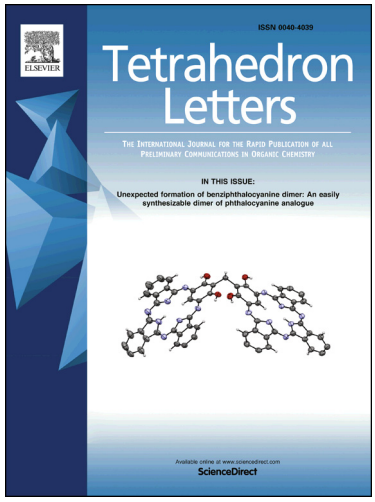


A Fast Route for the Synthesis of Tetrazolyl Oximes by a Novel Multicomponent Reaction between Z-Chlorooximes, Isocyanides and Trimethylsilyl Azide

Mariateresa Giustiniano, Sveva Pelliccia, Ana Belen Muñoz-Garcia, Michele Pavone, Bruno Pagano, Ubaldina Galli, Ettore Novellino, Gian Cesare Tron

PII: S0040-4039(17)30967-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2017.07.098
Reference: TETL 49180

To appear in: *Tetrahedron Letters*

Received Date: 6 July 2017
Revised Date: 26 July 2017
Accepted Date: 28 July 2017

Please cite this article as: Giustiniano, M., Pelliccia, S., Muñoz-Garcia, A.B., Pavone, M., Pagano, B., Galli, U., Novellino, E., Tron, G.C., A Fast Route for the Synthesis of Tetrazolyl Oximes by a Novel Multicomponent Reaction between Z-Chlorooximes, Isocyanides and Trimethylsilyl Azide, *Tetrahedron Letters* (2017), doi: http://dx.doi.org/10.1016/j.tetlet.2017.07.098

Tetrahedron Letters
journal homepage: www.elsevier.com

A Fast Route for the Synthesis of Tetrazolyl Oximes by a Novel Multicomponent Reaction between Z-Chlorooximes, Isocyanides and Trimethylsilyl Azide.

Mariateresa Giustiniano,*[a,d] Sveva Pelliccia,[a,d] Ana Belen Muñoz-Garcia,[b] Michele Pavone,[b] Bruno Pagano,[a] Ubaldina Galli,[c] Ettore Novellino,[a] and Gian Cesare Tron*[c]

[a] *Dipartimento di Farmacia, Università degli Studi di Napoli "Federico II", via D. Montesano 49, 80131, Naples, Italy.*
[b] *Dipartimento di Scienze Chimiche, Università degli Studi di Napoli "Federico II", Via Cintia 21, 80126, Naples, Italy.*
[c] *Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale "A. Avogadro", Largo Donegani 2, 28100, Novara, Italy*
[d] *These authors contributed equally to this work.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Multicomponent Reactions
Isocyanides
Z-Chlorooximes
[3+1] cycloaddition
(1*H*-tetrazol-5-yl)methanone oximes

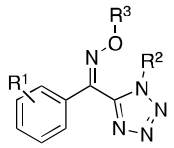
ABSTRACT

A library of twenty variously decorated 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes was prepared in one single synthetic step exploiting the combination of (*Z*)-chlorooximes, isocyanides and trimethylsilylazide. The formal [3+1] cycloaddition between isocyanides and nitrile *N*-oxides with respect to the [3+1] cycloaddition between isocyanides and azides prevails, while the direct attack of azide onto nitrile *N*-oxides remains competitive. Finally, an intramolecular cyclization of a (1*H*-tetrazol-5-yl)methanone oxime to a benzoisoxazole tetrazole is reported for the first time.

