Rapid, Microwave Accelerated Synthesis of [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazoles from 4-Acylamino-1,2,4-Triazoles

Stephanie L. Breunig, Margaret E. Olson, Daniel A. Harki

PII: S0040-4039(16)30950-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.07.082
Reference: TETL 47944

To appear in: *Tetrahedron Letters*

Received Date: 26 June 2016
Revised Date: 19 July 2016
Accepted Date: 27 July 2016

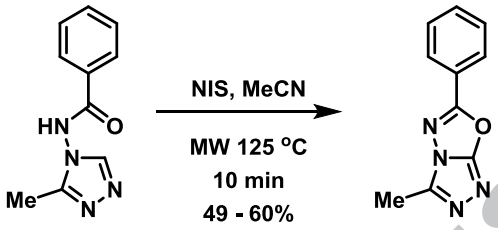
Please cite this article as: Breunig, S.L., Olson, M.E., Harki, D.A., Rapid, Microwave Accelerated Synthesis of [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazoles from 4-Acylamino-1,2,4-Triazoles, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.07.082

Graphical Abstract

Rapid, Microwave Accelerated Synthesis of [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazoles from 4-Acylamino-1,2,4-Triazoles

Leave this area blank for abstract info.

Stephanie L. Breunig, Margaret E. Olson, Daniel A. Harki
Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN 55455, USA



Tetrahedron Letters
journal homepage: www.elsevier.com

Rapid, Microwave Accelerated Synthesis of [1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazoles from 4-Acylamino-1,2,4-Triazoles

Stephanie L. Breunig, Margaret E. Olson, and Daniel A. Harki*

Department of Medicinal Chemistry, University of Minnesota, Minneapolis, MN, 55455, USA

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
1,2,4-Triazole
1,3,4-Oxadiazole
[1,2,4]Triazolo[3,4-*b*][1,3,4]oxadiazole
Microwave Chemistry
Intramolecular Cyclization

ABSTRACT

1,2,4-Triazoles and 1,3,4-oxadiazoles are prevalent moieties in pharmaceutical agents, yet fused [1,2,4]-triazolo[3,4-*b*][1,2,4]oxadiazoles are surprisingly under-represented for both synthesis and biological application. We report a rapid, two-step synthesis of [1,2,4]-triazolo[3,4-*b*][1,2,4]oxadiazoles from commercial 4-amino-1,2,4-triazoles that is highlighted by a microwave accelerated intramolecular cyclization to generate the fused ring system. Our efforts to optimize reaction conditions and elucidate reaction mechanism are also described.

* Corresponding author. Tel.: +1-612-625-8687; fax: +1-612-625-4749; e-mail: daharki@umn.edu

Introduction

1,2,4-Triazoles are represented in diverse molecules with antimicrobial,[1-2] antitubercular,[3] anticancer,[4] analgesic,[5] and anticonvulsant[6] activities. Notably, the antiviral drug ribavirin and antifungal drugs fluconazole, itraconazole, and voriconazole possess a 1,2,4-triazole. In a similar vein, 1,3,4-oxadiazoles, are present in compounds bearing antimicrobial,[7-8] antifungal,[9] anxiolytic,[10] antidepressant,[11] antiproliferative,[12-17] hypoglycemic,[18] and antiviral activities. Raltegravir, an FDA-approved HIV-1 integrase inhibitor, incorporates a 1,3,4-oxadiazole. However, [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazoles (**1**) are surprisingly under-investigated. In the few assays executed, compounds containing this moiety exhibited antibacterial activity similar to that of streptomycin,[19] herbicidal activity comparable to the commercially available 2,4-dichlorophenoxyacetic acid (2,4-D), and fungicidal activity akin to the commercial Dithane M-45.[20] Furthermore, in a library of oxadiazole derivatives screened for antimicrobial activity, the triazolo-oxadiazole was considered the most active.[21]

