Tetrahedron Letters 59 (2018) 1760–1762

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Exploring azide-enolate cycloaddition in the synthesis of novel Rufinamide analogs

José G. Aguirre-De Paz, Davir González-Calderón *, Aydeé Fuentes-Benítes, Carlos González-Romero *

Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Paseo Colón/Paseo Tollocan s/n, Toluca, Estado de México 50120, Mexico

ARTICLE INFO

Article history:
Received 6 November 2017
Revised 22 March 2018
Accepted 25 March 2018
Available online 27 March 2018

Keywords:
1,2,3-Triazoles
β-Ketonitriles
Rufinamide analogs
Azide-enolate cycloaddition

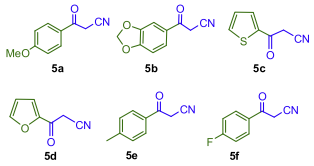
ABSTRACT

The exploration of azide-enolate cycloaddition in the synthesis of novel Rufinamide analogs is reported for the first time. A very simple procedure involving the use of β-ketonitriles as dipolarophiles afforded 5-aril/heteroayl Rufinamide derivatives in two steps.

Rufinamide, approved by the FDA in 2008 and marketed under the brand name *Banzel*, is one of the best-selling triazol-based antiepileptic pharmaceuticals used to treat Lennox-Gastaut syndrome. Since its discovery by Novartis pharmaceuticals, several synthetic routes have been described in literature.[1,2b] As with any drug leader, analogues have been developed and studied to resolve problems of pharmacological resistance, to achieve greater effectiveness, or to counteract adverse effects.

In this sense, only a few Rufinamide analogues (**2**–**4**, Scheme 1) have been reported,[2] and these involve the cycloaddition of a dipolarophile and phenyl azide **1**. Unfortunately, these methods suffer from drawbacks that limit their scope, such as the use of drastic conditions (4 days at 150 °C), tediously obtainable trihalomethylated enone precursors [Eq. (a) and (b)], a mixture of regioisomers (**2a**/**2b**), or a stoichiometric excess of expensive and dangerous reagents [e.g. trimethyl(trifluoromethyl)silane in Eq. (c)].

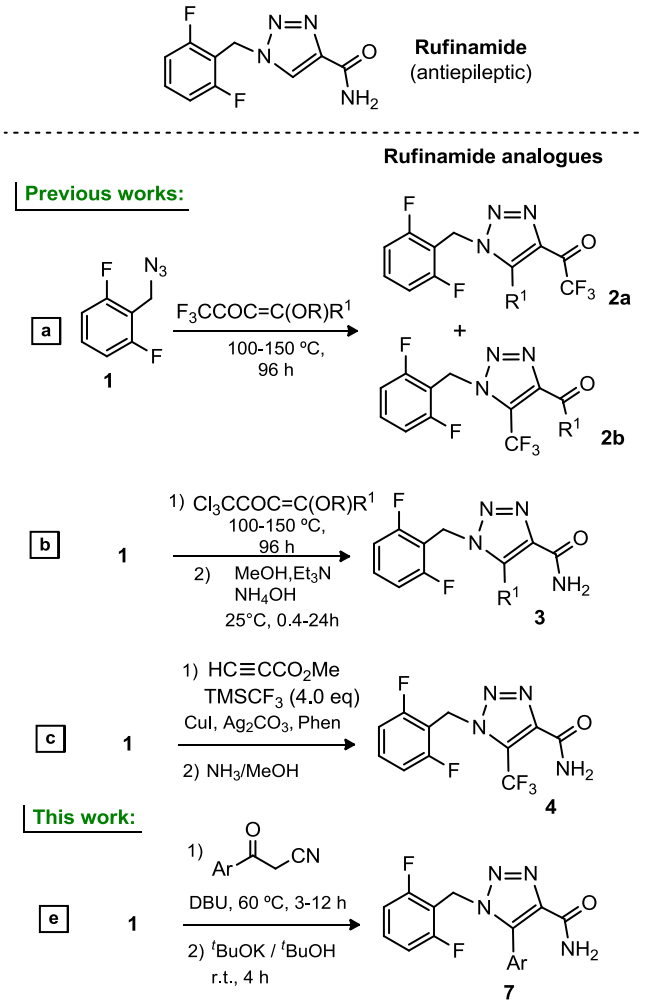
Evidently, these complex or cumbersome experimental procedures are a consequence of the inefficiency of CuAAC (the most reliable method for assembling triazoles)[3] for the synthesis of 1,4,5-trisubstituted derivatives. Very recently,[4] azide-enolate (3 + 2) cycloaddition has emerged as a novel way to generate 1,2,3-triazole moieties, facilitated by the use of a broad series of carbonyl derivatives (e.g., ketones, esters, aldehydes and nitriles) that are easily prepared and inexpensive. This represents a significant advantage over the CuAAC, especially for producing 1,4,5-trisubstituted triazoles. Hence, we herein describe the utility of the azide–enolate cycloaddition for the coupling of azides with β-ketonitriles as the dipolarophile to achieve the synthesis of novel Rufinamide analogues. [Eq. (e)].



