Practical synthesis of 3-(2-arylethylidene)isoindolin-1-ones (analogues of AKS-182) and 3-(2-arylethylidene)isobenzofuran-1(3*H*)-ones

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Graphical Abstract.

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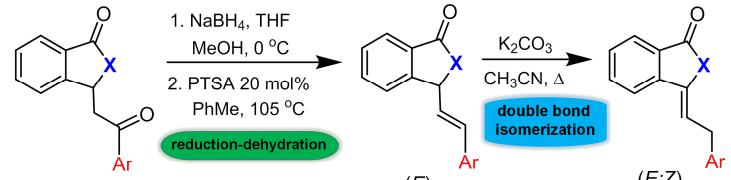

X = N-Bn, N-PMB, O
Ar = C_6H_5, 4-$MeOC_6H_5$, 4-MeC_6H_5, 4-HOC_6H_5

Tetrahedron
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We dedicate this paper to Professor Stephen Davies in recognition of his contributions to stereoselective synthesis

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ABSTRACT

A simple and practical method is reported for the synthesis of 3-(2-aryl-ethylidene)isoindolin-1-ones and 3-(2-arylethylidene)isobenzofuran-1(3*H*)-ones, proceeding with good to excellent yields and (*E:Z*) selectivity. This methodology involves the sequential reduction-dehydration reaction of readily obtained 3-(2-oxo-2-arylethyl)isoindolin-1-ones and 3-(2-oxo-2-arylethyl)isobenzofuran-1(3*H*)-ones followed by a base-catalyzed double bond isomerization with K_2CO_3 in acetonitrile. The development of a concise synthesis of AKS-182 has been achieved using this methodology.

1. Introduction

The 3-substituted isoindolin-1-ones are important compounds in organic and medicinal chemistry. They are present in numerous bioactive natural products and are also key intermediates in the preparation of numerous functionalized derivatives. For example, the 3-(2-phenylethylidene)isoindolin-1-one derivatives AKS-186 and AKS-182 inhibit vasoconstriction induced by thromboxane A2 (TXA2).[1] Additionally, isobenzofuran-1(3*H*)-ones (also known as phthalides) such as (*Z*)-3-butylideneisobenzofuran-1(3*H*)-one [(*Z*)-butylidenephthalide] and (*Z*)-3-*iso*-butylideneisobenzo-furan-1(3*H*)-one [(*Z*)-*iso*-butylidenephthalide], have been found in natural products exhibiting several pharmacological activities and are also versatile building blocks[2] (Fig. 1).

Despite the high pharmacological potential of 3-(2-arylethylidene)isoindolin-1-ones and 3-(2-arylethylidene)isobenzofuran-1(3*H*)-ones, the synthesis of these compounds have not been widely explored. Specifically, for the synthesis of 3-(2-phenylethyl-idene)isoindolin-1-ones AKS-186, AKS-182 and **4a**, only three methods have been reported in the literature; (a) the Wittig-Horner reaction of 3-diphenylphosphynylisoindolin-1-one **1** with phenyl-acetaldehyde,[3] (b) the nucleophilic addition of phenethylmagnesium bromide to phthalimide **2** followed by dehydration,[1] and (c) the photodecarboxylative cyclization reaction of phthalimide derivative **3** with the potassium salt of 3-phenylpropanoic acid[4] (Scheme 1).

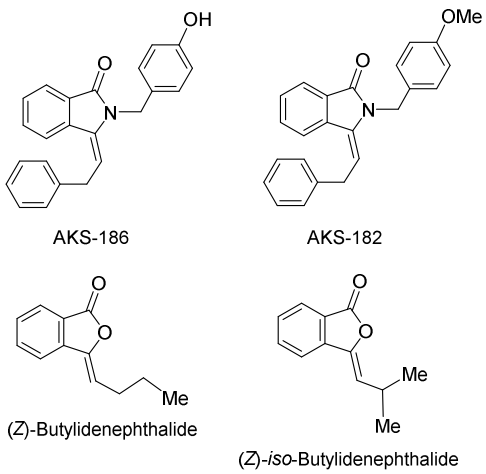

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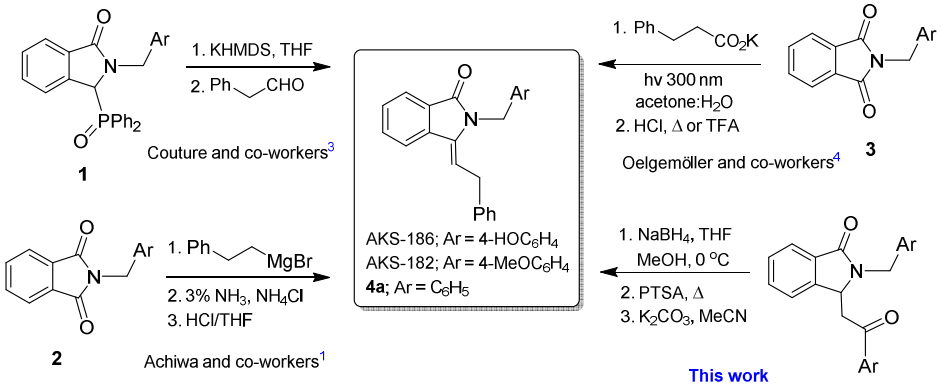
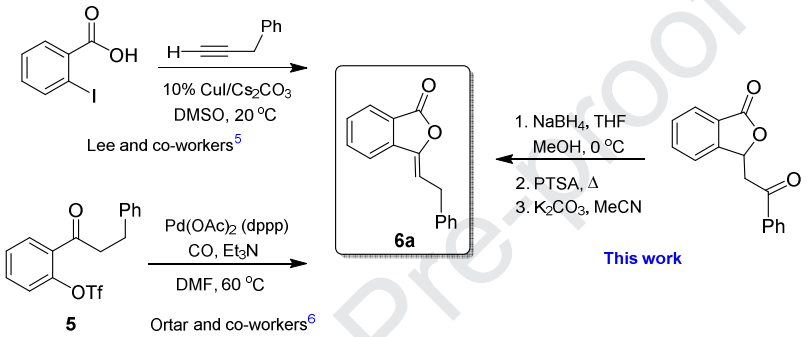
Figure 1. Structures of AKS-182, AKS-186 and representative butylidenephthalides.



Scheme 1. Synthesis of 3-(2-phenylethylidene)isoindolin-1-ones.



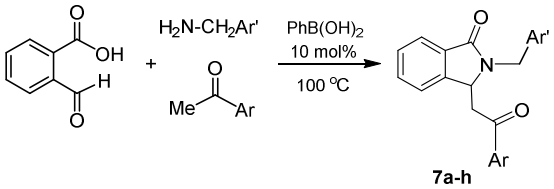
Scheme 2. Synthesis of 3-(2-phenylethylidene)isobenzofuran-1(3*H*)-one **6a**.

