Metal-Free Phosphorylations of 1,3,4-Oxadiazoles and Related Heterocycles

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Abstract: 1,3,4-Oxadiazoles have been phosphorylated at C5 in yields of >90% under mild metal-free reactions conditions using triethylamine as base. Other azoles undergo analogous phosphorylations albeit in lower yields.

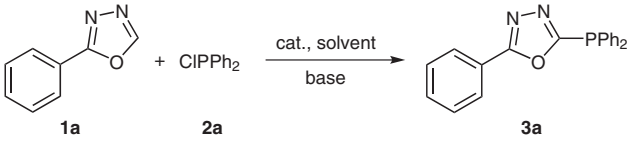
Key words: 1,3-azole, base-promoted, metal-free substitution, 1,3,4-oxadiazole, phosphorylation

1,3,4-Oxadiazoles are relevant core structures in medicinal chemistry[1] and material sciences.[2] Recently, transition-metal catalysis has been used for advanced CH-functionalizations of such key heterocycles.[3] For example, Miura and co-workers established nickel-catalyzed alkenylations and -alkylations of 1,3,4-oxadiazoles with alkynes and styrenes, respectively, which allow selective cross-couplings at C5.[4] Other mostly copper-based catalyses allowed related site-selective transformations such as alkynylations,[5a–c] arylations,[5d] benzylations,[5e] aminations,[5f–h] and homocouplings.[5i] In collaboration with Miura and co-workers we reported copper-catalyzed direct dehydrogenative sulfoximinations of azoles including 1,3,4-oxadiazole derivatives.[6]

An alternative route to C5-functionalized 1,3,4-oxadiazoles is the base-mediated electrophilic substitution, which, for example, was utilized by Zarudnitskii et al. for the preparation of silylated derivatives.[7] When applied in a 1:1 mixture of pyridine and toluene, triethylamine proved sufficiently basic for the deprotonation leading to 5-substituted derivatives upon treatment with trimethylsilyl bromide in good to excellent yields.[7,8]

Aryl phosphines are ubiqueous ligands in metal catalysis.[9] Modifying the aryl group can have a major impact on the catalytic performance. Commonly, azole-derived phosphines are prepared starting from the parent heterocycles by deprotonation–phosphorylation sequences, and in most cases strong bases such as *n*-BuLi in the presence or absence of TMEDA are applied for the first step.[10] On the basis of the findings by Zarudnitskii et al. on the silylation reactions of 1,3,4-oxadiazoles mentioned above,[6] we wondered if also phosphorylations of such heterocycles could be performed under those comparably mild reaction conditions. This assumption was supported by a brief report by Tolmachev et al. (lacking details of yield and full product characterization), which included two examples of 1,3,4-oxadiazole phosphorylations with chloro diphenylphosphine and triethylamine as base. With the goal to evaluate the opportunities offered by the ease of this azole functionalization, we decided to optimize the reaction conditions and to expand the substrate scope. The results are reported here.

As starting point the phosphorylation of 2-phenyl-1,3,4-oxadiazole (**1a**) with chloro diphenylphosphine (**2**) under basic conditions to give 1,3,4-oxadiazole **3a** was chosen (Scheme 1).



Scheme 1 Phosphorylation of 2-phenyl 1,3,4-oxadiazole (**1a**)

Using a 1:1 ratio of starting materials **1a** and **2a** (1 mmol scale), one equivalent of triethylamine, and pyridine as solvent, 1,3,4-oxadiazole **3a** was obtained in a yield of 40% after stirring the reaction mixture at 25 °C for 24 hours. Raising the temperature to 40 °C increased the yield of **3a** to 51%. Neither the addition of $Ni(COD)_2$ (0.05 equiv), as suggested by the chemistry of Miura and co-workers,[4] nor the presence of $PdCl_2$ in solvents such as toluene, THF, pyridine, and dichloromethane (CH_2Cl_2) led to significant improvements. Among those experiments the combination of $Ni(COD)_2$, Et_3N, and CH_2Cl_2 proved best providing **3a** in 76% yield. The attempt to use DMSO as solvent [in the presence of $Ni(COD)_2$ and Et_3N] was unsuccessful, and **3a** was not obtained at all. Also inorganic bases such as Cs_2CO_3 and K_3PO_4 instead of Et_3N could not be used. Major advances in the metal-free version of the reaction were achieved by changing the solvent from pyridine to CH_2Cl_2 and by varying the reagent ratios. Under the initial conditions (ratio of 1:1:1 for **1a**/**2a**/Et_3N) product **3a** was obtained in 75% when the reaction was performed in CH_2Cl_2 instead of pyridine. With a slight excess of **1a** (1.2 equiv) and two equivalents of base (in CH_2Cl_2) the yield raised to 82%. Finally, 90% of **3a** was obtained (after 48 h at 40 °C in CH_2Cl_2) when the chlorophosphine (**2**) and the base (Et_3N) were used in a twofold excess with respect to azole **1a** (Table 1, entry 1).

