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Chloroform-Based Atherton-Todd-Type Reactions of Alcohols and Thiols with Secondary Phosphine Oxides Generating Phosphinothioates and Phosphinates

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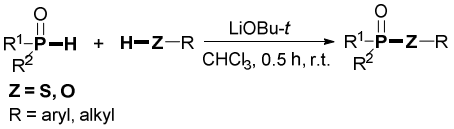

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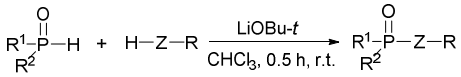
Chloroform-based Atherton-Todd-type reactions of alcohols and thiols with secondary phosphine oxides, generating phosphinothioates and phosphinates, respectively, are described. Various valuable phosphinothioates and phosphinates including those with functional groups are readily prepared under mild reaction conditions.

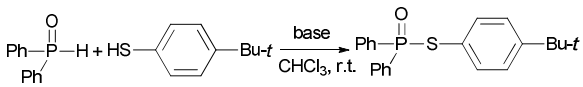
Because of the unique properties, phosphinothioates and phosphinates are widely applied in organic synthesis, pharmacochemistry and agrochemistry.[1-6] The reaction of P(O)-H compounds with alcohols and thiols, namely Atherton-Todd reaction, is one of the most powerful methods for the preparation of these compounds.[7-23] Unfortunately, however, this reaction usually requires the use of the toxic tetrachloromethane as the halogenating reagent and solvent. Although other reactive halocompounds such as $CHBr_3$, CHI_3 could also serve well for this reaction,[19-22] the Atherton-Todd reaction hardly took place in simple $CHCl_3$ under similar reaction conditions.[21,22] However, there is a practical need to replace CCl_4 with $CHCl_3$ since $CHCl_3$ is cheaper and easier handling than CCl_4.



(1)

Herein, we report the phosphorylation of alcohols and thiols with secondary phosphine oxides could be accomplished in chloroform, producing the corresponding phosphinothioates and phosphinates in moderate to high yields (eqn 1). This transformation is very facile and is complete in half an hour. Moreover, aliphatic thiols are applicable to this reaction to produce the corresponding products in high yields. It is known that aliphatic thiols react with CCl_4. Therefore, these substrates could not be used under the traditional Todd-conditions.[16]

Table 1 Chloroform-based Atherton-Todd-type reaction of 4-*tert*-butylphenyl thiol with diphenylphosphine oxides.[a]



1a 2a 3a

Run	1a	Base	Yield[b]
1	1 equiv	2 equiv LiOH	17%
2	1 equiv	2 equiv Li_2CO_3	N.R.
3	1 equiv	2 equiv NaOBu-*t*	4%
4	1 equiv	2 equiv KOBu-*t*	N.R.
5	1 equiv	2 equiv LiOBu-*t*	28%
6	1.5 equiv	2 equiv LiOBu-*t*	59%
7	2 equiv	2 equiv LiOBu-*t*	96%
8	2 equiv	1.5 equiv LiOBu-*t*	84%
9	2 equiv	1 equiv LiOBu-*t*	64%
10[c]	2 eauiv	2 equiv LiOBu-*t*	98%

[a] Conditions: **1a**, **2a** (0.1 mmol), base and 1 mL $CHCl_3$ were stirred at room temperature (25 °C) for 3 h. [b] ^{31}P NMR yield using triphosphine oxide as an internal standard.. [c] 0.5 h.

