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Alkylation of *H*-Phosphinate Esters under Basic Conditions

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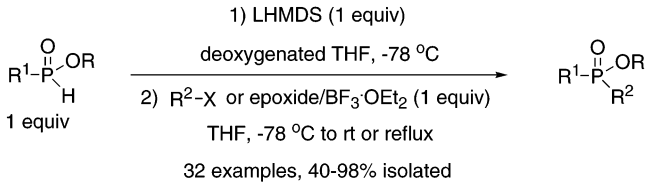
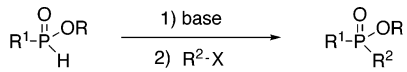


An efficient and general procedure was developed for the direct alkylation of *H*-phosphinate esters with LHMDS at low temperature. The simplicity of the reaction allows the use of various *H*-phosphinate esters and takes place with a wide range of electrophiles. The approach can be employed to access some GABA analogues or precursors to GABA analogues. The isolated yields are moderate to good. This is the first report of an alkylation with a secondary iodide or a primary chloride.

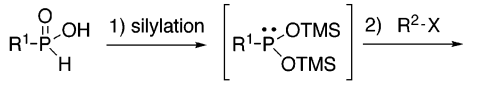
Introduction

Over the years, many examples of base-promoted *H*-phosphinate alkylation (eq 1) have been reported in the literature.[1] However, there does not appear to be a standard set of conditions, and surprisingly, we have not found any general



(1)

study of this reaction. Various bases (RONa, NaH, BuLi, LDA, KHMDS) and stoichiometries have been employed.[1] A somewhat more widely employed approach (eq 2) consists of



(2)

silylating *H*-phosphinic acids followed by an Arbuzov-like reaction with alkyl halides.[2] This method also has its limitations, and it often requires esterification of the dialkylphosphinic acid products when further manipulations are desired.

Functionalized, differentially substituted phosphinate esters $R^1R^2P(O)(OR)$ are important organophosphorus intermediates, particularly in the synthesis of medicinally relevant protease inhibitors and ATP-dependent ligases.[3] Over the past few years, our laboratory has been developing various approaches to prepare *H*-phosphinic acids and esters.[4] With these compounds becoming more widely available, we are turning our focus to

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(1) Base-promoted alkylations of *H*-phosphinate esters: (a) Baillie, A. C.; Cornell, C. L.; Wright, B. J.; Wright, K. *Tetrahedron Lett.* **1992**, *33*, 5133 (NaH). (b) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385 (Na). (c) Froestl, W.; Mickel, S. J.; von Sprecher, G.; Diel, P. J.; Hall, R. G.; Maier, L.; Strub, D.; Melillo, V.; Baumann, P. A.; Bernasconi, R.; Gentsch, C.; Hauser, K.; Jaekel, J.; Karlsson, G.; Klebs, K.; Maitre, L.; Marescaux, C.; Pozza, M. F.; Schmutz, M.; Steinmann, M. W.; van Riezen, H.; Vassout, A.; Mondadori, C.; Olpe, H.-R.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3313 (NaH, BuLi). (d) Froestl, W.; Mickel, S. J.; Hall, R. G.; von Sprecher, G.; Diel, P. J.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihs, G.; Vassout, A.; Waldmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297. (NaH); (e) Magnin, D. R.; Biller, S. A.; Dickson, J. K., Jr.; Logan, J. V.; Lawrence, R. M.; Chen, Y.; Sulsky, R. B.; Ciosek, C. P., Jr.; Harrity, T. W.; Jolibois, K. G.; Kunselman, L. K.; Rich, L. C.; Slusarchyk, D. A. *J. Med. Chem.* **1995**, *38*, 2596 (NaHMDS). (f) Gallagher, M. J.; Ranasinghe, M. G.; Jenkins, I. D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *115*, 255 (*i*-PrONa). (g) Fairhurst, R. A.; Collingwood, S. P.; Lambert, D.; Taylor, R. J. *Synlett* **2001**, 467 (KHMDS). (h) Larenco, C.; Villien, L.; Kaufmann, G. *Tetrahedron* **1984**, *40*, 2731 (NaH). (i) McKittrick, B. A.; Stamford, A. W.; Weng, X.; Ma, K.; Chackalamannil, S.; Czarniecki, M.; Cleven, R. M.; Fawzi, A. B. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1629 (NaH, LDA) (j) Froestl, W.; Bettler, B.; Bittiger, H.; Heid, J.; Kaupmann, K.; Mickel, S. J.; Strub, D. *Farmaco* **2003**, *58*, 173 (NaH). (k) Kehler, J.; Ebert, B.; Dahl, O.; Krogsgaard-Larsen, P. *Tetrahedron* **1999**, *55*, 771 (LDA, *t*-BuOK). (l) Hemmi, K.; Takeno, H.; Hashimoto, M.; Kamiya, T. *Chem. Pharm. Bull.* **1982**, *30*, 111 (BuLi). (m) Lindell, S. D.; Turner, R. M. *Tetrahedron Lett.* **1990**, *31*, 5381 (NaH). (n) Gallagher, M. J.; Honegger, H. *Tetrahedron Lett.* **1977**, 2987 (MeONa). (o) Hall, R. G.; Kane, P. D.; Bittiger, H.; Froestl, W. *J. Labelled Compd. Radiopharm.* **1995**, 129.

