Development of Novel Covalent Inhibitors and Other Scaffolds Through Multicomponent Reactions
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CHAPTER 5

Sequential Multicomponent Synthesis of 2-(Imidazo[1,5-A]Pyridin-1-YL)-1,3,4-Oxadiazoles

This chapter is published

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ABSTRACT

A 21 membered library of 2-(imidazo[1,5-α]pyridine-1-yl)-1,3,4-oxadiazoles is synthesized in an unprecedented short sequence starting from an Ugi tetrazole reaction with a cleavable isocyanide component. The intermediate tetrazole is subjected to an acetic anhydride-mediated cyclization, followed by a Huisgen-type rearrangement with acyl chlorides to afford the imidazopyridine-oxadiazole bis-heterocycles. The scope and limitations of the methodology were investigated with substitutions on both the oxadiazole and the imidazopyridine rings. The herein introduced enabling technology for imidazopyridine oxadiazole synthesis combines a short reaction sequence with high scaffold diversity, based on commercially available starting materials and high functional groups tolerance.
INTRODUCTION

Undoubtedly, heterocycles are the rings mostly used in drug discovery. New, elegant synthetic routes towards heterocycles are still of high demand in order to shorten reaction schemes, simplify synthetic routes and in some cases discover greener approaches with high atom economy. Most of the above attributes are fulfilled by multicomponent reaction chemistry (MCR), which in contrast to traditional step-wise synthesis, allows the synthesis of complex structures in a few synthetic steps, starting from commercially available or easily accessible starting materials. For instance, multicomponent reaction chemistry has been used extensively for the diverse synthesis of tetrazole derivatives, leading to complex scaffolds that cannot be accessed via the nitrile precursors. In this communication, we show a short, sequential reaction scheme that leads via multicomponent reaction chemistry with a cleavable isocyanide and a subsequent Huisgen rearrangement to the general synthesis of 2-(imidazo[1,5-α]pyridine-1-yl)-1,3,4-oxadiazoles (Scheme 1).

The bis-heterocycle scaffold was recently described in a series of 5-HT4 receptor partial agonists with applications in Alzheimer’s disease. The original imidazo[1,5-α] pyridine scaffold was further developed by changing its amide substituent to its stable bioisostere, 1,3,4-oxadiazole. The series were further improved, however the synthesis schemes remain quite lengthy and this could be a deterrent factor for the development of the scaffold in the future. Compounds with the same bis-heterocycles were also described as topoisomerase IIα inhibitors (Scheme 1). It should be noted that in both cases the two heterocycles are constructed separately in a multi-step synthesis.

Moreover, 1,3,4-oxadiazole derivatives have been extensively studied due to a broad spectrum of biological activities, including mainly antiviral, anti-inflammatory, analgetic, antimicrobial, anti-convulsant, anti-depressant, antipsychotic and anticancer. In medicinal chemistry, they
are well-established bioisosteres for esters, amides, carbamates and hydroxamic esters and they act, quite often, as hydrogen bond acceptors in ligand–receptor interactions. Furthermore, 1,3,4-oxadiazoles find applications as charge carrier transporting molecular materials and as fluorescent sensors due to their spectral luminescent properties. Regarding the synthetic routes for 1,3,4-oxadiazoles the most common procedures include the oxidative cyclization of N-acylhydrazones, the cyclodesulfurization of N-acyl-thiocarbazides, the cyclodehydration of aldehydes and hydrazides, and the reaction of carboxylic acids and acyl hydrazines with a great variety of reagents and conditions.

Recently, a mild synthetic route was described for 1,3,4-oxadiazoles using (isocyanooiminophosphorane). The transformation occurs through an aza-Wittig reaction leading to the desired 1,3,4-oxadiazole scaffold, with triphenylphosphine oxide as side-product.

Of note, the transformation of tetrazoles to 1,3,4-oxadiazoles, also called Huisgen reaction, is significantly less common. The Huisgen reaction is performed with tetrazoles and acyl chlorides, usually in refluxing pyridine or o-xylene. A few examples are reported for microwave-assisted synthesis either from acyl chlorides or anhydrides. In all those cases, the tetrazoles are formed from nitrile precursors. To the best of our knowledge, tetrazoles deriving from the Ugi-tetrazole reaction are not explored in the concept of Huisgen reaction.

RESULTS AND DISCUSSION

Herein, we present the synthesis of 2-(imidazo[1,5-α]pyridine-1-yl)-1,3,4-oxadiazoles starting from an Ugi-tetrazole reaction with a cleavable isocyanide. Example 7a (Table 1, entry 1) was selected for establishing the methodology. Equimolar amount of picolinaldehyde (1), tritylamine (2), tert-octyl-isocyanide (3) and trimethylsilylazide (4) were combined sequentially in methanol (0.5 M) at 50 °C. The corresponding Ugi-tetrazole product (5) was isolated after 48 h by a quick filtration with diethylether and was directly subjected to acid mediated trityl group deprotection. The obtained amine HCl salt (6) was treated with acetic anhydride (0.5 M) and 4 N HCl/dioxane (3.0 equiv). The reaction mixture was heated at 120 °C for 2 h in a heating metal block and after column chromatography afforded the corresponding 1,3,4-oxadiazole in 60% yield. The one pot–one step example intermediate 6 was subjected in-situ to an acetic anhydride – mediated N-acylation-cyclization, tert-octyl group deprotection and rearrangement of the tetrazole towards an oxadiazole (Scheme 2).
Next, we were keen to investigate the R₁ substitutions on the imidazo[1,5-α]pyridine ring by using a one pot–two step procedure. For this aim, the amine HCl intermediate 6 was treated with acyl chlorides, triethylamine and DCM at room temperature for 24 h to afford the amide intermediates A. The solvents were removed and intermediates A were directly treated with acetic anhydride (0.5 M) and 4 N HCl/dioxane (1.0 equiv). The reaction mixtures were heated at 120 °C for 2 h in a heating metal block to afford the cyclized R₁ – substituted oxadiazoles 7b–7j (Table 1).

