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Synthesis of 2-Pyridylphosphinate and Thiophosphinate Derivatives by Nucleophilic Aromatic Substitution of *N*-Methoxypyridinium Tosylates

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We developed a straightforward and cost-effective method for the synthesis of 2-pyridylphosphinate derivatives based on a nucleophilic aromatic substitution of *N*-methoxypyridinium salts. The method proved to be useful for synthesizing various 2-pyridylphosphinates and thiophosphinates, including an optically active compound, from *H*-phosphinate precursors.

2-Pyridylphosphine oxides and 2-pyridylphosphonates have been used as ligands for many applications such as the extraction of lanthanide ions,[1] preparation of luminescent metal complexes,[2] and transition-metal-catalyzed reactions.[3] Biological activities of these compounds have also attracted attention.[4] In contrast, 2-pyridylphosphinates categorized "in between" have attracted little attention,[5] and only a few studies on their application have been reported to date.[5e,5f]

2-Pyridylphosphinates in the literature have been synthesized by Pd-catalyzed cross-coupling between the corresponding *H*-phosphinates and 2-halopyridines exclusively.[5] However, 2-halopyridines are generally less reactive than other aryl halides, and thus, high catalyst loadings or highly reactive but expensive catalysts are essential. Therefore, the development of a cost-effective alternative method is required. For this purpose, we sought to develop a new method based on a nucleophilic aromatic substitution (S_NAr) of *N*-methoxypyridinium salts, which would not require an expensive transition-metal catalyst. This type of reaction has been used to synthesize 2-pyridylphosphonates.[3a,4,6] However, to the best of our knowledge, it has not been applied to the synthesis of 2-pyridylphosphinate derivatives. Therefore, we first investigated the reaction between methyl phenylphosphinate (**1a**) and *N*-methoxypyridinium tosylate (**2**) to verify the applicability of this reaction to the synthesis of 2-pyridylphosphinates (Table 1). Compound **2** can be easily synthesized from inexpensive pyridine *N*-oxide and methyl *p*-toluenesulfonate.[7]

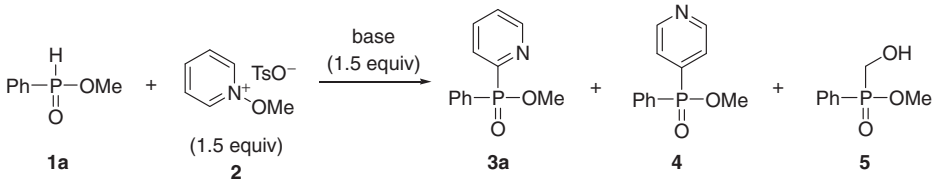
When the reaction between compounds **1a** and **2** was carried out in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at rt under similar conditions used for the synthesis of dialkyl 2-pyridylphosphonates by Stawinski et al.,[4] compound **1a** was completely consumed within 5 min and the desired 2-pyridylphosphinate **3a** as well as two by-products **4** and **5** were formed (Table 1, Entry 1). ^{31}P NMR analysis of the crude mixture showed that the ratio of compounds **3a**:**4**:**5** was 80:4:16. By-products **4** and **5** were identified by comparing the ^{1}H and ^{31}P NMR spectra with those of an authentic sample synthesized by Pd-catalyzed cross-coupling between compound **1a** and 4-iodopyridine[8] and with those in the literature,[9] respectively. Concomitant formation of 2- and 4-pyridyl derivatives is common in the syntheses of pyridylphosphonates.[6] *P*-Hydroxymethylation has also been reported by Stawinski et al. in the reaction of diethyl *H*-phosphonate with compound **2**.[4a] Because it was difficult to separate compounds **3a** and **5** by silica gel column chromatography, compound **3a** was isolated in only 46%.

It has been reported that such *P*-hydroxymethylation reactions are attributed to the base-promoted decomposition of *N*-methoxypyridinium salts (e.g., compound **2**), which generates formaldehyde.[4a,10] However, the addition of a base is necessary for the S_NAr reaction. In addition, it has been reported that the decomposition of *N*-methoxypyridinium salts is promoted even by a weak base.[4a] We speculated that the decomposition of **2** might be suppressed by lowering the reaction temperature because we found that the reaction was extremely exothermic. In fact, the formation of compound **5** was reduced at 0 °C (Entry 2) and completely suppressed at −40 °C (Entry 3). Practically the same result was obtained when the reaction was conducted in CH_2Cl_2 (Entry 4). The formation of **4** was not as temperature dependent as that of **5**; it was minimized at −40 °C (Entries 3 and 4) and was not further improved at −78 °C (Entry 5). Although the formation of **4** was not completely suppressed, compound **3a** was easily isolated in excellent yield (Entry 3). We also found that the relatively strong base DBU was necessary for the reaction; the conversion of **1a** was reduced from >99% to 41% and 14% when DBU was replaced by Et_3N and *i*-Pr_2NEt, respectively, even with an extended reaction time (Entries 3 vs. 6, 7).

