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Diels–Alder chemistry of 2-diethoxyphosphinylcyclohex-2-enones. A new approach to complex phosphonates and synthetic applications of the β-keto phosphonate system

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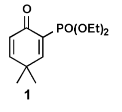
Received (in Cambridge, UK) 25th October 2001, Accepted 23rd November 2001
First published as an Advance Article on the web 17th January 2002

Enone phosphonates 1 and 2 were found to be excellent dienophiles for the Diels–Alder reaction, giving phosphonate-containing polycycles, and the phosphonate group of the resulting adducts facilitated both the installation of an angular alkyl group *via* a reductive alkylation process and the regioselective generation of a ring junction double bond *via* an intramolecular Wadsworth–Horner–Emmons reaction.

Extensive efforts have been devoted to the enhancement of the dienophilicity of cycloalk-2-enones by placing an electron-withdrawing group, such as carbalkoxyl,[1] formyl,[2] bromo,[3] phenylselenenyl,[4] nitro,[5] phenylthio,[6] cyano,[7] *etc.*, to the C-2 or C-3 carbon of the conjugated enone system. This has resulted in a remarkable increase of the reactivity of the otherwise poorly dienophilic carbon–carbon double bond. As well, the additional group can act as a handle for regio- and stereocontrol of the Diels–Alder addition and for further elaboration of the cycloaddition product. Recently we have investigated the possible use of phosphonate as an activating group for the Diels–Alder reaction to provide a new access to phosphonate-containing compounds. Many phosphonate-containing compounds have been shown to exhibit useful medicinal properties.[8] At the same time, the phosphonate group, being α to a ketone carbonyl, may serve as a leaving group to facilitate the introduction, *via* a reductive alkylation process, of various substitutents to the angular position of the polycyclic adducts. Perhaps more interestingly, after the ketone carbonyl of the Diels–Alder adduct is converted to a hydroxy, the resulting β-hydroxy phosphonate moiety may serve as a latent carbon–carbon double bond *via* an intramolecular Wadsworth–Horner–Emmons process. These expectations have now been experimentally realized and preliminary results are described herein.

Enone phosphonates **1**† and **2**‡ were used for the present study. These compounds were readily prepared from the corresponding β-keto phosphonates **3**[9] and **4**[10] using the phenylselenenylation-oxidative elimination process,[11] were used for the present study. Under Lewis acid catalysis, both compounds **1** and **2** were found to undergo facile Diels–Alder reaction. Of the Lewis acids studied ($AlCl_3$, $ZnCl_2$, $SnCl_4$, $BF{\cdot}Et_2O$, $TiCl_4$, $FeCl_3$) for the reaction of **1** and *trans*-piperylene, stannic chloride was found to be particularly effective in terms of the amount required, the reaction rate, and the yield of cycloadduct **5**. By the use of this Lewis acid, the Diels–Alder reactions of **1** and **2** with a variety of 1,3-dienes were effectively carried out, whereby a series of interesting phosphonates became readily accessible. An examination of the experimental results compiled in Table 1 reveals that most of the reactions, where applicable, follow the *ortho*- and *para*-rule (Table 1, Entries 1, 3, 5, 6, and 8). In terms of stereoselectivity, the addition follows consistently the *cis*-principle and *endo*-addition with respect to the ketone carbonyl (Table 1, Entries 1, 3, 5, and 6) suggesting the greater importance of the ketone carbonyl over the phosphonate group in directing the *endo*-addition. It is also noteworthy that in almost all of the cases studied, the Diels–Alder reaction of **1** involves the doubly activated double bond. The only exception was the addition of cyclopenta-1,3-diene (Table 1, Entry 4). In this case, exclusive addition to the less reactive double bond occurred. This abnormality was most likely due to a thermodynamic process similar to that observed for the addition of 2-cyano-4,4-dimethylcyclohexa-2,5-dienone to cyclopentadiene.[7b]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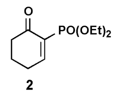
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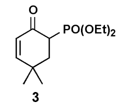
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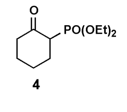
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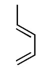
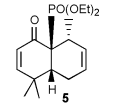
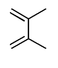
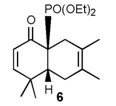
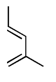
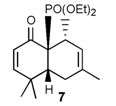
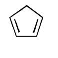
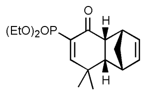
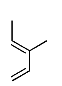
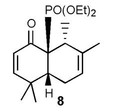
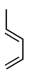
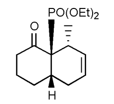
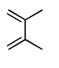
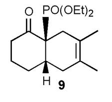
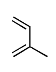
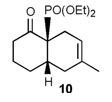
In addition to providing a direct access to some phosphonate-containing polycyclic compounds which are otherwise difficult

Table 1 Diels–Alder reactions of enone phosphonates **1** and **2**

$$\text{Dienophile} + \text{Diene (10 eq)} \xrightarrow[\text{Et}_2\text{O, r.t.}]{\text{SnCl}_4\text{ (0.5 eq)}} \text{Adduct}$$