Table 1. Substrate scope for one pot – two step procedure R₁ – substituted 2-(imidazo[1,5-α]pyridine-1-yl)-1,3,4-oxadiazoles.
<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tr>
<td>3</td>
<td><img src="attachment" alt="Chemical Structure" /></td>
<td>7c</td>
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<td>4</td>
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<td>5</td>
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<td>55%</td>
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<td>44%</td>
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<tr>
<td>7</td>
<td><img src="attachment" alt="Chemical Structure" /></td>
<td>7g</td>
<td>32%</td>
</tr>
<tr>
<td>8</td>
<td><img src="attachment" alt="Chemical Structure" /></td>
<td>7h</td>
<td>17%</td>
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For the $R_1$-substitution, both aromatic and aliphatic acyl chlorides were tolerated. Functional groups, including esters and thioethers reacted smoothly. Lower yields were observed with pivaloyl chloride (16 %, $7j$) and isobutyryl chloride (17 %, $7h$), whereas cyclopropanecarbonyl chloride gave a better yield (42 %, $7i$) and 2-cyclohexylacetyl chloride led to an excellent yield (92 %, $7c$). High yields were obtained in the cases where a methylene group was between the imidazopyridine ring and either an aromatic (85 %, $7b$) or aliphatic ring (92 %, $7c$). However, in the absence of the methylene, both for linear (17 %, $7h$, 16 %, $7j$) and cyclic acyl chlorides (42 %, $7i$) or aromatic acyl chlorides (32 %, $7g$) the observed yields were lower. One plausible explanation for the variation of those yields is steric hindrance, either in the initial N-acylation step or in the ring closure of the imidazopyridine ring.

For the product $7b$ an X-ray single crystal structure was obtained, confirming the structure. In the solid state, the rings of 1,3,4-oxadiazole and imidazo[1,5-α]pyridine are flat and coplanar. The $o$-fluorophenyl rings of two molecules are showing T-shaped pi stacking (Figure 1).

**Figure 1.** X-ray structure of compound $7b$.

Moreover, we investigated further to increase diversity by changing the methyl substituent of the oxadiazole ring to more general $R_2$-substituted 1,3,4-oxadiazoles. The obtained amine HCl salt ($6$) was treated with acetic anhydride [0.5 M] at 75 ºC for 1 h, following our previously reported
methodology.\textsuperscript{[19]} No base was required, only acetic anhydride and heating. The imidazopyridine intermediate $B$ was treated with 4N HCl / dioxane to deprotect the tert-octyl group and to give 3-methyl-1-(1H-tetrazol-5-yl)imidazo[1,5-$\alpha$]pyridine (compound 8a). This intermediate tetrazole 8a was directly dissolved in pyridine (0.5 M) and was reacted with 4-chlorobenzoyl chloride. The reaction mixture was heated at 120 °C overnight and after column chromatography the product 9 was isolated with 80% yield (Scheme 3).

![Scheme 3](image)

**Scheme 3.** Establishing the methodology for substitution on the oxadiazole ring.

Next, we investigated the scope of R$_2$-substitutions and at the same time changed the methyl substituent of the imidazo-pyridine system towards an isobuturyl group to further diversify the products (Scheme 4). The isobuturyl substituent was a key feature in a series of 2-imidazo[1,5-$\alpha$]pyridine-1,3,4-oxadiazole derivatives described as 5-HT$_4$ receptor partial agonists.\textsuperscript{[3]}

![Scheme 4](image)

**Scheme 4.** Synthetic route for products 10a-j.
## Table 2. Substrate scope for R₂-substituted 2-(imidazo[1,5-α]pyridine-1-yl)-1,3,4-oxadiazoles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acyl chloride</th>
<th>Product (Structure)</th>
<th>Product entry</th>
<th>Yield</th>
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<tbody>
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<td><img src="image1" alt="Acyl chloride" /></td>
<td><img src="image2" alt="Product" /></td>
<td>9</td>
<td>80%</td>
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<tr>
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<td><img src="image4" alt="Product" /></td>
<td>10a</td>
<td>66%</td>
</tr>
<tr>
<td>13</td>
<td><img src="image5" alt="Acyl chloride" /></td>
<td><img src="image6" alt="Product" /></td>
<td>10b</td>
<td>90%</td>
</tr>
<tr>
<td>14</td>
<td><img src="image7" alt="Acyl chloride" /></td>
<td><img src="image8" alt="Product" /></td>
<td>10c</td>
<td>40%</td>
</tr>
<tr>
<td>15</td>
<td><img src="image9" alt="Acyl chloride" /></td>
<td><img src="image10" alt="Product" /></td>
<td>10d</td>
<td>76%</td>
</tr>
<tr>
<td>16</td>
<td><img src="image11" alt="Acyl chloride" /></td>
<td><img src="image12" alt="Product" /></td>
<td>10e</td>
<td>72%</td>
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<tr>
<td>17</td>
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<td><img src="image14" alt="Product" /></td>
<td>10f</td>
<td>64%</td>
</tr>
</tbody>
</table>
Overall, both aliphatic and aromatic acid chlorides were well tolerated (Table 2). Excellent yields were observed with halogen-substituted aromatic acyl chlorides (9, 10a and 10j), whereas the presence of electron-donating methoxy groups (10i) significantly reduced the yield. In particular, compound 10a, bearing the 3,5-bis(trifluoromethyl)phenyl moiety, which is common feature in neurokinin-1 (NK1) receptor antagonists\[20\] reacted with high yield. Aliphatic acyl chlorides, such as 2-cyclohexylacetyl chloride (10b), isobutyryl chloride (10e) and 3-(methylthio)propanoyl chloride (10d) led to very good yields. On the other hand, the cyclopropanecarbonyl chloride (10g) and 2-(2-fluorophenyl)acetyl chloride (10h) reacted with a low yield. Regarding acyl chlorides with ester groups, methyl 5-chloro-5-oxopentanoate (10c) gave the expected product with 40 % yield, whereas ethyl 2-chloro-2-oxoacetate unexpectedly resulted in the cleavage of the ester group towards the mono-substituted oxadiazole (10f) with a yield of 64 %. This type of oxadiazoles are usually formed from the reaction of the corresponding hydrazide and triethylorthoformate and are useful intermediates for arylation reactions with boronic acids, \[21\] iodination \[22\] and C-H bond thiolation. \[23\] Only one acyl chloride failed to react in these conditions, the tert-butyl 1-(chlorocarbonyl)piperidine-4-carboxylate, which was prepared in situ from the corresponding carboxylic acid with thionyl chloride. In this case, unreacted intermediate 8b was recovered.

