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Synthesis of Highly Substituted Imidazole Uracil Containing Molecules via Ugi-4CR and Passerini-3CR

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3 Supporting Information

ABSTRACT: The synthesis of uracil/thymine containing tetra/trisubstituted imidazole derivatives was demonstrated using Ugi/Passerini-reaction followed by a postcyclization reaction sequence. The approach enables the one-pot facile construction of diverse compounds in moderate to excellent yields (47−82%). The S-fluorouracil and S-methyluracil moieties afford potentially bioactive molecules with drug-like properties. These scaffolds are currently being utilized in the screening deck of the European Lead Factory.

KEYWORDS: Ugi-4CR, Passerini-3CR, uracil/thymine, imidazole, one-pot

Figure 1. Thymine and uracil are important anchoring moieties toward protein receptors displaying a distinct universal hydrogen bonding network. Above: schematic hydrogen bonding network of U derivatives with hydrogen bond donors and acceptors shown as blue and red dotted lines, respectively. Below: Mycobacterium tuberculosis dUTPase complexed with dUTP (PDB ID SMC) as an archetypical nucleobase receptor interaction.
discovery research. Hence, the synthesis of imidazole scaffold by Ugi- and Passerini-reactions could be an interesting subject to study and explore through IMCRs.

Initially, the Ugi four-component reaction (U-4CR) of phenylglyoxal \(1\{1\}\), 3,4-dimethoxyphenethylamine \(2\{1\}\), cyclohexyl isocyanide \(3\{1\}\), and uracil derived acetic acid \(4\{1\}\) in methanol (1.0 M) furnished the corresponding product in poor yields even after 48 h. After a thorough investigation, it was found that a mixture of DCM/DMF (1:1) was the appropriate combination for this Ugi-reaction to yield up to 90% within 48 h. After completion of the Ugi reaction, we aimed to convert the Ugi products to the corresponding tetra-substituted imidazoles \(h\). After a thorough investigation, it was found that a mixture of DCM/DMF (1:1) was the appropriate combination for this Ugi-reaction to yield up to 90% within 48 h. After completion of the Ugi reaction, we aimed to convert the Ugi products to the corresponding tetra-substituted imidazoles (Table 1). Products \(6\{1,1,1,1\}\) were obtained from 5-tri- and tetra-substituted imidazole libraries reported within the study and explore through IMCRs.

All isocyanides afforded the corresponding imidazoles in good yields (Table 1). Interestingly, even the bulky adamantine \(3\{9\}\) and camphor \(3\{9\}\) derived isocyanides reacted nicely. The U-4CR and post cyclization reaction worked with all aliphatic and aliphatic-aromatic amines resulting in a variety of tetra-substituted imidazoles, we planned to synthesize oxazoles by employing the Passerini reaction as an initial step. The above optimized reaction conditions were used in the Passerini reaction as well followed by the cyclization reaction sequence. Phenylglyoxal, cyclohexyl isocyanide and uracil derived acetic acid were reacted in DCM:DMF (1:1) for 48 h. The crude mixtures were treated with \(\text{NH}_4\text{OAc} (15 \text{ equiv})\) in \(\text{AcOH}\) at 120 °C for 1 h furnishing the desired product \(6\{1,1,1,1\}\) in 60% overall yield.

**Figure 2.** Chemset 1 consisting of phenyl glyoxal.

**Figure 3.** Chemset 2 consisting of amines.

**Figure 4.** Chemset 3 consisting of isocyanides.

After careful elucidation of the X-ray structures of compounds \(8\{1,9,1\}\) and \(8\{1,11,1\}\), we concluded that the free NH-imidazole was formed instead of the expected trisubstituted oxazole. The formation of the imidazole instead of the oxazole can be attributed to the excess of ammonia used during the reaction. A proposed mechanism involves the initial formation of the oxazole followed by the nucleophilic attack of ammonia at the C2. Subsequently the oxazole ring opens through the intermediacy of an amide at C-2 and a ketone at C-5 followed by dehydration which leads to the unexpected free NH-imidazole (Scheme 1).

The postcyclization step of the Passerini products was also performed with 1.0 equiv of \(\text{NH}_4\text{OAc} \) in \(\text{AcOH}\) at 120 °C, but still the formation of imidazole along with oxazole (22% and 16% yield respectively) and incomplete starting material was observed, even after 12 h of reaction time. With these results in hand, we decided to investigate the synthesis of a library of NH-imidazoles.