In a similar way, only two methods have been reported for the synthesis of 3-(2-phenylethylidene)isobenzofuran-1(3*H*)-one **6a**: (a) the copper-catalyzed coupling reaction of 2-iodobenzoic acid with benzylacetylene,[5] and (b) the cyclocarbonylation reaction of 2-triflyloxyacetophenone derivative **5** with carbon monoxide catalyzed by palladium(II) acetate and 1,3-bis(diphenylphosphino)-propane (dppp)[6] (Scheme 2).

Due to the high pharmacological potential of 3-(2-arylethylidene)isoindolin-1-ones and 3-(2-arylethylidene)isobenzofuran-1(3*H*)-ones, and in connection with our current research interest in the synthesis of 2,3-disubstituted isoindolin-1-ones,[7] herein we describe a practical method for the synthesis of these compounds. Our synthetic strategy involves the sequential reduction-dehydration reaction of 3-(2-oxo-2-arylethyl)isoindolin-1-ones and 3-(2-oxo-2-arylethyl)isobenzofuran-1(3*H*)-ones followed by double bond isomerization with K_2CO_3 in acetonitrile.

2. Results and Discussion

For the synthesis of 3-(2-arylethylidene)isoindolin-1-ones **4a-g**, AKS-182 and 3-(2-arylethylidene)isobenzofuran-1(3*H*)-ones **6a-c**, our strategy began with the preparation of 3-(2-oxo-2-arylethyl)isoindolin-1-ones **7a-h** and 3-(2-oxo-2-arylethyl)iso benzofuran-1(3*H*)-ones **11a-c**, which were obtained *via* the $PhB(OH)_2$-catalyzed Mannich-lactamization sequence reaction of 2-formylbenzoic acid with benzylamine or *p*-methoxybenzylamine and aryl methyl ketones, and by the one-pot aldol-lactonization cascade reaction of 2-formylbenzoic acid with aryl methyl ketones under solvent free-conditions, according to our recent publication (Scheme 3).[7a]

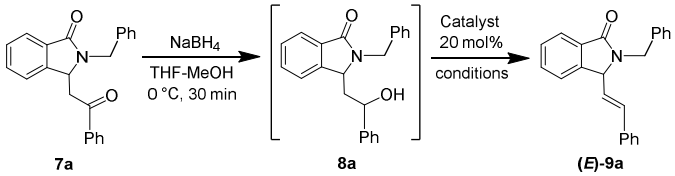


Scheme 3. Synthesis of 3-(2-oxo-2-arylethyl)isoindolin-1-ones **7a-h**.

With the required 3-(2-oxo-2-arylethyl)isoindolin-1-ones **7a-h** in hand, we turned our attention to the sequential reduction-dehydration reaction to obtain the corresponding 3-styrylisoindolin-1-ones **9a-h**. Chemoselective reduction of the ketone group in 3-(2-oxo-2-phenylethyl)isoindolin-1-one **7a** with sodium borohydride in a tetrahydrofuran-methanol solution at 0 °C, gave 2-benzyl-3-(2-hydroxy-2-phenylethyl)isoindolin-1-one **8a**, which without further purification was reacted with 20 mol% $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature, giving (*E*)-2-benzyl-3-styrylisoindolin-1-one **9a** in 60% yield after 4.0 h (Table 1, entry 1). In order to improve the yield, the dehydration reaction of **8a** was carried out with 20 mol% *p*-toluenesulfonic acid (PTSA) in dichloromethane at room temperature, to give the target compound **9a** in 62% yield after 8.0 h (Table 1, entry 2).[8] In the next experiment, compound **8a** was reacted with PTSA in benzene at 50 °C, to obtain the desired (*E*)-3-styrylisoindolin-1-one **9a** in 80% yield after 12.0 h (Table 1, entry 3). In order to find the optimum temperature, the reaction of **8a** was performed with PTSA in benzene at 100 °C; under these conditions the yield of the desired (*E*)-3-styrylisoindolin-1-one **9a** increased to 85% (Table 1, entry 4). The dehydration reaction of **8a** with PTSA in toluene at 105 °C, gave (*E*)-3-styrylisoindolin-1-one **9a** in 88% yield in only 4.0 h (Table 1, entry 5). Finally, when the dehydration reaction of **8a** was carried with 10 mol% PTSA in

toluene at 105 °C, the target compound **9a** was obtained in 85% yield but a longer reaction time was required (Table 1, entry 6).

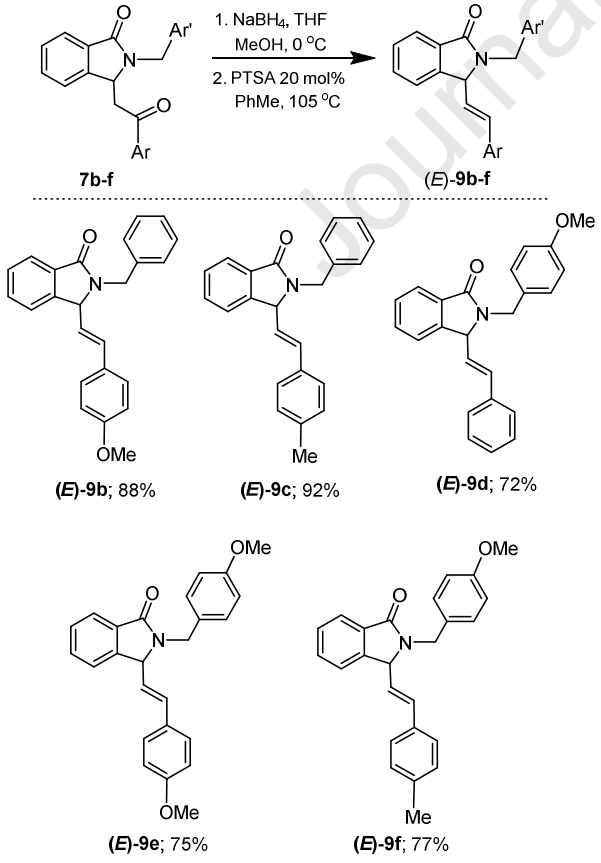
Table 1. Optimization for the synthesis of (*E*)-2-benzyl-3-styrylisoindolin-1-one **9a**.



Entry	Catalyst	Solvent	Conditions	Yield **9a** (%)[a]
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	25 °C, 4.0 h	60
2	PTSA	CH_2Cl_2	25 °C, 8.0 h	62
3	PPTS	PhH	50 °C, 12.0 h	80
4	PTSA	PhH	100 °C, 8.0 h	85
5	PTSA	PhMe	105 °C, 4.0 h	88
6	PTSA[b]	PhMe	105 °C, 7.0 h	85

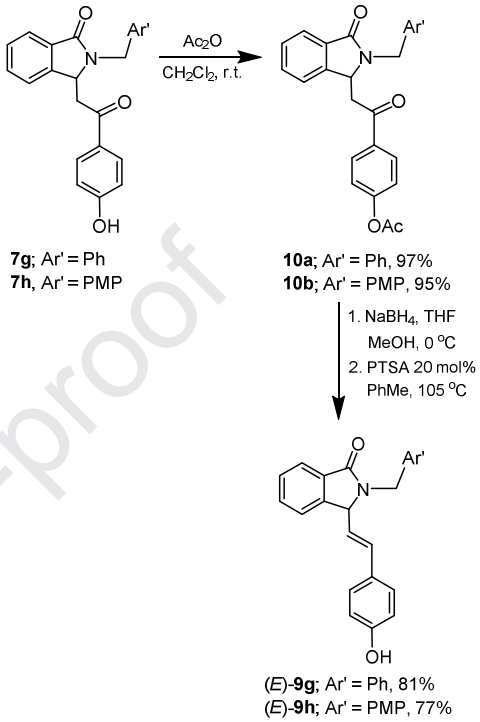
[a] Isolated yield after chromatographic purification.
[b] 10 mol% of PTSA was used.

