The 20th International Electronic Conference on Synthetic Organic Chemistry

Synthesis of 1,5-disubstituted-1H-tetrazole methane-linked bis-heterocycles via Ugi-azide

Submission ID: sciforum-009501

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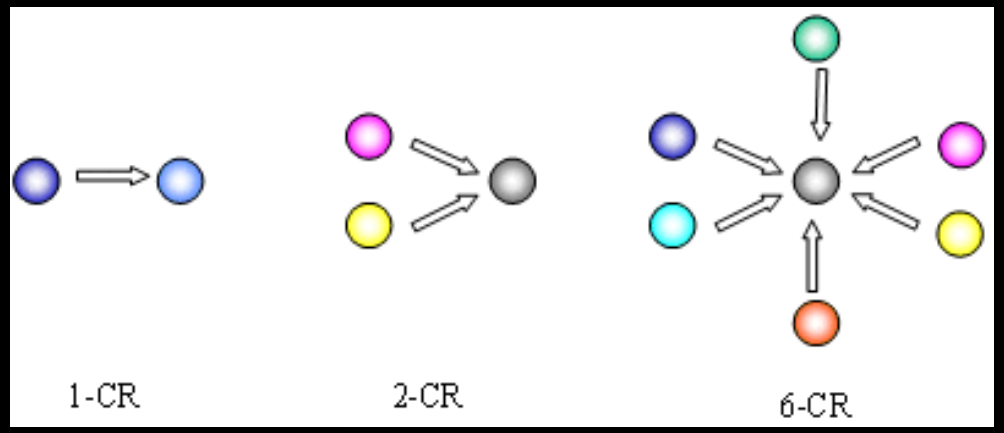
Rocío Gámez-Montaño*

MULTICOMPONENT REACTIONS

Multicomponent reactions (MCR) are those in which, in the same flask, combine three or more reactive sequentially to form a product which contains all or most of the atoms of the starting materials.



(a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168–3210; (b) Rentería-Gómez, A.; *et. al. Bioorg. Med. Chem. Lett*. **2016,** 26, 2333-2338;

WHY MCR?

Readily Available Starting Materials

Better yields

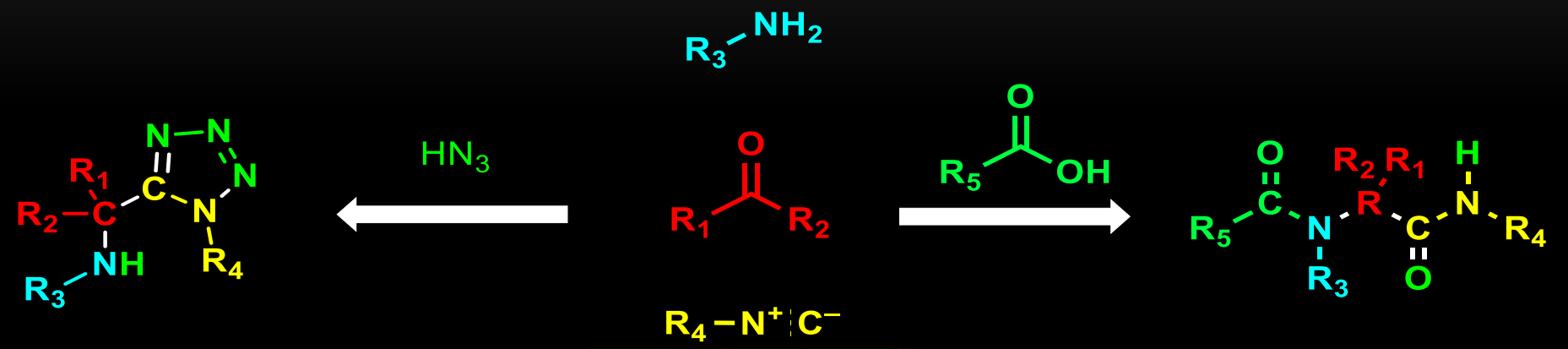
One pot

Reduced costs

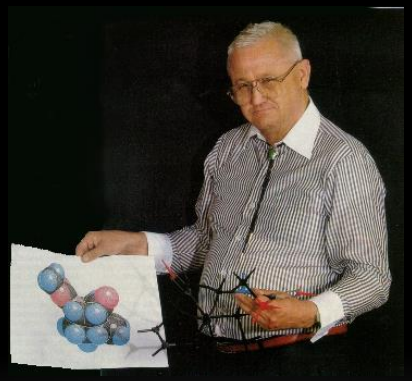
environmentally friendly

(a) Zhu, J. *et al*. *Eur. J. Org. Chem*. **2003**, 1133-1144 (c) Cortes-García, et. al. *Monatsh Chem*. **2016**, 147: 1277; (d) Rentería-Gómez, A.; *et. al*. *Bioorg. Med. Chem. Lett*. **2016,** 26, 2333-2338; (d) Kishore, K; *et. al. Tetrahedron Lett*, **2015**, 56, 155-158.

