UNIVERSIDAD DE GUANAJUATO

SECTION: *GENERAL ORGANIC SYNTHESIS*
SUBMISSION ID: *Sciforum-009497*

Synthesis of 2-tetrazolylmethyl-tetrahydro-1*H*-β-carboline methane-linked bis-heterocycles via one pot Ugi-azide / Pictet-Spengler process

Nancy V. Alvarez-Rodríguez, Alejandro Islas Jácome, Rocío Gámez-Montaño*

Universidad de Guanajuato (México)

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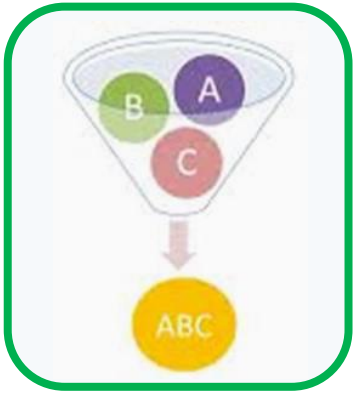
INTRODUCTION

One Pot Processes

tandem

domino

zipper



multicomponent reactions

cascade

Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

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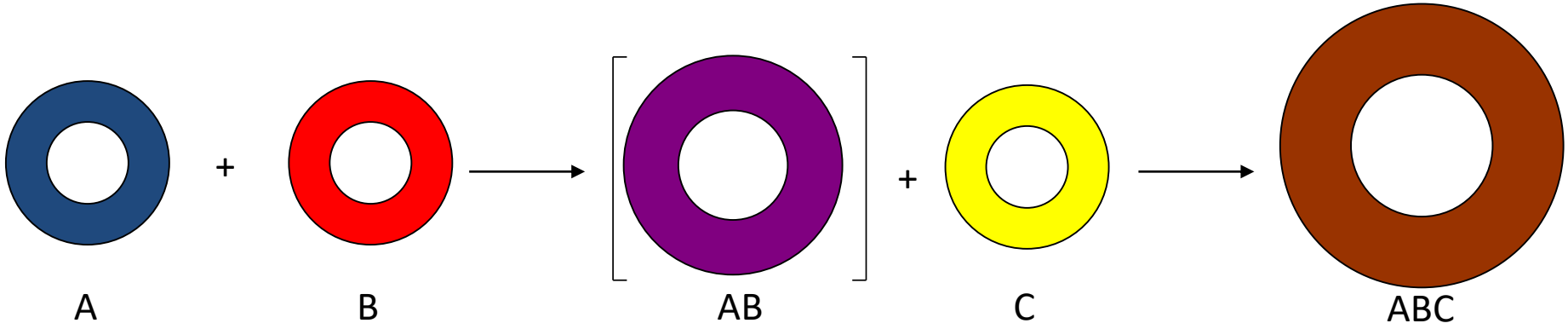
INTRODUCTION

Multicomponent Reactions



Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

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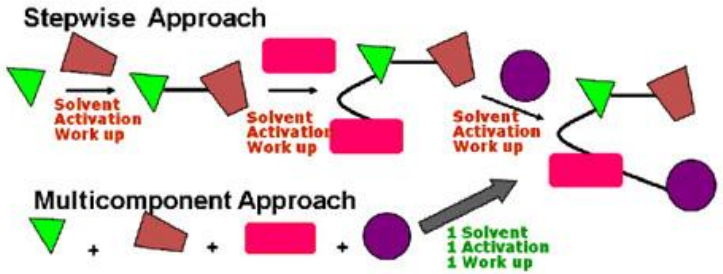
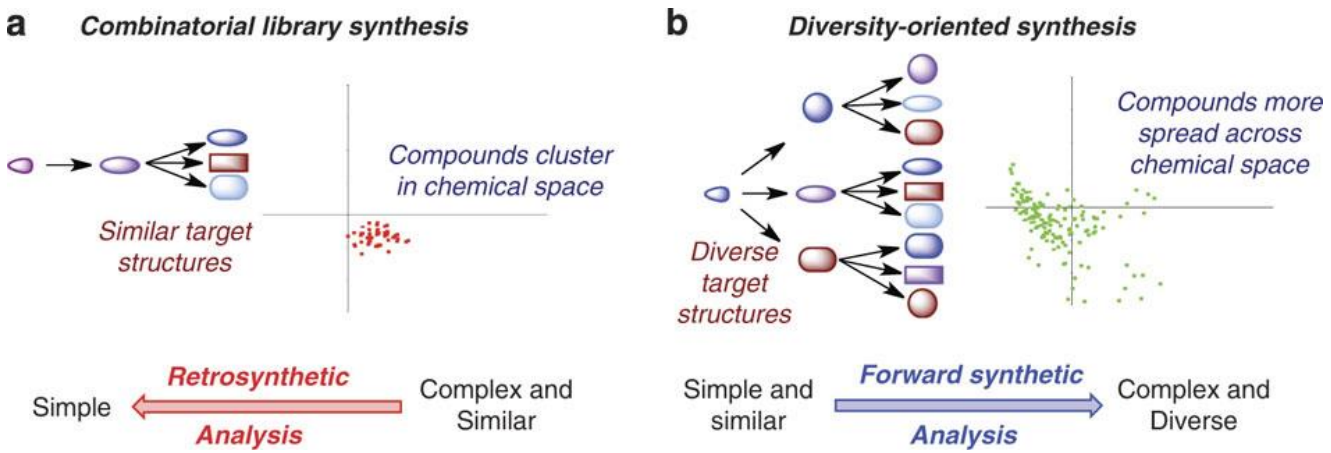
INTRODUCTION