The [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole heterocycle, **1**, was first suggested in 1961;[22] and since then, multiple synthetic approaches have been reported (**Figure 1A**). In nearly all approaches to **1** the oxadiazole is first prepared and the triazole is formed in the final step. For instance, 1,3,4-oxadiazoles functionalized at the 2-position with acylhydrazines (**2**),[19,23-25] hydrazones (**3**),[26-27] and unsubstituted hydrazines (**4**)[20,28-29] can be directly converted to **1** via triazole cyclization. The triazole has also been formed by reacting hydrazine hydrate with either EtOH and amino oxadiazoles (**5**),[21] *N*-substituted oxadiazolines (**6**),[30] or *N*-acylated oxadiazolones (**7**).[31] Butler et al. found that hydrazonyl bromides (**8**) could be cyclized via nucleophilic attack of the oxadiazole.[32] Bypassing the formation of **8**, Scott et al. found that tribromo-diazobutadienes (**9**) could afford **1** when refluxed with benzhydrazine and Et_3N.[33] Conversely, only two reports of [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole formation via late-stage generation of the oxadiazole ring have been reported. Tsuge et al. observed the formation of **1** when carbamoyl chloride (**10**) was treated with anhydrous sodium azide, and proposed the reaction proceeded via a triazolone intermediate able to react with a second equivalent of **10**.[34] They, along with Milcent et al., also formed **1** from a pre-functionalized triazole (**11**) using Na_2CO_3[34] or $POCl_3$,[35] respectively. Herein, we report a rapid, microwave accelerated synthesis of **1** from readily synthesized 4-acylamino-1,2,4-triazoles (**12**) that are iodinated *in situ* (**Figure 1b**).

In an effort to synthesize reversible covalent inhibitors of APOBEC3 DNA cytosine-to-uracil deaminases, we discovered the [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole synthesis presented herein. In

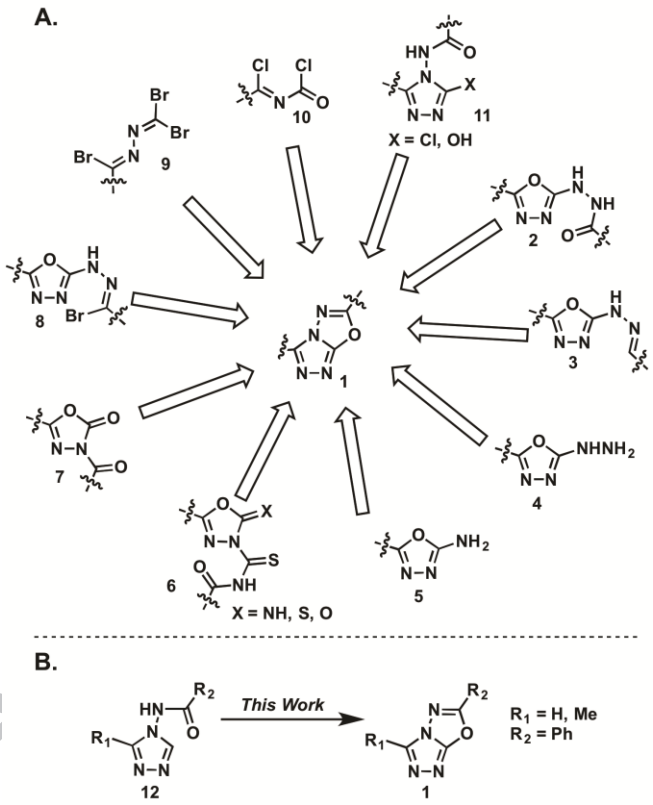
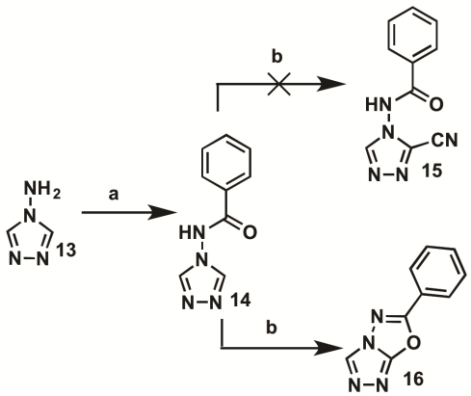


Figure 1. (A) Previously reported methods for the preparation of heterocycles represented by **1**. (B) Our strategy for the synthesis of **1** from readily accessible precursors, such as **12**.

previous studies by our laboratory, we found that substituted 4-amino-1,2,4-triazole-3-thiols inhibit APOBEC3G (A3G) DNA cytosine-to-uracil deaminase activity by covalently engaging A3G Cys321, a critical residue proximal to the active site.[36] As thiols are inherently reactive functional groups, we sought to replace this moiety on our inhibitor with a nitrile, compound **15**, to achieve a more drug-like scaffold with tuneable reactivity. The nitrile functional group has gained significant attention as an electrophile for reversible covalent inhibition of therapeutic targets due to its weak reactivity with nucleophiles in solution. For instance, when appropriately positioned in an enzyme, a



