A Versatile Synthesis of Poly- and Diversely Substituted Isoindolin-1-ones

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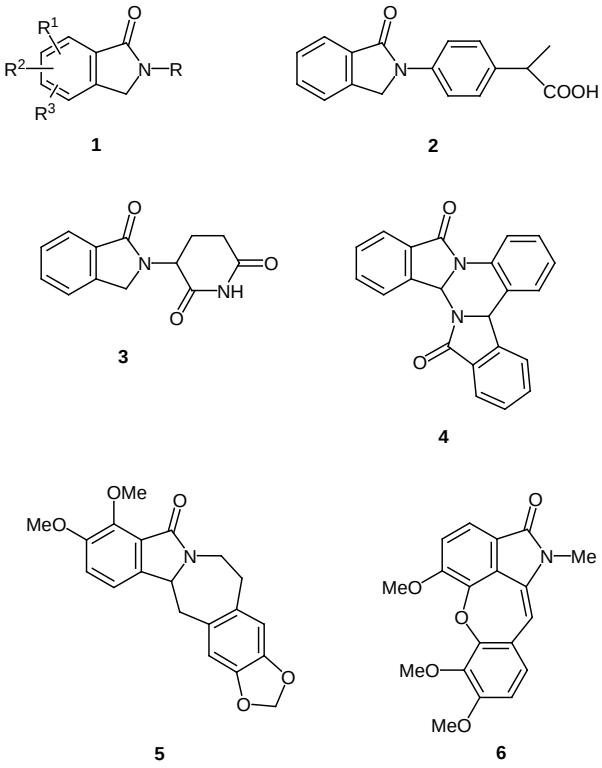
Abstract: A variety of diversely substituted isoindolin-1-ones have been prepared by alkaline cleavage of the C–P bond in the corresponding phosphorylated lactams obtained by base-induced aryne-mediated cyclization of *o*-halogeno-*N*-(phosphinylmethyl)benzamide derivatives.

Key words: isoindolinones, arynes, carbanions, cyclizations, dephosphorylation, heterocycles, cleavage, phosphorus

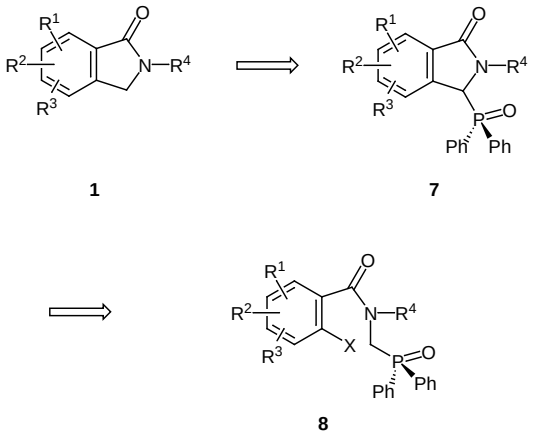
The chemistry of isoindolin-1-ones (phthalimidines **1**) has been the focus of new synthetic methodologies in many research groups during the last few years.[1] The interest demonstrated by the scientific community for these heterobicyclic compounds stems mainly from their diverse biological activities.[2] Indeed, bioactive compounds such as indoprofen[3] (**2**, anti-inflammatory agent), deoxythalidomide[4] (**3**, reductor of tumour necrosis factor production), batracyclin[5] (**4**, neoplasm inhibitor) as well as architecturally more sophisticated compounds known for their activity as non-nucleosidic HIV-reverse transcriptase inhibitors[2b] and vasodilatators[6] are based on the isoindolinone structure. In addition the isoindolinone skeleton constitutes the framework of many naturally occurring substances as exemplified by lennoxamine **5** and aristoyagonine **6**.



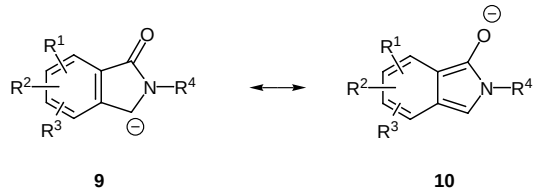
Almost all the new synthetic routes to these (fused)polycyclic isoindolinones have been secured by exploring the reactivity and selective functionalization of the parent phthalimidines. Unfortunately despite the fact that syntheses of phthalimidine derivatives have been investigated previously, the applicability of past methods is generally unsatisfactory because of drastic reaction conditions, difficulties in purification and above all restrictions in the choice of substituents namely in their nature, their number and their position on the aromatic nucleus.[7–11] The most convenient routes to these bicyclic lactams involve (i) the free radical bromination of 2-methylbenzoyl ester derivatives followed by addition of an appropriate primary amine,[7] (ii) the condensation of a primary amine with the corresponding 1(3*H*)-isobenzofuranones,[8] (iii) the reduction of phthalimides under various conditions[9] via their aminals or more recently their thioaminals[10] and finally (iv) the reaction of *o*-phthalaldehyde with a primary amine.[11] All these synthetic approaches are of procedural simplicity and generally proceed in satisfactory yields. However, these methods suffer from several drawbacks and are notably inadequate for the synthesis of models carrying specific substituents in particular positions on the basic benzene nucleus. Thus the first method does not tolerate the presence in the parent models of substituents that will not survive the bromination step (e.g. simply a methyl group). Issues raised by elaboration of diversely substituted isoindolinones by applying the second method may not be simply addressed from their corresponding oxo analogs. Finally, the last two synthetic approaches genuinely lack selectivity since the presence of one or several different substituents on the aromatic nucleus of the parent compounds would invariably induce the formation of difficultly separable regioisomers. Consequently, we understand why these routes have been mainly confined to the synthesis of bare models.