Multicomponent Reactions



In the first example, three distinct reactions are necessary, and require solvents, catalysts, purification and is not time-cost efficient. With an MCR approach, the same compound can be obtained in a single step.



Zhu, J.; Bienaymé, H. *Multicomponent Reactions* ©Wiley-VCH, Weinheim, **2005**. ISBN: 3-527-30806-7.

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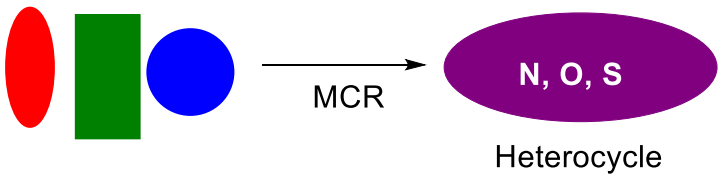
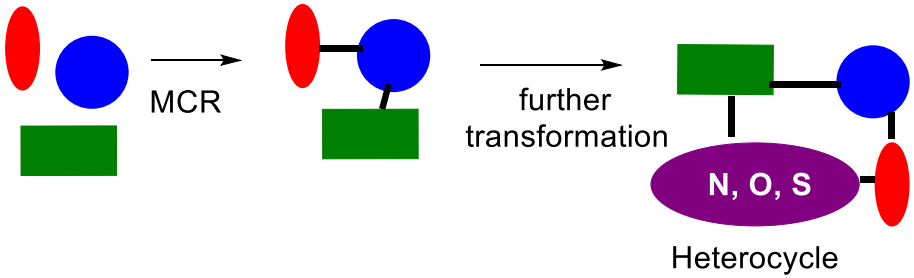
INTRODUCTION

Multicomponent Reactions In Heterocyclic Chemistry

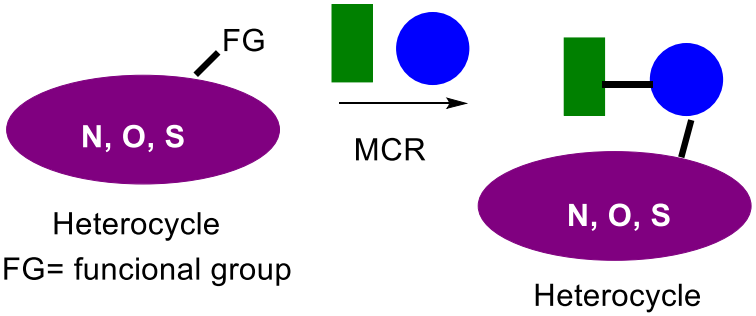
(a) Synthesis oh heterocycles by MCR



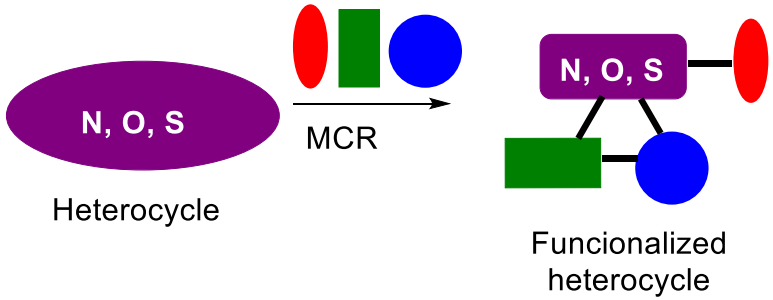
(c) Synthesis of heterocycles by MCR / further trasformation



