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Metal-Free Entry to Phosphonylated Isoindoles by a Cascade of 5-*exo*-dig Cyclization, a [1,3]-Alkyl Shift, and Aromatization under Microwave Heating

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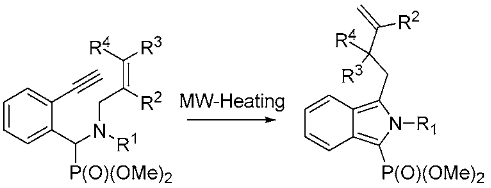
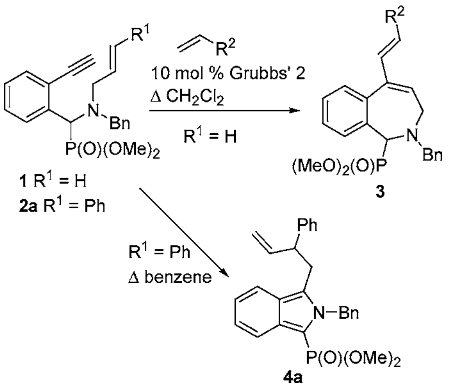
ABSTRACT



When *o*-ethynylbenzyl α-aminophosphonates are heated under microwave conditions, a rearrangement occurs which results in the formation of phosphonylated isoindoles. The rearrangement consists of a 5-*exo*-dig cyclization followed by a [1,3]-alkyl shift and finally aromatization.

Recently, we reported on the synthesis of phosphonylated benzazepines **3** via a domino enyne metathesis−cross-metathesis between an appropriately functionalized aminophosphonate **1** and an alkene (Scheme 1).[1] Studying the reactivity of **2a**, bearing a nonterminal alkene, it became apparent that this compound was quite inert toward the second-generation Grubbs' catalyst,[2] even in refluxing benzene. After two weeks of refluxing, however, spectroscopic analysis revealed the formation of a trace amount of a new compound with a ^{31}P NMR shift around 15 ppm. From previous experience in azaheterocyclic phosphonates, this was recognized as a phosphorus attached to an sp^2 carbon.[3] The trace amount was isolated and identified as isoindole **4a**. Phosphonylated isoindoles and related compounds are rarely described in the literature. In fact, only one entry to phosphonylated isoindoles could be found from the reaction of 2,3-benzoxazin-1-ones with trialkyl phosphites at high temperature.[4] Few entries toward phosphonylated dihydro isoindoles[5] and isoindolinones[6] have been reported in the literature. The latter are known for their plant growth regulating properties.[7] Isoindoles possessing an alkoxycar-

Scheme 1



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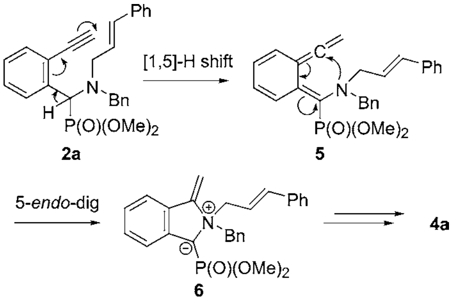
bonyl group, the bioisosteric counterpart of the phosphonate,[8] on the 1-position have been patented as appetite depressants.[9]

The presence of the terminal free double bond in **4a** suggests that the metathesis catalyst is no longer active because otherwise the product should have been dimerized. This points to the fact that the rearrangement is thermally driven rather then catalyzed by a metallic species. Indeed, it was found that refluxing **2a** in benzene results in a very slow conversion to **4a**. This conversion proceeded faster in CH$_3$CN. Almost all annulations of alkynes require activation of the triple bond. This can be achieved by a variety of transition metals such as Au(III),[10] Au(I),[11] Cu(II),[12] Cu(I),[13] Pd,[14] Ag,[15] and others (W, Pt, Ru).[16] Activation can also be achieved by TBAF,[17] TFA,[18] and certain electrophiles.[19] Addition to an unactivated carbon−carbon triple bond is rather uncommon but not unknown.[20] At first, it was thought that the reaction proceeded via a [1,5]-shift of the acidic proton in the α-position of the phosphonate of **2a** followed by 5-*endo*-dig attack of the nitrogen atom onto the central allene carbon atom of **5**.[21] The zwitterionic form **6** could then further rearrange toward the final product (Scheme 2). The first step in this sequence is assumed to be rate determining because aromaticity is lost. The addition of NEt$_3$ to a refluxing solution of **2a** in CH$_3$CN, to facilitate the proton shift, did not result in an increased reaction rate and caused decomposition of **4a**.