We therefore considered that for the convenient synthesis of a range of contiguously or uncontiguously and differentially substituted isoindolin-1-ones a more versatile procedure would be necessary. The present work originated with the following premises (i) the isoindolinone template, variously equipped with one or several groups, namely phenolic methyl and benzyl protected hydroxy groups present in a wide range of alkaloids and drugs, should be readily accessible by taking advantage of a re-

cently developed aryne-mediated cyclization methodolgy applied to *o*-halogeno-*N*-(phosphinylmethyl)benzamide derivatives **8**[12] (Scheme 1), (ii) once prepared the phosphorylated appendage of the initial annulated product **7** should be easily removed by alkaline cleavage owing to the sensitivity of the phosphoryl group with respect to nucleophilic attack, a rarely exploited property[13] and (iii) the formation of the transient carbanion **9** should be strongly facilitated since such a species can be represented as *o*-quinodimethane resonance structure **10** owing to electronic delocalization (Scheme 2).



Scheme 1



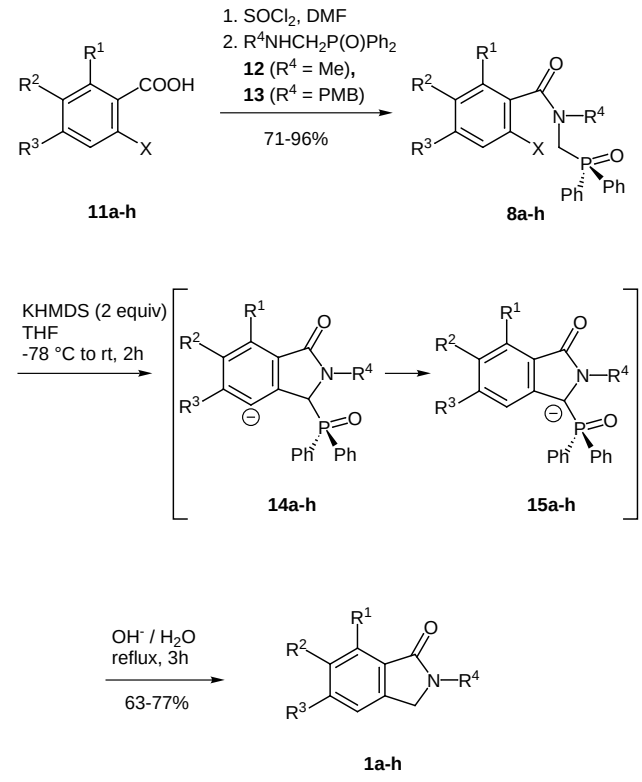
Scheme 2

The first facet of this synthesis, the elaboration of the required *o*-halogeno-*N*-(phosphinylmethyl)benzamide derivatives **8a−h**, was readily accomplished by coupling the *N*-[(diphenylphosphinyl)methyl]-*N*-alkylamines **12** and **13** with the acid chlorides derived from the diversely substituted *o*-halogenobenzoic acid derivatives **11a−h** (Scheme 3, Tables 1 and 2). The resulting phosphorylated halogenobenzamide derivatives were then exposed to potassium bis(trimethylsilyl)amide (KHMDS, 2 equiv) at −78°C in THF. The reaction mixture was then warmed to room temperature and subsequently refluxed over a short period in the presence of aqueous NaOH solution (2.5 M, 2 equiv) to generate the target isoindolinones **1a−h**. A representative series of annulated products which have been prepared by this method are presented in the Tables 1 and 3 where it may be seen that this protocol affords excellent yields of the polysubstituted isoindolin-1-ones **1a−h**. It is likely that these reactions proceed via the intermediacy of the carbanionic phosphorylated lactam **15** arising from the metal counterion shift from the initially formed aromatic anionic species **14**. Protonation and subsequent alkaline cleavage of the P−C bond of the resulting phosphane oxides then complete the synthesis of the desired isoindolinones. The progress of these reactions has some obvious implications and thus electrophile introduction prior to dephosphorylation gives rise to models equipped with various substituents at the 3-position of the heterocyclic nucleus as illustrated by the straightforward one-pot synthesis of the 2,3-dialkylisoindolinones **16i** and **16j** from the opened models **8a** and **8e** (Scheme 4, Table 3).