Over the last decades, isocyanide-based multicomponent reactions (IMCRs) have demonstrated to be viable short-cuts for the rapid assembly of medium-complexity molecular skeletons usually accessible via two-component chemistry through a multistep approach.[1] Indeed, mixing three or four components in the same vessel can alter the typical course of a two-component reaction, as the third and/or the fourth component may be able to intercept unstable intermediates channeling the transformation toward different outcomes. A multicomponent approach is particularly viable and welcomed even when the reaction yield appeared to be moderate. Indeed, as recently highlighted, the synthetic efficiency of a MCR with moderate yield (35 %) is by far higher than a three steps synthesis with yield higher than 70 % for each step.[2]

In continuation with our research for the discovery of novel multicomponent reactions[3] we envisaged the possibility to set up a novel multicomponent transformation for the synthesis of tetrazolyl oximes, a class of very potent fungicides exemplified by compounds of general formula **1** (Figure 1).[4] Usually, tetrazolyl oximes are synthesized from the corresponding 5-aroyl-1-aryltetrazoles **4** by condensation with hydroxylamine giving a mixture of *Z* and *E* isomers.[5]

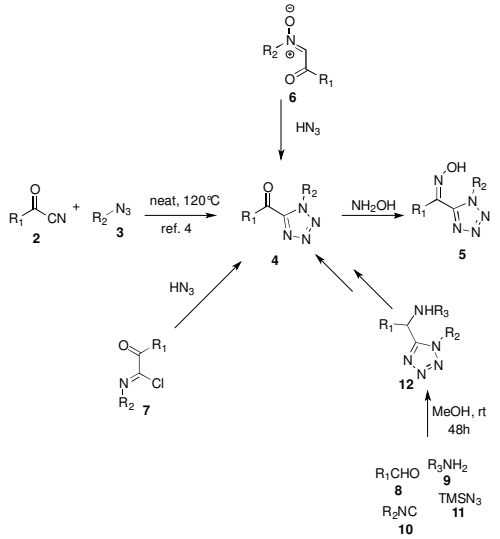
As only the *Z* geometrical isomer has fungicide activity, several patents tried to solve the problem of the oxime regioselectivity.[6]



1

Figure 1. General formula of tetrazolyl oximes endowed with fungicide activity.

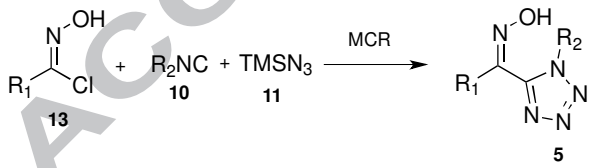
Different synthetic procedures for the synthesis of intermediates **4** have been reported so far. For example, a thermal [3+2] cycloaddition between acyl cyanides (**2**) and organic azides (**3**) have been described (Scheme 1).[7]



Scheme 1. Literature reported syntheses of the 5-oxo-tetrazole precursors.

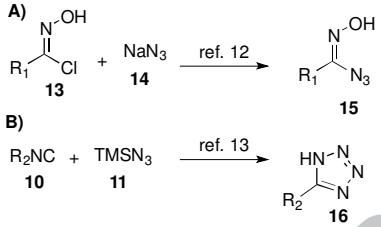
Anyway, the reaction fails with aromatic azides preventing the formation of 5-aroyl-1-aryltetrazoles (**4**). Reaction between nitrones (**6**) or α-ketoimidoylchlorides (**7**) and hydrazoic acid have also been reported although they were very poor in scope (Scheme 1).[8,9] Furthermore, the use of hydrazoic acid, an unstable, extremely explosive, and very toxic liquid, raises concerns about its use on industrial scale. An alternative and convergent approach for the obtainment of 5-aroyl-1-aryltetrazole derivatives was based on the use of an Ugi reaction between an aldehyde or a ketone (**8**), an amine (**9**), an isocyanide (**10**) and a source of azide (**11**). In this case, the Ugi-azide reaction affords derivative **12** (Scheme 1) in very good yields. However, further elaborations were needed to give 5-aroyltetrazoles (**4**).[10]

Understanding the difficulties associated with the synthesis of 5-aroyl-1-aryltetrazoles and the problems associated with the formation of the single *Z*-isomer of oxime, and in connection with our studies on the use of nitrile *N*-oxides in isocyanide-mediated multicomponent reactions,[11] we became intrigued in testing the one-pot reaction between *Z*-chlorooximes (**13**), isocyanides (**10**) and trimethylsilyl azide (**11**), in order to obtain *Z*-1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes (**5**) in one single chemical operation as exemplified in Scheme 2.