(b) Heterocycles as substituents in a MCR starting reagent



(d) Funcionalization of heterocycles by MCR



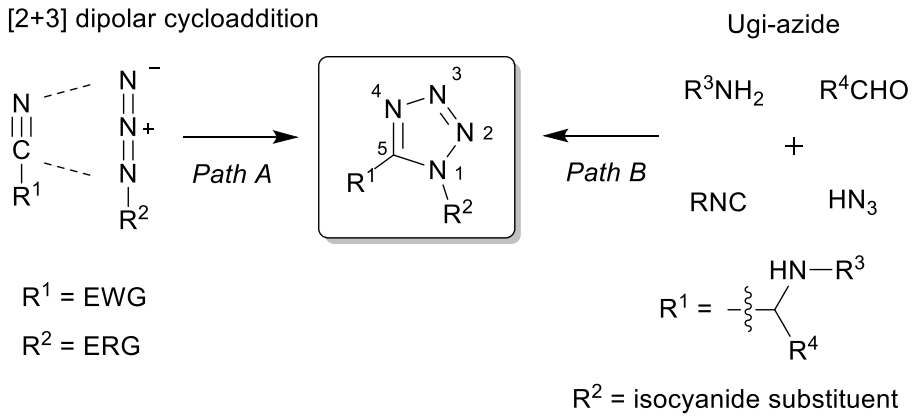
Zhu, J.; Wang, Q.; Wang, M.-X. *Multicomponent Reactions in Organic Synthesis*. Wiley-VCH. Weinheim **2015**. ISBN: 978-3-527-33237-3. Chapter 6.

BACKGROUND

Synthesis of 1,5-Disubstituted-tetrazoles (1,5-DS-T)

General method

MCR method



Gámez-Montaño *et al. Org. Biomol. Chem.* **2013**, *11*, 6470.

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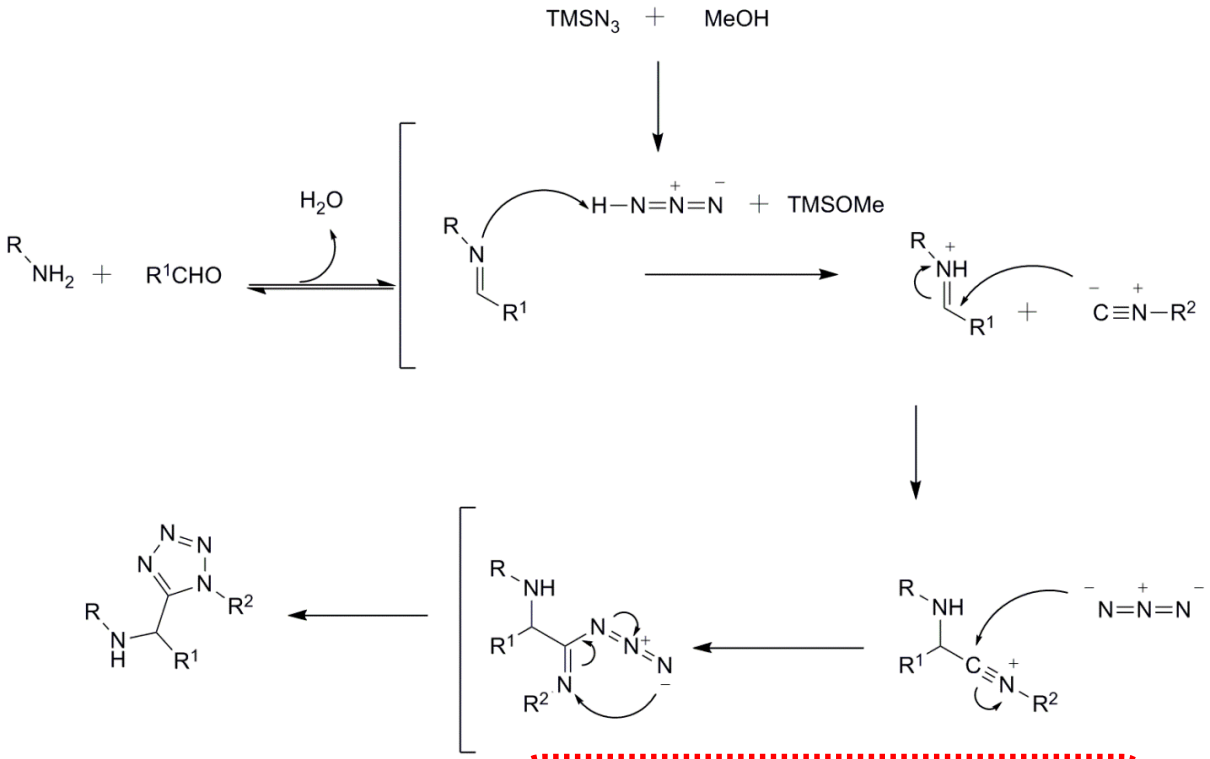
BACKGROUND