Table 1 Compounds **1, 8, 11** and **16** Prepared

1, 8, 11, 16	R^1	R^2	R^3	R^4	R^5	X
a	–	OMe	–	PMB[a]	–	Br
b	–	OBn	–	PMB[a]	–	Br
c	–	OBn	OMe	PMB[a]	–	Br
d	OMe	–	–	Me	–	F
e	OMe	OMe	–	Me	–	F
f	–	–	OBn	Me	–	Cl
g	OMe	–	OMe	Me	–	F
h	–	Me	–	Me	–	F
i	–	OMe	–	PMB[a]	Me	–
j	OMe	OMe	–	Me	Bn	–

[a] PMB = *p*-methoxybenzyl.



Scheme 3

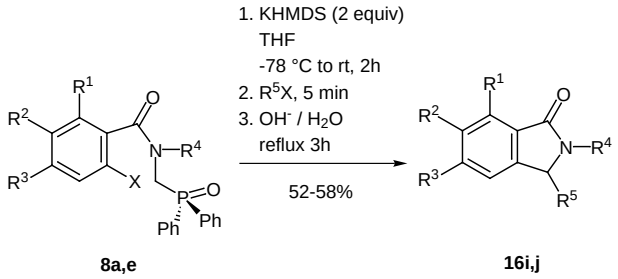
Table 2 Spectroscopic and Physical Data of the Phosphorylated Amides **8a**–**h**