With the optimized sequential reduction-dehydration reaction conditions established (Table 1), the scope and generality of this method for the synthesis of several (*E*)-3-styrylisoindolin-1-ones derivatives was investigated. Thus, the sequential reduction-dehydration reaction was tested with 2-benzyl-3-(2-oxo-2-arylethyl)isoindolin-1-ones **7b,c** and 2-*p*-methoxybenzyl-3-(2-oxo-2-arylethyl)isoindolin-1-ones **7d-f**, containing methylene aryl ketones bearing *para*-electron donating substituents. In all cases, the reaction proceeded efficiently affording the target (*E*)-3-styryl-isoindolin-1-one derivatives **9b-f** in 72-92% yield (Scheme 4).



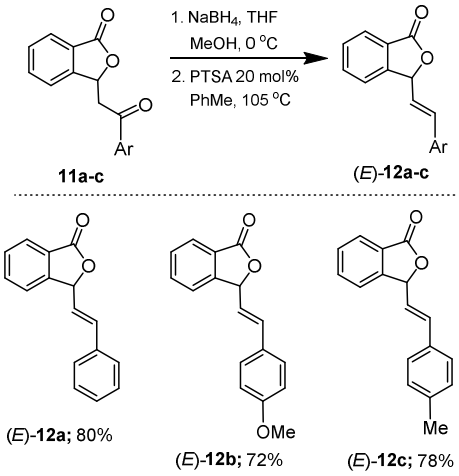
Scheme 4. Scope of the synthesis of (*E*)-3-styrylisoindolin-1-ones **9b-f**.[9]

When 3-(2-oxo-2-arylethyl)isoindolin-1-ones containing an OH group in the *para*-position were used, protection was necessary. Thus, the reaction of 3-(2-oxo-2-arylethyl)isoindolin-1-ones **7g,h** with anhydride acetic in dichloromethane at room temperature, produced the acetylated products **10a,b** in excellent yields, which upon reduction with $NaBH_4$ in a tetrahydrofuran-methanol mixture at 0 °C followed by dehydration with 20 mol% PTSA in toluene at 105 °C, provided the (*E*)-3-styrylisoindolin-1-one derivatives **9g,h** in 81% and 77% yield, respectively (Scheme 5).



Scheme 5. Synthesis of (*E*)-3-styrylisoindolin-1-one derivatives **9g,h**.

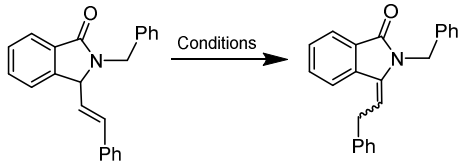
With the optimized sequential reduction-dehydration reaction conditions in hand for the preparation of (*E*)-3-styrylisoindolin-1-ones **9a-h**, we next investigated the scope and potential of this method for the synthesis of (*E*)-3-styrylisobenzofuran-1(*3H*)-ones. For this purpose, we carried out the reduction of 3-(2-oxo-2-arylethyl)isobenzofuran-1(3*H*)-ones **11a-c** with $NaBH_4$ in a tetrahydrofuran-methanol mixture at 0 °C followed by the dehydration reaction with 20 mol% PTSA in toluene at 105 °C, obtaining the corresponding (*E*)-3-styrylisobenzofuran-1(*3H*)-one derivatives **12a-c** in 72-80% yield (Scheme 6).[10]



Scheme 6. Synthesis of (*E*)-3-styrylisobenzofuran-1(*3H*)-ones **12a-d**.

In order to obtain the target compound AKS-182 and analogues, we next investigated the possibility to induce double bond isomerization in (*E*)-3-styrylisoindolin-1-ones **9a-h**. To prove the viability of double bond isomerization, we first examined the reaction of (*E*)-3-styrylisoindolin-1-one **9a** with strong bases such as *n*-BuLi, *sec*-BuLi, *t*-BuOK and NaH in dry tetrahydrofuran at different temperatures; however, after several attempts, the desired product was not obtained (Table 2, entries 1-6). However, the reaction of (*E*)-3-styrylisoindolin-1-one **9a** with K_2CO_3 in acetonitrile at reflux, produced the desired 2-benzyl-3-(2-phenylethylydene)isoindolin-1-one **4a** in 84% yield with a 86:14 (*E*:*Z*) selectivity, which was determined directly from the ^{1}H NMR spectra of the crude reaction mixture (Table 2, entry 7). Other bases such as DBU, Et_3N and K_2CO_3/DBU did not give satisfactory results.

Table 2. Optimization for the synthesis of (*E*/*Z*)-2-benzyl-3-(2-phenyl-ethylydene)isoindolin-1-one **4a**.



(*E*)-**9a** (*E*:*Z*)-**4a**

Entry	Base/Solvent	Temp./Time	Yield **4a** (%)[a]	(*E*:*Z*) ratio
1	*n*-BuLi/THF	-78 °C, 1.0 h	-	-
2	*n*-BuLi/THF	0 °C, 1.0 h	-	-
3	*s*-BuLi/THF	-78 °C, 3.0 h	-	-
4	*s*-BuLi/THF	0 °C, 1.0 h	-	-
5	*t*-BuOK/THF	25 °C, 1.0 h	-	-
6	NaH/THF	25 °C, 3.0 h	-	-
6	NaH/THF	70 °C, 1.0 h	-	-
7	K_2CO_3/MeCN	70 °C, 6.0 h	84	86:14

[a] Isolated yield after chromatographic purification.

