Sequential Multicomponent Synthesis of 2-(Imidazo[1,5-alpha]pyridin-1-yl)-1,3,4-Oxadiazoles

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Sequential multicomponent synthesis of 2-(imidazo[1,5-*α*]pyridin-1-yl)-1,3,4-oxadiazoles

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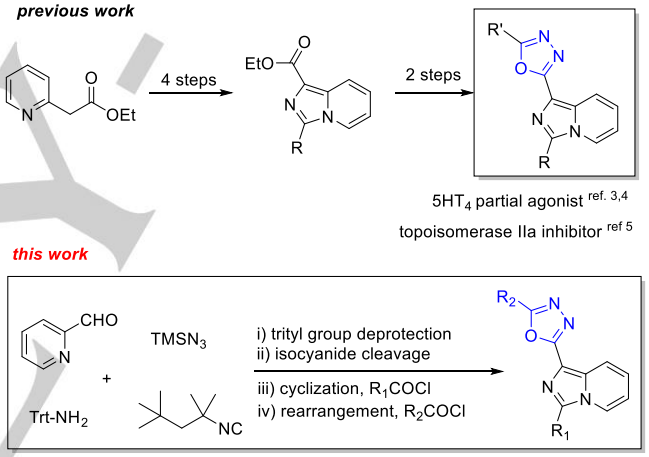
Dedication ((optional))

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.

Undoubtfully, heterocycles are the cycles 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 multi-component reaction chemistry (MCRs), 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.[1] For instance, multi-component reaction chemistry has been used extensively for the diverse synthesis of tetrazole derivatives,[2] 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 multi-component 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-HT_4 receptor partial agonists with applications in Alzheimer's disease.[3] 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,[4] 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).[5] It should be noted that in both cases the two heterocycles are constructed separately in a multi-step synthesis.



Scheme 1.

Moreover, 1,3,4-oxadiazole derivatives have been extensively studied due to a broad spectrum of biological activities, including mainly antiviral,[6] anti-inflammatory,[7] analgetic,[7] antimicrobial,[8] anti-convulsant,[8] anti-depressant,[8] antipsychotic and anticancer.[8] 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.[9] Moreover, 1,3,4-oxadiazoles find applications as charge carrier transporting molecular materials[10] and as fluorescent sensors,[11] due to their spectral luminescent properties.[12] 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-thiosemicarbazides, the cyclodehydration of aldehydes and hydrazides, and the reaction of carboxylic acids and acyl hydrazines with a great variety of reagents and conditions.[13]
Recently, a mild synthetic route was described for 1,3,4-oxadiazoles using (isocyanoimino)triphenylphosphorane.[14a-d] More specifically, a two-component reaction synthesis of 2-aryl-1,3,4-oxadiazoles is described using the above mentioned reagent and benzoic carboxylic acids under ultrasound irradiation.[14a] Variations of this procedure include a three-component reaction with the same reagent, a carboxylic acid

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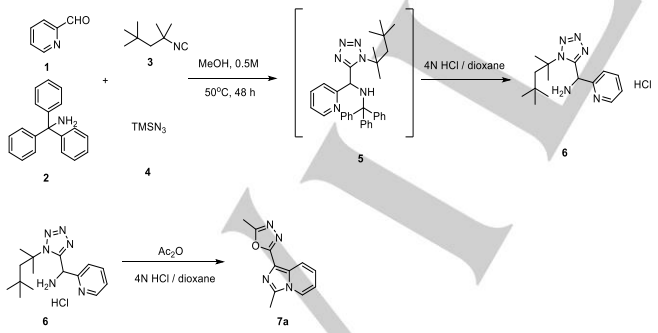
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

and acenaphthoquinone under ultrasound irradiation[14b] or four-component reactions with (isocyanoimino)triphenylphosphorane, chloroacetone, a primary amine and a carboxylic acid[14c] or a benzylamine, pyrrole-2-carbaldehyde and a carboxylic acid at room temperature.[14d] In all those cases, the transformation occurs through an aza-Wittig reaction leading to the desired 1,3,4-oxadiazole scaffold, with triphenylphosphine oxide as side-product. Moreover, a one-pot synthesis of α-keto-1,3,4-oxadiazoles was described using an isocyanide-Nef reaction through a sequential intermolecular dehydrochlorination / intramolecular aza-Wittig reaction.[15]

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[[16] or *o*-xylene.[17] A few examples are reported for microwave-assisted synthesis either from acyl chlorides or anhydrides. [18] 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.

