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Heteroannulation through Combined Palladium Catalysed and Friedel-Crafts Reactions Strategy : Synthesis of 3-Alkylidene Isoindolin-1-ones[1]

Nitya G. Kundu,* M. Wahab Khan[2] and Rupa Mukhopadhyay

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, India.

E-mail: ocngk@mahendra.iacs.res.in

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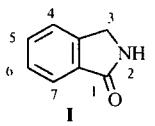
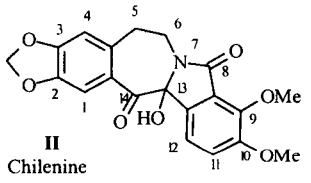
Abstract. The palladium-catalysed reactions of 2-iodobenzamides **1-5** with trimethylsilyl acetylene **6** led to 2-(2-trimethylsilyl)ethynyl benzamides **7-11** in excellent yields. The 2-(2-trimethylsilyl)ethynyl benzamides **7-11** underwent Friedel-Crafts reactions with acid chlorides **12-17** or anhydride **18** smoothly under mild conditions yielding the 3-alkylidene isoindolin-1-ones **19-38**.

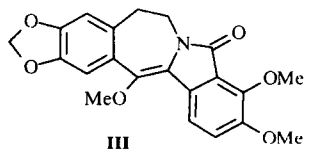
The isoindolin-1-one or 2,3-dihydro-1H-isoindol-1-one (phthalimidine) **I** skeleton is an integral part of many naturally occurring substances like chilenine **II**, pictonamine **III**, isolated from the Chilean Barberis species,[3] staurosporine **IV**, an alkaloid isolated from saccharothrise sp.[4] and cytochalasins **V**, isolated from various molds and microorganism.[5]



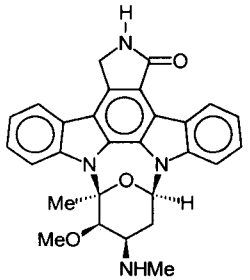
I
Isoindolin-1-one



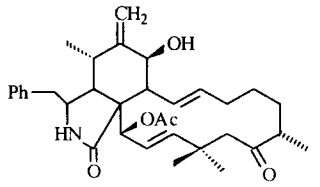
II
Chilenine



III
Pictonamine



Staurosporine **IV**



Cytochalasin D **V**

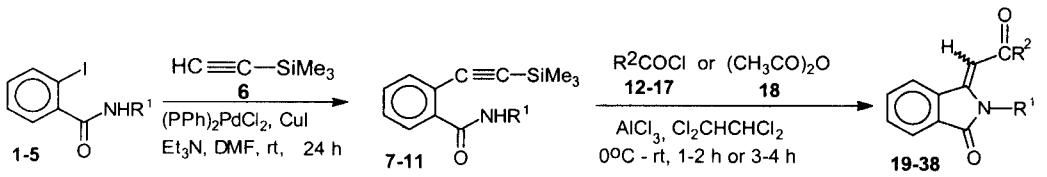
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00719-X

Also, many compounds containing the isoindolinone moiety have shown antiviral, antileukemic, antiinflammatory, antipsychotic and antiulcer properties.[6] Isoindolin-1-ones have also been useful in the synthesis of various drugs[7] and naturally occurring compounds.[8] Starting with the classical Gabriel method[9] for the synthesis of phthalides and phthalimidines, there are a number of methods available for the synthesis of isoindolinones which are based on (i) the Grignard procedure[10] (ii) lithiation procedures[11] (iii) Diels-Alder reactions[12] (iv) Wittig reagent[13] (v) reduction processes[14] (vi) rearrangement processes[15] and photochemical reactions.[16]

Palladium-catalysed reactions[17] have been extensively utilised for carbannulation[18] and heteroannulation[19] processes, but palladium-catalysed synthesis of isoindolinones are limited in number.[20] In connection with our syntheses of various benzo-fused heterocyclic structures, *e.g.* benzofurans,[21a] quinolines,[21b] phthalides,[21c] benzodioxins[21d] and benzoxazines[21e] through palladium-catalysed reactions with terminal alkynes, we recently reported[22] a facile synthesis of (Z)-3-alkylidene isoindolin-1-ones through palladium-catalysed reactions of 2-iodobenzamides with various terminal alkynes. In this paper, we report an alternative novel approach for the synthesis of 3-alkylidene isoindolin-1-ones in good yield under very mild conditions.[1]

Results and Discussion.

We report a novel approach where a palladium-catalyzed reaction is followed by Friedel-Crafts acylation and simultaneous cyclization to obtain 3-alkylidine isoindolin-1-ones in good to excellent yields. *N*-Alkyl or *N*-aryl-2-iodo benzamides **1-5** underwent facile reaction with trimethylsilyl acetylene **6** in the presence of $(PPh_3)_2PdCl_2$ and CuI at room temperature to yield 2-(trimethylsilyl)ethynyl benzamides **7-11** in excellent yields (83-88%). 2-Trimethylsilyl ethynyl benzamides **7-11** were then subjected to Friedel-Crafts reaction with acid chlorides **12-17** or acetic anhydride **18** to afford the 3-alkylidene isoindolin-1-ones **19-38** in good yields as shown in Scheme 1.



Compound	R^1
1, 7, 19-25	H
2, 8, 26-29	Me
3, 9, 30, 31	C_6H_4Me-*p*
4, 10, 32-35	C_6H_4OMe-*p*
5, 11, 36-38	C_6H_4Cl-*m*

Compound	R^2
12, 18, 19, 25, 26, 30, 32, 35, 36	CH_3
13, 20	CH_2CH_3
14, 20	$CH_2CH_2CH_3$
15, 22, 27, 33	C_6H_5
16, 23, 28, 34, 37	*p*-MeC_6H_4
17, 24, 29, 31, 38	*p*-$MeOC_6H_4$

Scheme-1

The palladium-catalyzed reactions between the 2-iodo-*N*-substituted benzamides **1-5** and trimethylsilyl acetylene **6** afforded the trimethylsilyl ethynyl benzamides **7-11** in good yields (83-88%). However, the Friedel-Crafts reaction between the 2-trimethylsilyl ethynyl benzamides **7-11** and the acid chlorides **12-17** or acetic anhydride **18** gave variable yields (50-84%) of 3-alkylidene isoindolin-1-ones **19-38** (Table 1).

Friedel-Crafts acylation reactions of 2-trimethylsilyl ethynyl benzamide with maleic anhydride, phthalic anhydride, oxalyl chloride, and *p*-fluorobenzoyl chloride under the same conditions, gave none of the desired products. Acylation reactions with trifluoroacetic anhydride and *p*-chlorobenzoyl chloride yielded very small amounts of the cyclized products. In the case of trifluoroacetic anhydride a small amount of 3-methylene isoindolinone was obtained.