[a] Reaction scale was 0.5 mmol. [b] Isolated yield after column chromatography.
A possible mechanism is proposed in Scheme 5. The trityl group of the Ugi-tetrazole product (5) is cleaved under acidic conditions. The intermediate amine salt (6) is N-acylated by the acyl chloride and further undergoes an O-acylation by the acetic anhydride (intermediates A-i, A-ii), followed by an elimination of acetic acid that leads to a nitrilium intermediate (intermediate A-iii). The latter, after an attack of the pyridine nitrogen’s electron lone pair on the triple bond, affords the cyclic intermediate (intermediate A-iv) that aromatizes (intermediate B-i).
deprotection of the tert-octyl group under acidic conditions gives the mono-substituted tetrazole (intermediate 8), which is N-acylated by the corresponding acyl chloride (intermediate 8-i). The unstable N-acylated tetrazole, undergoes the Huisgen rearrangement with nitrogen elimination, ring opening (intermediate 8-ii) and final cyclization towards the 2-(imidazo[1,5-α]pyridine-1-yl)-1,3,4-oxadiazole (10). In particular, for the formation of compound 10f, the N-acylation of intermediate 8 by ethyl 2-chloro-2-oxoacetate leads to an unstable intermediate, where it is likely for saponification to occur and in this case decarboxylation would happen under heating conditions, leading to the mono-substituted product 10f.

CONCLUSIONS

Overall, we have developed an efficient synthetic procedure for the synthesis of the 2-(imidazo[1,5-α]pyridine-1-yl)-1,3,4-oxadiazoles based on the Ugi–tetrazole reaction and the Huisgen rearrangement. The current methodology allowed the diverse library synthesis from simple building blocks in a short fashion and with great functional group compatibility. The final products show applicability in medicinal chemistry, materials chemistry and fluorescent probes.
REFERENCES


EXPERIMENTAL SECTION

Experimental procedures

Procedure A (Synthesis of pyridin-2-yl(1-(2,4,4-trimethylpentan-2-yl)-1H-tetrazol-5-yl) methanamine) (6): In a 50 ml round-bottom flask, picolinaldehyde (1, 1 g, 9.3 mmol, 881 μl, 1 equiv) and tritylamine (2, 2.4 g, 9.3 mmol, 1 equiv) were stirred at 50 °C in MeOH (0.5 M) for 30 minutes. Then, tert-octyl isocyanide (3, 1.29 g, 9.3 mmol, 1.6 ml, 1 equiv) and trimethylsilylazide (4, 1.22 ml, 9.3 mmol, 1 equiv) were added and further stirred for 24 h at 50 °C. Another equivalent of isocyanide (3) and trimethylsilylazide (4) was added and the heating at 50 °C was continued for 24 h. The reaction mixture was allowed to reach room temperature, diethyl ether was added (10 ml) and the intermediate (5) was collected by quick filtration as a solid. The intermediate (5) was dissolved in DCM (5 ml) and 4N HCl in dioxane (3.0 equiv) were added. The reaction mixture was stirred for 10 min at room temperature. The solvent was removed, diethyl ether (3 ml) was added and the amine-HCl salt (intermediate 6) was collected as a solid by filtration (2.6 g, 8.0 mmol, yield 86 %, white solid). Intermediate 6 was used directly in the next step without further purification.

Procedure B (Synthesis of R1-substituted imidazo[1,5-a]pyridin-1-yl)-1,3,4-oxadiazoles)

One pot – one step procedure (7a): In a 4 ml screwcap glass vial containing 1 mmol of intermediate (6) acetic anhydride [0.5 M] and 4 N HCl in dioxane (3.0 equiv) were added. The vial was closed and the reaction mixture was heated at 120 °C on a heating metal block for 2 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography [petroleum ether : ethyl acetate, 0-100% EtOAc in PE] to afford product 7a.

One pot – two step procedure (7b – 7j): In a 4 ml screwcap glass vial containing a suspension of intermediate (6) (1 mmol, 1 equiv) in DCM (2 ml), triethylamine (2.2 equiv) and acyl chloride (1.2 equiv) were added at room temperature. The reaction mixture was stirred at room temperature for 24 h to obtain intermediates A; then the solvent was removed and acetic anhydride [0.5 M] and 4 N HCl in dioxane (1.0 equiv) were added. The vial was closed and the reaction mixture was heated at 120 °C on a heating metal block for 2 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography [petroleum ether : ethyl acetate, 0-100% EtOAc in PE] to afford products 7b – 7j.

Procedure C (Synthesis of 3-methyl-1-(1H-tetrazol-5-yl)imidazo[1,5-a]pyridine) (8a): The reaction was carried out at 0.5 mmol scale in a 4 ml screwcap glass vial. Intermediate 6 (0.5 mmol, 1 equiv) was treated with acetic anhydride [0.5 M] at 75 °C for 1 h in a heating metal block. The solvent was removed under reduced pressure and toluene (4 x 5 ml) was added in order to completely remove acetic anhydride. The cyclized intermediate B was treated with 4 N HCl / dioxane in the same screwcap glass vial. The vial was closed and the reaction mixture was heated at 120 °C on a heating metal block for 4 h. Then, the reaction mixture was allowed to reach room temperature and the solvent was removed under reduced pressure. The residue was triturated
with diethyl ether to obtain intermediate 8a as a light brown solid, which was used directly in the next step.