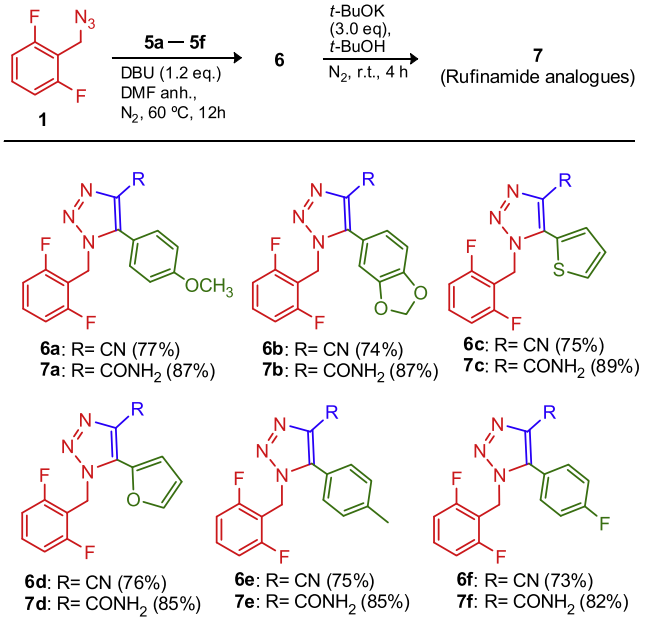
The initial study began by obtaining starting materials, β-ketonitriles[5] **5** and 2,6-difluorobenzyl azide[6] **1**, according to previously described methodologies. Based on our experience in this field, we decided to generate synthetic intermediates 5-CN substituted triazoles **6,** which are novel products such as the Rufinamide analogues reported in this paper, through an azide-enolate cycloaddition (Scheme 2).[7,8] Under mild reaction conditions, we utilized DBU as base in order to promote the *in situ* formation of the enolate from the corresponding β-ketonitriles **5**. Triazole scaffolds were furnished in good yields (73–77%). Subsequently, the hydrolysis of the nitrile group was attained by following the synthetic procedure of Dash et al.,[9,10] employing *t*-BuOK (3.0 eq) in *ter*-butanol at room temperature. Hence, 5-aril/heteroaryl Rufinamide analogues were efficiently synthesized and isolated in good yields (82–89%).

* Corresponding authors.
E-mail addresses: qfb_dgonzalez@yahoo.com.mx (D. González-Calderón), cgonzalezr@uaemex.mx (C. González-Romero).

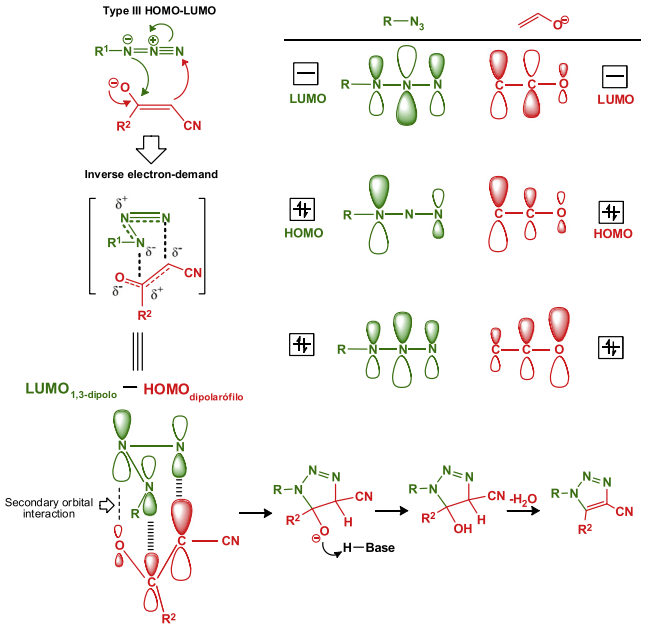
https://doi.org/10.1016/j.tetlet.2018.03.075
0040-4039/



