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COMMUNICATION

Copper-Catalyzed Cycloaddition between Hydrogen Phosphonates and Activated Alkenes: Synthesis of Phosphonoisoquinolinediones

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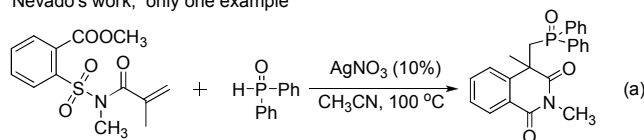
A new, general method for the synthesis of phosphonoisoquinolinediones has been achieved via copper-catalyzed phosphonation-cyclization of various methacryloylbenzamides with P(O)H compounds. This transformation allows the direct formation of a P-C bond and the construction of an isoquinolinedione ring in one reaction.

As one of the most important heterocyclic compounds, substituted isoquinolinedione derivatives are important scaffolds in a broad array of biologically active compounds. Over the last 20 years, more isoquinolinedione-containing compounds as drug candidates have increased greatly.¹ Thus, the development of new methods for their synthesis has been a major focus of study.² Among the synthetic methods to obtain isoquinolinedione derivatives, the difunctionalization reaction of alkenes through a radical process is well known, including direct intramolecular aryltrifluoromethylation^{2d} and arylphosphonylation³ of activated alkenes.

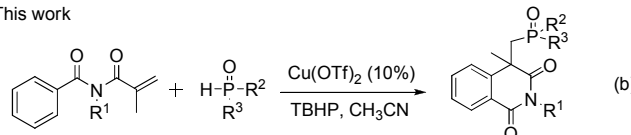
As we know, organophosphorus compounds have broad applications in the fields of organic synthesis, pharmaceuticals and agrochemicals owing to its unique properties.⁴ Heterocyclic phosphonate compounds are ubiquitous and exhibit interesting biological activities and potential pharmaceutical applications.⁵ If both phosphonyl group and isoquinolinedione structural motif can be simultaneously introduced into organic compounds, a series of new isoquinolinedione-containing organophosphorus compounds might be expected, and might provide an opportunity to introduce phosphonyl group into the original lead compounds or drugs to adjust their bioactivity. However, the efficient synthesis of molecules bearing both isoquinolinedione motif and phosphonyl group is quite rare. In 2014, Nevado group reported that the reaction of methyl 2-(N-methacryloyl-N-methylsulfamoyl)benzoate with diphenylphosphine oxide in the presence of silver salt led to phosphonoisoquinolinedione.³ Only one example was provided (Scheme 1 a). Herein, we report the successful realization of this concept with the introduction of phosphonyl radicals for the flexible synthesis of unprecedented phosphonoisoquinolinediones with a quaternary carbon centre. This transformation allows the direct

formation of a P-C bond and the construction of a heterocyclic ring in one reaction.

Nevado's work, only one example

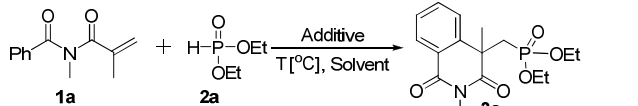


This work



Scheme 1. Synthetic routes to phosphonoisoquinolinediones.

