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Synthesis of phosphorus containing medium ring heterocycles by sequential Claisen rearrangement and ring closing metathesis

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ABSTRACT

An efficient method for the synthesis of novel medium ring phosphorus containing heterocycles starting from phenol derivatives by ruthenium catalyzed ring closing metathesis is described. This work deals with a sequential aromatic Claisen-rearrangement, coupling of an allyl/vinyl phosphonate, and ring closing metathesis reaction. All of these reactions were carried out at ambient temperature to afford the medium-sized phosphorus heterocycles in excellent yields.

Due to their ubiquity in biological systems[1] and potential to serve as novel pharmaceuticals and agrochemicals,[2] phosphorus containing heterocyclic compounds continue to receive widespread attention by the synthetic organic chemists. Catalytic antibody developer Haptens and anti-cancer agent cyclophosphamide are well known examples of phosphorus containing compounds.[3] 1,4-Dihydropyridine-5-cyclic phosphonate derivatives (such as compound **A**) are known to be an anti-hypertensive agent,[4a] besides these, several phosphorus analogues of sugars (as for example **B**) are also known for their different bioactivities.[4b–d] Addition to their bioactivities nowadays different *P*-heterocycles (as for example **C**) are used as catalyst[5] for asymmetric synthesis, Lewis bases,[6] and also as chiral auxiliaries ligand.[7] As a part of our continuing effort toward the development of new protocols for the expeditious synthesis of biologically relevant heterocyclic compounds,[8] we became interested to explore newer methodologies for the synthesis of phosphorus containing heterocycles. Considering their broad spectrum of bio-activity synthetic organic chemists have provided different protocols including different metal-catalyzed synthesis of phosphorus heterocycles.[9] Nevertheless these methods worked nicely but having some drawbacks. During the last two decades, after the discovery of Grubbs' catalyst,[10] RCM protocol has been used enormously in the construction of structurally diverse phosphorus containing heterocycles viz.; small ring and regular ring phosphorus heterocycles.[11]

However, synthesis of phosphorus containing medium ring heterocycles especially benzo-fused heterocycles has largely remained unexplored, this might, in part, be due to the lack of general methods for their synthesis. This has prompted us to investigate for an effective and compatible synthetic methodology to achieve the synthesis of some hitherto unreported benzo-fused oxophosphocine and oxophosphopine derivatives of biological interest.

In continuation with our work on the synthesis of medium ring by the implementation of sequential Claisen rearrangement followed by ring closing metathesis reaction,[8a,b] we have undertook a study to synthesize the hitherto unreported benzo-fused oxophosphocine and oxophosphopine derivatives from the substrates containing unsymmetrical alkenyl groups directly linked to the phosphorus atom. Herein, we report the results of our investigation.

Unsymmetrical alkenyl derivatives **4a–j** were used as metathetic precursors. For the synthesis of starting materials we have used the century old thermal Claisen rearrangement[12] of *O*-allylated derivatives of **1a–j** as one of the steps to access C-allylated phenol derivatives **2a–j** according to the published procedure.[13] The synthesis of unsymmetrical allyl arylphosphonate derivatives **4a–j** was accomplished according to Scheme 1.

The phosphonate derivatives **4a–j** were prepared in 72–93% yields by coupling of C-allylated phenol derivatives **2a–j** and the corresponding allylphosphonochloridate **3**.

For the synthesis of benzo-oxophosphocin derivatives the corresponding metathetic precursors **6a–d** were derived by the S_N2 displacement of chloride anion of vinylphosphonochloridate **4** by

