Catalytic Direct Regioselective Synthesis of Phosphonylated Tetrazoles from Aryl Diazonium Salts and Seyferth-Gilbert Reagent

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Supporting Information

ABSTRACT: Here we report a Ag-catalyzed [3 + 2] cycloaddition reaction between aryl diazonium salts and Seyferth-Gilbert reagent in a regioselective manner. This operationally simple transformation proceeds in an atom-economical way under mild reaction conditions, providing facile access to a broad set of phosphonylated tetrazoles. The synthetic utility of this method is further showcased by a straightforward procedure from upstream aromatic amines, denitrogenation transformations, and preparation of a phosphonylated drug scaffold.

Organophosphonates are an important class of chemical entities possessing extensive applications in synthetic chemistry, medical chemistry, and material science. In this context, the Seyferth-Gilbert reagent along with its modified version (Ohira-Bestmann reagent) have been recognized as extremely versatile building blocks in accessing various phosphonylated molecules. In particular, the 1,3-dipolar cycloaddition (DPC) reactions between the diazophosphonates and alkenes or alkynes or imines have enabled efficient synthetic routes to diverse phosphorus-functionalized pyrazolines, pyrazoles, and triazolines. Among them, the direct utilization of Seyferth-Gilbert reagent in DPC reactions has received much less attention compared with Ohira-Bestmann reagent, despite the fact that Seyferth-Gilbert reagent meets the criteria of atom-economic point better. Moreover, to the best of our knowledge, the DPC transformation of any diazophosphonate reagent and arenediazonium dipolarophiles has not yet been reported. Note that the implementation of such transformation would allow straightforward access to tetrazoles, which have been identified as an important type of core azoles in many pharmaceutically relevant small molecules. Recently, our group discovered that aryl diazonium salts can be employed as effective partners in cycloaddition reactions with trifluorodiazoethane or diazoacetates or masked difluorodiazoethane. On the basis of these primary findings, we conceived that a novel class of phosphorylated tetrazoles might be obtained by virtue of the DPC reaction with diazophosphonates and arenediazonium salts. Thus, we now present the development of a regioselective DPC reaction by utilizing Seyferth-Gilbert reagent with a wide array of arenediazonium salts (Scheme 1b). This transformation constitutes the first example of DPC reaction between diazophosphonates and N≡N triple bonds, meanwhile offering rapid access to phosphorylated tetrazoles with high tolerance of functional groups under mild reaction conditions.

Received: October 25, 2019
proved to be indispensable for the progress of this transformation (entries 2 and 3). The change of silver acetate (AgOAc) to a list of other silver salts, or the replacement of Cs2CO3 by a few other potassium bases, has no significant influence on the reaction performance (entries 4–8). In addition, this cycloaddition reaction can undergo well in other solvents such as diethyl ether (Et2O), 2-Me-THF, and 1,4-dioxane (entries 9–11). Moreover, the superiority of employing Seyferth-Gilbert reagent 1a instead of the Ohira-Bestmann reagent was evidenced by the observation that cycloadduct 3a was not detected in the latter case (entry 12).15

Having established the optimal conditions, we then proceeded to probe the generality of this reaction (Scheme 2). Phenyl diazonium salts possessing various electron-donating groups, including alkyl, alkoxyl, and amino motifs, at different locations of the phenyl ring (-para, -meta, and -ortho), underwent cycloaddition and gave corresponding tetr azoles 3b−3k in 54−94% yields. A variety of halogen-substituted products 3l−3u were obtained in practical to good yields, thus offering the possibility for downstream cross-couplings. In addition, substrates bearing strong electron-withdrawing groups (−NO2, −CF3, −Ac, and −CO2Me) are also compatible in this reaction (products 3v−3y). Notably, diazonium salt equipped with an electron-withdrawing alkenyl moiety did not affect the chemo- and regioselective reaction at N=N site, still delivering 3z in practical yield. This reaction platform is also tolerant of (hetero)aromatic systems including 1-naphthyl, 3-thienyl, and 3-quinolyl (products 3aa−3ae). The alteration on phosphate group is accommodated well and provided tetr azole 3ad in 85% yield. Furthermore, phenylalanine-derived diazonium salt underwent the cycloaddition under identical conditions and gave tetr aza cholino acid 3ae in 79% yield, which may offer potential bioorthogonal chemical handles for fluorescent labeling.16 The accurate structures of these phosphorylated tetr azoles are assigned by analogy based on X-ray analysis of compound 3x.15,16