Product[a]	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{31}P NMR δ
8a	96	165–166	1639 (C=O), 1242 (P=O)	3.65 (3 H, s, CH_3O), 3.76 (3 H, s, CH_3O), 4.44 (2 H, ddd, *J* = 5.6, 6.1, 15.1, CH_2P), 4.53 (1 H, d, *J* = 15.1, NC*H*$_2$Ar), 4.77 (1 H, d, *J* = 15.1, NC*H*$_2$Ar), 6.27 (1 H, d, *J* = 3.0, H_{arom}), 6.71 (1 H, dd, *J* = 3.0, 8.8, H_{arom}), 6.83 (2 H, d, *J* = 8.8, H_{arom}), 7.24 (2 H, d, *J* = 8.8, H_{arom}), 7.35 (1 H, d, *J* = 8.8, H_{arom}), 7.48–7.63 (6 H, m, H_{arom}), 7.87–8.00 (4 H, m, H_{arom})	C: 109.5, 127.0, 130.7 (d, J_{CP} = 98), 131.7, 137.7, 158.8, 159.3, 168.6 (C=O), CH: 113.3, 113.9, 116.9, 128.7 (d, J_{CP} = 11), 130.0, 131.3 (d, J_{CP} = 9), 132.3, 133.9, CH_2: 41.9 (d, J_{CP} = 76), 52.6, CH_3: 55.3, 55.6	30.7
8b	73	179–180	1635 (C=O), 1241 (P=O)	3.78 (3 H, s, CH_3O), 4.45 (2 H, ddd, *J* = 5.4, 6.3, 15.3, CH_2P), 4.51 (1 H, d, *J* = 15.2, NC*H*$_2$Ar), 4.74 (1 H, d, *J* = 15.2, NC*H*$_2$Ar), 4.84 (1 H, d, *J* = 11.7, OC*H*$_2$Ar), 4.91 (1 H, d, *J* = 11.7, OC*H*$_2$Ar), 6.36 (1 H, d, *J* = 3.0, H_{arom}), 6.70 (1 H, dd, *J* = 3.0, 8.5, H_{arom}), 6.82 (2 H, d, *J* = 8.7, H_{arom}), 7.22 (2 H, d, *J* = 8.7, H_{arom}), 7.25 (1 H, d, *J* = 8.5, H_{arom}), 7.32–7.41 (5 H, m, H_{arom}), 7.45–7.56 (6 H, m, H_{arom}), 7.88–8.01 (4 H, m, H_{arom})	C: 109.9, 127.0, 131.1 (d, J_{CP} = 98), 136.0, 137.7, 157.9, 159.3, 168.6 (C=O), CH: 114.1, 114.3, 118.0, 127.4, 128.2, 128.7 (d, J_{CP} = 11), 128.8, 130.0, 131.3 (d, J_{CP} = 9), 132.3 (d, J_{CP} = 3), 134.0, CH_2: 42.0 (d, J_{CP} = 76), 52.6, 70.4, CH_3: 55.3	30.7
8c	91	184–185	1649 (C=O), 1258 (P=O)	3.78 (3 H, s, CH_3O), 3.84 (3 H, s, CH_3O), 4.29–4.57 (2 H, m, CH_2P), 4.47 (1 H, d, *J* = 15.0, NC*H*$_2$Ar), 4.61 (1 H, d, *J* = 15.0, NC*H*$_2$Ar), 4.82 (1 H, d, *J* = 12.1, OC*H*$_2$Ar), 4.97 (1 H, d, *J* = 12.1, OC*H*$_2$Ar), 6.25 (1 H, s, H_{arom}), 6.80 (2 H, d, *J* = 8.6, H_{arom}), 7.05 (1 H, s, H_{arom}), 7.15 (2 H, d, *J* = 8.6, H_{arom}), 7.31–7.59 (11 H, m, H_{arom}), 7.85–8.00 (4 H, m, H_{arom})	C: 110.7, 127.2, 128.7, 136.0, 147.2, 150.8, 159.3, 168.8 (C=O), CH: 113.5, 114.1, 116.0, 127.4, 128.2, 128.6 (d, J_{CP} = 11), 128.7, 129.8, 131.3 (d, J_{CP} = 8), 131.3 (d, J_{CP} = 8), 132.3 (d, J_{CP} = 3), CH_2: 42.0 (d, J_{CP} = 76), 52.6, 71.1, CH_3: 55.3, 56.2	30.8