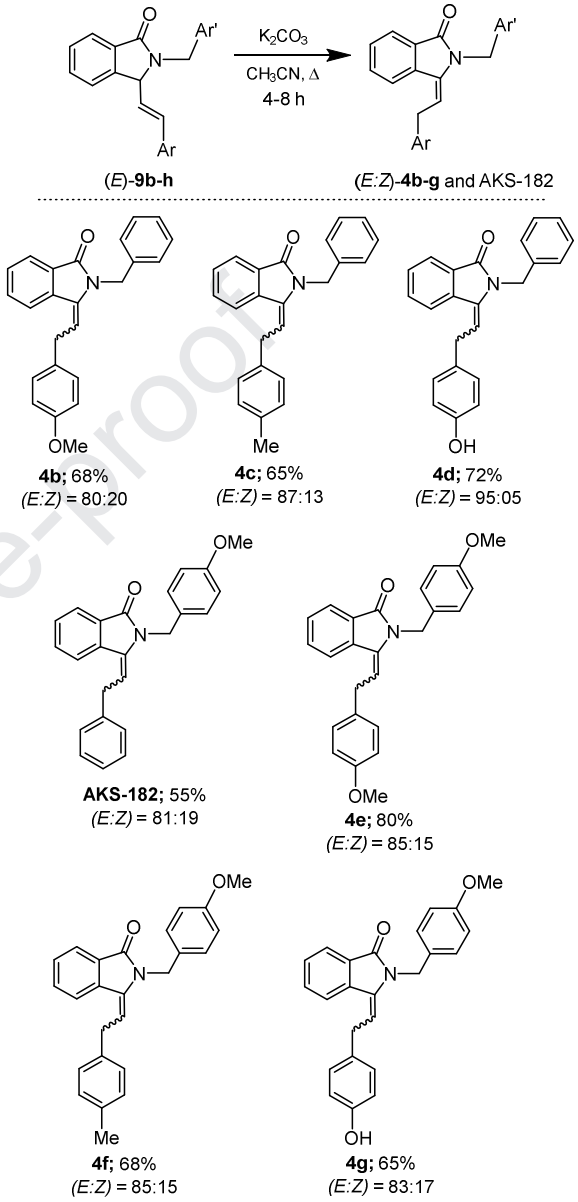
The stereochemistry assignment for (*E*)-**4a** was assigned by ^{1}H NMR spectroscopy according to our recently published results,[7b,11] and confirmed by comparison with spectroscopic data reported in the literature.[1,3,4] Additionally, X-ray crystallographic analysis permitted us to unambiguously assign it as the (*E*)-isomer.[12]

After optimization of the experimental conditions for the double bond isomerization in (*E*)-3-styrylisoindolin-1-one **9a**, we extended this protocol to (*E*)-3-styrylisoindolin-1-ones **9b-h**, obtaining our target 3-(2-arylethylydene)-isoindolin-1-ones **4b-g** and AKS-182 in 55-80% yield and good (*E*:*Z*) selectivity, with the *E* isomer as the major product (Scheme 7).

Finally, the double bond isomerization in (*E*)-3-styryl-isobenzo-furan-1(*3H*)-ones **12a-c** with K_2CO_3 CH_3CN at reflux, gave the target compounds 3-(2-arylethylydene)isobenzofuran-1(*3H*)-ones **6a-c** in 64-80% and very good (*Z*:*E*) selectivity, with the *Z* isomer as the major product (Scheme 8).[13,14]

3. Conclusion

In summary, we have developed an efficient and practical method for the synthesis of (*E*)-3-styrylisoindolin-1-ones and (*E*)-3-styrylisobenzofuran-1(*3H*)-ones through a sequential reduction-dehydration reaction. Additionally, we found that the double bound isomerization in (*E*)-3-styrylisoindolin-1-ones and (*E*)-3-styrylisobenzofuran-1(*3H*)-ones using K_2CO_3 as a base, is an excellent method for the preparation of several 3-(2-aryl-ethylydene)isoindolin-1-ones, AKS-182 analogues and 3-(2-arylethylydene)isobenzofuran-1(*3H*)-ones in good yield and (*E*:*Z*) selectivity.



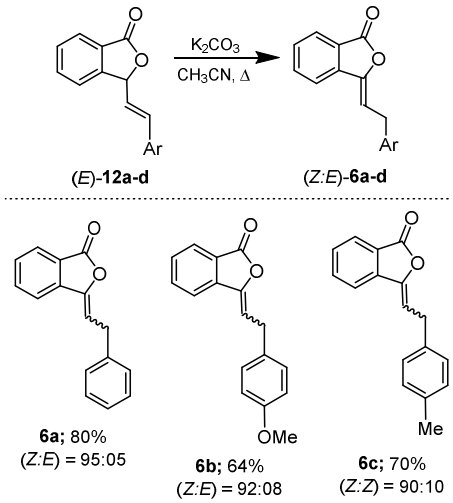
Scheme 7. Synthesis of 3-(2-arylethylydene)isoindolin-1-ones **4b-g** and AKS-182.

4. Experimental Section

4.1 General Methods

All commercial materials were used as received unless otherwise noted. Flash chromatography was performed with 230-400 mesh Silica Flash 60®. Thin layer chromatography was performed on pre-coated TLC sheets of silica gel (60 F_{254}, Merck) and the plates were visualized with UV-light, iodine vapors and submersion in a solution of ninhydrin or *para*-anisaldehyde. Melting points were determined in a Fisher–Johns apparatus and are uncorrected. NMR spectra were recorded on a Varian instrument (400 MHz for ^{1}H) or a Bruker instrument (500 MHz

for ^{1}H) and calibrated using the TMS and the residual solvent signal as internal standards; chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (J) in Hertz. High Resolution FAB$^+$ Mass Spectra (HRMS) were obtained on a JEOL MStation MS-700.



Scheme 8. Synthesis of 3-(2-arylethylydene)isobenzofuran-1(*3H*)-ones **6a-c**.

4.2. Experimental details and characterization data

*4.2.1. Typical procedure for the synthesis of (E)-3-styrylisoindolin-1-ones derivatives (**9a-h**) and (E)-3-styrylisobenzofuran-1(3H)-ones (**12a-c**).* To a solution of 3-(2-oxo-2-arylethyl)isoindolin-1-ones **7a-h** (1 mmol) or 3-(2-oxo-2-arylethyl)isobenzofuran-1(3*H*)-ones **11a-c** in tetrahydrofuran-methanol (7:3) (10 mL), was added $NaBH_4$ (1.2 mmol) and stirred for 20 min at 0 ^oC. After completion of the reaction, the mixture was warmed to room temperature and quenched with NH_4Cl solution, stirred for 5 min at room temperature and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with water (20 mL), dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. PTSA (0.2 mmol) was added to the crude product in toluene (15 mL) and stirred at 105 ^oC. After completion of the reaction, the mixture was cooled to room temperature, the solvent was evaporated and the resulting crude product was purified by flash column chromatography using hexane-ethyl acetate mixture as eluent, to give the pure products **9a-h** and **12a-c**. The ^{1}H and ^{13}C NMR spectroscopic data for the compounds **9a**[9b], **12a**[10] and **12c**[10a] are identical with those described in the literature.

*4.2.2. (E)-2-Benzyl-3-(4-methoxystyryl)isoindolin-1-one (**9b**).* Yellow oil, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.82 (s, 3H, CH_3O), 4.21 (AB system, J = 14.9 Hz, 1H, CH_2), 4.87 (d, J = 9.2 Hz, 1H, CHN), 5.31 (AB system, J = 14.9 Hz, 1H, CH_2), 5.65 (dd, J = 15.7, 9.2 Hz, 1H, CH=CH), 6.70 (d, J = 15.7 Hz, 1H, CH=CH), 6.87 (AA'BB', J = 8.8 Hz, 2H, H_{arom}), 7.17-7.38 (m, 8H, H_{arom}), 7.38-7.55 (m, 2H, H_{arom}), 7.87-8.00 (m, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 44.1 (CH_2), 55.4 (CH_3O), 63.0 (CHN), 114.3 (2C), 123.2, 123.3, 123.8, 127.5, 128.0 (2C), 128.5 (2C), 128.6 (2C), 128.8 (2C), 131.7, 131.9, 135.5, 137.5, 144.9, 159.9, 168.1 (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{22}NO_2$ $[M+H]^+$, *m/z* 356.1651; found for $[M+H]^+$, *m/z* 356.1620.

