Synthesis of 6-triazolylmethyl-pyrrolo[3,4-*b*]pyridin-5-ones by an efficient MW-assisted (Ugi-3CR / aza Diels-Alder) / Click process

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Introduction

Tetrahydroisoindolo[1,2-*a*]isoquinoline-amides are tetracyclic lactams with occurrence in nature, for example the (±)-nuevamine,[1] which is an alkaloid isolated from *Berberis Darwinii* Hook (**Figure 1**).

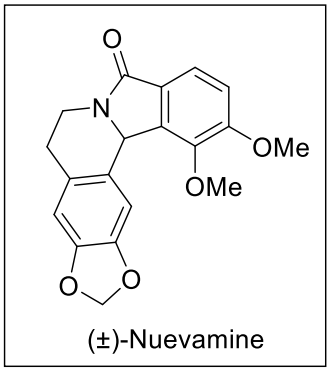


Figure 1: Natural alkaloid with the tetrahydro[1,2-*a*]isoindoisoquinolinone moiety.

We reported two methodologies for synthesizing series of novel pyrrolo[3,4-*b*]pyridine-5-ones using Ugi reactions combined with further condensation processes. In the first, a series of tetrahydroisoquinolin-pyrrolopyridinones was prepared by a sequence: Ugi-3CR / aza Diels-Alder / Pummerer.[2] In the second, aza-analogs of the natural alkaloid (±)-nuevamine were prepared by a sequence: Ugi-3CR / aza Diels-Alder / Pictet-Spengler.[3]
In this work, we describe the synthesis of novel triazolylmethyl-pyrrolo[3,4-*b*]pyridin-5-ones by a sequence: Ugi-3CR / aza Diels-Alder / Click. There are several reports about pyrrolo[3,4-*b*]pyridin-5-ones related to various type of biological activity. For example, some 5-oxo-pyrrolopyridine compounds (**A**) have been used as DPP-4 inhibitors.[4] (**Figure 2**)

1. Mertens, A.; Zilch, H.; Koenig, B.; Schaefer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H.; *J. Med. Chem.*, **1993**, *36*, 2526.
2. Islas-Jácome, A.; González-Zamora, E.; Gámez-Montaño, R. *Tetrahedron Lett*. **2011**, *52*, 5245.
3. Islas-Jácome, A.; Cárdenas-Galindo, L. E.; Jerezano, V. A.; Tamariz, J.; González-Zamora, E.; Gámez-Montaño, R. Synlett., **2012**, *23*, 2951.
4. Devasthale, P.; Wang,Y.; Wang, W.; Fevig, J.; Feng, J.; Wang, A.; Harrity, T.; Egan, D.; Morgan, N.; Cap, M.; Fura, A.; Klei, H. E.; Kish, K.; Weigelt, C.; Sun, L.; Levesque, P.; Moulin, F.; Li, Y. X.; Zahler, R.; Kirby, M. S.; Hamann, L. G.; *J. Med. Chem.*, **2013**, *56*, 7343.