8d	81	108–109	1639 (C=O), 1273 (P=O)	3.05 (3 H, s, CH_3N), 3.51 (3 H, s, CH_3O), 4.49–4.64 (2 H, ddd, *J* = 5.9, 6.0, 15.5, CH_2P), 6.51–6.52 (2 H, m, H_{arom}), 7.18 (1 H, ddd, *J* = 6.6, 8.4, 8.5, H_{arom}), 7.41–7.49 (6 H, m, H_{arom}), 7.82–7.95 (4 H, m, H_{arom})	C: 113.3 (d, J_{CF} = 22), 130.9 (d, J_{CP} = 99), 156.7 (d, J_{CF} = 8), 158.9 (d, J_{CF} = 248), 164.6 (C=O), CH: 106.6 (d, J_{CP} = 2.5), 108.0 (d, J_{CF} = 21), 128.5 (d, J_{CP} = 12), 128.7 (d, J_{CP} = 12), 130.9 (d, J_{CF} = 10), 131.1 (d, J_{CP} = 10), 131.3 (d, J_{CP} = 10), 132.1 (d, J_{CP} = 3), 132.2 (d, J_{CP} = 3), CH_2: 46.6 (d, J_{CP} = 77), CH_3: 37.2, 55.9	31.1
8e	85	126–127	1637 (C=O), 1281 (P=O)	3.09 (3 H, s, CH_3N), 3.55 (3 H, s, CH_3O), 3.76 (3 H, s, CH_3O), 4.51–4.66 (2 H, ddd, *J* = 5.8, 6.1, 15.0, CH_2P), 6.67 (1 H, dd, *J* = 8.0, 9.1, H_{arom}), 6.77 (1 H, dd, *J* = 5.2, 9.1, H_{arom}), 7.43–7.50 (6 H, m, H_{arom}), 7.82–7.95 (4 H, m, H_{arom})	C: 119.0 (d, J_{CF} = 22), 131.6 (d, J_{CP} = 97), 145.7 (d, J_{CF} = 6), 149.0 (d, J_{CF} = 3), 153.8 (d, J_{CF} = 266), 164.4 (C=O), CH: 110.3 (d, J_{CF} = 22), 113.3 (d, J_{CF} = 9), 128.6 (d, J_{CP} = 12), 128.7 (d, J_{CP} = 12), 131.1 (d, J_{CP} = 9), 131.3 (d, J_{CP} = 9.5), 132.1, 132.2, CH_2: 46.6 (d, J_{CP} = 77), CH_3: 37.4, 56.3, 61.3	31.0
8f	96	143–144	1629 (C=O), 1289 (P=O)	3.08 (3 H, s, CH_3N), 4.34–4.81 (2 H, br. d, *J* = 5.2, CH_2P), 5.00 (2 H, s, OC*H*$_2$Ar), 6.64 (1 H, d, *J* = 8.6, H_{arom}), 6.77 (1 H, dd, *J* = 2.4, 8.6, H_{arom}), 6.89 (1 H, d, *J* = 2.4, H_{arom}), 7.29–7.41 (5 H, m, H_{arom}), 7.46–7.59 (6 H, m, H_{arom}), 7.88–7.89 (4 H, m, H_{arom})	C: 127.7, 130.9 (d, J_{CP} = 98), 131.1, 135.9, 159.7, 168.4 (C=O), CH: 113.9, 115.8, 127.4, 128.3, 128.6, 128.7 (d, J_{CP} = 12), 128.8, 131.3 (d, J_{CP} = 9), 132.3, CH_2: 42.0 (d, J_{CP} = 77), 70.3, CH_3: 38.0	31.7

Table 2 (continued)