(2) For some representative examples of the silicon method: (a) Boyd, E. A.; Regan, A. C.; James, K. *Tetrahedron Lett.* **1994**, *35*, 4223. (b) Boyd, E. A.; Corless, M.; James, K.; Regan, A. C. *Tetrahedron Lett.* **1990**, *31*, 2933. (c) Malachowski, W. P.; Coward, J. K. *J. Org. Chem.* **1994**, *59*, 7625. (d) Reck, F.; Marmor, S.; Fisher, S.; Wuonola, M. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1451. (e) Ribière, P.; Altamirano-Bravo, K.; Antczak, M. I.; Hawkins, J. D.; Montchamp, J.-L. *J. Org. Chem.* **2005**, *70*, 4064. See also refs 1c, 1d, and 1h.

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TABLE 1. Role of the Base in the Alkylation of Butyl Octyl-*H*-phosphinate with Butyl Iodide[a]

entry	substrate	conditions	base	NMR conversion %[b]
1	BuI	THF, 0 °C to rt	Na	16
2	BuI	THF, −78 °C to rt	*i*-PrMgCl	64
3	BuI	THF, −78 °C to rt	MeLi	56
4	BuI	THF, −78 °C to rt	BuLi	60
5	BuI	THF, −78 °C to rt	LDA	89
6	BuI	THF, −78 °C to rt	LHMDS	100

[a] All reactions were conducted in freshly distilled anhydrous THF and under N_2. [b] NMR conversion yields are determined by integration of all the resonances in the crude ^{31}P NMR spectra.

the functionalization of these intermediates with the formation of a second phosphorus−carbon bond. Our literature survey uncovered the lack of general conditions for the base-promoted alkylation of *H*-phosphinates with alkyl halides. Therefore, we decided to investigate the scope and limitations of this transformation. Herein, we report a detailed investigation which led to a standardized set of conditions allowing the preparation of functionalized dialkylphosphinates.

Results and Discussion

Butyl octyl-*H*-phosphinate was selected as a test substrate to determine the choice of base, with *n*-butyl iodide as the electrophile (Table 1). The phosphorus nucleophile, butyl iodide, and base were used in equimolar quantities, and the results were studied by ^{31}P NMR of the crude reaction mixtures. Although alkylation takes place in all cases, significant differences are observed. Not surprisingly, nucleophilic bases, such as MeLi and BuLi (entries 3 and 4), give lower yields due to the competing direct substitution of the butyl ester to form a secondary phosphine oxide, whereas the strong non-nucleophilic bases (entries 5 and 6) give better results. After this initial screening, LHMDS was selected to investigate the influence of the electrophile.

Table 2 summarizes the results obtained in the LHMDS-mediated alkylation of PhP(O)(OEt)H with various alkyl halides. Under otherwise identical conditions, a clear erosion in yield is observed as the reactivity of the electrophile decreases. ^{31}P NMR analysis of these reaction mixtures indicates the formation of PhP(O)(OEt)OLi (δ 17.2 ppm), along with the P(III) anion PhP(OEt)(OLi) (δ 149 ppm), and the alkylation product PhP(O)(OEt)Oct (δ 44.8 ppm). The low reactivity of the electrophile requires heating the reaction mixture during which competitive oxidation of the anion takes place, so a deoxygenation protocol was investigated.[5] Instead of a rigorous freeze−thaw−degas cycle, we opted for a simpler, more practical, deoxygenation method consisting of placing the reaction flask containing the *H*-phosphinate ester and THF under vacuum for 5 min at −78 °C and filling it with nitrogen prior to adding the other reagents. This moderate deoxygenation is sufficient to provide good alkylation yields with unreactive electrophiles (X = Cl, OTs). To the best of our knowledge, this is the first example of successful alkylation with an alkyl chloride. Unlike primary iodides, which are sufficiently reactive to not necessitate deoxygenation, isopropyl iodide behaves like *n*-octyl chloride and tosylate. This is also the first time a secondary halide is employed in the alkylation of a *H*-phosphinate.