Ugi rection and Ugi-azide



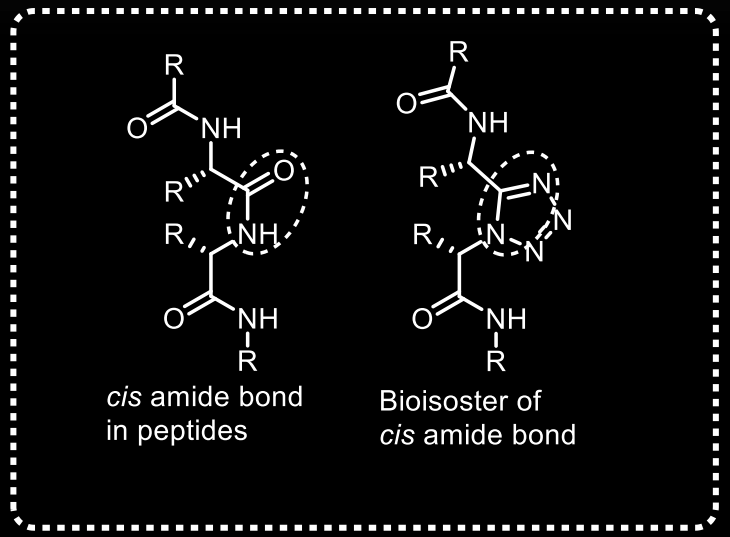
$R_4-N^+\equiv C^-$

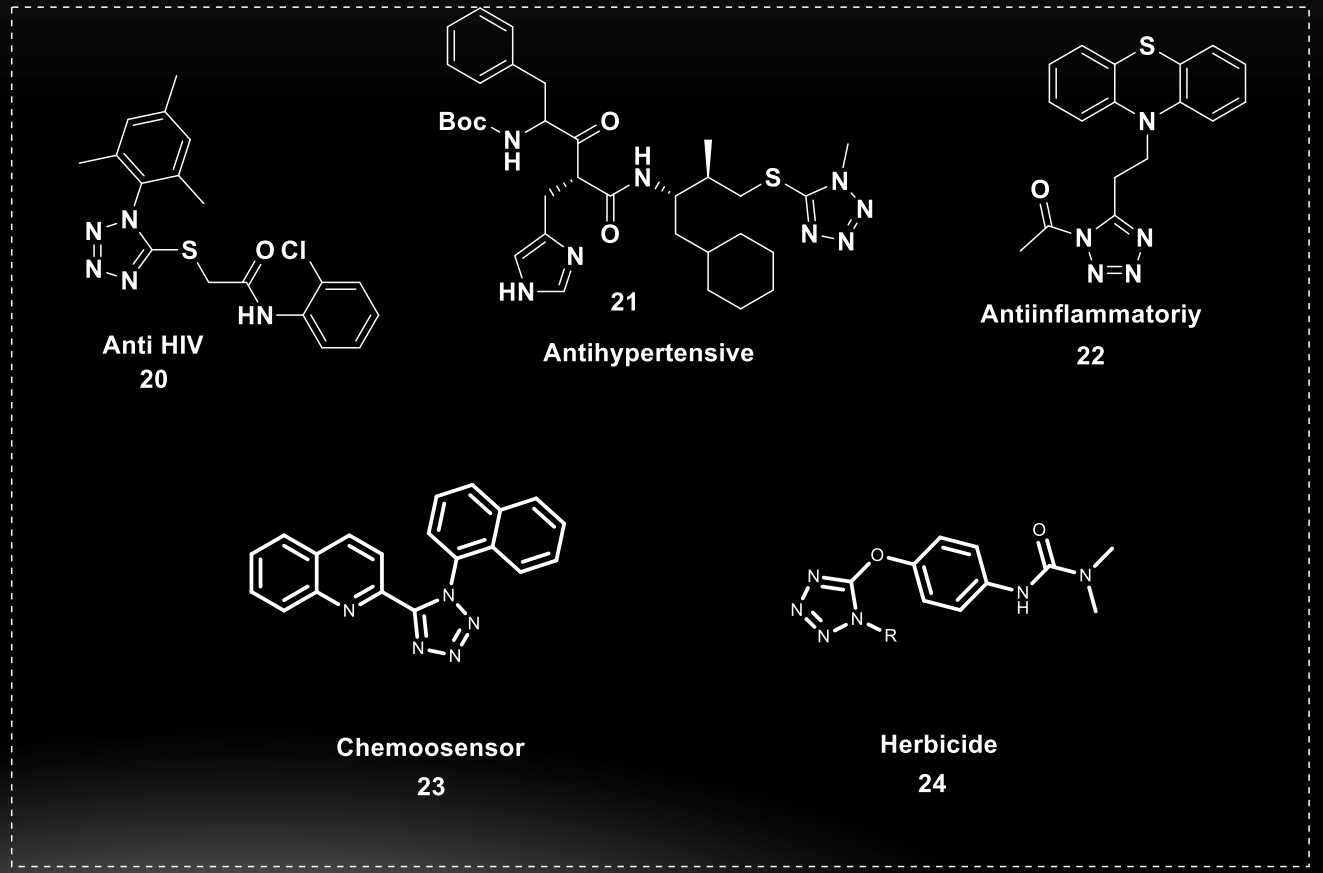


Ivar Karl Ugi
(1930-2005)

Ugi, I. *et al*. Angew.*Chem. Int. Ed.* **2000**,*39*, 3168-3210.

