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A Modular Rearrangement Approach toward Medicinally Relevant Phosphinic Structures

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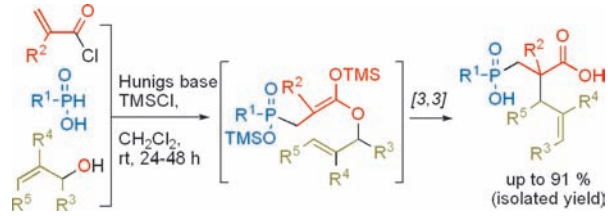
ABSTRACT



An unprecedented coupling of a P−C and a C−C bond-forming event in a practical operation was developed to access medicinally relevant phosphinic structures. The strategy relies on an Ireland−Claisen rearrangement triggered by the phospha-Michael addition of silyl phosphonites to allyl acrylates. This protocol was extended to a more versatile three-component variant that utilizes phosphinic acids, acryloyl chlorides, and allylic alcohols as starting materials.

The conjugate addition of phosphorus nucleophiles to activated alkenes (phospha-Michael reaction) holds a fundamental position in organophosphorus chemistry.[1] The formation of a stable P−C bond through this process has allowed access to a wide range of medicinally relevant phosphorus peptidomimetics (Figure 1) that act as transition-state analogue inhibitors of various proteases.[2] In recent years, several phosphinopeptidic Zn−metalloprotease inhibitors with excellent selectivity profiles have been developed,

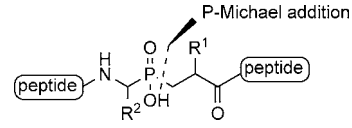


Figure 1. Generic structure of a phosphinic peptide and standard P−C bond disconnection.

and in most of these cases, a P-Michael reaction stands at the heart of their synthesis.[3]

On the other hand, the reversible addition of P(III) nucleophiles to 1,4-conjugated systems is one of the most prominent techniques to trigger transformation events on the parent substrate, i.e., the formation of a new C−C bond.[1b,c,4] Interestingly, coupling of P−C and C−C bond-forming events during a P-Michael addition represents a challenge hitherto scarcely addressed.[5] As part of our ongoing research on phosphinic peptidomimetics, we envisioned that the

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(1) For reviews, see: (a) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(2) For reviews on phosphorous-containing peptidomimetics, see: (a) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; John Wiley & Sons: Chichester, 2000. (b) Collinsová, M.; Jiráček, J. *Curr. Med. Chem.* **2000**, *7*, 629. (c) Yiotakis, A.; Georgiadis, D.; Matziari, M.; Makaritis, A.; Dive, V. *Curr. Org. Chem.* **2004**, *8*, 1135. (d) Palacios, F.; Alonso, C.; de los Santos, J. M. *Chem. Rev.* **2005**, *105*, 899.

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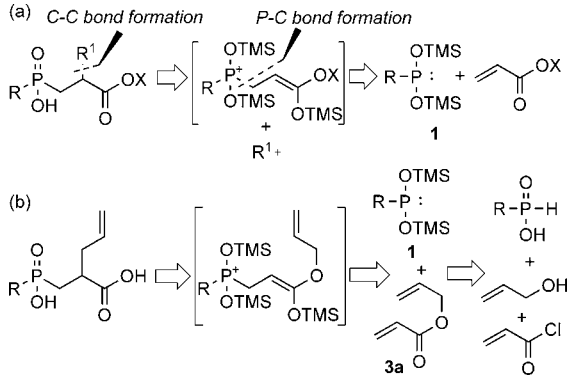
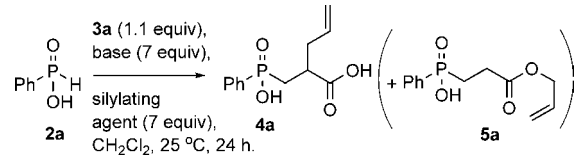
development of a modular protocol that would involve tandem P−C/C-C bond formation would pave the way for the combinatorial synthesis of diversified phosphinic scaffolds in a single operation (Scheme 1a). In this paper, we report a novel tandem P−C/C−C bond-forming reaction based on the sequential P-Michael addition of silyl phosphonites to allyl acrylates followed by Ireland−Claisen rearrangement and the extension of this transformation to a more convergent three-component variant.