Scheme 1. Attempted synthesis of nitrile **15** via **14** under previously published conditions[38] for direct cyanation of heterocycles and isolated **16**. (a) Benzoyl chloride, 1,4-dioxane, reflux, 24 h, 60-79% (b) CuCN (0.7 equiv.), NaCN (1.2 equiv.), I_2 (1.5 equiv.), *t*BuOLi (1.2 equiv.), 1,10-phenanthroline (1.0 equiv.), *m*-xylene, 1,4-dioxane, MW 125 °C, 18%.

Table 1. Initial studies to determine necessary reagents for conversion of **14** to **16** based on previously reported[38] direct cyanation conditions.[a,b]

Reagents	Solvent(s)	Temp (°C)	Time (min)	% Yield[c]
CuCN, *t*BuOLi, I_2, NaCN, Phenanthroline	1,4-dioxane/ *m*-xylene	125	30	18
CuCN, *t*BuOLi, I_2	1,4-dioxane/ *m*-xylene	125	30	12
CuCN, *t*BuOLi	1,4-dioxane/ *m*-xylene	125	30	N/A[d]
CuCN, *t*BuOLi, I_2	1,4-dioxane/ *m*-xylene	125	5	13
CuCN, *t*BuOLi, I_2	DMF	125	30	16
CuCN, *t*BuOLi, I_2	MeOH	125	30	12
CuCN, *t*BuOLi, I_2	MeOH	50	30	N/A

[a]Reactions were typically performed on 0.4 mmol scale (for **14**)

[b]Microwave conditions, 200 W maximum

[c]Isolated yields

[d]N/A = No product observed

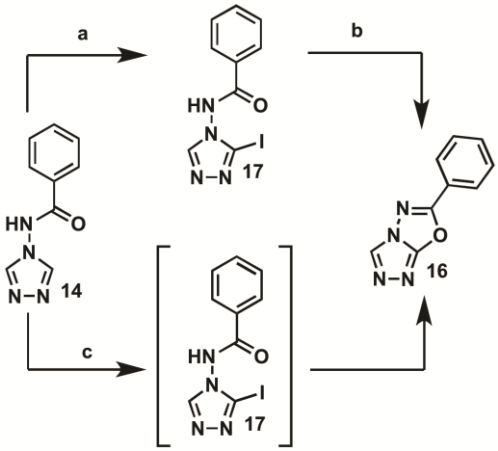
nitrile can undergo nucleophilic attack from a cysteine residue, forming a transient thioimidate adduct that is stabilized by hydrogen bonding with the enzyme.[37]

Accordingly, we acylated the commercially available 4-amino-4*H*-1,2,4-triazole (**13**) with benzoyl chloride, then attempted direct triazole cyanation of the resulting amide **14**. Direct heterocycle cyanation conditions with CuCN, NaCN, I_2, *t*BuOLi, and 1,10-phenanthroline in *m*-xylene and 1,4-dioxane at 110 °C have been reported[38] and similar conditions were attempted with our system. However, the presence of the pendant amide carbonyl instead promoted cyclization into the triazole to yield the [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole **16**, as opposed to target compound **15** (**Scheme 1**). Given the synthetic ease of elaborating a simple triazole, such as **13**, into a substituted triazolo-oxadiazole such as **16**, especially in comparison to other methods that require more transformations (see **Figure 1**), we instead turned our attention to optimizing this reaction and examining its mechanism.

Results and Discussion

Our initial efforts focused on determining which reagents were necessary to promote cyclization of **14** to **16** based on the direct cyanation conditions published by Do and Daugulis.[38] Systematic removal of the various reaction components revealed that neither 1,10-phenanthroline nor NaCN were necessary to achieve **16** (**Table 1**). However, when I_2 was omitted, no cyclization occurred and only the amide starting material was recovered. Because starting material solubility was poor when dioxane and xylene were used as co-solvents, both DMF and methanol were also utilized to enhance solubility. However, despite the fact that a homogenous solution was obtained in both instances, these solvent changes appeared to have little effect on the transformation. Finally, it appeared that elevated temperatures (125 °C) were required for the transformation, as I_2, CuCN, and *t*BuOLi were unable to confer **16** at 50 °C, and only amide starting material was recovered under these conditions. At this juncture, we envisioned possible metal-catalyzed cross-couplings or S_NAr intramolecular cyclizations to yield **16**, and devised a series of experiments to probe the reaction mechanism (**Table 2**).