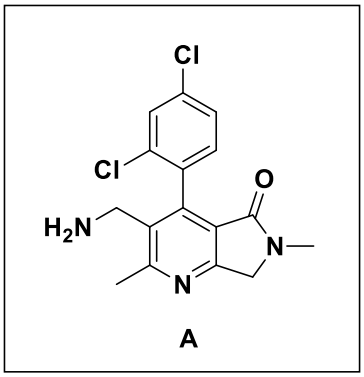
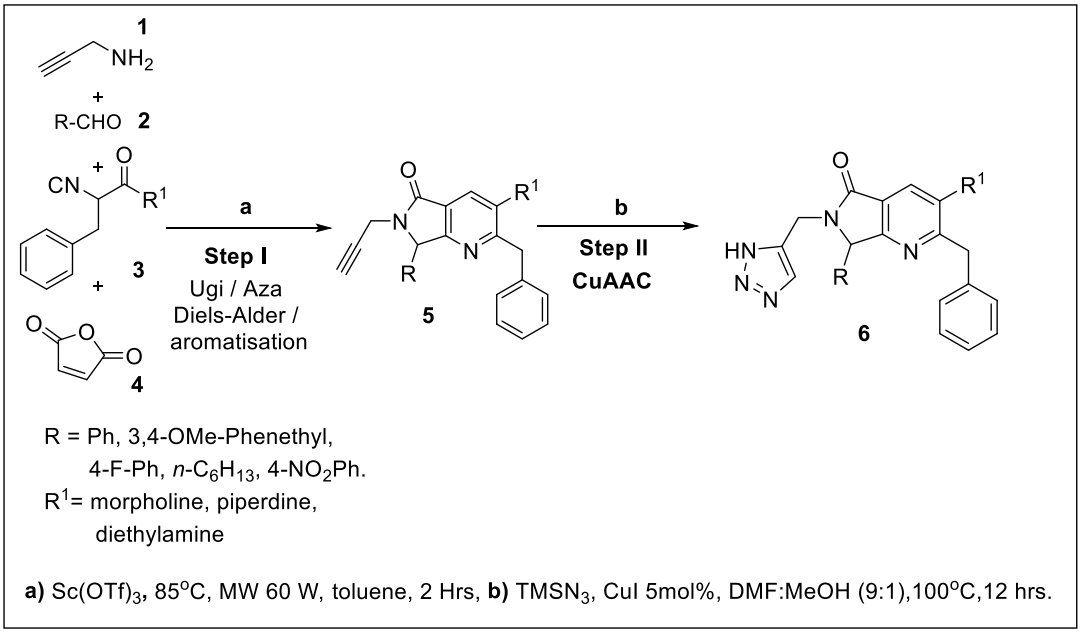


Figure 2: 5-oxo-pyrrolopyridine.

Objectives

- To synthesize a series of novel pyrrolo[3,4-*b*]pyridin-5-ones by an Ugi-3CR / aza Diels-Alder / 1,3-dipolar azide-alkyne cyclization.
- To assay final compounds *in vitro* for their antimycotic properties.

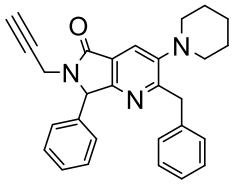
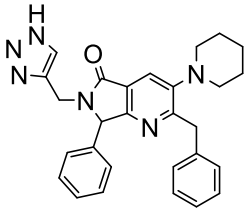
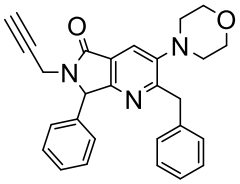
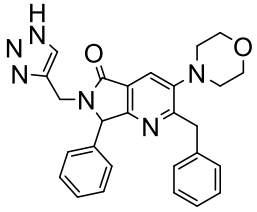
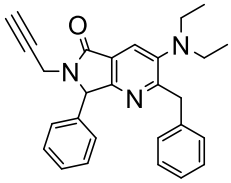
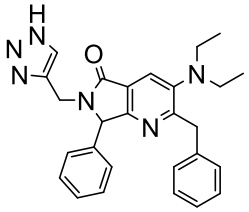
Methodology



Scheme 1: Synthesis of 6-triazolylmethyl-pyrrolo[3,4-*b*]pyridin-5-ones.

Results and discussion

We started the experimental part with the Ugi-3CR/ Aza Diels-Alder cycloaddition for the synthesis of intermediates **5 (step I)** by using the previously-well established conditions combining propargyl amine (**1**), aldehydes (**2**), α-isocyanoamides (**3**) and maleic anhydride (**4**) in toluene with $Sc(OTf)_3$ in MW followed by CuAAC sequence for the synthesis of triazolyl products **6 (step II)**. (**Scheme 1**)

Entry	Step I	%Yield	Entry	Step II	%Yield
5a		69	**6a**		73
5b		64	**6b**		77
5c		58	**6c**		72

Conclusion

We have successfully prepared the pyrrolo[3,4-*b*]pyridine-5-ones (**5**) in one step by using Ugi / aza Diels-Alder / aromatization sequence and 6-triazolylmethyl-pyrrolo[3,4-*b*]pyridine-5-ones (**6**) from pyrrolopiridines (**5**) followed by click process in good yields.