Synthesis of Tris-Heterocycles via a Cascade IMCR/Aza Diels-Alder + CuAAC Strategy

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6-Triazolylmethyl-pyrrolo[3,4-b]pyridin-5-one tris-heterocycles were synthesized in 43–57% overall yields. The two-stage synthesis involved a cascade process (Ugi-3CR/aza Diels-Alder/N-acylation/aromatization) followed by a copper-assisted alkyne-azide [3+2] cycloaddition (CuAAC). This efficient and convergent strategy proceeded via complex terminal alkynes functionalized with a fused bis-heterocycle at the α-position. The final products are ideal candidates for SAR studies as they possess two privileged scaffolds in medicinal chemistry: 4-substituted or 1,4-substituted 1H-1,2,3-triazoles and pyrrolo[3,4-b]pyridin-5-ones.

Keywords: nitrogen tris-heterocycles, cascade IMCR process, CuAAC, Ugi-3CR, aza Diels-Alder

INTRODUCTION

Polyheterocycles are organic molecules containing three or more heterocyclic moieties, which may be joined by one or more different kinds of connectivity (Ibarra et al., 2018). Nitrogen-containing polyheterocycles are of particular interest in the synthesis of bioactive molecules (Dener et al., 2006; Dolle et al., 2008; Atobe et al., 2013). Tris-heterocyclic molecules have been reported in optics and in coordination chemistry (Stibrany et al., 2003; Burling et al., 2007; Tahara et al., 2009).

The 4-substituted 1H-1,2,3-triazole is a heterocycle of high interest in medicinal chemistry, and it is well-documented that incorporation of this moiety into several bioactive compounds has resulted in advantages such as reduced toxicity or increased antibacterial or antimalarial activity (Shchepin et al., 2008; Zhou et al., 2008) [e.g., Figure 1, compound A (Dixit et al., 2012)]. Triazoles may also increase the stability and polarity of compounds by coordination of the N1 and N2 triazole nitrogens to active-site metal atoms in metalloproteases. The N3 nitrogen appears not to be directly involved in binding metals but can form hydrogen bonds with amino acid residues (Kallander et al., 2005; Huang et al., 2011; Röhrli et al., 2012; Borkin et al., 2016). Additionally, 4-substituted 1H-1,2,3-triazoles are precursors of bioactive disubstituted 1,2,3-triazoles (Duan et al., 2009; Oh et al., 2010; Yan et al., 2010; Hsu et al., 2013; Bakulev and Beryozkina, 2016) and of pyridyl-1H-1,2,3-triazolate complexes that have applications in optics and coordination chemistry (Sinn et al., 2014; Prabhath et al., 2015). On the other hand, 1,4-disubstituted 1H-1,2,3-triazoles display structural and electronic similarities with the trans-amide bond. Their overall dipolar moment and hydrogen-bonding properties are greater than those of an amide bond, making these heterocycles effective peptidomimetics (Tron et al., 2008). These triazoles also function as flat bivalent elements, imitating the rigid conformational constraints of double bonds in alkyl chains. 1,4-Disubstituted 1H-1,2,3-triazoles are also capable substitutes for other five-membered nitrogen-containing heterocycles.
such as imidazoles, pyrazoles, 1,2,4-triazoles, oxazoles, isoxazoles, and oxazolidinones. Finally, these rings can act as more stable isosteres of phosphate linkers (Bonandi et al., 2017).

