Synthesis of Adamantyl *H*-Phosphinate Esters

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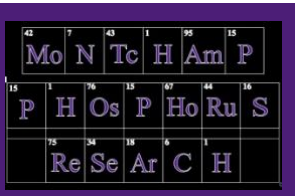
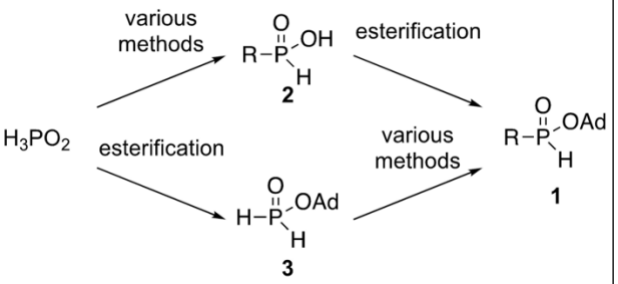


Abstract

Adamantyl *H*-phosphinate esters were first introduced by Yiotakis et al. as a protecting group in the synthesis of phosphinopeptides.[1] Gatineau et al. later found adamantyl *H*-phosphinate esters to be useful in the synthesis of *P*-stereogenic compounds.[2] Phosphorus compounds have a broad range of applications ranging from pharmaceuticals to agricultural products, making them an area of interest in synthetic chemistry. However, methods for the preparation of *P*-stereogenic compounds that achieve high enantioselectivity are limited.[3] Gatineau et al. discovered that adamantyl *H*-phosphinate esters serve as precursors that facilitate this preparation, which they attributed to the ability of the esters to resist racemization when displaced with organometallics.[2] However, their methods were limited by the necessity of chlorophosphine starting materials. In this project, we aimed at developing novel synthetic methods for the preparation of adamantyl *H*-phosphinate esters which are not limited in terms of available reagents and are less expensive than current known methods. EDC, PivCl, and T3P were utilized in the esterification reactions. Methods were developed to prepare these esters in good yield on a multigram scale without the need for chromatography. An alternative method to the esterification of *H*-phosphinic acids was also employed that involved the preparation of adamantyl hypophosphite and its conversion into a variety of *H*-phosphinate esters. However, adamantyl hypophosphite was shown to have limited reactivity.

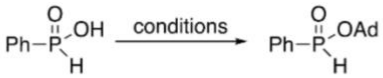
Methods



Method I: Esterification of *H*-phosphinic acids

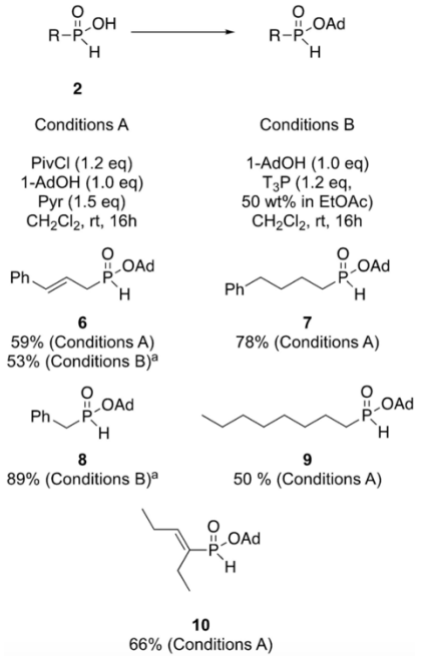
Phenyl *H*-phospinic acid was exposed to a variety of conditions in order to esterify it into the corresponding adamantyl ester. The highest yields were achieved under conditions using PivCl, T3P, a slight excess of $PhPO_2H_2$, and 1-AdOH as the limiting reagent. Esterification was then carried out on several different *H*-phosphinic acids under these conditions to generate a variety of adamantyl *H*-phosphinate esters.[4]

Table 1. Esterification of phenyl-*H*-phosphinic acid.