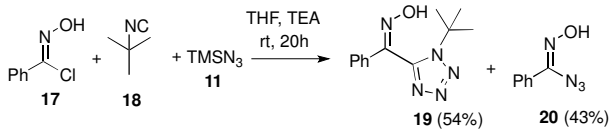
Scheme 2. Multicomponent reaction of *Z*-chlorooximes, isocyanides and trimethylsilylazide.

We have previously demonstrated that nitrile-*N*-oxides preferentially react with isocyanides in the presence of a third nucleophile independently from its nucleophilic strength, as the formal [3+1] cycloaddition reaction between isocyanides and nitrile *N*-oxides is energetically favorable.[11] In this case, anyway, the situation was even more puzzling as the third component, the azide, can behave both as strong nucleophile and reactive dipolar species. For this reason, the outcome of this three-component reaction could be *a priori* extremely chaotic with the formation of several products considering all the possible scenarios. For example, it is well-known that nitrile *N*-oxides, generated via base-deprotection of *Z*-chlorooximes (**13**), react with sodium azide **14** to give hydroxymoyl azides (**15**).[12] The same isocyanide function can also react with the azide in the Olivieri-Mandalà and Alagna reaction[13] to afford tetrazole derivatives (**16**) (Scheme 3).



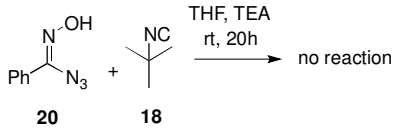
Scheme 3. Reported reactions of azide with *Z*-chlorooximes and isocyanides.

When Z-phenylchlorooxime **17**, *tert*-butylisocyanide **18** and trimethylilyl azide **11** were reacted in a test reaction we isolated, through chromatographic purification, the desired tetrazole **19**, along with a more lipophilic side product. Spectroscopic analyses revealed that the yield of **19** was lowered by the formation of hydroxymoyl azide **20** in 43% yield, deriving from the direct attack of the trimethylsilyl azide **11** to the nitrile *N*-oxide (Scheme 4). Interestingly, no sign of Olivieri-Mandalà and Alagna product was detected. Attempts to increase the yield of tetrazole **19** reducing the formation of compound **20**, by performing the reaction with more equivalents of isocyanide (1.5 eq. in place of 1 eq.), or at 0°C, had no success. Carrying out the reaction at reflux temperature overnight slightly increased the yield of **19** to 60%, but unfortunately a mixture of *Z* and *E* oximes was obtained. As the obtainment of pure *Z* geometrical isomers was a bonus of this transformation, we decided to explore the versatility of this reaction working at room temperature.



Scheme 4. Test reaction affording tetrazole **19** and hydroxymoyl azide **20**.

It is worth of note that any attempts to react isolated hydroxymoyl azide **20** with tert-butylisocyanide **18** in the presence of TEA did not give compound **19** (Scheme 5).



Scheme 5. Attempted reaction between hydroxymoyl azide **20** and *t*-butylisocyanide **18**.

To elaborate the scope and the limitations of this novel multicomponent reaction, different *Z*-chlorooximes (**17**, **21**-**27**) and isocyanides (**18**, **28**-**32**) were then used (Figure 2).

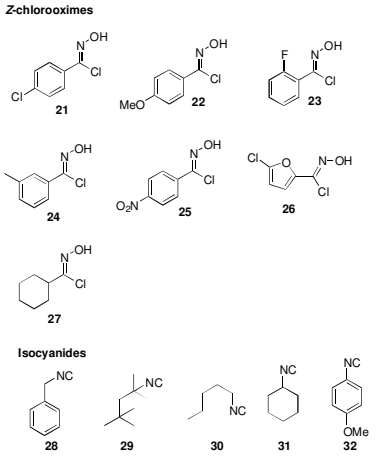


Figure 2. Starting materials used for the synthesis of a library of 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes.