**Procedure D (Synthesis of 2-(4-chlorophenyl)-5-(3-methylimidazo[1,5-α]pyridin-1-yl)-1,3,4 oxadiazole) (9):** In a 4 ml screwcap glass vial containing 3-methyl-1-(1H-tetrazol-5-yl) imidazo[1,5-α]pyridine (intermediate 8a, 1 equiv), pyridine (0.5 M) was added, followed by the addition of 4-chlorobenzoyl chloride (1.3 equiv). The vial was closed and after 10 min stirring at room temperature, the reaction mixture was heated overnight at 120 °C on heating metal block. The next day, ice was added in the reaction mixture. The reaction mixture was extracted with ethyl acetate (20ml x 3), dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by column chromatography [petroleum ether : ethyl acetate, 0-100% EtOAc in PE] to afford product 9.

**Procedure E (Synthesis of 3-isopropyl-1-(1H-tetrazol-5-yl)imidazo[1,5-α]pyridine) (8b):** In a 25-ml round-bottom flask, intermediate 6 (1 g, 2.8 mmol, 1 equiv) was suspended in 6 ml DCM (0.5 M). Triethylamine was added (0.85 ml, 6.16 mmol, 2.2 eq). The blue suspension was cooled in an ice-bath at 0 °C and isobutyryl chloride (0.35 ml, 3.36 mmol, 1.2 equiv) was added via the septum. The purple suspension was stirred at room temperature overnight. The reaction mixture was extracted with DCM (3 x 50 ml) and H₂O (60 ml) and then Brine (x2). The combined organic phases were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to obtain intermediate C as a purple solid. Intermediate C was transferred in a 25ml round-bottom flask and 5.6 ml of acetic anhydride (0.5 M) and 4 N HCl in dioxane (0.5 equiv, 0.35 ml) were added. The reaction mixture was heated at 85 °C (with condenser and CaCl₂ tube) overnight. The solvent was removed under reduced pressure. In order to completely remove acetic anhydride, toluene was added in the residue (4 x 20 ml) and the solvent was removed under reduced pressure to obtain intermediate D as a dark blue solid. Intermediate D was equally distributed in four 4-ml screwcap glass vials and 4 N HCl in dioxane was added (4 equiv). The vials were closed and the reaction mixture was heated at 120 °C on a heating metal block for 4 h. The progress of the reaction was monitored by TLC (petroleum ether – ethyl acetate 1:1). Then, the reactions mixtures were allowed to reach room temperature and the solvents were removed under reduced pressure. The brown solids were suspended in diethyl ether and filtered to obtain intermediate 8b as a light brown solid.

**Procedure F (Synthesis of R₂-substituted imidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazoles) (10a – 10j):** The reactions were carried out at 0.5 mmol scale. In a 4 ml screwcap glass vial containing 3-isopropyl-1-(1H-tetrazol-5-yl)imidazo[1,5-α]pyridine (intermediate 8b, 1 equiv), pyridine (0.5 M) was added, followed by the addition of the acyl chloride (1.3 equiv). The vial was closed and after 10 min stirring at room temperature, the reaction mixture was heated overnight at 120°C on heating metal block. The next day, ice was added in the dark brown reaction mixture. The reaction mixture was extracted with ethyl acetate (20ml x 3), dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The residues were purified by column chromatography [petroleum ether : ethyl acetate, 0-100% EtOAc in PE] to afford products 10a- 10j.
Characterization data

2-methyl-5-(3-methylimidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (7a)

Obtained using procedure B (one pot – one step) with acetyl chloride on 1mmol scale, 128 mg, 0.60 mmol, yield 60%, green solid, m.p. 184 - 185 °C. 1H NMR (500 MHz, DMSO- d6) δ 8.31 (td, J = 7.2, 1.2 Hz, 1H), 7.99 (dt, J = 9.2, 1.3 Hz, 1H), 7.17 (ddd, J = 9.2, 6.6, 0.9 Hz, 1H), 6.93 (td, J = 6.8, 1.2 Hz, 1H), 2.67 (s, 3H), 2.57 (s, 3H). 13C NMR (126 MHz, DMSO-d6) δ 161.7, 161.0, 137.3, 130.5, 123.4, 123.3, 117.7, 113.6, 113.4, 12.2, 10.5. HRMS calcd for C11H11N4O [M+H]+: 215.09274, found [M+H]+: 215.09283.

2-(3-(2-fluorobenzyl)imidazo[1,5-α]pyridin-1-yl)-5-methyl-1,3,4-oxadiazole (7b)

Obtained using procedure B (one pot – two steps) with 2-(2-fluorophenyl) acetyl chloride on 1 mmol scale, 262 mg, 0.85 mmol, yield 85%, brown solid, m.p. 96 - 97 °C. 1H NMR (500 MHz, CDCl3) δ 8.23 (dt, J = 9.1, 1.1 Hz, 1H), 7.82 (dt, J = 7.3, 1.1 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.15 – 7.06 (m, 2H), 7.06 – 7.00 (m, 2H), 6.73 (ddd, J = 7.2, 6.5, 1.1 Hz, 1H), 4.52 (s, 2H), 2.63 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 162.0, 161.3, 160.5 (d, J = 245.0 Hz), 137.6, 131.6, 130.3 (d, J = 3.5 Hz), 128.9 (d, J = 8.1 Hz), 124.6, 122.7, 122.3 (d, J = 15.2 Hz), 121.4 (d, J = 6.2 Hz), 119.4, 115.5 (d, J = 22.0 Hz), 115.2, 114.2, 25.6 (d, J = 4.2 Hz), 11.0. HRMS calcd for C17H14F6N4O [M+H]+: 309.1146, found [M+H]+: 309.1145.