Tetrazoles and their aplications

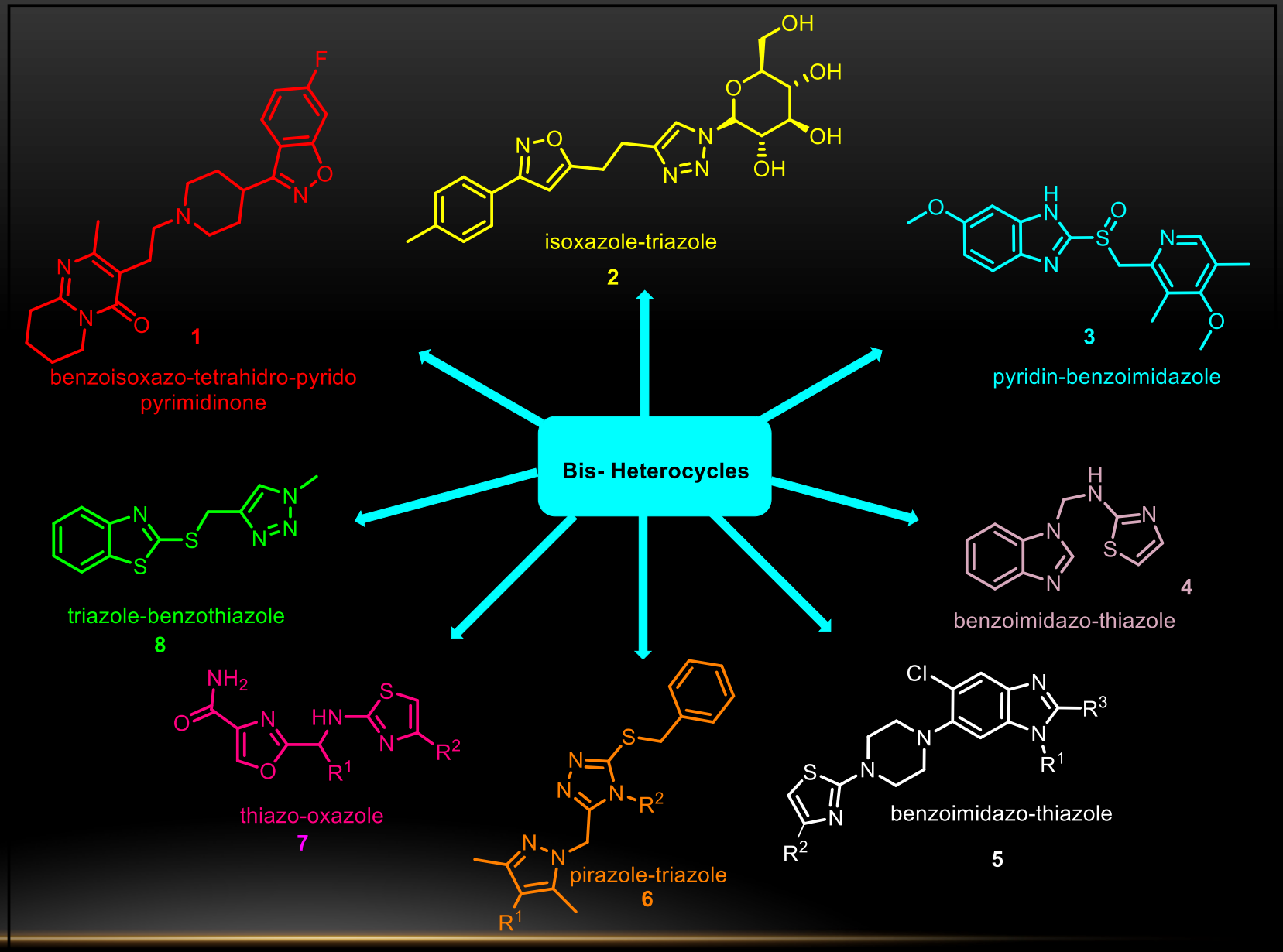




Demko, Z.; Sharpless, B. *Org. Lett.* **2002**, 4, 2525-2527; (b) Herr, R. J. *Bioorg. Med. Chem.* **2002**, 10, 3379-3393; (c) Ostrovskii, V. A. *et. al. Russ. Chem. Bull. Int. Ed.* **2012**, 61 , 768-780; (d) Ponnuvel, K.; *et. al. Sensors and Actuators B: Chemical*. **2016,** 222, 605-611.

