Pergamon

Tetrahedron 56 (2000) 4777–4792

TETRAHEDRON

Palladium-Catalysed Heteroannulation with Terminal Alkynes: a Highly Regio- and Stereoselective Synthesis of (*Z*)-3-Aryl(alkyl)idene Isoindolin-1-ones[1]

Nitya G. Kundu* and M. Wahab Khan

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

Dedicated to the late Professor P. C. Dutta, Head (1951–1977), Department of Organic Chemistry, IACS, Jadavpur on the occasion of the Golden Jubilee celebration of the Department

Received 28 October 1999; revised 4 April 2000; accepted 20 April 2000

Abstract—A highly regio- and stereoselective method for the synthesis of (*Z*)-3-aryl(alkyl)idene isoindolin-1-ones through palladium-copper catalysis is described. 2-Iodobenzamide **1** and its substituted derivatives **2**–**10** were reacted with terminal alkynes **11**–**19** in the presence of $(PPh_3)_2PdCl_2$, CuI, and Et_3N in DMF mostly at 80°C for 16 h to yield the 2-alkynyl substituted benzamides **20**–**38**, **40**–**45**, **77** which could then be cyclised with NaOEt in EtOH to the 3-aryl(alkyl)idene isoindolin-1-ones **46**–**49**, **51**, **53**–**55**, **57**, **59**–**71**, **73** and **75**. In certain cases, the isoindolin-1-ones **50**, **52**, **56** and **58** could be directly obtained by the palladium-catalysed reactions.

Introduction

Isoindoline (2,3-dihydro-*1H*-isoindole) **Ia** and isoindolin-1-one or 2,3-dihydro-*1H*-isoindol-1-one (phthalimidine) **Ib**, moieties are an integral part of some naturally products. For example, chilenine(**II**), lennoxamine(**III**) and other isoindolobenzazepines, nuevamine(**IV**), an isoindoloisoquinoline and magallanesine(**V**), an isoindolobenzazocine have been isolated by Shamma and co-workers[3] from various Berberis species. Similarly, staurosporine(**VI**), an alkaloid containing the isoindolinone moiety, isolated from a saccharothrise sp. has antimicrobial, hypotensive and cytotoxic activities.[4] Also, cytochalasins(**VII**) containing a perhydro isoindolone ring fused to an 11 to 14 membered macrocyclic ring have been isolated from varieties of molds and microorganisms.[5] Naturally occurring and synthetic isoindolin-1-ones have a range of biological activities[6] including antihypertensive,[7] antipsychotic,[8] antiinflammatory,[9] anesthetic,[10] antiulcer,[11] vasodilatory,[12] antiviral,[13] and antileukemic[14] properties. A number of isoindolin-1-ones have been found to be potent herbicides.[15] Isoindolin-1-ones have also been extensively used for the synthesis of various drugs[16,17] and naturally occurring compounds (Fig. 1).[18]

A number of methods have been developed for the synthesis of isoindolines and isoindolinones (phthalimidines). They fall under the following categories: (I) high temperature procedures based on Gabriel's method[19] for the synthesis of phthalides and phthalimidines, involving the reaction of phthalides with substituted amines[20] or the reaction of phthalimides with aryl acetic acids;[21] (ii) a Grignard procedure;[22] (iii) lithiation procedures;[23] (iv) Wittig reactions on phthalimides or benzamides;[24] (v) Diels–Alder reactions;[14,25] (vi) reduction[26] of N-substituted phthalimides to the corresponding phthalimidines; (vii) condensation of phthalaldehyde with phenyl isocyanate, amines, α-amino-acids;[27] boroxazolidenes,[28] or iminophosphoranes;[29] (viii) rearrangement reactions of benzofurans or phthalides;[18d,30] (ix) photochemical reactions[31] and (x) miscellaneous procedures.[32,33] Besides the above classical methods, several metal (e.g. cobalt or rhodium carbonyl complexes) mediated syntheses of isoindolinones have also been reported,[34] but few examples of palladium catalysis[35] have appeared.

Palladium-catalysed reactions[36] have been extensively utilised for carboannulation[37] and heteroannulation.[38] Aromatic heterocycles can be accessed via palladium-catalysed annulation of internal alkynes[39] and palladium-catalysed cyclisations allow synthesis of a wide variety of heterocycles[40] using vinylic compounds, terminal alkynes and allenes. We have developed methods for the synthesis of benzofurans,[41a] and phthalides[41b] by palladium catalysed reactions with terminal alkynes. In continuation of these studies we became interested in the palladium-catalysed heteroannulation for the synthesis of isoindolinones.[1,42]

Keywords: isoindolinones; heteroannulation; palladium-catalysis; terminal alkynes.