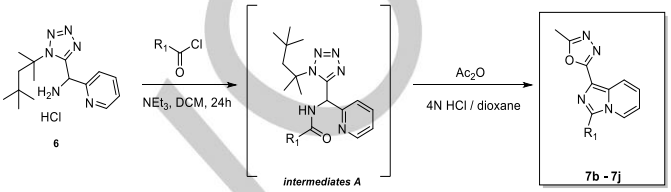
Herein, we present the synthesis of 2-(imidazo[1,5-*α*]pyridine-1-yl)-1,3,4-oxadiazoles starting from an Ugi-tetrazole reaction with a cleavable isocyanide. Example **7a** (Table 1, entry 1) was selected for establishing the methodology. Equimolar amount of picolinaldehyde (**1**), tritylamine (**2**), *tert*-octyl-isocyanide (**3**) and trimethylsilylazide (**4**) were combined sequentially in methanol (0.5M) 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). [19] 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).

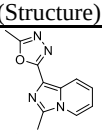
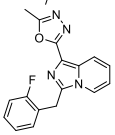
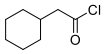
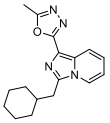
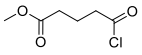
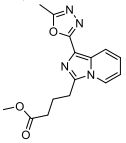
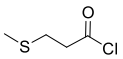
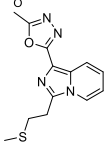
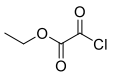
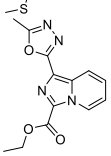
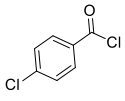
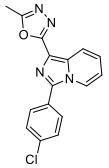
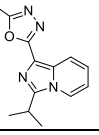


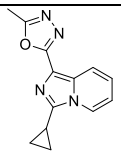
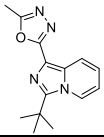
Scheme 2. Establishing the methodology and the one pot – one step procedure.

Next, we were keen to investigate the R_1 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 R_1 – substituted oxadiazoles (**7b- 7j**).

Table 1. Substrate scope for one pot – two step procedure R_1 – substituted imidazo[1,5-*α*]pyridine-1-yl)-1,3,4-oxadiazoles



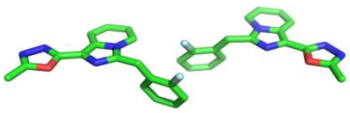
Entry [a]	Acyl chloride	Product (Structure)	Product entry	Yield[b]
1	-[c]		**7a**	60%
2			**7b**	85%
3			**7c**	92%
4			**7d**	33%
5			**7e**	55%
6			**7f**	44%
7			**7g**	32%
8			**7h**	17%

9			**7i**	42%
10			**7j**	16%

[a] Reaction scale was 1mmol. [b] Isolated yield after column chromatography. [c] Product was obtained using acetic anhydride.

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 isobuturyl 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 (7g, **32%**) 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.



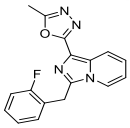
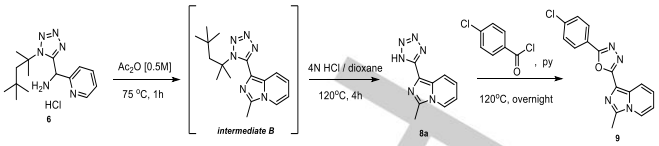


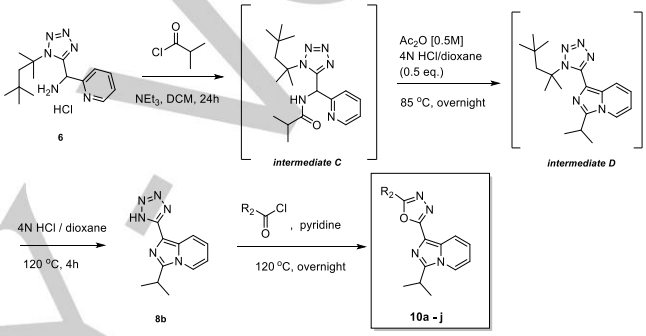
Figure 1. X-ray structure of compound **7b**.

Moreover, we investigated 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 [0.5M] at 75 °C for 1h, following our previously reported methodology.[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-(1*H*-tetrazol-5-yl)imidazo[1,5-*α*]pyridine (compound **8a)**. This intermediate tetrazole **8a** was directly dissolved in pyridine (0.5M) 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.



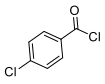
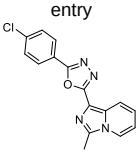
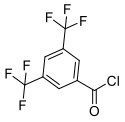
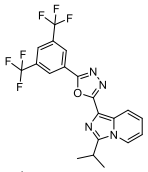
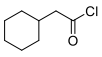
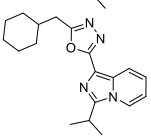
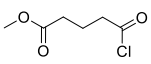
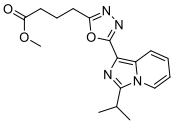
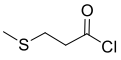
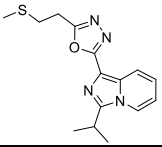
Scheme 3. Establishing the methodology for substitution on the oxadiazole ring.