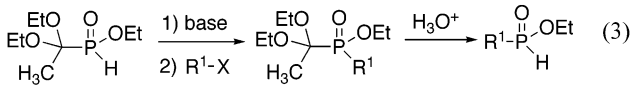
TABLE 2. Role of the Electrophile in the Alkylation of PhP(O)(OEt)H with LHMDS

entry	RX	deoxygenation[a]	temperature	NMR conversion %[b]	isolated yield %[c]
1	CH_3I	no	−78 °C to rt	100	98
2	OctI	no	−78 °C to rt	100	80
3	OctBr	no	−78 °C to rt	80	57
4	OctBr	yes	−78 °C to rt	92	71
5	OctCl	no	−78 °C to reflux	1	
6	OctCl	yes	−78 °C to reflux	77	51
7	OctOTs	yes	−78 °C to reflux	88	62
8	*i*-PrI	yes	−78 °C to reflux	87	45

[a] Deoxygenation was conducted by placing a THF solution of the *H*-phosphinate under vacuum at −78 °C for 5 min and then adding N_2. [b] NMR conversion yields are determined by integration of all the resonances in the ^{31}P NMR spectra. [c] Isolated yield of pure compounds after chromatography on silica gel.

The next stage in this study was to investigate the scope with respect to both the *H*-phosphinate starting material and the electrophile (Table 3).

As shown in Table 3, the general conditions can be successfully applied to a range of *H*-phosphinate/electrophile pairs. The alkylation of the "Ciba-Geigy reagent", $(CH_3C(OEt)_2P(O)(OEt)H)$,[6] was examined in some detail (entries 1−9), in part because it is a representative *H*-phosphinate ester but also because the ketal group can be cleaved to unmask a P(O)H functional group (eq 3).[7] While we[8] and Gallagher[9] have



(3)

reported the direct alkylation of phosphinates $ROP(O)H_2$ under basic conditions which would provide the *H*-phosphinate esters in one step (eq 4). The scope of this reaction is limited to

(3) Representative examples: (a) Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. *J. Med. Chem.* **2003**, *46*, 2641. (b) Lloyd, J.; Schmidt, J. B.; Hunt, J. T.; Barrish, J. C.; Little, D. K.; Tymiak, A. A. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1323. (c) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, E. W., Jr.; Powell, J. R. *J. Med. Chem.* **1988**, *31*, 204. (d) Qiao, L.; Nan, F.; Kunkel, M.; Gallegos, A.; Powis, G.; Kozikowski, A. P. *J. Med. Chem.* **1998**, *41*, 3303. (e) Tokutake, N.; Hiratake, J.; Katoh, M.; Irie, T.; Kato, H.; Oda, J. *Bioorg. Med. Chem.* **1998**, *6*, 1935. (f) Manthey, M. K.; Huang, D. T. C.; Bubb, W. A.; Christopherson, R. I. *J. Med. Chem.* **1998**, *41*, 4550. (g) Ebetino, F. H.; Berk, J. D. *J. Organomet. Chem.* **1997**, *529*, 135. (h) Vayron, P.; Renard, P.-Y.; Valleix, A.; Mioskowski, C. *Chem.—Eur. J.* **2000**, *6*, 1050. (i) Jackson, P. F.; Cole, D. C.; Slusher, B. S.; Stetz, S. L.; Ross, L. E.; Donzati, B. A.; Trainor, D. A. *J. Med. Chem.* **1996**, *39*, 619. (j) Hiratake, J. *Chem. Rec.* **2005**, *5*, 209. (k) Bartley, D. M.; Coward, J. K. *J. Org. Chem.* **2005**, *70*, 6757. (l) Valiaeva, N.; Bartley, D.; Konno, T.; Coward, J. K. *J. Org. Chem.* **2001**, *66*, 5146. (m) Jackson, P. F.; Tays, K. L.; Maclin, K. M.; Ko, Y.-S.; Li, W.; Vitharana, D.; Tsukamoto, T.; Stoermer, D.; Lu, X.-C. M.; Wozniak, K.; Slusher, B. S. *J. Med. Chem.* **2001**, *44*, 4170. (n) Collinsova, M.; Jiracek, J. *Curr. Med. Chem.* **2000**, *7*, 629. (o) Flohr, A.; Aemissegger, A.; Hilvert, D. *J. Med. Chem.* **1999**, *42*, 2633. (p) Chen, S.; Coward, J. K. *J. Org. Chem.* **1998**, *63*, 502. (q) Hiratake, J.; Kato, H.; Oda, J. *J. Am. Chem. Soc.* **1994**, *116*, 12059.