Scheme 1. Background and proposed approach to the synthesis of novel Rufinamide analogues.



Scheme 2. Synthesis of Rufinamide analogues *via* azide-enolate cycloaddition. The products were confirmed by ^{1}H, ^{13}C NMR and HRMS. Yields refer to chromatographically pure isolated compounds.



Scheme 3. Proposed plausible mechanism for Rufinamide analogues intermediates synthesis.

Since the azide-enolate 1,3-dipolar cycloaddition is a very well-known reaction,[4] the regioselectivity has been understood since its first report in 1902.[11] Such regioselectivity between 1,3-dipole and dipolarophile can be explained by a *type III* HOMO-LUMO interaction (EWG substituents in the 1,3-dipole or EDG substituents in the dipolarophile).[12] (Scheme 3). The 1,3-dipole has a low LUMO that overlaps with the HOMO of the dipolarophile leading to a dipole LUMO-controlled process. The overlap of molecular orbitals for all 1,3-dipolar cycloadditions is always suprafacial.

Unlike other 1,3-dipolar cycloadditions with *exo* interaction, probably this reaction occurs through an *endo*-type interaction due to a possible *secondary orbital interaction* between the *p* orbital of O (dipolarophile) and the *p* orbital of the central N (1,3-dipole), interactions widely known in the literature[13] which does not lead to bond, but it does make a contribution to lowering the energy of this transition structure relative to that of the *exo* reaction, where it must be absent.

In summary, a highly regioselective azide-enolate cycloaddition has been implemented for the first time in the synthesis of novel Rufinamide analogues under a simple protocol involving the use of β-ketonitriles as dipolarophiles.

Acknowledgments

Financial support from the Secretaría de Investigación y Estudios Avanzados/UAEMéx (project No. 3804/2014/CID) and CONACyT (postgraduate scholarship) is gratefully acknowledged. The authors would like to thank the referee for valuable comments and suggestions, as well as M.N. Zavala-Segovia and L. Triana-Cruz (CCIQS UAEMéx– UNAM) for technical support.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.03.075.

