A Convenient Synthesis of 4-Alkoxylated Isoindolin-1-ones

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Abstract: A short synthesis of 4-alkoxylated isoindolin-1-ones based upon the S_NAr reaction applied to phosphorylated 2-methoxybenzamides followed by alkaline cleavage of the phosphoryl auxiliary is reported.

Key words: metalations, carbanions, nucleophilic aromatic substitutions, ring closure, cleavage

The isoindolinone ring system has featured in recent years as a desirable synthetic target since it represents the core unit of a wide range of natural compounds as exemplified by fumaridine,[1] nuevamine,[2,3] lennoxamine[3] and chilenine,[4] and of synthetic pharmaceuticals with biological activity such as indoprofen[5] and DN 2327 (pazinaclone).[6]

Within this family of 6,5-fused heterobicyclic compounds, model compounds bearing alkoxy or hydroxy groups at the 4-position of the aromatic nucleus occupy a place of choice as witnessed by a great number of recent patents emphasizing the biological potential of the piperidinyl derivatives **1** (sigma receptor ligand),[7] **2** (microsomal triglyceride transfer protein inhibitor),[8] **3** (psychoses treatment)[9] and of the anilinoethyl derivative **4** (inflammation and allergy inhibitor).[10] The 4-alkoxyisoindolinone moiety is also present in a wide array of natural products such as zinnimidine (**5**),[11] porritoxin (**6**),[12] and constitutes the framework of architecturally sophisticated cularines as exemplified by aristoyagonine (**7**)[13] (Figure 1).

Organic chemists have at their disposal a great number of synthetic methods for the preparation of substituted isoindolinones but their applicability is quite insufficient because of restrictions in the choice of substituents namely in their nature, their number and above all their position on the aromatic nucleus.[14–21] The most convenient routes to these bicyclic lactams involve (i) the treatment of brominated alkyl *ortho*-toluate with a primary amine,[14] (ii) the reductive amination process applied to *ortho*-acylbenzoic acids,[15] (iii) the partial reduction of phthalimides via their aminals or thioaminals,[16] and (iv) the reaction of *ortho*-phthalaldehyde[17] or isobenzofuranones[18] with a primary amine. Isoindolinones can also be synthesized by reaction of *ortho*-bromobenzylamines with carbon monoxide in the presence of *n*-Bu_3N, $Pd(OAc)_2$ and

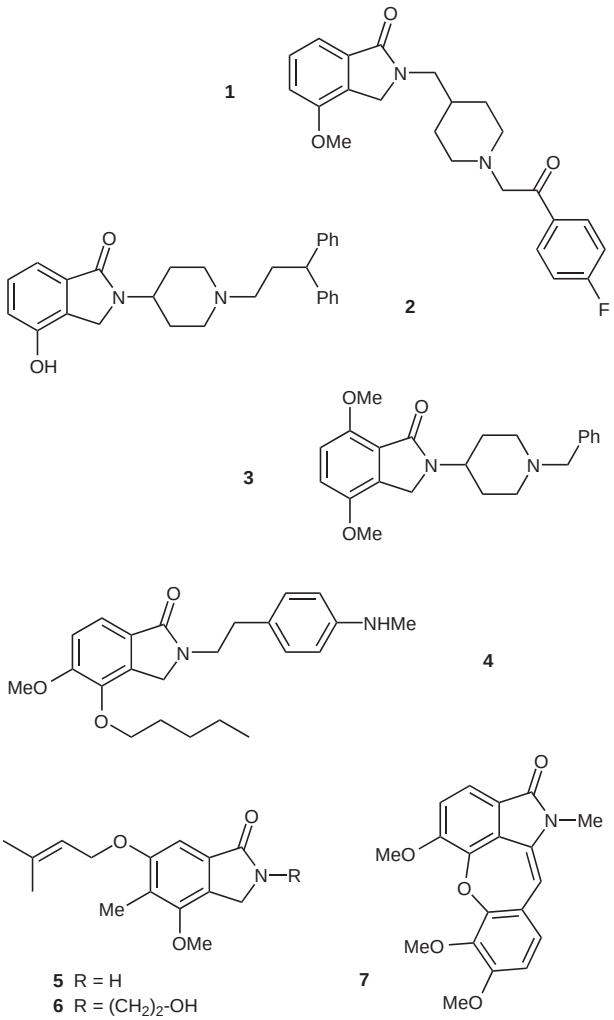

Figure 1 Some compounds of biological interest containing the isoindolino ring system

Ph_3P[19] and by base-induced cyclization of *ortho*-halomethylbenzamide derivatives.[20] Finally, they have been recently prepared by a palladium-catalyzed 3-component carbonylation-amination cascade process.[21] However, these strategies have been mainly confined to the elaboration of 2- and/or 3- substituted isoindolinones and in most cases are inadequate for the synthesis of models with diverse and dense functionality, particularly with hydroxy or alkoxy functions in specific positions on the basic benzene nucleus. They are notably plagued by difficulties associated with the presence of such functions at the 4-position of the aromatic unit. As a representative example, partial reduction of 4-alkoxyphthalide derivatives affords