Plausible Ugi-azide Reaction Mechanism



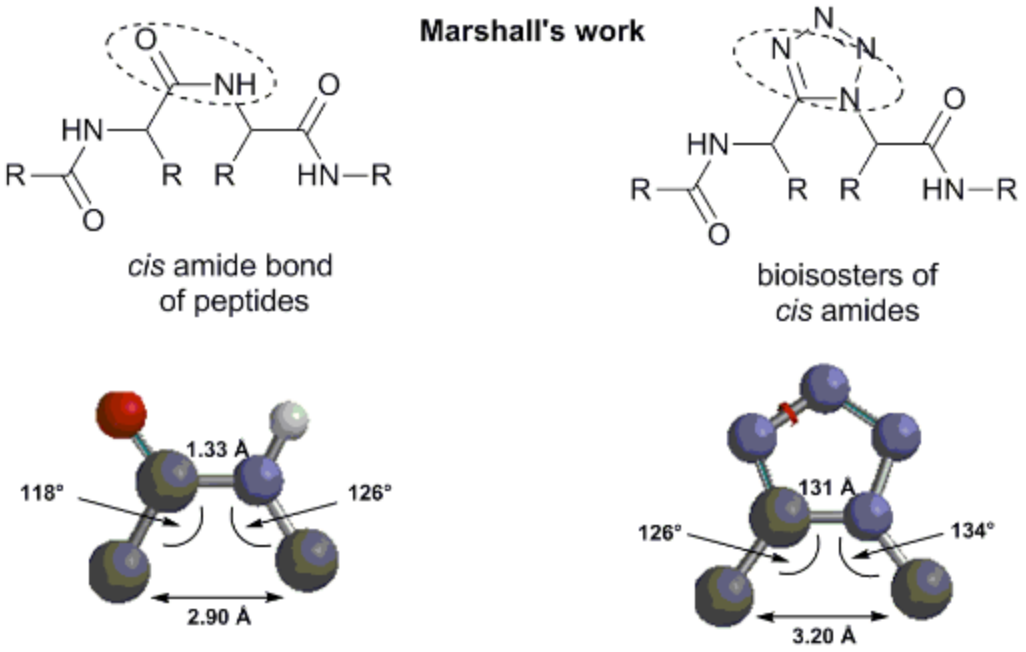
Gámez-Montaño *et al.*

J. Mex. Chem. Soc. **2013**, *57(4)*, 283-289

ISSN 1870-249X

BACKGROUND

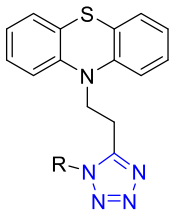
Bioisosterism between 1,5-DS-T and *cis*-amide bonds in peptides



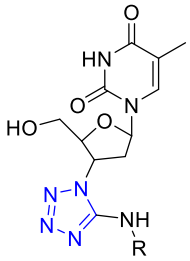
G. R. Marshall *et al. J. Am. Chem. Soc.*, 1988, **110**, 5875.

BACKGROUND

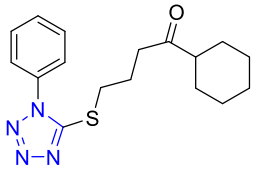
Bioactive 1,5-DS-T



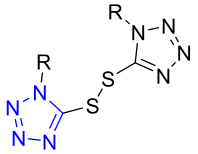
Antiinflammatories



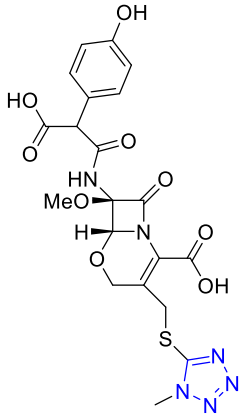
Antivirals (HIV)



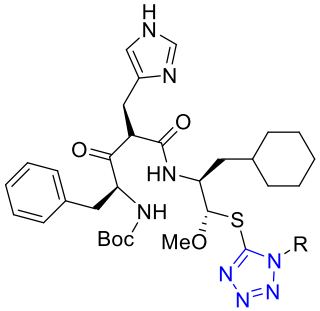
Antibiotics



Antiulcers

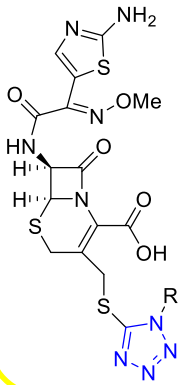


Antitubercular



Antihypertensives

LATAMOXEB®



β–lactam cephalosporin-type antibiotics

Gámez-Montaño et al. Bioorg. Med. Chem. **2014**, *22*, 1370.

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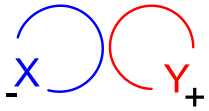
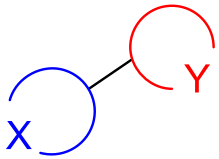
BACKGROUND