2-(3-(cyclohexylmethyl)imidazo[1,5-α]pyridin-1-yl)-5-methyl-1,3,4-oxadiazole (7c)

Obtained using procedure B (one pot – two steps) with 2-cyclohexylacetyl chloride on 1 mmol scale, 272 mg, 0.92 mmol, yield 92 %, brown oil. 1H NMR (500 MHz, CDCl3) δ 8.21 (dt, J = 9.2, 1.2 Hz, 1H), 7.88 (dt, J = 7.2, 1.1 Hz, 1H), 7.02 (ddd, J = 9.2, 6.5, 0.9 Hz, 1H), 6.75 (ddd, J = 7.4, 6.5, 1.2 Hz, 1H), 2.95 (d, J = 7.3 Hz, 2H), 2.61 (s, 3H), 1.89 (ttt, J = 10.7, 7.1, 3.2 Hz, 1H), 1.69 – 1.61 (m, 4H), 1.24 – 1.07 (m, 6H). 13C NMR (126 MHz, CDCl3) δ 161.9, 161.3, 160.5 (d, J = 245.0 Hz), 137.6, 131.6, 130.3 (d, J = 3.5 Hz), 128.9 (d, J = 8.1 Hz), 124.6, 122.7, 122.3 (d, J = 15.2 Hz), 121.4 (d, J = 6.2 Hz), 119.4, 115.5 (d, J = 22.0 Hz), 115.0, 113.8, 37.2, 34.2, 33.3, 26.1, 26.0, 11.0. HRMS calcd for C17H21N4O [M+H]+: 297.17099, found [M+H]+: 297.17077.

methyl 4-(1-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-α]pyridin-3-yl)butanoate (7d)

Obtained using procedure B (one pot – two steps) with methyl 5-chloro-5-oxopentanoate on 1 mmol scale, 100 mg, 0.33 mmol, yield 33 %, green semi-solid. 1H NMR (500 MHz, CDCl3) δ 8.20 (dt, J = 9.2, 1.3 Hz, 1H), 8.01 (dt, J = 7.3, 1.1 Hz, 1H), 7.04 (ddd, J = 9.2, 6.5, 0.9 Hz, 1H), 6.79 (ddd, J = 7.5, 6.6, 1.2 Hz, 1H), 3.66 (s, 3H), 3.16 – 3.09 (m, 2H), 2.61 (s, 3H), 2.49 (t, J = 6.9 Hz, 2H), 2.16 (dt, J = 14.4, 6.9 Hz, 2H). 13C NMR (126 MHz, CDCl3) δ 173.5, 161.9, 161.5, 139.5, 131.3, 122.6, 121.6, 119.5, 114.9, 114.1, 51.7, 32.8, 25.8, 22.0, 11.0. HRMS calcd for C15H17N4O3 [M+H]+: 301.12952, found [M+H]+: 301.12952.
SEQUENTIAL MULTICOMPONENT SYNTHESIS OF 2-(IMIDAZO[1,5-α]PYRIDIN-1-YL)-1,3,4-OXADIAZOLES

2-methyl-5-(3-(methylthio)ethyl)imidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (7e)

Obtained using procedure B (one pot – two steps) with 3-(methylthio) propanoyl chloride on 1 mmol scale, 150 mg, 0.55 mmol, yield 55%, brown solid, m.p. 108 – 109 °C.

1H NMR (500 MHz, CDCl3) δ 8.21 (dt, J = 9.2, 1.2 Hz, 1H), 7.94 (dt, J = 9.1, 6.5, 0.9 Hz, 1H), 7.05 (ddd, J = 9.1, 6.6, 0.9 Hz, 1H), 6.82 – 6.77 (m, 1H), 3.34 (dd, J = 8.3, 7.0 Hz, 2H), 3.03 (dd, J = 8.4, 6.9 Hz, 2H), 2.61 (s, 3H), 2.12 (s, 3H).


ethyl 1-(5-methyl-1,3,4-oxadiazol-2-yl)imidazo[1,5-α]pyridine-3-carboxylate (7f)

Obtained using procedure B (one pot – two steps) with ethyl 2-chloro-2-oxoacetate on 1 mmol scale, 120 mg, 0.44 mmol, yield 44 %, yellow solid, m.p. 159 – 160 °C.

1H NMR (500 MHz, CDCl3) δ 9.43 (dt, J = 7.2, 1.2 Hz, 1H), 8.46 (dt, J = 9.0, 1.3 Hz, 1H), 7.36 (ddd, J = 9.1, 6.6, 1.0 Hz, 1H), 7.10 (td, J = 6.9, 1.3 Hz, 1H), 4.53 (q, J = 7.1 Hz, 2H), 2.62 (s, 3H), 1.47 (t, J = 7.1 Hz, 3H).


2-(3-(4-chlorophenyl)imidazo[1,5-α]pyridin-1-yl)-5-methyl-1,3,4-oxadiazole (7g)

Obtained using procedure B (one pot – two steps) with 4-chlorobenzoyl chloride on 1 mmol scale, 100 mg, 0.32 mmol, yield 32%, light brown solid, m.p. 203 – 204 °C.

1H NMR (500 MHz, CDCl3) δ 8.33 (dt, J = 9.2, 1.2 Hz, 1H), 8.28 (dt, J = 7.2, 1.1 Hz, 1H), 7.77 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.12 (ddd, J = 9.1, 6.5, 0.9 Hz, 1H), 6.82 (ddd, J = 7.3, 6.4, 1.2 Hz, 1H), 2.64 (s, 3H).


2-(3-isopropylimidazo[1,5-α]pyridin-1-yl)-5-methyl-1,3,4-oxadiazole(7h)

Obtained using procedure B (one pot – two steps) with isobutyryl chloride on 1 mmol scale, 40 mg, 0.17 mmol, yield 17 %, brown solid, m.p. 101 – 103 °C.

1H NMR (500 MHz, CDCl3) δ 8.24 (dt, J = 9.2, 1.2 Hz, 1H), 7.91 (dt, J = 7.1, 1.1 Hz, 1H), 7.04 (ddd, J = 9.2, 6.5, 0.9 Hz, 1H), 6.78 (ddd, J = 7.4, 6.5, 1.2 Hz, 1H), 3.39 (hept, J = 6.9 Hz, 7H), 2.63 (s, 3H), 1.51 (d, J = 6.9 Hz, 6H).