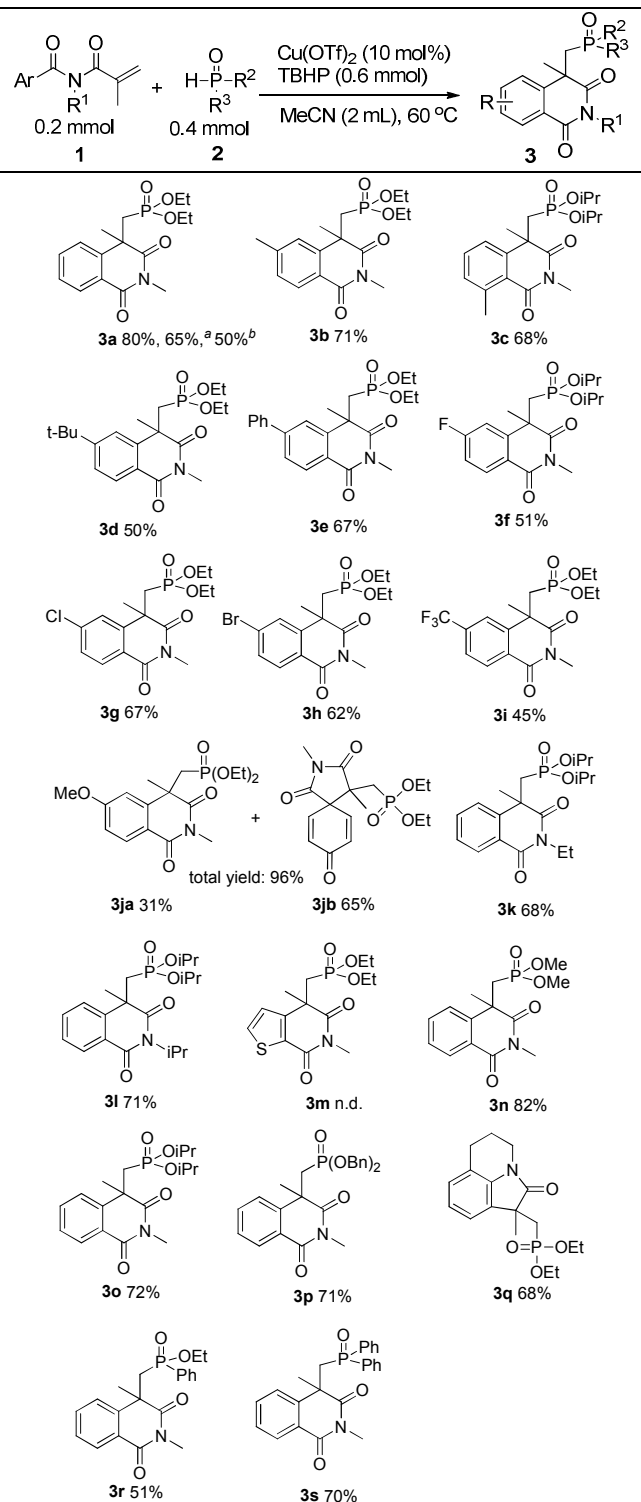
This idea was first examined by using N-methacryloyl-N-methylbenzamide (**1a**) and diethyl *H*-phosphonate (**2a**) as reaction partners (table 1). It has been found that many salts such as copper,⁶ silver⁷ and manganese⁸ can work with R₂P(O)H to form the corresponding phosphonyl radical which promoted phosphonyl radical addition chemistry. In the beginning, various silver and manganese catalysts were tested and all gave moderate yields (entries 1-4, Table 1). In these processes, manganese is used in excess (3 equivalents), which is quite wasteful. For a practical reaction, using readily available and low-cost catalyst for this transformation would be appealing. Gratifyingly, the combined use of Cu(OAc)₂ and TBHP (*tert*-butylhydroperoxide) gave **3a** in 40% yield (entry 6). Subsequently, various Cu(II) salts were further checked and the results showed that Cu(OTf)₂ was more effective to give the desired product (entries 5-9). However, the attempt to decrease the amount of Cu(OTf)₂ was failed (entry 10). Moreover, the yield was reduced to 43% under air (entry 11). Low yield was afforded without copper salt or TBHP (entries 12 and 13). Cu(I) salt and Cu powder couldn't execute this reaction efficiently (entries 14 and 15). After optimization of the reaction conditions, we established an efficient route to the phosphonation-annulation of methacryloylbenzamides (entry 9, table 1).