bis-Heterocycles

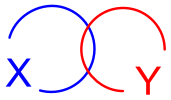
merged *bis*-Het



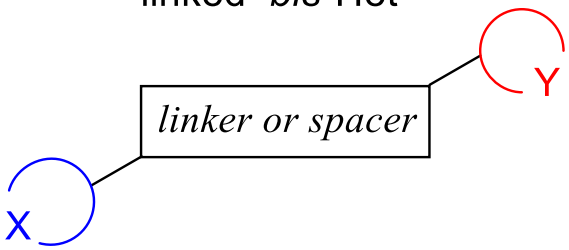
bound *bis*-Het



fused *bis*-Het



linked *bis*-Het



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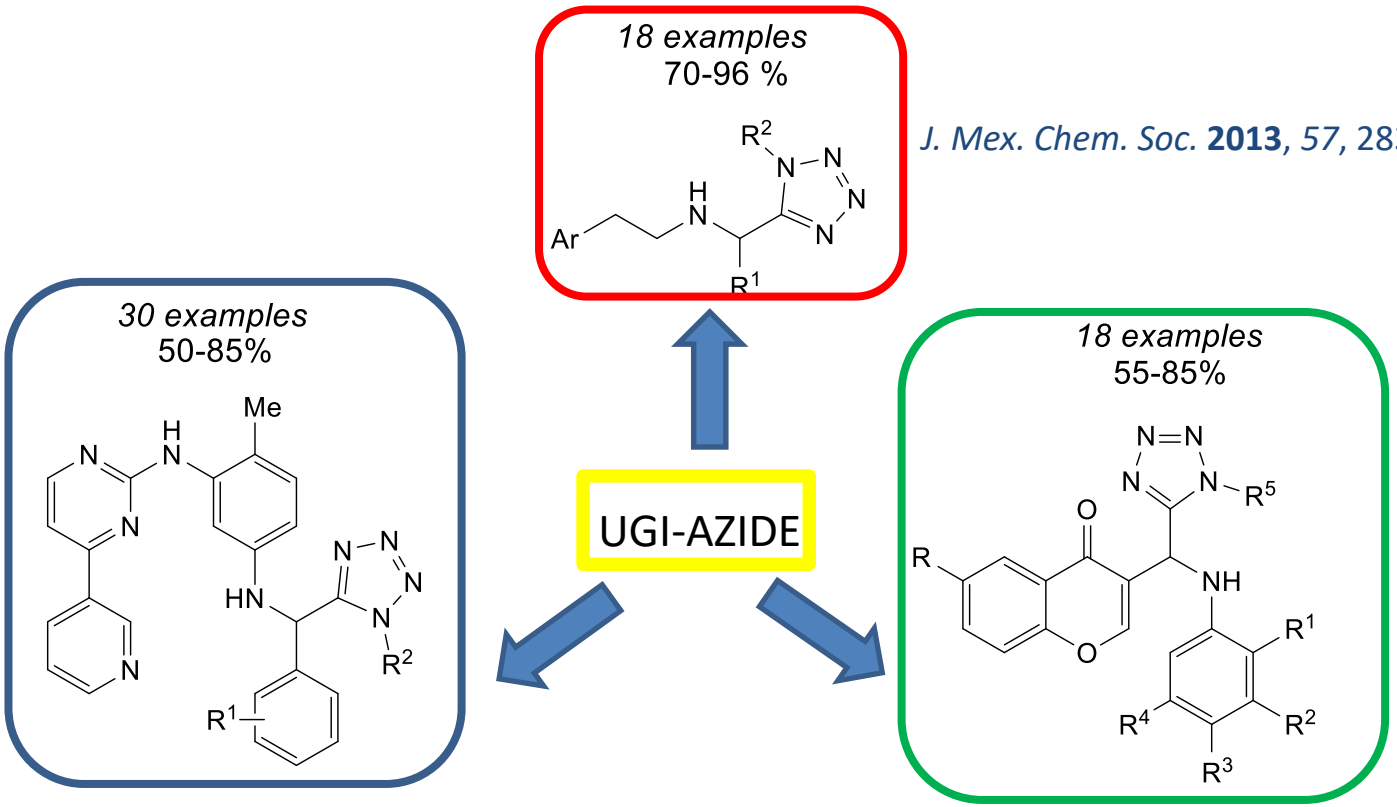
OWN BACKGROUND

Ugi-azide



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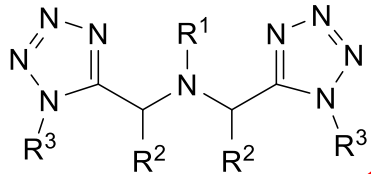
OWN BACKGROUND

Ugi-Azide / Further Cyclization

5 examples
88-95%

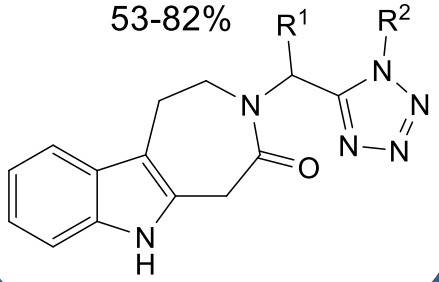


Molecules **2015**, *20*, 1519.

UGI-AZIDE / FURTHER PROCESS

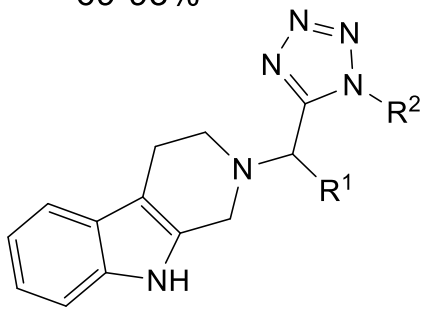
R^1, R^2 = alkyl or aryl

9 examples
53-82%



Org. Biomol. Chem. **2013**, *11*, 6470.

