Multicomponent Reaction Based Synthesis of 1-Tetrazolylimidazo[1,5-a]pyridines

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Supporting Information

ABSTRACT: A series of unprecedented tetrazole-linked imidazo[1,5-a]pyridines are synthesized from simple and readily available building blocks. The reaction sequence involves an azido-Ugi-deprotection reaction followed by an acetic anhydride-mediated N-acylation-cyclization process to afford the target heterocycle. Furthermore, the scope of the methodology was extended to diverse R₃-substitutions by employing commercial anhydrides, acid chlorides, and acids as an acyl component. The scope for the postmodification reactions are explored and the usefulness of the synthesis is exemplified by an improved three-step synthesis of a guanylate cyclase stimulator.

The design and synthesis of new bis-heterocyclic systems are highly appreciated in modern drug discovery to achieve specific drug–receptor interactions.¹ Tetrazole-linked imidazo[1,5-a]pyridine is such an unprecedented class of bis-heterocycles. Individually, the imidazo[1,5-a]pyridine heterocycle is the core of naturally occurring antimicrobial and antineoplastic agent cribrostatin 62 as well as many bioactive molecules, for example 5-hydroxytryptamine₄ receptor (5-HT4R) antagonists² and partial agonists,³ CB2 agonists,⁴ HIV protease inhibitors,⁵ thromboxane A₂ synthesis inhibitors,⁶ and guanylate cyclase stimulators.⁷ It has also found applications in material chemistry,⁷ and 1,5-disubstituted tetrazoles (1,5-DS-T’s) are bioisosteres of the cis-amide bond of peptides,¹⁰ which are highly appreciated in modern drug discovery to achieve specific drug–receptor interactions.¹ Therefore, developing more practical and efficient synthetic approaches for tetrazole-linked imidazo[1,5-a]pyridines is highly desirable. Our synthetic strategy for such a bis-heterocyclic system involves the Ugi-azole four component reaction (azido-Ugi 4CR)-deprotection to obtain the corresponding pyridin-2-yl(1H-tetrazol-5-yl)methanamine intermediate.¹³ The intermediate amine is then converted to tetrazolyl-imidazo[1,5-a]pyridine via an N-acylation-cyclization process (Figure 1).¹⁴

Thus, we describe the Ugi-azole four-component reaction (azido-Ugi 4CR) mediated synthesis of diverse analogues of 1-tetrazolylimidazo[1,5-a]pyridines.

Example 6a (Table 1, entry 1a) was selected as a model for screening and optimizing the reaction conditions. Equimolar amounts of aldehyde (1, R¹ = H), tritylamine 2, isocyanide (3, R² = benzyl), and azidotrimethylsilane 4 were combined sequentially in MeOH (0.5 M) at room temperature. The corresponding azido-Ugi product 5 was isolated in high yield of 85% after 18 h. Trityl group removal under acidic conditions (4 N HCl/dioxane) gave the (1-benzyl-1H-tetrazol-5-yl)(pyridin-2-yl)methanamine hydrochloride. We then tested the cyclization reaction under different reaction conditions using Ac₂O to form 6a. We screened several conditions and varied reaction parameters such as temperature, base, and Ac₂O concentration. To our surprise, no base was required, only Ac₂O (0.5 M) and warming (75 °C). A reaction time of 1 h was found to be optimal, with 6a being isolated in quantitative yield. With these optimized conditions in hand, we decided to switch to a one-pot protocol to avoid the isolation of the azido-Ugi intermediate. Here, the generally observed precipitation of trityl Ugi-azides