Table 1. Optimization for the DPC Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>base</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AgOAc</td>
<td>Cs2CO3</td>
<td>THF</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>AgNO3</td>
<td>Cs2CO3</td>
<td>THF</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>AgOAc</td>
<td>THF</td>
<td>nr</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>AgBF4</td>
<td>Cs2CO3</td>
<td>THF</td>
<td>89</td>
</tr>
<tr>
<td>5</td>
<td>AgO</td>
<td>Cs2CO3</td>
<td>THF</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>AgOAc</td>
<td>K2CO3</td>
<td>THF</td>
<td>77</td>
</tr>
<tr>
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<td>THF</td>
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<td>8</td>
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<td>K2PO4</td>
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<td>9</td>
<td>AgOAc</td>
<td>Cs2CO3</td>
<td>Et2O</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>AgOAc</td>
<td>Cs2CO3</td>
<td>2-Me-THF</td>
<td>89</td>
</tr>
<tr>
<td>11</td>
<td>AgOAc</td>
<td>Cs2CO3</td>
<td>1.4-dioxane</td>
<td>66</td>
</tr>
<tr>
<td>12</td>
<td>AgOAc</td>
<td>Cs2CO3</td>
<td>THF</td>
<td>0</td>
</tr>
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</table>

“General reaction conditions: To a stirred solution of indicated solvent (3.0 mL) containing 2a (0.5 mmol), the diazo reagent 1a (0.75 mmol), catalyst (0.025 mmol), and base (1.0 mmol) were successively added. The resulting mixture was reacted at 0°C for 10 h unless otherwise noted. Yield of isolated product. "nr" indicates no reaction. "Ohira-Bestmann reagent (1.0 mmol) was employed instead of 1a, and 1.5 mmol of Cs2CO3 was used.

A straightforward procedure directly from commercially available aniline derivatives to phosphorylated tetr azoles is also viable (Scheme 3). Particularly noteworthy is that this convenient one-pot process performed much better than the two-step approach for aromatic amines possessing a free hydroxyl or carboxylic group and gave the corresponding cycloadducts 3ag−3ai in decent to good yield. 3-Amino-pyridine is also tolerated and generated 3-pyridyl tetr azole 3aj in 72% yield. In addition, this silver-catalyzed straightforward procedure is also applicable for structurally complex substrate, thereby furnishing tocopherol derivative 3ak in good yield.

Subsequently, a gram-scale experiment was conducted and afforded compound 3e in a comparable yield of 88% (Scheme 4a). The tetr azole core can undergo photoinduced DPC reaction with different dipolarophiles, as demonstrated by the formation phosphorylated pyrazoline 5 and pyrazole 6 in 83% and 74% yield, respectively (Scheme 4b). Furthermore, by using the newly developed cycloaddition protocol, a phosphorylated analogue of P2X3 receptor antagonist was rapidly prepared from aromatic amine 7 with moderate total yield (Scheme 4c).
In summary, a silver-catalyzed [3 + 2] cycloaddition reaction of Seyferth-Gilbert reagent with arenediazonium salts was realized in a regioselective manner. This protocol represents the first example of rendering N≡N triple bond as feasible dipolarophile in DPC reactions with diazophosphonates. The high tolerance of functional groups, gentle reaction conditions, viable straightforward one-pot procedure from upstream aromatic amines, and denitrogenation transformations further showcased the promising synthetic utility of this method. Mechanistic study, substrate scope expansion, and other relevant applications are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03800.

Experimental details, compound characterization data, and NMR spectra of all the new compounds (PDF)

Accession Codes

CCDC 1958721 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Nos. 21532008, 21772142, and 21901181) and Tianjin Municipal Science & Technology Commission (No. 19JQNJ04700).

REFERENCES


(12) See the Supporting Information for detailed screening results.

(13) This is probably attributed to the difficult generation of corresponding silver-diazo species when Ohira-Bestmann reagent was used as the starting material. For our previous findings, see: Chen, Z.; Ren, N.; Ma, X.; Nie, J.; Zhang, F.-G.; Ma, J.-A. Silver-Catalyzed [3 + 3] Dipolar Cycloaddition of Trifluorodiazoethane and Glycine Imines: Access to Highly Functionalized Trifluoromethyl-Substituted Triazines and Pyridines. ACS Catal. 2019, 9, 4600–4608.


(15) See the Supporting Information for X-ray details under CCDC No. 1958721.

(16) As demonstrated in previous mechanistic studies, the silver-diazo species is speculated to be generated in these silver-mediated cycloaddition reactions. We hypothesized that the regioselectivity could be controlled by the enhanced electron density distribution attributed to the concurrence of electron-withdrawing phosphonate group and silver. However, deep understanding for the excellent regiocontrol is still under investigation via combined experimental and computational methods, the results of which will be disclosed in due course. For relevant refs, see: (a) Jia, F.; Luo, J.; Zhang, B. Using a traceless directing group for the silver-mediated synthesis of 3-trifluoromethylpyrazoles: a computational study on the mechanism and origins of regioselectivity. Org. Chem. Front. 2018, 5, 3374–3381. (b) Ríos-Gutiérrez, M.; Domingo, L. R. Unravelling the Mysteries of the [3 + 2] Cycloaddition Reactions. Eur. J. Org. Chem. 2019, 2019, 267–282.

(17) The deprotection of the phosphonate moiety with compound 3a was performed with TMSBr and gave the free phosphonic acid 3a’ in 70% yield. See the Supporting Information for experimental details.

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