7 examples
69-93%

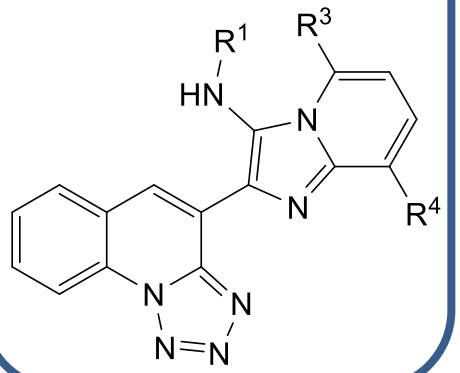


Synthesis **2014**, *46*, 49.

OWN BACKGROUND

Ugi-Azide / Further Cyclization

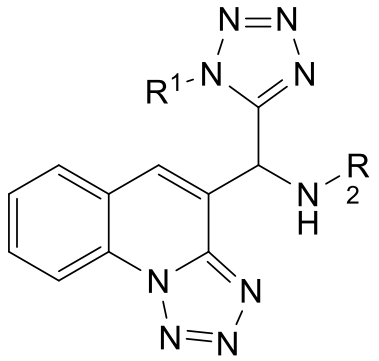
10 examples
65-94%



UGI-AZIDE / FURTHER PROCESS

R^1, R^2 = alkyl or aryl

12 examples
62-90%



J. Org. Chem. **2016** *ASAP (DOI: 10.1021/acs.joc.6b01576).*

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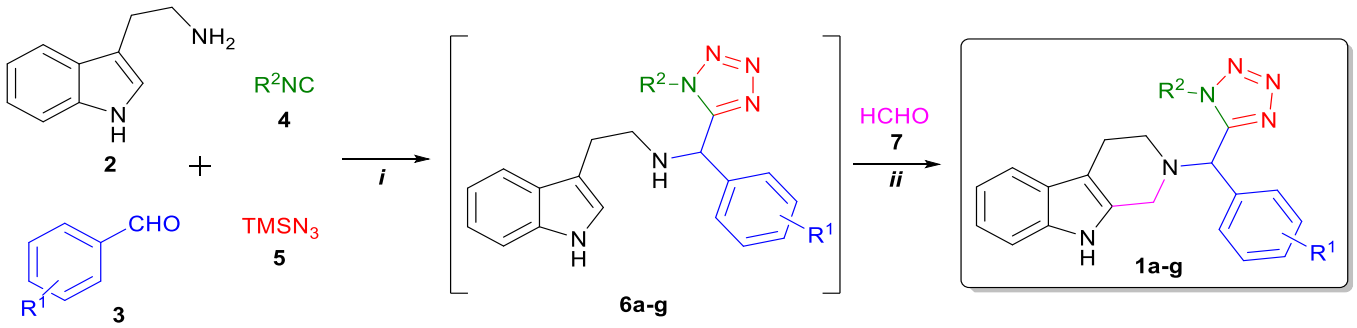
RESULTS

Substrate Scope

One pot: (*i*-Ugi-azide / *ii*-Pictet-Spengler)



i) MeOH [1.0 M], rt. *ii)* MeOH [1.0 M], 65 °C.

Product	R^1	R^2	Time (h)	Yield[a] (%)
6a	2-F	t-Bu	5	90
1a	2-F	t-Bu	3	94[b]
1a	2-F	t-Bu	8	91
1b	2,3-F	t-Bu	8	93
1c	2,3,4-F	t-Bu	8	97
1d	H	t-Bu	8	92
1e	2-F	2,6-MePh	8	89
1f	2,3-F	2,6-MePh	8	74
1g	2,3,4-F	2,6-MePh	8	nr
1h	H	2,6-MePh	8	90

[a] Measured after purification by silica-gel column chromatography. [b] from 6a. nr = no reaction

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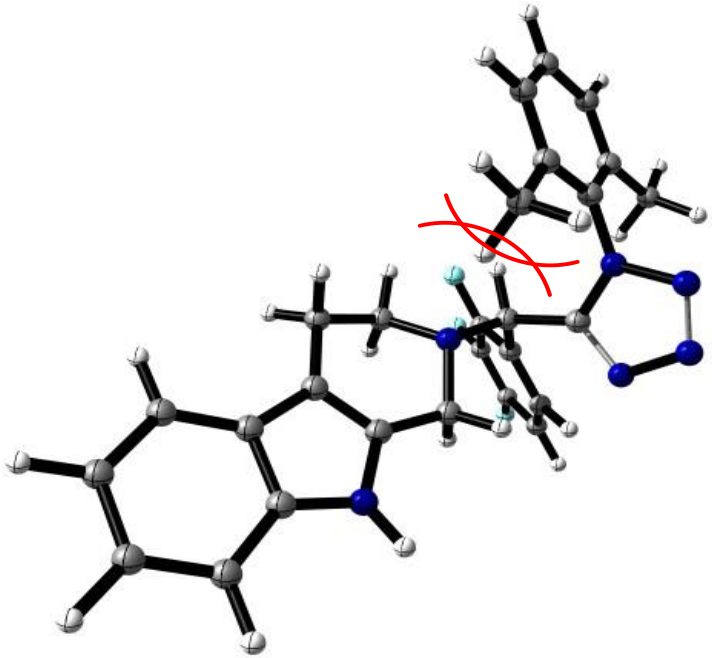
RESULTS