Our previous studies suggested that **16** may result from a Cu^I-catalyzed cross coupling between the benzamide oxygen and the 3-position of the triazole, either via an iodinated intermediate or C-H activation. To determine if other metal catalysts could afford **16**, we screened $Pd(OAc)_2$, $Pd(PPh_3)_4$, and $Pd(PPh_3)_2Cl_2$ under identical conditions as that used for CuCN. However, little-to-no **16** was observed. Recently, the synthesis of 2-arylbenzoxazoles through oxidative C-O coupling with $Cu(OTf)_2$ under an O_2 atmosphere has been reported,[39] which lead us to evaluate if similar conditions can be employed to deliver **16** from **14** using either CuCN or $Cu(OTf)_2$ as catalysts. In both instances no increase in yield was observed for the transformation of **14** to **16**, and the condition in which I_2 was omitted, $Cu(OTf)_2$ as catalyst, resulted in no product formation. Additionally, a similar iodine-mediated oxadiazole formation using Oxone, NaOH, and I_2 has been reported;[40] however, no cyclization occurred when these published conditions were applied to our system. We further found that nucleophilic iodine sources (e.g., KI) were insufficient to promote cyclization, whereas electrophilic iodine sources (e.g., I_2) resulted in product formation. These results, taken with the fact that cyclization was also observed when only *t*BuOLi and I_2 were utilized (**Table 2**), suggested a mechanism



Scheme 2. Two-step synthesis of **16** leads to a proposed mechanism of [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole formation via **17**. (a) NIS, MeCN, MW, 70 °C, 20 min, 36%. (b) MeCN, MW, 125 °C, 10 min, 32-35%. (c) NIS, MeCN, MW, 125 °C, 10 min, 29%

alternative to metal-catalyzed cross-coupling, and inspired us to investigate I_2-mediated intramolecular cyclization.

In an attempt to explore a step-wise synthesis of **16** – iodination followed by cyclization – we aimed to synthesize the mono-iodinated **17** using previously reported conditions.[41] To our surprise, subjecting **14** to *N*-iodosuccinimide (NIS) in THF at 70 °C not only resulted in the target molecule **17** (**Scheme 2a**), but was also sufficient to promote cyclization to **16**. Replacing THF with MeCN as solvent increased the solubility of **14**, and together with an increased microwave temperature of 125 °C, conferred **16** in a 29% isolated yield. Importantly, **17** was not observed at these higher temperatures.

To probe the mechanism of the cyclization, purified **17** was simply dissolved in MeCN and subjected to microwave irradiation at 125 °C. **16** was isolated from this reaction mixture in 32-35% yield (**Scheme 2**). These results led us to propose the following mechanism: NIS or I_2 mediates the formation of iodinated intermediate **17**, which undergoes intramolecular cyclization through the amide oxygen via a S_NAr mechanism to form **16**. Our data suggests that microwave irradiation at 70 °C is sufficient for iodination to occur, but higher temperatures (125 °C) are required for **17** to cyclize completely to **16**. It is also possible that a second mechanism involving an iodonium species across the C-N double bond of **14** followed by cyclization and elimination of HI is involved in the formation of **16**; however, no experimental evidence has yet been found to support this pathway.

Interestingly, the addition of base (*t*BuOLi) to the NIS-mediated reaction did not enhance the formation of the cyclized product (**Table 3**), suggesting that succinimide, ambient water, or the iodide anion released after substitution is sufficiently basic for proton abstraction and re-aromatization. Additionally, **14** heated at reflux overnight in MeCN using conventional heating methods (i.e. an oil bath) did allow for cyclization to **16** to occur, but in much lower yield (~9% isolated yield) compared to optimized microwave conditions (29% yield) that require only 10 min reaction times.

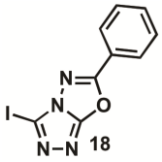


Figure 2. Isolated byproduct **18** (yields are shown in Table 3).

