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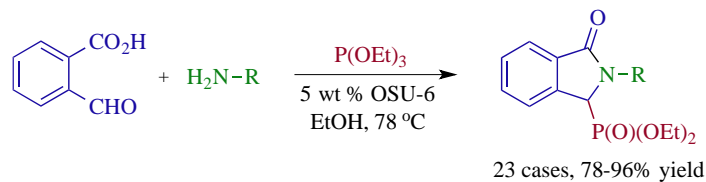
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Expeditious synthesis of (±)-diethyl 2-alkyl- and 2-aryl-(3-oxoisindolin-1-yl)phosphonates catalysed by OSU-6

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COMMUNICATION

Expeditious synthesis of (\pm)-diethyl 2-alkyl- and 2-aryl-(3-oxoisindolin-1-yl)phosphonates catalysed by OSU-6

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A one-step strategy to prepare (\pm)-diethyl 2-alkyl- and 2-aryl-(3-oxoisindolin-1-yl)phosphonates is reported *via* a modified Kabachnik-Fields condensation of 2-carboxybenzaldehyde with an amine and triethyl phosphite using OSU-6, an MCM-41 type mesoporous hexagonal silica, as the catalyst. The reaction proceeds to form the target compounds in high yields with minimal purification requirements. The method is successful for benzylic, aromatic and aliphatic amines. An additional advantage of the current method is that the catalyst can be recycled up to four times with useful activity.

α -Amino phosphonates are known to act as bioisosteres of α -amino acids and can play a crucial role in the inhibition of peptides and enzymes that involve amino acid metabolism.¹ Amino phosphonates exhibit a broad range of therapeutic activity as anticancer, anti-HIV, antibacterial, antifungal, and antithrombotic agents.^{1a, 2} Apart from their medicinal value, these compounds have applications in agricultural sector as plant growth regulators and pesticides.³

Isoindolinones are also important biological scaffolds. Core isoindolinone rings are present in several natural alkaloids⁴ as well as numerous drugs (Figure 1).⁵ These drugs have proven useful in ameliorating conditions associated with cancer, inflammation and psychosis. Further study has revealed that several halogenated isoindolinones have potential as insecticides.⁶

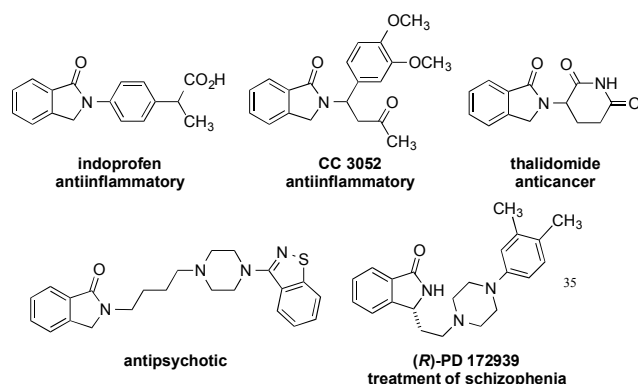


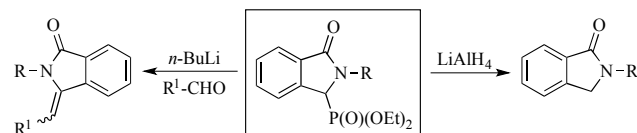
Figure 1. Biologically active isoindolinones

Though both α -amino phosphonates and isoindolinones have been studied as separate entities, few researchers have reported structures incorporating both subunits.⁷ One area where these compounds have demonstrated promise is in agrochemicals, where the (3-oxoisindolin-1-yl)phosphonate moiety is a central structural component of an important class of plant growth regulators.⁸ This finding, as well as the known importance of constrained amino acids in drug design and biomechanistic investigations,⁹ has inspired us to develop an efficient synthesis for these systems.