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Figure 1. Conceiving the idea.
was of great help. The azido-Ugi product 5 was quickly isolated by filtration to remove the solvent methanol and subjected to cyclization without any further purification with 4 N HCl/dioxane (3.0 equiv), Ac$_2$O [0.5 M] at 75 °C for 1 h, affording 6a in 85% overall yield. The reaction proceeds via in situ trityl deprotection followed by Ac$_2$O-mediated N-acylation—cyclization to form 6a. Using the optimized conditions, we next synthesized a series of novel 1-tetrazolyl-3-methylimidazo[1,5-a]pyridines 6b−m in a one-pot, two-step manner (Table 1, entries 1b−m). The scope of the substrate was evaluated using diverse isocyanides (3) and picolinaldehydes (1). Overall good to excellent yields were obtained. The highest yield of 90% was observed for product 6h (Table 1, entry 1b). Additionally, a lower yield was observed for the product 6g (65%, entry 1g) and 6i (60%, entry 1d).

Encouraged by the initial results, we investigated more diverse synthesis by changing the R3-substitutions on tetrazolylimidazo[1,5-a]pyridine core 8 according to our two-step procedure. According to the initial results, we investigated more diverse synthesis by changing the R3-substitutions on tetrazolylimidazo[1,5-a]pyridine core 8 according to our two-step procedure. Accordingly, step 1 involved the trityl deprotection of the azido-Ugi 4CR product 5 under acidic conditions (4 N HCl/dioxane, 10 min) to give the corresponding intermediate pyridin-2-yl(1H-tetrazol-5-yl)methanamine (intermediate a) as a HCl

Anhydrides including cyclic glutaric anhydride (entries 2a−c) worked well under the optimized conditions and produced 8a−c in 70−85% overall yield. A diverse set of acid chlorides (entries 2d−i) as the acyl component worked well, and the corresponding products were formed in generally very good yield. We observed a drop in overall yields in the case of acids (40−79%, entries 2k−o) compared to anhydrides and acid chlorides, which may reflect worse coupling yields. In the case of N-Boc-protected amino

Table 1. Substrate Scope of the 1-Tetrazolyl-3-methylimidazo[1,5-a]pyridine Synthesis

| Entry* | Aldehyde 1 $R_1$ | Isocyanide 3 $R_2$ | Product 6 | Yield(%) |
|--------|-----------------|-------------------|-----------|----------|
| 1a     | H               |                   | 6a        | 85       |
| 1b     | H               |                   | 6b        | 88       |
| 1c     | H               |                   | 6c        | 82       |
| 1d     | H               |                   | 6d        | 75       |
| 1e     | H               |                   | 6e        | 87       |
| 1f     | H               |                   | 6f        | 80       |
| 1g     | H               |                   | 6g        | 65*      |
| 1h     | H               |                   | 6h        | 90       |
| 1i     | H               |                   | 6i        | 60       |
| 1j     | H               | MeO               | 6j        | 75       |
| 1k     | H               |                   | 6k        | 77       |
| 1l     | 6-Me            |                   | 6l        | 78       |
| 1m     | 5-Br            |                   | 6m        | 74       |

*Reaction scale 1.0 mmol. †Isolated yield. *Indole N-acylated product was isolated in 15% yield. †Azide—Ugi product (5) was isolated in 62% yield along with tetryazole regiosymmetric product 20% yield.

Table 2. R$_3$-Substitutions on Tetrazolylimidazo[1,5-a]pyridine

| Entry* | $R_3$ | 7 | Product 8 | Yield(%) |
|--------|-------|---|-----------|----------|
| 2a     | Bu    | 8a | 85        |
| 2b     | Bu    | 8b | 78        |
| 2c     | Ph    | 8c | 70        |
| 2d     | Ph    | 8d | 87        |
| 2e     | Ph    | 8e | 85        |
| 2f     | Ph    | 8f | 80        |
| 2g     | Ph    | 8g | 82        |
| 2h     | Ph    | 8h | 70        |
| 2i     | Ph    | 8i | 85        |
| 2j     | Ph    | 8j | 80        |
| 2k     | MeO   | 8k | 67        |
| 2l     | MeO   | 8l | 79        |
| 2m     | MeO   | 8m | 60        |
| 2n     | MeO   | 8n | 40        |
| 2o     | MeO   | 8o | 45        |
| 2p     | MeO   | 8b | 70        |
| 2q     | MeO   | 8q | trace     |