Common synthetic approaches to 4-substituted 1H-1,2,3-triazoles involve a [3+2] cycloaddition between sodium azide (NaN₃) or hydrazoic acid (HN₃) and terminal alkynes activated with electron-withdrawing groups (EWGs) (Hartzel and Benson, 1954; Balle et al., 2003; Blass et al., 2006; Koszytkowska-Stawińska et al., 2012). A variation of this classical methodology using trimethylsilyl azide (TMSN₃) provides a much safer procedure. The use of a copper(I) catalyst allows the use of non-activated terminal alkynes in shorter reaction times and under milder conditions (Jin et al., 2004). For preparing 1,4-disubstituted 1H-1,2,3-triazoles, the classic synthetic approach is the regiospecific copper-assisted [3+2] cycloaddition between terminal alkynes with organic azides (Rostovtsev et al., 2002; Tornoe et al., 2002). The most common technique is in situ reduction of copper(II) salts, such as CuSO₄•5H₂O or Cu(OAc)₂, forming copper(I) salts using sodium ascorbate as the reducing agent. A second option is to use a copper(I) salt such as CuCl, CuBr, CuI, [Cu(CH₃CN)₄]OTf, or Cu(CH₃CN)₄PF₆ in a deoxygenated environment and in organic solvent, typically with an amine such as TEA, DIEA, DIPEA, or PMDETA (Bock et al., 2006; Hein and Fokin, 2010; Lauria et al., 2014).

On the other hand, the fused heterocycle pyrrolo[3,4-b]pyridin-5-one is an aza-analog of isoindolin-1-one natural products and is present in several bioactive molecules; for example: hypoglycemic [Figure 1, compound B (Devasthale et al., 2013)], analgesic, anticaner, and therapeutic agents for CNS-related diseases like Alzheimer’s, epilepsy, and schizophrenia (Unverferth et al., 2002; Chang et al., 2008; Pajouhesh et al., 2012; Lindsley et al., 2013). The synthesis of analogs with a brain-selective radioligand has also been reported [Figure 1, compound C (Wager et al., 2017)].

There are no previous reports of molecules containing 4-substituted or 1,4-disubstituted 1H-1,2,3-triazoles and pyrrolo[3,4-b]pyridin-5-ones, though there are a few examples of each of these ring systems connected to other heterocycles using multistep approaches [Figure 1, compounds A-C (Dixit et al., 2012; Devasthale et al., 2013; Mallemula et al., 2015; Marčić et al., 2015; Wager et al., 2017)].

Isocyanide-based multicomponent reactions (IMCRs) are the most efficient strategies to synthesize pyrrolo[3,4-b]pyridin-5-ones, and Zhu first reported a one-pot synthesis in 2001 (Sun et al., 2001). We synthesized various annulated polyheterocycles containing this fused bis-heterocycle via IMCR strategies (Islas-Jácome et al., 2011, 2012). However, there are no published reports of pyrrolo[3,4-b]pyridin-5-ones linked to other heterocycles in a non-annulated fashion using IMCRs. Recently, Van der Eycken reported a one-pot synthesis of
Previous work (Trang et al., 2015)

\[
\begin{align*}
\text{COOH} & \quad \text{N} \\
\text{Cl} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
R^1 & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{MeOH} & \quad \text{n, 24 h} \\
i & \quad \text{DMF, K}_2\text{CO}_3, N_2 \quad 110 ^\circ \text{C}, 24 h \\
\text{R}^1 & \quad \text{R}^2 \\
\text{MeOH} & \quad \text{n, 24 h} \\
\text{N} & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{MeOH} & \quad \text{n, 24 h} \\
\text{DMF, K}_2\text{CO}_3, \text{air} \quad 110 ^\circ \text{C}, 24 h \\
\text{10 examples} & \quad 21-88\% \\
\text{9 examples} & \quad 25-65\% \\
\end{align*}
\]

Previous work (Trang et al., 2015)

\[
\begin{align*}
\text{F} & \quad \text{Cl} \\
\begin{array}{c}
\text{NaN}_3, \text{Na-ascorbate (40 mol%), CuSO}_4\cdot\text{5H}_2\text{O (4 mol%)}
\end{array} \quad \text{DMF/H}_2\text{O, 6 h, 60 }^\circ \text{C} \\
\end{align*}
\]