Table 2. Alternative conditions to assess conversion of **14** to **16**.[a]

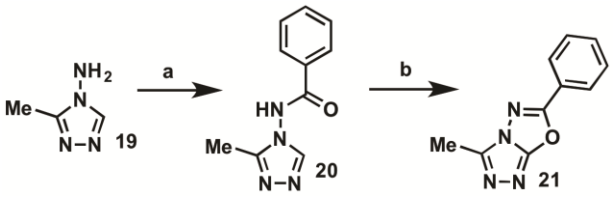
Reagents	Solvent(s)	Heat Source[b]	Temp (°C)	Time	% Yield[c]
$Pd(OAc)_2$, I_2, *t*BuOLi	DMF	MW	125	30 min	4
$Pd(PPh_3)_4$, I_2, *t*BuOLi	1,4-dioxane/ *m*-xylene	MW	125	30 min	N/A[d]
$Pd(PPh_3)_2Cl_2$, I_2, *t*BuOLi	MeOH	MW	125	30 min	1
CuCN, I_2, *t*BuOLi, O_2 (1 atm)	DMF	Oil bath	125	23 h	9
$Cu(OTf)_2$, O_2 (1 atm)	*o*-xylene	Oil bath	140	40 h	N/A
Oxone, I_2, NaOH	MeOH	-	r.t.	43 h	N/A
CuCN, KI, *t*BuOLi	1,4-dioxane/ *m*-xylene	MW	125	30 min	N/A
*t*BuOLi, I_2	MeCN	MW	125	10 min	11

[a]Reactions were typically performed on 0.4 mmol scale (for **14**)

[b]MW = Microwave heating, 200 W maximum. Oil bath = conventional heating.

[c]Isolated yields

[d]N/A = No



Scheme 3: Synthesis and subsequent cyclization of the 3-methyl analogue **20**. (a) benzoyl chloride, 1,4-dioxane, reflux, 24 h, 61-72%. (b) NIS, MeCN, MW 125 °C, 10 min, 49-60%.

Table 3. Optimization of NIS-mediated cyclization of **14** to **16**.[a,b]

Reagent(s)	Temp. (°C)	Time (min)	% Yield[c] (**16**)	% Yield[c] (**18**)	% Recovered[c] (**14**)
NIS (1.0 eq.), *t*BuOLi (1.2 eq.)[d]	125	10	13	1	66
NIS (0.9 eq.)	125	10	23	0	34
NIS (1.0 eq.)[e]	125	10	25	0	26
NIS (1.1 eq.)	125	10	29	7	18
NIS (1.2 eq.)	125	10	18	1	11
NIS (1.3 eq.)	125	10	22	9	31
NIS (2.0 eq.)	125	10	22	25	2
NIS (4.0 eq.)	125	10	18	37	0
NIS (1.0 eq.)	125	30	9	1	24
NIS (1.0 eq.)[d]	95	10	19	1	34
NIS (1.0 eq.)[d]	140	10	27	1	10

[a]Reactions were typically performed on 0.4 mmol scale (for **14**)

[b]Microwave conditions, 200 W maximum. Performed in duplicate in MeCN. Mean yields are shown.

[c]Isolated yields

[d]Single measurement

[e]Triplicate measurements

One explanation for the modest yield is the observation and isolation of the iodinated byproduct **18** with m/z = 312.9579 (calc'd = 312.9581, **Figure 2**). To push the reaction towards completion while avoiding over-iodination, we screened various equivalents of NIS, as well as varying reaction times and temperatures; however, of the conditions tested, none resulted in a significant improvement in yield (**Table 3**). Because both the byproduct **18** and starting material **14** could be isolated from the reaction mixture during optimization studies, this competing reaction, namely the formation of **18**, likely plays a role in low reaction yield. When the reaction mixture was treated with excess (4 eq.) of NIS, for instance, all starting material was consumed; however, recovery of the desired product **16** declined (18% yield) as the formation of the iodinated product **18** was promoted (37% yield). We found that 1.1 equivalents of NIS in MeCN heated to 125 °C for 10 min using microwave irradiation conferred the best yield of **16** (29% yield).

This limitation in transformation efficiency can be corrected by blocking the site of additional iodination by employing mono-substituted triazoles (e.g., 3-methyl; **19**) as starting materials. Acylation of **19** to amide **20**, followed by treatment with an excess (4.0 equiv.) of NIS under our established microwave conditions results in formation of **21** in reasonable yields (49-60%; **Scheme 3**). The substituted [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole **21** was synthesized from the triazole **19** in a 30-43% yield over two steps.

