 3288, 1684, 1638, 1589, 1527 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.61 (s, 1 H), 8.55 (s, 1 H), 7.99 (dd, *J* = 1.0, 7.9 Hz, 1 H), 7.54 (dd, *J* = 1.0, 7.8 Hz, 1 H), 7.32 (t, *J* = 7.9 Hz, 1 H), 6.02 (s, 1 H), 4.29 (m, 2 H), 3.79 (m, 2 H), 3.48 (s, 6 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.4, 162.7, 161.7, 158.4, 146.2, 145.4, 133.4, 126.3, 124.6, 124.5, 120.9, 103.8, 96.4, 69.5, 68.6, 58.8, 36.5.

HRMS (HESI): *m/z* [M – H][–] calcd for C₁₇H₁₅ClN₃O₄S: 392.0477; found: 392.0461.

N-(4-Cyanophenyl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10o)

From TMS-amine **9o**. The precipitated product was washed with MeOH to afford **10o** as a white solid; yield: 265 mg (81%); mp 249–251 °C.

IR (ATR): 3364, 2219, 1687, 1645, 1589, 1527 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.06 (s, 1 H), 8.40 (s, 1 H), 7.83 (s, 4 H), 5.99 (s, 1 H), 4.27 (m, 2 H), 3.78 (m, 2 H), 3.47 (s, 3 H), 3.33 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.3, 162.7, 161.4, 145.2, 142.8, 133.4, 119.6, 119.0, 105.9, 105.4, 96.3, 69.4, 68.0, 58.1, 36.4.

HRMS (HESI): *m/z* [M – H][–] calcd for C₁₇H₁₆N₃O₄: 326.1146; found: 326.1153.

N-[5-(2-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10p)

From TMS-amine **9p**. The precipitated product was washed with MeCN to afford **10p** as a pale yellow solid; yield: 255 mg (63%); mp 190–192 °C.

IR (ATR): 3289, 1698, 1667, 1594, 1528 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 11.09 (s, 1 H), 8.41 (s, 1 H), 7.93 (dd, *J* = 1.7, 7.7 Hz, 1 H), 7.64 (dddd, *J* = 1.2, 7.8, 15.0, 27 Hz, 3 H), 5.98 (s, 1 H), 4.22 (m, 2 H), 3.71 (m, 2 H), 3.46 (s, 3 H), 3.31 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.3, 162.7, 160.4, 158.9, 157.6, 145.6, 133.1, 131.6, 131.1, 131.0, 127.9, 122.5, 105.1, 96.3, 69.4, 68.4, 58.3, 36.5.

HRMS (ESI): *m/z* [M – H]⁻ calcd for C₁₈H₁₆ClN₄O₅: 403.0815; found: 403.0823.

N-(2-Chloropyridin-4-yl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10q)

From TMS-amine **9q**. The precipitated product was washed with MeCN to afford **10q** as a white solid; yield: 148 mg (44%); mp 228–229 °C.

IR (ATR): 3332, 1700, 1655, 1580, 1509 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.16 (s, 1 H), 8.41 (s, 1 H), 8.32 (d, *J* = 5.6 Hz, 1 H), 7.75 (d, *J* = 1.5 Hz, 1 H), 7.58 (dd, *J* = 1.7, 5.6 Hz, 1 H), 6.00 (s, 1 H), 4.26 (m, 2 H), 3.78 (m, 2 H), 3.47 (s, 3 H), 3.34 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.7, 163.1, 162.5, 151.5, 151.0, 148.2, 146.0, 113.5, 113.3, 106.0, 96.7, 69.9, 68.5, 58.5, 37.0.

HRMS (ESI): *m/z* [M – H]⁻ calcd for C₁₅H₁₅ClN₃O₄: 336.0757; found: 336.0764.

N-(6-Cyanopyridin-3-yl)-4-(2-methoxyethoxy)-1-methyl-6-oxo-1,6-dihydropyridine-3-carboxamide (10r)

From TMS-amine **9r**. The precipitated product was washed with MeCN/Et₂O (1:1) to afford **10r** as a pale yellow solid; yield: 220 mg (67%); mp 255–256 °C.

IR (ATR): 3312, 2225, 1684, 1648, 1580, 1540 cm⁻¹.

¹H NMR (400 MHz, DMSO-*d*₆): δ = 10.22 (s, 1 H), 8.87 (d, *J* = 2.1 Hz, 1 H), 8.43 (s, 1 H), 8.36 (dd, *J* = 2.3, 8.6 Hz, 1 H), 8.05 (d, *J* = 8.7 Hz, 1 H), 6.01 (s, 1 H), 4.27 (m, 2 H), 3.79 (m, 2 H), 3.47 (s, 3 H).

¹³C NMR (100 MHz, DMSO-*d*₆): δ = 163.2, 162.7, 161.9, 145.4, 142.3, 138.5, 129.8, 126.3, 126.2, 117.7, 105.5, 96.3, 69.4, 68.0, 58.0, 36.5.

