An Easy Approach for the Synthesis of N-Substituted Isoindolin-1-ones

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Abstract: A practical and efficient two-step synthesis of N-substituted isoindolin-1-ones was developed. The one-pot reaction of 2-formylbenzoic acid with amines and dimethyl phosphite proceeds in short time either with conventional heating or microwave irradiation under catalyst-free conditions to afford the corresponding N-substituted dimethyl 3-oxoisoindolin-1-ylphosphonates in good yield which, by means of a dephosphonylation reaction with lithium aluminum hydride, give the target N-substituted isoindolin-1-ones in moderate to good yield.

Key words: amino phosphonates, isoindolinones, C–P cleavage, microwave irradiation, one-pot reaction

Isoindolin-1-ones (2,3-dihydro-1*H*-isoindol-1-ones) have gained considerable attention recently due to their fascinating properties and potential applications in many fields, especially in biology and medicinal science.[1] The interest in these heterocyclic compounds stems mainly from their diverse biological activities. For example, isoindolin-1-ones **1**–**3** (Figure 1) have been tested as antimicrobial agents,[2] while indoprofen (**4**) has been shown to have anti-inflammatory activity[3,4] and deoxythalidomide (**5**) is an inhibitor of tumor necrosis factor production.[5] Additionally, the isoindolin-1-one skeleton is a key intermediate for the synthesis of many naturally occurring bioactive compounds.[6]

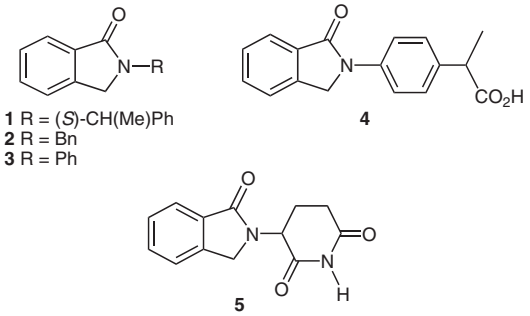

Figure 1

Consequently, the chemistry of isoindolinones has attracted much attention, and a number of synthetic strategies have been developed over the past few years including the reduction of phthalimides,[7] the condensation of anilines with *o*-phthalaldehydes,[8] amination and lactamization of 2-carbomethoxybenzaldehyde,[6h,9] palladium(0)-catalyzed carbonylation–amination,[10] synthesis from isocyanates[11] and base-induced aryne-mediated cyclization of *o*-halo-*N*-(phosphinylmethyl)benzamide derivatives;[12,13] however, despite their potential utility, these procedures typically suffer from one or more disadvantages, such as the use of harsh conditions or tedious multisteps which are necessary for these syntheses. Thus, there is still a need to develop versatile and flexible methods for the synthesis of isoindolin-1-ones. In this context, herein we describe an efficient method for the synthesis of N-substituted isoindolin-1-ones. Our synthetic strategy is based upon a one-pot reaction of 2-formylbenzoic acid with alkyl- or arylamines and dimethyl phosphite using conventional heating or microwave irradiation under catalyst-free conditions,[14] followed by a dephosphonylation reaction.

We have recently developed[15] an efficient and highly diastereoselective method for the synthesis of 3-oxoisoindolin-1-ylphosphonate **7a** by a three-component, one-pot reaction of 2-formylbenzoic acid (**6**), (*S*)-α-methylbenzylamine and dimethyl phosphite under catalyst- and solvent-free conditions (Table 1, entry 1). To establish the generality of this three-component, one-pot process we carried out the reaction of 2-formylbenzoic acid (**6**) with either alkyl- or arylamines and dimethyl phosphite. Thus, the reaction of 2-formylbenzoic acid (**6**) with *tert*-butylamine or benzhydrylamine and dimethyl phosphite at 80 °C under catalyst- and solvent-free conditions gave the corresponding 3-oxoisoindolin-1-ylphosphonates **7b**,**c**, but in low yield. Better results were obtained when the reaction was carried out in toluene at reflux; under these conditions, the phosphonates **7b**,**c** were obtained in 69% and 40% yield, respectively (Table 1, entries 2 and 3). On the other hand, the reaction of 2-formylbenzoic acid (**6**), aniline and dimethyl phosphite at 90 °C produced the desired 3-oxo-2-phenylisoindolin-1-ylphosphonate **7d** in 14% yield after five days (Table 1, entry 4). With this result, we decided to use microwave irradiation as an alternative heating source. Thus, the one-pot reaction of 2-formylbenzoic acid (**6**) with aniline under catalyst- and solvent-free conditions was irradiated at 70 °C for five minutes. After this time, dimethyl phosphite was added and the reaction mixture was again irradiated at 90 °C for five minutes, which gave the expected 3-oxoisoindolin-1-ylphosphonate **7d** in 77% yield (Table 1, entry 5). After the optimization of these experimental conditions, we explored the generality of this method with other arylamines, such as 4-methoxyaniline, 3,4-dimethoxyaniline,