Desired products **33**-**51** were obtained in yields ranging from 20 to 62% as shown in Figure 3. From a structure-reactivity relationship point of view, aromatic *Z*-chlorooximes bearing electron-withdrawing substituents such as the 4-nitrophenyl-chlorooxime **25** proved to be the better starting material, affording **41** in 62% yield and **42** in 57% yield, while electron-donor groups as the methoxy-group decreased the yields to 22, 20 and 35% as shown for products **36**, **40**, and **47** respectively.

Heteroaromatic (**26**) and aliphatic Z-chlorooximes (**27**) also afforded the desired products in 27 and 24% (**44** and **45**), and 37 and 48% yield (**50** and **51**), respectively. Primary, secondary and tertiary isocyanides (**18**, **30**-**31**) worked well, and also the bulky 1,1,3,3-tetramethylbutyl radical was well tolerated (**29**) as shown for products **34** and **44**. To note that only in one single case, i.e. with compound **50**, we obtained a mixture of *Z*/*E* geometrical isomers of the oxime in ratio *Z*/*E* 2:1.

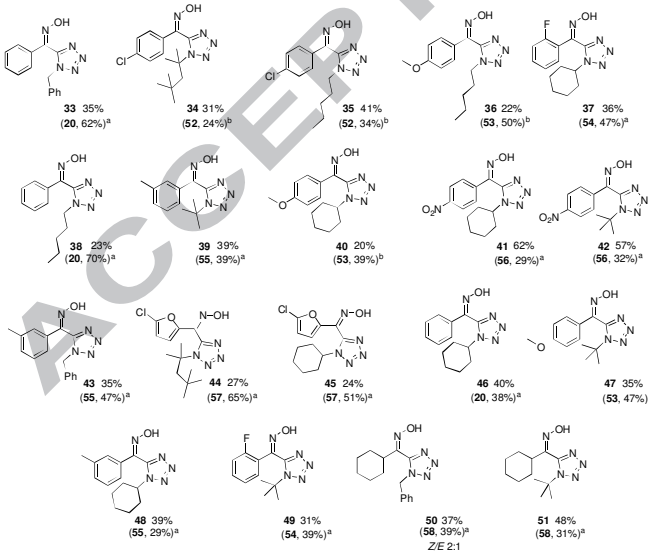
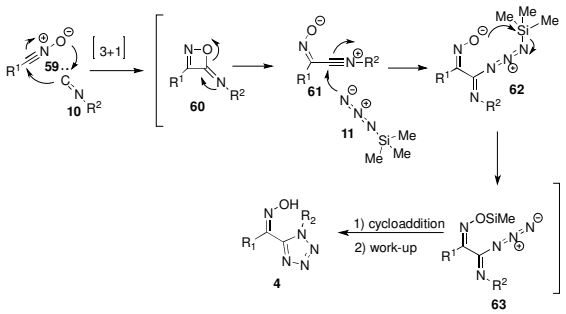


Figure 3. Library of synthesized 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes. In brackets are reported the yields of hydroxymoyl azides[a] or furoxans[b] (for structures and characterization see Supporting Information).

Benzyl isocyanide (**28**) gave the products **43** and **50** in 35 and 37% yield, while, not surprisingly,[10] aromatic isocyanides such as *p*-methoxyphenyl isocyanide (**32**) did not work. As already discussed above, the variable yields of 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes are to ascribe to the competing formation of hydroxymoyl azides or, in some cases, to the formation of furoxans through dimerization of nitrile *N*-oxides. On the other hand, the product deriving from Olivieri-Mandalà and Alagna reaction was never detected. The yields of these adducts seem to be influenced by both the substitution patterns of the same *Z*-chlorooxime and the reactivity of the isocyanide, with the *p*-methoxyphenyl-*Z*-chlorooxime **22** giving the major yields of furoxan **54** also in the presence of reactive tertiary and secondary isocyanides (**18** and **31,** respectively). The *Z*-phenylchlorooxime **17** and the primary *n*-pentylisocyanide (**30**) showed to be the less reactive and the reaction gave 70% of azidoxime **20**, while the combination of heteroaromatic chlorooxime **26** and Walborsky's isocyanide (**30**) gave azidoxime **57** in 65% yield. These results show that the unproductive reaction between trimethylsilylazide and nitrile *N*-oxides cannot be suppressed, but the electronic nature of substituted nitrile *N*-oxides plays a role in promoting selectivity towards the reaction between isocyanides and nitrile *N*-oxides. This behavior, however, cannot be simply explained comparing the energy of HOMO and LUMO orbitals (see Supporting Information). In particular, we calculated HOMO and LUMO energy differences in THF for three reactant combinations: a) the corresponding nitrile *N*-oxide of **19** and trimethylsilylazide **11**; b) the corresponding nitrile *N*-oxide of **19** and isocyanide **18**; c) trimethylsilylazide **11** and isocyanide **18.** However, HOMO and LUMO energy values (eV) are very similar, in accordance to the poor selectivity observed.