*4.2.3. (E)-2-Benzyl-3-(4-methylstyryl)isoindolin-1-one (**9c**).* Yellow oil, 92% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H, CH_3), 4.21 (AB system, J = 14.9 Hz, 1H, CH_2), 4.89 (d, J = 9.3 Hz, 1H, CHN), 5.32 (AB system, J = 14.8 Hz, 1H, CH_2), 5.75 (dd, J = 15.6, 9.3 Hz, 1H, CH=CH), 6.73 (d, J = 15.6 Hz, 1H, CH=CH), 7.14-7.16 (m, 2H, H_{arom}), 7.25-7.33 (m, 8H, H_{arom}), 7.46-7.52 (m, 2H, H_{arom}), 7.78-8.01 (m, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 44.2 (CH_2), 62.7 (CH_3), 123.3, 124.0, 126.5, 127.6, 128.0 (2C), 128.5 (2C), 128.8, 128.9 (2C), 131.9, 134.3 82C), 134.6, 137.4, 144.4, 168.2 (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{22}NO$ $[M+H]^+$, *m/z* 341.1701; found for $[M+H]^+$, *m/z* 341.1720.

*4.2.4. (E)-2-(4-Methoxybenzyl)-3-styrylisoindolin-1-one (**9d**).* Yellow oil, 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.78 (s, 3H, CH_3O), 4.16 (AB system, J = 14.8 Hz, 1H, CH_2), 4.89 (d, J = 9.3 Hz, 1H, CHN), 5.26 (AB system, J = 14.8 Hz, 1H, CH_2), 5.81 (dd, J = 15.7, 9.3 Hz, 1H, CH=CH), 6.77 (d, J = 15.7 Hz, 1H, CH=CH), 6.84 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.23 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.29-7.40 (m, 6H, H_{arom}), 7.46-7.53 (m, 2H, H_{arom}), 7.89-7.92 (m, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 43.6 (CH_2), 55.4 (CH_3O), 62.7 (CHN), 114.16 (2C), 123.3, 123.8, 125.7 (2C), 126.8, 128.5, 128.6, 128.8 (2C), 129.5 (2C), 130.0, 131.8, 132.0, 135.8, 135.9, 144.6, 159.0, 168.1 (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{22}NO_2$ $[M+H]^+$, *m/z* 356.1651; found for $[M+H]^+$, *m/z* 356.1676.

*4.2.5. (E)-2-(4-Methoxybenzyl)-3-(4-methoxystyryl)isoindolin-1-one (**9e**).* Yellow oil, 75% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.77 (s, 3H, CH_3O), 3.81 (s, 3H, CH_3O), 4.16 (AB system, J = 14.8 Hz, 1H, CH_2), 4.86 (d, J = 9.2 Hz, 1H, CHN), 5.24 (AB system, J = 14.8 Hz, 1H, CH_2), 5.64 (dd, J = 15.7, 9.2 Hz, 1H, CH=CH), 6.70 (d, J = 15.7 Hz, 1H, CH=CH), 6.83 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 6.88 (AA'BB', J = 8.8 Hz, 2H, H_{arom}), 7.22 (AA'BB', J = 8.6 Hz, 2H, H_{arom}), 7.31 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.33-7.35 (m, 1H, H_{arom}), 7.44-7.52 (m, 2H, H_{arom}) 7.88-7.89 (m, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 43.5 (CH_2), 55.4 (2 CH_3O), 62.7 (CHN), 114.1 (2C), 114.2 (2C), 123.3, 123.4, 123.7, 128.0 (2C), 128.5, 128.8, 129.6, 129.8 (2C), 131.7, 131.9, 135.4, 144.8, 159.0, 159.8, 168.0 (C=O). HRMS (FAB$^+$): calcd. for $C_{25}H_{24}NO_3$ $[M+H]^+$, *m/z* 386.1756; found for $[M+H]^+$, *m/z* 386.1734.

*4.2.6. (E)-2-(4-Methoxybenzyl)-3-(4-methylstyryl)isoindolin-1-one (**9f**).* Yellow oil, 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (s, 3H, CH_3), 3.78 (s, 3H, CH_3O), 4.15 (AB system, J = 14.8 Hz, 1H, CH_2), 4.87 (d, J = 9.3 Hz, 1H, CHN), 5.26 (AB system, J = 14.8 Hz, 1H, CH_2), 5.74 (dd, J = 15.7, 9.3 Hz, 1H, CH=CH), 6.74 (d, J = 15.7 Hz, 1H, CH=CH), 6.84 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.16 (AA'BB', J = 7.9 Hz, 2H, H_{arom}), 7.22 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.28 (AA'BB', J = 8.1 Hz, 2H, H_{arom}), 7.33 (AA'BB', J = 8.1 Hz, 2H, H_{arom}), 7.46-7.53 (m, 1H, H_{arom}) 7.88-7.90 (m, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.2 (CH_3), 43.5 (CH_2), 55.4 (CH_3O), 62.9 (CHN), 113.9 (2C), 123.3, 123.8, 124.5, 126.7 (2C), 128.6, 129.5 (2C), 129.6, 129.9 (2C), 131.7, 133.0, 135.9, 138.6, 144.5, 159.0, 158.6, 167.9 (C=O). HRMS (FAB$^+$): calcd. for $C_{25}H_{24}NO_2$ $[M+H]^+$, *m/z* 370.1807; found for $[M+H]^+$, *m/z* 370.1810.

*4.2.7. (E)-2-Benzyl-3-(4-hydroxystyryl)isoindolin-1-one (**9g**).* White oil, 81% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.45 (s, 1H, OH), 4.23 (AB system, J = 14.9 Hz, 1H, CH_2), 4.89 (d, J = 9.2 Hz, 1H, CHN), 5.31 (AB system, J = 14.9 Hz, 1H, CH_2), 5.60 (dd, J = 15.7, 9.3 Hz, 1H, CH=CH), 6.69 (d, J = 15.6 Hz, 1H, CH=CH), 6.86 (AA'BB', J = 8.6 Hz, 2H, H_{arom}), 7.23 (AA'BB', J = 8.6 Hz, 2H, H_{arom}), 7.25-7.34 (m, 6H, H_{arom}), 7.46-7.54 (m, 2H, H_{arom}), 7.90-7.93 (m, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 44.2 (CH_2), 63.2 (CHN), 115.8, 115.9 122.1, 123.3, 123.9, 127.7, 127.9, 128.2 (2C), 128.5 (2C), 128.7, 128.8 (2C), 131.6, 132.0, 136.1, 137.2, 144.9, 157.2, 168.6 (C=O). HRMS (FAB$^+$): calcd. for $C_{23}H_{20}NO_2$ $[M+H]^+$, *m/z* 342.1494; found for $[M+H]^+$, *m/z* 342.1469.