(4) Reviews: (a) Montchamp, J.-L. *J. Organomet. Chem.* **2005**, *690*, 2388. (b) Montchamp, J.-L. *Spec. Chem. Mag.* **2006**, *26*, 44.

(5) Other workers have used deoxygenation previously (see ref 1k).

(6) For applications of the "Ciba-Geigy reagents", see:(a) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G.; Jack, J. *Phosphorus Sulfur Relat. Elem.* **1987**, *30*, 571. (b) McCleery, P. P.; Tuck, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1319. (c) Dingwall, J. G.; Ehrenfreund, J.; Hall, R. G. *Tetrahedron* **1989**, *45*, 3787. (d) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9385. (e) Baylis, E. K. *Tetrahedron Lett.* **1995**, *36*, 9389. (f) Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1145. See also refs 1c and 1d.

TABLE 3. Reaction Scope[a]

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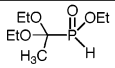
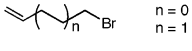
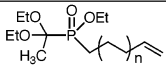
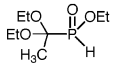
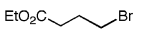
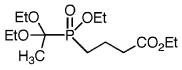
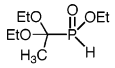
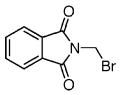
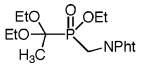
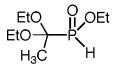
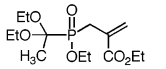
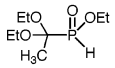
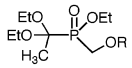
1a		 n = 0		68
1b		n = 1		66
2				62
3				70
4				48
5a		 R = Piv		50
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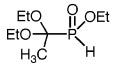
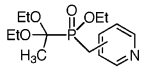
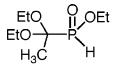
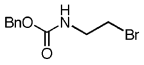
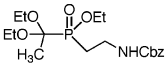
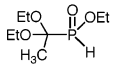
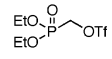
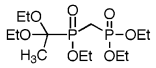
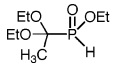
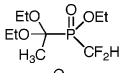
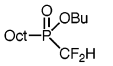
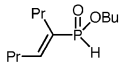
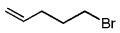
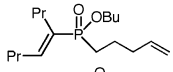
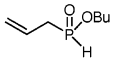
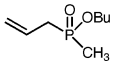
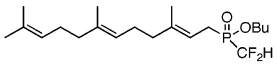
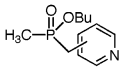
6a		 X=Cl, p		48
6b		X=Br, m		60
6c		X=Br, o		62
7				58
8				81
9		F_2CHCl		71
10		F_2CHCl		78
11		*i*-PrI		73
12				66
13		CH_3I		95
14		F_2CHCl		72
15a		 X=Cl, p		50
15b		X=Br, m		62
15c		X=Br, o		68

[a] Details are provided in the Experimental Section. [b] Electrophiles that did not react successfully under a variety of conditions (excess of base, heating) include CH_2I_2, $(CH_2Br)_2$, bromoacetates, and $(EtO)_2P(O)CF_2Br$. The reasons for failure are unclear. [c] Isolated yield of pure compounds after chromatography on silica gel.

(4)

reactive electrophiles, such as allylic halides, and it fails with most of the electrophiles used in Table 3.

The *H*-phosphinate starting materials were generally available through our various methodologies (radical, Ni- and Pd-catalyzed hydrophosphinylations, or Pd-catalyzed cross-coupling).[4] Various functional groups (esters, imides, carbamates) are tolerated under the reaction conditions (Table 3). This alkylation is comparable or superior to other conditions reported,[1] especially because it proceeds with equimolar amounts of reagents. In the literature, an excess of reagent (electrophile or *H*-phosphinate) is often employed.[1] For example, the product in Table 3, entry 2 was obtained in 42% yield using NaH as the base. With halomethylpyridine hydrohalides (Table 3, entries 6 and 15), an equivalent of LHMDS is employed prior to adding the electrophile to the lithium phosphinate solution. The products are precursors to GABA analogues, although none showed any significant activity on the GABA-B receptor after appropriate deprotection steps.[10]

Difluorochloromethane can be used to prepare the corresponding difluoromethylphosphinate. There was an example of such a reaction in the literature, although the product was not isolated.[11] We have extended this to several substrates (Table 3, entries 9, 10, and 14). Our results concerning the reactivity of these compounds for the synthesis of fluorinated phosphinates will be reported shortly.

Epoxides also react satisfactorily in the presence of a stoichiometric amount of boron trifluoride etherate (Scheme 1). Products **1** and **2** are obtained as nearly 1:1 mixtures of

(7) Cleavage of ketal protecting group to *H*-phosphinate: see ref 6.

