A straightforward and versatile approach to the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from alkyl halides *via* a one-pot, three-component reaction

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

PII: S0040-4039(15)00320-2
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.02.049
Reference: TETL 45918

To appear in: *Tetrahedron Letters*

Received Date: 7 January 2015
Revised Date: 9 February 2015
Accepted Date: 13 February 2015

Please cite this article as: González-Calderón, D., Aguirre-De Paz, J.G., González-González, C.A., Fuentes-Benítes, A., González-Romero, C., A straightforward and versatile approach to the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from alkyl halides *via* a one-pot, three-component reaction, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.02.049

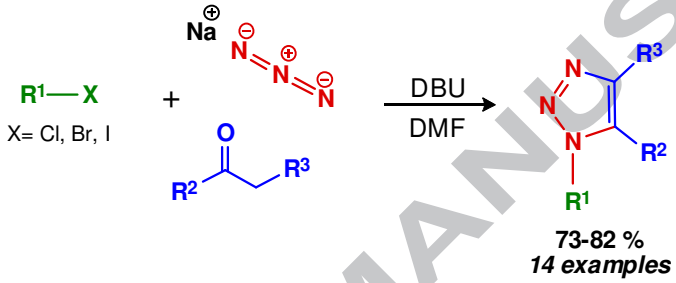
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

A straightforward and versatile approach to the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from alkyl halides *via* a one-pot, three-component reaction

Leave this area blank for abstract info.

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



Tetrahedron Letters
journal homepage: www.elsevier.com

A straightforward and versatile approach to the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from alkyl halides *via* a one-pot, three-component reaction

Davir González-Calderón [a,*], José G. Aguirre-De Paz [b], Carlos A. González-González [a], Aydeé Fuentes-Benítes [a], and Carlos González-Romero [a,*]

[a] *Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México, Paseo Colón/Paseo Tollocan s/n, Toluca, Estado de México, 50120, México.*

[b] *Universidad de Ixtlahuaca CUI, Carretera Ixtlahuaca-Jiquipilco km 1, Ixtlahuaca de Rayón, Estado de México, 50740, México.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Triazoles
Alkyl halides
Azide–enolate cycloaddition
Dimroth Cycloaddition

ABSTRACT

The preparation of 1,4,5-trisubstituted 1,2,3-triazoles by the coupling of three components (alkyl halides, sodium azide and active ketones) through an azide-enolate [3+2] cycloaddition (Dimroth Cycloaddition) has been developed for the first time. A wide variety of halides (including chlorides, bromides and iodides as well as primary and secondary derivatives) have demonstrated the versatility of this method, which is based on a one-pot system under mild reaction conditions.

In 1902[1] Otto Dimroth first described the azide-enolate [3+2] cycloaddition to obtain 1,4,5-trisubstituted 1,2,3-triazoles under strong basic conditions (NaOEt as base). For nearly 100 years this reaction remained *almost* forgotten.