Previous work (Hédou et al., 2013)

\[
\begin{align*}
\text{COOH} & \quad \text{NNH}_2 \\
\begin{array}{c}
\text{1. DMFDMA} \quad \text{DMF, 100 }^\circ \text{C (MW)} \quad 15 \text{ min} \\
\text{2. NBS, DMF, r.t. 4 h} \\
\text{3. AcOH, 100 }^\circ \text{C (MW)} \quad 15 \text{ min}
\end{array} \\
\end{align*}
\]

\[
\begin{align*}
\text{X} & \quad = \text{H} (97\%) \\
\text{X} & \quad = \text{Br} (94\%) \\
\begin{array}{c}
\text{TMSN}_3, \text{ CuI (5\% mol)} \quad \text{DMF/MeOH 130 }^\circ \text{C (MW)} \quad 40 \text{ min} \\
\text{1 example} & \quad 70\%
\end{array} \\
\end{align*}
\]

Besson reported the two-stage synthesis of tris-heterocycles with pyrido[2,3-d]pyrimidin-4(3H)-one linked to 1,2,3-triazoles via a one-pot DMFDMA-mediated cyclization followed by a CuAAC (Scheme 1; Hédou et al., 2013). However, only two heterocycles are constructed in this process and the scope of the alkynes is limited.

Our ongoing research program focuses on the design of rapid, convergent and efficient IMCR/post-transformation
strategies toward novel molecules containing privileged heterocycles: azepino[4,5-b]indol-4-ones (Rentería-Gómez et al., 2016b), 2-tetrazolylmethyl-isooxindolin-1-ones (Rentería-Gómez et al., 2016a), tetrazolo[1,5-a]quinolines (Unnamatla et al., 2016), 3-tetrazolylmethyl-azepino[4,5-b]indol-4-ones (Gordillo-Cruz et al., 2013), 2,3,4,9-tetrahydro-1H-β-carbolines (Cárdenas-Galindo et al., 2014), 4-(pyridine-3-yl)pyrimidines (Cortes-García et al., 2016), and spiro[pyrrolidine-3,3′-oxindoles] (Alvárez-Rodríguez et al., 2018). Herein we describe the first cascade IMCR process/post-transformation strategy toward the synthesis of 4-substituted 1H-1,2,3-triazoles linked to a fused, bis-heterocycle. Two fused rings were created in the process, resulting in pyrrolo[3,4-b]pyridin-5-ones 6a-m.

RESULTS AND DISCUSSION

In this work, we report the two-step synthesis of compounds 9a-m and 19a-d, which contain three different heterocycles: pyridine, pyrrolidin-2-one, and 1H-1,2,3-triazole (4-substituted and 1,4-disubstituted) (Scheme 3). The use of orthogonal, bifunctional reagents plays a central role in the IMCR/post-transformation strategy, leading to the rapid generation of molecular complexity in both bis-heterocycles 6a-m and final products 9a-l. In the first step, the synthesis of 6a-m occurs by a cascade process combining an Ugi-3CR with aza Diels-Alder, N-acylation, and aromatization reactions to give a complex terminal alkyne functionalized at the α-position with a fused bis-heterocycle. Two fused rings were created in the process, resulting in pyrrolo[3,4-b]pyridin-5-ones 6a-m.
To optimize the cascade process, we attempted to synthesize complex alkyne 6a by sequentially reacting propargylamine (1), benzaldehyde (2a), isocyanide 3a, and maleic anhydride (4) using toluene (Table 1). Performing the reaction without catalyst at 60–80 °C under conventional conditions produced 6a in 13% yield (entry 1, Table 1). When the reaction was carried out using catalytic amounts of NH₄Cl at 60–80 °C (Janvier et al., 2002), the product was isolated in 43% yield (entry 2, Table 1). Under microwave conditions, the yield increased to 57% (entry 3, Table 1). In previous reports, we used TsOH for the aromatization process after a Diels-Alder cycloaddition to construct the isoindolin-1-one moiety (Rentería-Gómez et al., 2016a). Unfortunately, bis-heterocycle 6a was not detected when TsOH was used; only decomposition was observed by TLC.