Scheme 2



If the reaction is thermally driven, increasing the temperature should result in a faster conversion to **4a**. Unfortunately, refluxing in DMF, DMSO, or NMP did not result in a clean reaction. Finally a high-temperature, short-time approach (185 °C/200 min) was achieved by heating **2a** in a 1:1 mixture of benzene/CH$_3$CN under microwave conditions resulting in a 95% conversion to **4a**. The proposed reaction mechanism is depicted in Scheme 3. The first step involves a direct addition onto the triple bond in a 5-*exo*-dig fashion. Although *endo*-dig cyclizations are more favored than *exo*-dig cyclizations, in this case the *endo*-cyclization would lead to a less stable secondary anion. The zwitterionic form **7** fragments into anion **8** and cation **9a** which is in resonance with cation **9b**.

As a result, anion **8** reacts with the allylic cation at the phenylated position and the overall result corresponds to a [1,3]-alkyl shift. Finally, aromatization occurs by a [1,5]-H shift of **10**. To establish the general nature of this rearrangement, a number of substrates **2a**−**i** were prepared by a one-pot, three-component coupling of 2-ethynylbenzaldehyde, secondary amines, and P(OMe)$_3$ mediated by LiClO$_4$.[22] Table 1 summarizes isolated yields of the isoindoles obtained under optimized conditions (165 °C).

We were pleased to find that in all cases the isoindoles were formed. This rearrangement is not limited to these examples where allylic cations can be formed. If a benzyl cation can be formed, the rearrangement also occurs. In these cases, however, an inseparable mixture of two isoindoles in a variable ratio depending on the applied temperature is produced in addition to decomposition material.[23] The first is the expected product **4j**,**k**, and the second compound is **11a**,**b**, formed by protonation and aromatization of intermediate **8** (Scheme 4). This seems to suggest that the benzyl cations do not survive long enough in the reaction mixture to quantitatively react with anions **8**.

We observed that during the synthesis of compounds **2** sometimes some isoindole (<10%) was formed if the reaction was allowed to stir for a prolonged time, probably by activation of the triple bond by LiClO$_4$. This observation, together with the fact that only allyl or benzyl cations migrate, prompted us to try to trap a zwitterionic intermediate of type **7**. A mixture of 2-ethynylbenzaldehyde, pyrrolidine,

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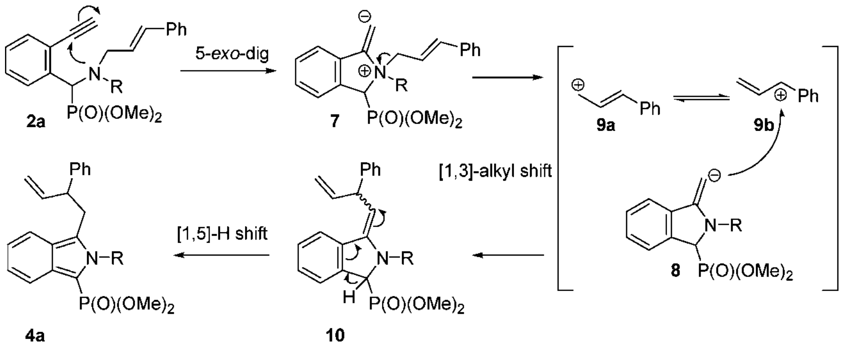
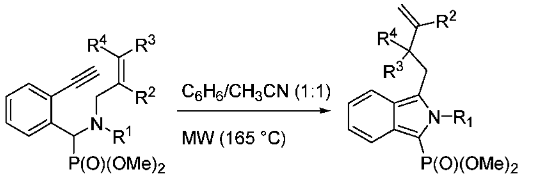
(23) This was also observed when heating **2b** to 180 °C.