* Corresponding author. Fax: +91-33-473-2805;
e-mail: ocngk@mahendra.iacs.res.in

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00359-8

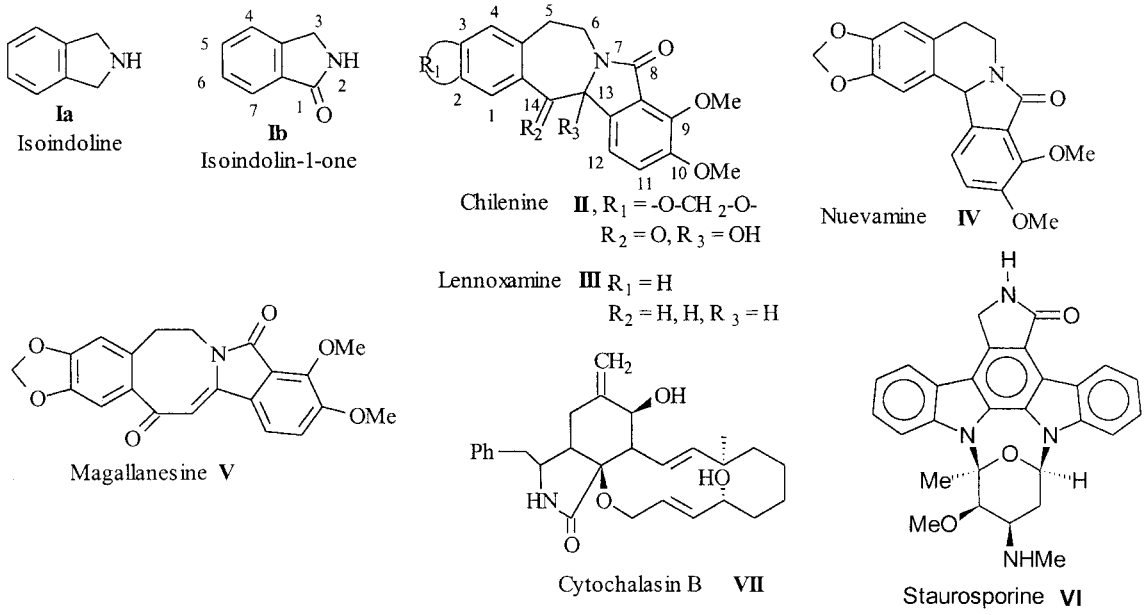
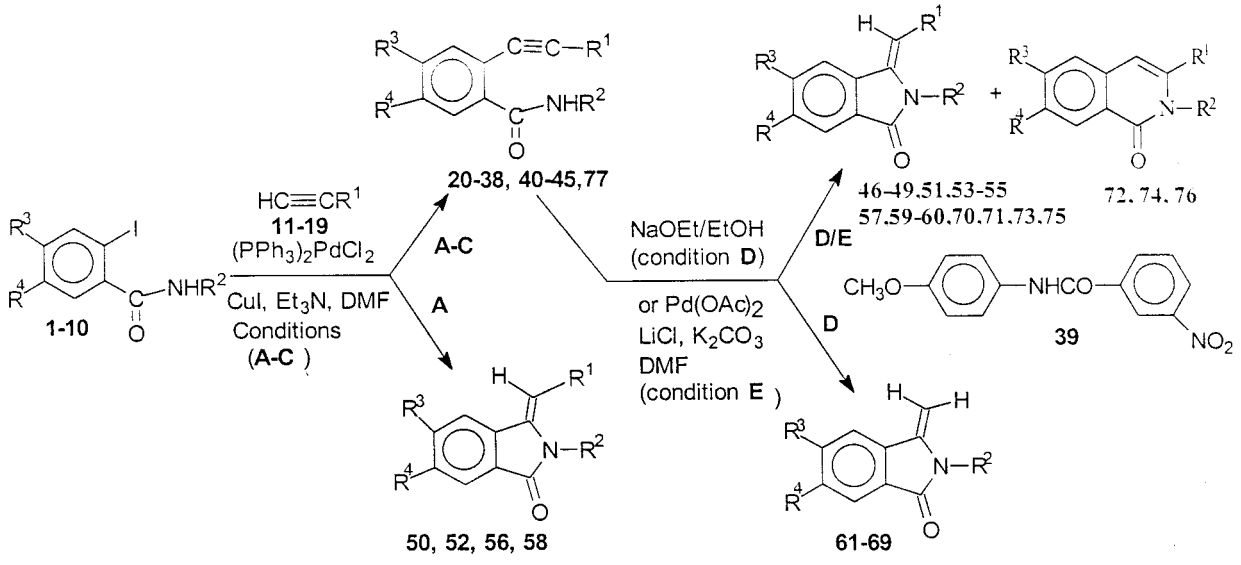


Figure 1.