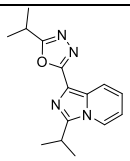
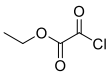
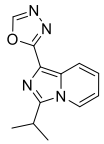
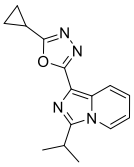
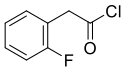
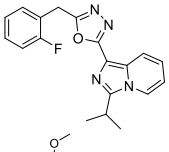
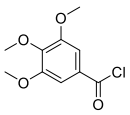
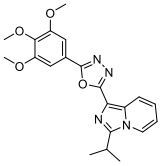
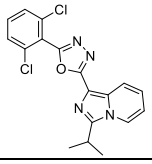
Next, we investigated the scope of R_2-substitutions and at the same time changed the methyl substituent of the imidazo-pyridine system towards an isobuturyl group to further diversify the products (Scheme 4). The isobuturyl substituent was a key feature in a series of 2-imidazo[1,5-a]pyridine-1,3,4-oxadiazole derivatives described as 5-HT_4 receptor partial agonists.[3]



Scheme 4. Synthetic route for products **10a**-j.

Table 2. Substrate scope for R_2-substituted imidazo[1,5-*α*]pyridine-1-yl)-1,3,4-oxadiazoles

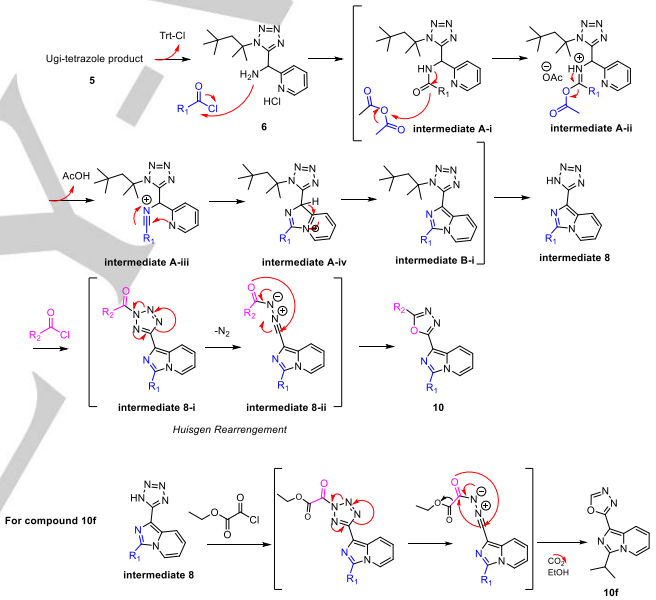
Entry [a]	Acyl chloride	Product (Structure)	Product entry	Yield[b]
11			**9**	80%
12			**10a**	66%
13			**10b**	90%
14			**10c**	40%
15			**10d**	76%

16			**10e**	72%
17			**10f**	64%
18			**10g**	29%
19			**10h**	23%
20			**10i**	26%
21			**10j**	80%

[a] Reaction scale was 0.5 mmol. [b] Isolated yield after column chromatography.

Overall, both aliphatic and aromatic acid chlorides were well tolerated. Excellent yields were observed with halogen-substituted aromatic acyl chlorides (products **9**, **10a** and **10j**), whereas the presence of electron-donating methoxy groups (**10i**) significantly reduced the 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, [20] iodination [21] and C-H bond thiolation. [22] 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 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)**. The deprotection of the *tert*-octyl group under acidic conditions gives the mono-substituted tetrazole **(intermediate B)**, 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 the elimination of nitrogen and ring opening are making the adjacent ethyl ester a good leaving group, which is eliminated as ethanol and carbon dioxide, thus affording the mono-substituted product **10f**.



Scheme 5. Proposed reaction mechanism.

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.

Experimental Section

Experimental Details (supporting information). General procedures, characterization data (^{1}H-NMR, ^{13}C-NMR, HRMS), single X-ray details (PDF file). CCDC 1869773 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif or by emailing data_request/cif@ccdc.cac.ac or by contacting the Cambridge

Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +441223336033.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgements

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Keywords:MCR chemistry•oxadiazole•Huisgen rearrangement•tetrazole•imidazopyridine

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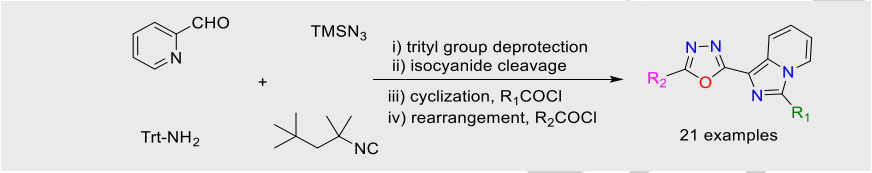

Text for Table of Contents: A short, unprecedented synthetic methodology for 2-(imidazo[1,5-*α*]pyridin-1-yl)-1,3,4-oxadiazoles is described, based on an Ugi tetrazole reaction with a cleavable isocyanide and a Huisgen-type rearrangement. Scope and limitations are discussed.

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Title Sequential multicomponent synthesis of 2-(imidazo[1,5-*α*]pyridin-1-yl)-1,3,4-oxadiazoles