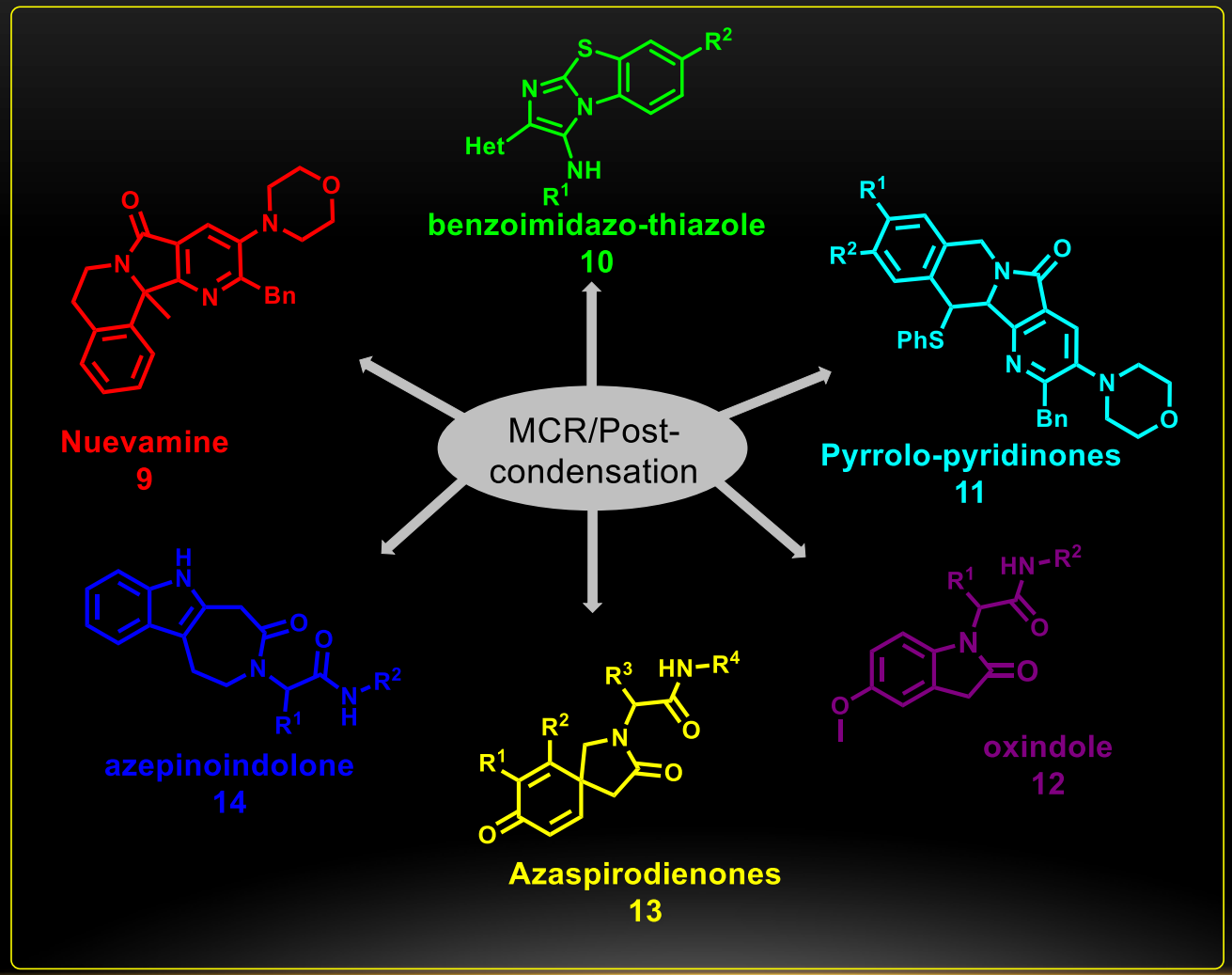
INTRODUCTION

Bis- heterocycles in Organic Chemistry



(a) Shafi, S. *et al .Eur. J. Med. Chem.* **2012**, 49, 324-333; (b) Murru ,S. *et al. ACS Comb. Sci.* **2013**,*16*, 39-45; (c) Shafi, S. *et al. J. Heterocycl. Chem.* 2013, *50*, 361-365; (d) Soural, M. et al. *J. Comb. Chem.* **2008,** *10,* 923–933.

Dra. Gámez research group in synthesis of bis heterocycles using MCR



(a) Islas-Jácome, A. *et al*. *Synlett* **2012**, 23, 2951-2956; (b) Kishore, K. et al. *Tetrahedron Lett*. **2016**, 57, 3556–3560; (c) Islas-Jácome, A. *et al*. *Tetrahedron Lett*. **2011**, 52, 5245-5248; (d) Rentería-Gómez, A. *et al*. *Tetrahedron Lett*. **2014**, 55, 6567-6570; (e) Gámez-Montaño R, *et al*. *Synthesis*. **2010**, 8, 1285-1290. (f) Rentería-Gómez, A. *et a*l. *Bioorg. Med. Chem. Lett*. **2016**, 26, 2333-2338.

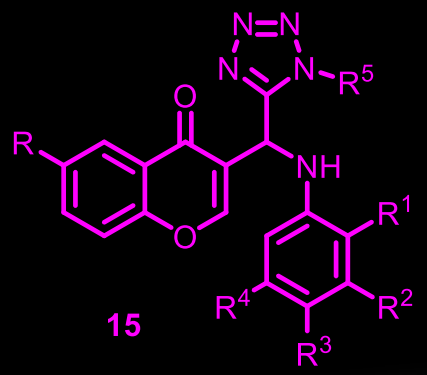
Bis heterocycles linked with 1,5-disubstituted tetrazoles in research group

12 examples
62-90%

14

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

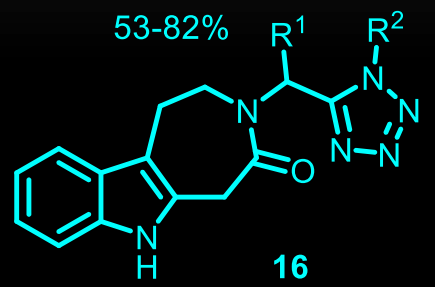
18 examples
55-85%



15

Bioorg. Med. Chem. **2014**, 22, 1370.
Molecules **2015**, 20, 12436.

9 examples
53-82%



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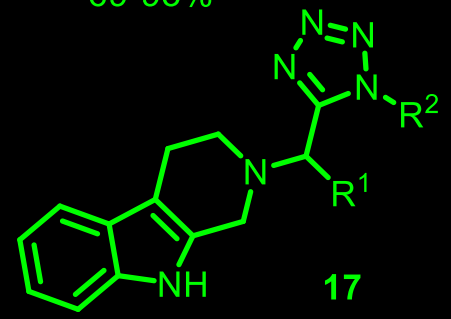
Org. Biomol. Chem. **2013**, 11, 6470.