*4.2.8. (E)-2-(4-Methoxybenzyl)-3-(4-hydroxystyryl)isoindolin-1-one (**9h**).* Yellow oil, 77% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.93 (s, 1H, OH), 3.77 (s, 3H, CH_3O), 4.17 (AB system, J = 14.6 Hz, 1H, CH_2), 4.88 (d, J = 9.1 Hz, 1H, CHN), 5.26 (AB system, J = 14.6 Hz, 1H, CH_2), 5.60 (dd, J = 15.5, 9.1 Hz, 1H, CH=CH), 6.70 (d, J = 15.5 Hz, 1H, CH=CH), 6.82-6.91 (m, 4H, H_{arom}), 7.02-7.37 (m, 5H, H_{arom}), 7.37-7.56 (m, 2H, H_{arom}), 7.89-7.93 (m, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 43.6 (CH_2), 55.0 (CH_3O), 62.9 (CHN), 114.2 (2C), 115.9 (2C), 122.1, 123.8, 127.8, 128.1, 128.28 (2C), 128.7, 129.3, 129.9 (2C), 130.0, 131.6, 132.0, 136.0, 144.8, 157.0, 168.2 (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{21}NO_3$ $[M+H]^+$, *m/z* 372.1600; found for $[M+H]^+$, *m/z* 372.1611.

*4.2.9. (E)-3-(4-Methoxystyryl)isobenzofuran-1(3H)-one (**12b**).* Yellow oil, 72% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.82 (s, 3H, CH_3O), 5.95-6.02 (m, 2H, CH-O and CH=CH), 6.82-6.88 (m, 2H, CH=CH and H_{arom}), 6.87 (AA'BB', J = 8.8 Hz, 2H, H_{arom}), 7.35 (AA'BB', J = 8.6 Hz, 2H, H_{arom}), 7.46 (d, J = 7.7 Hz, 1H, H_{arom}), 7.56 (t, J = 7.5 Hz, 1H, H_{arom}), 7.69 (t, J = 7.5 Hz, 1H, H_{arom}), 7.94 (d, J = 7.7 Hz, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.5 (CH_3O), 82.6 (CH-O), 114.2 (2C), 121.5, 122.8, 125.8, 125.9 (2C), 128.1, 128.3, 129.5, 134.3, 135.1, 149.1, 160.1, 170.5 (C=O). HRMS (FAB$^+$): calcd. for $C_{17}H_{14}O_3$ $[M+H]^+$, *m/z* 267.1021; found for $[M+H]^+$, *m/z* 267.1003.

*4.2.10. Typical Procedure for the synthesis of (E:Z)-3-(2-arylethylydene)isoindolin-1-ones (**4a-g**), AKS-182 and (E:Z)-3-(2-arylethylydene)isobenzofuran-1(3H)-ones (**6a-c**).* To a solution of the corresponding 3-styrylisoindolin-1-one or 3-styrylisobenzofuran-1(3*H*)-one (1 mmol) in CH_3CN (5 mL), K_2CO_3 (1 mmol) was added, stirred for 5.0 min at room temperature and then at 80 ^{o}C. After completion of the reaction, the mixture was cooled to room temperature then water (5 mL) and ethyl acetate (5 mL x 3) were added. The aqueous layer was extracted with ethyl acetate (5 mL x 3) and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The resulting crude product was purified by flash column chromatography using hexane-ethyl acetate mixture as eluent, to give (*E:Z*)-3-(2-arylethylydene)isoindolin-1-ones **4a-g** and (*E:Z*)-3-(2-arylethylydene)isobenzofuran-1(3*H*)-ones **6a-c**. The *E*:*Z* ratio was determined by ^{1}H-NMR spectroscopy for the crude product. The ^{1}H and ^{13}C NMR spectroscopic data for AKS-182 are identical with those described in the literature.[1a,3]

*4.2.11. (E)-2-Benzyl-3-(2-phenylethylidene)isoindolin-1-one (**4a**).* White solid, Mp: 102-104 ºC, 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.93 (d, J = 7.9 Hz, 2H, CH_2CH), 5.02 (s, 2H, NCH_2Ph), 5.56 (t, J = 7.9 Hz, 1H, $CHCH_2$), 7.03-7.14 (m, 2H, H_{arom}), 7.14-7.35 (m, 8H, H_{arom}), 7.41-7.63 (m, 2H, H_{arom}), 7.84 (d, J = 7.7 Hz, 1H, H_{arom}), 7.96 (d, J = 7.4 Hz, 1H, H_{arom} ^{13}C NMR (100 MHz, $CDCl_3$) δ: 33.2 (CH_2CH), 43.0 (CH_2Ph), 111.3 ($CHCH_2$), 123.3 (2C), 123.8 (2C), 126.9, 127.0 (2C), 127.3, 128.2 (2C), 128.7 (3C), 129.0, 130.9, 132.1, 135.5, 137.0, 139.9, 166.9 (C=O). HRMS (FAB$^+$): calcd. for $C_{23}H_{20}NO$ $[M+H]^+$, *m/z* 326.1545; found for $[M+H]^+$, *m/z* 326.1516.

*4.2.12. (E)-2-Benzyl-3-[2-(4-methoxyphenyl)ethylidene]isoindolin-1-one (**4b**).* Yellow solid, Mp: 60-62 ºC, 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.55 (d, J = 8.0 Hz, 2H, CH_2CH), 3.77 (s, 3H, CH_3O), 5.27 (s, 2H, NCH_2Ph), 5.72 (t, J = 8.0 Hz, 1H, $CHCH_2$), 6.78 (AA'BB', J = 8.4 Hz, 2H, H_{arom}), 6.85 (AA'BB', J = 8.4 Hz, 2H, H_{arom}) 7.16 (d, J = 7.5 Hz, 2H, H_{arom}), 7.23-7.34 (m, 3H, H_{arom}), 7.49 (t, J = 7.5 Hz, 1H, H_{arom}), 7.57 (t, J = 7.5 Hz, 1H, H_{arom}), 7.63 (d, J = 7.7 Hz, 1H, H_{arom}), 7.91 (d, J = 7.5 Hz, 1H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.7 (CH_2CH), 41.6 (CH_2Ph), 55.3 (CH_3O), 114.0 ($CHCH_2$), 123.3, 123.4, 123.7, 126.9, 127.8, 128.5 (2C), 128.6 128.7 (2C), 128.7, 128.9 (2C), 129.1, 132.1, 132.2, 134.0 (2C), 136.3, 168.1 (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{22}NO_2$ $[M+H]^+$, *m/z* 356.1651; found for $[M+H]^+$, *m/z* 356.1593.