Characterization of Products.

3-Alkylidene isoindolin-1-ones **19-38** were characterized by their spectroscopic (IR, UV, ^{1}H NMR and ^{13}C NMR) and satisfactory analytical data.

In IR spectra, C=O stretching vibration in the range 1690-1725 cm^{-1} indicated the presence of a γ-lactam (-CO-N-) ring *i.e* the isoindolinone moiety, and the stretching frequency in the range 1655-1660 cm^{-1} signified the presence of the α, β-unsaturated ketone functionality.

3-Alkylidene isoindolin-1-ones **27-29, 33, 34** and **38** showed the ^{1}H NMR signals for the vinylic proton (=CH-) as a singlet at δ 6.50-6.67, for the C-4 proton as a doublet at δ 8.80-8.93 and for the remaining aromatic protons at δ 6.93-8.04. But 3-alkylidene isoindolin-1-ones **19-21, 30, 32, 35** and **36** exhibited the ^{1}H NMR signals for the vinylic proton as a singlet at δ 5.93-6.15 and for the aromatic protons at δ 6.92-8.05. In the case of compounds **22-24, 31** and **37** vinylic proton signals in ^{1}H NMR spectra were observed as a singlet at δ 6.62 - 6.89 and the aromatic protons signals at δ 7.17-8.09.

An increase in chemical shifts (downfield) of the C-4 proton with respect to other aromatic protons characterized the (*E*)-configuration. The C-4 proton in the (*E*)-isomer is considerably deshielded or perturbed by the carbonyl group, whereas in the (*Z*) configuration the four aromatic protons were observed with similar chemical shifts.[23a-c] It has also been reported that the vinylic proton signal appears at lower field in the (*E*)-isomer than that of (*Z*)-isomer in case of the analogous lactones.[24] From the above observations we can identify **27-29, 33, 34** and **38** as (*E*)-isomers and **19-25, 30-32, 35-37** as (*Z*)-isomers. Compound **26** was obtained as a mixture of (Z) and (E) isomers **(1 : 1)**.

Table - 1 : Synthesis of 3-Alkylidene Isoindolin-1-ones from 2-Iodobenzamides (Scheme-1).

Entry	2-Iodobenzamides **1-5** (R^1)	2-Trimethylsilyl ethynylbenzamides **7-11** Yields (%)	Acid chlorides **12-17** / Acetic Anhydride **18** (R^2)	3-Alkylidene Isoindolin-1-ones **19-38**	(Z)/(E)-configuration	Yields (%)[a]
1	**1** (H)	**7** (86)	**12** (CH_3)	**19**[b]	(Z)	54 (47)
2	**1** (H)	**7** (86)	**13** (CH_2CH_3)	**20**	(Z)	53 (46)
3	**1** (H)	**7** (86)	**14** ($CH_2CH_2CH_3$)	**21**	(Z)	52 (44)
4	**1** (H)	**7** (86)	**15** (C_6H_5)	**22**	(Z)	52 (44)
5	**1** (H)	**7** (86)	**16** (*p*-MeC_6H_4)	**23**	(Z)	69 (60)
6	**1** (H)	**7** (86)	**17** (*p*-$MeOC_6H_4$)	**24**	(Z)	66 (57)
7	**1** (H)	**7** (86)	**18** (CH_3)	**25**[b]	(Z)	60 (52)
8	**2** (CH_3)	**8** (83)	**12** (CH_3)	**26**	(Z)+(E) (1:1)	60 (52)
9	**2** (CH_3)	**8** (83)	**15** (C_6H_5)	**27**	(E)	72 (62)
10	**2** (CH_3)	**8** (83)	**16** (*p*-MeC_6H_4)	**28**	(E)	52 (45)
11	**2** (CH_3)	**8** (83)	**17** (*p*-$MeOC_6H_4$)	**29**	(E)	50 (44)
12	**3** (C_6H_4Me-*p*)	**9** (87)	**18** (CH_3)	**30**	(Z)	67 (59)
13	**3** (C_6H_4Me-*p*)	**9** (87)	**17** (*p*-$MeOC_6H_4$)	**31**	(Z)	59 (49)
14	**4** (C_6H_4OMe-*p*)	**10** (88)	**12** (CH_3)	**32**[c]	(Z)	56 (50)
15	**4** (C_6H_4OMe-*p*)	**10** (88)	**15** C_6H_5	**33**	(E)	76 (68)
16	**4** (C_6H_4OMe-*p*)	**10** (88)	**16** (*p*-MeC_6H_4)	**34**	(E)	66 (59)
17	**4** (C_6H_4OMe-*p*)	**10** (88)	**18** (CH_3)	**35**[c]	(Z)	83 (74)
18	**5** (C_6H_4Cl-*m*)	**11** (86)	**12** (CH_3)	**36**	(Z)	52 (46)
19	**5** (C_6H_4Cl-*m*)	**11** (86)	**16** (*p*-MeC_6H_4)	**37**	(Z)	84 (74)
20	**5** (C_6H_4Cl-*m*)	**11** (86)	**17** (*p*-$MeOC_6H_4$)	**38**	(E)	86 (75)

[a]Yields are based on the 2-(trimethylsilyl)ethynyl benzamides **7-11**; yields in bracket are based on the 2-iodobenzamides **1-5.**

[b]Compounds **19** and **25** are identical; [c]Compounds **32** and **35** are identical.

The ^{13}C NMR spectra of the *(Z)-N-p*-methylphenyl-3-(2′-oxo)propylidene isoindolinone **30** and *(Z)-N-m*-chlorophenyl)-3-(2′-oxo)propylidene isoindolinone **36** showed signals for the vinylic carbon (=CH-) at δ 102, for the C-3 carbon at δ 124-125, for the γ-lactam carbon (-CO-N-) at δ 156-157 and for the carbon of acyl carbonyl group at δ 196. The other (Z)-3-alkylidene isoindolin-1-ones **19-25, 37** exhibited ^{13}C NMR signals for the vinylic carbon (=CH-) at δ 94.82 - 98.76, for the C-3 carbon at δ 129.41 - 131.59, for the γ-lactam carbon (-CO-N-) at 157.16 - 169.49 and for the carbon of the acyl carbonyl group at δ 189.06 - 202.63.