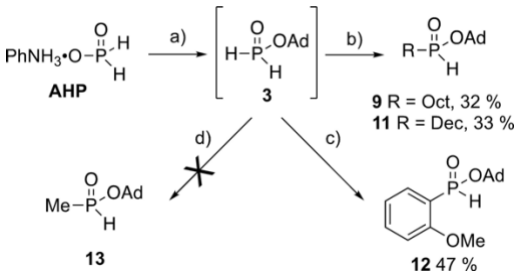


Entry	Conditions	Yield [%][a]
1	$PhPO_2H_2$ (1 eq) AdBr (2.4 eq), $CHCl_3$ and brought to reflux, Ag_2O (2.4 eq) added portion-wise. Refluxed for 2 h	42
2	$PhPO_2H_2$ (1.2 eq) AdBr (1 eq), $CHCl_3$, Ag_2O (1.0 eq) was added portion-wise, rt, 2 h	56
3	$PhPO_2H_2$ (1 eq) AdOH (1 eq) EDC (1.5 eq) DMAP (0.1 eq) CH_2Cl_2, 0 °C to rt, 16 h	55
4	$PhPO_2H_2$ (1.1 eq) AdOH (1.8 eq) EDC (1.5 eq) DMAP (0.1 eq) CH_2Cl_2, 0 °C to rt, overnight	72
5	$PhPO_2H_2$ (1 eq) PivCl (1.5 eq) Pyr (1 eq) AdOH (2 eq) CH_2Cl_2, rt, 16 h	84
6a	$PhPO_2H_2$ (1.2 eq) PivCl (1.2 eq) Pyr (1.5 eq) AdOH (1 eq)	80[b]
6b	CH_2Cl_2, rt, 16 h	94[b,c]
7a	$PhPO_2H_2$ (1.25 eq) T3P (1.5 eq, 50 wt% in EtOAc) AdOH	90[b]
7b	(1.0 eq) CH_2Cl_2, rt, 16 h	85[b,d]

[a] Isolated yield of pure **5** from **4** (1.5 mmol) after column chromatography, unless otherwise noted. [b] No chromatography. [c] 8.5 g (30 mmol) of **5**. [d] 13 g (48 mmol) of **5**.

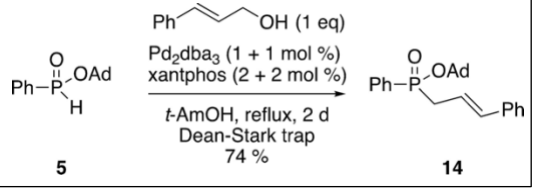


Method II: One-pot reactions with the novel adamantyl-hypophosphite



The novel adamantyl hypophosphite was first prepared and then used in a number of one-pot reactions with the aim of synthesizing a variety of adamantyl *H*-phosphinate esters. However, adamantyl hypophosphite was shown to have limited reactivity which is likely attributed to the bulky nature of the adamantyl group and its unfavorable tautomeric equilibrium.[4]

Despite its limited reactivity, Pd-catalyzed allylation with phenyl-*H*-phosphinate was successful and produced the corresponding adamantyl *H*-phosphinate ester.[4]



Conclusion

Two general methods for the synthesis of adamantyl *H*-phosphinate esters were developed. These methods are not limited in the availability of starting materials, reduce time, cost, and environmental impact, and expand the portfolio of adamantyl *H*-phosphinate esters. Future work could focus on finding a large-scale resolution method to avoid the limitations of chiral semipreparative HPLC.

References

1. Yiotakis, A.; Vassiliou, S.; Jiráček, J.; Dive, V. *Eur. J. Org. Chem.* **1996,** *61*, 6601–6605.
2. Gatineau, D.; Nguyen, D. H.; Hérault, D., Vanthuyne; N., Leclaire, J.; Giordano, L.; Buono, G. *J. Org. Chem.* **2015**, *80*, 4132–4141.
3. Lemouzy, S.; Giordano, L.; Hérault, D.; Buono, G. *Eur. J. Org. Chem.* **2020**, *23*, 3351–3366.
4. Winters, K. R.; Ricke, C.; Montchamp, J. L. *Eur. J. Org. Chem.* **2021**, *2022*, 1–6.

Acknowledgements

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