The evaluation of the substrate scope starting from functionalized 2-aryl 1,3,4-oxadiazoles (**1**) and chlorophosphine (**2a**, Table 1, entries 1–8) led to very satisfying results.[12] The yields of the corresponding 5-phosphorylated azoles ranged from 68–91% (for 2-dimethylamino- and 4-chloro-substituted derivatives **3f** and **3g**, respectively).

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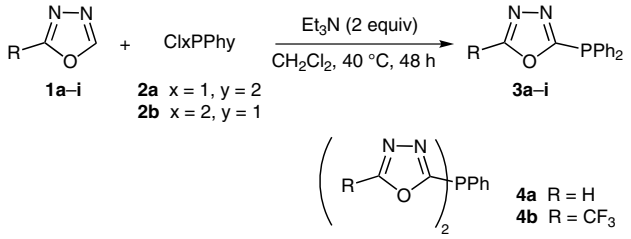
Steric and electronic factors on the arene group of the azole appeared to play only a minor role (if any). Also 2-benzyl-substituted 1,3,4-oxadiazole **1i** reacted well providing 5-phosphorylated product **3i** in 80% yield (Table 1, entry 9).

Table 1 Substrate Scope of the Metal-Free Phosphorylation of Azole Derivatives[a]



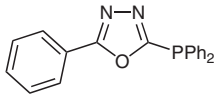
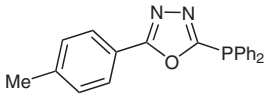
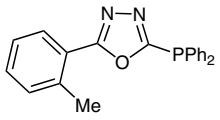
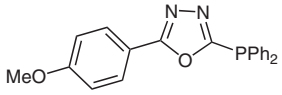
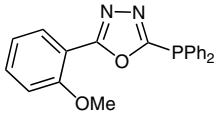
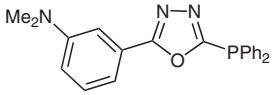
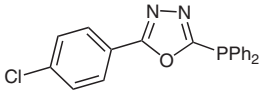
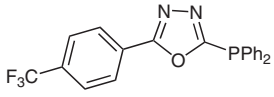
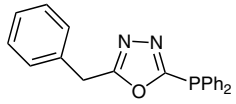
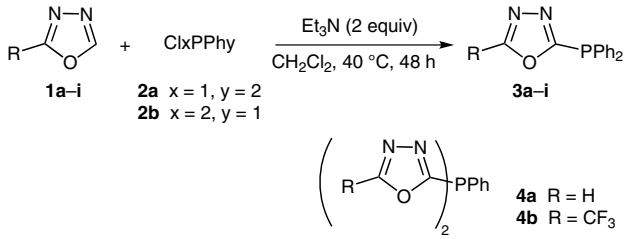
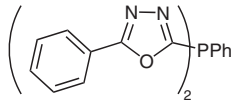
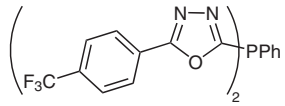
Entry	Substrate	R =	Product	Yield (%)
1	**1a**	Ph	 **3a**	90
2	**1b**	4-Tol	 **3b**	86
3	**1c**	2-Tol	 **3c**	89
4	**1d**	4-$MeOC_6H_4$	 **3d**	75
5	**1e**	2-$MeOC_6H_4$	 **3e**	74
6	**1f**	3-$Me_2NC_6H_4$	 **3f**	68
7	**1g**	4-ClC_6H_4	 **3g**	91
8	**1h**	4-$F_3CC_6H_4$	 **3h**	83
9	**1i**	Bn	 **3i**	80