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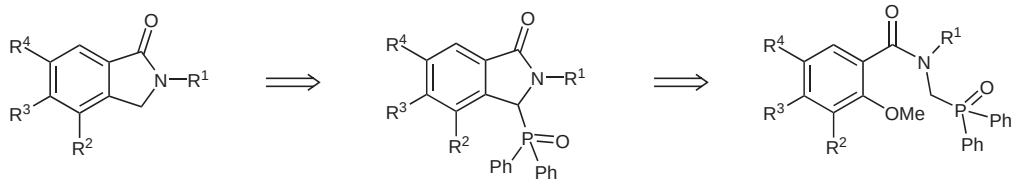


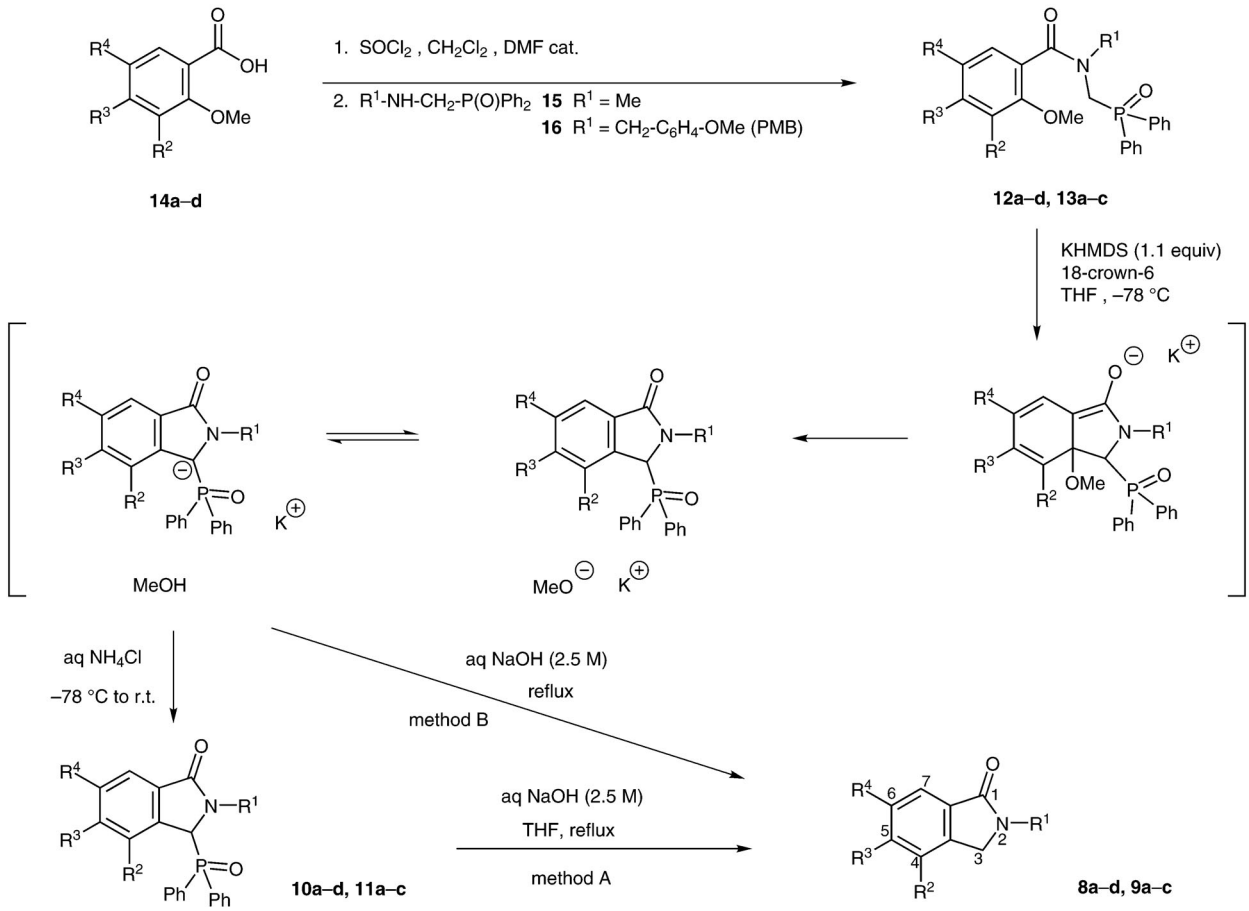
Scheme 1

exclusively the corresponding 7-substituted phthalimidines.[22] We therefore considered that the development of a more concise and efficient synthesis giving access to differentially substituted 4-alkoxyisoindolinones **8**, **9** was required.