Using catalytic Sc(OTf)₃ under conventional heating, 6a was obtained in 42% yield (entry 5, Table 1). Microwave heating with Sc(OTf)₃ or Yb(OTf)₃ (Islas-Jácome et al., 2011, 2012) raised the yield to 69 and 62%, respectively (entries 6-7, Table 1). We therefore used the optimal conditions (entry 6: 3 mol% Sc(OTf)₃, microwave heating 60–80 °C, 1.5 h) to synthesize the series of fused bis-heterocycles 6a-l (Table 2).

The scope of this cascade process was explored using alkyl and aryl aldehydes 2a-d and amide-containing isocyanides 3a-c (Table 2). The role of fluorine atoms in improving bioavailability, lipophilicity and metabolic resistance in bioactive molecules is well-documented (Purser et al., 2008). The products 6c, 6g, and 6k containing fluorine atom was synthesized. Piperidine, morpholine, and diethylamine were incorporated as substituents of isocyanides 3a-c. These fragments can act as structural bioisosteres, preferably interacting with some amino acids.

### Table 1: IMCR based cascade strategy screening conditions.

| Entry | Solvent | Additive | T (°C) | t (h) | Yield (%) |
|-------|---------|----------|--------|-------|-----------|
| 1     | PhMe    | ——       | 65–80  | 12    | 13        |
| 2     | PhMe    | NH₄Cl     | 65–80  | 12    | 43        |
| 3     | PhMe    | NH₄Cl     | 65–80  | 1.5   | 57        |
| 4     | PhMe    | TsOH      | 65–80  | 1.5   | —         |
| 5     | PhMe    | Sc(OTf)₃  | 65–80  | 12    | 42        |
| 6     | PhMe    | Sc(OTf)₃  | 65–80  | 1.5   | 57        |
| 7     | PhMe    | Yb(OTf)₃  | 65–80  | 1.5   | 62        |

- **Entry** a 1.0 equiv. 1, 1.0 equiv. 2a, 1.2 equiv. 3a, 1.4 equiv. 4.
- **Solvent** b 1.0 mL solvent.
- **Additive** c 1.4 equiv.
- **T (°C)** d 65–80.
- **t (h)** e MW (100 W).
- **Yield (%)** f 3.0 mol%.
- **g** Isolated products.
- **Bold** values indicate the best conditions.

### Table 2: Synthesis of the 6-propargyl-pyrrolo[3,4-b]pyridin-5-ones 5a-l.

| Product | R¹ | R² | Yield (%) |
|---------|----|----|-----------|
| 6a      | Ph | piperidine | 64        |
| 6b      | 3,4-diOMePh | piperidine | 72        |
| 6c      | 4-FPh | piperidine | 62        |
| 6d      | n-hexyl | piperidine | 64        |
| 6e      | Ph  | morpholine | 69        |
| 6f      | 3,4-diOMePh | morpholine | 66        |
| 6g      | 4-FPh | morpholine | 66        |
| 6h      | n-hexyl | morpholine | 67        |
| 6i      | Ph  | diethylamine | 59        |
| 6j      | 3,4-diOMePh | diethylamine | 63        |
| 6k      | 4-FPh | diethylamine | 64        |
| 6l      | n-hexyl | diethylamine | 66        |

- **Product** a Reactions performed with 1.0 equiv. propargylamine (1), 1.0 equiv. aldehyde 2a-d, 1.2 equiv. isocyanides 3a-c, 1.4 equiv. maleic anhydride (4), 3 mol% Sc(OTf)₃, 1 mL PhMe.
- **Isolated products.**
allowing in some cases improve biological activity (Kalinsky and Weinstein, 1954; Sander et al., 2008; Meng et al., 2011; El-Nassan, 2015; Yu et al., 2015; Sato et al., 2017).