CHAPTER 5

2-(3-cyclopropylimidazo[1,5-α]pyridin-1-yl)-5-methyl-1,3,4-oxadiazole (7i)

Obtained using procedure B (one pot – two steps) with cyclopropanecarbonyl chloride on 1mmol scale, 100 mg, 0.42 mmol, yield 42%, brown solid, m.p. 103-104 °C. 1H NMR (500 MHz, CDCl3) δ 8.19 (dt, J = 9.2, 1.2 Hz, 1H), 8.12 (dt, J = 7.2, 1.2 Hz, 1H), 7.05 (ddd, J = 9.2, 6.5, 1.0 Hz, 1H), 6.80 (ddd, J = 7.5, 6.5, 1.2 Hz, 1H), 2.60 (s, 3H), 2.08 – 2.04 (m, 1H), 1.16 – 1.12 (m, 4H). 13C NMR (126 MHz, CDCl3) δ 161.9, 161.6, 141.4, 131.4, 122.7, 121.5, 119.5, 114.4, 113.8, 111.1, 6.6, 6.3. HRMS calcd for C13H13N4O [M+H]+: 241.10839, found [M+H]+: 241.1084.

2-(3-(tert-butylimidazo[1,5-α]pyridin-1-yl)-5-methyl-1,3,4-oxadiazole (7j)

Obtained using procedure B (one pot – two steps) with pivaloyl chloride on 1mmol scale, 41 mg, 0.16 mmol, yield 16%, brown solid, m.p. 94 – 96 °C. 1H NMR (500 MHz, CDCl3) δ 8.25 (dt, J = 9.2, 1.3 Hz, 1H), 8.18 (dt, J = 7.3, 1.1 Hz, 1H), 7.01 (ddd, J = 9.1, 6.4, 0.9 Hz, 1H), 6.73 (ddd, J = 7.5, 6.3, 1.3 Hz, 1H), 2.61 (s, 3H), 1.59 (s, 9H). 13C NMR (126 MHz, CDCl3) δ 161.9, 161.6, 146.9, 132.5, 123.6, 121.9, 120.0, 14.3, 13.3, 33.6, 28.1, 1.1. HRMS calcd for C14H17N4O [M+H]+: 257.13969, found [M+H]+: 257.13963.

2-(4-chlorophenyl)-5-(3-methylimidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (9)

Obtained using procedure D with 4-chlorobenzoyl chloride on 0.5 mmol scale, 125 mg, 0.40 mmol, yield 80 %, yellow solid, m.p. 231 – 232 °C. 1H NMR (500 MHz, CDCl3) δ 8.28 (dt, J = 9.2, 1.2 Hz, 1H), 8.14 (d, J = 8.6 Hz, 2H), 7.85 (dt, J = 7.1, 1.1 Hz, 1H), 7.49 (d, J = 8.5 Hz, 2H), 7.10 (ddd, J = 9.1, 6.5, 1.0 Hz, 1H), 6.84 (t, J = 6.8 Hz, 1H), 2.76 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 162.3, 161.5, 137.4, 137.0, 131.8, 129.3, 128.2, 122.9, 122.6, 121.5, 119.6, 114.5, 114.2, 12.6. HRMS calcd for C16H12ClN4O [M+H]+: 311.06942, found [M+H]+: 311.06937.

3-isopropyl-1-(1H-tetrazol-5-yl)imidazo[1,5-α]pyridine (8b)

Obtained using procedure E on 2.8 mmol scale, 512 mg, 2.24 mmol, yield 80%, brown solid, m.p. 149 – 151 °C. 1H NMR (500 MHz, DMSO-d6) δ 8.42 (d, J = 7.1 Hz, 1H), 8.16 (dt, J = 9.2, 1.1 Hz, 1H), 7.15 (ddd, J = 8.7, 6.8 Hz, 1H), 6.90 (t, J = 6.7 Hz, 1H), 3.59 (hept, J = 7.0 Hz, 1H), 1.39 (d, J = 6.8 Hz, 6H). 13C NMR (126 MHz, DMSO-d6) δ 151.0, 145.3, 129.9, 123.0, 118.2, 113.8, 113.5, 25.1, 20.5, 20.4. HRMS calcd for C11H13N6 [M+H]+: 229.11962, found [M+H]+: 229.11954.
2-(3,5-bis(trifluoromethyl)phenyl)-5-(3-isopropylimidazo[1,5-a]pyridin-1-yl)-1,3,4-oxadiazole (10a)

Obtained using procedure F with 3,5-bis(trifluoromethyl)benzoyl chloride on 0.5 mmol scale, 145 mg, 0.33 mmol, yield 66 %, yellow solid, m.p 210-212 °C. Rotamers are observed, the major one is given: 1H NMR (500 MHz, CDCl₃) δ 8.63 (br, 2H), 8.32 (dt, J = 9.2, 1.2 Hz, 1H), 7.99 (br, 2H), 7.15 (ddd, J = 9.2, 6.5, 0.9 Hz, 1H), 6.87 (ddd, J = 7.4, 6.5, 1.2 Hz, 1H), 3.45 (hept, J = 6.9 Hz, 1H), 1.55 (d, J = 6.9 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 162.3, 160.8, 145.9, 133.0 – 131.9 (m), 130.04, 126.8 (d, J = 3.1 Hz), 126.3 – 126.0 (m), 124.5 – 124.3 (m), 123.60, 122.8 (q, J = 271 Hz), 121.7, 119.7, 114.4, 113.8, 26.4, 20.2. HRMS calcd for C₂₇H₂₅N₄O [M+H]+: 441.1145, found [M+H]+: 441.1144.