In case of isoindolinones of (*E*)-configuration, the ^{13}C NMR spectra showed the chemical shift positions of the vinylic carbon (=CH-) at δ 103-105, for the C-3 carbon at δ 129-133, for the γ-lactam carbon (-CO-N) at δ 163-169 and for the carbon of the acyl carbonyl group at δ 188-189. From the ^{13}C NMR spectra of the (*Z*) and (*E*) isoindolinones it was observed that the chemical shift positions for the vinylic carbons of (*E*) configuration were usually downfield compared with those of (*Z*)-configuration.

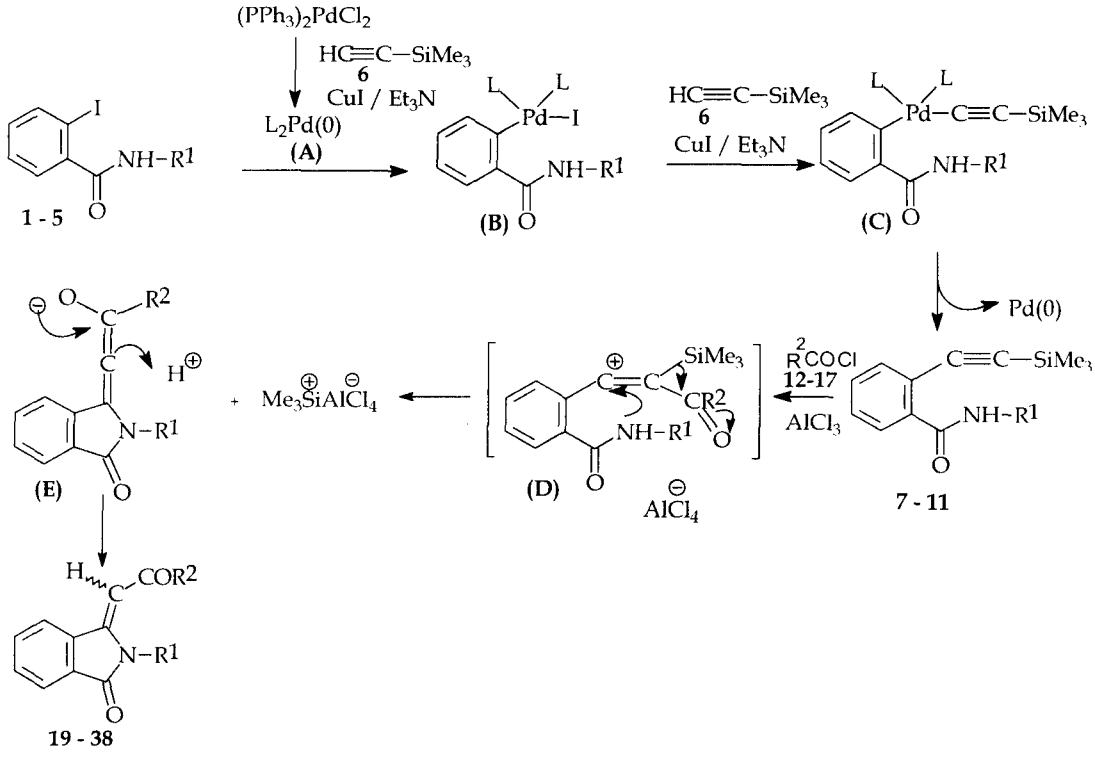
UV absorptions were found in the region λ_{max} 335-350 nm, 292-302 nm and 228-230 nm for the isoindolinones **27, 29, 33, 34, 38** which were found to be of similar pattern. But the UV absorptions were found in the region λ_{max} 373 nm and 258 nm for **36** and 341, 281 nm for **37**. From the UV absorption data it was revealed that the compound of (*E*)-configuration gave a different UV pattern than that of (*Z*)-configuration.

In our earlier preliminary communication [1] we claimed that all the 3-alkylidene isoindolin-1-ones **29-38** had the (*Z*)-configuration. However, on detailed investigation we have now established that some of the isoindolinones (**27-29, 33, 34, 38**) were indeed in the (*E*)-configuration, while the rest of the compounds (**19-25, 30-32, 35-37**) are in the *Z*-configuration. Finally the configuration of the 3-alkylidine isoindolinones was confirmed by X-ray crystallography. The X-ray diffraction pattern of **27** established it to have the E - configuration.[25]

All spectra (^1H NMR, ^{13}C NMR, IR and UV) of the isoindolinones **28, 29, 33, 34, 38** were compatible with the spectra of the isoindolinone **27** which confirmed the (*E*) - configuration of these compounds.

Mechanism

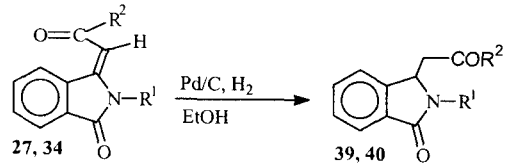
The mechanism of the reaction is as shown in Scheme **2.** Acylation of **7-11** generates the species **D** [26] which on elimination of the trimethylsilyl group and rearrangement leads to the 3-alkylidene isoindolin-1-ones **19-38**. The formation of the (*E*) or (*Z*) configuration depends on the relative stabilities of the isomers which are dictated by the substitution on the N-atom and also by the substitution at the C_3-position. When there was no substitution on the nitrogen atom only compounds of the *Z*-configuration were obtained.



Scheme 2

Hydrogenation.

(*E*)-*N*-Methyl-3-(2′-oxo-2′-phenyl)ethylidene isoindolin-1-one **27** and (*E*)-*N*-*p*-methoxyphenyl-3-(2′-oxo-2′-*p*-methyl phenyl)ethylidene isoindolin-1-one **34** were subjected to hydrogenation in the presence of Pd/C and H_2 in EtOH to yield *N*-methyl-3-(2′-oxo-2′-phenyl)ethyl isoindolinone **39** and *N*-*p*-methoxyphenyl-3-(2′-oxo-2′-*p*-methyl phenyl)ethyl isoindolin-1-one **40** respectively (Scheme 3).



27, 39 $R^1 = CH_3$, $R^2 = C_6H_5$

34, 40 $R^1 = C_6H_4OMe$-*p*, $R^2 = C_6H_4Me$-*p*

Scheme 3

The saturated isoindolin-1-ones 39 and 40 were characterished from their spectral (^{1}H NMR, ^{13}C NMR,IR and UV) and analytical data.

In IR spectra, γ-lactam peaks were found at 1695 and 1690 cm^{-1} and acyl carbonyl peaks at 1680 and 1665 cm^{-1}.