Table 1. Optimization of reaction conditions.^a


Entry	Additive (equiv)	Solvent	T (°C)	Yield(%)
1	Mn(OAc) ₃ ·2H ₂ O (3)	HOAc	60	63
2	Mn(OAc) ₃ ·2H ₂ O (3)	HOAc	70	59
3	AgNO ₃ (0.05)+Mg(NO ₃) ₂ ·6H ₂ O(0.5)	CH ₃ CN	100	62
4	AgNO ₃ (0.1)+Mg(NO ₃) ₂ ·6H ₂ O(0.5)	CH ₃ CN	100	65
5	Cu(OAc) ₂ (0.1)+TBHP (3)	CH ₃ CN	60	40
6	CuCl ₂ (0.1)+TBHP (3)	CH ₃ CN	60	15
7	CuSO ₄ ·5H ₂ O (0.1)+TBHP (3)	CH ₃ CN	60	20
8	Cu(NO ₃) ₂ ·3H ₂ O (0.1)+TBHP (3)	CH ₃ CN	60	48
9	Cu(OTf)₂ (0.1)+TBHP (3)	CH₃CN	60	83
10	Cu(OTf) ₂ (0.05)+TBHP (3)	CH ₃ CN	60	70
11 ^b	Cu(OTf) ₂ (0.1)+TBHP (3)	CH ₃ CN	60	43
12	TBHP (3)	CH ₃ CN	60	34
13	Cu(OTf) ₂ (0.2)	CH ₃ CN	60	0
14	CuCl (0.1)+TBHP (3)	CH ₃ CN	60	15
15	Cu powder(0.1)+TBHP (3)	CH ₃ CN	60	5

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), additive in solvent (2.0 mL) stirring under nitrogen for 24 h. Oil bath temperature. Yields were determined by ³¹P NMR based on Ph₃PO as internal standard. ^b Under air.

With this preliminary result in hand, the results of phosphonation–annulation for methacryloylbenzamides **1** with different H–phosphonates **2** can be summarized as follows. As shown in Table 2, a variety of functional groups on the phenyl ring of methacryloylbenzamides were compatible under this procedure, affording the desired products in moderate to good yields. The alkyl and phenyl substituted benzamide substrates, such as *para*-methyl, *ortho*-methyl, *para*-*tert*-butyl and *para*-phenyl on the aryl ring, reacted with **2a** efficiently and gave the desired products **3b–3e** in good yields. Halogen atoms such as fluoro, chloro, and bromo on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **3f–3h** in moderate to good yields, which could allow for further synthetic transformations. Benzamide substrates bearing CF₃ group reacted smoothly to give the corresponding product in moderate yield (**3i**). When N-methacryloyl-4-methoxy-N-methylbenzamide reacted with **2a**, we acquired both the normal coupling product **3ja** and the dearomatization product **3jb** as a 1:2 mixture in 96% total yield. The product **3jb** was formed by annulation of alkenyl radical with the aryl ring at the carbon atom directly attached to the carbonyl atom to form 1,3,8-trioxo-2-azaspiro compound.⁹ The reactivity of N-alkyl substituted substrates was further explored. More bulk alkyl groups at the nitrogen atom such as ethyl and isopropyl groups react with diethyl H-phosphonate (**2a**) furnishing the corresponding isoquinolinedione **3k** and **3l** in 68% and 71% yields, respectively. N-Methacryloyl-N-methylthiophene-2-carboxamide gave a complicated mixture, no **3m** was obtained. Dimethyl, diisopropyl, and dibenzyl H-phosphonates could be also used as substrates, generating the corresponding products (**3n–3p**) in good yields. 1-Methacryloyl-1,2,3,4-tetrahydroquinoline was also a suitable acceptor to extend the applicability of the current method, and led to the formation of product (**3q**) in 68% yield. It is worth noting that ethoxyphenylphosphine oxide and diphenylphosphine oxide can be also applied in the preparation of the corresponding phosphonoisoquinolinediones in moderate yields (**3r** and **3s**).

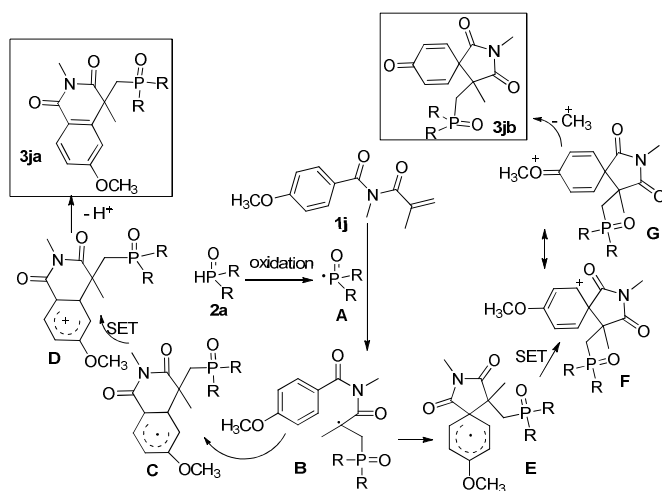
Table 2. Reaction scope study.