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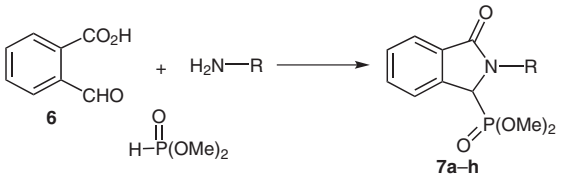
3-(trifluoromethyl)aniline and 2-aminopyridine, which produced the *N*-aryl-3-oxoisoindolin-1-ylphosphonates **7e–h** in good yield, except for the 2-aminopyridine derivative (Table 1, entries 6–9).

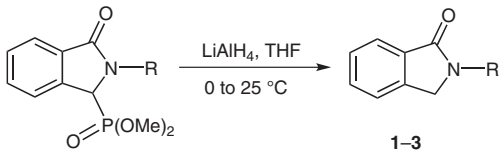
Table 1 Synthesis of 3-Oxoisoindolin-1-ylphosphonates **7a–h**



Entry	R	Conditions	Yield (%)
1	**7a**; (*S*)-CH(Me)Ph	80 °C, 60 min	75
2	**7b**; *t*-Bu	toluene, reflux	69
3	**7c**; $CHPh_2$	toluene, reflux	40
4	**7d**; Ph	90 °C, 5 d	14
5	**7d**; Ph	MW, 180 W[a]	77
6	**7e**; 4-$MeOC_6H_4$	MW, 180 W[a]	82
7	**7f**; 3,4-$(MeO)_2C_6H_3$	MW, 180 W[a]	75
8	**7g**; 3-$F_3CC_6H_4$	MW, 180 W[a]	73
9	**7h**; 2-pyridyl	MW, 180 W[a]	22

[a] Reaction conditions: (i) 70 °C, 5 min; (ii) dimethyl phosphite, 90 °C, 5 min.

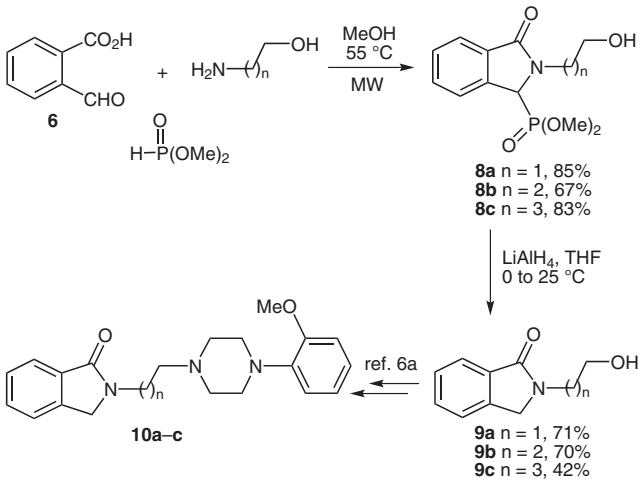
With the 3-oxoisoindolin-1-ylphosphonates **7a–h** in hand, in the next step we turned our attention to the reduction of the C–P bond to obtain the desired *N*-alkyl- and *N*-arylisoindolin-1-ones **1–3**. In this context, Oh and coworkers[16] have reported a method for C–P bond cleavage in β-oxo phosphonates by dephosphonylation of their lithium enolates with lithium aluminum hydride. Additionally, Amedjkouh and Grimaldi[17] have reported the dephosphonylation of 5-phosphonylpyrrolidines using the same reducing agent. According to these methods, we carried out the reaction of the 3-oxoisoindolin-1-ylphosphonates **7a–h** with lithium aluminum hydride in anhydrous tetrahydrofuran at 0 to 25 °C, whereupon the desired isoindolin-1-ones **1–3** were obtained in moderate to good yield (Scheme 1). Other reagents (such as DIBAL-H and $LiBH_4$) gave only poor yields of the corresponding isoindolin-1-ones **1–3**.