*4.2.13. (E)-2-Benzyl-3-[2-(4-methylphenyl)ethylidene]isoindolin-1-one (**4c**).* White solid, Mp: 130-132 ºC, 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.29 (s, 3H, CH_3), 3.88 (d, J = 7.9 Hz, 2H, CH_2CH), 5.00 (s, 2H, NCH_2Ph), 5.56 (t, J = 7.9 Hz, 1H, $CHCH_2$), 6.97 (AA'BB', J = 7.8 Hz, 2H, H_{arom}), 7.05 (AA'BB', J = 7.6 Hz, 2H, H_{arom}), 7.12-7.35 (m, 5H, H_{arom}), 7.48 (t, J = 7.4 Hz, 1H, H_{arom}), 7.55 (t, J = 7.5 Hz, 1H, H_{arom}), 7.82 (d, J = 7.5 Hz, 1H, H_{arom}), 7.94 (d, J = 7.5 Hz, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.0 (CH_3), 32.7 (CH_2CH), 43.0 (NCH_2Ph), 111.8 ($CHCH_2$), 123.3, 123.7, 127.0 (2C), 127.3, 128.0 (2C), 128.7 (2C), 128.9, 129.3 (2C), 132.1, 134.0, 135.3, 135.4, 136.0, 136.4, 137.0, 166.6 (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{22}NO$ $[M+H]^+$, *m/z* 340.1701; found for $[M+H]^+$, *m/z* 340.1680.

*4.2.14. (E)-2-Benzyl-3-[2-(4-hydroxyphenyl)ethylidene]isoindolin-1-one (**4d**).* White oil, 72% yield, (*E/Z*) 90:10 ratio. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.83 (d, J = 8.1 Hz, 2H, CH_2CH), 5.01 (s, 2H, NCH_2Ph), 5.22* (s, 2H, NCH_2Ph), 5.69 (t, J = 7.9 Hz, 1H, $CHCH_2$), 5.89* (t, J = 7.9 Hz, 1H, $CHCH_2$), 6.63 (d, J = 8.6 Hz, 2H, H_{arom}), 7.72* (d, J = 8.6 Hz, 2H, H_{arom}), 6.91 (d, J = 8.6 Hz, 2H, H_{arom}), 7.14* (d, J = 7.2 Hz, 1H, H_{arom}), 7.20 (d, J = 6.9 Hz, 2H, H_{arom}), 7.21-7.26 (m, 1H, H_{arom}), 7.28-7.32 (m, 2H, H_{arom}), 7.55* (t, J = 7.8 Hz, 1H, H_{arom}), 7.60 (t, J = 7.8 Hz, 1H, H_{arom}), 7.63* (t, J = 7.8 Hz, 1H, H_{arom}), 7.69 (t, J = 7.8 Hz, 1H, H_{arom}), 7.81* (d, J = 6.7 Hz, 1H, H_{arom}), 7.87 (d, J = 6.7 Hz, 1H, H_{arom}), 7.92* (d, J = 7.9 Hz, 1H, H_{arom}), 8.02 (d, J = 7.9 Hz, 1H, H_{arom}), 9.29 (s, 1H, OH). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 31.2 (CH_2CH), 42.2 (CH_2Ph), 112.6 ($CHCH_2$), 115.3, 123.1, 123.8, 125.6, 126.8 (2C), 127.3, 128.7 (2C), 129.1 (2C), 129.3, 129.7, 129.8, 132.7, 134.0, 134.9, 137.2, 155.7, 165.6 (C=O). HRMS (FAB$^+$): calcd. for $C_{23}H_{20}NO_2$ $[M+H]^+$, *m/z* 342.1494; found for $[M+H]^+$, *m/z* 342.1484.

*4.2.15. (E)-2-(4-Methoxybenzyl)-3-[2-(4-methoxyphenyl)ethylidene]-isoindolin-1-one (**4e**).* Yellow solid, Mp: 119-121 ºC, 80% yield, (*E/Z*) 85:15 ratio. ^{1}H NMR asterisk denotes minor isomer (500 MHz, $CDCl_3$) δ: 3.56* (s, 3H, CH_3O), 3.57* (s, 3H, CH_3O), 3.74 (s, 3H, CH_3O), 3.75 (s, 3H, CH_3O), 3.86 (d, J = 7.9 Hz, 2H, CH_2CH), 4.95 (s, 2H, NCH_2Ph), 5.18* (s, 1 H, NCH_2Ph), 5.57 (t, J = 7.9 Hz, 1H, $CHCH_2$), 5.70* (t, J = 8.1 Hz, 1H, $CHCH_2$), 6.79 (d, J = 7.8 Hz, 2H, H_{arom}), 6.80 (d, J = 7.8, Hz, 2H, H_{arom}), 6.83* (d, J = 8.3 Hz, 1H, H_{arom}), 6.88* (d, J = 8.3 Hz, 1H, H_{arom}), 7.02 (d, J = 8.5 Hz, 2H, H_{arom}), 7.07* (d, J = 8.5 Hz, 1H, H_{arom}), 7.15 (d, J = 8.5 Hz, 2H, H_{arom}), 7.43-7.61* (m, 1H, H_{arom}), 7.81 (d, J = 7.7 Hz, 1H, H_{arom}), 7.88* (d, J = 8.5 Hz, 1H, H_{arom}) 7.94 (d, J = 7.7 Hz, 1H, H_{arom}). NMR ^{13}C asterisk denotes minor isomer (125 MHz, $CDCl_3$) δ: 31.6* (CH_2CH), 32.3 (CH_2CH), 42.4 (CH_2Ph), 44.1* (CH_2Ph), 55.2 (CH_3O, 2C), 55.3* (CH_3O), 107.7* ($CHCH_2$), 111.8 ($CHCH_2$), 114.0, 114.14, 114.2*, 119.1, 123.3, 123.6, 127.0, 127.8, 127.9, 128.3, 128.5, 128.8, 129.1, 129.2, 129.6, 129.8, 130.5, 131.5, 131.9 (2C), 132.0, 134.0, 135.1, 135.4, 138.1, 158.2 (2C), 158.8, 166.5 (C=O), 168.3* (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{22}NO_2$ $[M+H]^+$, *m/z* 386.1756; found for $[M+H]^+$, *m/z* 386.1728.

*4.2.16. (E)-2-(4-Methoxybenzyl)-3-[2-(4-methylphenyl)ethylidene]-isoindolin-1-one (**4f**).* White solid, Mp: 73-75 ºC, 68% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.31 (s, 3H, CH_3), 3.77 (s, 3H, CH_3O), 3.91 (d, J = 7.9 Hz, 2H, CH_2CH), 4.96 (s, 2H, NCH_2Ph), 5.59 (t, J = 7.9 Hz, 1H, $CHCH_2$), 6.82 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.01 (AA'BB', J = 8.0 Hz, 2H, H_{arom}), 7.07 (AA'BB', J = 7.9 Hz, 2H, H_{arom}), 7.16 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.50 (d, J = 7.6 Hz, 1H, H_{arom}), 7.56 (d, J = 7.6 Hz, 1H, H_{arom}), 7.84 (d, J = 7.7 Hz, 1H, H_{arom}), 7.95 (d, J = 7.7 Hz, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.0 (CH_3), 32.8 (CH_2CH), 42.5 (CH_2Ph), 55.4 (CH_3O), 111.8 ($CHCH_2$), 114.1, 123.4, 123.8, 128.1, 128.4 (2C), 128.9, 129.2, 129.4 (2C), 130.2, 130.6, 132.1, 134.0, 135.4, 135.6, 136.1, 136.5, 158.9, 166.6 (C=O). HRMS (FAB$^+$): calcd. for $C_{25}H_{23}NO_2$ $[M+H]^+$, *m/z* 370.1807; found for $[M+H]^+$, *m/z* 370.1810.