Product[a]	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{31}P NMR δ
8g	81	139−140	1630 (C=O), 1291 (P=O)	3.07 (3 H, s, CH_3N), 3.60 (3 H, s, CH_3O), 3.69 (3 H, s, CH_3O), 4.57 (2 H, ddd, *J* = 6.1, 6.3, 14.0, CH_2P), 6.11 (1 H, s, H_{arom}), 6.13 (1 H, d, J_{CF} = 7.4, H_{arom}), 7.35–7.48 (6 H, m, H_{arom}), 7.81–7.93 (4 H, m, H_{arom})	C: 130.8 (d, J_{CP} = 95), 131.0 (d, J_{CP} = 98), 157.5 (d, J_{CF} = 11), 159.8 (d, J_{CF} = 245), 162.0 (d, J_{CF} = 13), 164.7 (C=O), CH: 93.2 (d, J_{CF} = 26), 94.5, 128.5 (d, J_{CP} = 12), 128.6 (d, J_{CP} = 12), 131.1 (d, J_{CP} = 10), 131.3 (d, J_{CP} = 10), 131.9 (d, J_{CP} = 2.5), 132.1 (d, J_{CP} = 2.5), CH_2: 46.7 (d, J_{CP} = 77), CH_3: 37.3, 55.6, 55.7	31.2
8h	71	120−121	1629 (C=O), 1275 (P=O)	2.19 (3 H, s, C*H*$_3$Ar), 3.08 (3 H, s, CH_3N), 4.56 (2 H, br d, *J* = 4.8, CH_2P), 6.57 (1 H, m, H_{arom}), 6.84 (1 H, t, *J* = 8.8, H_{arom}), 7.05 (1 H, s, H_{arom}), 7.47–7.50 (6 H, m, H_{arom}), 7.86–7.92 (4 H, m, H_{arom})	C: 123.1 (d, J_{CF} = 18), 130.7 (d, J_{CP} = 98), 134.1, 156.1 (d, J_{CF} = 246), 167.0 (C=O), CH: 115.4 (d, J_{CF} = 21), 128.6 (d, J_{CP} = 12), 128.7 (d, J_{CF} = 8), 131.2 (d, J_{CP} = 10), 131.8 (d, J_{CF} = 8), 132.3 (d, J_{CP} = 4.5), CH_2: 48.9 (d, J_{CP} = 76), CH_3: 20.4, 38.0	32.0

[a] Satisfactory microanalyses obtained: C ± 0.26, H ± 0.29, N ± 0.25.



Scheme 4

Examination of the Table 1 deserves some comment. The method is tolerant to a variety of substituents on the aromatic moiety and particularly with methyl, methoxy and also benzyloxy groups, which can be regarded as protected phenolic functions. The reaction can be indifferently performed with fluoro, chloro or the more easily accessible bromo derivatives. This new conceptual approach allows access to poly- and diversely substituted models at the 2, 3, 5, 6, 7 positions of the bicyclic framework and due to initial aryne formation only the 4-substituted analogues remain unobtainable by this method. The simplicity and versatility of this new synthetic route should be rewarded by giving easy access to a wide array of natural and biologically active compounds. Further exploitation along these lines is underway in our laboratories.

Melting point determinations were carried out on a Reichert-Thermopan apparatus and were recorded uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were measured at 300 MHz, 75 MHz 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 determined by the CNRS microanalysis centre. For flash chromatography, Merck silica gel 60 (230−400 mesh ASTM) was used. All solvents were dried and distilled according to standard procedures. Dry glassware for moisture-sensitive reactions was obtained by oven drying and assembly under Ar. An inert atmosphere was obtained with a stream of Ar and glassware equipped with rubber septa; reagent transfer was performed by syringe.

The *o*-halogenobenzoic acid derivatives **11a**,[14] **11c**,[15] **11d**,[16] **11e**,[17] **11f**,[18] **11g**,[16] were prepared according to already reported procedures. **11b** was prepared by oxidation (CrO_3/H_2SO_4/ H_2O/acetone) of 5-benzyloxy-2-bromobenzaldehyde.[19] Compound **11h** is commercially available. The phosphorylated amines **12**,[20] **13**,[12a] were synthesized according to the literature. The *o*-halogenobenzoic acid derivatives **11a-h** were converted by the conventional method ($SOCl_2$, DMF cat., CH_2Cl_2) into their corresponding acid chlorides which were used directly for the next step without further purification. The coupling reaction between the appropriately substituted *o*-halogenobenzoyl chlorides and the phosphorylated amines **12**, **13** was performed by following an already reported procedure.[12a]

Isoindolin-1-ones 1a-h and 16i,j; General Procedure

A solution of KHMDS (4 mL, 0.5 M in toluene, 2 mmol) was added dropwise to a stirred solution of the appropriate phosphorylated halogenobenzamides **8a−h** (1 mmol) in THF (25 mL) at −78 °C under Ar. The solution was stirred for 30 min at this temperature and then allowed to warm to r.t. over a period of 2 h. A solution of an electrophile (1 mmol) in THF (2 mL) was added by syringe at this stage. An aq NaOH solution (2.5 M, 0.8 mL) was slowly added to the reaction mixture which was subsequently 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 flash column chromatography with acetone/hexanes (40:60 for **1a−c** and **16i**; 80:20 for **1d**; 60:40 for **1f−h** and **16j**).

