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An efficient, three-component synthesis of isoindolin-1-one-3-phosphonates under mild and solvent-free conditions

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ABSTRACT

An efficient and mild three-component synthesis of isoindolin-1-one-3-phosphonates is described. The reaction between a 2-formylbenzoic acid, a primary amine, and a trialkyl phosphite proceeded at ambient temperature under catalyst- and solvent-free conditions to afford the desired compounds in excellent yields.

Recently, isoindolin-1-ones have attracted great attention as common structural motifs in naturally occurring compounds such as magallanesine,[1] lennoxamine,[2] and stachybotrin C,[3] as well as in pharmacologically important synthetic compounds such as Pagoclone (Fig. 1).[4] Compounds having the isoindolin-1-one scaffold have been shown to possess a broad range of biological activities including antimicrobial,[5] anti-viral,[6] HIV-1 inhibition,[7] sedative, and hypnotic.[8] Some isoindolin-1-ones have been claimed to assist in treating diabetes,[9] obesity and hyperlipidemia,[10] cancer,[11] and CNS diseases.[12] Also, several isoindoline derivatives have been proposed as dipeptidyl peptidase DPP8/9 inhibitors in immunohistochemical studies.[13] Isoindolin-1-ones have also been used in the Diels–Alder reaction and as building blocks in asymmetric synthesis.[14–16]

Due to the widespread biological activities of isoindoline derivatives, a variety of synthetic approaches have been reported for the preparation of these heterocycles.[17–22]

To date, a few synthetic routes have been reported for the preparation of dialkyl 3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)phosphonates. Kolodiazhnyi and co-workers have reported a three-step sequence including reduction of phthalimides to 3-hydroxyisoindolin-1-ones followed by treatment with trifluoroacetic anhydride and then triethyl phosphite to afford the corresponding phosphonates in moderate yields.[23] Ordóñez et al. reported the synthesis of chiral isoindolin-1-one-3-phosphonates via the Kabachnik–Fields three-component reaction of 2-formylbenzoic acid, an amine and dimethyl phosphite. The reactions were carried out in toluene at reflux[24] under microwave irradiation[24] or at 80 °C under solvent- and catalyst-free conditions[25] to give the phosphonates in low to excellent yields. Very recently, Bunce and co-workers have reported a modified Kabachnik–Fields condensation of 2-formylbenzoic acid with an amine and triethyl phosphite using OSU-6, a MCM-41 type mesoporous hexagonal silica, as the catalyst.[26]

Although the above mentioned syntheses have proved to be suitable routes to obtain dialkyl 3-oxo-2,3-dihydro-1*H*-isoindol-1-yl)phosphonates, these suffer from some drawbacks such as

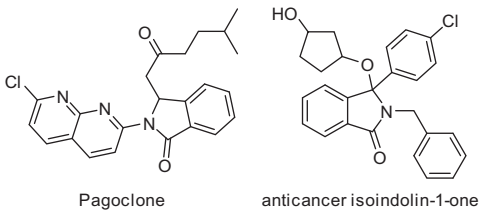

Figure 1. Examples of pharmacologically important compounds having the isoindolin-1-one core structure.

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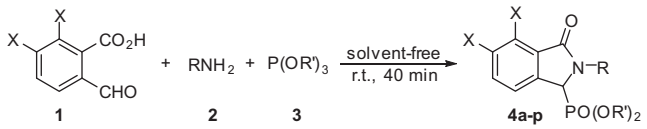