7 examples
69-93%

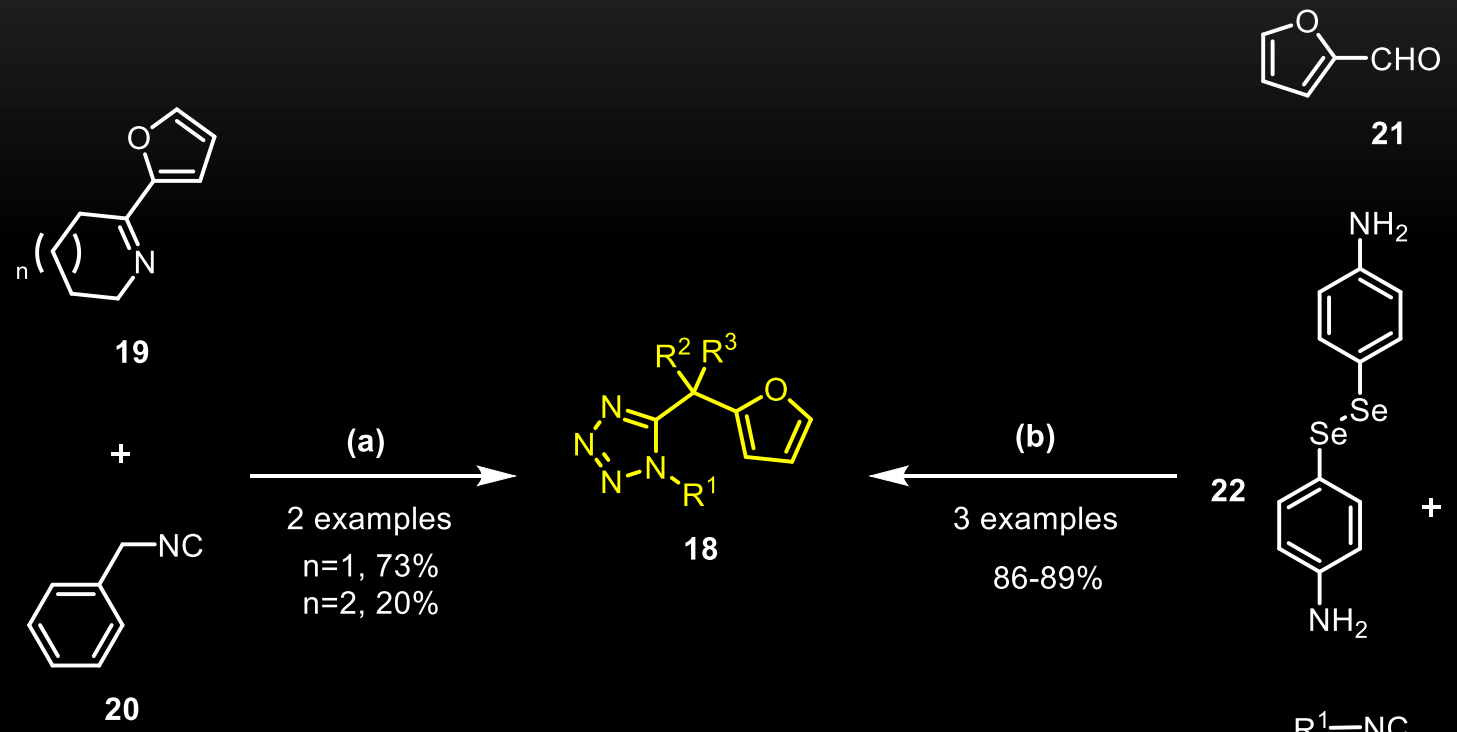


17

Synthesis **2014**, 46, 49.

R^1, R^2 = alkyl or aryl

Bis heterocycles linked with 1,5-disubstituted tetrazoles and furan



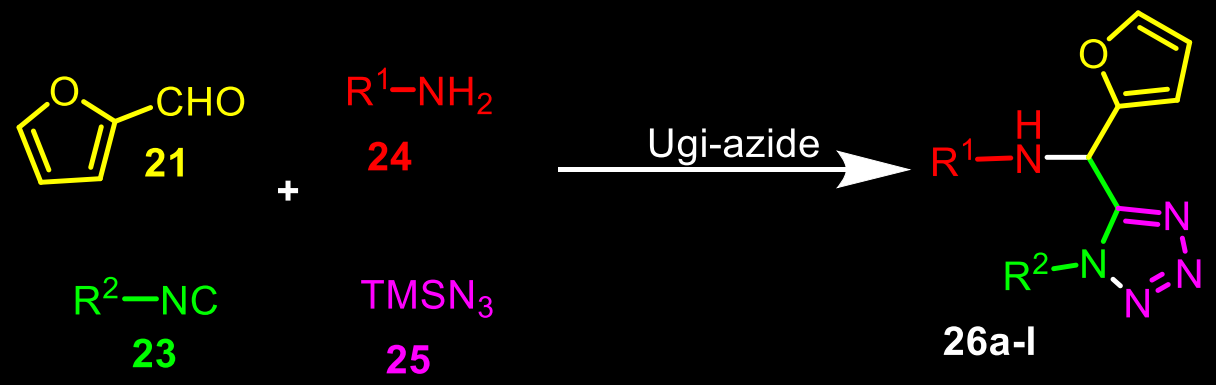
a) **$TMSN_3$**, MeOH, t.a, >24 h

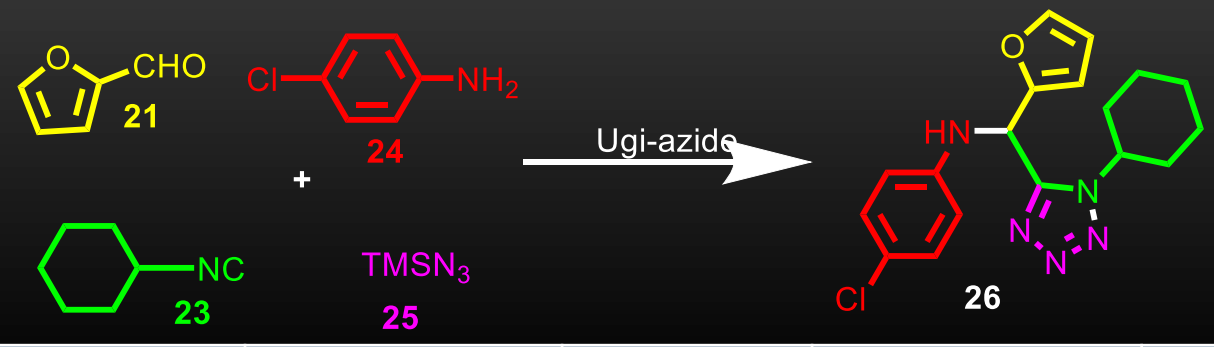
b) i.- $TMSN_3$, MeOH, 24 h, ii.- DCM

(a) Shmatova, O. I.; Nenajdenko, V. G.. *J. Org. Chem.***2013**, 78, 9214-9222; (b) Shaaban, S.; Negm, A.; Ashmawy, A. M.; Ahmed, D. M.; Wessjohann, L. A. *Eur. J.Med. Chem.* **2016**, 122, 55-71.