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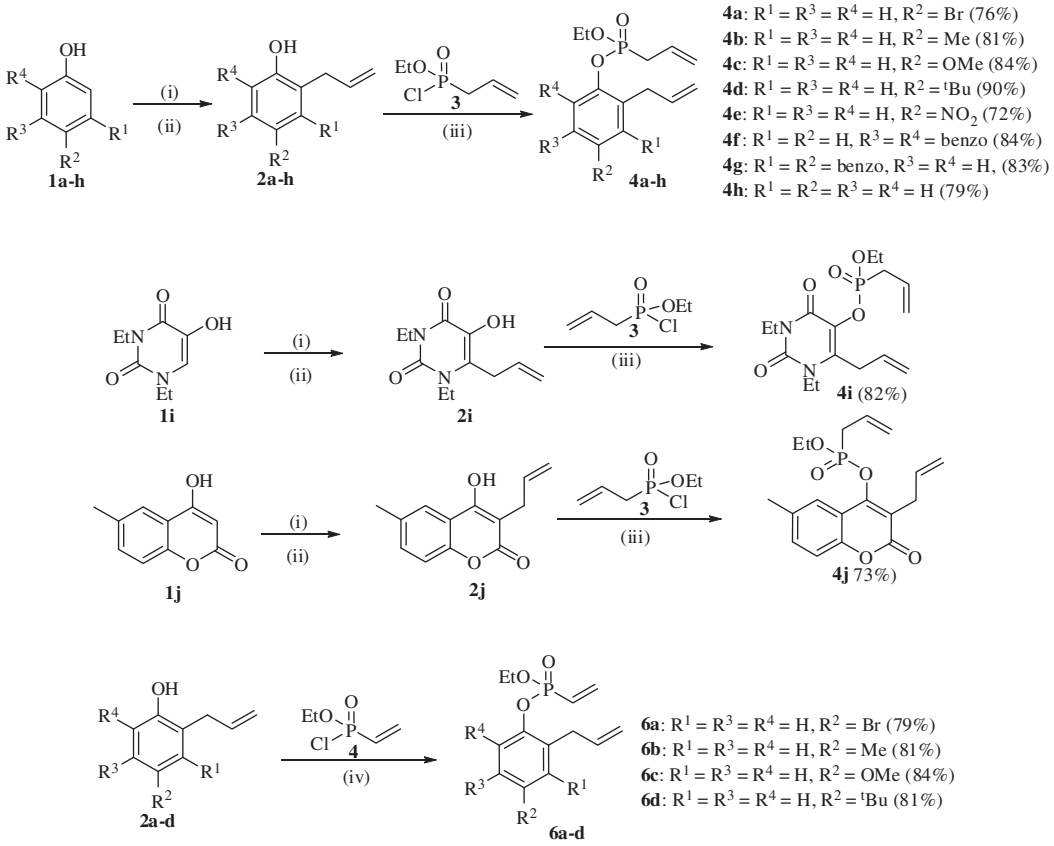


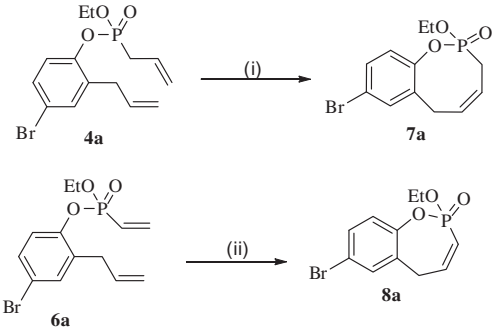
Scheme 1. Synthesis of unsymmetrical phosphorus tethered metathetic precursor. Reagents and conditions: (i) allyl bromide, K_2CO_3, dry acetone, reflux, 8 h; (ii) Dichlorobenzene, reflux 6 h; (iii) Dry Et_2O, Et_3N, 0 °C, 4 h; (iv) Dry Et_2O, Et_3N, 0 °C, 9 h.

the phenoxide anion of C-allylated aromatic precursors **2a–d**. The allylphosphonochloridate **3** and vinylphosphonochloridate **4** were prepared according to the published procedure[13] (scheme 1).

Finally, the ring closing metathesis was adopted for the synthesis of the target phosphorus containing medium ring heterocycles from the substrate **4a–j** and **6a–d**. Grubbs' first generation catalyst (**D**; Fig. 1) was used in the metathesis step for the formation of medium ring containing phosphorus.