1 R = (*S*)-CH(Me)Ph; 67%
2a R = *t*-Bu; 85%
2b R = $CHPh_2$; 60%
3a R = Ph; 90%
3b R = 4-$MeOC_6H_4$; 80%
3c R = 3,4-$(MeO)_2C_6H_3$; 43%
3d R = 3-$F_3CC_6H_4$; 58%
3e R = 2-pyridyl; 44%

Scheme 1

In order to establish the generality of this method, we carried out the synthesis of *N*-(2-hydroxyethyl)-, *N*-(3-hydroxypropyl)- and *N*-(4-hydroxybutyl)isoindolin-1-one (**9a–c**), which are key intermediates for the preparation of the piperazine derivatives **10a–c** (Scheme 2).[6a] Thus, the reaction of 2-formylbenzoic acid (**6**) with ethanolamine and dimethyl phosphite under catalyst- and solvent-free conditions was irradiated at 55 °C for five minutes to give the corresponding 3-oxoisoindolin-1-ylphosphonate **8a** in very poor yield, while the one-pot reaction of 2-formylbenzoic acid (**6**) with ethanolamine in methanol under microwave irradiation at 55 °C for five minutes, followed by addition of dimethyl phosphite and heating at 55 °C/180 W for five minutes, gave the desired phosphonate **8a** in 85% yield. Under these conditions, the reaction of 2-formylbenzoic acid (**6**), 3-aminopropan-1-ol or 4-aminobutan-1-ol and dimethyl phosphite provided the corresponding 3-oxoisoindolin-1-ylphosphonates **8b**,**c** in 67% and 83% yield, respectively (Scheme 2). Finally, the reaction of the 3-oxoisoindolin-1-ylphosphonates **8a–c** with lithium aluminum hydride in anhydrous tetrahydrofuran afforded the target isoindolin-1-ones **9a–c** in good yield.



Scheme 2

In summary, we have developed a practical and efficient synthetic approach to N-substituted isoindolin-1-ones. The synthetic route involves the one-pot reaction of 2-formylbenzoic acid with amines and dimethyl phosphite, followed by a dephosphonylation reaction. This two-step synthetic sequence is very efficient, affording the N-substituted isoindolin-1-ones in good yield. Considering the mild reaction conditions, we believe that this methodology could be of use in organic synthesis for the preparation of important isoindolin-1-ones.

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All commercial materials were used as received without further purification. Melting points were registered in a Fisher–Johns apparatus and are uncorrected. Flash chromatography was performed using silica gel 60 (230–400 mesh). Thin-layer chromatography was performed with precoated TLC sheets of silica gel 60 F_{254} (Merck). Microwave reactions were performed in a CEM Discover System. NMR spectra were recorded with a Varian System instrument (400 MHz for ^{1}H, 100 MHz for ^{13}C) or a Mercury instrument (81 MHz for ^{31}P) and calibrated with $CDCl_3$ as solvent and TMS as internal standard signal. Chemical shifts (δ) are reported in parts per million. Coupling constants (*J*) are given in Hz. High-resolution FAB$^+$ and CI$^+$ mass spectra (HRMS) were obtained with a JEOL HRMStation JHRMS-700 instrument. Compound **7a** was prepared according to the literature procedure.[15]

N-Alkyl-3-oxoisoindolin-1-ylphosphonates 7b,c; General Procedure

A mixture of 2-formylbenzoic acid (**6**, 1 equiv), an amine (1.06 equiv) and dimethyl phosphite (1.11 equiv) in toluene (7 mL) was heated under reflux for 4 h. The crude product was purified by simple column chromatography (EtOAc–hexane, 70:30).