Results And Discussion

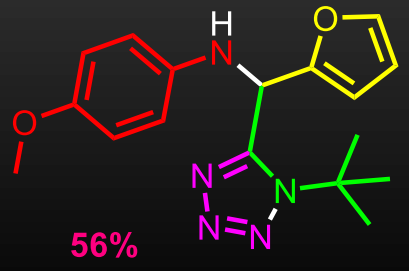
Synthesis of 1,5-disubstituted-1H-tetrazole via Ugi-azide





Entry	Temperature	Solvent	time	Catal.	Yield (%)
1	r.t	H_2O (1M)	24 h	------	45
2	r.t	CH_3CN (1M)	24 h	------	70
3	**r.t**	**MeOH (1M)**	**24 h**	**-----**	**90**
4	r.t	EtOH (1M)	24 h	------	80
5	r.t	*i*-PrOH (1M)	24 h	------	79
6	r.t	MeOH (1M)	6 h	$InCl_3$	24
7	r.t	----------	24 h	------	20
8	65°C	MeOH (1M)	1.5 h	------	80
9	65°C (MW)	MeOH (1M)	1 h	------	82
10	r.t. US	MeOH (1M)	1 h	------	83

Scope and formation of stable bis heterocyclic



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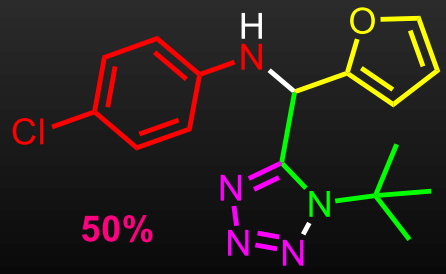

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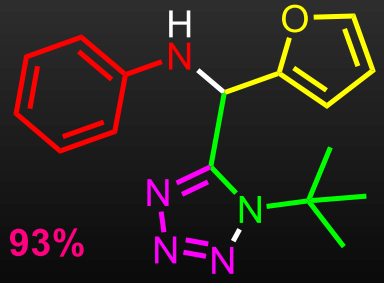
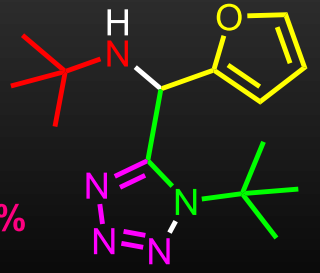


93%



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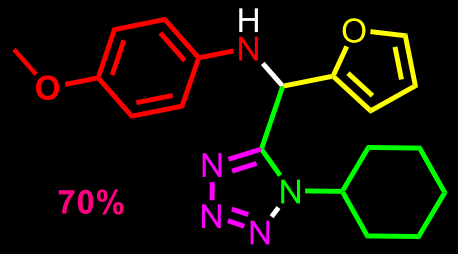
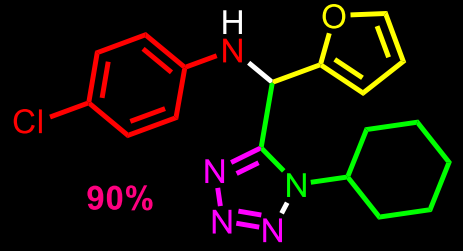


70%



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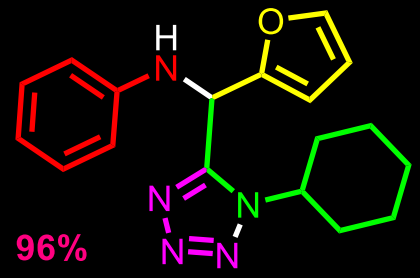

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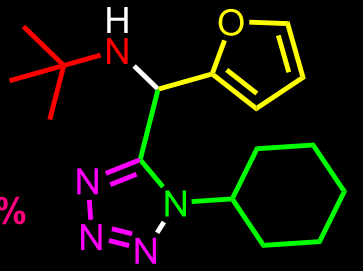

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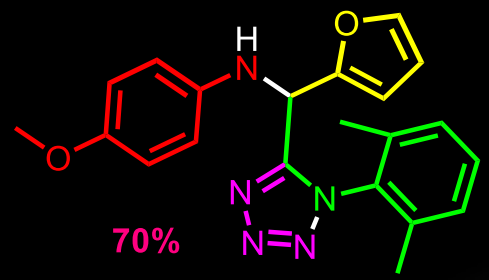

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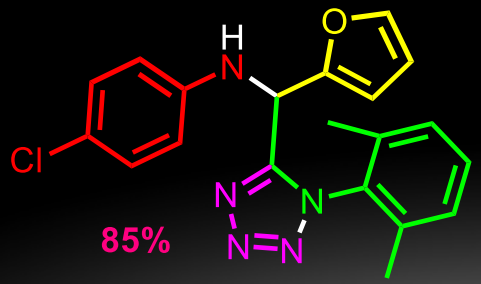
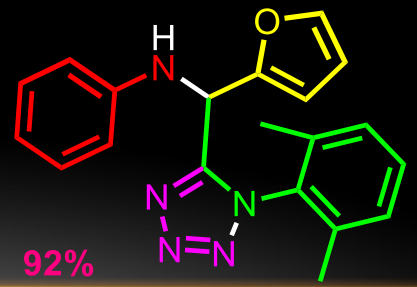
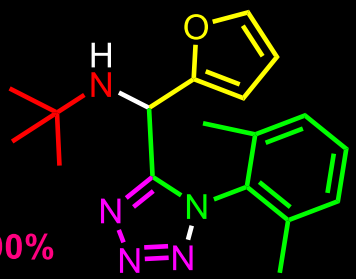