When unsymmetrical alkenyl derivative, substrate **4a** was allowed to react in the presence of 5 mol % Grubbs' first generation catalyst under a nitrogen atmosphere at room temperature (rt) in dichloromethane for 5 h, the corresponding 8-membered cyclized product **7a** was obtained in excellent yield without any contamination of the product (Scheme 2).

For the synthesis of benzo-oxophosphocine derivatives the metathetic precursor **6a** was subjected to the same protocol with Grubbs' catalyst I, but the reaction resulted in giving a poor yield (23%) at room temperature, the rest of the starting material remained unchanged. The seven-membered product **8a** was obtained in 79% yield under refluxing condition for 8 h.



Scheme 2. Synthesis of phosphorus containing heterocycles by RCM. Reagents and conditions: (i) Grubbs' Cat I, 5 mol %, rt, DCM, 5 h, 92%; (ii) Grubbs' Cat I, 5 mol %, reflux, DCM, 8 h, 79%.

Encouraged by this result, other substrates **4b–j** and **6b–d** were similarly treated with Grubbs' catalyst I in dichloromethane to afford the corresponding oxophosphocine (**7b–j**) and oxophosphopine (**8b–d**) derivatives in 67–93% and 65–79% yields, respectively.

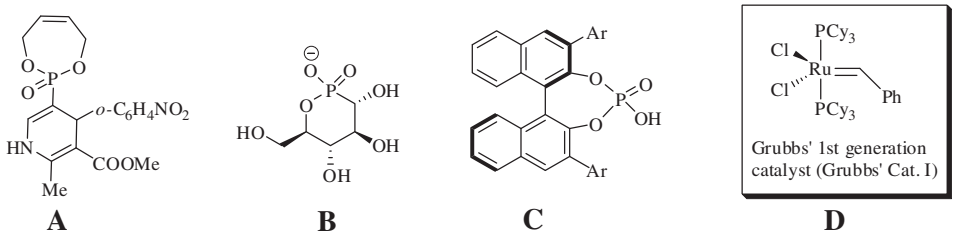
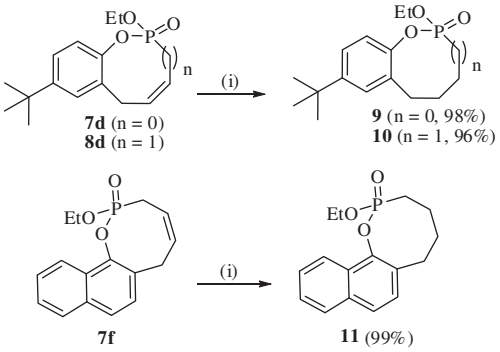


Figure 1. Some important phosphorus containing heterocycles and Grubbs' catalyst-I.

All oxophosphocine derivatives **8a–d** were obtained in improved yields (Table 1) under refluxing condition rather than room temperature. Variation has been done by introducing different types of electron demanding group. All structurally varied metathetic precursors gave the corresponding cyclized products by Grubbs' first generation catalyst, but the presence of electron withdrawing group (such as **4e**, **4i**, **4j**) gave comparable low yields than corresponding electron rich precursors.

The medium ring heterocycles obtained by ring closing metathesis reaction can further be easily converted to the corresponding saturated analogues by hydrogenation in the presence of 10 mol % Pd/C and. Seven-membered heterocycles **7d** gave the saturated analogue **9** in 98% yield. Other two eight-membered compounds **8d** and **7f** also gave the corresponding saturated analogue **10** and **11**, respectively under same reaction condition in almost quantitative yield (Scheme 3).



Scheme 3. Synthesis of saturated analogue of phosphorous containing heterocycles by hydrogenation. Reagent and condition: 10 mol % Pd–C, H_2, 2 h.