Dimethyl 2-*tert*-Butyl-3-oxoisoindolin-1-ylphosphonate (7b)

Yield: 682 mg (69%); white solid; mp 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68 [s, 9 H, $C(CH_3)_3$], 3.60 [d, *J* = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.62 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 5.10 [d, *J* = 10.4 Hz, 1 H, $CHP(OCH_3)_2$], 7.46–7.82 (m, 4 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [$(CH_3)_3C$], 53.6 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 54.4 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 56.6 [$C(CH_3)_3$], 58.2 [d, *J* = 151.7 Hz, $CHP(OCH_3)_2$], 123.5, 124.3, 128.8, 131.1, 134.2, 139.3, 169.3 (C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 22.00.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{14}H_{21}NO_4P$: 298.1208; found: 298.1203.

Dimethyl 2-(Diphenylmethyl)-3-oxoisoindolin-1-ylphosphonate (7c)

Yield: 214 mg (40%); white solid; mp 130–132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.46 [d, *J* = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.54 [d, *J* = 11.2 Hz, 3 H, $(CH_3O)_2P$], 4.94 [d, *J* = 12.8 Hz, 1 H, $CHP(OCH_3)_2$], 6.45 (s, 1 H, $CHPh_2$), 7.24–7.85 (m, 14 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.3 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 54.4 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 59.0 [d, *J* = 156.3 Hz, $CHP(OCH_3)_2$], 63.9 ($CHPh_2$), 124.3, 124.6, 127.5, 127.7, 128.3, 128.6, 128.7, 129.2, 129.3, 132.0, 132.9, 138.7, 139.0, 139.4, 169.5 (C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.60.

HRMS (FAB$^+$): *m*/*z* calcd for $C_{23}H_{23}NO_4P$: 408.1365; found: 408.1398.

N-Aryl-3-oxoisoindolin-1-ylphosphonates 7d–h; General Procedure

A mixture of 2-formylbenzoic acid (**6**, 1 equiv) and an amine (1 equiv) was irradiated using a CEM microwave at 70 °C/180 W for 5 min. After this time, dimethyl phosphite (1.1 equiv) was added and the reaction mixture was again irradiated at 90 °C/180 W for 5 min. The crude product was purified by column chromatography (EtOAc–hexane, 50:50).

Dimethyl 3-Oxo-2-phenylisoindolin-1-ylphosphonate (7d)

Yield: 1.3 g (77%); yellow solid; mp 145–147 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.28 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.47 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 5.58 [d, *J* = 12.4 Hz, 1 H, $CHP(OCH_3)_2$], 7.26–7.30 (m, 1 H, H_{arom}), 7.42–7.66 (m, 6 H, H_{arom}), 7.84–7.96 (m, 2 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.1 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 54.1 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 59.2 [d, *J* = 151.7 Hz, $CHP(OCH_3)_2$], 124.6, 124.7, 125.2, 126.6, 129.0, 129.4, 132.2, 132.4, 137.5, 138.1, 167.6 (C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 20.47.

HRMS (CI$^+$): *m*/*z* calcd for $C_{16}H_{17}NO_4P$: 318.0817; found: 318.0886.

Dimethyl 2-(4-Methoxyphenyl)-3-oxoisoindolin-1-ylphosphonate (7e)

Yield: 1.38 g (82%); yellow solid; mp 169–172 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.50 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.83 (s, 3 H, CH_3O), 5.47 [d, *J* = 12.8 Hz, 1 H, $CHP(OCH_3)_2$], 6.98 (AA′BB′ system, *J* = 6.8 Hz, 2 H, H_{arom}), 7.40 (AA′BB′ system, *J* = 6.8 Hz, 2 H, H_{arom}), 7.54–7.65 (m, 2 H, H_{arom}), 7.82–7.95 (m, 2 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.2 [d, *J* = 6.1 Hz, $(CH_3O)_2P$], 54.1 [d, *J* = 6.1 Hz, $(CH_3O)_2P$], 55.6 (CH_3O), 59.6 [d, *J* = 151.7 Hz, $CHP(OCH_3)_2$], 114.4, 124.5, 124.7, 126.9, 129.3, 130.3, 132.2, 138.0, 158.4, 167.9 (C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 20.67.