During the ongoing studies on the construction of P(O)-Z bonds via P(O)-H/Z-H bonds cross coupling,[15,16,24,25] we found that chloroform acted as the right halogenating reagent and solvent in the Atherton-Todd type reaction in the presence of LiOBu-*t*. Thus, in the presence of 2 equiv LiOBu-*t*, diphenylphosphine oxide coupled readily with equivalent 4-*tert*-butylphenyl thiol in chloroform at room temperature (25 °C) in 3 h, affording the corresponding phosphorothioate **3a** in 28% yield (Table 1, entry 5). The reaction efficiency could be further improved. When 1.5 equiv diphenylphosphine oxide was loaded, 59% yield of **3a** was obtained (Table 1, entry 6). By increasing the amount of diphenylphosphine oxide to 2 equiv, **3a** was generated almost quantitatively (Table 1, entry 7). Worth noting is that this reaction proceed rapidly and could complete in half an hour (Table 1, entry 10).

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Electronic Supplementary Information (ESI) available: [General information, experimental procedures, characterized data and copies of ^1H, ^{13}C and ^{31}P NMR spectra for products]. See DOI: 10.1039/x0xx00000x

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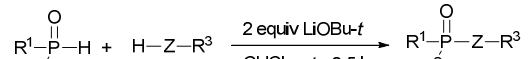
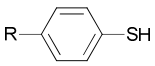
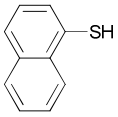
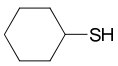
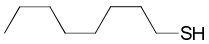
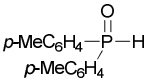
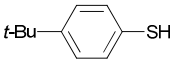
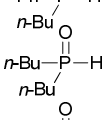
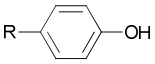
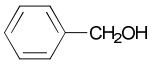
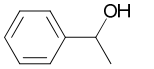
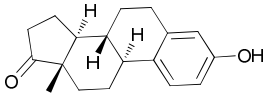
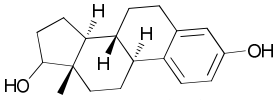
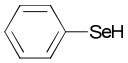
Table 2 Cross coupling of secondary phosphine oxides with Z-H compounds in chloroform.[a]



1 2 3-5

Run	1	2	3, Yield[b]
			
1		R = Bu-*t*	**3a**, 93%
2		R = Me	**3b**, 92%
3		R = OMe	**3c**, 94%
4		R = NHAc	**3d**, 83%
5		R = F	**3e**, 80%
6		R = CF_3	**3f**, trace
7			**3g**, 90%
8			**3h**, 72%
9			**3i**, 89%
10			**3j**, 80%
11			**3k**, 76%
12			**3l**, 23%
13			**3m**, 26%
			
14		R = H	**4a**, 82%
15		R = Bu-*t*	**4b**, 81%
16		R = OMe	**4c**, 90%
17		R = F	**4d**, 84%
18		R = CF_3	**4e**, 81%
19			**4f**, 70%
20			**4g**, 85%[c]
21			**4h**, 87%
22			**4i**, 73%[d]
23			**5a**, 72%

[a] Conditions: **1** (0.4 mmol), thiols or alcohols or selenol (0.2 mmol), LiOBu-*t* (0.4 mmol), $CHCl_3$ (1.0 mL), room temperature (25 °C), 0.5 h. [b] Isolated yield. [c] 0.3 mmol **1** was loaded. [d] regioselectivity: 10:1

This cross coupling is applicable to other substrates; various Z-H compounds including thiols, alcohols and selenols reacted with secondary phosphine oxides in chloroform under similar conditions, producing the corresponding organophosphorus compounds in good to high yields. Thus, the derivatives of benzenethiol with Me, *t*-Bu and MeO groups on the benzene ring all coupled with diphenylphosphine oxide to give the corresponding products in good yields (Table 2, entries 1-3). A substrate with amido group was phosphorylated to produce the expected phosphorothioate **3d** in 83% yield (Table 2, entry 4). 4-F-benzenethiol also reacted with diphenylphosphine oxide readily under similar reaction conditions (Table 2, entry 5). However, when benzenethiol analogue with electron-withdrawing CF_3 group was employed, only trace of product was generated (Table 2, entry 6). Phosphinothioate **3g** was also obtained in high yield from the cross coupling of naphthalene-1-thiol with diphenylphosphine oxide in chloroform (Table 2, entry 7). Worth noting is that aliphatic thiols, which did not react with H-phosphinates under the standard Atherton-Todd reaction conditions,[16] also served as the good substrates in the present reaction system. For example, both cyclohexanethiol and octane-1-thiol coupled with diphenylphosphijne oxide in chloroform to give the corresponding products **3h** and **3i** in 72% and 89% yields, respectively (Table 2, entries 8 and 9). Secondary phosphine oxides $(p\text{-}MeC_6H_4)_2P(O)H$ and $Cy_2P(O)H$ could also couple with thiols in chloroform, generating the expected products phosphinothioates in good yields (Table 2, entries 10 and 11). However, when secondary phosphine oxides with small alkyl group were used as substrate, low yields were given (Table 2, entries 12 and 13).