The ^{1}H NMR spectrum of the saturated isoindolin-1-one **40** exhibited a double doublet at δ 5.86 (J = 9, 3 Hz) for the C-3 proton and two double doublets at δ 3.14 (J = 3,18 Hz) and 3.44 (J = 9, 18 Hz) for the **CH_2CO** and aromatic protons at δ 6.94-7.93. Compound **39** gave a triplet at δ 5.24 (J = 6 Hz), for C-3 proton,the two double doublets at δ 3.27 and 3.54 (J = 6, 18 Hz) for the **CH_2CO** and aromatic protons at δ 7.43-7.96.

The ^{13}C NMR spectra of **39** and **40** showed the signals for ($\underline{C}H_2CO$) at δ 41, for the C-3 carbon at 57, for the γ-lactam carbon at 166-168 and for the carbon of the acyl carbonyl group at δ 197.

Conclusion.

We have described a convenient method for the synthesis of 3-alkylidene isoindolin-1-ones through palladium catalyzed reactions followed by Friedel-Crafts acylation.

Experimental.

Melting points were determined in open capillary tubes on Reichert (285980) Austria melting point apparatus and are uncorrected. UV spectra were recorded on a Hitachi 200-20 spectrometer using spectrophotometric grade ethanol (Baker). IR spectra were recorded on a Perkin-Elmer 298 instrument for samples as KBr plates or liquid films. ^{1}H NMR spectra were recorded on a Varian EM-360, a Varian XL-200 and a Bruker DPX-300 spectrometer with tetramethylsilane as internal reference. ^{13}C Spectra (75.5 MHz) were obtained on a Bruker DPX-300 spectrometer. Splitting patterns are designated as follows : s, singlet; d, doublet; t, triplet; q, quartet, m, multiplet; and br, broad. Analytical thin-layer chromatography (TLC) was performed on precoated 0.2 mm silica gel 60F-254 (E. Merck), and the spots were visualized with UV light. Column chromatography was performed on silica gel (60-120 mesh) or neutral alumina. Elemental analyses (C, H, N) were carried out on a Perkin-Elmer 240C Analyser.

Synthesis of 2-trimethylsilyl ethynyl benzamides (7-11).General Procedure.

To a solution of 2-iodobenzamide **1-5** (1 mmol) in DMF (5 mL), bis(triphenylphosphine) palladium(II)chloride (3.5 mol %), copper(I)iodide (8 mol %), and triethylamine (4 mmol) were added. The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then the trimethylsilyl acetylene **6** (2 mmol) was added dropwise to the mixture with continued stirring and allowed to stand for 23 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure. The residue was extracted with chloroform (3 x 5 mL). The organic extract was washed with distilled water (3 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under low pressure. The residue was purified by column chromatography on silica gel using chloroform as the eluent to afford the 2-trimethylsilyl ethynyl benzamides **7-11**.

2-(2′-Trimethylsilylethynyl)-benzamide 7.

Yield 86% . A colourless crystalline solid, m.p 62-63°C; [Found: C, 66.7; H, 6.9; N, 6.1. $C_{12}H_{15}SiNO$ requires C, 66.35; H, 6.97; N, 6.12%]; R_f (5% EtOAc/$CHCl_3$) 0.65; ν_{max} (KBr) 3420, 2160, 1660, 1600 cm^{-1}; δ_H (60 MHz, CCl_4) 8.38-8.10 (1H, m, Ar-H), 7.69 (1H, brs, NH), 7.51-7.30 (4H, m, Ar-H), 0.30 (9H, s, TMS-H).

2-[(2′-Trimethylsilylethynyl)-N-methyl] benzamide 8.

Yield 83% . A light yellow crystalline solid, m.p 80-82°C; [Found: C, 67.2; H, 7.0; N, 5.9. $C_{13}H_{17}SiNO$ requires C, 67.53; H, 7.35; N, 6.06%]; R_f (5% EtOAc/$CHCl_3$) 0.63; ν_{max} (KBr) 3360, 3170, 2950, 2160, 1640, 1560, 1480 cm^{-1}. δ_H (60 MHz, CCl_4) 8.10-8.07 (1H, m, Ar-H), 7.66 (1H, brs, NH), 7.53-7.38 (3H, m, Ar-H), 3.02 (3H, s, Me), 0.28 (9H, s, TMS-H).

2-[(2′-Trimethylsilylethynyl)N-*p*-methylphenyl] benzamide 9.

Yield 87%. A off white powder, m.p. 85-87 °C; [Found: C, 74.0; H, 6.7; N, 4.4. $C_{19}H_{21}SiNO$ requires C, 74.22; H, 6.88; N, 4.55%]; R_f (5% EtOAc/$CHCl_3$) 0.85; ν_{max} (KBr) 3340, 3000, 2160, 1665, cm^{-1}; δ_H (60 MHz, CCl_4) 9.10-8.90 (1H, brs, NH), 8.10-6.80 (8H, m, Ar-H), 2.10 (3H, s, Me), 0.15 (9H, s, TMS-H).

2-[2′-Trimethylsilylethynyl)-N-*p* methoxyphenyl] benzamide 10.

Yield 88% . Colourless small needles , m.p. 116-117 °C; [Found: C, 70.9; H, 6.8; N, 4.3. $C_{19}H_{21}SiNO_2$ requires C, 70.55; H, 6.54; N, 4.33%]; R_f (5% EtOAc/$CHCl_3$) 0.70; ν_{max} (KBr) 3330, 3000, 2150, 1660 cm^{-1}; δ_H (60 MHz, $CDCl_3$) 8.90 (1H, brs, NH), 8.00-6.80 (8H, m, Ar-H), 3.50 (3H, s, OMe), 0.30 (9H,s, TMS-H).

2-[(2′-Trimethylsilylethynyl)-N-m-chlorophenyl] benzamide 11.

Yield 86%. Colourless small needles, m.p. 70-77 °C; [Found: C, 66.1; H, 5.7; N, 4.0. $C_{18}H_{18}SiNO$ requires C, 65.93; H, 5.53; N, 4.27%]; R_f (5% EtOAc/$CHCl_3$) 0.80; ν_{max} (KBr) 3310, 2970, 2160, 1660, 1600 cm^{-1}; δ_H (60 MHz, CCl_4) 9.50-9.40 (1H, s, NH), 8.20-6.90 (8H, m, Ar-H), 0.20 (9H, s, TMS-H).