References

1. (a) Borukhova S, Noël T, Metten B, de Vos E, Hessel V. *Green Chem*. 2016;18:4947–4953. https://doi.org/10.1039/C6GC01133K;
(b) Ott D, Borukhova S, Hessel V. *Green Chem*.. 2016;18:1096–1116. https://doi.org/10.1039/C5GC01932J;
(c) Zhang P, Russell MG, Jamison TF. *Org Process Res Dev*. 2014;18:1567–1570. https://doi.org/10.1021/op500166n;
(d) Tomás-Mendivil E, García-Álvarez R, Vidal C, Crochet P, Cadierno V. *ACS Catal*. 2014;4:1901–1910. https://doi.org/10.1021/cs500241p;
(e) Borukhova S, Noël T, Metten B, de Vos E, Hessel V. *ChemSusChem*. 2013;6:2220–2225. https://doi.org/10.1002/cssc.201300684;
(f) Mudd WH, Stvens EP. *Tetrahedron Lett*. 2010;51:3229. https://doi.org/10.1016/j.tetlet.2010.04.060;
(g) Meier, R. US Patent 4,789,680, 1988.;
(h) Attolino, E. P.; Colombo, L. P.; Mormino, I. M.; Allegrini, P. S. D. M.. US Patent 8198459 B2, 2012.;
(i) Kankan, R. N.; Rao, D. R.; Birari, D. R. Int. WO Patent 2010/043849 A1, 2010.;
(j) Siyan, R. S.; Aher, Y. S.; Nandu, B.; Singh, G. P.; Gohel, S. WO Patent 2013/105029 A1, 2013.;
(k) Zhang P, Russell MG, Timothy F. Jamison TF. *Org. Process Res Dev*. 2014;18:1567–1570. https://doi.org/10.1021/op500166n.
2. (a) Bonacorso HG, Moraes MC, Wiethan CW, et al. *J Fluorine Chem*. 2013;156:112–119. https://doi.org/10.1016/j.jfluchem.2013.09.005;
(b) Bonacorso HG, Moraes MC, Luz FM, Quintana PS, Zanatta N, Martins MAP. *Tetrahedron Lett*. 2015;56:441–444. https://doi.org/10.1016/j.tetlet.2014.11.125;
(c) Pak K, Cheung S, Tsui GC. *Org Lett*. 2017;19:2881–2884. https://doi.org/10.1021/acs.orglett.7b01116.
3. For complete Reviews about this issue see: Meldal M, Tornøe CW. *Chem. Rev*. 2008;108:2952–3015;
(b) Bock VD, Hiemstra H, van Maarseveen JH. *Eur J Org Chem*. 2006;51–68.
4. (a) For complete Reviews about this issue see: Lima CGS, Ali A, van Berkel SS, Westermann B, Paixão MW. *Chem Commun*. 2015;51:10784–10796;
(b) John J, Thomas J, Dehaen W. *Chem Commun*. 2015;51:10797–10806;
(c) Ramasastry SSV. *Angew Chem Int Ed*. 2014;53:14310–14312.
5. Shen J, Yang D, Liu Y, et al. *Org Lett*. 2014;16:350–353. https://doi.org/10.1021/ol403555n.
6. Rajadhyaksha, M. N.; Nair, R.; Ramesan, V.; Johnson, K.; Panandikar, A. M. Process for preparation of fluorinated triazole compound, WO 2012032540 A1, 2011 (Indoco Remedies Limited).
7. (a) González-Calderón D, Mejía-Dionicio MG, Morales-Reza MA, et al. *Eur J Med Chem*. 2016;112:60–65;
(b) González-Calderón D, Mejía-Dionicio MG, Morales-Reza MA, et al. *Bioorg Chem*. 2016;69:1–6.
8. General procedure for the synthesis of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazoles-4-carbonitriles derivatives (6a-f): To a solution of the β-ketonitrile 5a-f (0.57 mmol) in anhydrous DMF (1.0 mL) was added DBU (0.59 mmol) under nitrogen atmosphere. The solution was stirred for 1h at 60°C. Then, 2,6-difluorobenzyl azide 1 (0.88 mmol) was added to the reaction mixture with continuous stirring for 8 h. Brine (~30 mL) was added and then the reaction mixture was washed with EtOAc (3 × 10 mL). The organic layer was dried (Na2SO4) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the pure triazole.
9. Midya GC, Kapat A, Maiti S, Dash J. *J Org Chem*. 2015;80:4148–4151. https://doi.org/10.1021/jo502752u.
10. General procedure for the synthesis of 1-(2,6-difluorobenzyl)-1H-1,2,3-triazoles-4-carboxamides derivatives (7a-f). Triazole nitrile derivative 6a-f (0.31 mmol) was added to a solution of KOtBu (0.90 mmol) in dry tert-butyl alcohol. The reaction mixture was stirred at room temperature for 4 h under nitrogen atmosphere, and progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was treated with NH4Cl sat. sol. (30 mL). and then the reaction mixture was washed with EtOAc (3×10 mL). The organic layer was dried (Na2SO4) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the pure Rufinamide analogs.
11. (a) Dimroth O. *Ber Dtsch Chem Ges*. 1902;35:1029–1038. https://doi.org/10.1002/cber.190203501171; For a concise discussion about this issue see(b) Dimroth, M. D. Triazole Synthesis. In Name Reactions in Heterocyclic Chemistry II; Li, J. J., Ed.; John Wiley & Sons: New Jersey, 2011. Chapter 5. DOI: 10.1002/9781118092828.ch5.
12. Huisgen R. *J Org Chem*. 1976;41:403–419. https://doi.org/10.1021/jo00865a001.
13. I. Fleming, Pericyclic Reactions, Oxford Chemistry Primers, USA, 1998, pp. 49.