HRMS (CI$^+$): *m*/*z* calcd for $C_{17}H_{19}NO_5P$: 348.0923; found: 348.0993.

Dimethyl 2-(3,4-Dimethoxyphenyl)-3-oxoisoindolin-1-ylphosphonate (7f)

Yield: 0.55 g (75%); yellow solid; mp 110–113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.32 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.52 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.91 (s, 6 H, CH_3O), 5.52 [d, *J* = 12.8 Hz, 1 H, $CHP(OCH_3)_2$], 6.92–6.99 (m, 2 H, H_{arom}), 7.13 (s, 1 H, H_{arom}), 7.55–7.66 (m, 2 H, H_{arom}), 7.83 (d, *J* = 7.2 Hz, 1 H, H_{arom}), 7.94 (d, *J* = 7.2 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.2 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 54.1 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 56.2 (2 CH_3O), 59.6 [d, *J* = 154.7 Hz, $CHP(OCH_3)_2$], 110.0, 111.3, 117.7, 124.5, 124.6, 129.4, 130.6, 132.1, 132.3, 138.0, 148.0, 149.3, 167.9 (C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 20.80.

HRMS (CI$^+$): *m*/*z* calcd for $C_{18}H_{21}NO_6P$: 378.1128; found: 378.1120.

Dimethyl 3-Oxo-2-[3-(trifluoromethyl)phenyl]isoindolin-1-ylphosphonate (7g)

Yield: 0.50 g (73%); yellow solid; mp 124–128 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.31 [d, *J* = 11.2 Hz, 3 H, $(CH_3O)_2P$], 3.51 [d, *J* = 11.2 Hz, 3 H, $(CH_3O)_2P$], 5.63 [d, *J* = 12.0 Hz, 1 H, $CHP(OCH_3)_2$], 7.49–7.57 (m, 3 H, H_{arom}), 7.62–7.66 (m, 1 H, H_{arom}), 7.76–7.84 (m, 3 H, H_{arom}), 7.92 (d, *J* = 7.6 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.2 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 54.2 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 58.8 [d, *J* = 151.7 Hz, $CHP(OCH_3)_2$], 121.4, 122.9, 123.9 (d, *J* = 270.0 Hz), 124.7, 124.8, 128.1, 129.5, 129.6, 131.2, 131.7, 132.8, 137.9, 138.1 (d, *J* = 30.4 Hz), 167.5 (C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 20.06.

HRMS (CI$^+$): *m*/*z* calcd for $C_{17}H_{16}F_3NO_4P$: 386.0769; found: 386.0777.

Dimethyl 3-Oxo-2-(2-pyridyl)isoindolin-1-ylphosphonate (7h)

Two rotamers were observed for this compound.

Yield: 385 mg (22%); yellow solid; mp 105–108 °C.

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^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36 [d, *J* = 11.0 Hz, 3 H, $(CH_3O)_2P$], 3.60 [d, *J* = 10.4 Hz, 3 H, $(CH_3O)_2P$], 3.65 [d, *J* = 11.0 Hz, 3 H, $(CH_3O)_2P$], 3.92 [d, *J* = 10.4 Hz, 3 H, $(CH_3O)_2P$], 5.73 (d, *J* = 11.2 Hz, 1 H, $CHP(OCH_3)_2$], 6.36 (d, *J* = 13.6 Hz, 1 H, $CHP(OCH_3)_2$], 7.12–7.15 (m, 2 H, H_{arom}), 7.53–7.95 (m, 10 H, H_{arom}), 8.23–8.24 (d, *J* = 8.4 Hz, 2 H, H_{arom}), 8.44–8.46 (m, 2 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.7 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 53.8 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 54.2 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 54.5 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 56.3 [d, *J* = 151.7 Hz, $CHP(OCH_3)_2$], 75.3 [d, *J* = 163.8 Hz, $CHP(OCH_3)_2$], 117.2, 120.5, 123.7, 124.6, 124.8, 125.2, 125.3, 126.1, 129.1, 130.0, 132.0, 132.9, 134.6, 137.9, 139.1, 143.7, 147.6, 150.8, 167.7 (C=O), 169.6 (C=O).