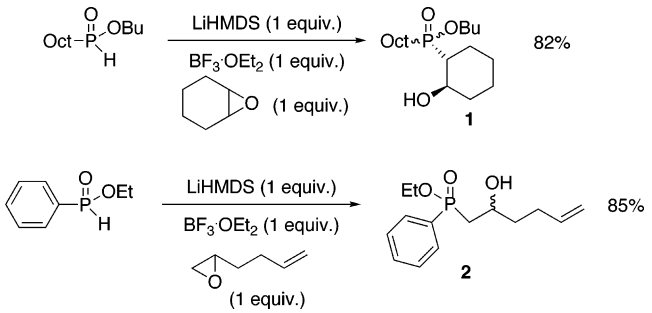
(8) Abrunhosa-Thomas, I.; Ribière, P.; Adcock, A. C.; Montchamp, J.-L. *Synthesis* **2006**, *2*, 325.

(9) Gallagher, M. J.; Ranasinghe, M. G.; Jenkins, I. D. *Phosphorus, Sulfur Silicon Relat. Elem.* **1996**, *115*, 255.

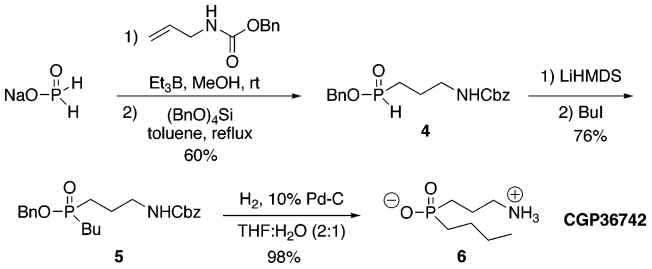
(10) The compounds were inactive.

(11) $CH_3C(OEt)_2P(O)(OEt)CF_2H$ has been prepared in 95% yield using NaH and was used in situ (see ref 1c). The synthetic use of this and other difluorophosphinates described herein will be reported separately.

SCHEME 1. Epoxide Opening

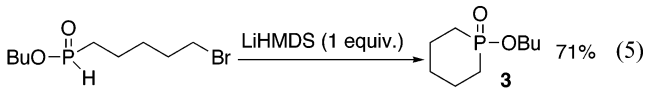


SCHEME 2. Synthesis of the GABA-B Antagonist CGP 36742



diastereoisomers because the phosphorus atom is stereogenic. Although epoxide-openings have been reported using the silylation approach, we could not find any report of this reaction under basic conditions.[12]

Equation 5 shows an example of an intramolecular alkylation



(5)

to form P-heterocycle **3** (1-butoxy-phosphinane-1-oxide).

The based-promoted alkylation can be applied to the synthesis of a variety of biologically active targets. For example, CGP 36742,[1c,13] a GABA-B antagonist which is currently undergoing phase II clinical trials, can be synthesized easily using our radical-based hydrophosphinylation,[14] followed by our alkoxysilane-based esterification to form **4**[15] and the present alkylation reaction to form intermediate **5** (see Scheme 2). Debenzylation affords CGP 36742, **6**, cleanly without the need for cumbersome ion-exchange purification.

Another example is shown in Scheme 3 for the rapid synthesis of the known kynureninase inhibitor **8**.[16] The key step of forming **7** proceeds in good yield.

A similar strategy could be applied for the preparation of protected phosphinothricin (Scheme 4).[17] The starting *H*-phosphinate **9** was prepared using our recently disclosed alkylation of phosphinate esters.[8] The base-promoted alkylation of **9** delivered protected phosphinothricin **10** in moderate yield.

Conclusion

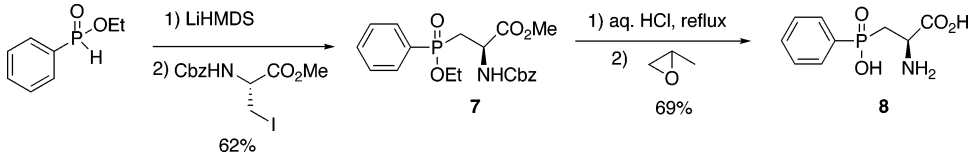
Our investigations of the base-promoted alkylation of *H*-phosphinate esters reveal that a standardized set of conditions can be established, using LHMDS as the base and stoichiometric amounts of the reagents. A moderate, yet practical, deoxygenation protocol is necessary with less reactive electrophiles. A wide variety of *H*-phosphinate esters can be alkylated, including the first successful examples with a primary alkyl chloride electrophile and a secondary alkyl iodide electrophile. The reaction provides a viable alternative to the Arbuzov-like silylation methodology, and it can be applied to the synthesis of functionalized disubstituted phosphinate esters. The method should be useful to phosphorus chemistry practitioners, particularly because the stoichiometry allows the use of valuable moieties present both in the phosphorus nucleophile and in the carbon electrophile.