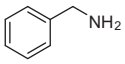
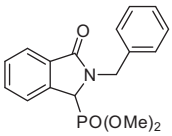
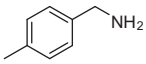
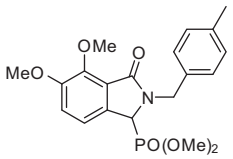
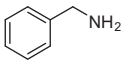
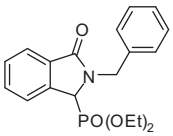
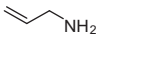
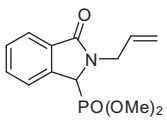
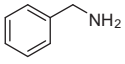
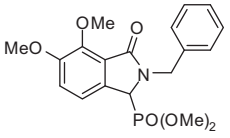
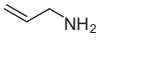
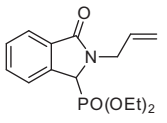
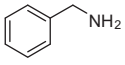
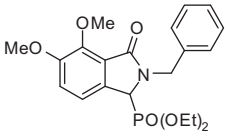
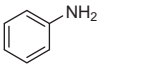
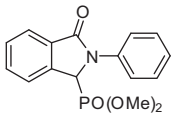
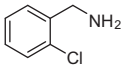
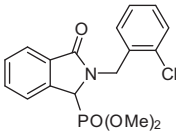
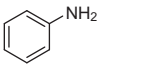
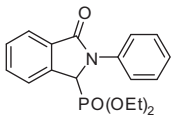
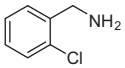
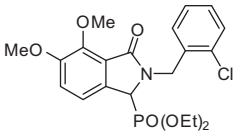
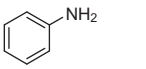
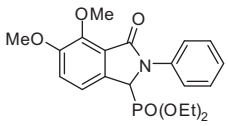
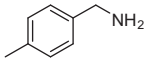
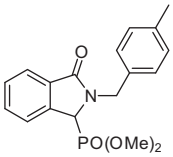
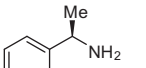
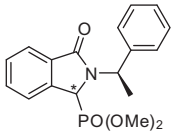
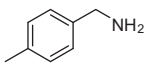
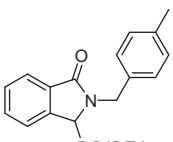
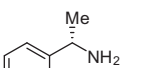
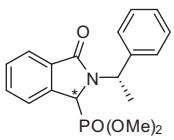
Scheme 1. Synthesis of *N*-substituted isoindolin-1-one-3-phosphonates **4**.

multistep reactions, high reaction temperatures, use of catalysts and solvents and in some cases fairly low product yields.

In connection with an ongoing research program concerned with the synthesis of biologically active heterocyclic compounds,[27] herein, we report an efficient and convenient method for the preparation of *N*-substituted isoindolin-1-one-3-phosphonates. Thus, a mixture of a 2-formylbenzoic acid **1**, a primary amine **2** and a trialkyl phosphite **3** was stirred at ambient temperature under solvent-free conditions.[28] The reactions proceeded to completion within 40 min to afford the corresponding isoindolin-1-one-3-phosphonates **4** in 89–98% yields (Scheme 1 and Table 1). ^{1}H NMR analysis of the reaction mixtures clearly indicated formation of compounds **4** without the formation of by-products.[29]

The structures of the isolated products were deduced by IR, ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, mass spectrometry, and elemental analyses. The IR spectrum of **4e** showed a stretching band for the C=O bond of the amide group at 1693 cm^{-1}. The mass spectrum of **4e** displayed the molecular ion (M^{+}) peaks at *m*/*z* 367 (^{37}Cl) and 365 (^{35}Cl) which were consistent with the 1:1:1 adduct of 2-formylbenzoic acid, 2-chlorobenzylamine, and trimethyl

Table 1
Synthesis of isoindolin-1-one-3-phosphonates **4a**–**p**[a]

X	Amine **2**	R′	Product		Yield[b] (%)	X	Amine **2**	R′	Product		Yield[b] (%)
H		Me		**4a**	98	OMe		Me		**4i**	93
H		Et		**4b**[23,26]	96	H		Me		**4j**	95
OMe		Me		**4c**	93	H		Et		**4k**[26]	98
OMe		Et		**4d**	92	H		Me		**4l**[24]	93
H		Me		**4e**	97	H		Et		**4m**[26]	93
H		Et		**4f**	97	OMe		Et		**4n**	92
H		Me		**4g**	94	H		Me		**4o**[25]	89[c]
H		Et		**4h**[26]	95	H		Me		**4p**[25]	90[d]

[a] Reaction conditions: 2-formylbenzoic acid (**1**, 1 mmol), amine (**2**, 1 mmol), trialkyl phosphite (**3**, 1.1 mmol); solvent-free, ambient temperature, 40 min.
[b] Isolated yield.
[c] Diastereoisomeric ratio: >97:3 (determined from the ^{31}P NMR of the crude product); (3*S*,1′*R*)-diastereoisomer was the major product.[25]
[d] Diastereoisomeric ratio: >97:3 (determined from the ^{31}P NMR of the crude product); (3*R*,1′*S*)-diastereoisomer was the major product.[25]