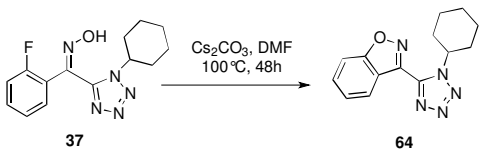
According to the obtained results, we can propose the following reaction mechanism for the formation of 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes. The nitrile *N*-oxide (**59**), in situ generated via base dehydrochlorination of *Z*-chlorooxime **(13),** reacts with the isocyanide **10** in its carbenic form in a formal [3+1] cycloaddition to give the highly strained four-membered ring **(60)**. The latter spontaneously opens to afford the nitrilium species **(61)** that is then intercepted by the trimethylsilylazide **11** to give intermediate **62**. The shift of trimethylsilyl group from the azide to the oxime, triggers an intramolecular cycloaddition to afford the tetrazole ring **4** (Scheme 6).



Scheme 6. Proposed reaction mechanism for the formation of 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes.

Notwithstanding the moderate yields, the obtainment of tetrazolyl oximes in a one chemical operation and as single stereoisomers, and using simple and safe reactants, represents an interesting advancement in the synthesis of this class of biologically active compounds. Importantly, the basic medium

prevents the formation of the toxic and explosive hydrazoic acid. Furthermore, this class of compound can be the starting point for the preparation of difficult-to-obtain class of compounds or novel heterocyclic systems. For example, hydrolysis of oximes can afford 5-aroyl-1-aryltetrazoles[15], whose synthesis is notoriously elaborate as discussed before. Alternatively, when we heated 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes bearing a fluorine atom at the *ortho* position (**37**), in presence of Cesium carbonate, an intramolecular aromatic nucleophilic substitution took place affording the unprecedented benzoisoxazole tetrazole **64** (Scheme 7).



Scheme 7. Synthesis of benzoisoxazole tetrazole **64.**

In conclusion, we disclosed a novel three-component reaction using three different dipoles: *Z*-chlorooximes, isocyanides and trimethylsilylazide to afford 1,5-disubstituted-(1*H*-tetrazol-5-yl)methanone oximes. One of the major features of this transformation is the selectivity of the formal [3+1] cycloaddition between isocyanides and nitrile *N*-oxides with respect to the [3+1] cycloaddition between isocyanides and azides, while the direct attack of azide onto nitrile *N*-oxides remains competitive and cannot be suppressed. Despite the yields of products remain moderate, they are comparable to or higher than overall yields in multistep reported procedures. Importantly, these yields do not affect the efficiency of the newly reported multicomponent reaction, as three new bonds were formed (one C-C, one C-N and one N-N) with an average yield of 30%, which corresponds to ~70% yield per bond formation. On the other hand, hydroxymoyl azides were formed through one single new C-N bond, so that their yield per new-formed bond is less noteworthy. Moreover, the stereoselectivity and the possibility to obtain this class of compounds in one single chemical operation and using accessible and safe chemical reagents cannot be underestimated and this method constitutes an improvement by comparison with the reported strategies.

Acknowledgments

Financial support from University of Naples Federico II and University of Piemonte Orientale, Novara, is acknowledged. M. G. acknowledges AIRC (MFAG 18793).