With the optimized conditions in Table 1, Entry 3, we examined the scope of the reaction by using various substrates. First, ethyl and isopropyl phenylphosphinates **1b** and **1c** were used in place of the methyl ester **1a** (Table 2). Compounds **1b** and **1c** were synthesized according to the literature with minor modifications.[8,11] The results were rather surprising; although the desired products **3b** and **3c** were formed in 90–93%, they were both contaminated with compound **3a**. Although the mechanism of this side reaction is not clear yet, it is most likely derived from the *N*-methoxy group of compound **2**. Because of this undesired transesterification, we carried out the following investigations by using methyl esters as starting materials.

Compound **1a** was allowed to react with 2- and 4-methylpyridinium salts **6a** and **6b**, which were expected to be less reactive than compound **2** owing to the electron-donating methyl group (Table 3). In fact, compound **6a** was significantly less reactive than compound **2**. Thus, only 68% of the starting material **1a** was consumed under the optimized conditions and the isolated yield of compound **7a** was less than 40% (Entry 1). The result was not practically improved by increasing the amounts of compound **6a** and DBU (Entry 2) and also extending the reaction time (Entry 3). In contrast, compound **6b** having a methyl group at the 4-position showed greater reactivity than the 2-methyl reagent **6a**, although still less reactive than the unsubstituted **2**, and the desired product **7b** was isolated in good yields (Entries 4 and 5).

Table 1. Optimization of reaction conditions for the synthesis of phenyl(2-pyridyl)phosphinates **3a**

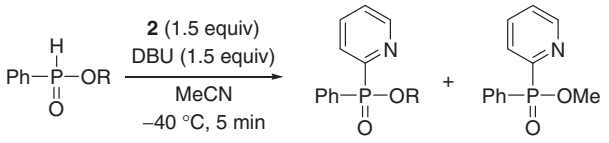


1a (1.5 equiv) **2** **3a** **4** **5**

Entry	Base	Conditions	Conversion[a]/%	**3a**:**4**:**5**[a]	Yield of **3a**[b]/%
1	DBU	MeCN, rt, 5 min	>99	80:4:16	46
2	DBU	MeCN, 0 °C, 5 min	>99	90:4:6	—
3	DBU	MeCN, −40 °C, 5 min	>99	98:2:0	93
4	DBU	CH_2Cl_2, −40 °C, 5 min	>99	98:2:0	—
5	DBU	CH_2Cl_2, −78 °C, 5 min	>99	98:2:0	—
6	Et_3N	MeCN, −40 °C, 2 h	41	—	—
7	*i*-Pr_2NEt	MeCN, −40 °C, 2 h	14	—	—

[a]Determined by ^{31}P NMR analysis of crude mixture. [b]Isolated yield.

Table 2. Transesterification during the synthesis of phenyl(2-pyridyl)phosphinates **3b** and **3c**

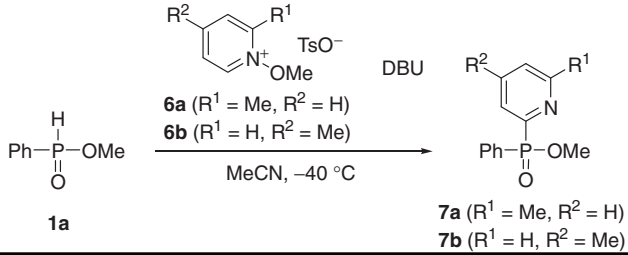


1b (R = Et) **1c** (R = *i*-Pr) **3b** (R = Et) **3c** (R = *i*-Pr) **3a**

Entry	**1**	Conversion[a]/%	**3b**,**c**:**3a**[a]
1	**1b**	>99	90:10
2	**1c**	>99	93:7

[a]Determined by ^{31}P NMR.

Table 3. Synthesis of methyl phenyl(methyl-2-pyridyl)phosphinates **7a** and **7b**

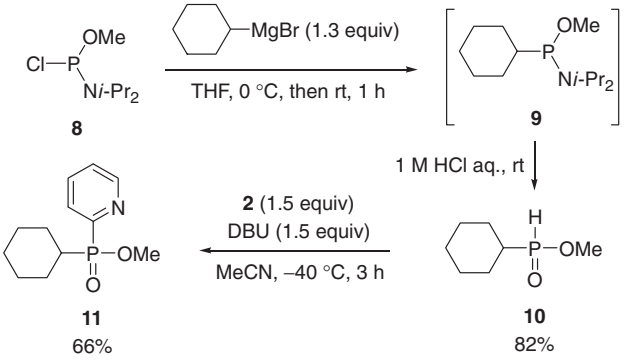


1a **7a** (R^1 = Me, R^2 = H) **7b** (R^1 = H, R^2 = Me)

Entry	**6** (equiv)	Equiv of DBU	Reaction time	**7**	Conversion[a] /%
1	**6a** (1.5)	1.5	5 min	**7a**	68 (37)[b]
2	**6a** (2.0)	2.0	5 min	**7a**	75 (35)[b]
3	**6a** (2.0)	2.0	3 h	**7a**	68 (33)[b]
4	**6b** (1.5)	1.5	5 min	**7b**	89 (69)[b]
5	**6b** (2.0)	2.0	5 min	**7b**	93 (61)[b]

[a]Determined by ^{31}P NMR. [b]Isolated yields of **7** are given in parentheses.