Interestingly, phosphinates can also be prepared from the facile cross coupling of alcohols with secondary phosphine oxide in chloroform by the aid of LiOBu-*t*. As shown as entries 14-21 in Table 2, both electron-rich and electron-deficient phenols acted as good coupling partners to yield the corresponding phosphinates in high yields. Thus, phenol coupled readily with diphenylphosphine oxide in chloroform to produce **4a** in 82% yield (Table 2, entry 14). Phenol analogues with *t*-Bu and MeO groups served well and were converted to the expected phosphinates in high yields (Table 2, entries 15 and 16). 4-Fulorophenol reacted with **1a** smoothly in this coupling system (Table 2, entry 17). Intriguingly, the substrate with electron-withdrawing CF_3 group also coupled with diphenylphosphine oxide to yield phosphinate **4e** in 81% yield (entry 18). Aliphatic alcohols like phenylmethanol and styralyl alcohol were also phosphorylated by diphenylphosphine oxide to give **4f** and **4g** in 70% and 85% yields, respectively (Table 2, entries 19 and 20). In the presence of LiOBu-*t*, chloroform also promoted the phosphorylation of complex molecules with diphenylphosphine oxide, facilitating the introduction of the $Ph_2P(O)$ group into the bioactive molecules estrone and estradiol (Table 2, antries 21 and 22). Worth noting is that a phenolic hydroxy group is more reactive than an alcoholic hydroxy group, resulting in the highly selective phosphorylation of the phenolic OH group under the present reaction conditions.[26] For example, product from the cross coupling of the phenolic hydrox group was produced predominately in the phosphorylation of estradiol with diphenylphosphine oxide (Table 2, entry 22). Benzeneselenol also worked well to couple with **1a**, furnishing the corresponding phosphinoselenoate **5a** in high yield (Table 2, entry 23).[27]

Conclusions

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In summary, we disclosed that chloroform served well in the Atherton-Todd-type reactions of alcohols and thiols with secondary phosphine oxides, replacing the highly toxic CCl_4, as the halogenating reagent and solvent. This transformation completed rapidly and provided an efficient method for the preparation of phosphinothioates and phosphinates under mild reaction conditions.