Scheme 1. (a) Tandem P−C/C−C Bond-Forming Approach. (b) Proposed Tandem P-Michael/Ireland−Claisen Sequence



At the onset of our study, prompted by the work of Inanaga et al. on the phosphine-catalyzed [3,3] rearrangement of allyl acrylates to α-methylene-γ,δ-unsaturated carboxylic acids,[6] we reasoned that a similar [3,3] Ireland−Claisen rearrangement could occur upon conjugate addition of in situ generated trivalent bis(trimethylsilyl)phosphonites (**1**) to an allyl acrylate. In this case, however, a stable P−C bond might be also formed (Scheme 1b).[7] Initial experiments to test our working hypothesis were carried out with phosphinic acid **2a** and allyl acrylate (**3a**) as the Michael acceptor. After extensive experimentation, it was revealed that the reaction outcome is dramatically affected by the choice of silylation conditions. Silylation of **2a** by HMDS and subsequent addition of **3a** at 25 °C led to the moderate conversion of **2a** to a 1:1 mixture of **4a** and **5a** (Table 1, entry 1). A significant improvement in both yield and **4a**/**5a** ratio (3:1) was observed upon silylation with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) (Table 1, entry 2). Interestingly, when TMSCl was used the product distribution was highly dependent on the amine employed each time. Gratifyingly, the combination of TMSCl and Hunig's base led to a **4a**/**5a** ratio of 10:1 when 7 equiv of each reagent were used (Table 1, entry 4). Furthermore, a wide screening of other amines in lieu of Hunig's base led to an unexpected observation: all the amines tested (except Et_3N) switched the **4a**/**5a** ratio in favor of the Michael adduct **5a** with *imidazole suppressing completely the formation of* **4a** (Table 1, entry 10). This remarkable tuning effect of the amine to the reaction outcome can offer easy access to both scaffolds **4a** and **5a** by using practically the same reaction setting.

Table 1. Condition Screening of Reaction between **2a** and **3a**



entry	silylating agent	base	**4a**/**5a**[a]	yield[a] (%)
1	HMDS		51:49	46
2	BSA		75:25	>99
3	TMSCl	Et_3N	77:23	>99
4	**TMSCl**	**i-Pr$_2$EtN**	**91:9**	>**99**[b]
5	TMSCl	DABCO	49:51	>99
6	TMSCl	DBU	29:71	>99
7	TMSCl	DMAP	33:67	>99
8	TMSCl	NMM	21:79	>99
9	TMSCl	DBN	3:97	85
10	**TMSCl**	**imidazole**	**0:100**	>**99**[c]

[a] Determined by ^{31}P NMR spectroscopy of the crude mixtures. [b] Yield of isolated product **4a**, 85%. [c] Yield of isolated product **5a**, 97%.

NMR monitoring of the reaction between **2a** and **3a** revealed that silyl ketene acetal **6** was the true precursor of the rearrangement (Scheme 2). We observed that at −30 °C, phosphonite **1a** (δ_P = 141.3 ppm) is slowly converted to an intermediate showing two signals at δ_P = 33.9 and 34.0 ppm which are within the typical range of chemical shifts for P(V) phosphinic esters (see the Supporting Information). Interestingly, when the reaction was quenched with D_2O after 48 h at −30 °C, compound **5a** that had undergone quantitative deuterium incorporation was obtained. This implies that the observed intermediate corresponds to silyl ketene acetal **6** (*E* and *Z*

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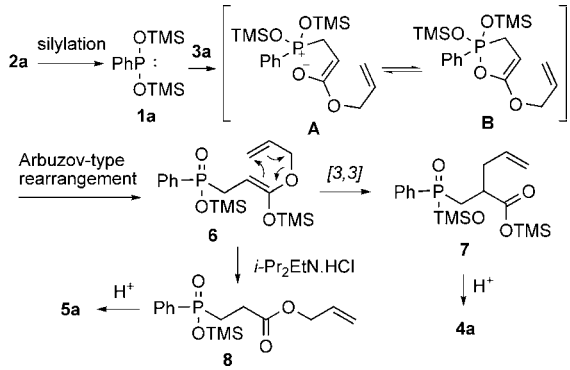
(7) For Ireland−Claisen rearrangements triggered by conjugate additions, see: (a) Aoki, Y.; Kuwajima, I. *Tetrahedron Lett.* **1990**, *31*, 7457. (b) Yamazaki, T.; Shinohara, N.; Kitazume, T.; Sato, S. *J. Org. Chem.* **1995**, *60*, 8140. (c) Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631. (d) Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 8728. (e) Bausch, C. C.; Johnson, J. S. *J. Org. Chem.* **2008**, *73*, 1575. For a relevant reaction with oxasilacyclopentenes, see: (f) Calad, S. A.; Woeprel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 2046.

Scheme 2. Proposed Mechanistic Pathway



isomers) which cannot rearrange at −30 °C. In addition, the absence of any other intermediates in the reaction mixture at −30 °C suggests that a rapid Arbuzov-type rearrangement of primary adducts (zwitterions **A** and oxaphosphalenes **B** have been proposed)[8] toward secondary adduct **6** precedes the sigmatropic rearrangement. This observation rules out possible rearrangement of **A** or **B**, a hypothesis that could be valid on the basis of recent work by Woerpel et al. on similar isosteric oxasilacyclopentenes.[7f] When imidazole was used as a deprotonating base, no deuterium incorporation was observed upon D_2O addition at −30 °C, which suggests that intermediate **6** is internally quenched by imidazole.HCl. This result may explain the absence of rearranged product observed at entry 10 of Table 1. When we followed the fate of **6** at room temperature in the TMSCl/*i*-Pr_2EtN system, we observed that this was fully consumed within 5 h to give a new major resonance at δ_P = 33.5 ppm and a minor at δ_P = 33.8 ppm. Upon quenching with D_2O, a 10:1 mixture of **4a**/**5a** was obtained in which **5a** was not labeled. Obviously, **6** affords **7** upon rearrangement or, to a lesser extent, **8** upon protonation by *i*-Pr_2EtN.HCl and the final product distribution reflects the relative rate of these two processes which is clearly in favor of the sigmatropic rearrangement under the described conditions.

The scope of this P-Michael/Claisen tandem process was studied by testing a wide range of acrylates with diverse substitution patterns. It should be emphasized that in all cases, target compounds of type **4** were easily isolated from minor Michael-adduct byproducts of type **5** by standard column chromatography, thus satisfying our initial requirement for a synthetically useful protocol. Substituents at C-1 or C-3 of the allylic part of **3** do not affect the efficiency of the formation of rearranged products **4** (Table 2, entries 1, 3, and 4).[9] Moreover, comparison of entries 3 and 4 of Table 2 shows that a phenyl group at C-3 position benefits the rearrangement process, possibly due to a better stabilization of the pericyclic reaction transition state. Slightly inferior yields for products of type **4** were observed with a C-2 substituent on the allylic chain (Table 2, entries 2 and 5). This protocol was also able to provide synthetically useful allenyl-substituted phosphinate **4g** by

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Table 2. P-Michael/Claisen Reaction between Phosphinic Acids and Allyl Acrylates[a]

entry	components	product	yield (%)[b]
1	**2a** + **3b**	**4b**	79
2	**2a** + **3c**	**4c**	69
3	**2a** + **3d**	**4d**	90[c]
4	**2a** + **3e**	**4e**	78[c]
5	**2a** + **3f**	**4f**	69[c]
6	**2a** + **3g**	**4g**	66
7[d]	**2a** + **3h**	**4h**	91
8[d]	**2a** + **3i**	**4i**	84
9	**2b** + **3a**	**4j**	52
10	**2c** + **3a**	**4k**	84

[a] Conditions: **2**, **3** (1.1 equiv), *i*-Pr_2EtN (7 equiv), CH_2Cl_2, then TMSCl (7 equiv) at −78 °C, warm to rt, 24 h. [b] Yield of isolated product. [c] dr: 70:30 (**4d**), 65:35 (**4e**), 90:10 (**4f**). [d] Reaction time 48 h.

replacing the starting allyl acrylate with propargyl acrylate. Furthermore, a very interesting application of this process relies on the preparation of phosphinic scaffolds with an all-carbon quaternary center at the α-position (Table 2, entries 7 and 8). Such structures can be of great medicinal interest since double substitution of peptidomimetics is a well-known medicinal

technique to obtain conformationally restricted bioactive compounds.[10] These unique phosphinic structures can be easily obtained by using allyl acrylates bearing an α-substituent. To our knowledge, this protocol represents the first general synthetic method for phosphinic peptide-like structures with a quaternary α-carbon.[11]

Cbz-protected α-aminophosphinic acids (**2b**) can be also used in this reaction, although the yield of the rearranged product is lower (**4j**/**5j** = 55:45 in the crude mixture) due to a negative effect of the vicinal amide hydrogen (Table 2, entry 9).[12] Although the role of this amide hydrogen in the final **4j**/**5j** ratio is not completely understood, the 6-atom distance between the amide hydrogen and the nucleophilic carbon of silyl ketene acetal **6j** could imply an increased susceptibility to protonation due to intramolecular proton transfer, as it is depicted in Figure 2. This is further supported

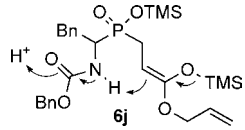


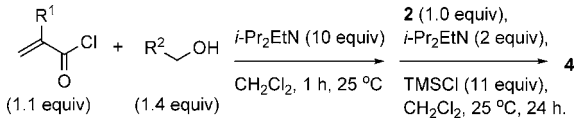
Figure 2. Intramolecular interaction at **6j** that may accelerate its deactivation.

by the fact that when the bis-protected aminophosphinic analogue **2c** was employed, the yield of the rearranged product was increased in levels comparable to those obtained with phenylphosphinic acid (Table 2, entry 10).

Although the development of the reported protocol follows the spirit of our initial concept, it still does not enable us to assemble the target compounds by three independent components that will correspond to the phosphinic part, the propionyl backbone part, and the side-chain part. Obviously, the two latter components are brought together in the final structure by an allyl acrylate that needs to be synthesized separately. Therefore, our next goal was to merge the allyl acrylate preparation with the P-Michael addition/Ireland−Claisen rearrangement protocol in an one pot three-component process. A crucial feature of the developed method that allowed us to perform this combination was the tolerance of the process to the presence of *i*-Pr_2EtN·HCl. We reasoned that such a characteristic would permit the in situ formation of allyl acrylates by acryloyl chloride and simple allylic alcohols mediated by Hunig's base. Indeed, addition of TMSCl and a phosphinic acid in a reaction mixture consisting of acryloyl chloride, an allylic alcohol, and Hunig's base successfully provided the target structures in high yields. In all cases, the desired products were obtained with high efficiency, comparable to that of the two-component protocol. Some examples of this novel transformation are shown in Table 3.

In conclusion, we have developed a novel and practical reaction sequence which enables the rapid assembly of medicinally relevant phosphinic structures starting from readily available acryloyl chlorides, allylic or propargylic alcohols and

Table 3. One-Pot Three-Component Synthesis of Compounds **4**[a]



entry	phosphinic acid	$-R^1$	$-R^2$	product	yield[a] (%)
1	**2a**	−H	$-CH=CH_2$	**4a**	80
2	**2a**	−H	$-C(Me)=CH_2$	**4c**	54
3	**2a**	−H	−CH=CHPh (*E*)	**4d**	91
4	**2a**	−H	−C≡CH	**4g**	67
5[b]	**2a**	−Bn	$-CH=CH_2$	**4h**	87
6	**2c**	−H	$-CH=CH_2$	**4k**	76

[a] Yield of isolated product. [b] Reaction time 48 h.

phosphinic acids. The reaction involves an Ireland−Claisen rearrangement triggered by the P-Michael addition of silyl phosphonites to allyl acrylates, both formed in situ. This unique tandem P−C/C−C bond-forming reaction allows the preparation of diverse phosphinic peptidomimetic structures in a single step and gives access to unprecedented α,α-disubstituted scaffolds that can be of great interest for the development of conformational-constrained bioactive compounds. In fact, all compounds of type **4** reported herein are potential inhibitors of zinc−metallocarboxypeptidases, a large family of exopeptidases that are involved in a wide range of physiological process, as well as, in numerous human pathologies.[13] It is also noteworthy that this method represents the first application of an Ireland−Claisen rearrangement in a three-component synthetic protocol. Studies on the scope and the development of an asymmetric version of this process are currently underway.

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Supporting Information Available: Full experimental details, characterization data, and copies of ^{1}H, ^{13}C and ^{31}P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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