Results and Discussion

We now report a new strategy for the regio and stereoselective synthesis of isoindolinones **46–71**, **73**, **75** through the palladium-catalysed condensation of *o*-iodobenzamides **1–10** with terminal alkynes **11–19** and subsequent cyclisation (Scheme 1).

Our results (Table 1) demonstrate that a number of (*Z*)-3-aryl(alkyl)idene isoindolin-1-ones were formed without any



Compounds	R^2	R^3	R^4	Compounds	R^1
1, 20, 27, 30, 32, 46, 54, 59, 61	H	H	H	**11, 20-26, 46-53**	Ph
2, 21, 31, 33, 45, 47, 60, 62, 75, 76	CH_3	H	H	**12, 27- 29, 54-57, 77**	C_6H_4OMe-*p*
3, 22, 28, 34, 48, 55, 63	CH_2Ph	H	H	**13, 58**	2,4-dimethoxy pyrimidin-5-yl
4, 23, 35, 49, 64	Ph	H	H	**14, 30, 59**	C_6H_4Cl-*m*
5, 24, 36, 42, 43, 50, 65, 70, 71, 72	C_6H_4Me-*p*	H	H	**15, 31, 60**	1-naphthyl
6, 25, 37, 44, 51, 56, 66, 73, 74, 77	C_6H_4OMe-*p*	H	H	**16, 32-38, 40, 41**	$SiMe_3$
7, 38, 52, 58, 67	C_6H_4Cl-*m*	H	H	**17, 42, 70**	CMe_2OH
8, 39	C_6H_4OMe-*p*	H	NO_2	**18, 43, 71, 72**	CH_2OH
9, 29, 40, 57, 68	CH_3	OCH_3	OCH_3	**19, 44, 45, 73, 74, 75, 76**	n-hexyne
10, 26, 41, 53, 69	C_6H_4Me-*p*	H	OH	**61-69**	H

Scheme 1.

Table 1. Palladium-catalysed reactions of 2-iodobenzamides (**1**–**10**) with terminal alkynes (**11**–**19**) leading to isoindolinones **46**–**71**, **73**, **75** and isoquinolinones **72**, **74** and **76** (Scheme 1) (R^3=R^4=H, except compounds **8**, **9**, **10**, **26**, **29**, **40**, **41**, **53**, **57**, **68** and **69** (Scheme 1))