References and notes

1. Zhu, J. and Bienayme, H. *Multicomponent reactions*, Wiley-VCH, Weinheim, 2005; (b) Zhu, J.; Wang, Q.; Wang, M. *Multicomponent reactions in organic synthesis*, Wiley-VCH, Weinheim, 2014; (c) Herrera, R. P. and Marquez-Lopez, E. *Multicomponent reactions*, Wiley-VCH, Weinheim, 2015. (d) Dömling, A. *Chem. Rev.* **2006**, *106*, 17-89; (e) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083–3135; (f) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 6234-6246; (g) Giustiniano, M.; Basso, A.; Mercalli, V.; Massarotti, A.; Novellino, E.; Tron, G. C.; Zhu, J. *Chem. Soc. Rev.* **2017**, *46*, 1295-1357.
2. Eckert, E. *Molecules* **2017**, *22*, 349.
3. (a) Giustiniano, M.; Novellino, E.; Tron, G. C. *Synthesis* **2016**, 2721-2731; (b) Giustiniano, M.; Meneghetti, F.; Mercalli, V.; Varese, M.; Giustiniano, F.; Novellino, E.; Tron, G. C. *Org. Lett.* **2014**, *16*, 5332-5335; (c) Giustiniano, M.; Mercalli, V.; Amato, J.; Novellino, E.; Tron, G. C. *Org. Lett.* **2015**, *17*, 3964-3967.
4. (a) Fréneau, M.; de Sainte Claire, P.; Hoffmann, N.; Vors, J.-P.; Geist, J.; Euvrard, M.; Richard, C. *RSC Adv.* **2016**, *6*, 5512-5522; (b) Beier, C; Benting, J.; Bernier, D.; Coqueron, P.-Y.; Desbordes, P.; Dubost, C.; Gary, S.; Genix, P.; Portz, D.; Wachendorff-Neumann, U. U.S. Patent, US 8796463, 2014; (c) Tomoyuki, S.; Kazushige, K.; Shinya, W.; Akie, F. PCT Int. Appl., WO 2014136603, 2014; (d) Ichirou, U. PCT Int. Appl., WO 2011115029, 2011.
5. (a) Matsuda, K.; Matsushita, M.; Noda, K.; Kajita, S. PCT Int. Appl. WO 2013137075, 2013; (b) Caillon-Morisseau, S.; Coqueron, P.-Y.; Heinrich, J.-D.; Lui, N. PCT Int. Appl. WO2011110651, 2011; (c) Beier, C.; Benting, J.; Bernier, D.; Christian, I.; Coqueron, P.-Y.; Desbordes, P.; Dubost, C.; Genix, P.; Portz, D.; Wachendorff-Neumann, U. PCT Int. Appl. WO201000084, 2010.
6. (a) Suzuki, T.; Sugiura, T.; Ito, Y. PCT Int. Appl., WO 2010103783, 2010; (b) Coqueron, P.-Y.; Dubost, C.; Ford, M.; Rebstock, A.-S. PCT Int. Appl., WO 2013117582, 2013; (c) Zaragoza, D. F. PCT Int. Appl., WO 2016142364, 2016; (d) Benting, J.; Coqueron, P.-Y.; Desbordes, P.; Dubost, C.; Wachendorff-Neumann, U. PCT Int. Appl., WO 2013026836, 2013; (e) Beier, C.; Bernier, D.; Coqueron, P.-Y.; Desbordes, P.; Dubost, C.; Lui, N.; Pazenok, S. PCT Int. Appl., WO 2011161076, 2011.
7. Demko, Z. P.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2113-2116.
8. Moderhack, D. *J. Heterocyclic Chem.* **1977**, *14*, 757-763.
9. (a) Zefirov, N. S.; Trach, S. S.; Chapovskaya, N. K. *Zh. Org. Khim.* **1972**, *8*, 629-634;(b) Ugi, I.; Fetzer, U. *Chem. Ber.* **1961**, *94*, 1116-1121.