Our new synthetic approach which is depicted in the retrosynthetic Scheme 1 hinges upon the exploitation of a number of chemical properties linked to the anions derived from the opened or cyclized phosphorylated benzamide derivatives **10**, **11** and **12**, **13**, respectively.

The key features of the method are based on: (i) The remarkable nucleophilicity of phosphorylated aminocarbanions, a property mainly used thus far in related systems for the synthesis of aromatic enamines[23] and enamides[24] (Horner protocol). These carbanionic entities have also been involved in the aryne-mediated cyclization of phosphorylated *ortho*-halobenzamide derivatives but this procedure inevitably gave rise to models which were unsubstituted at the 4-position of the aromatic nucleus;[25] (ii) The sensitivity of alkoxy groups activated by ester,[26] amide,[27] and above all oxazoline groups (the Meyers reaction)[28] to nucleophilic aromatic substitution by various nucleophiles, inter or intramolecularly, and (iii) The sensitivity of the phosphoryl group with respect to $S_NP(V)$ nucleophilic attack and consequently the possibility to trigger the formation of the target compound by its release from the phosphoryl appendage by alkaline cleavage.[29]

The first facet of the synthesis, the elaboration of polyalkoxylated and phosphorylated benzamide derivatives **12a**–**d**, **13a**–**c** was readily accomplished by coupling the suitably substituted benzoic acid derivatives **14a**–**d**, via their acyl chlorides, to the appropriate phosphorylated amines **15**, **16** (Scheme 2).



Scheme 2

Exposure of the phosphorylated *ortho*-methoxybenzamide derivatives **12a–d** and **13a–c** to potassium bis(trimethylsilyl)amide (KHMDS, 1.1 equiv) at –78 °C in the presence of 18-crown-6 induced the formation of the phosphoryl-stabilized α-aminocarbanion. Subsequent *ortho*-methoxy displacement by the transient carbanion, according to the nucleophilic aromatic substitution process (S_NAr) portrayed in Scheme 2, brought about the intramolecular arylation reaction and usual acidic workup delivered the phosphorylated isoindolinones **10a–d** and **11a–c**.

It is noteworthy that, while S_NAr reactions are usually carried out with two equivalents of base, the methoxylate released in the annulation step was of sufficient kinetic basicity to ensure deprotonation of the phosphorylated benzylic position (Scheme 2). Consequently this new cyclization process can be performed with one equivalent of base only. It is also worth noting that the methoxy displacement required in the annulation process is not conditioned by the presence of a vicinal alkoxy function as shown by the formation of the isoindolinone **10d** starting from **12d**.

The final removal of the temporary activating auxiliary was not problematic and basic treatment of the primary annulated compounds **10a–d** and **11a–c** with aqueous NaOH solution (2.5 M) afforded the desired polyalkoxylated isoindolinones released from the phosphoryl appendage (Scheme 2; Method A). A collection of annulated compounds which have been prepared by this method are presented in Table 1 where it may be seen that this protocol affords excellent yields of the target poly and diversely alkoxylated isoindolinones **8a–d** and **9a–c** (87–95%, Table 1). Interestingly, isolation of the phosphorylated isoindolinones is not a prerequisite for the conversion of the phosphorylated opened models into the desired lactam compounds. Thus the phosphorylated benzamides **12**, **13** could be treated with KHMDS at low temperature and then with aqueous NaOH in sequence (Scheme 2, Method B). Gratifyingly this protocol delivered straightforwardly the fused lactam compounds albeit in more modest yields (65–75%, Table 1). The analytical and spectral data of compounds **8–14** are assembled in Table 2.

Table 1 Compounds **8–14** Prepared

		R^1	R^2	R^3	R^4
8, 10, 12, 14	**a**	Me	OMe	H	H
	b	Me	OBn	H	H
	c	Me	OCH_2O		H
	d	Me	H	OMe	OMe
9, 11, 13	**a**	PMB	OMe	H	H
	b	PMB	OBn	H	H
	c	PMB	OCH_2O		H

Table 2 Spectroscopic and Physical Data of the Phosphorylated Amides **12, 13** and Isoindolin-1-ones **8–11** Prepared