Entry	2-Iodobenzamide (R^2)	Alkynes (R^1)	Conditions	2-Alkynyl benzamides [%][a]	Conditions	Isoindolinones +Isoquinolinones[b]	Yield (%)[a]
1	**1** (H)	**11** (Ph)	A	**20** [70]	D	**46**	50
2	**2** (CH_3)	**11** (Ph)	A	**21** [68]	D	**47**	52
3	**3** (Ch_2Ph)	**11** (Ph)	A	**22** [77]	D	**48**	60
4	**4** (Ph)	**11** (Ph)	A	**23** [67]	D	**49**	41
5[c]	**5** (C_6H_4Me-*p*)	**11** (Ph)	A	**24** [32]	-	**50**	34
6	**6** (C_6H_4OMe-*p*)	**11** (Ph)	A	**25** [91]	D	**51**	77
7[d]	**7** (C_6H_4Cl-*m*)	**11** (Ph)	A	-	-	**52**	86
8[e]	**10** (C_6H_4Me-*p*)	**11** (Ph)	A	**26** [43]	D	**53**	20
9	**1** (H)	**12** (C_6H_4OMe-*p*)	A	**27** [78]	D	**54**	75
10	**3** (CH_2Ph)	**12** (C_6H_4OMe-*p*)	A	**28** [83]	D	**55**	65
11[d]	**6** (C_6H_4OMe-*p*)	**12** (C_6H_4OMe-*p*)	A	-	-	**56**	82
12[e]	**9** (CH_3)	**12** (C_6H_4OMe-*p*)	A	**29** [91]	D	**57**	55
13[d]	**7** (C_6H_4Cl-*m*)	**13** (2,4-Dimethoxy pyrimidin-5-yl)	A	-	-	**58**	81
14	**1** (H)	**14** (C_6H_4Cl-*m*)	A	**30** [65]	D	**59**	50
15	**2** (CH_3)	**15** (1-Naphthyl)	A	**31** [50]	D	**60**	50
16	**1** (H)	**16** ($SiMe_3$)	B	**32** [77]	D	**61**	65
17	**2** (Me)	**16** ($SiMe_3$)	B	**33** [78]	D	**62**	66
18	**3** (CH_2Ph)	**16** ($SiMe_3$)	B	**34** [74]	D	**63**	61
19	**4** (Ph)	**16** ($SiMe_3$)	B	**35** [71]	D	**64**	67
20	**5** (C_6H_4Me-*p*)	**16** ($SiMe_3$)	B	**36** [82]	D	**65**	71
21	**6** (C_6H_4OMe-*p*)	**16** ($SiMe_3$)	B	**37** [96]	D	**66**	76
22	**7** (C_6H_4Cl-*m*)	**16** ($SiMe_3$)	B	**38** [87]	D	**67**	70
23[e,f]	**8** (C_6H_4OMe-*p*)	**16** ($SiMe_3$)	B	-	D	-	-
24[e]	**9** (CH_3)	**16** ($SiMe_3$)	B	**40** [91]	D	**68**	64
25[e]	**10** (C_6H_4Me-*p*)	**16** ($SiMe_3$)	B	**41** [86]	D	**69**	42
26	**5** (C_6H_4Me-*p*)	**17** (CMe_2OH)	B	**42** [75]	**E**	**70**	60
27[g]	**5** (C_6H_4Me-*p*)	**18** (CH_2OH)	C	**43** [81]	**E**	**71**+**72**[b]	60 (3:7)
28[g]	**6** (C_6H_4OMe-*p*)	**19** $(CH_2)_3CH_3$	B	**44** [92]	D	**73**+**74**[b]	61 (7:3)
29[g]	**2** (CH_3)	**19** $(CH_2)_3CH_3$	B	**45** [92]	D	**75**+**76**[b]	65 (1:1)

[a] Yields are based on 2-iodobenzamides.
[b] Isoquinolinones.
[c] Mixures of 2-alkyl benzamide **24** and isoindolin-1-one **50** was obtained.
[d] Isoindolin-1-ones were obtained directly in one step in excellent yields.
[e] 2-Iodo-5-nitro-*N*-*p*-anisyl benzamide **8**; 2-iodo-4,5-dimethoxy-*N*-methyl benzamide **9**; 2-iodo-5-hydroxy-*N*-*p*-tolyl benzamide **10**.
[f] The de-iodinated amide **39** was obtained.
[g] Mixtures of isoindolinones and isoquinolinones were obtained after cylisation.

formation of the corresponding isoquinolinones except in case of entries 27–29 where mixtures of isoindolinones and isoquinolinones were obtained.

The reactions were usually carried out by heating a mixture of 2-iodobenzamide or its *N*-substituted derivatives **1**–**10** (1 mmol) and alkynes **11**–**19** (1.2 mmol) in DMF (5 mL) at 80°C for 16 h in the presence of bis(triphenylphosphine)-palladium(II) chloride (2.5 mol%), copper(I) iodide (8 mol%)[43] and triethylamine (4 mmol) (entries 1–15, condition A).

However, with (trimethylsilyl)acetylene **16**, dimethyl-propargyl alcohol **17** and *n*-hexyne **19**, 2.0 equiv. of the alkyne were used and the reactions were performed at room temperature for 24 h (entries 16–25, 28, 29, condition B). In the case of entries 5,7,11 and 13 the cyclised products, e.g. the isoindolinones **50**, **52**, **56** and **58** were obtained directly usually in excellent yields. In the case of entry 5, the cyclic product **50** (34%) was obtained together with the acyclic product **24** (32%). But in other cases (all entries except 5, 7, 11, 13) the open chain condensation products **20**–**38**, **40**–**45** were the major products which were cyclised in the same pot, after removal of solvent, by refluxing with sodium ethoxide in ethanol (condition D) for 4 h to afford the isoindolinones **46**–**49**, **51**, **53**–**55**, **57**, **59**–**69**, **73**, **75**, respectively in good yields. The cyclisation was also carried out with pure open chain products which were isolated and characterised completely. The yields of the cyclised products were almost the same in both cases. In the case of entry 23 where there was a NO_2 group present in the iodobenzamide moiety, only the deiodinated amide **39** was obtained.