10. (a) Giustiniano, M.; Pirali, T.; Massarotti, A.; Biletta, B.; Novellino, E.; Campiglia, P.; Sorba, G.; Tron, G. C. *Synthesis* **2010**, 4107-4118; (b) Zhao, T.; Boltjes, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2013**, *15*, 639-641; (c) Butini, S.; Gabellieri, E.; Brindisi, M.; Casagni, A.; Guarino, E.; Huleatt, P. B.; Relitti, N.; La Pietra, V.; Marinelli, L.; Giustiniano, M.; Novellino, E.; Campiani, G.; Gemma, S. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 85-89.
11. (a) Pirali, T.; Mossetti, R.; Galli, S.; Tron, G. C. *Org. Lett.* **2011**, *13*, 3734-3737; (b) Mercalli, V.; Meneghetti, F.; Tron, G. C. *Org. Lett.* **2013**, *15*, 5902-5905; (c) Giustiniano, M.; Mercalli, V.; Cassese, H.; Di Maro, S.; Galli, U.; Novellino, E.; Tron, G. C. *J. Org. Chem.* **2014**, *79*, 6006-6014; (d) Mercalli, V.; Giustiniano, M.; Del Grosso, E.; Varese, M.; Cassese, H.; Massarotti, A.; Novellino, E.; Tron, G. C. *ACS Comb. Sci.* **2014**, *16*, 602-605; (e) Stornaiuolo, M.; La Regina, G.; Passacantilli, S.; Grassia, G.; Coluccia, A.; La Pietra, V.; Giustiniano, M.; Cassese, H.; Di Maro, S.; Brancaccio, D.; Taliani, S.; Ialenti, A.; Silvestri, R.; Martini, C.; Novellino, E.; Marinelli, L. *J. Med. Chem.* **2015**, *58*, 2135-2148; (f) Mercalli, V.; Massarotti, A.; Varese, M.; Giustiniano, M.; Meneghetti, F.; Novellino, E.; Tron, G. C. *J. Org. Chem.* **2015**, *80*, 9652-9661.
12. (a) Eloy, F. *J. Org. Chem.* **1961**, *26*, 952-954; (b) Hegarty, A. F.; Mullane, M. *J. Chem. Soc., Chem. Commun.* **1984**, 913; (c) Dignam, K. J.; Hegarty, A. F.; Quain, P. L. *J. Org. Chem.* **1978**, *43*, 388-393; (d) Tselinskii, I. V.; Mel'nikova, S. F.; Romanova, T. V. *Russ J. Org. Chem.* **2001**, *37*, 455-461.
13. Olivieri-Mandalà, E.; Alagna, B. *Gazz. Chim. Ita.* **1910**, *40*, 441-448.
14. The reaction was also tried in dichloromethane without yield modification. Due to the extreme concern in carrying out a reaction with a source of azide in dichloromethane, see Conrow, R. E.; Dennis Dean, W. *Org. Process Res. Dev.* **2008**, *12*, 1285-1286, we opted for the safer use of THF.
15. Kudose, K.; Kaneko, M.; Noda, K. JP 2016098214, 2016.

Supplementary Material

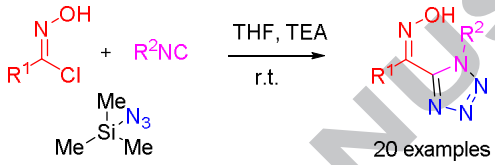
Experimental procedure, spectroscopic data, copies of ^{1}H and ^{13}C spectra, HOMO-LUMO calculations (PDF).

Graphical Abstract

A Fast Route for the Synthesis of Tetrazolyl Oximes by a Novel Multicomponent Reaction between *Z*-Chlorooximes, Isocyanides and Trimethylsilyl Azide.

Leave this area blank for abstract info.

Mariateresa Giustiniano, Sveva Pelliccia, Ana Belen Muñoz-Garcia, Michele Pavone, Bruno Pagano, Ubaldina Galli, Ettore Novellino, and Gian Cesare Tron



- A one-pot synthesis of (1*H*-tetrazol-5-yl)methanone oximes has been reported.
- The combination of (*Z*)-chlorooximes, isocyanides and $TMSN_3$ has been exploited.
- A cyclization to benzoisoxazole tetrazoles has been reported for the first time.