*4.2.17. (E)-2-(4-Methoxybenzyl)-3-[2-(4-hydroxyphenyl)ethylidene]-isoindolin-1-one (**4g**).* Yellow solid, Mp: 160-162 ºC, 65% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.69 (s, 1H, OH), 3.77 (s, 3H, CH_3O), 3.87 (d, J = 7.9 Hz, 2H, CH_2CH), 4.97 (s, 2H, NCH_2Ph), 5.58 (t, J = 7.9 Hz, 1H, $CHCH_2$), 6.74 (AA'BB', J = 8.5 Hz, 2H, H_{arom}), 6.81 (AA'BB', J = 8.5 Hz, 2H, H_{arom}), 6.96 (AA'BB', J = 8.4 Hz, 2H, H_{arom}), 7.16 (AA'BB', J = 8.5 Hz, 2H, H_{arom}), 7.51 (t, J = 7.5 Hz, 1H, H_{arom}), 7.57 (t, J = 7.5 Hz, 1H, H_{arom}), 7.84 (d, J = 7.5 Hz, 1H, H_{arom}), 7.96 (d, J = 7.5 Hz, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.9 (CH_2CH), 42.3 (CH_2Ph), 55.2 (CH_3O), 114.1 ($CHCH_2$), 114.2, 115.5, 115.8, 122.9 (2C), 123.5 (2C), 128.6 (2C), 129.0 (2C), 129.2 (2C), 129.3 (2C), 132.0 (2C), 135.0, 158.7, 166.4 (C=O). HRMS (FAB$^+$): calcd. for $C_{24}H_{22}NO_3$ $[M+H]^+$, *m/z* 372.1600; found for $[M+H]^+$, *m/z* 372.1574.

*4.2.18. (Z)-3-(2-Phenylethylydene)isobenzofuran-1(3H)-one (**6a**).* White soli, Mp: 89-91 ^{o}C, 80% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.81 (d, J = 7.9 Hz, 2H, CH_2CH), 5.78 (t, J = 7.9 Hz, 1H, $CHCH_2$), 7.20-7.25 (m, 1H, H_{arom}), 7.26-7.34 (m, 4H, H_{arom}), 7.51 (t, J = 7.8 Hz, 1H, H_{arom}), 7.61 (d, J = 7.8 Hz, 1H, H_{arom}), 7.66 (t, J = 7.8 Hz, 1H, H_{arom}), 7.90 (d, J = 7.8 Hz, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 32.1 (CH_2CH), 107.8, 119.9, 124.7, 125.4, 126.6, 128.7 (2C), 128.8 (2C), 129.7, 134.4, 139.3, 139.5, 145.8, 167.1 (C=O). HRMS (FAB$^+$): calcd. for $C_{16}H_{13}O_2$ $[M+H]^+$, *m/z* 237.0916; found for $[M+H]^+$, *m/z* 237.0918.

*4.2.19. (Z:E)-3-[2-(4-Metoxyphenyl)ethylydene]isobenzofuran-1(3H)-one (**6b**).* Yellow oil, 80% yield, (*Z*/*E*) 95:05 ratio. ^{1}H MR asterisk denotes minor isomer (500 MHz, $CDCl_3$) δ: 3.76 (d, J = 7.9 Hz, 2H, CH_2CH), 3.79 (s, 3H, CH_3O), 3.88* (d, J = 8.4 Hz, 2H, CH_2CH), 5.76 (t, J = 7.9 Hz, 1H, $CHCH_2$), 6.03* (t, J = 7.9 Hz, 1H, $CHCH_2$), 6.86 (AA'BB', J = 8.7, Hz, 2H, H_{arom}), 7.15* (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.20 (AA'BB', J = 8.7 Hz, 2H, H_{arom}), 7.48* (d, J = 7.5 Hz, 1H, H_{arom}), 7.53 (d, J = 7.5 Hz, 1H, H_{arom}), 7.59* (d, J = 7.8 Hz, 1H, H_{arom}), 7.62 (d, J = 7.8 Hz, 1H, H_{arom}), 7.67 (t, J = 7.8, 1H, H_{arom}), 7.91 (d, J = 7.8 Hz, H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 31.3 (CH_2CH), 55.4 (CH_3O), 108.3, 113.9, 114.2, 119.9, 124.6, 125.4, 129.4, 129.7 (2C), 131.3, 134.4, 139.6, 145.6, 158.3, 167.2 (C=O). HRMS (FAB$^+$): calcd. for $C_{17}H_{15}O_3$ $[M+H]^+$, *m/z* 267.1021; found for $[M+H]^+$, *m/z* 267.1005.

*4.2.20. (Z)-3-[2-(4-Mehylphenyl)ethylydene]isobenzofuran-1(3H)-one (**6c**).* Yellow oil, 70% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.32 (s, 3H, CH_3), 3.78 (d, J = 7.9 Hz, 2H, CH_2CH), 5.77 (t, J = 7.9 Hz, 1H, $CHCH_2$), 7.13 (AA'BB', J = 7.9, Hz, 2H, H_{arom}), 7.18 (AA'BB', J = 8.0, Hz, 2H, H_{arom}), 7.52 (t, J = 7.8 Hz, 1H, H_{arom}), 7.61 (d, J = 7.8 Hz, 1H, H_{arom}), 7.67 (t, J = 7.8 Hz, 1H, H_{arom}), 7.91 (d, J = 7.8 Hz, 1H, H_{arom}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.7 (CH_3), 31.7 (CH_2CH), 108.2, 119.9, 124.7, 125.4, 128.6 (2C), 128.7, 129.5, 129.7 (2C), 134.4, 136.2, 136.3, 145.7, 167.2 (C=O). HRMS (FAB$^+$): calcd. for $C_{17}H_{15}O_2$ $[M+H]^+$, *m/z* 251.1072; found for $[M+H]^+$, *m/z* 251.1086.

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Supplementary data

Supplementary data related to this article can be found online.

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12. CCDC 1961555 [for (*E*)-**4a**]; CCDC 1961556 [for (*E*)-**4e**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
13. For the synthesis of (*Z*)-3-(2-phenylethylidene)isobenzofuran-1(3*H*)-one **6a**, see: references 5a and 6b.

14. CCDC 1961557 [for (*E*)-**6a**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Practical synthesis of 3-(2-aryl-ethylidene)isoindolin-1-ones and 3-(2-arylethylidene)isobenzofuran-1(3*H*)-ones.

Concise synthesis of AKS-182

Sequential reduction-dehydration reaction

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: