OL Organic Letters

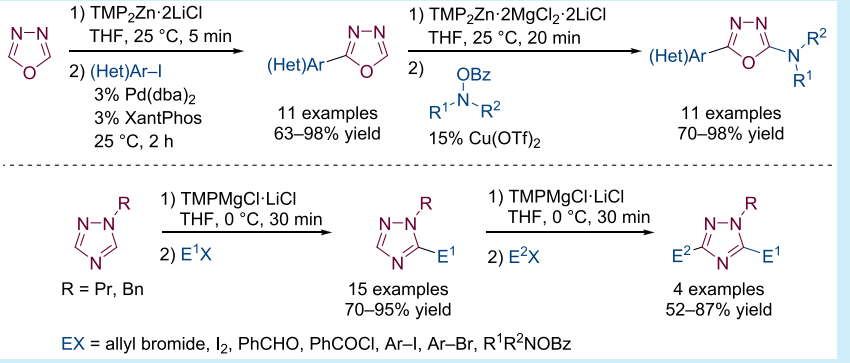
pubs.acs.org/OrgLett Letter

Functionalization of 1,3,4-Oxadiazoles and 1,2,4-Triazoles via Selective Zincation or Magnesiation Using 2,2,6,6-Tetramethylpiperidyl Bases

Kuno Schwärzer, Carl Phillip Tüllmann, Simon Graßl, Bartosz Górski, Cara E. Brocklehurst, and Paul Knochel*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00238 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: We report the metalation of the 1,3,4-oxadiazole and 1,2,4-triazole scaffolds via regioselective zincation or magnesiation using the TMP bases (TMP = 2,2,6,6-tetramethylpiperidyl) $TMP_2Zn{\cdot}2LiCl$, $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, TMPMgCl·LiCl, and TMPZnCl·LiCl under mild conditions in THF. Subsequent trapping with various electrophiles including hydroxylamino benzoates gives access to functionalized heterocycles while tolerating many functional groups.

Substituted five-membered heterocycles such as functionalized 1,3,4-oxadiazoles and 1,2,4-triazoles are common structural moieties in pharmaceutical compounds (Figure 1).[1] Examples include raltegravir (**1**)[2] and maraviroc (**2**),[3] which are used for the treatment of HIV, the iron chelator deferasirox (**3**),[4] as well as alprazolam (**4**),[5] which is used in the medication of anxiety disorders.

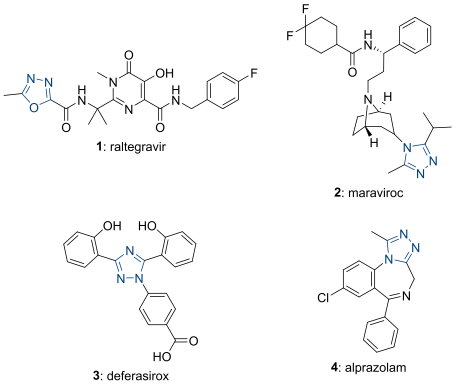


Figure 1. Pharmaceuticals containing a 1,3,4-oxadiazole or 1,2,4-triazole ring.

These heterocycles have also been utilized as functional materials such as electron-transporting, hole-blocking materials in the construction of organic light-emitting diodes (OLEDs).[6] Most synthetic approaches toward functionalized 1,3,4-oxadiazoles and 1,2,4-triazoles involve a late-stage formation of the heterocycle starting from a properly substituted precursor.[7] In consequence, the installation of various substituents may require multiple precursors, which complicates medicinal screening experiments. Therefore, we envisioned a more general approach involving the metalation of these scaffolds followed by trapping reactions with electrophiles. However, the metalation of 1,3,4-oxadiazole has not yet been reported, and in the case of N-substituted 1,2,4-triazoles, only the lithiation with BuLi is known from the literature.[8]

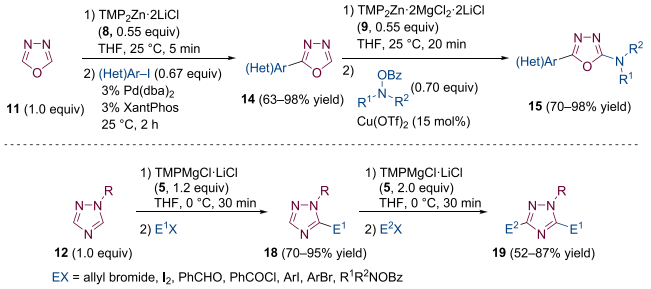
Previously, we have demonstrated that sterically hindered TMP-magnesium bases (TMP = 2,2,6,6-tetramethylpiperidyl) such as TMPMgCl·LiCl (**5**) or $TMP_2Mg{\cdot}2LiCl$ (**6**) and TMP-zinc bases like TMPZnCl·LiCl (**7**), $TMP_2Zn{\cdot}2LiCl$ (**8**),

