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.

Figure 1 IDC16 (indole compound 16) mimics: di(hetero)arylamide-type anti-HIV compounds 1–4

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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, 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. 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 (Figure 1) relatively little development of this scaffold in amide synthesis has been described.

Carboxylic acid 6 was prepared (Scheme 1) by O4-alkylation of 2-pyridinone ester 5 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) 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 competing formation of the symmetrical anhydride 8. Compound 7 was isolated pure as a colorless solid (90%) by washing the crude product mixture with hexane to remove the tetrathylurea 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 (Δδ 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 trimethylsil cyanide (TMSCN) (0.5 mL) at 70 °C (30 to 180 min) (Table 1). 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 software) (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 D(hetero)aryl amides 4 and 10 from TMS-Amines 9a–r

<table>
<thead>
<tr>
<th>TMS-amine 9</th>
<th>Electron density</th>
<th>N-Silylation time</th>
<th>Amide(^{a,b}) (yield, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMS-9a</td>
<td>140.1</td>
<td>7 (91%)</td>
<td>10a (78)</td>
</tr>
<tr>
<td>TMS-9b(^{12})</td>
<td>132.2</td>
<td>30</td>
<td>10b (7)</td>
</tr>
<tr>
<td>TMS-9c</td>
<td>120</td>
<td>30</td>
<td>10c (27)</td>
</tr>
<tr>
<td>TMS-9d</td>
<td>119.5</td>
<td>15</td>
<td>10d (34)</td>
</tr>
<tr>
<td>TMS-9e</td>
<td>115</td>
<td>30</td>
<td>10e (53)</td>
</tr>
<tr>
<td>TMS-9f(^{11a-d})</td>
<td>112.8</td>
<td>30</td>
<td>10f (55)</td>
</tr>
<tr>
<td>TMS-9g(^{11a})</td>
<td>105.9</td>
<td>180</td>
<td>10g (89)</td>
</tr>
<tr>
<td>TMS-9h(^{11a})</td>
<td>100.5</td>
<td>90</td>
<td>10h (42)</td>
</tr>
<tr>
<td>TMS-9i</td>
<td>98</td>
<td>120</td>
<td>10i (62)</td>
</tr>
<tr>
<td>TMS-9j</td>
<td>97.8</td>
<td>30</td>
<td>10j (71)</td>
</tr>
<tr>
<td>TMS-9k</td>
<td>96</td>
<td>180 (96%)</td>
<td>10k (85)</td>
</tr>
<tr>
<td>TMS-9l(^{11})</td>
<td>92.9</td>
<td>30</td>
<td>10l (87)</td>
</tr>
<tr>
<td>TMS-9m(^{11b})</td>
<td>88.8</td>
<td>30</td>
<td>4 (60)(^{a,b})</td>
</tr>
<tr>
<td>TMS-9n</td>
<td>88.7</td>
<td>30</td>
<td>10n (92)</td>
</tr>
<tr>
<td>TMS-9o(^{11a})</td>
<td>80.4</td>
<td>180</td>
<td>10o (81)</td>
</tr>
</tbody>
</table>
As alluded to already, reactions where the acid chloride derivative of carboxylic acid 6 (and the related compound containing a 4-OMe substituent) was coupled to amines 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 amide product yields beyond those indicated in Table 1. 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 method 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 (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 = 8.62 (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), 7.75 (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).

13C NMR (100 MHz, CDCl3): δ = 74.7, 70.1, 69.0, 59.6, 37.8.

1F 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 Me2SiCN (0.5 mL) was heated at 70 °C for the required time (1–120 min). Without removing the hot oil bath, the resulting solution was flushed with N2 by 1H NMR analysis in CDCl3 (passed through a basic alumina column to remove N2). Finally, 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%).

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 = 8.20 (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).

5-Methyl-N-(trimethylsilyl)isoxazol-3-amine (TMS-9b)
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)isoxazol-5-amine (TMS-9c)
Heated for 30 min; yellow oil; 100% conversion.

1H NMR (400 MHz, CDCl3): δ = 8.05 (s, 1 H), 7.03 (d, J = 7.8 Hz, 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).

5-Methyl-N-(trimethylsilyl)thiazol-2-amine (TMS-9d)
Heated for 15 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).

3-Methyl-N-(trimethylsilyl)thiazol-2-amine (TMS-9e)
Heated for 30 min; orange 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).

5-(2-Chlorophenyl)-N-(trimethylsilyl)-1,3,4-oxadiazol-2-amine (TMS-9f)
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)
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)
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)benz[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)
Heated for 30 min; yellow oil; 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)benz[d]isothiazol-3-amine (TMS-9m)
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)benz[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]benzonitrite (TMS-9o)
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.
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).

Diheteroarylamides 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 rt. This was quickly followed by addition of 1 M TBAF in THF (10 μL, 0.01 mmol). The reaction mixture/solution was stirred at 50 °C for 12 h. The precipitated product was collected by 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/ EtO (1:1) to afford 10a as a white solid; yield: 274 mg (78%); mp 187–188 °C.
IR (ATR): 3337, 1685, 1660, 1612, 1548 cm–1.

1H NMR (400 MHz, CDCl3): δ = 8.13 (d, J = 2.4 Hz, 1 H), 8.28 (m, 2 H), 7.78 (dd, J = 7.8, 2.2 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, CDCl3): 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.

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 (tt, 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, 57.7, 12.8.

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.
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 EtO to afford 10h as a white solid; yield: 128 mg (42%); mp 191–193 °C.

IR (ATR): 3356, 2227, 1684, 1638, 1589, 1527 cm–1.

1H NMR (400 MHz, DMSO-d6): δ = 9.98 (s, 1 H), 8.55 (d, J = 1.0 Hz, 1 H), 7.99 (dd, J = 1.0, 7.9 Hz, 1 H), 7.32 (t, J = 7.9 Hz, 1 H), 6.02 (s, 1 H), 4.29 (m, 2 H), 3.76 (m, 2 H), 3.47 (s, 3 H), 3.32 (s, 3 H), 2.97 (s, 3 H), 1.48 (s, 9 H), 0.91 (s, 3 H).

13C NMR (100 MHz, DMSO-d6): 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, 68.9, 59.7, 37.8.


N-(4-Chlorobenz[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-d6): δ = 11.51 (s, 1 H), 9.20 (s, 1 H), 8.51 (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, 3 H).

13C NMR (100 MHz, DMSO-d6): 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, 68.8, 58.8, 36.5.


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-d6): 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-d6): 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.
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, 1527 cm⁻¹.


Supporting Information
Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588603.

References


