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Manganese(III) Acetate Promoted Regioselective Phosphonation of Heteroaryl Compounds

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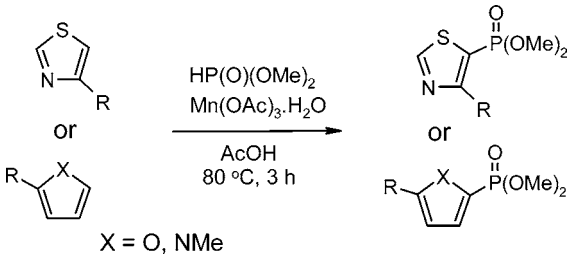
ABSTRACT



A new method for direct phosphonation of thiazoles, furans, and pyrroles is introduced. Reactions of the heteroaryl compounds with dimethyl or diethyl phosphites and $Mn(OAc)_3 \cdot 2H_2O$ under mild conditions give phosphonated products in high yield and good regioselectivity.

Aryl and heteroaryl phosphonates are an important class of compounds, and many of them possess biological activities.[1,2] They have also been widely used as ligands for transition-metal catalysis[2] and as building blocks for nanoarchitectures.[3] There are two general methods for the preparation of aryl carbon−phosphorus bonds: (i) $S_{RN}1$ reactions of aryl halides with Ph_2P^{-}[4] and (ii) metal complex catalyzed Arbuzov-type reactions.[5]

As part of our continuing efforts on the development of Mn(III) acetate based reactions,[6] we recently reported thio radical reactions of thioformanilides to form benzothiazole ring systems (Scheme 1). We have reasoned that Mn(III) acetate promoted phosphonyl radicals could also add to aryl compounds to form phosphonation products. Described in this paper is our effort toward the development of this new methodology for direct phosphonation of heteroaryl compounds using dimethyl or diethyl phosphites and $Mn(OAc)_3 \cdot 2H_2O$ as the coupling agents. While this project was in progress, the Ishii group reported the first example of phosphonation of aryl compounds using $Mn(OAc)_2/Co(OAc)_2/O_2$ as a redox couple.[7]

Scheme 1. Mn(III)-Promoted Thio Radical Cyclization

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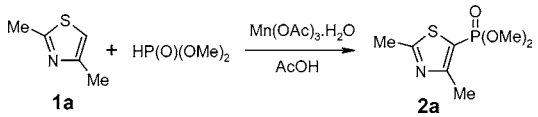
In our initial study, 2,4-dimethylthiazole **1a** was used as a model compound for method development. The reaction was first carried out in acetic acid in the absence of $Mn(OAc)_3{\cdot}2H_2O$. No reaction occurred at 20, 40, and 80 °C (Table 1, entries 1−3). Similar reactions were then attempted

Table 1. Phosphonation of 2,4-Dimethylthiazole



1a **2a**

entry	molar ratio Mn(III)/**1a**	solvent	temp (°C)	yield (%)[a]
1	0:1	AcOH	20	0
2	0:1	AcOH	40	0
3	0:1	AcOH	80	0
4	1:1	AcOH	20	trace
5	2:1	AcOH	20	trace
6	1:1	AcOH	80	22
7	2:1	AcOH	80	55
8	3:1	AcOH	80	92
9	3:1	CH_3CN	reflux	78
10	3:1	MeOH	reflux	67
11	3:1	EtOH	reflux	79
12	3:1	solvent-free	80	76

[a] Isolated yield.

in the presence of 1 or 2 equiv of $Mn(OAc)_3{\cdot}2H_2O$. Only a trace amount of product was detected at 20 °C (Table 1, entries 4 and 5). When the temperature increased to 80 °C, product **2a** was produced in 22% and 55% yields at different ratios of Mn(III) to **1a** (Table 1, entries 6 and 7). Further optimization of reaction conditions by using 3 equiv of $Mn(OAc)_3{\cdot}2H_2O$ obtained 92% yield of **2a** (Table 1, entry 8). In addition to acetic acid, MeCN, MeOH, and EtOH were also tested as the reaction solvents. In these cases, product **2a** was formed in slightly lower yield (Table 1, entries 9−11). We also conducted the reaction under solvent-free conditions. Compound **2a** was produced in 76% yield (Table 1, entry 12).