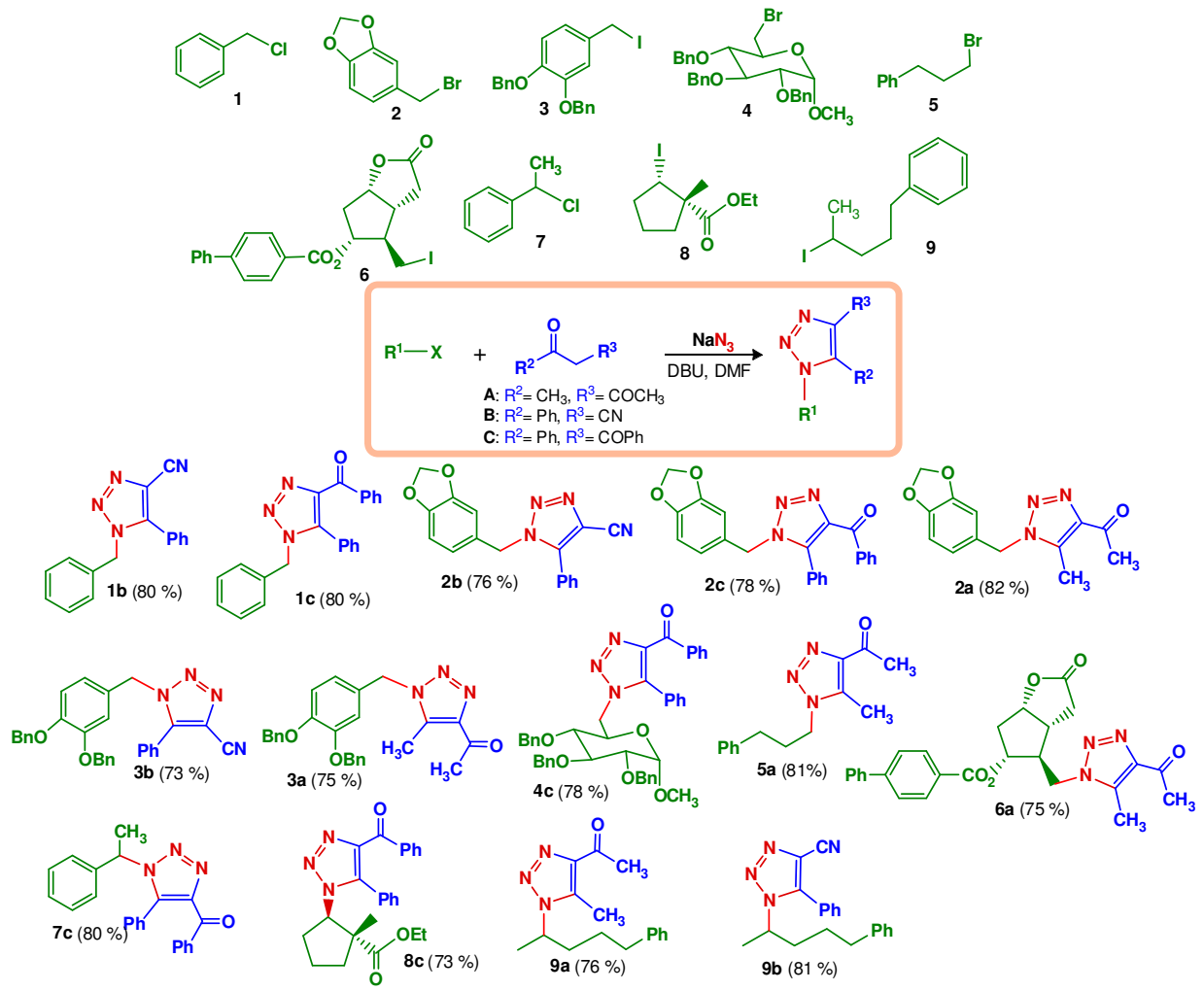
During the last decade several research groups[2] took renewed interest in this synthetic method and strove to improve it, because the 1,4,5-trisubstituted 1,2,3-triazole core had shown potent pharmacological activities.[3] Although these improved protocols have brought back this synthetic method in a new setting, there are still certain limitations. For instance, the use of azide substrate as the starting material requires that this uncommon reagent be obtained from other common functional group. Recently, Cao *et al*. reported a one-pot, three-component synthesis of 1,4,5-trisubstituted 1,2,3-triazoles starting from primary alcohols and using a NaN_3/TsIm/ TEA/TBAI/KOH system.[4] Unfortunately, the exclusive use of primary substrates and strongly basic conditions limits it use. Previously we published the use of a BnOH/DPPA/DBU system[5] as a facile approach to the synthesis of these compounds, but its scope is limited by the exclusive use of benzylic alcohols. Thus, there is a need to develop new alternatives for an effective approach to this important class of heterocycle compounds, preferably starting from conventional functional groups and using mild reaction conditions.