Received: January 16, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00238
Org. Lett. XXXX, XXX, XXX−XXX

$TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**9**), or TMPZnOPiv·LiCl (**10**) allow the metalation of a range of different heterocycles under mild conditions while tolerating a variety of functional groups.[9] Therefore, we envisioned a selective double functionalization of 1,3,4-oxadiazole (**11**) and N-substituted 1,2,4-triazoles (**12**) using TMP bases (Scheme 1).

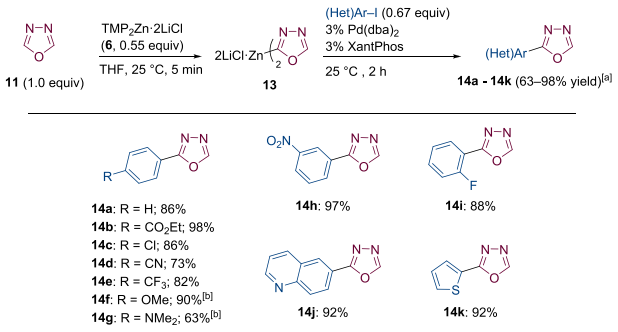
Scheme 1. Stepwise Functionalization of 1,3,4-Oxadiazole (11) and N-Substituted 1,2,4-Triazoles of Type 12 Using the TMP Bases 8, 9, and 5[a]



[a]R = Pr, Bn.

Preliminary studies have shown that in the case of 1,3,4-oxadiazole (**11**) the freshly prepared base $TMP_2Zn{\cdot}2LiCl$ (**8**)[10] provided the best results, leading to a complete conversion after 5 min at 25 °C.[11] The resulting zincated 1,3,4-oxadiazole **13** was subsequently submitted to *Negishi* cross-coupling (Scheme 2).[12] A mixture of $Pd(dba)_2$ (3 mol %) and XantPhos[13] (3 mol %) provided excellent results with a variety of electron-poor aryl iodides at 25 °C, producing the desired cross-coupling products **14a**−**14e**, **14h**, and **14i** in 73−98% yield. When employing electron-rich aryl iodides, $Pd(PPh_3)_4$[14] (7.5 mol %) was the best catalyst and afforded the heterocycles **14f** and **14g** in 63−90% yield (50 °C, 2 h). Due to the relatively low reactivity of the intermediate organozinc species **13**, various functional groups were tolerated, including an ester (**14b**), a chloride (**14c**), a nitrile (**14d**), an amine (**14g**), and a nitro group (**14h**). In addition, heterocyclic iodides, such as 6-iodoquinoline and 2-iodothiophene, have been successfully coupled, providing the heterocycles **14j** and **14k** in 92% yield.

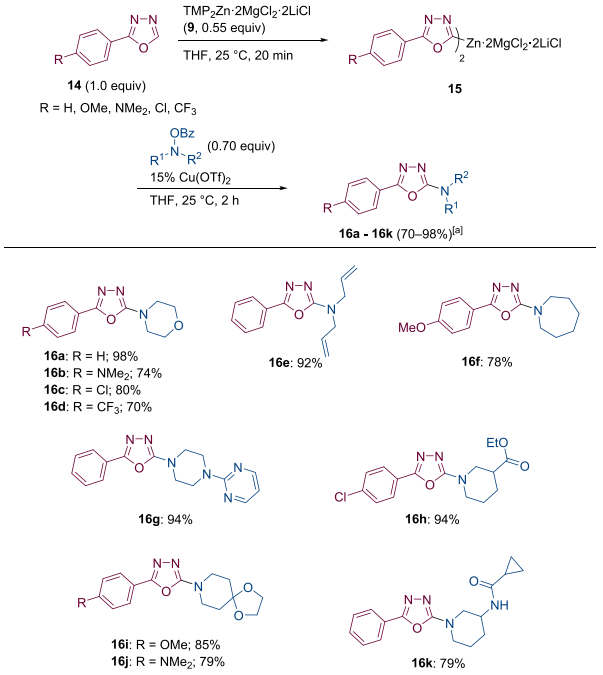
Scheme 2. Zincation of 1,3,4-Oxadiazole (11) Using $TMP_2Zn{\cdot}2LiCl$ (6) Followed by Negishi Coupling Leading to Monosubstituted 1,3,4-Oxadiazoles of Type 14



[a]Isolated yields of analytically pure product. [b]Using 7.5% $Pd(PPh_3)_4$ at 50 °C.