^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.40.

HRMS (CI^+): *m*/*z* calcd for $C_{15}H_{16}N_2O_4P$: 319.0848; found: 319.0853.

N-(ω-Hydroxyalkyl)-3-oxoisoindolin-1-ylphosphonates 8a–c; General Procedure

A mixture of 2-formylbenzoic acid (**6**, 6.6 mmol) and an amine (6.6 mmol) in MeOH (1 mL) was irradiated using a CEM microwave at 55 °C/180 W for 5 min. After this time, dimethyl phosphite (7.3 mmol) was added and the reaction mixture was again irradiated at 55 °C/180 W for 5 min. The crude product was purified by column chromatography (EtOAc).

Dimethyl 2-(2-Hydroxyethyl)-3-oxoisoindolin-1-ylphosphonate (8a)

Yield: 1.59 g (85%); white solid; mp 92–94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.58 [d, *J* = 11.2 Hz, 3 H, $(CH_3O)_2P$], 3.71 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.74–3.82 (m, 1 H, CH_2N), 3.86 (br s, 1 H, OH), 3.88–3.90 (m, 2 H, CH_2), 4.13–4.19 (m, 1 H, CH_2OH), 5.19 [d, *J* = 13.2 Hz, 1 H, $CHP(OCH_3)_2$], 7.47–7.51 (m, 1 H, H_{arom}), 7.55–7.59 (m, 1 H, H_{arom}), 7.70–7.72 (m, 1 H, H_{arom}), 7.82–7.84 (m, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.4, 53.8 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 54.0 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 58.7 [d, *J* = 154.7 Hz, $CHP(OCH_3)_2$], 61.6, 123.9, 124.3, 129.0, 131.9, 132.0, 138.9, 169.8.

^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.51.

HRMS (CI^+): *m*/*z* calcd for $C_{12}H_{17}NO_5P$: 286.0769; found: 286.0852.

Dimethyl 2-(3-Hydroxypropyl)-3-oxoisoindolin-1-ylphosphonate (8b)

Yield: 1.37 g (67%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78–1.88 (m, 1 H, CH_2), 1.93–2.00 (m, 1 H, CH_2), 3.36 (br s, 1 H, OH), 3.50–3.56 (m, 1 H, CH_2), 3.60 [d, *J* = 11.2 Hz, 3 H, $(CH_3O)_2P$], 3.60–3.65 (m, 1 H, CH_2), 3.75 [d, *J* = 10.8 Hz, 3 H, $(CH_3O)_2P$], 3.82–3.88 (m, 1 H, CH_2), 4.05–4.12 (m, 1 H, CH_2), 4.94 [d, *J* = 13.6 Hz, 1 H, $CHP(OCH_3)_2$], 7.51–7.55 (m, 1 H, H_{arom}), 7.58–7.62 (m, 1 H, H_{arom}), 7.75–7.77 (m, 1 H, H_{arom}), 7.85–7.87 (m, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.0, 39.0, 53.9 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 54.0 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 57.8 [d, *J* = 154.7 Hz, $CHP(OCH_3)_2$], 59.0, 124.0, 124.5, 129.2, 132.0, 132.1, 138.5, 170.1.

^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.14.

HRMS (CI^+): *m*/*z* calcd for $C_{13}H_{19}NO_5P$: 300.0923; found: 300.0970.