Product[a,b]	Yield (%)	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{31}P NMR ($CDCl_3/H_3PO_4$) δ
12a	91	118–119	3.05 (s, 3 H, NCH_3), 3.58 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.33 (br s, 1 H, NCH_2P), 4.85 (br s, 1 H, NCH_2P), 6.19 (dd, *J* = 7.6, 1.7, 1 H_{arom}), 6.84 (dd, *J* = 8.1, 1.6, 1 H_{arom}), 6.93 (t, *J* = 7.9, 1H_{arom}), 7.42–7.54 (m, 6 H_{arom}), 7.84–7.99 (m, 4 H_{arom})	38.1, 46.9 (d, $J_{C,P}$ = 77), 55.7, 61.2, 113.1, 118.6, 124.5, 128.7 (d, $J_{C,P}$ = 12), 130.6, 130.9 (d, $J_{C,P}$ = 97), 131.2 (d, $J_{C,P}$ = 10), 132.2 (d, $J_{C,P}$ = 2), 144.9, 152.6, 169.0 (d, $J_{C,P}$ = 3)	31.0
12b	88	119–120	3.06 (s, 3 H, NCH_3), 3.62 (s, 3 H, OCH_3), 4.37 (br s, 1 H, NCH_2P), 4.84 (br s, 1 H, NCH_2P), 5.06 (s, 2 H, OCH_2Ph), 6.23 (t, *J* = 4.6, 1 H_{arom}), 6.90 (d, *J* = 4.6, 1 H_{arom}), 7.28–7.42 (m, 6 H_{arom}), 7.46–7.59 (m, 6 H_{arom}), 7.82–8.06 (m, 4 H_{arom})	38.2, 46.9 (d, $J_{C,P}$ = 76), 61.2, 70.8, 115.2, 119.1, 124.4, 127.3, 128.0, 128.6, 128.7 (d, $J_{C,P}$ = 13), 130.8, 131.1 (d, $J_{C,P}$ = 98), 131.2 (d, $J_{C,P}$ = 10), 132.2 (d, $J_{C,P}$ = 2), 136.6, 145.4, 151.7, 169.1 (d, $J_{C,P}$ = 2)	31.2
12c	86	oil	3.06 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 4.56 (br s, 2 H, NCH_2P), 5.87 (s, 2 H, OCH_2O), 6.17 (d, *J* = 8.0, 1 H_{arom}), 6.40 (d, *J* = 8.0, 1 H_{arom}), 7.47–7.55 (m, 6 H_{arom}), 7.87–7.93 (m, 4 H_{arom})	38.0, 47.0 (d, $J_{C,P}$ = 76), 59.5, 101.1, 102.8, 120.8, 122.0, 128.6 (d, $J_{C,P}$ = 12), 128.6 (d, $J_{C,P}$ = 12), 130.9 (d, $J_{C,P}$ = 98), 131.1 (d, $J_{C,P}$ = 10), 132.1 (d, $J_{C,P}$ = 2), 135.9, 139.7, 150.1, 168.7 (d, $J_{C,P}$ = 2)	31.6
12d	84	84–85	3.00 (s, 3 H, NCH_3), 3.50 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 4.54 (br s, 2 H, NCH_2P), 6.17 (s, 1 H_{arom}), 6.34 (s, 1 H_{arom}), 7.41–7.45 (m, 6 H_{arom}), 7.83–7.90 (m, 4 H_{arom})	37.9, 47.3 (d, $J_{C,P}$ = 76), 56.0, 56.1, 56.4, 97.1, 111.1, 115.8, 128.6 (d, $J_{C,P}$ = 12), 130.9 (d, $J_{C,P}$ = 98), 131.3 (d, $J_{C,P}$ = 10, 132.1 (d, $J_{C,P}$ = 3), 143.1, 149.8, 150.6, 169.1 (d, $J_{C,P}$ = 2)	31.9

Table 2 Spectroscopic and Physical Data of the Phosphorylated Amides **12, 13** and Isoindolin-1-ones **8**–**11** Prepared (continued)

