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Metathesis studies to cyclic enol phosphonamidates

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Abstract

The development of cyclic, six membered enol phosphonamidates utilizing the ring-closing metathesis (RCM) reaction is discussed. Phosphonamidic monochloridates are generated and further functionalized to an array of acyclic, enol phosphonamidates. Subsequent metathesis affords both desired RCM product and corresponding cross metathesis (CM) dimer. Efforts to optimize formation of desired RCM product, while minimizing CM products are discussed, with interesting steric and electronic factors governing reactivity patterns. This strategy allows for generation of cyclic enol phosphonamidates, with ultimate application to C(6)-substituted analogs of the anti-cancer agent, cyclophosphamide.

Keywords: Metathesis; Enolphosphonamidate; Cyclophosphamide

Organophosphorus [1] compounds continue to be popular targets due to their ubiquity in biological systems [2] and their potential to serve as novel pharmaceutical [3], agricultural [4], and chemical agents [5]. Until 1996, general methods to access phosphorus heterocycles (*P*-heterocycles) employing transition metal-catalyzed processes were primarily limited to Pd(0)-catalyzed protocols [6]. The advent of ring-closing metathesis [7] as a common synthetic tool has led to numerous advances in the preparation of unique small molecules [8]. In particular, a number of strained *P*-heterocycles has been reported utilizing ruthenium-based catalysts [$(PCy_3)_2(Cl)_2Ru{=}CHPh$] cat-**A** and [$(ImesH_2)(PCy_3)$–$(Cl)_2Ru{=}CHPh$] cat-**B** [9]. A number of noteworthy examples addressing olefinic substitution patterns and thus expanding the scope of RCM have emerged, including RCM with chlorine [10] and fluorine-substituted olefins [11]. Recently, Shibasaki and coworkers have carried out successful examples of RCM with enol silanes employing Grubbs catalyst (cat-**B**) [12], while RCM of various enol phosphates [13], and cross metathesis (CM) of vinyl phosphonates [14] have also been achieved. As part of our continued studies employing transition metal-catalysis to new *P*-heterocycles, we herein report the use of RCM en route to cyclic enol phosphonamidates, with potential application to cyclophosphamide (CP)-like analogs.

Among the more notable *P*-heterocycles displaying biological activity to emerge is cyclophosphamide (CP), a widely used anti-cancer alkylating agent that requires activation in vivo (Fig. 1). The chemistry and pharmacology of CP have been extensively studied and reviewed [15]. Cyclophosphamide is a prodrug and its cytotoxicity is attributed to the formation of an aziridinium ion, which is derived from release of a phosphoramide mustard; this mustard is able to crosslink interstrand DNA. The byproduct, acrolein, is also produced, though it does not contribute to anti-cancer activity within CP. However, acrolein is responsible for a number of undesired side effects associated with CP, including hemorrhagic cystitis [16]. A variety of CP analogs have been developed with substitution at various positions of the heterocycle. However, to-date, no analog has shown the success of CP itself. With this in mind, we set out to use RCM in the construction of a relatively unexplored class of CP-analogs displaying C(6)-substitution [17].

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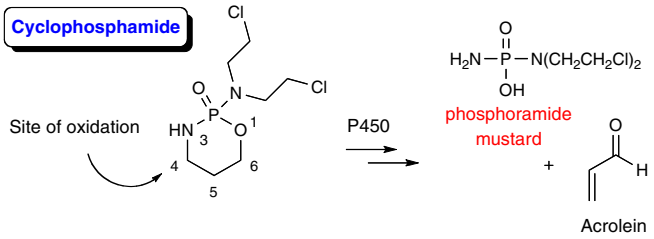


Fig. 1. Cyclophosphamide.

We initially began our study with the phosphorylation of allylbenzyl amine (**1**) using methylphosphonic dichloride to afford monochloridate **2** (Scheme 1). Due to the tendency of the monochloridate to undergo dimerization after purification, **2** was immediately reacted with the potassium enolate of acetophenone **3** to yield acyclic enol-phosphonamidate **4**. Subjection of **4** to olefin metathesis conditions using Grubbs cat-**B** afforded target six-membered phosphonamidate **5** as the major product (64%), along with acyclic dimer [18] **6** (26%) resulting from olefin CM [19]. Not surprisingly, no CM was seen between the enolic olefin partners [20], but instead occurred only between two allylic amine partners. To the best of our knowledge, this represents the first example of RCM on an enolphosphonamidate-containing substrate.