Experimental Section

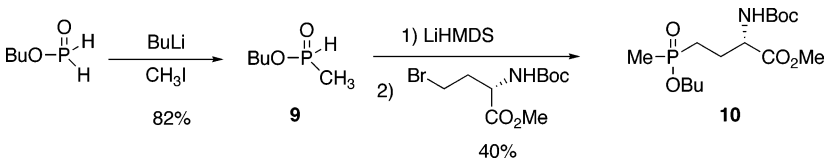
Typical Alkylation Procedure. Neat alkyl *H*-phosphinate ester (1.0 equiv, 1.5 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (5 mL) was then added under nitrogen. The flask was then placed at −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was backfilled with nitrogen, and LHMDS (1.0 M in THF, 1.0 equiv, 1.5 mmol) was added at −78 °C. After 15 min, the electrophile (1 equiv, 1.5 mmol) was added under N_2 as a neat liquid or as a 0.5 M THF solution for solids. (In the case of the bromomethyl- or chloromethylpyridine hydrobromide or -chloride, the pyridine was first deprotonated at −78C in dry THF with LHMDS (1 equiv) under N_2 for 15 min and then added to the solution of the lithium phosphinate.) After the addition of the electrophile, the temperature of the solution was slowly allowed to warm to room temperature (rt). (The temperature and reaction time after the solution reaches rt depend on the reactivity of the electrophile.) Once at rt, the reaction mixture was quenched with a saturated solution of NH_4Cl/brine, extracted with ethyl acetate (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography over silica gel.

For the alkyl iodides and alkyl triflate, the mixture reacted for 10 min at rt, except for the hindered iodides that were refluxed for 6 h. The alkyl bromides were reacted for 2−4 h at rt. The alkyl chlorides and tosylates were refluxed for 6 h or reacted at rt

SCHEME 3. Synthesis of a Known Kynureninase Inhibitor



SCHEME 4. Synthesis of a Phosphinothricin Precursor



overnight (except for BOMCl, which reacted for 10 min at rt). For HCF_2Cl, the reaction mixture is warmed up and quenched at 0 °C.

General Procedure for Alkyl Chlorides and Tosylates (Table 2, Entry 6): Octyl-phenyl-phosphinic Acid Ethyl Ester.[18] Neat ethyl phenyl-*H*-phosphinate (0.510 g, 3 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (10 mL) was then added under nitrogen. The flask was placed at −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, and LHMDS (1.0 M in THF, 3 mL, 3 mmol) was added at −78 °C. After 10 min, *n*-octyl chloride (510 μL, 3 mmol) was added under N_2. After addition, the reaction mixture was slowly allowed to warm up to rt. The solution was then refluxed overnight under N_2. After cooling, the reaction mixture was quenched with NH_4Cl/brine, extracted with ethyl acetate (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography (silica, EtOAc/hexanes 40:60) to afford the desired product (51%). RN: [119079-17-3]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85 (t, J = 6.7 Hz, 3 H), 1.22−1.35 (m, 10 H), 1.29 (t, J = 7.0 Hz, 3 H), 1.46−1.60 (m, 2 H), 1.81−2.04 (m, 2 H), 4.84 and 4.08 (m, 2 H), 7.45−7.60 (m, 3 H), 7.76−7.85 (m, 2 H).

General Procedure for Alkyl Bromides (Table 2, Entry 4). Neat ethyl phenyl-*H*-phosphinate (0.510 g, 3 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (10 mL) was then added under nitrogen. The flask was placed at −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, and LHMDS (1.0 M in THF, 3 mL, 3 mmol) was added at −78 °C. After 10 min, *n*-octyl bromide (520 μL, 3 mmol) was added under N_2. After addition, the temperature of the solution was slowly allowed to warm to rt. After 3 h at rt, the reaction mixture was quenched with NH_4Cl/brine, extracted with ethyl acetate (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography (silica, EtOAc/hexanes 40:60) to afford octyl-phenyl-phosphinic acid ethyl ester in 71% yield.