Dimethyl 2-(4-Hydroxybutyl)-3-oxoisoindolin-1-ylphosphonate (8c)

Yield: 1.70 g (83%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54–1.61 (m, 2 H, CH_2), 1.69–1.76 (m, 1 H, CH_2), 1.84–1.91 (m, 1 H, CH_2), 2.75 (br s, 1 H, OH), 3.57–3.64 (m, 5 H), 3.66–3.69 (m, 1 H, CH_2), 3.72 [d, *J* = 10.4 Hz, 3 H, $(CH_3O)_2P$], 4.07–4.15 (m, 1 H, CH_2), 4.94 [d, *J* = 13.6 Hz, 1 H, $CHP(OCH_3)_2$], 7.50–7.60 (m, 2 H, H_{arom}), 7.72–7.74 (m, 1 H, H_{arom}), 7.85–7.87 (m, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.4, 29.7, 41.7, 53.7 [d, *J* = 7.6 Hz, $(CH_3O)_2P$], 53.9 [d, *J* = 6.0 Hz, $(CH_3O)_2P$], 57.2 [d, *J* = 154.7 Hz, $CHP(OCH_3)_2$], 61.9, 124.0, 124.4, 129.2, 131.8, 132.4, 138.4, 169.0.

^{31}P NMR (81 MHz, $CDCl_3$): δ = 21.14.

HRMS (CI^+): *m*/*z* calcd for $C_{14}H_{21}NO_5P$: 314.1079; found: 314.1154.

N-Substituted Isoindolin-1-ones 1–3 and 9a–c; General Procedure for the Dephosphonylation of 7a–h and 8a–c

To a suspension of $LiAlH_4$ (3 equiv) in anhyd THF (5 mL) at 0 °C was added slowly a 3-oxoisoindolin-1-ylphosphonate (1 equiv) in anhyd THF (5 mL). The reaction mixture was allowed to warm to r.t. and was stirred for 30 min. EtOAc (5 mL) and H_2O (5 mL) were added, and the resulting mixture was refluxed for 1 h. The reaction mixture was extracted with EtOAc (3 × 5 mL), and the combined organic layer was washed with H_2O (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (hexane–EtOAc, 50:50).

2-[(*S*)-1-Phenylethyl]isoindolin-1-one (1)

Yield: 135 mg (67%); white solid; mp 143–145 °C (Lit.[10e] 142–144 °C for the *R*-enantiomer).

$[\alpha]_D$ –161.3 (*c* 1.33, $CHCl_3$) [Lit.[10e] $[\alpha]_D$ +144 (*c* 1.33, $CHCl_3$) for the *R*-enantiomer].

The spectroscopic data were identical with those reported in the literature for the *R*-enantiomer.[10e]

2-*tert*-Butylisoindolin-1-one (2a)

Yield: 136 mg (85%); white solid; mp 62–63 °C.

The spectroscopic data were identical with those reported in the literature.[18]

2-(Diphenylmethyl)isoindolin-1-one (2b)

Yield: 108 mg (60%); white solid; mp 115–117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (s, 2 H, CH_2N), 6.91 (s, 1 H, $NCHPh_2$), 7.21–7.92 (m, 14 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.6 (CH_2N), 58.8 ($NCHPh_2$), 123.0, 124.2, 127.8, 128.2, 128.7, 128.8, 131.6, 132.5, 139.4, 141.6, 168.6 (C=O).

HRMS (FAB^+): *m*/*z* calcd for $C_{21}H_{18}NO$: 300.1388; found: 300.1382.

2-Phenylisoindolin-1-one (3a)

Yield: 178 mg (90%); yellow solid; mp 160–163 °C (Lit.[10c,19] mp 162–163 °C).

The spectroscopic data were identical with those reported in the literature.[10c,19]

2-(4-Methoxyphenyl)isoindolin-1-one (3b)

Yield: 100 mg (80%); yellow solid; mp 130–134 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H, CH_3O), 4.79 (s, 2 H, CH_2), 6.93–6.97 (m, 2 H, H_{arom}), 7.47–7.50 (m, 2 H, H_{arom}), 7.55–

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7.59 (m, 1 H, H_{arom}), 7.70–7.75 (m, 2 H, H_{arom}), 7.89–7.91 (m, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.4 (CH_3O), 55.7 (CH_2), 114.6, 121.7, 122.7, 124.2, 128.5, 131.9, 132.9, 133.5, 140.4, 156.9, 167.4 (C=O).

HRMS (CI^+): *m/z* calcd for $C_{15}H_{14}NO_2$: 240.1025; found: 240.1015.