13a	84	oil	3.64 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.20 (dd, J = 16.0, $J_{H,P}$ = 6.2, 1 H, NCH_2P), 4.54–4.68 (m, 3 H, NCH_2P + NCH_2Ar), 6.25 (dd, J = 7.6, 1.3, 1 H_{arom}), 6.82 (d, J = 8.5, 2 H_{arom}), 6.86 (dd, J = 8.3, 1.2, 1 H_{arom}), 6.95 (t, J = 8.0, 1 H_{arom}), 7.24 (d, J = 8.3, 2 H_{arom}), 7.42–7.58 (m, 6 H_{arom}), 7.86–7.98 (m, 4 H_{arom})	41.9 (d, $J_{C,P}$ = 76), 52.6, 55.2, 55.8, 61.5, 113.1, 114.0, 118.9, 124.5, 127.3, 128.7 (d, $J_{C,P}$ = 12), 313.2 (d, $J_{C,P}$ = 10), 131.3, 131.4 (d, $J_{C,P}$ = 97), 132.2 (d, $J_{C,P}$ = 3), 136.2, 145.0, 152.9, 159.2, 161.6	31.1
13b	81	113–114	3.66 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 4.28 (dd, J = 15.1, $J_{H,P}$ = 5.6, 1 H, NCH_2P), 4.58–4.74 (m, 3 H, NCH_2P + NCH_2Ar), 5.03 (s, 2 H, OCH_2Ph), 6.30 (t, J = 4.6, 1 H_{arom}), 6.82 (d, J = 8.3, 2 H_{arom}), 6.89 (d, J = 3.9, 2 H_{arom}), 7.26–7.47 (m, 13 H_{arom}), 7.87–7.96 (m, 4 H_{arom})	41.8 (d, $J_{C,P}$ = 76), 52.7, 55.2, 61.4, 114.0, 115.2, 119.4, 124.4, 127.3, 127.5, 128.0, 128.4, 128.6 (d, $J_{C,P}$ = 12), 129.9, 130.1, 130.9, 131.3 (d, $J_{C,P}$ = 10), 131.9 (d, $J_{C,P}$ = 97), 145.7, 151.9, 159.2, 168.9 (d, $J_{C,P}$ = 2)	31.0
13c	85	148–149	3.74 (s, 6 H, 2 OCH_3), 4.36–4.77 (m, 4 H, NCH_2P + NCH_2Ar), 5.86 (s, 2 H, OCH_2O), 6.22 (d, J = 8.0, 1 H_{arom}), 6.41 (d, J = 8.1, 1 H_{arom}), 6.81 (d, J = 8.5, 2 H_{arom}), 7.19 (d, J = 8.5, 2 H_{arom}), 7.45–7.51 (m, 6 H_{arom}), 7.83–7.97 (m, 4 H_{arom})	42.1 (d, $J_{C,P}$ = 76), 52.6, 55.2, 59.7, 101.2, 102.9, 114.0, 121.2, 121.9, 128.6 (d, $J_{C,P}$ = 12), 127.7, 129.7, 131.2 (d, $J_{C,P}$ = 10), 132.1 (d, $J_{C,P}$ = 2), 132.1 (d, $J_{C,P}$ = 97), 136.2, 140.1, 150.2, 159.2, 168.7 (d, $J_{C,P}$ = 2)	31.4
10a	75	250–252	3.06 (s, 3 H, NCH_3), 3.15 (s, 3 H, OCH_3), 5.37 (d, $J_{H,P}$ = 8.1, 1 H, NCHP), 6.72 (d, J = 7.3, 1 H_{arom}), 7.23–7.50 (m, 10 H_{arom}), 7.71–7.77 (m, 2 H_{arom})	30.7, 54.6, 63.8 (d, $J_{C,P}$ = 70), 112.6 (d, $J_{C,P}$ = 2), 115.8 (d, $J_{C,P}$ = 1), 126.6 (d, $J_{C,P}$ = 3), 127.4 (d, $J_{C,P}$ = 98), 128.2 (d, $J_{C,P}$ = 12), 128.3 (d, $J_{C,P}$ = 12), 131.4 (d, $J_{C,P}$ = 10), 131.6 (d, $J_{C,P}$ = 9), 131.7 (d, $J_{C,P}$ = 2), 132.0 (d, $J_{C,P}$ = 93), 132.1 (d, $J_{C,P}$ = 2), 132.4 (d, $J_{C,P}$ = 2), 134.8 (d, $J_{C,P}$ = 3), 154.1 (d, $J_{C,P}$ = 2), 168.4	30.0