Synthesis of 3-alkylidene isoindolinones 19-38 : General procedure

Anhydrous aluminium(III) chloride (4 mmol) and acid chloride or anhydride (1.2-1.5 mmol) were added to an ice-cold solution of 2-trimethylsilyl ethynyl benzamides **7-11** (1 mmol) in tetrachloroethane (10 mL).The mixture was stirred under a nitrogen atmosphere for 1-2 h (acid chloride) or 3-4 h (acid anhydride) and the temperature of the reaction bath was raised from 0°C to 25°C. Then the mixture was poured into an ice cold solution of dilute hydrochloric acid (20 mL, 1-1.5 N HCl) and the organic layer was separated. The aqueous layer

was extracted with $CHCl_3$ (2 x 25 mL). The combined organic extracts were washed with distilled H_2O (2 x 25 mL), saturated $NaHCO_3$ solution (2 x 25 mL) and distilled H_2O (25 mL). After drying over anhydrous Na_2SO_4 and removal of the solvent, a deep yellow solid was obtained, which was purified by chromatography on neutral alumina or silica gel using 5-10% EtOAc/$CHCl_3$ as the eluent. Finally the product was crystallized from EtOH to yield pure 3-alkylidene isoindolinones **19-38**.

(*Z*)-3-[(2′-Oxo)propylidene] isoindolin-1-one 19

Yield 54%.Light yellow crystals (EtOH), m.p. 108°C; [Found: C, 70.5; H, 4.9; N, 7.2. $C_{11}H_9NO_2$ requires C, 70.58; H, 4.81; N, 7.48%]; R_f (5% EtOAc/$CHCl_3$) 0.30; ν_{max} (KBr) 3320, 1720, 1670, 1610, 1450, 1400, 1350, 1290, 1270, 1180, 1090, 970, 820, 760, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.29 (1H, s, NH).7.85-7.29 (4H, m, Ar-H), 6.15 (1H, s, =CH), 2.35 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) : 201.7, 169.3, 146.7, 137.3, 133.2, 132.2, 129.8, 124.5, 121.4, 98.7, 31.4.

(*Z*)-3-[(2′-Oxo)butylidene] isoindolin-1-one 20

Yield 53%. Light yellow crystalline solid (EtOH), m.p. 64°C; [Found: C, 71.3; H, 5.5; N, 7.1. $C_{12}H_{11}NO_2$ requires C, 71.64; H, 5.47; N, 6.96%]; R_f (5%EtOAc/$CHCl_3$) 0.30; ν_{max} (KBr) 3360, 1720, 1670, 1600, 1510, 1450, 1400, 1340, 1290, 1250, 1190, 1100, 1030, 990, 900, 830, 760, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.17 (s, 1H, -NH), 7.76-7.16 (4H, m, Ar-H), 6.03 (1H, s, =CH), 2.51 (2H, q *J* 7.4 Hz, CH_2), 1.09 (3H, t *J* 6.0 Hz, Me); δ_C (75.5 MHz, $CDCl_3$) 202.6, 169.4, 146.5, 137.4, 133.2, 132.1, 129.8, 124.5, 121.4, 98.2, 37.5, 8.8.

(*Z*)-3-[(2′-Oxo)pentylidene] isoindolin-1-one 21

Yield 52%. Light yellow solid (EtOH), m.p. 58°C; [Found: C, 72.2; H, 6.4; N, 6.7. $C_{13}H_{13}NO_2$ requires C, 72.55; H, 6.05; N, 6.51%]; R_f (5% EtOAc/$CHCl_3$) 0.35; ν_{max} (KBr) 3280, 2940, 1710, 1660, 1600, 1460, 1400, 1330, 1290, 1190, 1090, 1030, 760, 690 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.31 (1H, s, NH), 7.89-7.26 (4H, m, Ar-H), 6.13 (1H, s, =CH), 2.57 (2H, t, *J* 6.0 Hz, CH_2), 1.73 (2H, m, CH_2), 0.99 (3H, t *J* 7.3 Hz, Me); δ_C (75.5 MHz, $CDCl_3$) 202.3, 146.6, 137.4, 133.2, 132.8, 129.9, 124.6, 121.4, 98.4, 46.3, 18.5, 14.2.

(*Z*)-3-[(2′-Oxo-2′-phenyl)ethylidene] isoindolin-1-one 22

Yield 52%. Light yellow powder (EtOH), m.p. 165°C; [Found: C, 77.3; H, 4.4; N, 5.3. $C_{16}H_{11}NO_2$ requires C, 77.10; H, 4.41; N, 5.62%]; R_f (5% EtOAc/$CHCl_3$) 0.50; ν_{max} (KBr) 3300, 1720, 1640, 1600, 1460, 1410, 1300, 1260, 1220, 1090, 1040, 1010, 890, 830 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.62 (1H, s, NH), 8.07-7.28 (9H, m, Ar-H),

6.89 (1H, s, =CH); δ_C (75.5 MHz, $CDCl_3$) 191.5, 169.5, 148.8, 138.8, 137.5,133.4, 133.3, 132.4, 129.7, 129.1, 128.4, 124.6, 121.5, 95.2.

(*Z*)-3-[(2′-Oxo-2′ *p*-methylphenyl)ethylidene] isoindolin-1-one 23

Yield 69%. Light yellow crystalline solid (EtOH), m.p. 192-193°C; [Found: C, 77.2; H, 5.0; N, 5.3. $C_{17}H_{13}NO_2$ requires C, 77.56; H, 4.94; N, 5.32%]; R_f (5% EtOAc/$CHCl_3$) 0.45; ν_{max} (KBr) 3350, 1710, 1640, 1600, 1460, 1420, 1300, 1260, 1230, 1190, 1020, 810, 760, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.60 (1H, s, NH), 7.95-7.26 (8H, m, Ar-H), 6.86 (1H, s, =CH), 2.43 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) 190.6, 169.0, 148.0, 143.8, 137.1, 135.8, 132.8, 131.8, 129.4, 129.3, 128.0, 124.1, 121.0, 94.8, 21.6.

(*Z*)-3-[(2′-Oxo-2′-*p*-methoxyphenyl)ethylidene] isoindolin-1-one 24

Yield 66%. Light yellow solid (EtOH), m.p. 148°C; [Found: C, 73.4; H, 4.6; N, 4.8. $C_{17}H_{13}NO_3$ requires C, 73.11; H, 4.65; N, 5.01%]; R_f (5% EtOAc/$CHCl_3$) 0.75; ν_{max} (KBr) 3320, 1720, 1640, 1600, 1560, 1500, 1425, 1300, 1260, 1230, 1180, 1110, 1010, 820, 760, 690, 660, 620 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.54 (1H, s, NH), 7.97-6.77 (8H, m, Ar-H), 6.76 (1H, s, =CH), 3.81(3H, s, OMe); δ_C (75.5 MHz, $CDCl_3$) 189.9, 169.4, 163.9, 148.2, 137.6, 133.2, 132.2, 131.7, 130.7, 129.8, 124.6, 121.4, 114.3, 95.2, 55.9.