General Procedure for Alkyl Iodides and Triflates (Table 3, Entry 8): [(1,1-Diethoxy-ethyl)-ethoxy-phosphinoylmethyl]-phosphonic Acid Diethyl Ester.[19] Neat ethyl (l,l-diethoxyethyl)-phosphinate (630 mg, 3 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (10 mL) was then added under nitrogen. The flask was placed at −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, and LHMDS (1.0 M in THF, 3 mL, 3 mmol) was added at −78 °C. After 10 min, alkyl triflate (0.945 g, 3.15 mmol) dissolved in THF (6 mL) was added under N_2. After addition, the temperature of the solution was slowly allowed to warm to rt. After 1 h at rt, the reaction mixture was quenched with NH_4Cl/brine, extracted with ethyl acetate (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography (silica, EtOAc/MeOH 95:5) to afford the desired product (81%). RN: [179015-83-9]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 and 1.21 (2 × t, J = 7.0 Hz, 6H), 1.34 (m, 9H), 1.53 (d, J_{HP} = 12.6 Hz, 3H), 2.41 (ddd, J_{HP} = 20.8 Hz, J_{HP} = 14.4 Hz, J = 15.2 Hz, 1H), 2.68 (ddd, J_{HP} = 21.7 Hz, J_{HP} = 12.9 Hz, J = 15.2 Hz, 1H), 3.61−3.78 (m, 5H), 4.08−4.41 (m, 5H). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 22.1 and 40.09 (2 × d, J_{PP} = 20.0 Hz).

Representative Procedure for Hindered Iodides (Table 2, Entry 8): Isopropyl-phenyl-phosphinic Acid Ethyl Ester.[20] Neat ethyl phenyl-*H*-phosphinate (510 mg, 3 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (10 mL) was then added under nitrogen. The flask was placed at −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, and LHMDS (1.0 M in THF, 3 mL, 3 mmol) was added at −78 °C. After 10 min, isopropyl iodide (300 μL, 3 mmol) was added under N_2. After addition, the temperature of the solution was slowly allowed to warm to rt. The solution was then refluxed for 6 h. After cooling, the reaction mixture was quenched with NH_4Cl/brine, extracted with ethyl acetate (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography (silica, EtOAc/hexanes 80:20) to afford the desired product (45%). RN: [53716-14-6]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.04 (d, J = 7.0 Hz, 1.5H), 1.10 (d, J = 7.0 Hz, 1.5H), 1.16 (d, J = 7.0 Hz, 1.5H), 1.22 (d, J = 7.0 Hz, 1.5H), 1.32 (t, J = 7 Hz, 3H), 2.0−2.15 (m, 1H), 3.80−3.95 (m, 1H), 4.05−4.20 (m, 1H), 7.45−7.60 (m, 3H), 7.70−7.80 (m, H). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 54.60 (s).

Representative Procedure with Pyridinium Salts (Table 3, Entry 6b): (1,1-Diethoxy-ethyl)-pyridin-3-ylmethyl-phosphinic Acid Ethyl Ester. Neat ethyl (l,l-diethoxyethyl)phosphinate (0.630 g, 3 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (10 mL) was then added under nitrogen. The flask was placed at −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, and LHMDS (1.0 M in THF, 3 mL, 3 mmol) was added at −78 °C. In a second dry two-neck flask, LHMDS (1.0 M in THF, 3 mL, 3mmol) was added to a solution of 2-(bromomethyl)-pyridine hydrobromide (0.759 g, 3 mmol) in anhydrous THF (5 mL), at −78 °C under N_2. After 10 min, the first solution was added to the second one. After 10 min at −78 °C, the temperature of the solution was slowly allowed to warm to rt. After 3 h at rt, the reaction mixture was quenched with NH_4Cl/brine, extracted with ethyl acetate (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography (silica, EtOAc 100%) to afford the desired product (60%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12−1.29 (m, 9H), 1.50 (d, J_{HP} = 11.4 Hz, 3H), 3.11 and 3.23 (ABX system, J_{AB} = 14.6 Hz, J_{BX} = 8.2 Hz, J_{AX} = 8.6 Hz, 2H), 3.58−3.88 (m, 4H), 4.08 (qt, J = 7.3 Hz, 2H), 7.25 (dd, J = 7.9 Hz, J = 3.5 Hz, 1H), 7.67−7.74 (m, 1H), 8.48−8.51 (m, 2H). ^{13}C {^{1}H} NMR ($CDCl_3$, 75.45 MHz) δ 15.6 (d, J_{POCC} = 20.7 Hz), 16.7 (d, J_{PCC} = 5.2 Hz), 20.6 (d, J_{POCC} = 12.4 Hz), 30.0 (d, J_{PC} = 78 Hz), 57.9 (d, J_{POC} = 7.8 Hz), 58.7 (d, J_{POC} = 4.6 Hz), 62.3 (d, J_{POC} = 6.9 Hz), 101.5 (d, J_{PC} = 142 Hz), 123.4, 127.3 (d, J_{PCC} = 8.3 Hz), 137.8 (d, J_{PCCCC} = 4.6 Hz), 148.2 (d, J_{PCCC} = 3.2 Hz), 151.1 (d, J_{PCCCC} = 6.0 Hz). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 44.21 (s). HRMS ($[M + H]^+$ ion by direct probe): calcd for $C_{14}H_{25}O_4P$ 302.1521, obsd 302.1526.