Conclusions

In conclusion, we report a rapid, microwave accelerated method for the synthesis of [1,2,4]triazolo[3,4-*b*][1,3,4]-oxadiazoles from readily available commercial building blocks. This method, despite modest yields, offers an alternative approach for synthesizing this interesting heterocycle in only two synthetic steps. We believe our method expands the synthetic accessibility of this heterocycle, which may enable its evaluation for a variety of biological applications.

Acknowledgments

We gratefully acknowledge funding by the National Institutes of Health (R01-GM110129) and the University of Minnesota, Office of the Vice President for Research (Equipment Grant-in-Aid to purchase the CEM Discover SP Microwave Synthesizer). S.L.B. thanks the University of Minnesota, Undergraduate Research Opportunities Program (UROP) and the Department of Chemistry Heisig/Gleysteen Summer Undergraduate Research Fellowship Program for financial support. M.E.O. acknowledges the National Institutes of Health for a Ruth L. Kirschstein NRSA Predoctoral Fellowship (F31-CA18324). Mass spectrometry was performed at the Analytical Biochemistry Core Facility of the Masonic Cancer Center (University of Minnesota), which is supported in part by the National Institutes of Health (P30-CA77598).

Supplementary Material

Supplementary data (experimental procedures and NMR spectra) associated with this article can be found online at XXXXX.