^a Reaction conditions: **1a** (10 mmol), **2a** (20 mmol), Cu(OTf)₂ (1.0 mmol), TBHP (30 mmol), CH₃CN (30 mL) stirring under nitrogen for 30 h. ^b **1a** (10 mmol), **2a** (20 mmol), Cu(OTf)₂ (0.5 mmol), TBHP (30 mmol), CH₃CN (30 mL) stirring under nitrogen for 30 h.

In order to demonstrate the practical application of this method, N-methacryloyl-N-methylbenzamide (**1a**, 10 mmol) was employed

in a gram-scale reaction and delivered **3a** in 65% yield (Table 2). When the loading of Cu(OTf)₂ was reduced to 5 mol%, the reaction also afforded **3a** in 50% yield.

No desired product was obtained when 2.0 equiv of TEMPO was added in the reaction of **1a** with **2a** under the optimal conditions. This result indicates that the phosphonyl radicals may be intercepted by TEMPO. According to our previous Cu(II)–TBHP catalytic reaction mechanism study,^[6a,c] a plausible mechanism is proposed as shown in Scheme 2. Initially, the reaction of P(O)H **1** with Cu(II) salt and TBHP generates phosphonyl radical **A** which then goes through intermolecular addition onto the carbon-carbon double bond of **2** to produce alkyl radical **B**. Followed by intramolecular attack of the radical **B** on the pendant aromatic ring subsequently provides radical **C**. Subsequently, phosphonoisoquinolinedione **3ka** is formed through oxidation-deprotonation reaction. Alternatively, alkyl radical **B** attacks the aryl ring at the carbon atom directly attached to the carbonyl group to form radical **E**. Cationic intermediate **F** is formed through single-electron oxidation which could afford resonance structure **G**. The intermediate **G** converts into the product **3kb** via demethylation.



Scheme 2. Proposed reaction mechanism.

In conclusion, we have successfully developed a facile catalytic method for the preparation of phosphonoisoquinolinediones *via* phosphonation-cyclization of various methacryloylbenzamides with P(O)H compounds. This method provides a rapid access to a broad spectrum of phosphonoisoquinolinediones in moderate to good yields. Moreover, the use of inexpensive Cu(II) catalyst, using readily-prepared methacryloylbenzamides and P(O)H compounds mean that this facile protocol will be attractive for academia and industry.

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Notes and references

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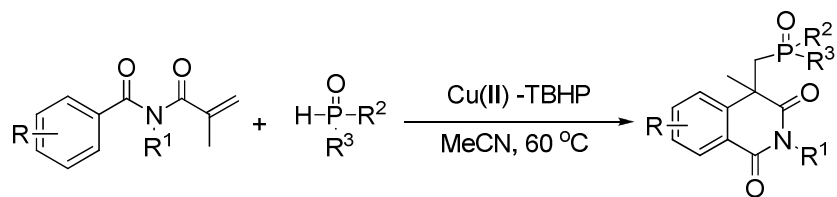
Electronic Supplementary Information (ESI) available: Experimental procedures for the synthesis, spectral data and NMR spectra of compounds **3a-3s**. See DOI: 10.1039/c000000x/

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Copper-Catalyzed Cycloaddition between Hydrogen Phosphonates and Activated Alkenes: Synthesis of Phosphonoisoquinolinediones

Ju Wu,^a Yuzhen Gao,^a Xin Zhao,^a Liangliang Zhang,^a Weizhu Chen,^{a,b} Guo Tang,^{a,*} and Yufen Zhao^a



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