2-(cyclohexylmethyl)-5-(3-isopropylimidazo[1,5-a]pyridin-1-yl)-1,3,4-oxadiazole (10b)

Obtained using procedure F with 2-cyclohexylacetyl chloride on 0.5 mmol scale, 146 mg, 0.45 mmol, yield 90 %, dark green oil. ¹H NMR (500 MHz, CDCl₃) δ 8.19 (dt, J = 9.2, 1.3 Hz, 1H), 7.89 (dt, J = 7.2, 1.1 Hz, 1H), 7.00 (ddd, J = 9.1, 6.5, 0.9 Hz, 1H), 6.74 (ddd, J = 7.4, 6.6, 1.3 Hz, 1H), 3.37 (hept, J = 6.9 Hz, 1H), 2.79 (d, J = 7.2 Hz, 2H), 1.93 (ttt, J = 10.9, 7.2, 3.5 Hz, 1H), 1.83 – 1.73 (m, 2H), 1.69 (dt, J = 12.5, 2.8 Hz, 2H), 1.66 – 1.60 (m, 1H), 1.48 (d, J = 6.9 Hz, 6H), 1.24 (qt, J = 12.6, 3.2 Hz, 2H), 1.15 (tt, J = 12.5, 3.0 Hz, 1H), 1.05 (qd, J = 12.6, 3.4 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 164.5, 161.5, 145.1, 131.3, 122.3, 121.3, 119.7, 115.0, 113.8, 36.1, 33.0, 32.9, 26.3, 26.1, 25.9, 20.3. HRMS calcd for C₁₉H₂₃N₅O [M+H]+: 325.20229, found [M+H]+: 325.20229.

methyl 4-(5-(3-isopropylimidazo[1,5-a]pyridin-1-yl)-1,3,4-oxadiazol-2-yl)butanoate (10c)

Obtained using procedure F with methyl 5-chloro-5-oxopentanoate on 0.5 mmol scale, 66 mg, 0.20 mmol, yield 40 %, off-white semi-solid. ¹H NMR (500 MHz, CDCl₃) δ 8.20 (dt, J = 9.3, 1.3 Hz, 1H), 7.90 (dd, J = 7.3, 1.1 Hz, 1H), 7.02 (ddd, J = 9.2, 6.5, 0.9 Hz, 1H), 6.76 (ddd, J = 7.5, 6.6, 1.3 Hz, 1H), 3.66 (s, 3H), 3.37 (hept, J = 6.9 Hz, 1H), 3.00 (t, J = 7.4 Hz, 2H), 2.49 (t, J = 7.3 Hz, 2H), 2.21 (p, J = 7.3 Hz, 2H), 1.48 (d, J = 6.9 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 173.1, 164.3, 161.7, 145.1, 131.4, 122.4, 121.3, 119.7, 114.7, 113.8, 51.6, 32.9, 32.7, 26.2, 24.6, 21.7, 20.3. HRMS calcd for C₁₇H₂₁N₅O₃ [M+H]+: 329.16082, found [M+H]+: 329.16076.

2-(3-isopropylimidazo[1,5-a]pyridin-1-yl)-5-(2-(methylthio)ethyl)-1,3,4-oxadiazole (10d)

Obtained using procedure F with 3-(methylthio)propanoyl chloride on 0.5 mmol scale, 115 mg, 0.38 mmol, yield 76 %, dark green oil. ¹H NMR (500 MHz, CDCl₃) δ 8.20 (dd, J = 9.1, 1.3 Hz, 1H), 7.90 (dd, J = 7.1, 0.9 Hz, 1H), 7.03 – 7.00 (m, 1H), 6.77 – 6.74 (m, 1H), 3.40 – 3.34 (m, 1H), 3.22 (t, J = 7.7 Hz, 2H), 2.98 (t, J = 7.7 Hz, 2H), 2.15 (s, 3H), 1.47 (d, J = 6.8 Hz, 6H). ¹³C NMR (126 MHz, CDCl₃) δ 163.4, 161.7, 145.2, 131.5, 122.5, 121.3, 119.6, 113.8, 30.6, 26.2, 25.9, 20.2, 20.1, 15.4. HRMS calcd for C₁₅H₁₉N₄S [M+H]+: 303.12741, found [M+H]+: 303.12728.
2-isopropyl-5-(3-isopropylimidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (10e)

Obtained using procedure F with isobutyryl chloride on 0.5 mmol scale, 97 mg, 0.36 mmol, yield 72 %, yellow solid, 100-102 °C. 'H NMR (500 MHz, DMSO-d$_6$) δ 8.44 (td, J = 7.2, 1.2 Hz, 1H), 8.02 (dt, J = 9.2, 1.3 Hz, 1H), 7.18 (dd, J = 9.2, 6.6, 0.9 Hz, 1H), 6.93 (td, J = 6.8, 1.2 Hz, 1H), 3.56 (hept, J = 7.0 Hz, 1H), 3.28 (hept, J = 7.0 Hz, 1H), 1.36 (dd, J = 6.9, 4.9 Hz, 12H). 13C NMR (126 MHz, DMSO-d$_6$) δ 168.5, 161.0, 145.3, 130.7, 123.5, 123.2, 118.0, 113.7, 113.5, 25.5, 25.1, 20.4, 20.3, 20.0, 19.9. HRMS calcd for C$_{15}$H$_{19}$N$_4$O [M+H]+: 271.15534, found [M+H]+: 271.15528.

2-(3-isopropylimidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (10f)

Obtained using procedure F with ethyl 2-chloro-2-oxoacetate on 0.5 mmol scale, 73 mg, 0.32 mmol, yield 64 %, yellow solid, m.p. 131-133 °C. 'H NMR (500 MHz, CDCl$_3$) δ 8.41 (s, 1H), 8.22 (dt, J = 9.2, 1.2 Hz, 1H), 7.91 (dt, J = 7.1, 1.0 Hz, 1H), 7.05 (dd, J = 9.1, 6.5, 0.9 Hz, 1H), 6.78 (td, J = 6.9, 1.3 Hz, 1H), 3.37 (hept, J = 6.9 Hz, 1H), 1.48 (d, J = 6.8 Hz, 6H). 13C NMR (126 MHz, CDCl$_3$) δ 161.5, 151.0, 145.4, 131.8, 122.8, 121.4, 1 19.5, 1 14.3, 1 13.9, 26.1, 20.3. HRMS calcd for C$_{12}$H$_{13}$N$_4$O [M+H]+: 229.10839, found [M+H]+: 229.10845.