With the monosubstituted 1,3,4-oxadiazoles of type **14** in hand, we performed a second metalation using the freshly prepared base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**9**),[10] resulting in a complete zincation within 20 min at 25 °C (Scheme 3). The zincated heterocycles **15** were then aminated at 25 °C using hydroxylamino benzoates[15a,b] in the presence of 15% $Cu(OTf)_2$, providing a variety of aminated 1,3,4-oxadiazoles of type **16** in 54−98% yield.[15] This sequence proceeded well with both electron-rich (**16b**, **16f**, **16i**, **16j**) as well as electron-deficient (**16c**, **16d**, **16h**) 1,3,4-oxadiazoles. The scope of hydroxylamino benzoates was also explored, including reagents derived from morpholine, diallyl amine, azepane, and piperazine, leading to the products **16a**−**16g** in 70−98% yield. In addition, a variety of amines bearing functional groups such as an ester (**16h**), a protected ketone (**16i**−**16j**), or an amide (**16k**) could be prepared in 79−94% yield.

Scheme 3. Zincation of Monosubstituted 1,3,4-Oxadiazoles of Type 14 Using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (9) Followed by Electrophilic Amination Leading to Aminated 1,3,4-Oxadiazoles of Type 16



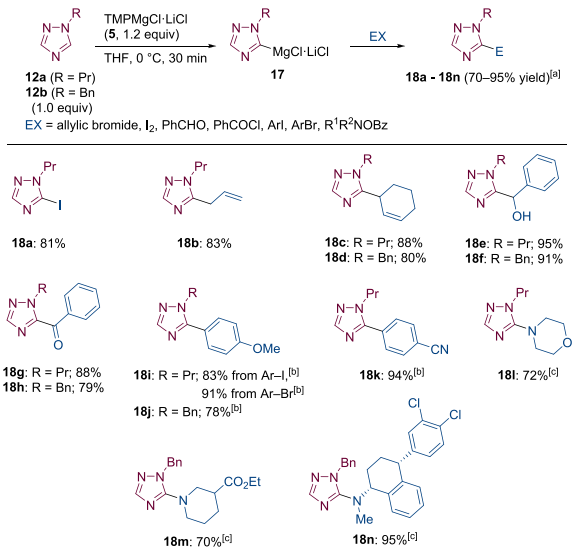
[a]Isolated yields of analytically pure product.

In the case of *N*-propyl and *N*-benzyl 1,2,4-triazoles (**12a,b**), complete magnesiation was achieved within 30 min at 0 °C using TMPMgCl·LiCl (**5**) (Scheme 4). The resulting magnesiated triazoles of type **17** were trapped with a variety of electrophiles such as iodine, allylic bromides, benzaldehyde, and benzoyl chloride, providing the 5-substituted 1,2,4-triazoles **18a**−**18h** in 79−95% yield. In addition, a metalation with TMPZnCl·LiCl (**7**) under the same conditions enabled Pd-catalyzed *Negishi* cross-couplings with both electron-rich (**18i**−**18j**) as well as electron-poor aryl halides (**18k**) in 78−94% yield. Finally, zincation followed by copper-catalyzed electrophilic amination with hydroxylamino benzoates derived from morpholine, nipecotic acid, and sertraline[16] led to the 5-aminated 1,2,4-triazoles **18l**, **18m**, and **18n** in 70−95% yield.

To prepare fully functionalized 1,2,4-triazoles of type **19**, two approaches have been developed (Scheme 5). On one hand, a double magnesiation of *N*-propyl 1,2,4-triazole (**12a**) was achieved by using an excess of TMPMgCl·LiCl (**7**, 4.0

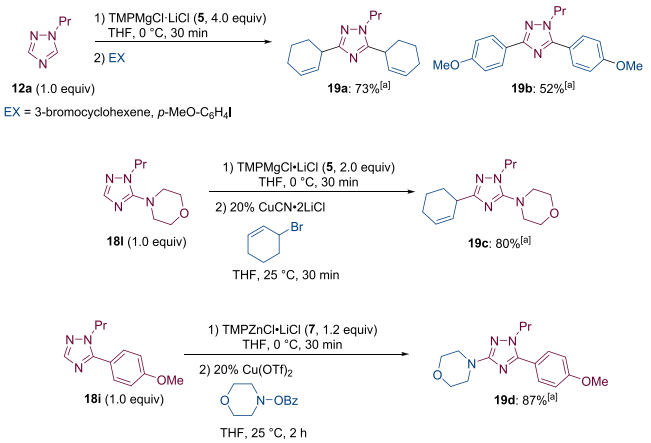
https://dx.doi.org/10.1021/acs.orglett.0c00238
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Metalation of N-Substituted 1,2,4-Triazoles of Type 12 Using TMPMgCl$_2$·LiCl (5) Followed by Electrophile Trapping Leading to Functionalized 1,2,4-Triazoles of Type 18



[a]Isolated yields of analytically pure product. [b]Zincation using TMPZnCl·LiCl (7) and subsequent cross-coupling catalyzed with 5% Pd(OAc)$_2$ and 10% SPhos. [c]Zincation using TMPZnCl·LiCl (7) and subsequent amination catalyzed with 15% Cu(OTf)$_2$.

Scheme 5. Double Functionalization of *N*-Propyl 1,2,4-Triazole (12a) Leading to Fully Functionalized 1,2,4-Triazoles of Type 19

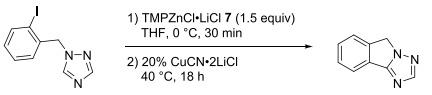


[a]Isolated yields of analytically pure product.

equiv, 0 °C, 30 min). Subsequent trapping with cyclohexyl bromide provided the double allylated triazole **19a** in 73% yield. Also, transmetalation to zinc followed by a *Negishi* cross-coupling with 4-iodoanisole led to the formation of the double arylated triazole **19b** in 52% yield. On the other hand, a second metalation of monosubstituted 1,2,4-triazoles of type **18** could be achieved using TMPMgCl·LiCl (**5**, 2.0 equiv, 0 °C, 30 min) or TMPZnCl·LiCl (**7**, 1.2 equiv, 0 °C, 30 min). This procedure was used to allylate the 3-amino triazole **18l** as well as to aminate the 3-anisyl triazole **18i**, giving access to the fully functionalized triazoles **19c** and **19d** in 80% and 87% yield.

Using the *N*-2-iodobenzyl-protected 1,2,4-triazole **12c**, a copper-catalyzed cyclization was performed after a zincation with TMPZnCl·LiCl (**7**, 1.5 equiv, 0 °C, 30 min, Scheme 6). The cyclization was completed after 18 h at 40 °C and afforded 5*H*-[1,2,4]triazolo[5,1-*a*]isoindole[17] (**20**) in 94% yield.

Scheme 6. Copper-Catalyzed Cyclization of a Zincated 1,2,4-Triazole



In summary, we achieved the full functionalization of both 1,3,4-oxadiazole (**11**) as well as 1,2,4-triazoles (**12**) utilizing the sterically hindered TMP-magnesium and TMP-zinc bases TMP$_2$Zn·2LiCl (**8**), TMP$_2$Zn·2MgCl$_2$·2LiCl (**9**), TMPMgCl·LiCl (**5**), and TMPZnCl·LiCl (**7**). The metalations were achieved under mild conditions (0 or 25 °C) in THF, and the subsequent trappings with various electrophiles, including electrophilic amination reagents, gave access to substituted heterocycles while tolerating many functional groups. Further extensions are currently explored in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00238.

Additional screening data, experimental procedures, and compound characterization data, including copies of ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Paul Knochel − *Department Chemie, Ludwig-Maximilians-Universität München, 81377 München, Germany;* orcid.org/0000-0001-7913-4332; Email: paul.knochel@cup.uni-muenchen.de

Authors

Kuno Schwärzer − *Department Chemie, Ludwig-Maximilians-Universität München, 81377 München, Germany*

Carl Phillip Tüllmann − *Department Chemie, Ludwig-Maximilians-Universität München, 81377 München, Germany*

Simon Graßl − *Department Chemie, Ludwig-Maximilians-Universität München, 81377 München, Germany*

Bartosz Górski − *Faculty of Chemistry, University of Warsaw, 02-093 Warsaw, Poland*

Cara E. Brocklehurst − *Global Discovery Chemistry, Novartis Institutes for BioMedical Research, 4057 Basel, Switzerland;* orcid.org/0000-0002-0484-5540

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00238

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the LMU Munich and the DFG for financial support. We thank Albemarle (Hoechst, Germany) for the generous gift

https://dx.doi.org/10.1021/acs.orglett.0c00238
Org. Lett. XXXX, XXX, XXX−XXX

of chemicals. Bartosz Górski thanks the Erasmus+ program of the European Union for financial support.

REFERENCES

(1) (a) Khalilullah, H.; Ahsan, M. J.; Hedaitullah, M.; Khan, S.; Ahmed, B. *Mini-Rev. Med. Chem.* **2012**, *12*, 789. (b) Kharb, R.; Sharma, P. C.; Yar, M. S. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 1.
(2) Summa, V.; Petrocchi, A.; Bonelli, F.; Crescenzi, B.; Donghi, M.; Ferrara, M.; Fiore, F.; Gardelli, C.; Paz, O. G.; Hazuda, D. J.; Jones, P.; Kinzel, O.; Laufer, R.; Monteagudo, E.; Muraglia, E.; Nizi, E.; Orvieto, F.; Pace, P.; Pescatore, G.; Scarpelli, R.; Stillmock, K.; Witmer, M. V.; Rowley, M. *J. Med. Chem.* **2008**, *51*, 5843.
(3) Dorr, P.; Westby, M.; Dobbs, S.; Griffin, P.; Irvine, B.; Macartney, M.; Mori, J.; Rickett, G.; Smith-Burchnell, C.; Napier, C.; Webster, R.; Armour, D.; Price, D.; Stammen, B.; Wood, A.; Perros, M. *Antimicrob. Agents Chemother.* **2005**, *49*, 4721.
(4) Heinz, U.; Hegetschweiler, K.; Acklin, P.; Faller, B.; Lattmann, R.; Schnebli, H. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 2568.
(5) Hester, J. B.; Rudzik, A. D.; Kamdar, B. V. *J. Med. Chem.* **1971**, *14*, 1078.
(6) (a) Hughes, G.; Bryce, M. R. *J. Mater. Chem.* **2005**, *15*, 94. (b) Han, J. *J. Mater. Chem. C* **2013**, *1*, 7779. (c) Sasabe, H.; Kido, J. *Chem. Mater.* **2011**, *23*, 621.
(7) (a) Jakopin, Ž.; Dolenc, M. S. *Curr. Org. Chem.* **2008**, *12*, 850. (b) Moulin, A.; Bibian, M.; Blayo, A.-L.; El Habnouni, S.; Martinez, J.; Fehrentz, J.-A. *Chem. Rev.* **2010**, *110*, 1809.
(8) (a) Micetich, R. G.; Spevak, P.; Hall, T. W.; Bains, B. K. *Heterocycles* **1985**, *23*, 1645. (b) Ohta, S.; Kawasaki, I.; Fukuno, A.; Yamashita, M.; Tada, T.; Kawabata, T. *Chem. Pharm. Bull.* **1993**, *41*, 1226.
(9) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. (c) Wunderlich, S. H.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7685. (d) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837. (e) Stathakis, C. I.; Bernhardt, S.; Quint, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9428. (f) Stathakis, C. I.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2013**, *15*, 1302.
(10) The base was prepared according to the procedure detailed in the Supporting Information and used within 3 h. A longer storage of the base reduces the yields significantly.
(11) For a detailed description of the preliminary studies, see the Supporting Information.
(12) King, A. O.; Okukado, N.; Negishi, E.-I. *J. Chem. Soc., Chem. Commun.* **1977**, *19*, 683.
(13) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.
(14) Friesen, R. W.; Allouche, E. M. D. *e-EROS Encyclopedia of Reagents in Organic Synthesis*; Wiley: Hoboken, NJ, 2017; p 1.
(15) (a) Graßl, S.; Chen, Y.-H.; Hamze, C.; Tüllmann, C. P.; Knochel, P. *Org. Lett.* **2019**, *21*, 494. (b) Chen, Y.-H.; Graßl, S.; Knochel, P. *Angew. Chem., Int. Ed.* **2018**, *57*, 1108. Chen, Y.-H. *Angew. Chem.* **2018**, *130*, 1120. (c) McDonald, S. L.; Hendrick, C. E.; Wang, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 4667. (d) Bouarfa, S.; Graßl, S.; Ivanova, M.; Langlais, T.; Bentabed-Ababsa, G.; Lassagne, F.; Erb, W.; Roisnel, T.; Dorcet, V.; Knochel, P.; Mongin, F. *Eur. J. Org. Chem.* **2019**, *2019*, 3244.
(16) Koe, B. K.; Weissmann, A.; Welch, W. M.; Browne, R. G. *Psychopharmacol. Bull.* **1983**, *19*, 687.
(17) Barbero, N.; SanMartin, R.; Domínguez, E. *Org. Biomol. Chem.* **2010**, *8*, 841.

https://dx.doi.org/10.1021/acs.orglett.0c00238
Org. Lett. XXXX, XXX, XXX−XXX