(*Z*)-3-[(2′-Oxo)propylidene] isoindolin-1-one 25

The compound **25** was obtained from the Friedel-Crafts reaction of 2-trimethylsilyl ethynyl benzamide **7** with acetic anhydride and was found identical with compound **19**.

***N*-Methyl-3-[(2′-oxo)propylidene] isoindolin-1-one 26**

Yield 60%.The compound **26** was obtained as a mixture of (*E*) and (*Z*) isomers (1:1). Light yellow solid (EtOH), m.p. 120-124°C. R_f (5% EtOAc/$CHCl_3$) 0.25 and 0.30 respectively. δ_H (300 MHz $CDCl_3$) 9.09-9.06 (1H, m, Ar-H), 7.88-7.82 (2H, m, Ar-H), 7.65-7.59 (5H, m, Ar-H), 6.37 (1H, s, =CH), 5.88 (1H, s, =CH), 3.44 (3H, s, N-Me), 3.37 (3H, s, N-Me), 2.61 (3H, s, Me), 2.37 (3H, s, Me).

(*E*)-*N*-Methyl-3-[(2′-oxo-2′-phenyl)ethylidene] isoindolin-1-one 27

Yield 72%. Light yellow small needles (EtOH), m.p. 115-116°C; [Found: C, 77.3; H, 5.1; N, 5.6. $C_{17}H_{13}NO_2$ requires C, 77.55; H, 4.97; N, 5.32%]. R_f (5% EtOAc/$CHCl_3$) 0.40. ν_{max} (KBr) 3000, 1700, 1665, 1615, 1585, 1480, 1300, 1240, 1200, 990, 810, 770, 660 cm^{-1}; λ_{max} (EtOH) 349 (log ε 4.21), 300 (4.17), 229 (4.32) nm; δ_H (300 MHz, $CDCl_3$) 8.89-8.86 (1H, m, Ar-H), 8.04-8.01 (2H, m, Ar-H), 7.85-7.83 (1H, m, Ar-H), 7.62-7.48 (5H,

m, Ar-H), 6.66 (1H, s, =CH), 3.36 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) 183.5, 167.3, 149.3, 139.3,133.8, 133.2, 132.8, 131.4, 130.1, 128.6, 128.2, 127.2, 123.1, 103.2, 26.3.

(*E*)-*N*-Methyl-3-[(2′oxo-2′-*p*-methylphenyl)ethylidene] isoindolin-1-one 28

Yield 52%. Light yellow small needles (EtOH), m.p. 124-125°C; [Found: C, 77.9; H, 5.5; N, 5.0. $C_{18}H_{15}NO_2$ requires C, 77.95; H, 5.45; N, 5.05%]; R_f (5% EtOAc/$CHCl_3$) 0.45; ν_{max} (KBr) 3000, 1720, 1650, 1610, 1580, 1430, 1350, 1240, 1090, 1010, 810, 770, 700, 680 cm^{-1}; λ_{max} (EtOH) 348 (4.18), 300 (4.13), 229 (4.29) nm; δ_H (300 MHz, $CDCl_3$) 8.85 (1H, d *J* = 9 Hz, Ar-H), 7.94 (2H, d *J* 6 Hz, Ar-H), 7.86-7.83 (1H, m, Ar-H), 7.65-7.54 (2H, m, Ar-H),7.28 (2H, d *J* 6.0 Hz, Ar-H), 6.67 (1H, s, =CH), 3.37 (3H, s, N-Me), 2.44 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) 189.3, 169.4, 148.9,143.7,136.7, 133.9,133.2, 131.5, 130.2, 129.4, 128.4, 127.2, 123.1, 103.6, 26.4, 21.7.

(*E*)-*N*-Methyl-3-[(2′-oxo-2′-*p*-methoxyphenyl)ethylidene] isoindolin-1-one 29

Yield 50%. Light yellow powder (EtOH), m.p. 131-132°C; [Found: C, 73.8; H, 5.1; N, 4.5. $C_{18}H_{15}NO_3$ requires C, 73.70; H, 5.15; N, 4.77%]; R_f (5% EtOAc/$CHCl_3$) 0.30; ν_{max} (KBr) 3000, 1720, 1650, 1600, 1585, 1565, 1440, 1350, 1230, 1190, 1020, 820, 700, 610 cm^{-1}; λ_{max} (EtOH) 351 (log ε 4.31), 302 (4.12), 228 (4.36) nm; δ_H (300 MHz, $CDCl_3$) 8.80 (1H, d *J* 9 Hz, Ar-H), 8.04 (2H, d *J* 9.0 Hz, Ar-H), 7.75 (1H, d *J* 6.0 Hz, Ar-H), 7.65-7.54 (2H, m, Ar-H), 7.00 (2H, d *J* 9.0 Hz, Ar-H), 6.66 (1H, s, Ar-H), 3.90 (3H, s, Ar-OMe)), 3.39 (3H, s, N-Me); δ_C (75.5 MHz, $CDCl_3$) 188.3, 163.4, 156.5, 148.2, 133.9, 133.1, 131.2, 130.7, 130.6, 130.5, 127.1, 123.1, 113.8, 103.6, 55.5, 26.3.

(*Z*)-*N*-*p*-Methylphenyl-3-[(2′-oxo)propylidene] isoindolin-1-one 30

Yield 67%. Light yellow small needles (EtOH), m.p. 166-168°C; [Found: C, 77.7; H, 5.4; N, 5.3. $C_{18}H_{15}NO_2$ requires C, 77.96; H, 5.45; N, 5.05%]; R_f (5% EtOAc/$CHCl_3$) 0.45; ν_{max} (KBr) 3000, 1700, 1660, 1610, 1580, 1470, 1300, 1230, 1200, 990, 800, 760, 660 cm^{-1}; λ_{max} (EtOH) 378 (log ε 3.98), 258 (4.09), 223 (4.12) nm; δ_H (300 MHz, $CDCl_3$) 8.07-8.04 (1H, m, Ar-H), 7.72-7.66 (3H, m, Ar-H), 7.39 (2H, d *J* 8.1 Hz, Ar-H), 7.23 (2H, d *J* 8.4 Hz, Ar-H),5.93 (1H, s, =CH), 2.52 (3H, s, Me),2.38 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) 196.4, 157.1, 135.8, 135.7, 132.5, 132.2, 131.4 129.4, 124.1, 123.9, 121.2, 102.0, 31.1, 31.0.