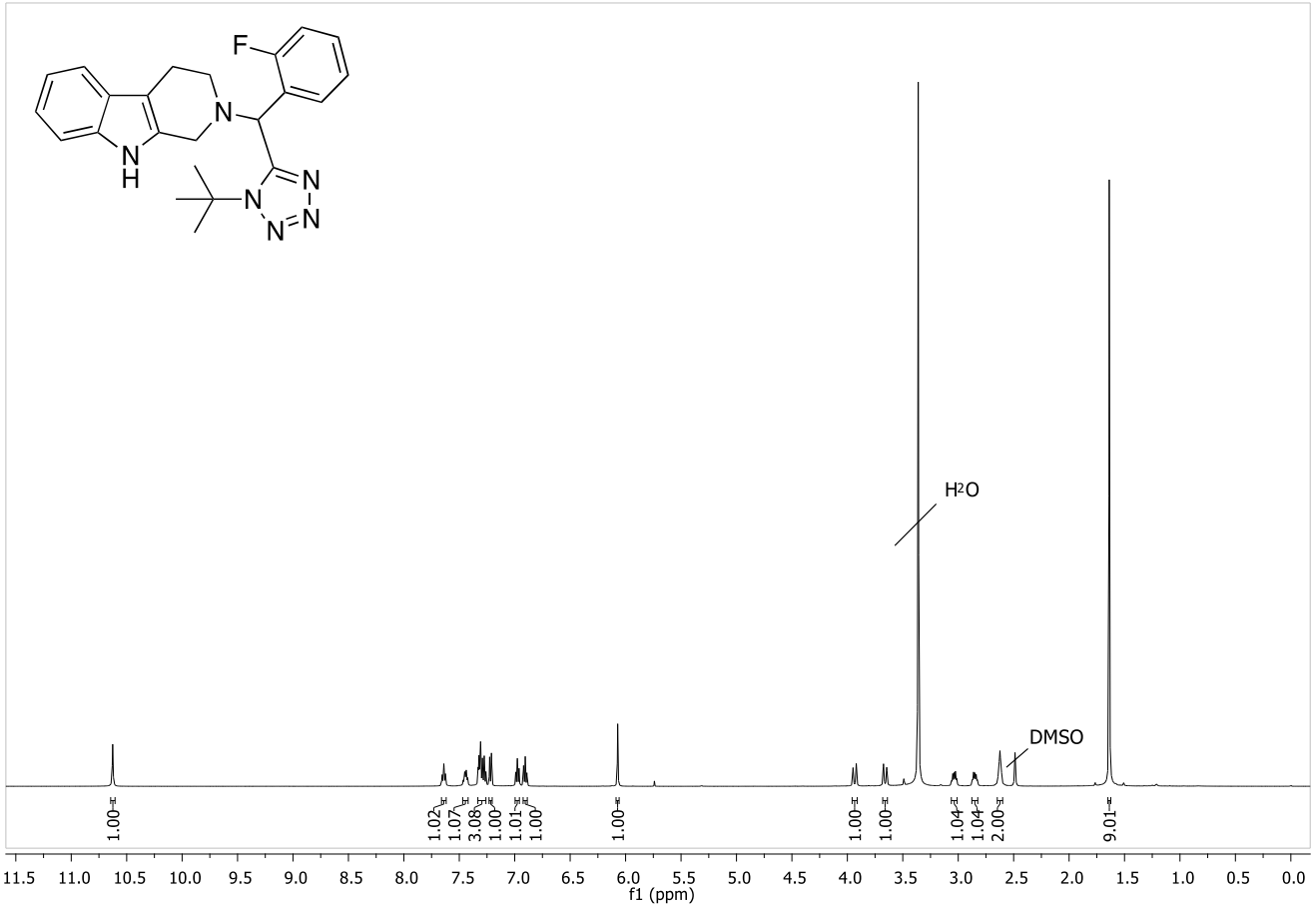
Non-synthesized *bis*-heterocycle **1g**