The optimized procedure for phosphonation of 2,4-dimethylthiazole was found to be as follows: To a solution of dimethyl phosphite (4 mmol) in 10 mL of acetic acid were added 2,4-dimethylthiazole (2 mmol) and $Mn(OAc)_3{\cdot}2H_2O$ (6 mmol). The mixture was then heated at 80 °C, and the reaction was completed in 3 h. The general phosphonation procedure was used for reactions of 2-ethyl-4-methylthiazole **1b** and 2-methyl-4-phenylthiazole **1c.** Corresponding products **2b** and **2c** were produced in 90% and 87% yields, respectively (Table 2, entries 2 and 3). The reaction of 2-methoxythiazole **1d** was carried out to study the regioselectivity. To our surprise, only a single product **2d** was isolated in 90% yield (Table 2, entry 4). Compound **2d** was

(7) Kagayama, T.; Nakano, A.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* **2006**, *8*, 407−409.

Table 2. Phosphonation of Thiazoles

1a-i **2a-i**

R = Me, Et

entry	substrate **1**	product **2**[a]	yield (%)[b]
1	**1a**	**2a**	92
2	**1b**	**2b**	90
3	**1c**	**2c**	87
4	**1d**	**2d**	90
5	**1e**	**2e**	89
6	**1f**	**2f**	88
7	**1g**	**2g**	80
		2g'	9
8	**1h**	**2h**	10
		2h'	78
9	**1i**	**2i**	83

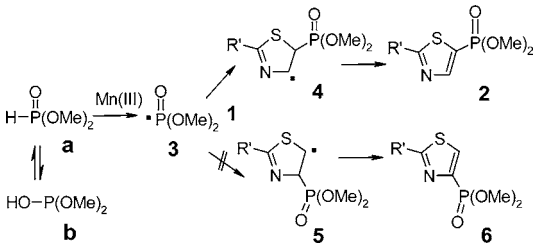
[a] Characterized by NMR and MS. [b] After flash column chromatography.

identified as 2-methoxy-5-dimethylphosphonothiazole on the basis of ^{1}H NMR and HRMS analyses. The aromatic proton at 7.66 ppm is the one at the 4-position of the thiazole. This result suggests that the phosphonation of thiazole is regioselective at the 5-position. Reactions of 2-ethoxythiazole **1e** and 2-acetylthiazole **1f** also afforded single products. The ^{1}H NMR spectra of **2e** and **2f** show the chemical shifts of the aromatic protons at 7.66 and 8.31 ppm, respectively (Table 2, entries 5 and 6).

To have a better understanding of phosphonation regioselectivity, we tested several different thiazoles. The reaction of 4-methylthiazole **1g** produced 5-phosphonation product **2g** as the major product in 80% yield and 2-phosphonation product **2g′** as the minor one in 9% yield (Table 2, entry 7). In the case of thiazole **1h**, the 5- and 2-phosphonation products **2h** and **2h′** were produced in a ratio of 10:78 (Table 2, entry 8). When 4,5-dimethylthiazole **1i** was used as the substrate, the phosphonation performed smoothly to give **2i** in 83% yield (Table 2, entry 9).