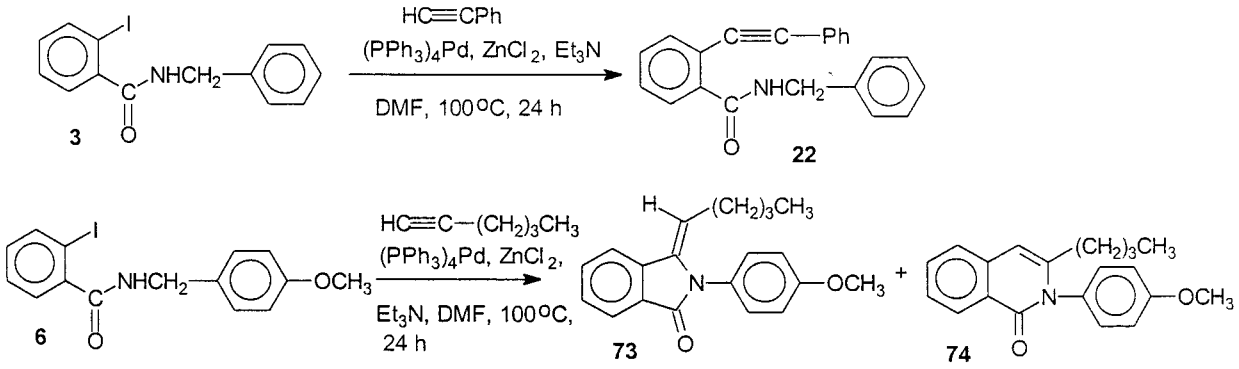
When trimethylsilyl acetylene **16** was used as the alkyne (entries 16–25), the trimethylsilyl group was completely removed under the cyclisation condition D to afford 3-methylene isoindolinones **61**–**69**. During the reaction with propargyl alcohol **18**, the reaction mixture was heated at 60°C for 6 h (entry 27, condition C) to yield the acyclic product **43**. The cyclisation was also carried out by heating the open chain condensation products **42**, and **43** (1 mmol) (entries 26, 27) with palladium(II) acetate (5 mol%), LiCl (1 mmol) and K_2CO_3 (2.5 mmol) in DMF (5 mL) for 16 h at 100°C[39a] (condition E).

Role of catalysts

In general for the palladium-catalysed reactions of 2-iodo-benzamides with alkynes we have used the same catalyst

Table 2. Effects of catalyst, co-catalyst, solvent, base and temperature on the palladium-catalysed reactions of 2-iodobenzamides with terminal alkynes

Entry	2-Iodobenzamides (R^2)	Alkynes (R^1)	Catalyst	Co-catalyst	Solvent/Base	Conditions T (°C); *t* (h)	Compounds	Yield (%)
1	**6**(C_6H_4OMe-*p*)	**11** (Ph)	$Pd(OAC)_2$	CuI	DMF, Et_3N	80; 16	**25**	55
2	**6**(C_6H_4OMe-*p*)	**11** (Ph)	$Pd(OAC)_{2,}$	CuI	DMF, Et_3N	80; 16	**25**	79
3	**3**(CH_2Ph)	**11** (Ph)	PPh_3	$ZnCl_2$	DMF, Et_3N	100; 24	**22**	65
4	**6**(C_6H_4OMe-*p*)	**19** $(CH_2)_3CH_3$	$(PPh_3)_4Pd$	$ZnCl_2$	DMF, Et_3N	100; 24	**73**+**74** (1:1)	62
5	**6**(C_6H_4OMe-*p*)	**11** (Ph)	$(PPh_3)_4Pd$	-	DMF, Et_3N	80; 16	**25**	71
6	**6**(C_6H_4OMe-*p*)	**11** (Ph)	-	CuI	DMF, Et_3N	80; 16	**25**	10
7	**3**(CH_2Ph)	**11** (Ph)	$(PPh_3)_4PdCl_2$-	$ZnCl_2$	DMF, Et_3N	100; 24	**48**	21
8	**6**(C_6H_4OMe-*p*)	**11** (Ph)	$(PPh_3)_4PdCl_2$	CuI	DMF, Et_3N	80; 16	**25**	30
9	**6**(C_6H_4OMe-*p*)	**11** (Ph)	$(PPh_3)_4PdCl_2$	CuI	DMSO-H_2O (1:1), Et_3N	80; 16	**25**	10
10	**6**(C_6H_4OMe-*p*)	**11** (Ph)	$(PPh_3)_4PdCl_2$	CuI	DMF, $NaHCO_3$	80; 16	**25**	20
11	**5**(C_6H_4Me-*p*)	**11** (Ph)	$(PPh_3)_4PdCl_2$	CuI	DMF, K_2CO_3	80; 16	-	-
12	**5**(C_6H_4Me-*p*)	**11** (Ph)	$(PPh_3)_4PdCl_2$	CuI	DMF, Et_3N	rt; 24	**24**	35
13	**6**(C_6H_4OMe-*p*)	**12** (C_6H_4OMe-*p*)	$(PPh_3)_4PdCl_2$	CuI	DMF, Et_3N	rt; 24	**77**	90
14	**6**(C_6H_4OMe-*p*)	**11** (Ph)	$(PPh_3)_4PdCl_2$	CuI	DMF, Et_3N	rt; 24	**25**	40