The highest yield (72%) was obtained for product 6b, which contains 2,3-dimethoxyphenyl and piperidine as substituents at R₁ and R₂, respectively. Contrarily, bis-heterocycle 6i, with phenyl and diethylamine substituents, was obtained in the lowest yield (59%). In fact, among all products, the diethylamine-containing analogs 6i-l were synthesized in lower yields, which can be attributed to the lower stability of this isocyanide in acidic media. In all cases, the primary byproducts were the corresponding 5-aminooxazoles resulting from Lewis-acid-catalyzed chain-ring tautomerization of the isocyanides 3a-c (Gao et al., 2016). Consistent with reports by Zhu (Cuny et al., 2004; Wang et al., 2007), we also observed, as minor byproducts, the alcohols resulting from isocyanide addition to the aldehydes prior to oxazole formation (7) (Scheme 4). The plausible reaction mechanism for the formation of pyrrolo[3,4-b]pyridin-5-ones 6a-l is supported by computational calculations performed previously using DFT methods (Scheme 4) (Islas-Jácome et al., 2016).

Conditions were screened for the [3+2] cycloaddition using terminal alkyne 6a (Table 3). Heating at 100 °C for 12 h with 1.0 equiv. TMSN₃ and 3 mol% CuI provided tris-heterocycle 9a in a modest 48% yield (entry 1, Table 2). Increasing the equivalents of the volatile TMSN₃ to 1.5 or 2.0 raised the

| Entry | TMSN₃ (equiv) | CuI (mol%) | T (°C) | t (h) | Yield (%)a |
|-------|--------------|------------|--------|------|------------|
| 1     | 1.0          | 3          | 100    | 12   | 48         |
| 2     | 1.5          | 3          | 100    | 12   | 69         |
| 3     | 2.0          | 3          | 100    | 12   | 77         |
| 4     | 2.0          | 5          | 100    | 18   | 75         |
| 5     | 2.0          | 3          | 100b   | 0.5  | 62         |

a isolated products.
b MW (100 W).
Bold values indicate the best conditions.
yield of 9a to 69 and 77%, respectively (entries 2-3, Table 2). Using additional CuI (5% mol) and increasing the reaction time to 18 h did not improve the yield (entry 4, Table 2).

Table 4: Synthesis of 4-substituted 1H-1,2,3-triazoles 9a-l.

| Product | R¹ | R²         | Yield (%) |
|---------|----|------------|-----------|
| 9a      | Ph | piperidine | 77        |
| 9b      | 3,4-diOMePh | piperidine | 75        |
| 9c      | 4-FPh | piperidine | 80        |
| 9d      | n-hexyl | piperidine | 70        |
| 9e      | Ph | morpholine | 63        |
| 9f      | 3,4-diOMePh | morpholine | 73        |
| 9g      | 4-FPh | morpholine | 80        |
| 9h      | n-hexyl | morpholine | 75        |
| 9i      | Ph | diethylamine | 73       |
| 9j      | 3,4-diOMePh | diethylamine | 70       |
| 9k      | 4-FPh | diethylamine | 78       |
| 9l      | n-hexyl | diethylamine | 75       |

a 1.0 equiv. alkyne 6a-l, 2.0 equiv. TMSN₃, 3% mol CuI in MeOH/DMF (9:1 v/v, 0.5 M) at 100 °C for 12 h.
b Isolated products.

Microwave heating reduced both the reaction time and the yield to 52%, as high amounts of byproducts were detected (entry 5, Table 2).

Table 5: Synthesis of 1,4-disubstituted 1H-1,2,3-triazoles 19a-e.

| Product | R³ | t (min) | Yield (%) |
|---------|----|---------|-----------|
| 19a     |    | 90      | 83        |
| 19b     |    | 30      | 89        |
| 19c     |    | 45      | 93        |
| 19d     |    | 45      | 90        |
| 19e     |    |         |           |

a 1.0 equiv. azide 20a-e, 5% mol Cu₂SO₄·5H₂O, 20% mol Na-ascorbate in H₂O/tert-BuOH (1:1 v/v, 0.3 M) at rt (USI) for 30-90 min.
b Isolated products.