We found that the reaction was also applicable to the synthesis of an alkyl(2-pyridyl)phosphinate. Thus, the reaction of methyl cyclohexylphosphinate (**10**), which was synthesized from the chlorophosphoramidite **8**, with compound **2** afforded



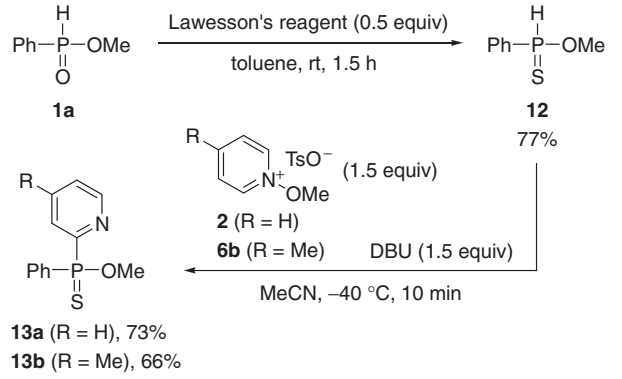
8 **9** **10** 82% **11** 66%

Scheme 1. Synthesis of methyl cyclohexyl(2-pyridyl)phosphinate (**11**).

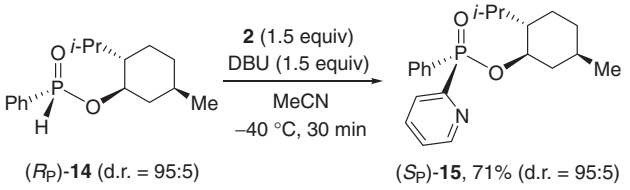
the 2-pyridylphosphinate **11** in good yield, though the reaction required a longer reaction time than that for compound **1a** (Scheme 1).

Oxygen to sulfur exchange has been one of the major transformations in organophosphorus chemistry, which can dramatically change properties of molecules such as coordination ability to metal ions and biological activity.[12] Synthesis of 2-pyridylthiophosphinates from the 2-pyridylphosphinates we already obtained would therefore significantly extend the scope of the reaction. For this reason, we sought to develop a method to synthesize 2-pyridylthiophosphinates. First, we attempted to convert compound **3a** to the corresponding thiophosphinate by treatment with Lawesson's reagent (1.5 equiv) for 6 h at rt.[13] However, the reaction did not give the desired product and multiple unidentified by-products were formed instead.

Therefore, we next conducted the O to S exchange prior to the introduction of the 2-pyridyl group (Scheme 2) and found that compound **1a** was successfully converted into the corresponding thiophosphinate **12** in contrast to compound **3a**. 0.5 equiv of Lawesson's reagent was sufficient for the complete consumption of compound **1a**. It was also found that the optimal reaction time was ca. 1–2 h and a prolonged treatment of **1a** with Lawesson's reagent resulted in the formation of some highly polar by-products, which were probably derived from the oversulfurization of **12**. The reaction of compounds **12** and **2** under



Scheme 2. Synthesis of phenyl(2-pyridyl)thiophosphinate esters **13a** and **13b** via methyl phenylthiophosphinate (**12**).



Scheme 3. Synthesis of optically active 2-pyridylphosphinate derivative (S_P)-**15**.

similar conditions as above gave the desired 2-pyridylthiophosphinate **13a** in good yield. The reaction with 4-methyl reagent **6b** was also successful, producing the corresponding thiophosphinate **13b**.

The 2-pyridylphosphinate derivatives produced by this method are *P*-chiral. Considering the potential applications of these compounds, i.e., ligands for transition-metal catalysts and biologically active compounds, it is important to open a way to the synthesis of these compounds in optically active forms.[14] We also envisage that optically active 2-pyridylphosphinate derivatives would work as Lewis basic organocatalysts for asymmetric reactions in analogy with bidentate phosphine oxides and pyridine derivatives.[15] As a preliminary study in this pursuit, we conducted the reaction of (R_P)-**14**[16] (R_P:S_P = 95:5) (Scheme 3) and found that the reaction proceeded smoothly to afford the desired product **15** in good yield, though taking a little longer time than the methyl ester **1a**. The reaction was completely stereospecific. In analogy with the reaction of dialkyl *H*-phosphonates reported by Stawinski et al.,[4] we speculate that the reaction proceeded with retention of configuration at the phosphorus atom. Although the transesterification described above (Table 2) also occurred in this case and a small amount of the methyl ester **3a** (3% by ^{31}P NMR) was observed in the crude mixture, it was easily removed from the desired product (S_P)-**15** by silica gel column chromatography.

In conclusion, we developed a straightforward method for the synthesis of 2-pyridylphosphinates and thiophosphinates using the S_NAr reaction of *N*-methoxypyridinium salts. This method would be a cost-effective alternative for the synthesis of various 2-pyridylphosphinate derivatives, which are currently synthesized by rather costly Pd-catalyzed cross-coupling. Further extension of this study, particularly on the synthesis of optically active compounds, is in progress.

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