10b	72	171–172	3.13 (s, 3 H, NCH_3), 4.24 (d, J = 12.5, 1 H, OCH_2Ar), 4.68 (d, J = 12.5, 1 H, OCH_2Ar), 5.45 (d, $J_{H,P}$ = 7.1, 1 H, NCHP), 6.76 (d, J = 7.3, 1 H_{arom}), 7.03–7.46 (m, 15 H_{arom}), 7.63–7.77 (m, 2 H_{arom})	30.8, 63.9 (d, $J_{C,P}$ = 69), 69.7, 114.3, 116.1, 127.0, 127.4, (d, $J_{C,P}$ = 3), 128.0, 128.15 (d, $J_{C,P}$ = 12), 128.2 (d, $J_{C,P}$ = 12), 128.4 (d, $J_{C,P}$ = 102), 128.5, 130.7 (d, $J_{C,P}$ = 2), 131.4 (d, $J_{C,P}$ = 95), 131.5 (d, $J_{C,P}$ = 9), 132.1 (d, $J_{C,P}$ = 3), 132.3 (d, $J_{C,P}$ = 3), 134.8 (d, $J_{C,P}$ = 3), 135.9, 153.4 (d, $J_{C,P}$ = 3), 168.5	29.8
10c	69	oil	3.03 (s, 3 H, NCH_3), 5.35 (d, $J_{H,P}$ = 9.0, 1 H, NCHP), 5.41 (d, J = 1.1, 1 H, OCH_2O), 5.72 (d, J = 1.1, 1 H, OCH_2O), 6.84 (d, J = 8.0, 1 H_{arom}), 7.27 (d, J = 8.0, 1 H_{arom}), 7.35–7.54 (m, 8 H_{arom}), 7.71–7.80 (m, 2 H_{arom})	30.5, 62.6 (d, $J_{C,P}$ = 72), 102.0, 109.3, 118.5 (two peaks overlapping), 127.6 (d, $J_{C,P}$ = 98), 127.7 (d, $J_{C,P}$ = 2), 128.5 (d, $J_{C,P}$ = 12), 128.6 (d, $J_{C,P}$ = 12), 129.6 (d, $J_{C,P}$ = 96), 131.7 (d, $J_{C,P}$ = 9), 131.75 (d, $J_{C,P}$ = 9), 132.6 (d, $J_{C,P}$ = 3), 132.9 (d, $J_{C,P}$ = 3), 142.0 (d, $J_{C,P}$ = 3), 150.7 (d, $J_{C,P}$ = 2), 167.8 (d, $J_{C,P}$ = 1)	29.3
10d	71	206–207	3.04 (s, 3 H, NCH_3), 3.53 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 5.22 (d, $J_{H,P}$ = 11.0, 1 H, NCHP), 6.19 (s, 1 H_{arom}), 7.12 (s, 1 H_{arom}), 7.34–7.39 (m, 4 H_{arom}), 7.45–7.58 (m, 4 H_{arom}), 7.64–7.69 (m, 2 H_{arom})	30.7, 55.9, 56.2, 63.6 (d, $J_{C,P}$ = 73), 105.0, 105.8 (d, $J_{C,P}$ = 2), 127.3 (d, $J_{C,P}$ = 98), 128.8 (d, $J_{C,P}$ = 12), 128.85 (d, $J_{C,P}$ = 12), 129.3 (d, $J_{C,P}$ = 98), 130.0, 131.7 (d, $J_{C,P}$ = 9), 131.75 (d, $J_{C,P}$ = 19), 131.9, 132.8 (d, $J_{C,P}$ = 2), 133.0 (d, $J_{C,P}$ = 2), 150.1, 151.9 (d, $J_{C,P}$ = 2), 169.0 (d, $J_{C,P}$ = 2)	30.6
11a	69	144–145	3.02 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 4.52 (d, J = 14.7, 1 H, NCH_2Ar), 5.26–5.30 (m, 2 H, NCH_2Ar + NCHP), 6.68–6.70 (m, 1 H_{arom}), 6.75 (d, J = 8.4, 2 H_{arom}), 7.13 (d, J = 8.4, 2 H_{arom}), 7.23–7.54 (m, 10 H_{arom}), 7.69–7.75 (m, 2 H_{arom})	45.0, 54.5, 55.2, 59.8 (d, $J_{C,P}$ = 70), 112.7 (d, $J_{C,P}$ = 2), 114.0, 116.1, 127.0 (d, $J_{C,P}$ = 3), 127.8 (d, $J_{C,P}$ = 98), 128.1 (d, $J_{C,P}$ = 1), 128.3 (d, $J_{C,P}$ = 12), 129.0, 130.1, 130.7 (d, $J_{C,P}$ = 2), 131.4 (d, $J_{C,P}$ = 11), 131.7 (d, $J_{C,P}$ = 8), 132.0 (d, $J_{C,P}$ = 95), 132.2 (d, $J_{C,P}$ = 3), 132.3 (d, $J_{C,P}$ = 3), 134.7 (d, $J_{C,P}$ = 3), 154.1 (d, $J_{C,P}$ = 2), 159.0, 168.3	30.5