Alkyl halides in presence of sodium azide (NaN_3) have been highly efficient in Cu-catalyzed azide-alkyne cycloaddition (CuAAC) for the synthesis of 1,4-disubstituted 1,2,3-triazoles through a one-pot, three-component system.[6] This has proven to be a very rapid and *elegant* way to access triazole building blocks. The reasons are evident, the azide substrate generated *in situ* require only a simple and rapid displacement (S_N2) of a halide by an azide ion, providing this potential functional group in a one-pot reaction.

Rationalizing these facts, we decided to investigate the use of alkyl halides in the synthesis of 1,4,5-trisubstituted 1,2,3-triazoles *via* a one-pot, three-component reaction. The aim was to improve the synthetic strategies for the total synthesis of triazole carbocyclic nucleosides.[7]

Optimization studies for this coupling synthesis were carried out on benzyl chloride **1** and benzoylacetonitrile **B**. Mixing halide with a 1.1 equivalent of sodium azide in anhydrous DMF solution produced the desired alkyl azide in quantitative yield with short reaction times at 50 °C. The reaction with the enolate substrate, which was generated *in situ* by the action of a 1.1

* Corresponding author: Tel: +52 722 217 5109x113; Fax: +52 722 217 3890; e-mail: cgonzalezr@uaemex.mx (C. González-Romero) and qfb_dgonzalez@yahoo.com.mx (D. González-Calderón).



Scheme 1. Synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from alkyl halides by coupling with sodium azide and active ketones. The products were confirmed by ^{1}H-NMR, ^{13}C-NMR, MS and HRMS.

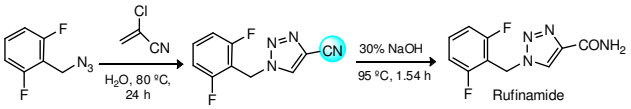
equivalent of 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) on a 1.1 equivalent of active ketone **A** led the building of the desired 1,4,5-trisubstituted 1,2,3-triazole block in 80 % yield. In contrast with Khurana's procedure,[2f] the catalytic use of DBU failed under our protocol. Optimized conditions were then used to study the coupling of a series of halide compounds in the presence of acetylacetone **A,** benzoylacetonitrile **B**, and/or dibenzoylmethane **C** as active ketones (Scheme 1).[8]

As the data in Scheme 1 indicate, acceptable yields of 1,4,5-trisubstituted 1,2,3-triazoles were obtained by using chlorides (**1** and **7**), bromides (**2**, **4** and **5**), and iodides (**3**, **6**, **8** and **9**) as well as primary (**1**–**6**) and secondary (**7**–**9**) derivatives. The inversion of configuration in an asymmetric center (*e.g.* **8**→**8c**) must be expected in order to a S_N2 mechanism.[9]

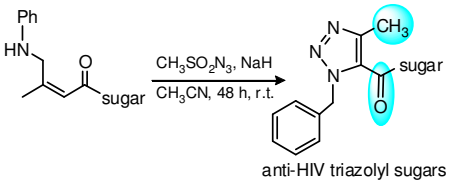
Rufinamide is an anticonvulsant medication approved by the FDA in 2008 which was discovered by Novartis Pharmaceuticals and is currently manufactured by Eisai Co., Japan, and marketed under the brand name Banzel. Classical approach to rufinamide is described in Scheme 2.[10] Synthetically, the use of benzoylacetonitrile **B** under our method may represent the obtaining of potential intermediates (**1b**, **2b**, **3b**, and **9b**) for the synthesis of rufinamide analogues.

On the other hand, the formation of 1,2,3-triazole core in carbohydrates has become one of the most important issue in medicinal chemistry to obtain 1,2,3-triazole nucleosides, nucleotides and oligonucleotides.[11] Triazolyl saccharide derivative **4c** obtained from halosugar **4** represent an interesting reaction for the synthesis of aforementioned compounds. Furthermore, this protocol is a facile alternative to obtain 4-acetyl-5-methyl-triazole derivatives (*e.g.* **2a**, **3a**, **5a**, **6a**, and **9a**) which are very functionalizable intermediates to obtain anti-HIV triazolyl sugars, previously reported by Ferreira *et. al*. (Scheme 3).[3c]

In summary, we report the first one-pot procedure for the direct conversion of alkyl halides to 1,4,5-trisubstituted 1,2,3-triazoles *vía* an azide-enolate [3+2] cycloaddition. These reactions were efficiently performed under mild conditions. The method circumvents the problems encountered with the isolation of organic azides, and complements the library of synthetic methods for obtaining these valuable heterocycles.