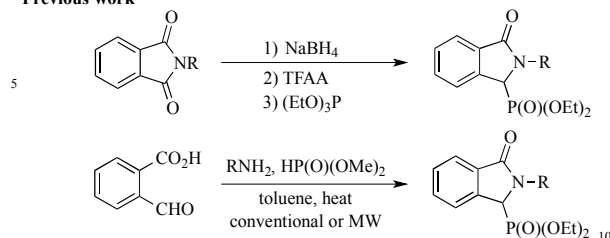
In addition to their potential commercial uses, the target phosphonates also have significant value as synthetic precursors.^{7c, 10} For example, lithium aluminum hydride reduction of (3-oxoisindolin-1-yl)-phosphonates yields the dephosphorylated isoindolinone ring system (Figure 2).^{7d} Additionally, these compounds permit access to the 3-methyleneisoindolin-1-one system *via* a Horner-Wadsworth-Emmons protocol involving treatment with *n*-BuLi followed by an aldehyde. Despite their utility, (3-oxoisindolin-1-yl)phosphonates have received relatively little attention due to limitations of the existing syntheses to prepare them.

To date, only two routes to diethyl 2-alkyl- and 2-aryl-(3-oxoisindolin-1-yl)phosphonates have been reported (see Figure 2). The first synthesis involved a three-step sequence starting from phthalimide. This method required reduction to the 3-hydroxyisoindolin-1-one followed by sequential treatment with trifluoroacetic anhydride and triethyl phosphite to afford the phosphonates in overall yields of 56-72%.^{7f} A second strategy utilized 2-carboxybenzaldehyde, an amine and diethyl hydrogen phosphonate (known commercially as dimethyl phosphite) in toluene at 120 °C or under microwave irradiation.^{7d} This reaction generated products in low to moderate yields and required extended periods of heating under both sets of conditions. Furthermore, poor yields were reported for a limited number of cases employing aromatic amines. In order to overcome these problems and improve the breadth of possible substrates, we have developed a synthesis from 2-carboxybenzaldehyde, amines and triethyl phosphite using a new heterogeneous acid catalyst. Our modified conditions permit the conversion of a broad range of structurally diverse amines to the target phosphonates.

2-Alkyl-(3-oxoisindolin-1-yl)phosphonates in synthesis



Previous work



Current work

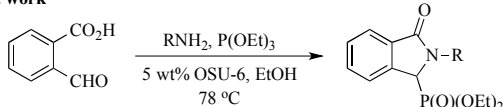


Figure 2. 2-Alkyl-(3-oxoisindolin-1-yl)phosphonates in synthesis and comparison with previous synthetic approaches

The Kabachnik-Fields reaction is a multicomponent condensation between an aldehyde, an amine and a dialkyl hydrogen phosphonate, that provides a one-step, high-yield synthesis of α -amino phosphonates.^{2c} The reaction is facilitated by the use of Lewis acids and occasionally dehydrating agents. Over the years, it has proven to be an important tool for generating valuable peptidomimetic compounds.¹¹ As part of our on-going research to identify environmentally friendly synthetic approaches to bioactive heterocycles,¹² we sought to employ a modified Kabachnik-Fields strategy to prepare a series of (3-oxoisindolin-1-yl)phosphonates.

Our synthesis involves reaction of 2-carboxybenzaldehyde with an amine and triethyl phosphite in the presence of catalytic acid. A selection of Bronsted and Lewis acids was examined for this reaction in refluxing EtOH and compared to the process without catalyst (**Table 1**). In the absence of catalyst, the reaction gave a poor yield and required heating for extended periods. Several additives (InCl_3 , NH_4Cl , $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ and wet Amberlyst-15) proved ineffective. Other acids ($\text{Bi}(\text{OTf})_3$, $p\text{-TsOH} \cdot \text{H}_2\text{O}$, dry Amberlyst-15, SiO_2 and $\text{CF}_3\text{CO}_2\text{H}$) afforded moderate to good yields, but the resulting products contained varying amounts of unreacted materials that were difficult to remove. Among the catalysts screened, OSU-6, an MCM-41 type hexagonal mesoporous silica with strong Lewis and Bronsted acid properties,¹³ provided the best results with high yields in a shorter time frame. This material is reported to have superior hydrothermal stability compared with traditional MCM-41 due to its greater channel wall thickness. As part of its preparation, OSU-6 is aged in the presence of HCl (pH 2) for 14 days at 25 °C. During this period, protons from the acid are trapped on the surface and in the pores of the catalyst by hydrogen bonding with the hydroxyl groups of the silica. The material is finally washed with H_2O and EtOH, dried under vacuum, and calcinated in air at 550 °C for 12 h. This final treatment removes the HCl,

but presumably leaves behind protons, which are held by the hydroxyl groups of the silica. We assume these protons are responsible for the acidity of the catalyst. MCM-41 is not acidic unless it is doped with alumina or used in combination with added Lewis or Bronsted acids.¹⁴ In the current study, OSU-6 was used directly with no added acid.