The structures exhibit interesting hydrogen bonding patterns. In \(8\{1,9,1\}\), the Uracil undergoes a bifurcated hydrogen bonding to the Uracil of a neighboring molecule. Moreover, a hydrogen bond from the imidazole NH to a DMSO solvent molecule is formed. In \(8\{1,11,1\}\), a hydrogen bonding between the imidazole NH to the U-CO of a neighboring molecule is formed. In general, the free NH-imidazoles were obtained in good yields regardless of their steric and electronic properties. First, a wide variety of aliphatic and aliphatic-aromatic isocyanides were reacted with phenylglyoxal \(1\{1\}\) and uracil derived acetic acid in

**Figure 5.** Chemset 4 consisting of acids.
DCM:DMF (1:1) followed by an excess of NH₄OAc (15 equiv) and treatment in acetic acid at 120 °C for 1 h, providing the desired free NH-imidazoles in very good yield. On the other hand, indole and amino acid derived isocyanides were also valid substrates in the Passerini/cyclization sequence (8{1,1,1,1} and 8{1,1,3,1}). 5-Fluoro and 5-methyl uracil acetic acids along with phenylglyoxal and isocyanides also furnished the expected trisubstituted imidazoles (8{1,1,1,1}, 8{1,8,3}, and 8{1,8,2}) in 47%, 57%, and 63% yields, respectively.

Imidazole rings are the second most common five-membered aromatic nitrogen heterocycles U.S. FDA approved drugs. The imidazole ring is considered to be an attractive isostere of a triazole, oxazole, pyrazole, thiazole, and tetrazole because of its capability to coordinate with a variety of inorganic metal ions, as well as biological molecules in the human body. In this report, along with the imidazole ring, we have grafted an attractive extra uracil part and based on the interesting scaffold properties they are now part of the screening decks of the European Lead Factory (ELF). In summary, we have described a novel method for the synthesis of Uracil containing tetra- and trisubstituted imidazoles. This simple and mild procedure is a valuable addition to MCR chemistry and expands its unique scaffold diversity. Work is ongoing to identify biological targets for our compound libraries and will be reported in due course.

### EXPERIMENTAL PROCEDURES

Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer (1H NMR (500 MHz), 13C NMR (126 MHz)). Chemical shifts for 1H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = double of doublet, ddd = double of doublet of doublets, m = multiplet. Chemical shifts for 13C NMR were reported in ppm relative to the solvent peak. Thin layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 μm). Flash chromatography was performed on a Teledyne ISCO CombiFlash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230−400 mesh) and on a Reveleris X2 Flash Chromatography, using Grace Reveleris Silica flash cartridges (12 g). Reagents were available from commercial suppliers (Sigma-Aldrich, ABCR, Acros, and AK Scientific) and used without any purification unless otherwise noted. All microwave irradiation reactions were carried out in a Biotage Initiator Microwave Synthesizer. Electrospray ionization mass
spectra (ESI-MS) were recorded on a Waters Investigator Semiprep 15 SFC-MS instrument.

**Typical Procedures for the Synthesis of Compounds 6 and 8. Procedure A.** General procedure for the synthesis of imidazole derivatives 6: In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of DCM:DMF (1:1) (0.5 M) were added amine (1.0 mmol) and 2-oxo-2-phenylacetaldehyde (1.0 mmol). After stirring for a minute, were added isocyanide (1.0 mmol) and acid (1.0 mmol). The reaction mixture was stirred at 25 °C for 24 to 48 h. The crude mixture was filtered through a pad of silica eluting with DCM:MeOH (9:1). Resulting mixture was treated with NH₄OAc (15 equiv) in AcOH (0.5 M) at 120 °C for 1 h. The crude reaction mixture was worked up with saturated NaHCO₃ solution and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. Pure products were obtained through column chromatography (silica gel, mixture of DCM/MeOH).

**Procedure B.** General procedure for the synthesis of free NH-imidazole derivatives 8: In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of DCM:DMF (1:1) (0.5 M) were added 2-oxo-2-phenylacetaldehyde (1.0 mmol) isocyanide (1.0 mmol) and acid (1.0 mmol). The reaction mixture was stirred at 25 °C for 24 to 48 h. The crude mixture was filtered through a pad of silica eluting with DCM:MeOH (9:1), evaporated to dry and resulting mixture was treated with NH₄OAc (15 equiv) in AcOH (0.5 M) at 120 °C for 1 h. The crude reaction mixture was worked up with saturated NaHCO₃ solution and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na₂SO₄), filtered and concentrated. Pure products were obtained through column chromatography (silica gel, mixture of DCM/MeOH).

**ASSOCIATED CONTENT**

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.7b00145.

Crystallographic information file for compound 5j (CIF)
Crystallographic information file for compound 5k (CIF)
General experimental procedures, compound characterization data, and ¹H and ¹³C spectra of all compounds (PDF)

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Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Author Contributions
K. K. and K-T. J contributed for crystal structure analysis.

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Notes
The authors declare no competing financial interest.

REFERENCES

(1) (a) Longley, D. B.; Harkin, D. P.; Johnston, P. G. S-Fluorouracil: Mechanisms of action and clinical strategies. Nat. Rev. Cancer 2003, 3, 330−338. (b) Al Safarjalani, O. N.; Zhou, X. J.; Rais, R. H.; Shi, J. X.; Schinazi, R. F.; Naguib, F. N. M.; el Kouni, M. H. S-(Phenylthio)-acyclobutidine: a powerful enhancer of oral uridine bioavailability: relevance to chemotherapy with 5-fluorouracil and other uridine rescue regimens. Cancer Chemother. Pharmacol. 2005, 55, 541−551.