85%

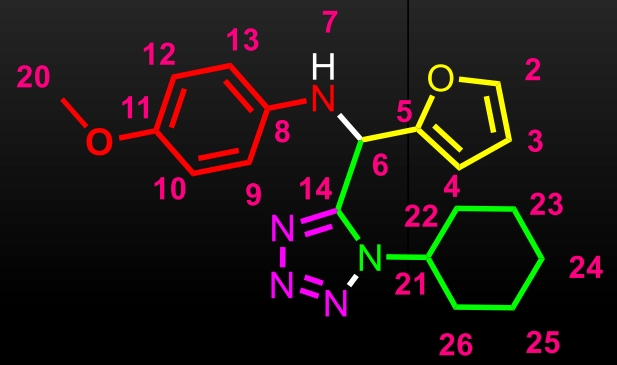


92%



90%

^{1}H NMR


20
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7
H
N
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O
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4
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23
N
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N
21
24
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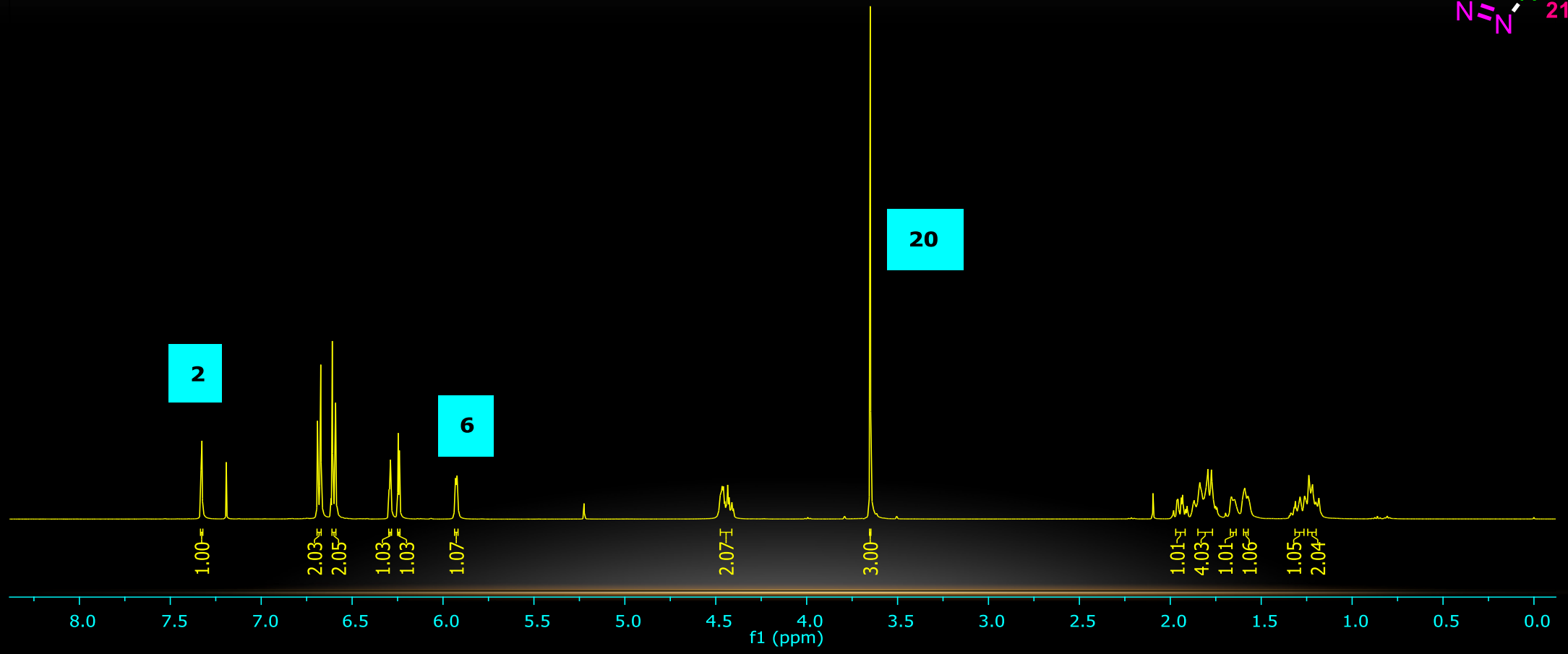
25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1.00
2.03
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1.06
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8.0
7.5
7.0
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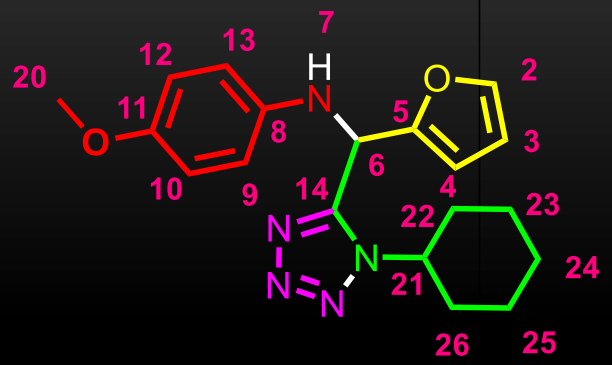
f1 (ppm)

