Efficient Horner–Wadsworth–Emmons intramolecular cyclisation of a N-substituted phthalimide promoted by KF-Alumina: a general tool for the synthesis of functionalised isoindolinones

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Abstract

An intramolecular Horner–Wadsworth–Emmons reaction promoted by KF-Alumina involving a N-substituted phthalimide, cleanly and efficiently furnishes an interesting α,β-unsaturated tricyclic enone which may undergo selective alkylations at the α-position.

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Isoindolinones constitute the core of several natural compounds, such as magallanesine1 (Fig. 1), an isoidolobenzazocine isolated from the South-American plant Berberis darwinii, a pentacyclic nucleus with a characteristic benzazocine ring system in which the nitrogen is present as a vinyllogous imide, and could be formally derived by the intramolecular cyclisation of an appropriate phthalimide derivative. Moreover, the interest towards isoindolinones from a medicinal chemistry perspective is prompted because of their presence in 5-HT1A,2a 5-HT2,2a,b or D2 antagonists,2a,b as well as in antileukemic drugs.2c

Considerable efforts have been directed towards the synthesis of isoindolinones (phthalimidines). They have been prepared via Grignard3 or lithiation4 procedures, as well as by Diels–Alder cycloaditions,5c rearrangement6 and photochemical reactions.7 The reduction of N-substituted phthalimides6 and the condensation of phthalaldehyde8 also afford isoindolinones. In addition, different palladium-catalysed syntheses of isoindolinones have been reported,10 while, on the other hand, isoindolin-1-ones have also been prepared via electrophilic cyclisation of o-(1-alkynyl)benzamides,3 or by the addition of in situ generated organoalanes to acyliminium ions.11

All the methodologies above reported involve the employment of some reagents, such as organometallic compounds, which should be avoided in order to promote an eco-friendlier process, according to modern synthetic chemistry principles; thus, we considered that a Wittig-type process could be more appropriate for preparing such structures.

In fact, the Wittig reaction of compounds different from aldehydes and ketones has been extensively studied;12 more concretely, Wittig reaction of imides is applicable to intramolecular processes and has been employed in the preparation of a wide range of heterocyclic systems.13 An useful alternative to classical Wittig reaction is represented by the Horner–Wadsworth–Emmons reaction (HWE),14 in which the nucleophilic ylid is obtained from a β-ketophosphonate. However, to the best of our knowledge, only a few examples have applied this attractive methodology to imide chemistry, generally reporting low reaction yields.15 On the contrary, related carbonyl compounds such as lactones, may...
undergo intramolecular HWE type-condensation, thus providing an useful synthetic route to analogous five-membered ring structures.16

In this Letter we wish to report a convenient procedure, based on a HWE intramolecular cyclisation of a \( \beta \)-ketophosphonate 1, prepared from N-substituted phthalimides, for the construction of the heterofused isoidololinone 2, namely 2H-pyrrolo[2,1-\( a \)]isoidole-2,5(3\( H \))-dione. As can be seen in Scheme 1, mechanism reaction involves the nucleophilic intramolecular addition of carbanion \( 1a \) generated from the phosphonate 1 to the phthalimide carbonyl, followed by spontaneous elimination of phosphate from the oxaphosphetane \( 1b \) and formation of the highly stable \( \alpha,\beta \)-unsaturated cyclic ketone 2.

Previously, compound 2 has been prepared by flash vacuum pyrolysis (FVP) of stabilized phosphorous ylides under drastic reaction conditions: in particular, performing the cyclisation at 750 \(^\circ\)C (as described by Aitken,17a) represents a major drawback, because of the severe complexity of reaching those extreme conditions in normal laboratories. Alternatively, Caballero et al. obtained this tricyclic system as an undesired product of the Wittig reaction between a phosphorane and \( N \)-phenylsulfonylindole-3-carbalddehyde.17b Finally, Bestmann and co-workers noticed the formation of pyrroloisoindolediones as the consequence of the intramolecular cyclisation promoted by heating of an appropriate phosphoranylideneketenimine.17c

The effective precursor of \( \beta \)-ketophosphonate 118 is 3-phthalimido-1-iodopropan-2-one 4, easily obtained in quantitative yield by an interesting new route consisting in ring opening of 2,3-epoxypropylphthalimide 3 with concentrated HCl, subsequent oxidation of the resulting chlorohydrine using the Jones reagent and, finally, a Finkelstein process to afford the desired \( \alpha \)-iodoketone 4, which underwent a subsequent Arbuzov reaction19 to yield phosphonate 1, as depicted in Scheme 2. It is worth noting that carrying out the Arbuzov reaction on \( \alpha \)-iodoketone 4 without solvent under reflux allows eliminating any Perkow side reaction, which usually is obtained along with the desired nucleophile displacement,20 so that, under these reaction conditions, we obtained \( \beta \)-ketophosphonate 1 exclusively.

We examined the possibility to promote the cyclisation of the \( \beta \)-ketophosphonate under basic conditions, as depicted in Scheme 1. Table 1 shows the experimental results obtained using different bases. The first choice was supported KF, which had previously allowed us to report high chemoselective procedures in \( N \)-allylation of anilines.21 So we checked the viability of the reaction on the \( \beta \)-ketophosphonate by using KF-Alumina.22 This catalyst had been already employed in such HWE chemistry by different authors,23 although they described the limitation of its use in classical reactions involving aldehydes and ketones.