2-(3,4-Dimethoxyphenyl)isoindolin-1-one (3c)
Yield: 73 mg (43%); white solid; mp 138–140 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3 H, CH_3O), 3.94 (s, 3 H, CH_3O), 4.81 (s, 2 H, CH_2), 6.88 (d, *J* = 8.8 Hz, 1 H, H_{arom}), 7.03 (d, *J* = 8.4 Hz, 1 H, H_{arom}), 7.49 (m, 2 H, H_{arom}), 7.57 (m, 1 H, H_{arom}), 7.88 (m, 2 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 51.4 (CH_2), 56.2 (CH_3O), 56.3 (CH_3O), 105.3, 111.4, 111.8, 122.7, 124.2, 128.5, 132.0, 133.5, 140.2, 146.5, 149.6, 167.5.

HRMS (CI^+): *m/z* calcd for $C_{16}H_{16}NO_3$: 270.1052; found: 270.1126.

2-[3-(Trifluoromethyl)phenyl]isoindolin-1-one (3d)
Yield: 200 mg (58%); white solid; mp 158–160 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.88 (s, 2 H, CH_2), 7.40–7.43 (m, 1 H, H_{arom}), 7.50–7.56 (m, 3 H, H_{arom}), 7.60–7.64 (m, 1 H, H_{arom}), 7.91–7.93 (m, 1 H, H_{arom}), 8.11–8.18 (m, 2 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.8 (CH_2), 115.7 (q, *J* = 0.46 Hz), 121.0 (q, *J* = 3.1 Hz), 122.3, 122.9, 124.5, 128.8, 129.9, 131.7 (d, *J* = 31.8 Hz), 132.7, 132.9, 139.9, 140.0, 167.9 (C=O).

HRMS (CI^+): *m/z* calcd for $C_{15}H_{11}F_3NO$: 278.0714; found: 278.0790.

2-(2-Pyridyl)isoindolin-1-one (3e)
Two rotamers were observed for this compound.

Yield: 40 mg (44%); yellow solid; mp 128–130 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.08 (s, 2 H, CH_2), 7.04–7.07 (m, 1 H, H_{arom}), 7.47–7.62 (m, 3 H, H_{arom}), 7.74 (t, *J* = 8.0 Hz, 1 H, H_{arom}), 7.91 (d, *J* = 8.0 Hz, 1 H, H_{arom}), 8.38 (s, 1 H, H_{arom}), 8.65 (d, *J* = 8.8 Hz, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.0 (CH_2), 114.4, 119.6, 123.1, 124.4, 128.4, 132.7, 133.2, 138.0, 141.2, 147.9, 152.1, 168.9.

HRMS (CI^+): *m/z* calcd for $C_{13}H_{11}N_2O$: 211.0793; found: 211.0878.

2-(2-Hydroxyethyl)isoindolin-1-one (9a)
Yield: 222 mg (71%); white solid; mp 116–118 °C (Lit.[1k] 117–119 °C).

The spectroscopic data were identical with those reported in the literature.[1k]

2-(3-Hydroxypropyl)isoindolin-1-one (9b)
Yield: 89 mg (70%); colorless oil.

The spectroscopic data were identical with those reported in the literature.[1k]

2-(4-Hydroxybutyl)isoindolin-1-one (9c)
Yield: 122 mg (42%); colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.58–1.65 (m, 2 H, CH_2), 1.75–1.82 (m, 2 H, CH_2), 2.31 (br s, 1 H, OH), 3.66–3.72 (m, 4 H, CH_2), 4.39 (s, 2 H, CH_2), 7.43–7.47 (m, 2 H, H_{arom}), 7.50–7.54 (m, 1 H, H_{arom}), 7.82–7.84 (m, 1 H, H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.2 (CH_2), 29.7 (CH_2), 42.3 (CH_2), 50.1 (CH_2), 62.5 (CH_2), 122.8, 123.9, 128.2, 131.4, 133.1, 141.3, 168.9.

HRMS (CI^+): *m/z* calcd for $C_{12}H_{16}NO_2$: 206.1102; found: 206.1179.

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