Table 2 Spectroscopic and Physical Data of the Phosphorylated Amides **12, 13** and Isoindolin-1-ones **8**–**11** Prepared (continued)

11b	66	oil	3.75 (s, 3 H, OCH_3), 4.21 (d, J = 12.5, 1 H, NCH_2Ar), 4.45 (d, J = 14.9, 1 H, OCH_2Ar), 4.64 (d, J = 12.2, 1 H, NCH_2Ar), 5.29-5.34 (m, 2H, OCH_2Ar + NCHP), 6.73–6.78 (m, 3 H_{arom}), 7.06–7.12 (m, 4 H_{arom}), 7.24–7.46 (m, 13 H_{arom}), 7.66–7.73 (m, 2 H_{arom})	45.1, 55.2, 60.0 (d, $J_{C,P}$ = 70), 69.9, 114.0, 114.3, 116.5, 127.2, 127.7 (d, $J_{C,P}$ = 3), 128.0 (d, $J_{C,P}$ = 12), 128.1 (d, $J_{C,P}$ = 13), 128.4, 128.5, 128.9, 128.95 (d, $J_{C,P}$ = 98), 130.1, 130.6 (d, $J_{C,P}$ = 2), 131.4 (d, $J_{C,P}$ = 95), 131.5 (d, $J_{C,P}$ = 9), 131.6 (d, $J_{C,P}$ = 8), 132.2 (d, $J_{C,P}$ = 3), 132.25, 134.6 (d, $J_{C,P}$ = 3), 135.8, 153.5, 159.0, 168.3	30.4
11c	74	159–160	3.73 (s, 3 H, OCH_3), 4.23 (d, J = 14.9, 1 H, NCH_2Ar), 5.23 (d, J = 14.9, 1 H, NCH_2Ar), 5.26 (d, $J_{H,P}$ = 8.3, 1 H, NCHP), 5.35 (d, J = 0.7, 1 H, OCH_2O), 5.63 (d, J = 0.7, 1 H, OCH_2O), 6.77 (d, J = 8.6, 2 H_{arom}), 6.82 (d, J = 7.8, 1 H_{arom}), 7.09 (d, J = 8.6, 2 H_{arom}), 7.30 (d, J = 7.8, 1 H_{arom}), 7.33–7.54 (m, 8 H_{arom}), 7.69–7.75 (m, 2 H_{arom})	55.2, 58.8 (d, $J_{C,P}$ = 73), 102.0, 109.4, 118.9 (d, $J_{C,P}$ = 2), 127.7 (d, $J_{C,P}$ = 2), 127.8 (d, $J_{C,P}$ = 98), 128.7, 129.9, 129.9 (d, $J_{C,P}$ = 96), 131.7 (d, $J_{C,P}$ = 9), 131.9 (d, $J_{C,P}$ = 9), 132.6 (d, $J_{C,P}$ = 3), 132.8 (d, $J_{C,P}$ = 3), 142.2 (d, $J_{C,P}$ = 3), 150.7 (d, $J_{C,P}$ = 2), 159.1, 167.8 (d, $J_{C,P}$ = 2)	29.6
8a	72[c] 92[d]	60–61	3.18 (s, 3 H, NCH_3), 3.87 (s, 3 H, OCH_3), 4.23 (s, 2 H, NCH_2Ar), 6.97 (d, J = 7.3, 1 H_{arom}), 7.36–7.43 (m, 2 H_{arom})	29.6, 50.0, 55.4, 112.6, 115.8, 129.0, 129.7, 134.5, 154.3, 168.8	–
8b	65[c] 87[d]	130–131	3.17 (s, 3 H, NCH_3), 4.34 (s, 2 H, NCH_2Ar), 5.15 (s, 2 H, $ArCH_2O$), 7.04 (d, J = 7.6, 1 H_{arom}), 7.25–7.41 (m, 7 H_{arom})	29.5, 50.0, 70.1, 113.9, 116.0, 122.9, 127.3, 128.2, 128.7, 129.6, 134.7, 153.5, 159.7, 170.9	–
8c	70[c] 89[d]	184–185	3.09 (s, 3 H, NCH_3), 4.23 (s, 2 H, NCH_2Ar), 6.00 (s, 2 H, OCH_2O), 6.84 (d, J = 7.7, 1 H_{arom}), 7.30 (d, J = 7.7, 1 H_{arom})	29.5, 48.6, 102.0, 108.5, 117.8, 120.5, 128.0, 141.5, 150.3, 167.8	–
8d	68[c] 89[d]	133–134	–[e]	–[e]	–
9a	65[c] 88[d]	91–92	3.77 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.17 (s, 2 H, NCH_2Ar), 4.71 (s, 2 H, NCH_2Ar), 6.84 (d, J = 8.8, 2 H_{arom}), 6.96 (d, J = 7.6, 1 H_{arom}), 7.23 (d, J = 8.8, 2 H_{arom}), 7.40 (t, J = 7.6, 1 H_{arom}), 7.47 (d, J = 7.6, 1 H_{arom})	45.8, 47.2, 55.3, 112.6, 114.1, 115.9, 129.2, 129.3, 129.6, 129.7, 134.4, 154.4, 168.5	–
9b	70[c] 89[d]	104–105	3.78 (s, 3 H, OCH_3), 4.22 (s, 2 H, NCH_2Ar), 4.73 (s, 2 H, NCH_2Ar), 5.10 (s, 2 H, OCH_2Ar), 6.85 (d, J = 8.5, 2 H_{arom}), 7.03 (d, J = 8.1, 1 H_{arom}), 7.14–7.42 (m, 8 H_{arom}), 7.50 (d, J = 7.6, 1 H_{arom})	45.8, 47.3, 55.3, 70.1, 113.9, 114.1, 116.2, 127.4, 128.2, 128.7, 129.2, 129.5, 129.6, 129.7, 134.6, 136.3, 153.7, 159.1, 168.4	–
9c	75[c] 95[d]	146–147	3.73 (s, 3 H, OCH_3), 4.13 (s, 2 H, NCH_2Ar), 4.65 (s, 2 H, NCH_2Ar), 5.96 (s, 2 H, OCH_2O), 6.81 (d, J = 8.5, 2 H_{arom}), 6.85 (d, J = 8.0, 1 H_{arom}), 7.18 (d, J = 8.5, 2 H_{arom}), 7.37 (d, J = 7.8, 1 H_{arom})	45.8, 45.9, 55.2, 102.0, 108.6, 114.1, 118.1, 120.8, 127.8, 129.0, 129.5, 141.7, 150.4, 159.1, 167.6	–