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Table 3 Spectroscopic and Physical Data of the Isoindol-1-ones **1a–h** and **16i,j**

Product[a]	Yield (%)	mp (°C)	IR (KBr) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ, *J* (Hz)
1a	77	oil	1679 (C=O)	3.75 (3 H, s, CH_3O), 3.83 (3 H, s, CH_3O), 4.14 (2 H, s, NCH_2Ar), 4.69 (2 H, s, NCH_2Ar), 6.83 (2 H, d, *J* = 8.6, H_{arom}), 7.04 (1 H, dd, *J* = 2.5, 8.0, H_{arom}), 7.20 (2 H, d, *J* = 8.6, H_{arom}), 7.22 (2 H, d, *J* = 8.0, H_{arom}), 7.34 (1 H, d, *J* = 2.5, H_{arom})	C: 129.1, 134.0, 136.0, 159.1, 159.9, 168.4 (C=O), CH: 106.6, 114.1, 119.7, 123.5, 129.5, *CH_2:* 45.9, 48.9, CH_3: 55.3, 55.6
1b	73	oil	1674 (C=O)	3.78 (3 H, s, CH_3O), 4.16 (2 H, s, NCH_2Ar), 4.71 (2 H, s, NCH_2Ar), 5.11 (2 H, s, OCH_2Ar), 6.85 (2 H, d, *J* = 8.7, H_{arom}), 7.14 (1 H, dd, *J* = 2.4, 8.3, H_{arom}), 7.22 (2 H, d, *J* = 8.7, H_{arom}), 7.28–7.44 (7 H, m, H_{arom})	C: 128.6, 129.1, 133.6, 136.5, 159.1, 168.3 (C=O), CH: 107.7, 114.1, 120.4, 123.6, 127.5, 128.1, 128.6, 129.5, CH_2: 45.9, 48.9, 70.3, CH_3: 55.3
1c	67	oil	1661 (C=O)	3.79 (3 H, s, CH_3O), 3.88 (3 H, s, CH_3O), 4.05 (2 H, s, NCH_2Ar), 4.55 (2 H, s, NCH_2Ar), 5.11 (2 H, s, OCH_2Ar), 6.87 (2 H, d, *J* = 8.7, H_{arom}), 7.00 (1 H, s, H_{arom}), 7.25–7.42 (8 H, m, H_{arom})	C: 125.5, 127.9, 129.7, 141.9, 147.5, 151.5, 166.5 (C=O), CH: 114.1, 115.1, 116.2, 127.5, 128.1, 128.6, 129.3, CH_2: 43.8, 45.8, 71.1, CH_3: 55.3, 56.3
1d	71	84–85	1669 (C=O)	3.10 (3 H, s, CH_3N), 3.92 (3 H, s, CH_3O), 4.27 (2 H, s, NCH_2Ar), 6.84 (1 H, dd, *J* = 0.6, 8.3, H_{arom}), 6.95 (1 H, dd, *J* = 0.6, 7.5, H_{arom}), 7.42 (6 H, dd, *J* = 7.5, 8.3, H_{arom})	C: 120.1, 134.8, 157.2, 167.4 (C=O), CH: 110.1, 114.7, 132.7, CH_2: 51.5, CH_3: 29.2, 55.8
1e	68	107–108[b]	1683 (C=O)	3.10 (3 H, s, CH_3N), 3.85 (3 H, s, CH_3O), 4.03 (3 H, s, CH_3O), 4.29 (2 H, s, NCH_2Ar), 7.02 (2 H, m, H_{arom})	C: 125.0, 134.3, 152.2, 166.8 (C=O), CH: 116.1, 117.6, CH_2: 51.0, CH_3: 29.3, 56.7, 62.5
1f	63	151–152	1671 (C=O)	3.13 (3 H, s, CH_3N), 4.27 (2 H, s, NCH_2Ar), 5.09 (2 H, s, OCH_2Ar), 6.96 (1 H, d, *J* = 2.0, H_{arom}), 7.02 (1 H, dd, *J* = 2.0, 8.4, H_{arom}), 7.32–7.43 (5 H, m, H_{arom}), 7.72 (1 H, d, *J* = 8.4, H_{arom})	C: 125.8, 136.3, 143.2, 161.6, 168.5 (C=O), CH: 107.7, 108.6, 115.2, 124.8, 127.4, 128.2, 128.6, CH_2: 51.8, 70.3, CH_3: 29.4
1g	72	139–140	1665 (C=O)	3.01 (3 H, s, CH_3N), 3.77 (3 H, s, CH_3O), 3.84 (3 H, s, CH_3O), 4.16 (2 H, s, NCH_2Ar), 6.33 (2 H, s, H_{arom}), 6.41 (1 H, s, H_{arom})	C: 113.4, 145.6, 158.1, 164.0, 167.4 (C=O), CH: 98.1, 98.9, CH_2: 51.6, CH_3: 29.1, 55.6, 55.8
1h	69	75–76	1685 (C=O)	2.38 (3 H, s, ArCH_3), 3.13 (3 H, s, CH_3N), 4.27 (2 H, s, NCH_2Ar), 7.26 (2 H, s, H_{arom}), 7.58 (1 H, s, H_{arom})	C: 125.8, 136.3, 143.2, 161.6, 168.5 (C=O), CH: 107.7, 108.6, 115.2, 124.8, 127.4, 128.2, 128.6, CH_2: 51.8, 70.3, CH_3: 29.4
16i	52	oil	1680 (C=O)	1.37 (3 H, d, *J* = 6.7, CH_3), 3.75 (3 H, s, CH_3O), 3.85 (3 H, s, CH_3O), 4.16 (1 H, d, *J* = 15.0, NCH_2Ar), 4.28 (1 H, q, *J* = 6.7, C*H*Me), 5.25 (1 H, d, *J* = 15.0, NCH_2Ar), 6.82 (2 H, d, *J* = 8.7, H_{arom}), 7.05 (1 H, dd, *J* = 2.5, 7.7, H_{arom}), 7.19 (2 H, d, *J* = 8.7, H_{arom}), 7.22 (1 H, d, *J* = 7.7, H_{arom}), 7.35 (1 H, d, *J* = 2.5, H_{arom})	C: 129.3, 133.1, 136.3, 159.0, 156.0, 167.9 (C=O), CH: 53.9, 106.5, 114.1, 119.7, 122.8, 129.3, CH_2: 55.2, 43.2, CH_3: 18.1
16j	58	86–87	1674 (C=O)	2.84 (1 H, dd, *J* = 7.5, 13.8, CH_2Ph), 3.07 (3 H, s, CH_3N), 3.28 (1 H, dd, *J* = 4.9, 13.8, CH_2Ph), 3.85 (3 H, s, CH_3O), 3.98 (3 H, s, CH_3O), 4.54 (1 H, dd, *J* = 4.9, 7.5, C*H*Bn), 6.59 (1 H, d, *J* = 8.2, H_{arom}), 6.93 (1 H, d, *J* = 8.2, H_{arom}), 7.02–7.07 (2 H, m, H_{arom}), 7.18–7.27 (3 H, m, H_{arom})	C: 136.0, 138.7, 152.3, 166.6 (C=O), CH: 61.6, 115.6, 117.8, 126.9, 128.4, 129.5 CH_2: 39.0, CH_3: 28.1, 56.6, 62.5