*Reaction scale 1.0 mmol. †Isolated yield. *The reaction scale was 5.0 mmol; reaction mixture was heated at 75 °C for 8 h.
acids, the corresponding N-acyl products 8m–o (entries 2m–p) were isolated in 40–60% yields. Deborlation was observed in the case of the 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid, and 8b was isolated with 70% yield. Thus, Boc and pinacol—borane groups were found to be labile under the optimized condition. In case of cyanoacetic acid, a trace amount of product 8q was formed (Table 2, entry 2q).

Several structures have been confirmed by X-ray single-crystal analyses (Figure 2 and Supporting Information). The following interesting motifs could be observed in the solid state: the scaffold in general is flat, and therefore, stacking interactions with neighboring molecules are always observed. In 6b the tetrazole and in 6l the imidazopyridine moieties stack antiparallel. In 6m, a halogen bond with 3.1 Å between the p-Br and N3 of an adjacent tetrazole can be found.

A mechanism is proposed in Scheme 1. The Azido-Ugi reaction mechanism has been documented.13 Then the azido-Ugi product 5 undergoes N-acylation and forms intermediate 5-I via acid-mediated trityl group deprotection. Further, 5-I undergoes an O-acylation—elimination process and provides nitritium intermediate 5-II. Attacking the ring nitrogen lone pair of electrons from 5-II leads to the cyclic intermediate 5-III, which upon aromatization leads to the formation of the target product 6 (Scheme 1).

As an application of the methodology, we could improve upon the synthetic route of the guanylate cyclase stimulator 9 in three simple steps with 76% overall yield, via acid mediated tert-octyl group deprotection13 of 8j in the final step (Scheme 2). After demonstrating the successful synthesis of diverse substituted tetrazolylimidazo[1,5-a]pyridines, we wanted to further demonstrate the scope of the method by synthesizing unsubstituted (R3 = H) examples and explore their postmodification.

Examples 8r and 8s were prepared from intermediates 6r and 6s in 74% and 78% yields, respectively, via one pot N-formylation followed by POCl3-mediated dehydration—cyclization process (Scheme 3).16 While attempting the debenzylation of 8r under hydrogenation condition, we observed the selective pyridyl ring saturation product, and 10 was isolated in 98% yield. The interesting low molecular weight free tetrazole 11 building block was obtained in 88% yield by deprotection of the tert-butyl group of 8s under acidic conditions (Scheme 3).17

In continuation of exploring the post modification scope, the phthalimide group in 8i was deprotected to form the free amine 12 (90% yield), which was subjected to three different types of reactions: (i) sulfonamide, (ii) urea, and (iii) thiourea formation.18 All three types of reactions worked well and furnished the desired products 13a-c in very good yields of 75–85% (Scheme 3).

Taken together, we have developed a novel, simple, and efficient two-step method for the synthesis of tetrazolylimidazo-

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**Scheme 1. Proposed Mechanism**

![Scheme 1](image1.png)

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**Scheme 2. Improved Route to the Guanylate Cyclase Stimulator (9)**

![Scheme 2](image2.png)

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**Scheme 3. Postmodification Scope**

![Scheme 3](image3.png)
[1,5-α]pyridines, a bis-heterocyclic system via the well-known azido-Ugi 4CR reaction, and an unprecedented acetic anhydride mediated post cyclization reaction. Work is ongoing to investigate the further synthetic applications and biological properties of the new compound class.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01452.

General procedures, characterization data, spectra (H, 13C NMR, HRMS), single crystal X-ray details (PDF)

Accession Codes

CCDC 1828260–1828262 and 1839326 contain 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@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**Notes**

The authors declare no competing financial interest.

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