^{13}C NMR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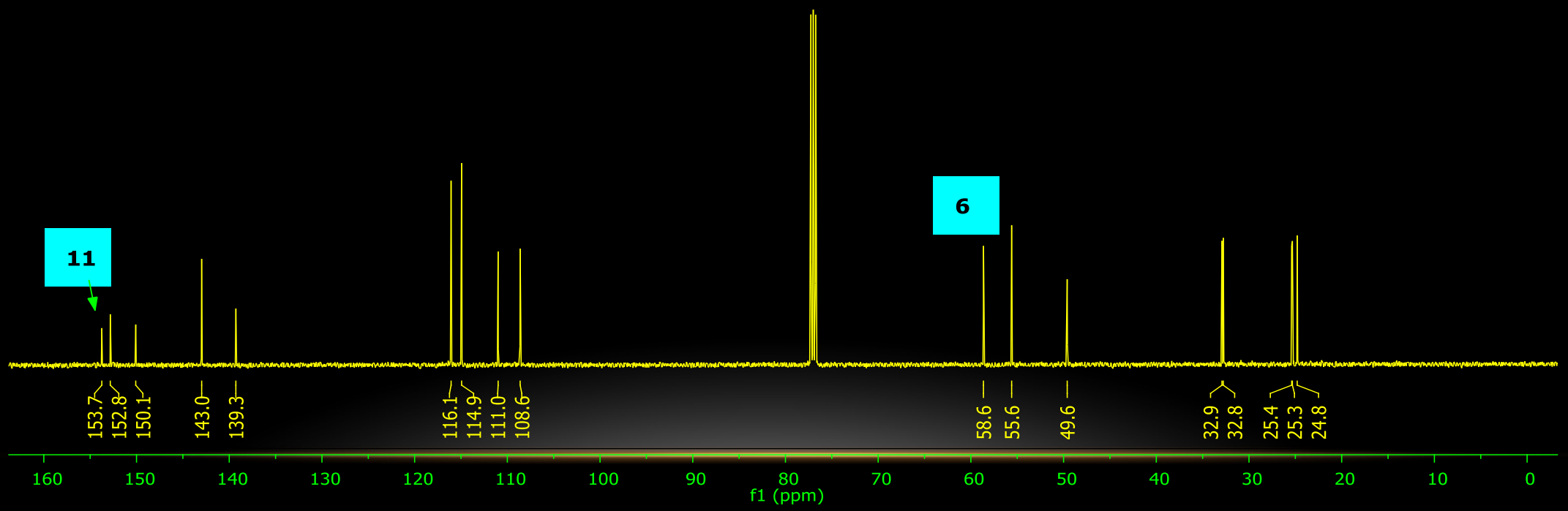
11
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153.7
152.8
150.1
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139.3
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114.9
111.0
108.6
58.6
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49.6
32.9
32.8
25.4
25.3
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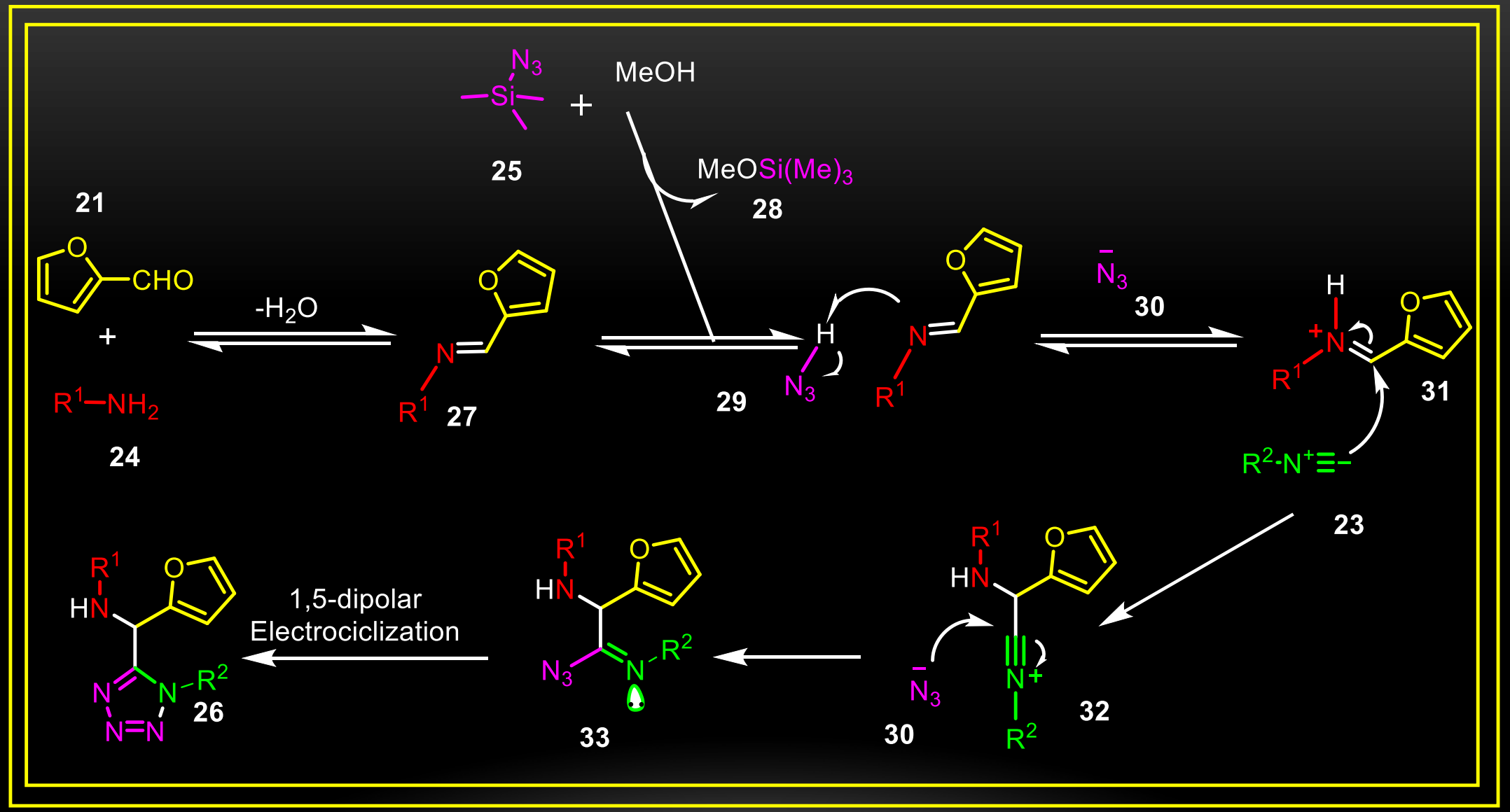
f1 (ppm)



Proposed mechanism of the reaction

CONCLUSIONS

- The objective of this work was accomplished by synthesizing a family of bis heterocycles which contain in their structure two rings: 1,5- disubstituted tetrazole and furan in moderate to good yields by a Ugi azide reaction.
- This work represents a contribution in the area of synthesis of bis-heterocycles via MCR. This strategy is useful in the synthesis of nitrogen heterocycles of interest in medicinal chemistry, part of the research developed in the working group.

ACKNOWLEDGEMENTS

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Our Research Group