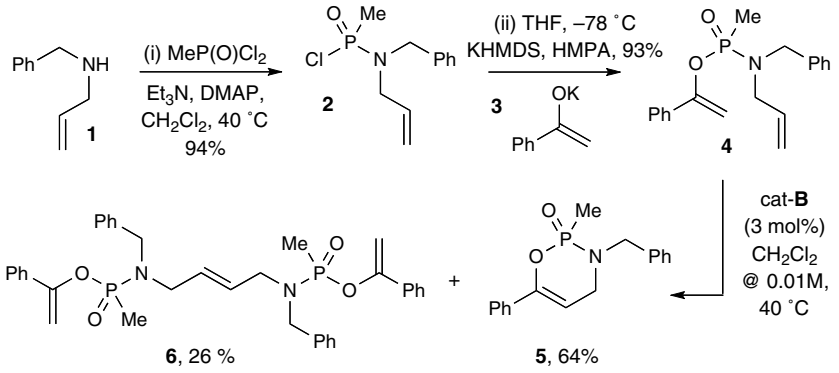
In order to provide eventual late-stage introduction of the mustard portion of CP, we explored the installation of a labile group at phosphorus. Utilizing a variety of P(V) dichlorides, successful generation of corresponding mono chloridates (**7a**–**c**) was achieved in a straight-forward manner (Scheme 2). Unlike **2**, monochloridates **7a**–**c** are quite stable and can be stored for prolonged periods of time. Subsequent *O*-phosphorylation with acetophenone gave acyclic enol phosphonamidates **8a**–**c**, which underwent RCM (0.01 M) with cat-**B** to form the corresponding RCM (**9a**–**c**) and CM (**10a**–**c**) products. Replacing $R^1 = CH_3$ with other groups however, led to increased conversion to the undesired CM product (**10a**–**c**) in all but one case, which contrasts with the initial results outlined in Scheme 1. Only the chloro-substituted phosphoryl acyclic diene (**8c**) gave RCM product **9c** as the major product (albeit slightly). Furthermore, reaction times in these systems were slow, typically taking between 24 and 48 h compared to 6 h for the methyl-substituted ($R^1 = Me$) system.

In attempting to optimize this reaction, we examined a number of factors, ranging from reaction concentration (0.005–0.5 M), catalyst load (1–10 mol%), and solvent (CH_2Cl_2, benzene, toluene). After surveying an array of combinations it was found that 3 mol% of cat-**B**, run in 0.01 M CH_2Cl_2, gave optimal results.

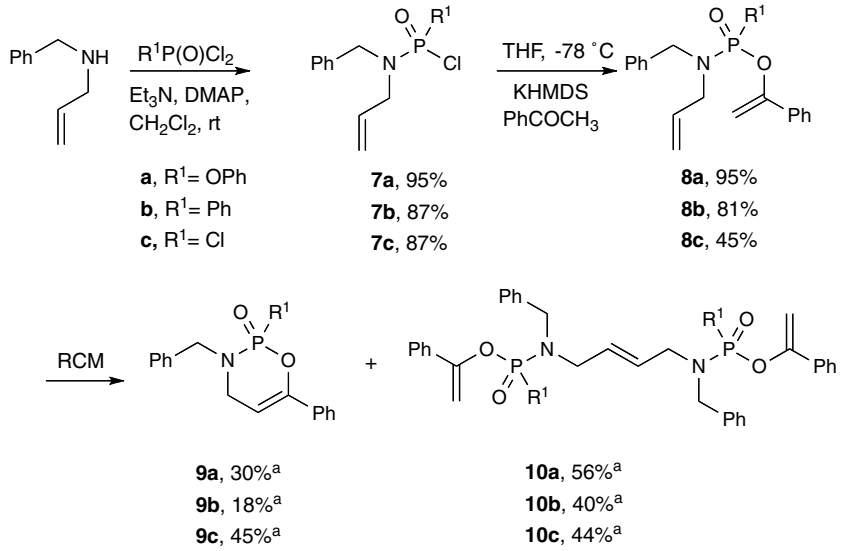
Substitution at nitrogen was next probed. Thus monochloridate **12** was generated using the previously mentioned protocol. Subsequent *O*-alkylation with acetophenone yielded acyclic enol phoshphonamidate **13**. Exposure of **13** to the optimized metathesis conditions, resulted in exclusive CM product formation (**14**) (*E*/*Z* 97:3) (Scheme 3) with no desired cyclized product detected. Thus the benzyl group at nitrogen seems to be essential to inhibit dimer formation, presumably through a steric effect, however the exact origin of this result is unclear.

In order to probe potential electronic effects, we next turned our attention to metathesis studies containing precursors possessing substitution within the aromatic ring (Table 1). Both electron withdrawing and donating groups were examined in this study, with the reactions conveniently monitored using ^{31}P NMR analysis [21]. Again in order to accommodate late-stage introduction of the mustard segment, we began this portion of our study by looking at acyclic enol phosphonamidates possessing a labile group at phosphorus (i.e., –Cl or –OPh, entries 1–6). As shown in Table 1, metathesis of precursors containing a *para*-substituted Cl- (entries 3 and 6) or MeO- (entries 2 and 5) aromatic ring led to an erosion of the RCM/CM ratio. With these interesting results in hand we reexamined the Me-substituted phosphonyl system. In stark contrast, aromatic-substitution in these systems (entries 8–10) resulted in a dramatic increase in conversion to the RCM product. Both electron donating- (–OMe, entry 8) and electron withdrawing-substituted (–NO_2, entry 10) [22] precursors gave substantial increases in the RCM manifold. The highest conversion occurred in entry 8 with 88% conversion to the desired cyclic system.

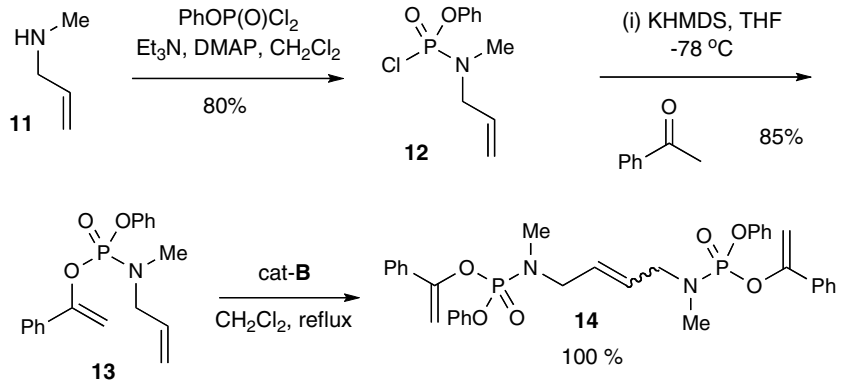
In order to further optimize this promising result we reexamined our enol phosphonamidate systems utilizing



Scheme 1.

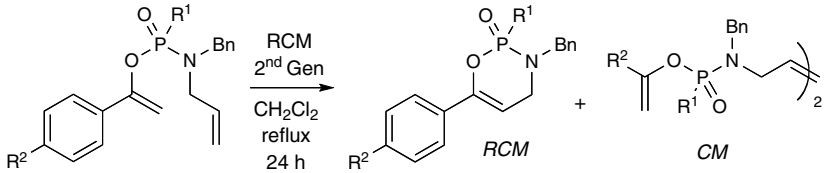


Scheme 2.



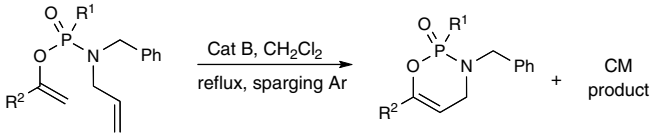
Scheme 3.

Table 1
Substitution effects



Entry	R^1	R^2	% RCM	% CM	SM
1	Cl	H	45	44	
2	Cl	OMe	16	54	30
3	Cl	Cl	11	41	48
4	OPh	H	30	56	
5	OPh	OMe	11	41	47
6	OPh	Cl	13	41	45
7	Me	H	64	26	
8	Me	OMe	88	6	6
9	Me	Cl	84	7	8
10	Me	NO_2	75	3	21

Table 2
Sparging effects on RCM



Entry	R^1	R^2	Time (h)	% RCM	% CM
1	Me	C_6H_5	3	82	17
2	OPh	C_6H_5	20	39	42
3	Me	*p*-Cl–C_6H_5	3	75	2

the sparging technique reported by Reiser and co-workers [23]. Sparging with argon resulted in substantial increases in conversion to the desired RCM products (Table 2). Moreover, dramatic decreases in reaction times were observed. Entry 1 shows improvement to 82% RCM product in 3 h when the reaction is purged with argon, compared to the original observation of 64% conversion after 6 h (Scheme 1). Furthermore, when the aromatic group is substituted (entry 3) even less CM product (only 2%) formation was seen after 3 h. We also reexamined one of the systems where the phosphoryl group is substituted with a labile group. When R^1 is OPh (Entry 2, Table 2), constant Ar purge resulted in a 1:1 mixture of RCM:CM which was achieved after 20 h. This improved result compares with a resulting 1:2 mixture after 48 h (Entry 4, Table 1) using static Ar conditions. When subjecting the RCM products to the reaction conditions both with and without ethylene, no ring-opening or CM was observed after 72 h.

In conclusion, the first examples of RCM with an enol-phosphonamidate-containing substrate to yield C(6)-substituted precursors to cyclophosphamide analogs has been accomplished. During this investigation a number of interesting steric and electronic factors were uncovered. Further studies elucidating the origins of these intriguing results are underway and will be reported in due course.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2006.09.035.

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