Table 1 Substrate Scope of the Metal-Free Phosphorylation of Azole Derivatives[a] (continued)



Entry	Substrate	R =	Product	Yield (%)
10[b]	**1a**	Ph	 **4a**	68 (70)[c]
11[b]	**1h**	4-$F_3CC_6H_4$	 **4b**	46

[a] Conditions: azole (1.0 mmol), $ClPPh_2$ (2.0 mmol), Et_3N (2 mmol), CH_2Cl_2 (1.5 mL), 40 °C, 48 h.
[b] Use of 3.0 mmol of azole and Cl_2PPh instead of $ClPPh_2$.
[c] In parentheses: result of a 10 mmol scale reaction.

With dichlorophenylphosphine (**2b**) as electrophile and an excess of azole (3 equiv), double phosphine arylations were possible. Two examples are shown in Table 1, entries 10 and 11. In the first transformation involving 2-phenyl 1,3,4-oxadiazole (**1a**), the corresponding product **4a** was obtained in 68% yield. Raising the scale from (the standard) 1 mmol to 10 mmol led to a slight increase in yield (70% of **4a**). Using trifluoromethyl-substituted **1h** as starting material gave **4b** in 46% yield.

Attempts to use other azole derivatives than 1,3,4-oxadiazoles proved the general applicability of the metal-free phosphorylation, but also showed that conversions of benzoxazole (**5**, Figure 1) and *N*-phenyl benzimidazole (**7**) were more difficult. In both cases the yields of the corresponding phosphorylated products, **6** (30%) and **8** (20%), respectively, were only moderate.

In order to examine whether aliphatic phosphine chlorides could be used as well, compound **1a** was reacted with chloro diisopropyl phosphine (**9**) under standard reaction conditions. In this manner, product **10** was obtained in 59% yield.

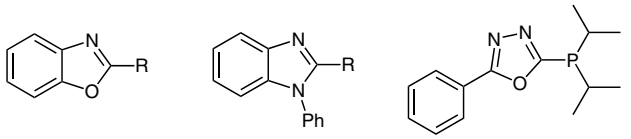


Figure 1 Benzoxazole- and *N*-phenyl benzimidazole based starting materials and products; diisopropylphosphino-substituted 1,3,4-oxadiazole **10**

In conclusion, 2-substituted 1,3,4-oxadiazoles can be phosphorylated at C5 under metal-free conditions. Using triethylamine as base, various new heteroaryl phosphines have been prepared under mild conditions in high yields.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure for the Phosphorylation of Azoles – Examplified by the Synthesis of 2-Phenyl-1,3,4-oxadiazolyldiphenylphosphine (3a)[11]**

In a Schlenk tube filled with argon 2-phenyl-1,3,4-oxadiazole (**1a**, 1 mmol), Et_3N (277 μL, 2 mmol), $ClPPh_2$ (2, 180 μL, 2 mmol), and CH_2Cl_2 (1.5 mL) were added. The mixture was stirred at 40 °C for 48 h. After full conversion of **1a** (as confirmed by TLC), the mixture was filtered through a pad of silica gel, concentrated and purified by silica gel column chromatography providing **3a** in 90% yield. White solid, mp 85.2–86.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96–8.00 (m, 2 H), 7.62–7.55 (m, 4 H), 7.47–7.43 (m, 2 H), 7.42–7.36 (m, 7 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.8 ($^1J_{C–P}$ = 32.6 Hz), 167.0, 134.0 ($^2J_{C–P}$ = 21.1 Hz), 132.0 ($^1J_{C–P}$ = 6.3 Hz), 131.9, 130.2, 129.0 ($^3J_{C–P}$ = 2.3 Hz), 128.9, 127.2, 123.7. ^{31}P NMR (122.0 MHz, $CDCl_3$): δ = –25.0 ppm. MS (EI): *m/z* = 330 [M^+]. HRMS: *m/z* [M^+] calcd for $C_{20}H_{15}ON_2NaP$: 353.0814; found: 353.0813.