Scheme 2. Reported synthetic approach to Rufinamide.



Scheme 3. Ferreira's synthesis for anti-HIV triazolyl sugars.

Acknowledgments

Financial support from UAEMéx (project No. 3512/2013CHT) and CONACYT-Mexico (postgraduate scholarship) is gratefully acknowledged. The authors would like to thank the referee for valuable comments and suggestions, Signa S.A. de C.V. for some graciously donated solvents and reagents, M.N. Zavala-Segovia and L. Triana-Cruz (CCIQS UAEMéx–UNAM) for technical support.

Supplementary Material

Supplementary material (characterization data of all compounds and copies of ^{1}H–NMR, ^{13}C–NMR and HRMS) associated with this article can be found in the online version.

References and Notes

1. (a) Dimroth, O. *Ber. Dtsch. Chem. Ges.* **1902,** *35,* 1029-1038. (b) For a concise discussion about this issue see: Hill, M. D. *Dimroth Triazole Synthesis* in: *Name Reactions in Heterocyclic Chemistry II*, Chapter 5, (Ed: Li, J. J.), John Wiley & Sons: New Jersey, **2011**.
2. (a) Seus, N.; Goldani, B.; Lenardão, E. J.; Savegnago, L.; Paixão, M. W.; Alves, D. *Eur. J. Org. Chem.* **2014**, 1059–1065. (b) Kamalraj, V. R.; Senthil, S.; Kannan, P. *J. Mol. Structure*, **2008**, *892*, 210–215. (c) Pokhodylo, N.; Matiychuk, V. S.; Obushak, M. D. *Synthesis*, **2009**, 2321–2323. (d) Danence, L. J. T.; Gao, Y.; Li, M.; Huang, Y.; Wang, J. *Chem. Eur. J*. **2011**, *17*, 3584–3587. (e) Rozin, Y. A.; Leban, J.; Dehaen, W.; Nenajdenko, V. G.; Muzalevskiy, V. M.; Eltsov, O. S.; Bakulev, V. A. *Tetrahedron* **2012**, *68*, 614–618. (f) Singh, H.; Sindhu, J.; Khurana, J. M. *RSC Adv*. **2013**, *3*, 22360–22366. (g) Zhang, J.; Jin, G.; Xiao, S.; Wu, J.; Cao, S. *Tetrahedron*, **2013**, *69*, 2352–2356.
3. (a) Demchuk, D. V.; Samet, A. V.; Chernysheva, N. B.; Ushkarov, V. I.; Stashina, G. A.; Konyushkin, L. D.; Raihstat, M. M.; Firgang, S. I. Philchenkov, A. A.; Zavelevich, M. P.; Kuiava, L. M.; Chekhun, V. F.; Blokhin, D. Y.; Kiselyov, A. S.; Semenova, M. N.; Semenov, V. V. *Bioorg. Med. Chem*. **2014**, *22*, 738–755. (b) Kamal, A.; Shankaraiah, N.; Devaiah, V.; Reddy, K. L.; Juvekar,A.; Sen, S.; Kurian, N.; Zingde, S. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 1468–1473. (c) Da Silva, F. C.; De Souza, M. C. B. V.; Frugulhetti, I. I. P.; Castro, H. C.; De O. Souza, S. L.; De Souza, T. M. L.; Rodrigues, D. Q.; Souza, A. M. T.; Abreu, P. A.; Passamani, F.; Rodrigues, C. R.; Ferreira, V. F. *Eur. J. Med. Chem.* **2009**, *44*, 373–383. (d) Jordão, A. K.; Afonso, P. P.; Ferreira, V. F.; De Souza, M. C. B. V.; Almeida, M. C. B.; Beltrame, C. O.; Paiva, D. P.; Wardell, S. M. S. V.; Wardell, J. L.; Tiekink, E. R. T.; Damaso, C. R.; Cunha, A. C. *Eur. J. Med. Chem*. **2009**, *44*, 3777–3783. (e) Campos, V. R.; Abreu, P. A.; Castro, H. C.; Rodrigues, C. R.; Jordão, A. K.; Ferreira, V. F.; De Souza, M. C.B.V.; Santos, F. C.; Moura, L. A.; Domingos, T. S.; Carvalho, C.; Sanchez, E. F.; Fuly, A. L.; Cunha, A. C. *Bioorg. Med. Chem.