In conclusion, we have demonstrated a straightforward synthetic approach for a series of novel phosphorus containing medium ring heterocycles by applying the sequential Claisen rearrangement and RCM protocol. The methodology is simple, avoids hazardous steps, and uses easily available starting materials. The methodology is sufficiently flexible to permit the preparation of various ring sizes. This type of ring closing metathesis and its tolerance to both electron releasing and electron withdrawing groups may find this process complementary to those that exist in the literature.

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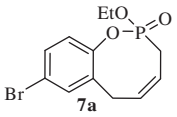
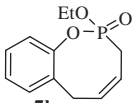
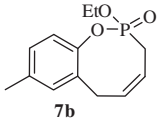
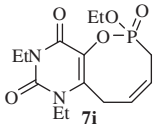
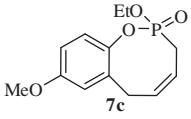
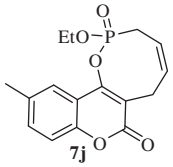
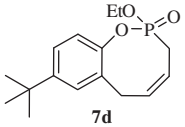
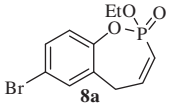
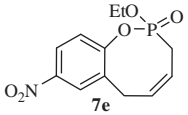
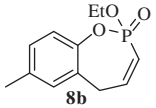
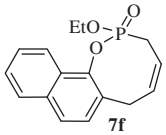
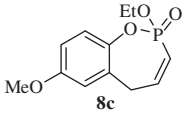
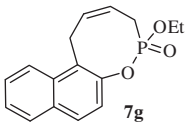
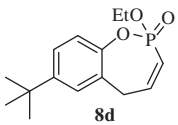
Table 1
Reaction condition, yield (%) of products (**7a–8d**)

Entry	Substrate	Product	Time	Yield[a] (%)	Entry	Substrate	Product	Time	Yield[a] (%)
1	**4a**	 **7a**	**5h** (rt)	92	8	**4h**	 **7h**	**6h** (rt)	87
2	**4b**	 **7b**	**4.5h** (rt)	89	9	**4i**	 **7i**	**4h** (rt)	82
3	**4c**	 **7c**	**4.5h** (rt)	93	10	**4j**	 **7j**	**6h** (rt)	73
4	**4d**	 **7d**	**5.5h** (rt)	82	11	**6a**	 **8a**	**8h** (reflux)	23[b] 79[c]
5	**4e**	 **7e**	8h (rt)	67	12	**6b**	 **8b**	**8.5h** (reflux)	19[b] 71[c]
6	**4f**	 **7f**	**6h** (rt)	87	13	**6c**	 **8c**	**8h** (reflux)	16[b] 73[c]
7	**4g**	 **7g**	**5.5h** (rt)	84	14	**6d**	 **8d**	**12h** (reflux)	18[b] 65[c]

[a] Isolated yield.
[b] Isolated yield in room temperature.
[c] Isolated yield under refluxing condition.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.008.