HRMS (ESI): *m/z* [M – H]⁻ calcd for C₁₆H₁₅N₄O₄: 327.1099; found: 327.1106.

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Supporting Information

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References

- (1) (a) Cheung, P. K.; Horhant, D.; Bandy, L. E.; Zamiri, M.; Rabea, S. M.; Karagiosov, S. K.; Matloobi, M.; McArthur, S.; Harrigan, P. R.; Chabot, B.; Grierson, D. S. *J. Med. Chem.* **2016**, *59*, 1869. (b) Grierson, D. S.; Cheung, P. K.; Chabot, B.; Harrigan, P. R.; Cochrane, A. W. PCT Int. Appl WO 2015164956, **2015**.
- (2) (a) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. (b) El-Faham, A.; Albericio, F. *Chem. Rev.* **2011**, *111*, 6557. (c) Humphrey, J. M.; Chamberlin, R. A. *Chem. Rev.* **1997**, *97*, 2243.
- (3) Quelever, G.; Burlet, S.; Garino, C.; Pietrancosta, N.; Laras, Y.; Kraus, J.-L. *J. Comb. Chem.* **2004**, *6*, 695.
- (4) Dehe, D.; Munstein, I.; Reis, A.; Theil, W. R. *J. Org. Chem.* **2011**, *76*, 1151.
- (5) (a) Lippert, J. W. III *ARKIVOC* **2005**, (xiv), 87. (b) Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M. *Acc. Chem. Res.* **1996**, *29*, 268. (c) Carpino, L. A.; Sadat-Aalae, D.; Chao, H. G.; DeSelms, R. H. *J. Am. Chem. Soc.* **1990**, *112*, 9651.
- (6) (a) Rajeswari, S.; Jones, R. J.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 5099. (b) Wenschuh, H.; Bayermann, M.; Winter, R.; Bienert, M.; Ionescu, D.; Carpino, L. A. *Tetrahedron Lett.* **1996**, *37*, 5483. (c) Kim, H.-O.; Gardner, B.; Kahn, M. *Tetrahedron Lett.* **1995**, *36*, 6013. (d) For a related reaction, see: Sakamoto, K.; Nakahara, Y.; Ito, Y. *Tetrahedron Lett.* **2002**, *43*, 1515.
- (7) Wallace, E. M.; Lyssikatos, J.; Blake, J. F.; Seo, J.; Yang, H. W.; Yeh, T. C.; Perrier, M.; Jarski, H.; Marsh, V.; Poch, G.; Livingston, M. G.; Otten, J.; Hingorami, G.; Woessner, R.; Lee, P.; Winkler, J.; Koch, K. *J. Med. Chem.* **2006**, *49*, 441.
- (8) (a) Carpino, L. A.; El-Faham, A. *J. Am. Chem. Soc.* **1995**, *117*, 5401. (b) El-Faham, A.; Abdul-Ghani, M. *Org. Prep. Proced. Int.* **2003**, *35*, 369.
- (9) (a) Joullié, M. M.; Lassen, K. M. *ARKIVOC* **2010**, (viii), 189. (b) Carpino, L. A.; Ionescu, D.; El-Faham, A.; Beyermann, M.; Henklein, P.; Hanay, C. W. H.; Bienert, M. *Org. Lett.* **2003**, *5*, 975.
- (10) Mai, K.; Patil, G. *J. Org. Chem.* **1986**, *51*, 3545.
- (11) *Spartan Version 6.1.7*; Wavefunction Inc: Irvine (CA, USA), **2014**.
- (12) Sircar, J. C.; Capiris, T.; Bobovski, T. P.; Schwender, C. F. *J. Org. Chem.* **1985**, *50*, 5723.
- (13) (a) Bryce, M. R.; Heaton, J. N.; Taylor, P. C.; Anderson, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1935. (b) El-Tamany, E.-S. H.; Sowellim, S. Z.; Hamed, A. A.; Radwan, A. S. *Res. Chem. Intermed.* **2015**, *41*, 2675. (c) El-Tammany, E.-S. H.; Hamed, A. A.; Sowellim, S. Z. A.; Radwan, A. S. *Natural Sci.* **2012**, *4*, 1013. (d) Schmidt, U.; Schwochau, M. *Monatsh. Chem.* **1967**, *98*, 1492.
- (14) Fuchter, M. J.; Smith, C. J.; Tsang, M. W. S.; Boyer, A.; Saubern, S.; Ryan, J. H.; Holmes, A. B. *Chem. Commun.* **2008**, 2152.
- (15) Kricheldorf, H. R. *Justus Liebigs Ann. Chem.* **1971**, 745, 81.
- (16) (a) Garcia-Alvarez, R.; Crochet, P.; Cadierno, V. *Green Chem.* **2013**, *15*, 46. (b) Gernignon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386. (c) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471.