Notes and references

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1 L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley Interscience, New York, 2000.
2 P. J. Murphy, *Organophosphorus Reagents*, Oxford University Press, Oxford, U.K., 2004.
3 N. N. Melnilkov, *Chemistry of Pesitcides*, Springer-Verlag, New York, 1971.
4 M. W. Loranger, S. A. Beaton, K. L. Lines and D. L. Jakeman, *Carbohydr. Res.*, 2013, **379**, 43.
5 D. M. Bartley and J. K. Coward, *J. Org. Chem.*, 2005, **70**, 6757.
6 F.-R. Alexandre, A. Amador, S. Bot, C. Caillet, T. Convard, J. Jakubik, C. Musiu, B. Poddesu, L. Vargiu, M. Liuzzi, A. Roland, M. Seifer, D. Standring, R. Storer and C. B. Dousson, *J. Med. Chem.*, 2011, **54**, 392.
7 F. R. Atherton, H. T. Openshaw and A. R. Todd, *J. Chem. Soc.*, 1945, 660.
8 F. R. Atherton and A. R. Todd, *J. Chem. Soc.*, 1947, 674.
9 G. M. Steinberg, *J. Org. Chem.*, 1950, 637.
10 A. Kong and R. Engel, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3671.
11 S. Cao, Y. Guo, J. Wang, L. Qi, P. Gao, H. Zhao and Y.-F. Zhao, *Tetrahedron Lett.*, 2012, **53**, 6302.
12 R. A. Ashmus and T. L. Lowary, *Org. Lett.*, 2014, **16**, 2518.
13 K. Troev, V. Mitova and I. Ivanov, *Tetrahedron Lett.*, 2010, **51**, 6123.
14 A. Bogomilova, M. Hohn, M. Gunther, K. Troev, E. Wagner and L. Schreiner, *Eur. J. Pharm. Sci.*, 2013, **50**, 410.
15 B. Xiong, Y. Zhou, C. Zhao, M. Goto and S.-F. Yin, *Tetrahedron*, 2013, **69**, 9373.
16 G. Wang, R. Shen, Q. Xu, M. Goto, Y. Zhao and L.-B. Han, *J. Org. Chem.*, 2010, **75**, 3890.
17 N. K. Gusarova, P. A. Volkov, N. I. Ivanova, L. I. Larina and B. A. Trofimov, *Synthesis*, 2011, **22**, 3723.
18 M. Neisius, S. Liang, H. Mispreuve and S. Gaan, *Ind. Eng. Chem. Res.*, 2013, **52**, 9752.
19 G. Mielniczak and A. Lopusinski, *Synth. Commun.*, 2003, **33**, 3851.
20 S. Wagner, M. Rakotomalala, Y. Bykov, O. Walter and M. Döring, *Heteroatom Chem.*, 2012, **23**, 216.
21 E. Georgiev, D. M. Roundhill and K. Troev, *Inorg. Chem.*, 1992, **31**, 1965.
22 E. M. Georgiev, J. Kaneti, K. Troev and D. M. Roundhill, *J. Am. Chem. Soc.*, 1993, **115**, 10964.
23 S. S. L. Corre, M. Berchel, H. Couthon-Gourvés, J.-P. Haelters and P.-A. Jaffrés, *Beilstein J. Org. Chem.*, 2014, **10**, 1166.
24 Y. Zhou, G. Wang, Y. Saga, R. Shen, M. Goto, Y. Zhao and L.-B. Han, *J. Org. Chem.*, 2010, **75**, 7924.
25 T. Chen, J.-S. Zhang and L.-B. Han, *Dalton Trans.*, 2015, DOI: 10.1039/C5DT01896J.
26 Similar phenomenon was shown in the reaction of H-phosphonates with alcohols under Atherton-Todd reaction conditions, see: L. J. Silverberg, J. L. Dillon and P. Vemishetti, *Tetrahedron Lett.*, 1996, **37**, 771.
27 For synthesis of phosphinothioates and phosphinoselenoates, also see: (a) N. Liu, L.-L. Mao, B. Yang and S.-D. Yang, *Chem. Commun.*, 2014, **50**, 10879; (b) M. Arisawa, T. Ono and M. Yamaguchi, *Tetrahedron Lett.*, 2005, **46**, 5669; (c) M. Grayson, C. E. Farley and C. A. Streuli, *Tetrahedron*, 1967, **23**, 1065; (d) Y. Kobiki, S. Kawaguchi and A. Ogawa, *Tetrahedron Lett.*, 2013, **54**, 5453; (e) S. Kawaguchi, M. Kotani, S. Atobe, A. Nomoto, M. Sonoda and A. Ogawa, *Organometallics*, 2011, **30**, 6766.