[a] Satisfactory microanalyses obtained: C ±0.29, H ±0.30, N ±0.27.
[b] IR: 1629–1665 (C=O), 1241–1275 (PO) cm^{-1} for **12**, **13**; 1663–1688 (C=O), 1215–1285 (PO) cm^{-1} for **10**, **11**; 1660–1680 (C=O) cm^{-1} for **8**, **9**.
[c] Method A.
[d] Method B.
[e] See Ref.[36]

In conclusion, we have developed a new and concise one-step method for the preparation of various mono and poly-alkoxylated 4-alkoxyisoindolinones from phosphorylated 2-methoxybenzamides through metalation, S_NAr mediated cyclization and ultimate alkaline cleavage of the phosphorylated auxiliary.

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. ^1H, ^{13}C and ^{31}P NMR spectra were measured at 300, 75 and 121 MHz, respectively, on a Bruker AM 300 spectrometer as solutions in $CDCl_3$ with TMS as internal standard or H_3PO_4 as external standard. Elemental analyses were performed at the CNRS microanalysis centre. For flash chromatography, silica gel 60 M (230–400 mesh ASTM) was used. All solvents were dried and distilled according to standard procedures. Dry glassware for moisture-sensitive reactions were oven dried and assembled under argon. An inert atmosphere was obtained with a stream of argon and glassware equipped with rubber septa; reagent transfer was performed by syringe.

Compounds **14a** and **14d** are commercially available. The 2-methoxybenzoic acid derivatives **14b**[30] and **14c**[31] were obtained by oxidation ($CrO_3/H_2SO_4/H_2O$/acetone) of the corresponding benzaldehydes. Beforehand, the aromatic carboxaldehyde precursor[32] of **14b** was obtained by sequential O-methylation (K_2CO_3, MeI, DMF) and O-benzylation (K_2CO_3, BnBr, EtOH) of

commercially available dihydroxy-2,3-benzaldehyde. The methylenedioxybenzaldehyde precursor[33] of **14c** was synthesized by O-methylation (K_2CO_3, MeI, DMF) of the phenolic parent compound prepared according to a reported procedure.[34]

The phosphorylated amines **15**,[35] **16**,[25a] were synthesized according to the literature. The 2-methoxybenzoic acid derivatives were converted by the conventional method ($SOCl_2$, DMF cat., CH_2Cl_2) into their corresponding acid chlorides which were used directly with the phosphorylated amines **15**, **16** by following an already reported procedure.[35]

Phosphorylated Isoindolin-1-ones 10a–d and 11a–c; General Procedure

A solution of KHMDS (8.8 mL, 0.5 M in toluene, 4.4 mmol) was added dropwise to a carefully degassed and stirred solution of the phosphorylated 2-methoxybenzamide derivative **12** or **13** (4.0 mmol) in THF (50 mL) in the presence of 18-crown-6 (1.16 g, 4.4 mmol) at –78 °C under argon. The solution was stirred for 15 min at this temperature and then allowed to warm to r.t. over a period of 2 h. Aq NH_4Cl solution (10%, 10 mL) was added and after dilution with H_2O, the mixture was extracted with Et_2O (2 × 25 mL) and CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with H_2O and brine, dried (Na_2SO_4) and evaporated in vacuo. Flash column chromatography on silica gel with EtOAc–hexanes (90:10) as eluent allowed isolation of the phosphorylated isoindolinones **10a**–**d** and **11a**–**c** which were finally purified by recrystallization from hexane–toluene (Table 2).

Isoindolin-1-ones 8, 9; General Procedures

Method A: An aq NaOH solution (2.5 M, 0.8 mL, 2 mmol) was added to a solution of the phosphorylated isoindolin-1-ones **10, 11** (1 mmol) in THF (30 mL) and the mixture was then refluxed for 3 h. H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated in vacuo to a residue which was purified by recrystallization from hexane–toluene (Table 2).

Method B: The annulation reaction was carried out as described above for the synthesis of **10**, **11** but the crude reaction mixture obtained after warming to r.t., was treated with aq NaOH (2.5 M, 8 mmol) by dropwise addition before refluxing the solution for an additional 3 h. The crude reaction mixture was then treated as described above in Method A (Table 2).

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