A possible mechanism is proposed in Scheme 2 which explains the regioselective phosphonation of thiazoles. Di-

Scheme 2. Proposed Mechanism for Regioselective Phosphonation

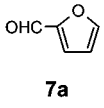
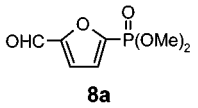
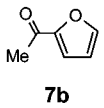
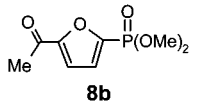
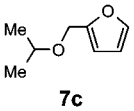
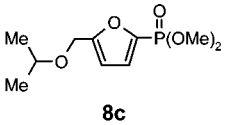
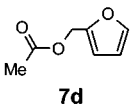
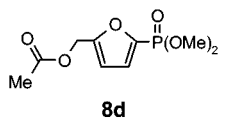
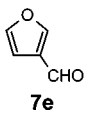
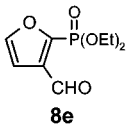
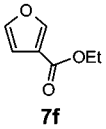
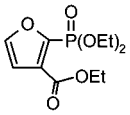
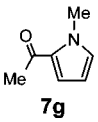
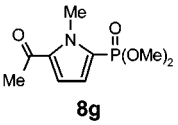


methyl phosphite has tautomeric forms **a** and **b**.[8] The reaction of $Mn(OAc)_3$ with tautomer **a** gives phosphonyl radical **3**. This radical could attack the thiazole ring at the 4- or 5-position. In compound **4**, the radical is next to an imine which is more stable than the radical in compound **5** which is next to a sulfur. Formation of **4** is more favorable which leads to 5-phosphonated thiazole **2** via air or Mn(III) oxidation to regain the aromaticity of the thiazole ring. Results generated from the unsubstituted thiazole (Table 2, entry 8) indicate that the 2-position of thiazole is most reactive for phosphonation, followed by the 5-position. The 4-position is the least reactive site. Interestingly, no double or triple phosphonation products were detected from the reaction of thiazole **1h**.

Other heterocyclic substrates such as furans and pyrroles were employed to study the scope and regioselectivity of the phosphonation reactions. Under the general reaction conditions described above, reaction of 2-formylfuran **7a** produced a single product **8a** in 95% yield (Table 3, entry 1). The regiochemistry of compound **8a** was also established by ^{1}H NMR analysis; two aromatic protons at 7.30−7.27 ppm suggest they are at the 3- and 4-positions. Similarly, using 2-substituted furans **7b**−**d** as starting materials, 5-phosphonation products **8b**−**d** were obtained in 86−89% yields (Table 3, entries 2−4). In comparison with 2-substituted furans, when 3-substituted furans **7e**,**f** reacted with diethyl phosphite, only 2,3-disubstituted furans **8e**,**f** were obtained in 84−89% yields (Table 3, entries 5 and 6). Finally, 1-methyl-2-acetyl pyrrole **7g** was used for the reaction. A single 5-phosphonation product **8g** was isolated in 91% yield (Table 3, entry 7).

(8) Han, L. B.; Tanaka, M. *J. Am. Chem. Soc.* **1996**, *118*, 1571−1572.

Table 3. Phosphonation of Furans and Pyrroles

entry	substrate **7**	product **8**[a]	yield (%)[b]
1	 **7a**	 **8a**	95
2	 **7b**	 **8b**	89
3	 **7c**	 **8c**	87
4	 **7d**	 **8d**	86
5	 **7e**	 **8e**	84
6	 **7f**	 **8f**	89
7	 **7g**	 **8g**	91

[a] Characterized by NMR and MS. [b] After flash column chromatography.

In summary, independent from the first example of direct phosphonation of aryl compounds reported by the Ishii group, we have developed a simple yet highly efficient method for phosphonation of heteroaryl compounds including thiazole, furan, and pyrrole derivatives. The reactions are performed under mild conditions using dimethyl or diethyl phosphites and $Mn(OAc)_3{\cdot}2H_2O$ as the reagents. Our protocol has demonstrated broad synthetic scope, and more importantly, the phosphonation process is regioselective.

Acknowledgment. We thank the Key Laboratory of Organic Synthesis of Jiangsu Province and the Suzhou Scientific Committee for financial support (JSK016 and SG 0219).

Supporting Information Available: Experimental procedures and NMR and HRMS spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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