Minimal energy conformation calculated at *TPSSh/6-311g(d)* level of theory

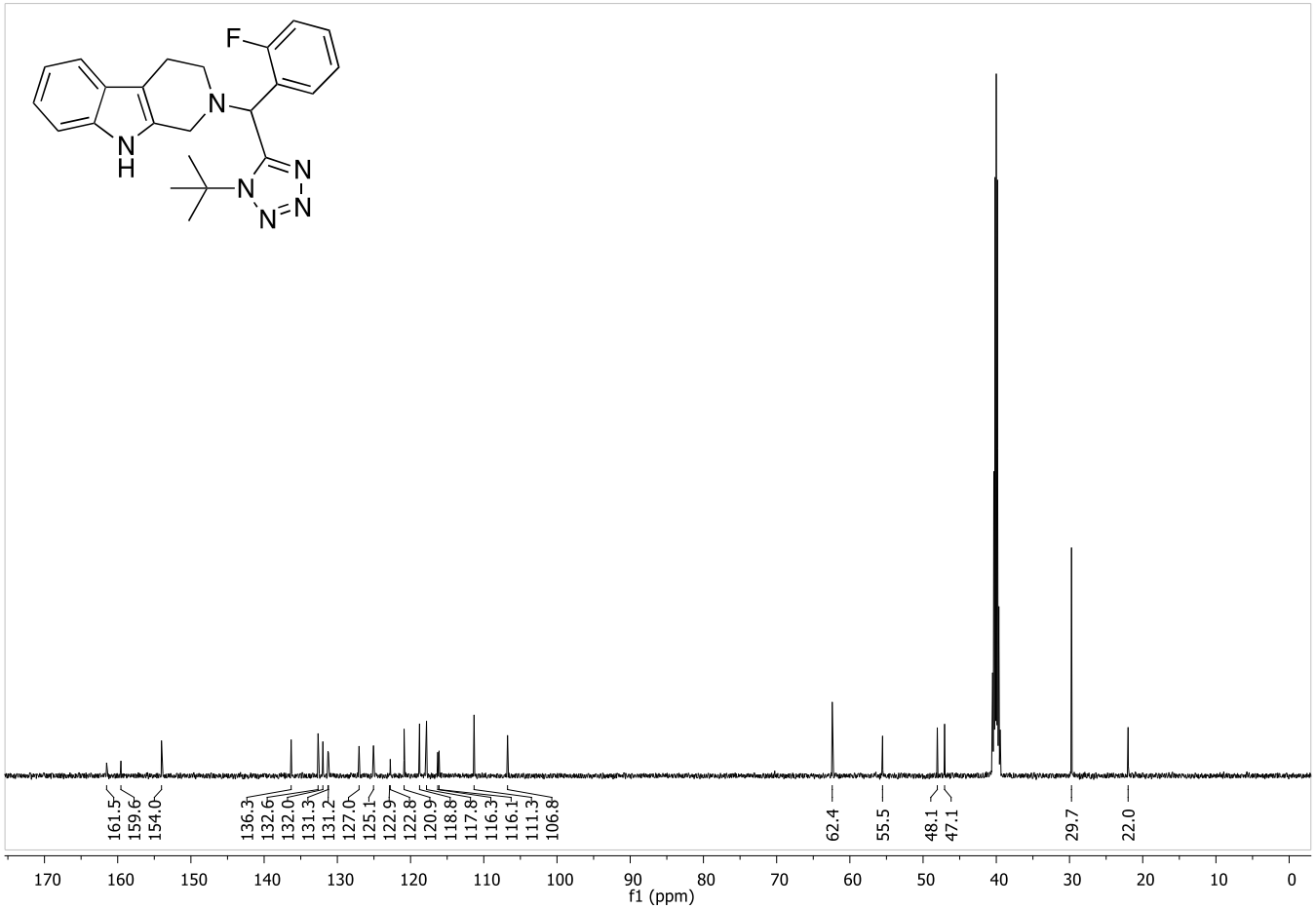
RESULTS

H-NMR spectrum of product **1a**



RESULTS

C-NMR spectrum of product **1a**



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CONCLUSIONS

• This work is a contribution to the synthesis of methane-linked *bis*-heterocycles via Ugi-azide based one pot MCR methodologies as well as to the synthesis of *bis*-heterocycles via MCR/cyclization.

• An Ugi-azide product was isolated and fully characterized to confirm the reaction pathway.

• The Pictet-Spengler reaction worked well using formaldehyde instead *para*-formaldehyde becoming milder the reaction conditions.

• A final *bis*-heterocycle could not be synthesized due to a high steric strain coming from its three bulky moieties.

• The products herein described may find application in medicinal chemistry because they have two heterocyclic cores (1,5-DS-T and THbC) present in numerous bioactive products and drugs, even contain one or more fluorine atoms, which can be reflected by improving some interesting features like metabolic resistance, lipophilicity, and bioavailability.

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THANK YOU VERY MUCH

Rocío Gámez-Montaño's group

$$$

CIO-UG (009/2015)
DAIP (859/2016)
CONACYT (CB-2011-166747-Q)