(*Z*)-*N*-*p*-Methylphenyl-3-[(2′-oxo-2′-*p*-methoxyphenyl)ethylidene] isoindolin-1-one 31

Yield 59%. Light yellow needles (EtOH), m.p. 167-170°C; [Found: C, 77.8; H, 5.2; N, 3.5. $C_{24}H_{19}NO_3$ requires C, 78.03; H, 5.18; N, 3.79%]; R_f (5% EtOAc/$CHCl_3$) 0.38; ν_{max} (KBr) 3000, 1690, 1655, 1600, 1590, 1260, 1240, 1210, 1170, 980, 810, 760 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.09-8.04 (1H, m, Ar-H), 7.98 (2H, d *J* 8.77 Hz, Ar-H), 7.85-7.78 (1H, m, Ar-H), 7.64-6.68 (2H, m, Ar-H). 7.51 (2H d *J* 8.1 Hz, Ar-H), 7.17 (2H, d *J* 8.1 Hz, Ar-H), 6.95 (2H, d *J* 9.0 Hz, Ar-H), 6.62 (1H, s, =CH), 3.87 (3H, s, OMe), 2.33 (3H, s, Me).

(*Z*)-*N*-*p*--Methoxyphenyl-3-[(2′-oxo)propylidene] isoindolin-1-one 32

Yield 56%. Light yellow powder (EtOH), m.p. 178-181°C; [Found: C, 74.0; H, 5.0; N, 4.8. $C_{18}H_{15}NO_3$ requires C, 73.71; H, 5.15; N, 4.77%]; R_f (5% EtOAc/$CHCl_3$) 0.30; ν_{max} (KBr) 3000, 1690, 1660, 1640, 1510, 1300, 1250, 1170, 1020, 960, 830, 760, 670 cm^{-1}; λ_{max} (EtOH) 374 (log ε 3.97), 286 (4.10), 258 (4.18), 248 (4.20), 224 (4.35) nm; δ_H (300 MHz, $CDCl_3$) 8.03-8.00 (1H, m, Ar-H), 7.69-7.62 (3H, m, Ar-H), 7.57-7.52 (2H, m, Ar-H), 6.93-6.47 (2H, m, Ar-H), 5.94 (1H, s, =CH), 3.85 (3H, s,OMe), 2.54 (3H, s, Me).

(*E*)-*N*-*p*-Methoxyphenyl-3-[(2′-oxo-2′-phenyl)ethylidene] isoindolinone 33

Yield 76%. Light yellow small needles (EtOH), m.p. 172-175°C; [Found: C, 77.4; H, 4.7; N, 4.0. $C_{23}H_{17}NO_3$ requires C, 77.73; H, 4.82; N, 3.94%]; R_f (5% EtOAc/$CHCl_3$) 0.40; ν_{max} (KBr) 3000, 1725, 1650, 1600, 1585, 1510, 1410, 1300, 1250, 1180, 1020, 830, 770, 640 cm^{-1}; λ_{max} (EtOH) 336 (4.09), 301 (4.14), 231 (4.48) nm; δ_H (300 MHz, $CDCl_3$) 8.96 (1H, d *J* 7.2 Hz, Ar-H), 7.94 (1H, d *J* 6.6 Hz, Ar-H), 7.92-7.82 (2H, m, Ar-H), 7.74-7.62 (2H, m, Ar-H), 7.55-7.39 (3H, m, Ar-H), 7.34-7.29 (2H, m, Ar-H), 7.12-7.06 (2H, m, Ar-H), 6.54 (1H s, =CH), 3.88 (1H, s, OMe); δ_C (75.5 MHz, $CDCl_3$), 189.7, 167.3, 159.8, 150.1, 139.0, 133.8, 133.5, 132.8, 131.8, 129.9 129.7, 128.6, 128.2, 127.3, 126.2, 123.5, 115.1, 105.3, 55.5.

(*E*)-*N*-*p*-Methoxyphenyl-3-[(2′-oxo-2′-*p*-methylphenyl)ethylidene] isoindolin-1-one 34

Yield 66%. Light yellow needles (EtOH), m.p. 175-176°C; [Found: C, 77.8; H, 5.2; N, 3.7. $C_{24}H_{19}NO_3$ requires C, 78.03; H, 5.18; N, 3.79%]; R_f (5% EtOAc/$CHCl_3$) 0.35; ν_{max} (KBr) 3000, 1720, 1650, 1610, 1580, 1510, 1300, 1250, 1180, 1030, 1020, 740, 700 cm^{-1}; λ_{max} (EtOH) 335 (log ε 4.20), 302 (4.24), 230 (4.56) nm; δ_H (300 MHz, $CDCl_3$) 8.93 (1H, d *J* 7.5 Hz, Ar-H), 7.93 (1H, d *J* 7.8 Hz, Ar-H), 7.75-7.64 (4H, m, Ar-H), 7.33-7.30 (2H, m, Ar-H), 7.22 (2H, d, *J* 7.8 Hz, Ar-H), 7.10-7.07 (2H, m, Ar-H), 6.52 (1H, s, =CH), 3.88 (3H, s, OMe), 2.39 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) 189.5, 167.3, 159.8, 149.7, 143.7, 136.5, 133.9, 133.4, 131.7, 129.9, 129.8,

129.3, 128.3, 126.3, 123.5, 115.1, 105.5, 55.5, 21.6; DEPT-135 : 133.61, 131.87, 130.10, 129.46, 128.52, 127.48, 123.68, 115.27 (Ar-CH), 105.74 (=CH-), 55.70 (OMe), 21.79 (N-Me).

(*Z*)-*N*-*p*-Methoxyphenyl-3-[(2′-oxo)propylidene] isoindolin-1-one 35

The compound **35** was obtained from the Friedel-Crafts reaction of 2-trimethylsilyl ethynyl-*N*-*p*-methoxyphenyl benzamide with acetic anhydride and was found identical with compound **32**.

(*Z*)-*N*-*m*-Chlorophenyl-3-[(2′-oxo)propylidene] isoindolin-1-one 36

Yield 52%. Light yellow needles (EtOH), m.p. 178-180°C; [Found: C, 68.8; H, 4,2; N, 4.9. $C_{17}H_{12}ClNO_2$ requires C, 68.58; H, 4.06; N, 4.70%]; R_f (5% EtOAc/$CHCl_3$) 0.50; ν_{max} (KBr) 3040, 1700, 1660, 1630, 1590, 1465, 1265, 985, 780, 670 cm^{-1}; λ_{max} (EtOH) 325 (logε 4.08), 274 (4.50), 265 (4.33) nm; δ_H (300 MHz, $CDCl_3$) 8.06-8.03 (1H, m, Ar-H), 7.70-7.69 (3H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.36-7.18 (3H, m, Ar-H), 5.95 (1H, s, =CH), 2.48 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) δ 196.1, 156.4, 145.7, 135.9, 134.2, 132.9, 130.1, 129.7, 125.5, 124.1, 123.8, 122.0, 121.2, 102.6, 30.9.