A previous study identified 100% EtOH as an excellent medium for reactions catalysed by OSU-6.¹⁵ Nevertheless, alternative solvents such as methanol (MeOH), dichloromethane (DCM), acetonitrile, toluene, *p*-xylene, dioxane and tetrahydrofuran (THF) were also examined, but EtOH generally offered superior conversions to the product (**Figure 3**). Thus, we used EtOH to optimize the reaction parameters and catalyst loading. Following a number of trial runs, we found that OSU-6 at an optimized loading of 5-wt% (relative to mg of **1**) in EtOH at reflux rapidly and cleanly produced the desired phosphonates in high yields.

Table 1. Reaction optimization

Entry	Catalyst	Time (h)	Yield (%)
1	no catalyst	18	73
2	5-wt% InCl_3	6	22
3	5-wt% NH_4Cl	5	28
4	5-wt% $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	5	20
5 ^a	5-wt% OSU-6	1	92
6	10-wt% OSU-6	1	85
7	5-wt% $\text{Bi}(\text{OTf})_3$	1	56
8	5-wt% $p\text{-TsOH} \cdot \text{H}_2\text{O}$	6	79
9	5-wt% dry Amberlyst-15	2	68
10	5-wt% wet Amberlyst-15	8	25
11	5-wt% SiO_2	12	72
12	2-wt% $\text{CF}_3\text{CO}_2\text{H}$	8	70

^aOptimized conditions

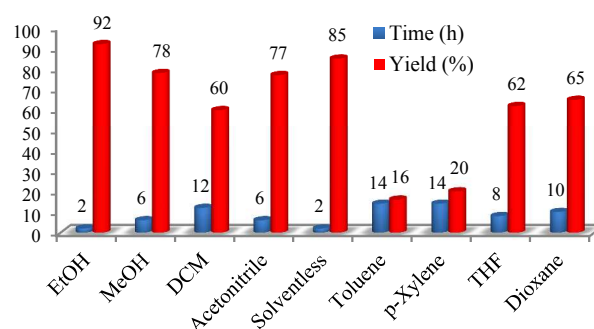
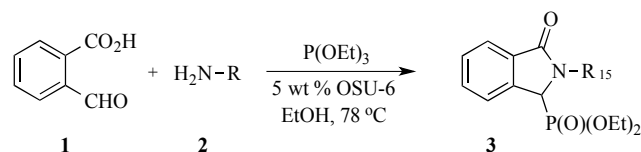


Figure 3. Solvent optimization for the preparation of **3a** with OSU-6

A convenient washing and drying procedure was also developed to regenerate the catalyst without significant loss of activity. This allowed the catalyst to be recycled for the same reaction up to four times.

Once our synthetic protocol was established, the method was applied to 23 substrates to study the scope of the process. The reaction proceeded nominally for all of the amines employed. Our results are summarized in **Table 2**.

Table 2. Synthesis of (±)-diethyl 2-alkyl- and 2-aryl-(3-oxoisindolin-1-yl)phosphonates



Entry	R	Time (h)	Yield (%)
1	a: C ₆ H ₅ CH ₂	2.5	92
2	b: 4-CH ₃ C ₆ H ₄ CH ₂	2.5	93
3	c: 4-CF ₃ C ₆ H ₄ CH ₂	3	82
4	d: 4-ClC ₆ H ₄ CH ₂	2.5	90
5	e: 3-FC ₆ H ₄ CH ₂	2	87
6	f: 3-CH ₃ OC ₆ H ₄ CH ₂	2.5	96
7	g: 4-CH ₃ OC ₆ H ₄ CH ₂	2.5	94
8	h: C ₆ H ₅	3	88
9	i: 2-CH ₃ C ₆ H ₄	3.5	92
10	j: 4-CH ₃ C ₆ H ₄	3	90
11	k: 4-ClC ₆ H ₄	3.5	85
12	l: 2-FC ₆ H ₄	3.5	82
13	m: 4-FC ₆ H ₄	3.5	80
14	n: 3-CH ₃ OC ₆ H ₄	3	95
15	o: 4-CH ₃ OC ₆ H ₄	3	96
16	p: 4-CF ₃ OC ₆ H ₄	4.5	78
17	q: C ₆ H ₅ CH ₂ CH ₂	3.5	87
18	r: 5,6,7,8-tetrahydro-naphth-1-yl	3.5	84
19	s: <i>i</i> -butyl	4	79
20	t: <i>n</i> -hexyl	4	86
21	u: allyl	3.5	85
22	v: cyclopropyl	4	82

The cyclocondensation was successful for benzylic, aromatic and aliphatic amines. The reaction accommodated a range of electron-donating and electron-withdrawing groups on the aromatic rings for both the benzylamine and aniline substrates. These included alkyl (CH₃, CF₃), halogen (Cl, F) and ether (OCH₃, OCF₃) substituents. Previous reports have documented only poor results from aniline substrates. In this

variant, arylamines provided 2-aryl-(3-oxoisindolin-1-yl)phosphonates in high yields and purity, and thus, the OSU-6 promoted transformation has broader scope and utility. In all cases, the reactions afforded products requiring minimal purification. Most of the 2-alkyl- and 2-benzyl-(3-oxoisindolin-1-yl)phosphonates were obtained as oils and required purification by passing through a short silica gel column. Products derived from anilines were solids that could be purified by recrystallization.

Most of the reactions were completed within a period of 2-4.5 h. For benzyl amines, the transformation required about 2-3 h for complete conversion, while anilines and aliphatic amines were more sluggish and required 3-4.5 h. Finally, some of the more volatile amines were used in slight excess to compensate for evaporative loss.

The OSU-6 catalyst was further evaluated for recyclability and reusability. Following some experimentation, it was found that the catalyst could be reused following careful regeneration of the catalyst. Initially, the reaction mixture was filtered, thoroughly washed with ethanol and air-dried. Attempts to reuse this catalyst directly resulted in a significant (≥ 25%) reduction in the yield. However, if the filtered catalyst was washed with several portions of EtOH:H₂O (1:1) followed by drying at 200 °C under vacuum for 14 h, the activity was almost fully restored (**Figure 4**).

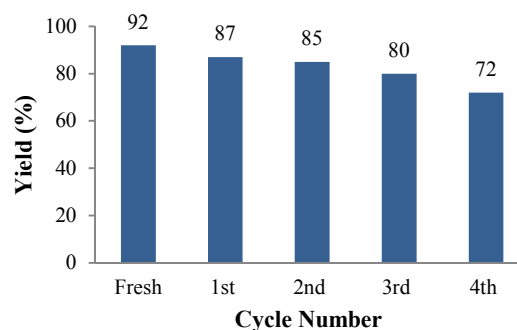


Figure 4. Reusability of OSU-6 for the preparation of **3a** in EtOH

The mechanism of these cyclizations has long been assumed to involve initial formation of the aldimine, followed by addition of the nucleophile to the carbon-nitrogen double bond, and closure of the amine adduct on the carboxyl group. While it is known that aldimine intermediates in the Strecker synthesis react with cyanide to give α-aminonitriles,^{12c} and aldimines from simple aromatic aldehydes add trimethyl phosphite,¹⁶ 2-carboxybenzaldehyde (**1**) is a unique substrate due to the proximity of reactive groups in the compound. In a recent project,¹⁵ the OSU-6 promoted condensation of **1** with anilines and trimethylsilyl cyanide produced 3-(arylamino)isobenzofuranones rather than the expected 2-aryl-3-oxoisindoline-1-carbonitriles. These products have been previously reported from **1** and aniline under neutral and acidic conditions.¹⁷ Additionally, reaction of **1** with diethyl hydrogen phosphonate and aniline in the

absence of an acid catalyst gave only low yields of the 2-aryl-(3-oxoisindolin-1-yl)phosphonates, even after prolonged heating.^{7d} These observations contraindicated aldimine intermediates for these processes. In the reaction of **1** with aniline and triethyl phosphite in the presence of OSU-6, however, high yields of the phosphonate-substituted isindolinones were isolated, suggesting that a different mechanism was operating. Additional control experiments demonstrated that the 3-(arylamino)isobenzofuranones, isolated during our earlier study using cyanide,¹⁵ gave 2-aryl-(3-oxoisindolin-1-yl)phosphonates in nearly quantitative yields when treated with triethyl phosphite in the presence of OSU-6. This observation confirmed that 3-(arylamino)-isobenzofuranones were intermediates in this transformation when anilines were employed.

Our proposed mechanism for the condensation of **1** with anilines is presented in **Figure 5**. It is widely recognized that 2-carboxybenzaldehyde exists as an equilibrium between **1A** and **1B**, with **1A** being the predominant species.¹⁸ One might also assume that **4A** and **4B** exist in a similar equilibrium, but this does not appear to be the case.^{17c} If **4B** was present, reaction with cyanide or phosphite should have given the 3-cyano- or 3-phosphonate-substituted isindolinones directly; however, this was not observed. Thus, only **4A** is available to react. Following formation of **4A** from anilines **2**, attack by triethyl phosphite at the aminoacetal carbon under acid catalysis would open the furanone ring to give **5**, and water generated during the formation of **4A** would convert the phosphonium group to the phosphonate **6**. Finally, lactam closure with loss of water would deliver the final products **3**. We presume that OSU-6 serves as a proton source throughout the path from **4A** to **3**. Without catalyst, the reactions

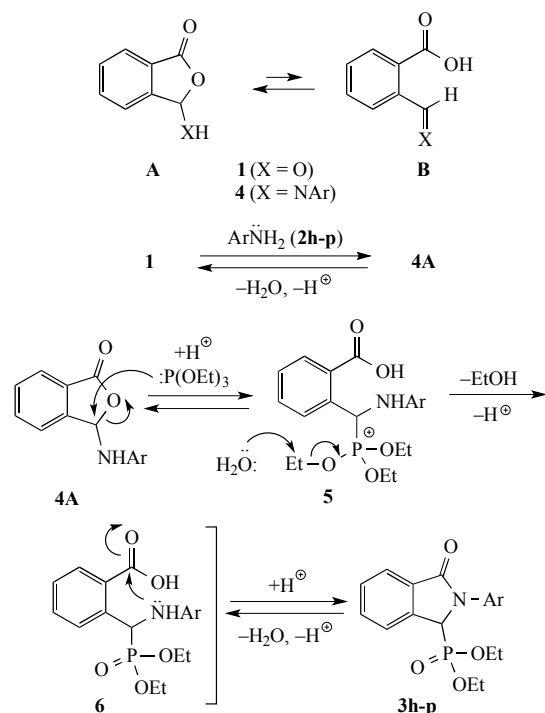


Figure 5. Proposed mechanism for the reaction of anilines with 2-carboxybenzaldehyde

proceeded to ca 15-20% conversion in 48 h. When OSU-6 was present, however, the reactions were complete within 2 h. While the exact chronology of events has not been rigorously established, the poor reactivity of **4A** toward cyanide and triethyl phosphite suggests that aldimine **4B** is not involved in the transformation. Furthermore, though no formal study has been reported, the successful addition of phosphite but not cyanide in the acid catalysed reaction could be a reflection of superior nucleophilicity of phosphite or decreased reversibility of the addition, especially after its conversion to the phosphonate group. By comparison, benzylic and aliphatic amines could proceed *via* this pathway or by the accepted aldimine mechanism. These amines are sufficiently basic to deprotonate the hemiacetal **1A** to give the ring-opened carboxylate of **1B**. This ring-opened anion would then be expected to react through the aldimine intermediate.

Conclusion

In summary, we have developed an efficient strategy for the synthesis of (\pm)-diethyl 2-alkyl- and 2-aryl-(3-oxoisindolin-1-yl)phosphonates using OSU-6 to promote the reaction. This catalyst affords clean conversion and high yields in 2-4.5 h with minimum purification requirements. Furthermore, the greater pore thickness of this catalyst allows for repeated regeneration and reuse for up to four reaction cycles without significant loss of activity. The process proceeded optimally with 5-wt% catalyst loading in 100% EtOH at reflux. The reaction can be successfully performed on benzylic, aromatic and aliphatic amines. This method is the first to produce high yields of 2-aryl-(3-oxoisindolin-1-yl)phosphonates from anilines and is successful with electron-donating and electron-withdrawing groups on the aromatic rings. An alternative mechanism, circumventing an aldimine intermediate, has been proposed for the transformation involving arylamines.

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