Representative Procedure with Epoxides (Scheme 1): (2-Hydroxy-hex-5-enyl)-phenyl-phosphinic Acid Ethyl Ester 2. Neat ethyl phenyl-*H*-phosphinate (0.510 mg, 3 mmol) was placed under vacuum in a dry two-neck flask 10 min before use. Anhydrous THF (10 mL) was then added under nitrogen. The flask was placed at −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, and LHMDS (1.0 M in THF, 3 mL, 3 mmol) was added at −78 °C. After 10 min, 1,2-epoxy-

(12) For examples of epoxide-opening using the silicon method, see refs 1c and 1k.

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5-hexene (340 μL, 3 mmol) was added followed by the addition of boron trifluoride etherate (380 μL, 3 mmol) under N_2. After addition, the temperature of the solution was slowly allowed to warm to rt. After 2 h at rt, the reaction mixture was quenched with NH_4Cl/brine, extracted with ethyl acetate (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography (silica, EtOAc 100%) to afford the desired product (85%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J = 7.0 Hz, 3H), 1.53−1.72 (m, 2H), 1.91−2.19 (m, 5H), 3.87 (m, 1H), 4.07−4.23 (m, 2H), 4.88−5.06 (m, 2H), 5.78 (tqd, J = 6.4 Hz, J = 10.5 Hz, 1H), 7.46−7.83 (m, 5H). ^{13}C {^{1}H} NMR ($CDCl_3$, 75.45 MHz) δ 16.7 (d, J_{POCC} = 6.6 Hz), 29.82, 36.2, 37.2 (d, J_{PC} = 84.9 Hz), 37.5 (d, J_{PCCCC} = 3.5 Hz), 37.6 (d, J_{PCCCC} = 3.2 Hz), 61.1 (d, J_{POCC} = 6.9 Hz), 61.2 (d, J_{POCC} = 6.6 Hz), 65.6, 66.4 (d, J_{POCC} = 6.0 Hz), 128.9 (d, J_{PCC} = 2.3 Hz), 129.1 (d, J_{PCC} = 2.0 Hz), 130.4 (d, J_{PC} = 128 Hz), 131.5 (d, J_{PCCC} = 10.4 Hz), 131.8 (d, J_{PCCC} = 10.1 Hz), 132.1, 132.8, 132.9, 138.2 (d, J_{PCCCC} = 5.5 Hz). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 44.26 (s), 55.74 (s). HRMS (M^+ by EI^+): calcd for $C_{14}H_{21}O_3P$ 268.1228, obsd 268.1228.

Representative Procedure with Freon (Table 3, Entry 9): Difluoromethyl-(1,1-diethoxy-ethyl)-phosphinic Acid Ethyl Ester.[1d] Neat ethyl (l,l-diethoxyethyl)phosphinate (12.0 g, 57.1 mmol) was placed under vacuum in a dry two-neck flask equipped with a cold finger 10 min before use. Anhydrous THF (80 mL) was then added under N_2. The flask was cooled to −78 °C and deoxygenated under vacuum for 5 min. The reaction flask was back-filled with nitrogen, then LHMDS (1.0 M in THF, 57.1 mL, 57.1 mmol) was added at −78 °C. After 15 min, condensed chlorodifluoromethane (around 5.0 g, 58.0 mmol) was added under N_2. After addition, the temperature of the solution was kept at −78 °C for 10 min, then slowly allowed to warm to 0 °C. After 10 min at 0 °C, the reaction mixture was quenched with a saturated solution of NH_4Cl/brine, extracted with EtOAc (3×), and then dried over anhydrous $MgSO_4$. Concentration in vacuo gave an oil that was purified by column chromatography (silica, EtOAc/hexanes 30:70) to afford the desired product (71%). RN: [139474-89-8]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J = 7.0 Hz, 6H), 1.39 (t, J = 7.0 Hz, 3H), 1.58 (d, J_{HP} = 12.0 Hz, 3H), 3.63−3.87 (m, 4H), 4.29−4.39 (m, 2H), 6.08 (dt, J_{HF} = 27.5 Hz, J_{HF} = 48.9 Hz, 1H). ^{31}P NMR ($CDCl_3$, 121.47 MHz) δ 27.5 (t, J_{FP} = 71.4 Hz). ^{19}F NMR ($CDCl_3$, 282.30 MHz) δ −135.31 (ddt, J_{FH} = 21.8 Hz, J_{FP} = 71.4 Hz, J_{FH} = 49.5 Hz).

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Supporting Information Available: Representative NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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