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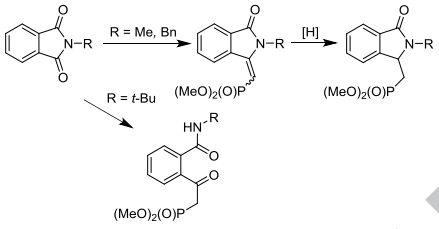

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A hitherto undescribed addition of the lithium salt of dimethyl methylphosphonate to *N*-substituted phthalimides.

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ABSTRACT

The hitherto unknown addition of the lithium salt of dimethyl methylphosphonate **6** to the *N*-substituted phthalimides **7** is described. This reaction allows the synthesis of new systems in which the phosphono group is connected to the heterocyclic skeleton of an isoindolinone at the 3-position by one methylene group.

1. Introduction

Molecules containing the isoindolinone ring system have a variety of biological activities and are part of the structure of many natural products. For example, alkaloids such as Lennoxamine (**1**)[1], Nuevamine[2] and Magallanesine[3] have been isolated from *Berberidaceae* plants, which have been used in the past as anti-inflammatory and antirheumatic agents. It has also been shown that the presence of a phosphonyl group can influence the biological function of aza-heterocyclic systems. For example, proline derivatives **2** and **3** play an important role in biochemical processes: compound **2** has antifungal, antibacterial and herbicidal activity, while compound **3** is used as an antibiotic against the bacteria *Pseudomonas aeruginosa* and *Proteus vulgaris*.[4-5]

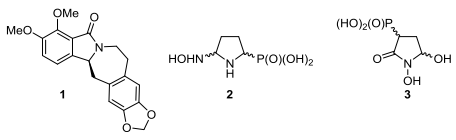


Figure 1

Phosphono derivatives of isoindolinones **A**, **B** and **C** can be considered as belonging to two pre-specified classes of compounds. Substances having such a structure in which the phosphono group is linked directly to the heterocyclic ring (structure **A**) or *via* two or three methylene groups (structure **B**) have already been reported in the literature.[6-17] The aim of our study was to develop a method of synthesis which would enable the preparation of new systems in which the heterocyclic ring is connected to the phosphonic moiety by one methylene group (structure **C**). Such systems have the potential to show biological activity that can be of use in medicine.

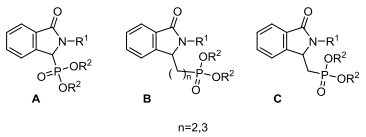
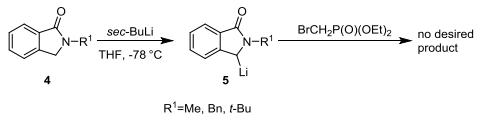


Figure 2

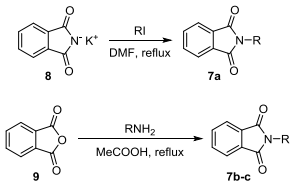
2. Results and discussion

Alkylation of the lithium derivative **5** (resulting from lithiation at the 3-position of isoindolinone **4**), using diethyl bromomethylphosphonate is potentially an easy way to access compounds in which the phosphono moiety is separated from the isoindolinone skeleton by one methylene group (structure **C**). Unfortunately, using this procedure, we did not isolate the desired products; only the starting material **4** and products that did not contain the isoindolinone skeleton, which were not further investigated, were formed (Scheme 1). The reaction was probably unsuccessful since the bromomethylphoshonate protons are much more acidic than the phthalimide protons, resulting in the phthalimide anion deprotonating the phosphonate and starting material isolation.



Scheme 1

This result forced us to look for other methods to synthesise structure **C**. Our retrosynthetic approach leads to the lithiated synthon of the phosphonomethylene fragment instead of the lithiated heterocyclic ring. We decided to investigate a method, which to the best of our knowledge has not yet been described in the literature, based on the addition of the lithium salt of dimethyl methylphosphonate **6**, obtained from the reaction of dimethyl methylphosphonate with *n*-BuLi,[18] to *N*-substituted phthalimides.[19] *N*-Methylphthalimide **7a** was obtained by the reaction of the potassium phthalimide **8** with methyl iodide.[20] *N*-Benzyl, and *N*-*tert*-butyl phthalimides **7b-c** were obtained by the reaction of phthalic anhydride **9** with the corresponding primary amines (Scheme 2).[21]



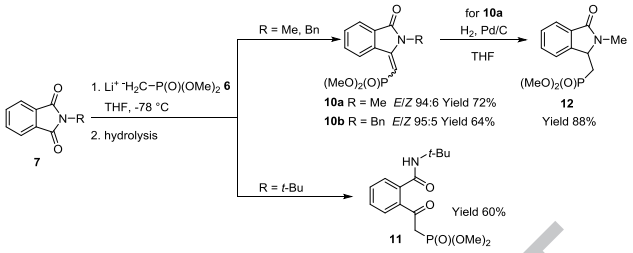
Product	R	Yield (%)
7a	Me	71
7b	Bn	82
7c	*t*-Bu	55

Scheme 2. Synthesis of *N*-substituted phthalimides **7a-c**

Utilization of these phthalimides in the reaction with the lithium salt of dimethyl methylphosphonate **6** turned out to be a successful solution. When *N*-methylphthalimide **7a** or *N*-benzylphthalimide **7b** were used, after hydrolysis of the reaction mixture, the final unsaturated phosphonates **10a** or **10b** were isolated as *E*/*Z* diastereomeric mixtures. The *E* configuration of the major diastereomer was confirmed by the nuclear Overhauser effect spectroscopy (NOESY) correlation between the vinylic and the *N*-methyl or *N*-methylene protons. However, attempts to separate the mixtures of isomers proved unsuccessful. We also observed that the addition of lithium dimethyl methylphosphonate **6** to phthalimide **7c** followed by hydrolysis of the reaction mixture resulted in the formation of compound **11**. Thus, it is probable that the steric hindrance caused by the bulky *tert*-butyl group forces the formation of the open product **11**. As an example, we have demonstrated the suitability of compound **10a** in the synthesis of the phosphonic derivative isoindolinone of type **C** in which the phosphono group is separated from the isoindolinone skeleton by one methylene group. Thus, reduction of compound **10a** with hydrogen in the presence of a palladium catalyst led to the target compound **12** (Scheme 3).

3. Conclusions

In summary, we have demonstrated a strategy for the synthesis of new phosphono-functionalized isoindolinone systems in which the phosphono group is connected to the heterocyclic skeleton of an isoindolinone at the 3-position by one methylene group. The method requires the novel addition of a lithium salt of dimethyl methylphosphonate to the *N*-substituted phthalimides. We plan to further investigate the scope of this method, along with its diastereoselectivity and applicability to



Scheme 3

the synthesis of a broad class of isoindolinone derivatives of potential pharmacological importance.

Acknowledgment

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4. References and notes

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Captions

Figure 1. Structure of Lennoxamine (1) and bioactive phosphonoprolines 2 and 3.

Figure 2. Structure of phosphono derivatives of isoindolinones A, B (reported in literature) and C (new).

Scheme 1. Failed attempt to synthesise phosphono-functionalized structure C.

Scheme 2. Synthesis of N-substituted phthalimides 7a-c.

Scheme 3. Addition of lithium salt of 6 to N-substituted phthalimides 7 and reduction of unsaturated phosphonate 10a to phosphonomethylisoindolinone 12.

1) Addition of the lithium salt of dimethyl methylphosphonate to a phthalimide system
2) Synthesis of the 3-phosphonomethyl substituted isoindolinone system
3) Catalytic reduction of the 3-oxoisoindolin-1-ylidene system