2-cyclopropyl-5-(3-isopropylimidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (10g)

Obtained using procedure F with cyclopropanecarbonyl chloride on 0.5 mmol scale, 39 mg, 0.145 mmol, yield 29 %, yellow oil. 'H NMR (500 MHz, CDCl$_3$) δ 8.17 (dt, J = 9.2, 1.2 Hz, 1H), 7.88 (dt, J = 7.1, 1.0 Hz, 1H), 7.00 (dd, J = 9.0, 6.6, 0.9 Hz, 1H), 6.74 (td, J = 6.8, 1.3 Hz, 1H), 3.37 (hept, J = 6.9 Hz, 1H), 2.22 – 2.20 (m, 1H), 1.49 (d, J = 6.9 Hz, 6H), 1.27 – 1.23 (m, 2H), 1.17 – 1.08 (m, 2H). 13C NMR (126 MHz, CDCl$_3$) δ 166.9, 161.0, 145.0, 131.2, 122.2, 121.3, 119.7, 114.9, 113.7, 26.3, 20.2, 8.1, 6.3. HRMS calcd for C$_{15}$H$_{17}$ON$_4$ [M+H]+: 269.13969, found [M+H]+: 269.13919.

2-(2-fluorobenzyl)-5-(3-isopropylimidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (10h)

Obtained using procedure F with 2-(2-fluorophenyl)acetyl chloride on 0.5 mmol scale, 39 mg, 0.12 mmol, yield 23 %, yellow oil. 'H NMR (500 MHz, CDCl$_3$) δ 8.18 (dt, J = 9.1, 0.9 Hz, 1H), 7.90 (dt, J = 7.2, 1.0 Hz, 1H), 7.37 – 7.34 (m, 1H), 7.30 – 7.27 (m, 1H), 7.12 – 7.07 (m, 2H), 7.00 (dd, J = 9.0, 6.6, 0.9 Hz, 1H), 6.76 (td, J = 6.8, 1.3 Hz, 1H), 4.34 (s, 2H), 3.37 (hept, J = 6.9 Hz, 1H), 1.49 (d, J = 6.9 Hz, 6H). 13C NMR (126 MHz, CDCl$_3$) δ 162.7, 162.0, 160.8 (d, J = 246.0 Hz), 145.2, 131.6, 130.9 (d, J = 3.6 Hz), 129.3 (d, J = 8.0 Hz), 124.3 (d, J = 3.7 Hz), 122.5, 121.4 (d, J = 19.4 Hz), 119.7, 115.6 (d, J = 21.4 Hz), 114.6, 113.8, 113.4, 26.3, 24.9 (d, J = 4.3 Hz), 20.3. HRMS calcd for C$_{19}$H$_{18}$ON$_4$F [M+H]+: 337.14592, found [M+H]+: 337.14551.
2-(isopropylimidazo[1,5-α]pyridin-1-yl)-5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazole (10i)

Obtained using procedure F with 3,4,5-trimethoxybenzoyl chloride on 0.5 mmol scale, 50 mg, 0.13 mmol, yield 26%, yellow solid, m.p. 147 - 149 °C. ^1H NMR (500 MHz, CDCl₃) δ 8.30 (dt, J = 9.1, 1.1 Hz, 1H), 7.94 (dt, J = 7.1, 1.0 Hz, 1H), 7.42 (s, 2H), 7.08 (ddd, J = 9.1, 6.5, 0.9 Hz, 1H), 6.81 (td, J = 6.8, 1.3 Hz, 1H), 3.97 (s, 6H), 3.92 (s, 3H), 3.42 (hept, J = 6.9 Hz, 1H), 1.53 (d, J = 6.9 Hz, 6H). ^13C NMR (126 MHz, CDCl₃) δ 163.1, 161.5, 153.5, 145.3, 140.7, 131.9, 122.7, 121.5, 120.0, 119.3, 114.7, 114.0, 104.3, 61.0, 56.4, 26.4, 20.2. HRMS calcd for C_{21}H_{23}O_{4}N_{4} [M+H]^+: 395.17138, found [M+H]^+: 395.17078.

2-(2,6-dichlorophenyl)-5-(isopropylimidazo[1,5-α]pyridin-1-yl)-1,3,4-oxadiazole (10j)

Obtained using procedure F with 2,6-dichlorobenzoyl chloride on 0.5 mmol scale, 150 mg, 0.40 mmol, yield 80%, brown solid, m.p. 204 – 206 °C. ^1H NMR (500 MHz, CDCl₃) δ 8.28 (dt, J = 9.2, 0.9 Hz, 1H), 7.94 (dt, J = 7.2, 1.0 Hz, 1H), 7.44 – 7.42 (m, 3H), 7.08 (ddd, J = 9.1, 6.5, 0.9 Hz, 1H), 6.79 (td, J = 6.8, 1.3 Hz, 1H), 3.39 (hept, J = 6.9 Hz, 1H), 1.49 (d, J = 6.9 Hz, 6H). ^13C NMR (126 MHz, CDCl₃) δ 162.7, 157.9, 145.5, 136.8, 132.6, 132.0, 128.2, 128.0, 124.8, 122.9, 119.6, 114.3, 113.9, 26.2, 20.3. HRMS calcd for C_{18}H_{15}O_{4}N_{4}Cl_{2} [M+H]^+: 373.06174, found [M+H]^+: 373.06189.
CHAPTER 5

CRYSTAL STRUCTURE DETERMINATION

X-ray diffraction data for single crystals of compound 7b was collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus CuKα radiation source (λ = 1.5418 Å) The diffractometer was additionally equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments performed at 130(2) K. The obtained data sets were processed with CrysAlisPro software. The phase problem was solved with direct methods using SIR2004. Parameters of obtained models were refined by full-matrix least-squares on F² using SHELXL2014/6. Calculations were performed using WinGX integrated system (ver. 2014.1). Figure was prepared with Mercury 3.7 software.

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter Uiso[H] = 1.2 (or 1.5 (methyl groups only)) Ueq[C]. Crystal data and structure refinement results for presented crystal structures is presented in Table S1. The molecular geometry observed in crystal structure is shown in Figure S1.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC1869773 7b. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Figure S1. Molecular geometry observed in the crystal structures of compound 7b showing the atom labelling scheme (here asymmetric units, which consists of two independent molecules, related via pseudo-mirror plane). Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.
Table S1. Crystal data and structure refinement results for compound 7b.

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REFERENCES