As detailed in Table 1, the best result, 93% of cyclisation product, was obtained under KF-Alumina catalysis at 60 °C in only 1 h. It seemed that solvent effect was not dramatic, since at the same temperature acetonitrile and DME gave comparable results (entries 1 and 3). Remarkably, by increasing temperature the amount of cyclisation product decreased: this can be explained by the fact that, since reaction is an equilibrium, temperature could shift it towards the open form (entries 1 and 2). Interestingly, the milder basic nature of KF-Celite (entry 4) did not allow to achieve the cyclisation, and furthermore the use of unsupported KF (entry 5) was also ineffective. Ordinary bases used in organic synthesis (\( \text{BuOK}, \text{NaOMe} \) or \( \text{NaH} \)) were also effective to promote this transformation in analogous reaction times (entries 6–8) with slightly lower yields. Furthermore, the synthetic utility of the supported catalyst is readily demonstrable.22,24 All reactions can be carried out cleanly, rapidly and in high yield under mild conditions, whereas attempts to carry out the same reactions with unsupported catalyst frequently either fail or result in the formation of mixture of products. This not only becomes environmentally benign but also offers economically favourable situation as compared to cumbersome and cost-effective separation of the products in corresponding homogeneous procedures.

The simplicity of our reaction conditions led to higher yield of adduct 2 compared to before-mentioned methodologies based on a classical Wittig reaction.17b,c More concretely, we have maximised the yield and minimised the reaction time: Bestmann, reported only a 56% of isolated yield of 2 after 12 h.17c These results are in excellent agreement with the general higher reactivity of ylids derived from phosphonates towards those obtained from phosphoranes.25 Furthermore, work-up of HWE reactions is easier compared to that of their Wittig counterparts, as phosphonate esters are soluble in water and elimination of the supported KF is performed simply by filtering the reaction mixture in vacuo. Of particular synthetic value is the generation of the enolate of the cyclic \( \alpha,\beta \)-unsaturated enone so formed, which may be alkylated selectively at the \( \alpha \)-position of the ketone as described by
Scheme 2. Preparation of β-ketophosphonate 1. Reagents and conditions: (a) CHCl₃, HCl 37%, 0 °C, 30 min, quant.; (b) CrO₃, acetone 0 °C, 30 min, quant.; (c) NaI, acetone, rt, 2 h, quant.; and (d) PO(Et)₃, neat, reflux 4 h, 91%.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclisation product (%)</th>
<th>Conditions</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>93</td>
<td>KF-Alumina (1.0 equiv), MeCN, 60 °C, 1 h</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>KF-Alumina (1.0 equiv), MeCN, 82 °C, 1 h</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
<td>KF-Alumina (1.0 equiv), DMF, 60 °C, 1 h</td>
</tr>
<tr>
<td>4</td>
<td>—</td>
<td>KF-Celite (1.0 equiv), MeCN, 60 °C, 12 h</td>
</tr>
<tr>
<td>5</td>
<td>—</td>
<td>KF (1.0 equiv), MeCN, 60 °C, 12 h</td>
</tr>
<tr>
<td>6</td>
<td>86</td>
<td>BuOK (1.0 equiv), MeCN, 60 °C, 1 h</td>
</tr>
<tr>
<td>7</td>
<td>78</td>
<td>NaH (1.0 equiv), DMF, 0 °C to rt, 1.5 h</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>NaOMe (1.0 equiv), THF, rt, 2 h</td>
</tr>
</tbody>
</table>

* Isolated yield.

Scheme 3. α'-Functionalisation of cyclic enone 2.

Stork and Danheiser. In fact, the deprotonation at low temperature of isoindolinone 2 with the strong base LDA, followed by treatment with an appropriate alkyl halide (1.2 equiv), as shown in Scheme 3, smoothly affords a series of functionalised ketones 5a–e and 6 at the α'-position. The results are shown in Table 2.

Reaction is quite general, allowing the recovering of the products in high isolated yields (72–90%) within 3 h in all cases. It is worth noting that if the alkylating agent is employed in excess, α,β-dimethylated ketone 6, R' = Me is formed in high yield, as shown in Table 2.

Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>α'-Substituted cyclic enone (%)</th>
<th>Electrophiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>5a (82)</td>
<td>Methyl iodide (1.2 equiv)</td>
</tr>
<tr>
<td>10</td>
<td>5a (17) + 6 (61)</td>
<td>Methyl iodide (2.5 equiv)</td>
</tr>
<tr>
<td>11</td>
<td>5b (79)</td>
<td>Ethyl iodide (1.2 equiv)</td>
</tr>
<tr>
<td>12</td>
<td>5c (90)</td>
<td>Benzyl bromide (1.2 equiv)</td>
</tr>
<tr>
<td>13</td>
<td>5d (86)</td>
<td>Allyl iodide (1.2 equiv)</td>
</tr>
<tr>
<td>14</td>
<td>5e (72)</td>
<td>2-chloro-3-isoprop-1-ene (1.2 equiv)</td>
</tr>
</tbody>
</table>

* Isolated yield.

In conclusion, we have described the first use of KF-Alumina as an effective base to promote HWE intramolecular reaction on a phthalimide, obtaining selectively an isoindolinone, which represents a starting structure for further modifications at α'-position of the cyclic α,β-unsaturated ketone, by choosing appropriately the electrophile agent.

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Supplementary data


References and notes