(2) Berman, H. M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T. N.; Weissig, H.; Shindyalov, I. N.; Bourne, P. E. The Protein Data Bank.

(3) (a) Bossio, R.; Marcaccini, S.; Pepino, R. Synthesis of isocyanides and related compounds. Synthesis of oxazole and Morpholines and Piperazines.

(4) (a) Zhang, C.; Moran, E. J.; Woiwode, T. F.; Short, K. M.; Jalil, A. M. M. Synthesis of tetrasubstituted imidazoles via [alpha]-[N-acyl-N-alkylamino]-[beta]-ketoamides on Wang resin. Tetrahedron Lett. 1996, 37, 751−754. (b) Sung, K. S.; Wu, S. H.; Chen, P. I. Facile two-pot syntheses of novel alternating benzene/imidazole systems. Tetrahedron 2002, 58, 5599−5602. (c) Bossio, R.; Marccacini, S.; Pepino, R. Syntheses of isocyanides and related compounds. Synthesis of oxazole derivatives via the Passerini reaction. Liebig’s Ann. Chem. 1991, 1107−1108.

(5) (a) Wang, H. W.; Kumar, R. K.; Yu, Y.; Zhang, L.; Liu, Z. H.; Liao, P. Q.; Bi, X. H. Silver-Catalyzed Isocyanide-Isocyanide [3 + 2] Cross-Cycloaddition Involving 1,2-Group Migration: Efficient Synthesis of Trisubstituted Imidazoles. Chem. - Asian J. 2016, 11, 2841−2845. (b) Yu, L.; Deng, Y.; Cao, J. Regioselective Synthesis of Highly Substituted Imidazoles via the Sequential Reaction of Allenyl Sulfonamides and Amines. J. Org. Chem. 2015, 80, 4729−4735. (c) Pool, B.; Lee, J.; Choo, K.; Gong, H.; Hong, S. H. Tandem Insertion-Cyclization Reaction of Isocyanides in the Synthesis of 1,4-Diaryl-1H-imidazoles: Presence of N-Arylimidamidate Intermediate. J. Org. Chem. 2014, 79, 9231−9245.

(6) Zuliani, V.; Cocconcelli, G.; Fantini, M.; Ghiron, C.; Rivara, M. A practical synthesis of 2,4,5-[diaryl]imidazoles from simple building blocks. J. Org. Chem. 2007, 72, 4551−4553. (c) Langhammer, I.; Erker, T. Synthesis of 2,4-diarylimidazoles through Suzuki cocoupling reactions of imidazole halides with aryloboronic acids. Heterocycles 2005, 65, 1975−1984. (f) Li, B.; Chiu, C. K. F.; Hank, R. F.; Murry, J.; Roth, J.; Tobissens, H. An optimized process for formation of 2,4-disubstituted imidazoles from condensation of amidines and alpha-haloketones. Org. Process Res. Dev. 2002, 6, 682−683. (g) Lee, H. B.; Balasubramanian, S. Solid-phase synthesis of N-alkyl-N-(beta-keto)amides and 1,2,4,5-tetrasubstituted imidazoles using a traceless cleavage strategy. Org. Lett. 2000, 2, 323−326.

(7) Van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. Base-Induced Cycloaddition of Sulfonylmethyl Isocyanides to C, N Double Bonds - Synthesis of 1,5-Disubstituted and 1,4,5-Trisubstituted Imidazoles from Aldimines and Imidoyl Chlorides. J. Org. Chem. 1977, 42, 1153−1159.

(8) (a) Patil, P.; Madhavachary, R.; Kurpiewska, K.; Kalinowska-Tluscik, J.; Dömling, A. Recent developments in isocyanide based multicomponent reactions in applied chemistry. Chem. Rev. 2006, 106, 17−89. (b) Orru, R. V. A.; de Greef, M. Recent advances in solution-phase multicomponent methodology for the synthesis of heterocyclic compounds. Synthesis 2003, 1471−1499. (c) Bienayme, H.; Hulme, C.; O’Donn, G.; Schmitt, P. Maximizing synthetic efficiency: Multicomponent transformations lead the way. Chem. - Eur. J. 2000, 6, 3321−3329. (d) Dömling, A.; Ugi, I. Multicomponent reactions with isocyanides. Angew. Chem., Int. Ed. 2000, 39, 3168−3210.

(9) (a) Vitaku, E.; Smith, D. T.; Njardarson, J. T. Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among US FDA Approved Pharmaceuticals. J. Med. Chem. 2014, 57, 10257−10274. (b) Mullard, A. European Lead Factory opens for business. Nat. Rev. Drug Discovery 2013, 12, 173−175.