Scheme 5: Plausible CuAAC reaction mechanism.
Using the optimized conditions, a series of tris-heterocycles (9a-l) was synthesized from complex alkynes 6a-l via the [3+2] cycloaddition in good yields (70–80%, Table 4). The highest yields were obtained for the 4-fluorophenyl analogs. Alkynes 6a-l and triazole products 9a-l were fully characterized by IR, 1H and 13C NMR, and HRMS (see the Supplementary Material for further details). Several attempts to obtain adequate crystals for X-ray analysis were performed without success.

In Scheme 5, we show a plausible reaction mechanism for the alkyne-azide [3+2] cycloaddition to produce 4-substituted 1H-1,2,3-triazoles. The reaction likely proceeds through the formation of copper acetylide species 13a-l from terminal alkynes 6a-l with CuI (12) and in situ generation of HN3 (17) from the reaction of TMSN3 (15) and MeOH (14). Copper-assisted cycloaddition between 13a-l and HN3 (17) takes place to form intermediates 18a-l. Protonolysis of the C-Cu bond of 18a-l by terminal alkynes 6a-l, HI, or MeOH affords 4-substituted 1H-1,2,3-triazoles 9a-l (Jin et al., 2004).

Having the methodology for the synthesis of compounds 9a-l, we next explored the scope of use de terminal alkynes linked to bis-heterocycles using organic azides to obtain the 1,4-disubstituted 1,2,3-triazoles (19a-d) via CuAAC. Compound 6m was synthesized (60% yield) and selected as model. Phenyl azides with different stereo-electronic natures (20a-d) were prepared from aromatic amines via diazotization with sodium nitrite in water in the presence of p-TsOH followed by reaction with sodium azide at room temperature (Kutonova et al., 2013).

First, the reaction was carried out under constant stirring, at room temperature, using 6m and azide 20a obtaining an 85% yield of 1,4-disubstituted 1,2,3-triazole 19a after 5 h. When the reaction was carried out using ultrasound-assisted irradiation (USI) at room temperature, the product 19a was obtained in 1.5 h, with a yield of 83%. For this reason, we decided to use the USI protocol for the synthesis of 1,4-disubstituted 1H-1,2,3-triazoles (19a-d). The reactions under USI resulted in reduced reaction times (30–90 min) and good yields (83–93%) in the CuAAC for the synthesis of 19a-e (Table 5).

CONCLUSIONS

We have developed a new and efficient strategy to synthesize 4-substituted and 1,4-disubstituted 1H-1,2,3-triazoles linked to pyrrolo[3,4-b]pyridin-5-ones. Molecules containing these heterocycles together are novel. The molecules synthesized contain privileged tris-heterocycles which could have applications in medicinal chemistry and coordination chemistry.

The IMCR based cascade process coupled with CuAAC strategy, as convergent and powerful tool toward the synthesis of bis and tris heterocycles is unreported.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the Supplementary Files.

AUTHOR CONTRIBUTIONS

MR-G, RG-M, and DV have made a substantial, direct and intellectual contribution to the work. SP was responsible for performing the initial experiments. AI-J was responsible for designing and analyzing the results. All authors discussed the whole project, wrote the publication, and approved it for publication.

ACKNOWLEDGMENTS

RG-M is grateful for financial support from DAIP (193/2017) and CONACYT (CB-2016-28562) projects. MR-G (707974/585367) and SP (636753/573230) thank CONACYT for scholarships. DV is thankful for a Fulbright-Garcia Robles grant. The authors acknowledge Dr. Murali V. Unnamatla and Dr. Eduardo González-Zamora (UAM-I) for technical support with HRMS and NMR. All authors acknowledge the Laboratorio Nacional de Caracterización de Propiedades Fisiocquímicas y Estructura Molecular (CONACYT-México, Project: 123732) for the instrumentation time provided.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2019.00546/full#supplementary-material

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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