References and notes

1. (a) Melzer, M.; Chen, J. C.-H.; Heidenreich, A.; Gab, J.; Koller, M.; Kehe, K.; Blum, M.-M. *J. Am. Chem. Soc.* **2009**, *131*, 17226; (b) Chanda, A.; Khetan, S. K.; Banerjee, D.; Ghosh, A.; Collins, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 12058; (c) Seto, H.; Kuzuyama, T. *Nat. Prod. Rep.* **1999**, *16*, 589.
2. (a) Westheimer, F. H. *Science* **1987**, *235*, 1173; For more representative examples of phosphorus containing pharmaceutical agents, see: (b) Kafarski, P.; Lejczak, B. *Phosphorus Sulfur Silicon Relat. Elem.* **1991**, *63*, 193; (c) Colvin, O. M. *Curr. Pharm. Des.* **1999**, *5*, 555; (d) Zon, G. *Prog. Med. Chem.* **1982**, *19*, 205; (e) Fields, S. C. *Tetrahedron* **1999**, *55*, 12237; (f) Kafarski, P.; Lejczak, B. *Curr. Med. Chem.* **2001**, *1*, 301; (g) Mukherjee, S.; Huang, C.; Guerra, F.; Wang, K.; Oldfield, E. *J. Am. Chem. Soc.* **2009**, *131*, 8374.
3. (a) Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234; (b) Smith, A. B., III; Taylor, C. M.; Benkovic, S. J.; Hirschmann, R. *Tetrahedron Lett.* **1994**, *35*, 6853; (c) Stec, W. J. *Organophosphorus Chem.* **1982**, *13*, 145.
4. (a) Morita, I.; Kunimoto, K.; Tsuda, M.; Tada, S.-I.; Kise, M.; Kimura, K. *Chem. Pharm. Bull.* **1987**, *35*, 4144; (b) Jiang, X.; Minnaard, A. J.; Hessen, B.; Feringa, B. L.; Duchateau, A. L. L.; Andrien, J. G. O.; Boogers, J. A. F.; de Vries, J. G. *Org. Lett.* **2003**, *5*, 1503; (c) Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3690; (d) Rademacher, T. W.; Parekh, R. B.; Dwek, R. A. *Ann. Rev. Biochem.* **1988**, *57*, 785.
5. (a) Field, L. D.; Thomas, I. P. *Inorg. Chem.* **1996**, *35*, 2546; (b) Darrow, J. W.; Drueckhammer, D. G. *Bioorg. Med. Chem.* **1996**, *4*, 1341; (c) Harvey, T. C.; Simiand, C.; Weiler, L.; Withers, S. G. *J. Org. Chem.* **1997**, *62*, 6722; (d) Hanessian, S.; Rogel, O. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2441; (e) Hanessian, S.; Rogel, O. *J. Org. Chem.* **2000**, *65*, 2667.
6. (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763; (b) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825.
7. (a) Vries, A. H. M. D.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **1996**, *35*, 2374; (b) Molt, O.; Schrader, T. *Synthesis* **2002**, 2633.
8. (a) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B.; Nandi, R. K. *Synthesis* **2010**, 863; (b) Majumdar, K. C.; Mondal, S.; Ghosh, D. *Synthesis* **2010**, 1176; (c) Majumdar, K. C.; Ganai, S.; Nandi, R. K.; New, J. *Chem.* **2011**, *35*, 1355; (d) Majumdar, K. C.; Nandi, R. K.; Samanta, S.; Chattopadhyay, B. *Synthesis* **2010**, 985; (e) Majumdar, K. C.; Ponra, S.; Nandi, R. K. *Eur. J. Org. Chem.* **2011**, 6909; (f) Majumdar, K. C.; Nandi, R. K.; Ponra, S. *Synlett* **2012**, 113.
9. (a) Fourgeaud, P.; Vors, J. P.; Virieux, D. *Targets Heterocycl. Syst.* **2005**, *9*, 254; (b) Hetherington, L.; Greedy, B.; Gouverneur, V. *Tetrahedron* **2000**, *56*, 2053.
10. For reviews of RCM see: (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (b) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (c) Grubbs, R. H. *Handbook of metathesis*; Wiley-VCH: Weinheim, 2003; pp 1–1204. Vol. 3.
11. (a) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239; (b) Sieck, S. R.; McReynolds, M. D.; Schroeder, C. E.; Hanson, P. R. *J. Organomet. Chem.* **2006**, *691*, 5307; (c) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 8231; (d) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; Marel, G. A. V. D.; Boom, J. H. V. *Tetrahedron Lett.* **2000**, *41*, 8635; (e) Wu, X.; O'Brien, P.; Ellwood, S.; Secci, F.; Kelly, B. *Org. Lett.* **2013**, *15*, 192.
12. (a) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157; (b) Majumdar, K. C.; Chattopadhyay, B.; Sinha, B. *Lett. Org. Chem.* **2009**, *6*, 453.
13. Fourgeaud, P.; Midrier, C.; Vors, J.-P.; Volle, J.-N.; Pirat, J.-L.; Virieux, D. *Tetrahedron* **2010**, *66*, 758.