* **2009**, *17*, 7429–7434. (f) Jordão, A. K.; Ferreira, V. F.; Lima, E. S.; De Souza, M. C. B. V.; Carlos, E. C. L.; Castro, H. C.; Geraldo, R. B.; Rodrigues, C. R.; Almeida, M. C. B.; Cunha, A. C. *Bioorg. Med. Chem.* **2009**, *17*, 3713–3719.
4. Jin, G.; Zhang, J.; Fu, D.; Wu, J.; Cao, S. *Eur. J. Org. Chem*. **2012**, 5446–5449.
5. González-Calderón, D.; Santillán-Iniesta, I.; González-González, C. A.; Fuentes-Benítes, A.; González-Romero, C. *Tetrahedron Lett*. **2015**, *56*, 514–516
6. Odlo, K.; Høydahl, E. A.; Hansen, T. V. *Tetrahedron Lett.* **2007**, *48*, 2097–2099. (b) Kacprzak, K. *Synlett* **2005**, 943–946. (c) Huang, L.; Liu, W.; Wu, J.; Fu, Y.; Wang, K.; Huo, C.; Du, Z. *Tetrahedron Lett.* **2014**, *55*, 2312–2316. (d) Kumar, B. S. P. A.; Reddy, K. H. V.; Madhav, B.; Ramesh, K.; Nageswar, Y. V. D. *Tetrahedron Lett*. **2012**, *53*, 4595–4599. (e) Mukherjee, N.; Ahammed, S.; Bhadra, S.; Ranu, B. C. *Green Chem.* **2013**, *15*, 389–397. (f) Ladouceur, S.; Soliman, A. M.; Zysman-Colman, E. *Synthesis* **2011**, 3604–3611. (g) Sharghi, H.; Khalifeh, R.; Doroodmand, M. M. *Adv. Synth. Catal*. **2009**, *351*, 207–218.
7. González-González, C. A.; Fuentes-Benítez, A.; Cuevas-Yáñez, E.; Corona-Becerril, D.; González-Romero, C.; González-Calderón, D. *Tetrahedron Lett.* **2013**, *54*, 2726–2728.
8. *Experimental Procedure*: A 10-mL round-bottom flask was equipped with a magnetic stir bar and a reflux condenser. Then 0.4 mmol of alkyl halide and 0.44 mmol of sodium azide were added to 1.5 mL of anhydrous dimethylformamide. The reaction mixture was stirred at 60 °C for 2 h under nitrogen atmosphere. After cooling to room temperature, TLC indicated the disappearance of the starting material. 0.44 mmol of active ketone and 0.44 mmol of DBU were then added to the reaction mixture, which was stirred for 3 h at 60 °C. Brine (~40 mL) was added to the reaction mixture and washed with EtOAc (3×10 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Flash column chromatography afforded the pure triazole.
9. Rablen, P. R.; McLarney, B. D.; Karlow, B. J.; Schneider, J. E. *J. Org. Chem.* **2014**, *79*, 867–879.
10. Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; Del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2014**, *114*, 2432–2506 and references therein.
11. (a) For representative Reviews see: Aragão-Leoneti, V.; Campo, V. L.; Gomes, A. S.; Field, R. A.; Carvalho, I. *Tetrahedron* **2010**, *66*, 9475–9492. (b) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev*. **2009**, *109*, 4207–4220.