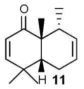
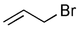
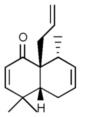
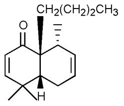
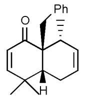
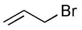
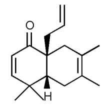
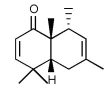
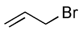
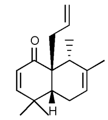
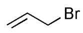
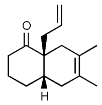
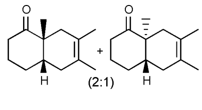
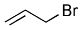
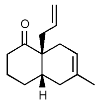
Entry	Dienophile	Diene	Time/h	Adduct	Yield (%)
1	**1**		5	 5	95
2	**1**		92	 6	82
3	**1**		35	 7	78
4	**1**		2.5		99
5	**1**		9	 8	99
6	**2**		16		78
7	**2**		13	 9	92
8	**2**		15	 10	84

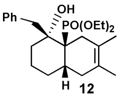
DOI: 10.1039/b109780f

to prepare, the above Diels–Alder process also found synthetic applications in the following two areas by modification of the phosphonate group. It was found that the phosphonate functionality, being α to a ketone carbonyl, could be reductively removed using lithium naphthalenide[12] and the ensuing enolate readily trapped by an alkylating agent, whereby providing a convenient route leading to angularly substituted decalin systems. This reductive alkylation process was found to be general as outlined in Table 2. With the exception of the reductive methylation of compound **9** (entry 9) which gave a fair amount of the *trans*-product, the reductive alkylation was found to be completely face selective, giving the *cis*-decalin system exclusively. As a typical example, sequential treatment of adduct **5** with lithium naphthalenide (THF, −25 °C, 10 min), and methyl iodide (−25 °C, 18 h) gave rise to product **11** in 84% yield after usual workup and flash chromatography. In another area of application, after the ketone carbonyl was first converted to a hydroxy group, the adjacent phosphonate group could be used for the introduction of a ring junction double bond with regiocontrol. This is illustrated by the following examples. Grignard addition of benzylmagnesium bromide to adducts **9** and **10** gave alcohols **12** and **13**, respectively. When each of these compounds was treated with potassium hydride in THF in the presence of 18-crown-6 ether at −25 °C for 5 h, dienes **14** and **15** were produced in modest yields (~40%). The formation of these dienes most likely involves a ring opening process followed by an intramolecular Wadsworth–Horner–Emmons reaction as shown in Scheme 1 with **13**. This mechanistic pathway is in accordance with the following experimental observations. When alcohol **13** was treated briefly (15 min) with potassium hydride, keto phosphonate **16** was isolated in 30% yield along with the starting material.

Table 2 Reductive alkylation of the Diels–Alder adducts

Adduct $\xrightarrow[\text{THF, -25 °C, 10 min, then RX (5 eq)}]{\text{Lithium naphthalenide (3.5 eq)}}$ Product(s)

Entry	Adduct	RX	Conditions (°C/h)	Product(s)	Yield (%)
1	**5**	CH_3I	−25/18	 11	84
2	**5**		20/20		72
3	**5**	$CH_3(CH_2)_2CH_2I$	65/18		87
4	**5**	$PhCH_2Br$	65/18		52
5	**6**		20/18		86
6	**7**	CH_3I	−25/18		72
7	**8**		20/20		81
8	**9**		20/18		75
9	**9**	CH_3I	20/24		85
10	**10**		20/18		72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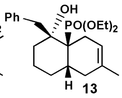
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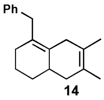
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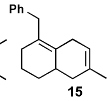
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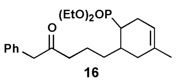
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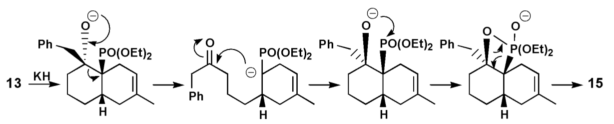
The aforementioned results show that the phosphonate group can be used to augment the dienophilicity of cyclohex-2-enones and to facilitate the preparation of phosphonate-containing polycyclic compounds. Moreover, the phosphonate group present in the adducts could serve as a latent alkyl group *via* reductive alkylation and to direct the formation of a ring junction double bond using an intramolecular Wadsworth–Horner–Emmons reaction. These interesting aspects may prove to be highly useful in the construction of complex polycyclic compounds.



Scheme 1

We are grateful to the Natural Science Council (NSC 89-2113-M-007-007) and the Ministry of Education (89-B-FA04-1-4) of the Republic of China for financial support.

Notes and references

† Satisfactory spectral and elemental or HRMS analytical data were obtained for all new compounds. The structure of several compounds was further confirmed by X-ray crystallography. All the compounds obtained, where applicable, are racemic mixtures.

‡ This compound was found to be rather unstable and easily oxidized in air to give 2-diethoxyphosphinyl-*p*-hydroquinone.

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