Scheme 3



and trimethyl phosphite was stirred in a concentrated solution of $LiClO_4$ for 4 h and was then quenched by the addition of 3 N HCl (Scheme 5). Under these conditions, intermediate **12** did not fragment, because a nonstabilized primary cation would have been formed, but instead reacted with HCl producing compound **13**.

Table 1. Microwave-Induced Rearrangement of **2a**−**i** to Isoindoles **4a**−**i**

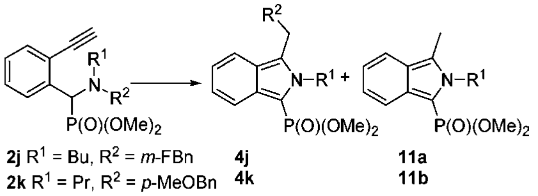


2a-i **4a-i**

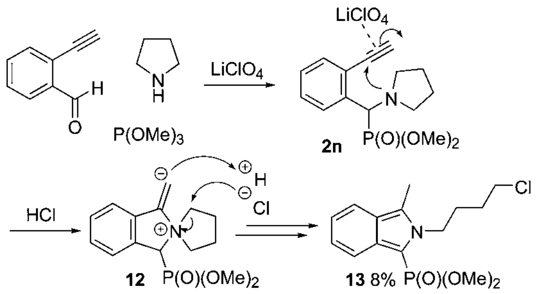
2	R^1	R^2	R^3	R^4	time (min)	yield of **4** (%)
a	Bn	H	Ph	H	90	82
b	Bn	H	H	H	70	76
c	Pr	H	*p*-$MeOC_6H_4$	H	90	68
d	*p*-MeBn	H	CH_3	CH_3	95	47
e	CH_2CH_2Ph	H	*i*Pr	H	80	71
f	*m*-FC_6H_4	H	H	H	150	63
g	CH_2CH_2-*p*-ClPh	$-CH_2CH_2CH_2CH_2-$		H	180	40
h	Bu	CH_3	Ph	H	80	40
i	allyl	H	H	H	60	98

It was also possible to prepare more complex isoindoles by incorporating the allyl group inside a ring structure (Scheme 6). When these derivatives (**2l**,**m**) were allowed to react, the allylic cation **15a**,**b** remains attached to the anion and can react intramolecularly to form an additional six-membered ring **14a**,**b**.

Scheme 4



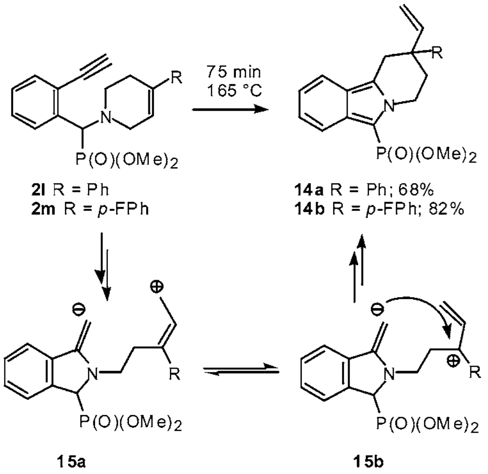
Scheme 5



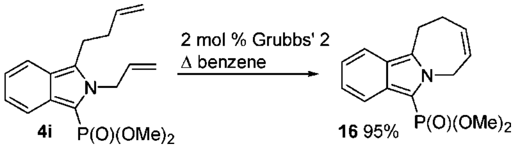
Finally, compound **4i** proved to be an excellent substrate for ring-closing metathesis and was cleanly converted to azepino isoindole **16** by treatment with 2% second-generation Grubbs' catalyst in refluxing benzene (Scheme 7).

In summary, we have uncovered a new unusual rearrangement leading to highly substituted isoindoles that occurs

Scheme 6



Scheme 7



under thermal conditions. The rearrangement starts with an attack of a tertiary nitrogen on a nonactivated carbon−carbon triple bond in a 5-*exo*-dig fashion, followed by a [1,3]-alkyl shift with eventual aromatization. This strategy is also suitable to prepare isoindoles that are fused with an extra six- or seven-membered ring.

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Supporting Information Available: Spectroscopic data and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds and general procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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