(*Z*)-*N*-*m*-Chlorophenyl-3-[(2′-oxo-2′-*p*-methylphenyl)ethylidene] isoindolin-1-one 37

Yield 84%. Light yellow needles (EtOH), m.p. 157-158°C; [Found: C, 73.5; H, 4.5; N, 3.6. $C_{23}H_{16}ClNO_2$ requires C, 73.89; H, 4.31; N, 3.74%]; R_f (5% EtOAc/$CHCl_3$) 0.53; ν_{max} (KBr) 3000, 1725, 1655, 1610, 1590, 1450, 1430, 1350, 1225, 1180, 1090, 1020, 860, 780, 700, 640 cm^{-1}; λ_{max} (EtOH) 341 (log ε 4.29), 281 (4.44) nm; δ_H (300 MHz, $CDCl_3$) 8.04-8.01 (1H, m, Ar-H), 7.87 (2H, d *J* 8.7 Hz, Ar-H), 7.84-7.81 (1H, m, Ar-H), 7.69-7.67 2H, m, Ar-H), 7.56-7.48 (2H, m, Ar-H), 7.30-7.17 (4H, m, Ar-H), 6.66 (1H, s, =CH), 2.42 (3H, s, Me); δ_C (75.5 MHz, $CDCl_3$) 189.1, 157.2, 153.0, 145.6, 143.9, 136.7, 134.7, 133.1, 132.6, 131.6, 129.6, 128.9, 126.4, 124.5, 123.6, 121.5, 98.0, 22.1.

(*E*)-*N*-*m*-Chlorophenyl-3-[(2′-oxo-2′-*p*-methoxyphenyl)ethylidene] isoindolin-1-one 38

Yield 86%. Light yellow small needles (EtOH), m.p. 179-181°C; [Found: C, 70.5; H, 4.0; N, 3.9. $C_{23}H_{16}ClNO_3$ requires C, 70.86; H, 4.14; N, 3.59%]; R_f (5% EtOAc/$CHCl_3$) 0.45; ν_{max} (KBr) 3000, 1725, 1650, 1600, 1580, 1480, 1350, 1245, 1180, 1025, 830, 700, 610 cm^{-1}; λ_{max} (EtOH) 350 (log ε 4.30), 292 (4.09), 228 (4.30) nm; δ_H (300 MHz, $CDCl_3$) 8.83 (1H, d *J* 7.5 Hz, Ar-H), 7.96 (1H, d *J* 7.2 Hz, Ar-H), 7.84 (2H, d *J* 9.0 Hz, Ar-H), 7.77-7.45 (5H, m, Ar-H), 7.33 (1H, dd *J* 1.8, 7.0 Hz, Ar-H), 6.93 (2H, d *J* 9.0 Hz, Ar-H), 6.50 (1H s, =CH),

3.86 (3H, s, OMe); δ_C 188.4, 166.7, 163.5, 148.1, 135.3, 135.1, 133.8, 133.6, 131.7, 131.6, 131.0, 130.8, 130.6, 129.3, 129.2, 127.2, 122.1, 123.6, 113.8, 105.9, 55.5.

_N_-Methyl-3-[(2′-oxo-2′-phenyl)ethyl] isoindolin-1-one 39

White powder (MeOH), m.p. 114-115°C; [Found: C, 76.7; H, 5.7; N,5.5. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.69; N, 5.27%]; ν_{max} (KBr) 3000, 1695, 1680, 1600, 1450, 1400, 1220, 760, 700; cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.94 (1H, d *J* 9.0 Hz, Ar-H), 7.85 (1H, d *J* 6.0 Hz, Ar-H), 7.60-7.40 (6H, m, Ar-H), 5.22 (1H, t *J* 6.0 Hz, C-3H), 3.52 (1H, dd *J* 6, 18 Hz, CH_2), 3.25 (1H, dd *J* 6, 18 Hz, Me), 3.12 (3H, s, N-Me); δ_C (75.5 MHz, $CDCl_3$) 197.4, 168.3, 145.5, 136.3, 133.9, 132.0, 131.6, 128.9, 128,4, 128.1, 123.6, 122.6, 57.7, 41.8, 27.8. DEPT-135 : 134.0,131.7,129.0,128.5, 128.2, 123.7, 122.8 (Ar-CH), 57.8 (C-3H), 42.0 (CH_2, inverted), 28.1 (N-Me).

_N-p_-Methoxyphenyl-3-[(2′-oxo-2′-_p_-methyl phenyl)ethyl] isoindolin-1-one 40

Colourless small needles (EtOH), m.p. 153-155°C; [Found: C, 77.2; H, 5.5; N, 3.4. $C_{24}H_{21}NO_3$ requires C, 77.60; H, 5.69; N, 3.77%]; ν_{max} (KBr) 2990, 1695, 1665, 1610, 1515, 1400, 1250, 1150, 1040, 840, 820, 750, 700; δ_H (300 MHz, $CDCl_3$) 7.93-7.90 (1H, m, Ar-H), 7.75 (2H, d *J* 9.0 Hz, Ar-H), 7.52-7.45 (5H, m, Ar-H), 7.25 (2H, d *J* 6.0 Hz, Ar-H), 6.92 (2H, d *J* 9.0 Hz, Ar-H), 5.80 (1H, dd *J* 3,9 Hz, C-3H), 3.99 (3H, s, Ar-OMe), 3.40 (1H, dd *J* 3,18 Hz, CH_2), 3.12 (1H, dd *J* 9, 18 Hz, CH_2), 2.35 (3H, s, Ar-Me); δ_C (75.5 MHz, $CDCl_3$) 197.3, 166.9, 156.5, 145.3, 144.7, 133.9, 132.1, 131.9, 129.4, 128.6, 128.2, 125.3, 124.0, 123.2, 114.5, 57.5, 55.5, 41.7, 21.6. DEPT-135: 132.2, 129.5, 128.7, 128.3, 125.4, 124.1, 123.3, 114.7 (Ar-CH), .57.6 (C-3H), 55.6 (Ar-OMe), 41.9 (CH_2, inverted), 21.8 (Ar-Me).

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