ORGANIC LETTERS

2013
Vol. 15, No. 24
6162–6165

Regioselective Functionalization of the Oxazole Scaffold Using TMP-Bases of Mg and Zn

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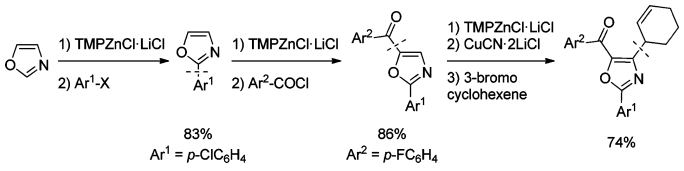
Received October 21, 2013

ABSTRACT



A general method for the synthesis of 2,4,5-trisubstituted oxazoles has been developed. Starting from commercially available oxazole, successive metalations using TMPMgCl·LiCl or TMPZnCl·LiCl led to the corresponding magnesiated or zincated species which were stable toward ring fragmentation. Furthermore, they readily reacted with various electrophiles, such as aryl and allylic halides, acid chlorides, TMSCl, and TMS-CN, providing highly functionalized oxazoles.

The synthesis of oxazoles is an important task in organic chemistry since these heterocycles are present in many biologically active compounds such as alkaloids, analgesics, antibiotics, and anticancers.[1] In addition, oxazoles are frequently utilized as building blocks in modern materials.[2] To date, the preparation of highly functionalized oxazoles involves condensation reactions such as the Robinson–Gabriel synthesis.[3] However, these methods have some limitations, such as poor regioselectivity in the ring construction, multistep syntheses for the starting materials, and harsh reaction conditions. C–H arylation is another approach to functionalize oxazoles. This method shows great potential, and its scope is constantly increasing.[4]

These difficulties have been addressed by the development of alternative methods, in particular metalations of the oxazole scaffold. Indeed, there are many reports of successful lithiations of oxazoles at position 2.[5] However, the direct functionalization of these heterocycles by lithiation is difficult due to side reactions such as ring fragmentation.[6] Although a few lithiation reactions of positions 5 and 4 have been reported,[7] these metalations require very low reaction temperatures and prefunctionalized starting

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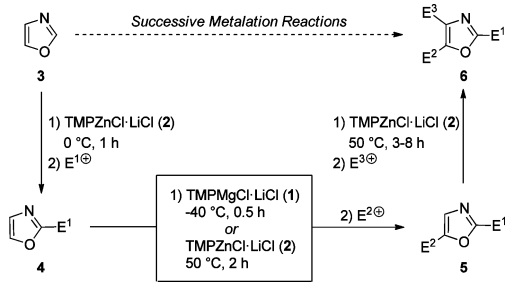
10.1021/ol403019c
Published on Web 11/18/2013

materials and do not allow the use of oxazole derivatives containing sensitive functional groups. Recently, we have reported a set of novel sterically hindered TMP-bases (TMP = 2,2,6,6-tetramethylpiperidyl) complexed by LiCl.[8] TMPMgCl·LiCl (**1**)[9] and TMPZnCl·LiCl (**2**)[10] have proven to be especially efficient for a broad range of metalations particularly for sensitive heterocycles.

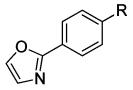
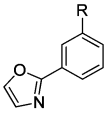
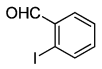
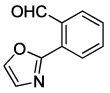
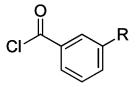
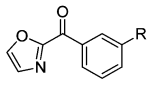
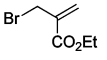
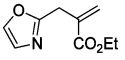
Herein, we report the full functionalization of oxazole (**3**) using successive metalations with TMP-bases **1** and **2** (Scheme 1).

Scheme 1. Successive Metalations of Oxazole (**3**) at Positions 2, 5, and 4 Using TMPMgCl·LiCl (**1**) and TMPZnCl·LiCl (**2**)



Thus, treatment of oxazole (**3**) with TMPZnCl·LiCl (**2**; 1.4 equiv, 0 °C, 1 h)[10] leads to the quantitative formation of the corresponding 2-oxazolylzinc reagent which successfully undergoes Negishi cross-couplings[11] using Farina's ligand ((*o*-furyl)$_3$P)[12] with various *ortho*-, *meta*- or *para*-substituted aryl iodides, as well as an aryl bromide furnishing the desired cross-coupling products **4a**–**h** in 74–94% yield (Table 1, entries 1–8). The 2-oxazolylzinc reagent also reacts well in Pd-catalyzed Negishi acylation reactions[13] with benzoyl chloride and 3-chlorobenzoyl chloride, providing the ketones **4i** and **4j** in 73–86% yield (entries 9 and 10). The 2-zincated oxazole also reacts after transmetalation with CuCN·2LiCl[14] in a copper(I)-mediated allylation reaction with ethyl 2-(bromomethyl)acrylate[15] to furnish the allylated oxazole **4k** in 78% yield (entry 11).

Table 1. 2-Substituted Oxazoles of Type **4** Obtained by Regioselective Zincation of Oxazole (**3**) Using TMPZnCl·LiCl (**2**) and Quenching with Electrophiles

entry	electrophile	product, yield[a]
		
1	R = CO_2Et	**4a**, 92%[a] (80%)[c]
2	R = Cl	**4b**, 83%[b]
3	R = CF_3	**4c**, 74%[b]
4	R = OMe	**4d**, 90%[b]
5	R = CN	**4e**, 87%[b]
		
6	R = NO_2	**4f**, 94%[b]
7	R = CN	**4g**, 82%[b]
8		 **4h**, 79%[b]
		
9	R = H	**4i**, 73%[d]
10	R = Cl	**4j**, 86%[d]
11		 **4k**, 78%[e]

[a] Isolated yield of analytically pure product. [b] Pd-catalyzed cross-coupling using 3 mol % Pd(dba)$_2$ and 6 mol % P(*o*-furyl)$_3$. [c] The aryl bromide was used as an electrophile for Pd-catalyzed cross-coupling using 4 mol % Pd(PPh$_3$)$_4$. [d] Pd-catalyzed acylation reaction using 4 mol % Pd(PPh$_3$)$_4$. [e] CuCN·2LiCl was used for the reaction with this electrophile.

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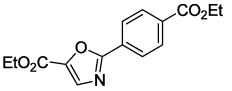
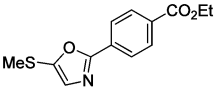
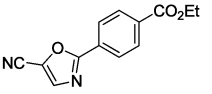
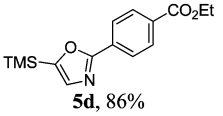
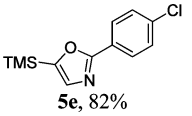
(15) Villieras, J.; Rambaud, M. *Synthesis* **1982**, 924.

A second metalation of the 2-substituted oxazoles of type **4** occurs at position 5 and is readily achieved by adding either TMPMgCl·LiCl (**1**)[9] or TMPZnCl·LiCl (**2**).[10] Thus, treatment of the 2-arylated oxazoles **4a** and **4b** with TMPMgCl·LiCl (**1**; 1.4 equiv, −40 °C, 0.5 h)[9] leads to the quantitative formation of the 5-magnesiated oxazole. These oxazolylmagnesium reagents readily react with various electrophiles, such as NC−CO_2Et, $MeSO_2SMe$,[16] TsCN, or TMSCl to provide the 2,5-disubstituted oxazoles **5a**−**e** in 72−93% yield (Table 2).[17]

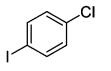
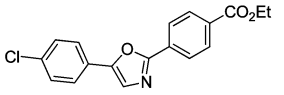
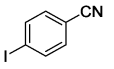
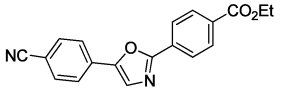
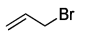
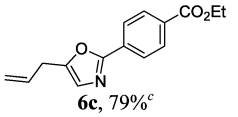
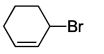
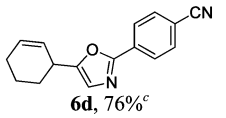
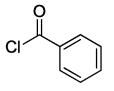
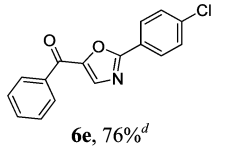
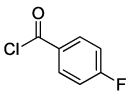
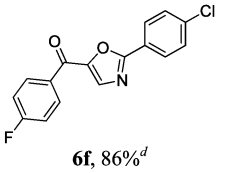
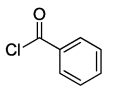
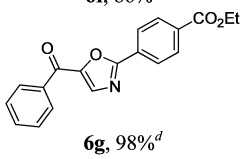
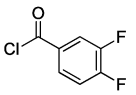
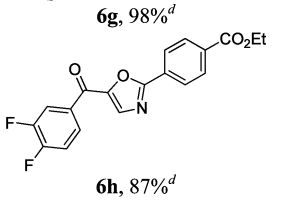
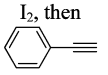
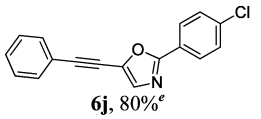
Table 2. 2,5-Disubstituted Oxazoles of Type **5** Obtained by Regioselective Magnesiation of Oxazole Derivatives of Type **4** Using TMPMgCl·LiCl (**1**) and Quenching with Electrophiles

entry	substrate	electrophile	product, yield[a]
1	**4a**	NC-CO_2Et	 **5a**, 93%
2	**4a**	$MeSO_2SMe$	 **5b**, 72%
3	**4a**	TsCN	 **5c**, 89%
4	**4a**	TMSCl	 **5d**, 86%
5	**4b**	TMSCl	 **5e**, 82%

[a] Isolated yield of analytically pure product.

Alternatively, the 5-zincated species can be prepared by reacting 2-substituted oxazoles of type **4** with TMPZnCl·LiCl (**2**; 1.4 equiv, 50 °C, 2 h).[10] The zinc derivative of **4a** is then subjected to Negishi cross-couplings with 1-chloro-4-iodobenzene or 4-iodobenzonitrile to provide the bis-arylated oxazoles **6a** and **6b** in 83−92% yield (Table 3, entries 1 and 2). After zincation of **4a** and **4e** and transmetalation with CuCN·2LiCl, a copper(I)-mediated allylation with allyl bromide or 3-bromocyclohexene leads to oxazoles **6c** and **6d** in 76−79% yield (entries 3 and 4). Pd-catalyzed acylation with benzoyl chloride, 4-fluorobenzoyl chloride, or 3,4-difluorobenzoyl chloride provides the oxazolyl ketones **6e**−**h** in 76−98% yield. Furthermore, after zincation and reaction with iodine, the 2-substituted oxazole **4b** undergoes a regioselective Sonogashira reaction[18] *in situ* with phenylacetylene in the presence of 3 mol %

Table 3. 2,5-Disubstituted Oxazoles of Type **5** Obtained by Regioselective Zincation of Oxazole Derivatives of Type **4** Using TMPZnCl·LiCl (**2**) and Quenching with Electrophiles

entry	substrate	electrophile	product, yield[a]
1	**4a**		 **6a**, 92%[b]
2	**4a**		 **6b**, 83%[b]
3	**4a**		 **6c**, 79%[c]
4	**4e**		 **6d**, 76%[c]
5	**4b**		 **6e**, 76%[d]
6	**4b**		 **6f**, 86%[d]
7	**4a**		 **6g**, 98%[d]
8	**4a**		 **6h**, 87%[d]
9	**4b**	I_2, then 	 **6j**, 80%[e]

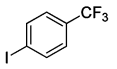
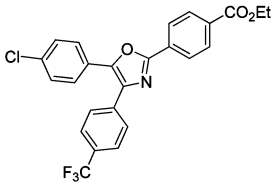
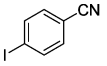
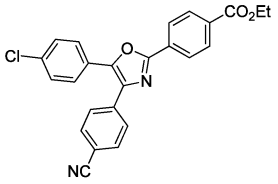
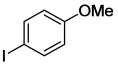
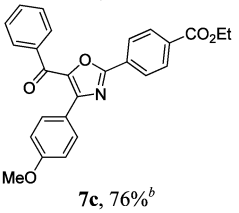
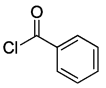
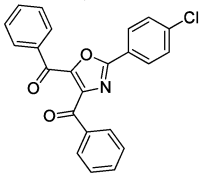
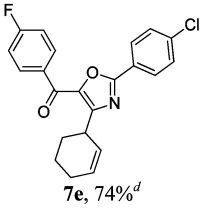
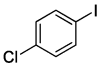
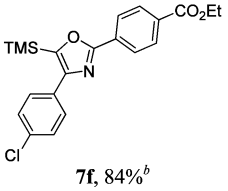
[a] Isolated yield of analytically pure product. [b] Pd-catalyzed cross-coupling using 3 mol % $Pd(dba)_2$ and 6 mol % P(*o*-furyl)$_3$. [c] CuCN·2LiCl was used for the reaction with these electrophiles. [d] Pd-catalyzed acylation reaction using 4 mol % $Pd(PPh_3)_4$. [e] Pd-catalyzed cross-coupling using 3 mol % $Pd(dba)_2$ and 6 mol % P(*o*-furyl)$_3$, 4 mol % CuI, and NEt_3.

(16) The thiomethyl group can be subjected to cross-coupling reactions; see: Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979.

(17) The regioselectivity of 2-substituted oxazole functionalization is supported by the X-ray data of compound **5c** (see Supporting Information).

(18) (a) Sonogashira, K.; Tohda, Y. M.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (c) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (d) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084. (e) Sonogashira, K. In *Metal-catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998.

Table 4. 2,4,5-Trisubstituted Oxazoles of Type **7** Obtained by Regioselective Zincation of Oxazole Derivatives of Type **5** or **6** Using TMPZnCl·LiCl (**2**) and Quenching with Electrophiles

entry	substrate	electrophile	product, yield[a]
1	**6a**		 **7a**, 82%[b]
2	**6a**		 **7b**, 73%[b]
3	**6f**		 **7c**, 76%[b]
4	**6e**		 **7d**, 78%[c]
5	**6h**		 **7e**, 74%[d]
6	**5d**		 **7f**, 84%[b]

[a] Isolated yield of analytically pure product. [b] Pd-catalyzed cross-coupling using 3 mol % $Pd(dba)_2$ and 6 mol % P(*o*-furyl)$_3$. [c] Pd-catalyzed acylation reaction using 4 mol % $Pd(PPh_3)_4$. [d] CuCN·2LiCl was used for the reaction with this electrophile.

$Pd(dba)_2$, 6 mol % P(*o*-furyl)$_3$, 4 mol % CuI, and Et_3N to afford the 2,5-disubstituted oxazole **6j** in 80% yield. Remarkably, the metalation of 2-substituted oxazole derivatives with TMPZnCl·LiCl can be performed at 50 °C, whereas the use of TMPMgCl·LiCl requires more accurate temperature control (reaction temperature should be −40 °C).

The prepared 2,5-disubstituted oxazoles of type **6** and **5** can be further regioselectively metalated at position 4 using TMPZnCl·LiCl (**2**; 1.4 equiv, 50 °C, 3−8 h)[9] to afford the expected 4-zincated species. These zincated polyfunctional oxazoles undergo Negishi cross-couplings, Pd-catalyzed acylation reactions, or copper(I)-mediated allylations. Thus, after the zincation of the 2,5-substituted oxazole **6a**, Negishi cross-couplings were performed with various aryl iodides, such as 1-iodo-4-(trifluoromethyl)benzene and 4-iodobenzonitrile, furnishing the desired 2,4,5-arylated oxazoles **7a** and **7b** in 73−82% yield (Table 4, entries 1 and 2). Similarly, the keto-substituted oxazole **6f** is an excellent substrate for a Negishi cross-coupling reaction with 4-iodoanisole and provides the desired trisubstituted oxazole **7c** in 76% yield. Furthermore, the 5-acylated oxazole **6e** undergoes a Pd-catalyzed Negishi acylation with benzoyl chloride, providing the trisubstituted oxazole **7d** in 78% yield (entry 4). Also, the allylation of the zincated oxazole derived from **6h** with 3-bromocyclohexene in the presence of CuCN·2LiCl leads to the expected trisubstituted oxazole **7e** in 74% (entry 5). Finally, the oxazole **5d** is arylated by our standard procedure with 1-chloro-4-iodobenzene, furnishing the 5-silyloxazole **7f** in 84% yield.[19]

In conclusion, we have developed a new general method for performing multiple regioselective metalations of oxazole (**3**) *via* successive reactions using TMPMgCl·LiCl (**1**) or TMPZnCl·LiCl (**2**) leading to a variety of new functionalized oxazole derivatives with the regiocontrolled introduction of all substituents. Further extension of this method toward the synthesis of biologically active oxazoles is currently underway in our laboratory.

Acknowledgment. The research leading to these results has received funding from the European Research Council under the European Community's Seventh Framework Programme (FP7/2007−2013) ERC Grant Agreement No. 227763. We thank the Fonds der Chemischen Industrie for financial support, as well as Heraeus Holding GmbH (Hanau), Rockwood Lithium (Frankfurt), and BASF SE (Ludwigshafen) for the generous gift of chemicals. We also thank Prof. Dr. Konstantin Karaghiosoff for the X-ray analysis.

Supporting Information Available. Experimental details and full spectroscopic data for all new compounds is given in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) For removal of the TMS-group on heterocycles, see: Dunst, C.; Knochel, P. *J. Org. Chem.* **2011**, *76*, 6972.

The authors declare no competing financial interest.