References

1. Holla, B. S.; Gonsalves, R.; Shenoy, S., *Farmaco* **1998**, *53*, 574-578.
2. Turan-Zitouni, G.; Kaplancıklı, Z. A.; Yıldız, M. T.; Chevallet, P.; Kaya, D., *Eur. J. Med. Chem.* **2005**, *40*, 607-613.
3. Walczak, K.; Gondela, A.; Suwiński, J., *Eur. J. Med. Chem.* **2004**, *39*, 849-853.
4. Holla, B. S.; Veerendra, B.; Shivananda, M. K.; Poojary, B., *Eur. J. Med. Chem.* **2003**, *38*, 759-767.
5. Amir, M.; Shikha, K., *Eur. J. Med. Chem.* **2004**, *39*, 535-545.
6. Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A., *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6057-6059.
7. Ahsan, M. J.; Samy, J. G.; Khalilullah, H.; Nomani, M. S.; Saraswat, P.; Gaur, R.; Singh, A., *Bioorg. Med. Chem. Lett.* **2011**, *21*, 7246-7250.
8. Şahin, G.; Palaska, E.; Ekizoğlu, M.; Özalp, M., *Farmaco* **2002**, *57*, 539-542.
9. Liu, F.; Luo, X.-Q.; Song, B.-A.; Bhadury, P. S.; Yang, S.; Jin, L.-H.; Xue, W.; Hu, D.-Y., *Bioorg. Med. Chem.* **2008**, *16*, 3632-3640.
10. Harfenist, M.; Heuser, D. J.; Joyner, C. T.; Batchelor, J. F.; White, H. L., *J. Med. Chem.* **1996**, *39*, 1857-1863.
11. Ergün, Y.; Orhan, Ö. F.; Özer, U. G.; Gişi, G., *Eur. J. Pharmacol.* **2010**, *630*, 74-78.
12. Jin, L.; Chen, J.; Song, B.; Chen, Z.; Yang, S.; Li, Q.; Hu, D.; Xu, R., *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5036-5040.
13. Abadi, A. H.; Eissa, A. A. H.; Hassan, G. S., *Chem. Pharm. Bull.* **2003**, *51*, 838-844.
14. Bajaj, S.; Asati, V.; Singh, J.; Roy, P. P., *Eur. J. Med. Chem.* **2015**, *97*, 124-141.
15. Du, Q.-R.; Li, D.-D.; Pi, Y.-Z.; Li, J.-R.; Sun, J.; Fang, F.; Zhong, W.-Q.; Gong, H.-B.; Zhu, H.-L., *Bioorg. Med. Chem.* **2013**, *21*, 2286-2297.
16. Shahzad, S. A.; Yar, M.; Bajda, M.; Jadoon, B.; Khan, Z. A.; Naqvi, S. A. R.; Shaikh, A. J.; Hayat, K.; Mahmmod, A.; Mahmood, N.; Filipek, S., *Bioorg. Med. Chem.* **2014**, *22*, 1008-1015.
17. Zheng, Q.-Z.; Zhang, X.-M.; Xu, Y.; Cheng, K.; Jiao, Q.-C.; Zhu, H.-L., *Bioorg. Med. Chem.* **2010**, *18*, 7836-7841.
18. Shingalapur, R. V.; Hosamani, K. M.; Keri, R. S.; Hugar, M. H., *Eur. J. Med. Chem.* **2010**, *45*, 1753-1759.
19. Sanjeeva Reddy, C.; Vani Devi, M.; Rajesh Kumar, G.; Sunitha, M.; Nagaraj, A., *J. Heterocyclic Chem.* **2013**, *50*, 557-562.
20. Singh, H.; Yadav, L. D. S.; Bhattacharya, B. K., *Indian J. Chem., Sect. B* **1979**, *17B*, 499-501.
21. Gad El-Karim, I. A.; Amine, M. S.; Mahmoud, A. A.; Gouda, A. S., *J. Surfactants Deterg.* **2014**, *17*, 509-523.
22. Potts, K. T., *Chem. Rev.* **1961**, *61*, 87-127.
23. EL-Saraf, G. A.; EL-Sayed, A. M., *Synth. Commun.* **1996**, *26*, 3827-3839.
24. Feng, X.-M.; He, X.; Jiang, Y.-Z., *Gaodeng Xuexiao Huaxue Xuebao* **1998**, *19*, 577-579.
25. Qiu, Z.-Z.; Dai, C.-F.; Chao, S.-J.; Xu, P.-F.; Zhang, Z.-Y., *J. Chin. Chem. Soc.* **2004**, *51*, 1343-1346.
26. Abdel-Aal, M. T.; El-Sayed, W. A.; El-Kosy, S. M.; El-Ashry, E. S. H., *Arch. Pharm. Chem. Life Sci.* **2008**, *341*, 307-313.
27. Vakula, T. R.; Srinivasan, V. R., *Indian J. Chem.* **1971**, *9*, 901-903.
28. El-Dean, A. M. K., *J. Chem. Res. Miniprint*, **1996**, 1401-1415.
29. Moustafa, O. S.; Badr, M. Z. A.; El-Emary, T. I., *Bull. Korean Chem. Soc.* **2002**, *23*, 567-570.
30. Aly, A. S.; Fahmy, A. A.; Zaki, M. E. A.; Abdel-Megeid, F. M. E., *Egypt. J. Pharm. Sci.* **1992**, *33*, 699-711.
31. Gogoi, P. C.; Kataky, J. C. S., *Heterocycles* **1991**, *32*, 237-244.
32. Butler, R. N.; Lambe, T. M.; Scott, F. L., *J. Chem. Soc., Perkin Trans. 1* **1972**, 269-273.
33. Scott, F. L.; Lambe, T. M.; Butler, R. N., *Tetrahedron Lett.* **1971**, *12*, 1729-1732.
34. Tsuge, O.; Yoshida, M.; Kanemasa, S., *J. Org. Chem.* **1974**, *39*, 1226-1228.
35. Milcent, R.; Redeuilh, C., *J. Heterocyclic Chem.* **1980**, *17*, 1691-1696.
36. Olson, M. E.; Li, M.; Harris, R. S.; Harki, D. A., *ChemMedChem* **2013**, *8*, 112-117.
37. Frizler, M.; Stirnberg, M.; Sisay, M. T.; Gutschow, M., *Curr. Top. Med. Chem.* **2010**, *10*, 294-322.
38. Do, H.-Q.; Daugulis, O., *Org. Lett.* **2010**, *12*, 2517-2519.
39. Ueda, S.; Nagasawa, H., *Angew. Chem. Int. Ed.* **2008**, *47*, 6411-6413.
40. Shinde, V. N.; Ugarkar, B. G.; Ghorpade, S. R., *J. Chem. Res.* **2013**, *37*, 53-54.
41. Katkevica, S.; Salun, P.; Jirgensons, A., *Tetrahedron Lett.* **2013**, *54*, 4524-4525.

Highlights

- [1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazoles were synthesized in two steps
- 10-min microwave-accelerated cyclization forms the oxadiazole ring
- 3-substituted 1,2,4-triazoles cyclize in higher yields without byproduct formation