[a] Satisfactory microanalyses obtained: C ± 0.25, H ± 0.24, N ± 0.36.
[b] Lit.[21] 107–108 °C.

References

(1) (a) Luzzio, F. A.; Piatt Zacherl, D. *Tetrahedron Lett.* **1998**, *39*, 2285.
(b) Campbell, J. B.; Dedinas, R. F.; Trumbower-Walsh, S. A. *J. Org. Chem.* **1996**, *61*, 6205.
(c) Decroix, B.; Pigeon, P. *Tetrahedron Lett.* **1996**, *37*, 7707
(d) Decroix, B.; Pigeon, P.; Othman, M. *Tetrahedron* **1997**, *53*, 2495.
(e) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1997**, *38*, 3627.
(f) Kundu, N. G.; Khan, M. W. *Tetrahedron Lett.* **1997**, *38*, 6937.
(g) Kitching, M. S.; Clegg, W.; Elsewood, M. R. J.; Griffin, R. J.; Golding, B. T. *Synlett* **1999**, 997.

(2) (a) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. E. *J. Org. Chem.* **1994**, *59*, 2623.
(b) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491.
(c) Taylor, E. C.; Zhou, P.; Jenning, L. D.; Mao, Z.; Hu, B.; Jun, J.-G. *Tetrahedron Lett.* **1997**, *38*, 521.
(d) Li, S.; Wang, X.; Guo, H.; Chen, L. *Yiyano Gougye* **1985**, *16*, 543; *Chem. Abstr.* **1986**, *105*, 63778.
(e) Zuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157.
(f) Lippmann, W. U.S. Patent 4267189, 1981; *Chem. Abstr.* **1981,** *95*, 61988.
(g) Norman, M. H.; Minick, D. J.; Rigdon, G. C. *J. Med. Chem.* **1996**, *39*, 149.
(3) (a) Nannin, G.; Griraldi, P. N.; Molgora, G.; Biasoli, G.; Spinelli, F.; Logemann, L.; Dradi, E.; Zanni, G.; Buttinoni, A.; Tommasini, R. *Arzneim. Forsch.* **1973**, *23*, 1090.
(b) Hisamitsu Pharmaceutical Co., Inc. Japan Kokai Tokkyo Koho 149257, 1980; *Chem. Abstr.* **1981**, *94*, 174879.
(4) Schmahl, H.-J.; Denker, L.; Plum, C.; Chahoud, I.; Nau, H. *Arch. Toxicol.* **1996**, *11*, 749.
(5) Plowman, J.; Paull, K. D.; Atassi, G.; Harrison, S.; Dykes, D.; Kabbe, N.; Narayan, V. L.; Yoder, O. *Inves. New Drugs* **1988**, *6*, 147.
(6) Kato, Y.; Takemoto, M.; Achiwa, K. *Chem. Pharm. Bull.* **1993**, *41*, 2003.
(7) (a) Anzani, M.; Capelli, A.; Vomero, S. *Heterocycles* **1994**, *38*, 103.
(b) Ganesan, A.; Wang, H. *Tetrahedron Lett.* **1998**, *39*, 9097.
(c) Taylor, E. C.; Jennings, L. D.; Mao, Z.; Hu, B.; Jun, J.-G.; Zhou, P. *J. Org. Chem.* **1997**, *62*, 5392.
(d) Anderson, P. S.; Christy, M. E.; Colton, C. D.; Shepard, K. L. *J. Org. Chem.* **1978**, *43*, 3719.
(e) Pendergast, W.; Dickerson, S. H.; Dev, I. K.; Ferone, R.; Duch, D. S.; Smith, G. K. *J. Med. Chem.* **1994**, *37*, 838.
(f) Norman, M. H.; Kelley, J. L.; Hollingsworth, E. B. *J. Med. Chem.* **1993**, *36*, 3417.
(8) (a) Hessert, J. *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1445.
(b) Rowe, F. M.; Levin, E.; Burns, A. C.; Davies, J. S. H. *J. Chem. Soc.* **1926**, 690.
(c) Stirling, C. J. M. *J. Chem. Soc.* **1960**, 255.
(d) BASF Brit. Patent 1049007, 1966; *Chem. Abstr.* **1967**, *66*, 37763.
(9) (a) Graebe, C.; Pictet, A. *Liebigs Ann. Chem.* **1888**, *247*, 302.
(b) Sugasawa, S.; Kodama, K. *J. Pharm. Soc. Japan* **1943**, *63*, 96; *Chem. Abstr.* **1951**, *45*, 5168.
(c) Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Haga, S.; Shirayama, K. Japan Kokai Tokkyo Koho 92954, 1979; *Chem. Abstr.* **1980**, *92*, 76287.
(10) Luzzio, F. A.; Piatt Zacherl, D.; Figg, W. D. *Tetrahedron Lett.* **1999,** *40*, 2087.
(11) (a) Thiele, J.; Schneider, J. *Liebigs Ann. Chem.* **1909,** *369*, 287.
(b) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *J. Chem. Soc., Chem. Commun.* **1985,** 1183.
(c) Tsuruta, Y.; Date, Y.; Kohashi, K. *J. Chromatogr.* **1990**, *502*, 178.
(d) Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamagushi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833.
(e) Takahashi, I.; Kawakani, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353.
(f) Takahashi, I.; Hirano, E.; Kawakani, T.; Kitajima, H. *Heterocycles* **1996**, *43*, 2343.
(12) (a) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128.
(b) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313.
(c) Couture, A.; Deniau, E.; Woisel, P.; Grandclaudon, P. *Synthesis* **1997**, 1439.
(13) (a) Allen, D. W.; Hutley, B. G.; Mellor, M. T. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1705.
(b) Aksnes, G.; Gierstae, R.; Wulvik, E. A. *Phosphorus, Sulfur* **1988**, *39*, 141.
(c) Eymery, F.; Iorga, B.; Savignac, P. *Tetrahedron* **1999**, *55*, 13109.
(14) Horton, W. J.; Robertson, D. E. *J. Org. Chem.* **1960**, *25*, 1016.
(15) Barton, D. H. R.; Boar, R. B.; Widdowson, D. A. *J. Chem. Soc. (C)* **1970**, 1208.
(16) Horne, S.; Russell, R. *J. Org. Chem.* **1990**, *55*, 4520.
(17) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, in press.
(18) Tighineanu, E.; Chiraleu, F.; Raoleanu, D. *Tetrahedron* **1980**, *36*, 1385.
(19) Keserü, G. M.; Mezey-Vándor, G.; Nógrádi, M.; Vermes, B.; Kajtár-Peredy, M. *Tetrahedron* **1992**, *48*, 913.
(20) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron Lett.* **1996**, *37*, 7749.
(21) (a) F. Hoffmann-La Roche & Co. A.-G. Ger. Patent 609244, 1935; *Chem. Abstr.* **1935**, *29*, 3116.
(b) Nekhlin, Y. G.; Glushkov, R. G.; Magidson, O. Y. *J. Org. Chem. USSR* **1965**, *1*, 1305; *Chem. Abstr.* **1965**, *63*, 13136.

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