Scheme 2.

system e.g. $(PPh_3)_2PdCl_2$ (3.5 mol%) with CuI (8 mol%) as a co-catalyst, which we utilised for the heteroannulation of terminal alkynes to benzofurans[41a] and phthalides,[41b] was found to be the catalyst of choice. The palladium-catalysed reactions of 2-iodo-*N*-*p*-anisyl benzamide **6** with the alkyne **11** in the presence of $Pd(OAc)_2$ (5 mol%) and copper(I) iodide (5 mol%) under the same reaction conditions gave **25** in 55% yield (Table 2, entry 1). The addition of 5 mol% of PPh_3 to the above reaction increased the yield to 79% (Table 2, entry 2) indicating the importance of PPh_3 as a ligand. We have also carried out the palladium-catalysed reactions of 2-iodobenzamides with terminal alkynes in the presence of tetrakis(triphenyl phosphine) palladium(0), Et_3N and $ZnCl_2$ in DMF at 100°C (Scheme 2).[44] Usually, the yield of the 2-alkynylated product **22** was higher (77%) from the reaction with $(PPh_3)_2PdCl_2$ and CuI than the yield of **22** (65%) with $(PPh_3)_4Pd$ and $ZnCl_2$ (Table 1, entry 3 *vs* Table 2, entry 3). In one case, the $ZnCl_2$ method yielded a mixture of isoindolinone **73** and isoquinolinone **74** (Table 2, entry 4) whereas with $(PPh_3)_2PdCl_2$ and CuI, the same reaction yielded the 2-alkynylated product **44** only (Table 1, entry 28) which could then be cyclised to a 7:3 mixture of **73** and **74**.

Role of co-catalysts

The *o*-alkynylated benzamide **25** was obtained from 2-iodo-*N*-*p*-anisyl benzamide **6** in 91% yield (Table 1, entry 6) in the presence of $(PPh_3)_2PdCl_2$ and with CuI as a co-catalyst. However, in the absence of CuI, the yield of **25** dropped to 71% (entry 5, Table 2). When the reaction was carried out only with CuI, without any palladium-catalyst, the yield was significantly lower (10%) (Table 2, entry 6). The use of $ZnCl_2$ instead of CuI as co-catalyst gave the cyclised product **48** in 21% yield with the starting material **3** being recovered (Table 2, entry 7).

Role of solvent

Palladium-catalysed reactions have been reported in Et_3N as a solvent and a base, but 2-iodobenzamides were sparingly soluble in Et_3N and did not undergo reaction in it. DMF was found to be the solvent of choice where yields of 60–96% were obtained. The use of other solvents e.g. DMSO, DMSO–water (1:1) led to poorer yields (10–30%) (Table 2, entries 8, 9), compared with 91% yield in DMF (Table 1, entry 6).

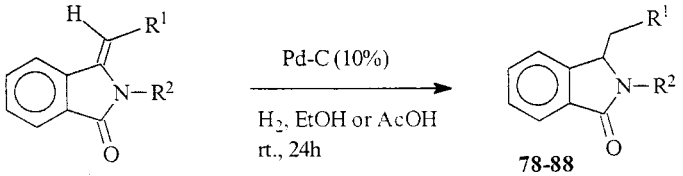
Role of base

Triethylamine was the base of choice as was observed previously.[41] The effects of other bases e.g. $NaHCO_3$ and K_2CO_3 were investigated (Table 2, entries 10 and 11). The use of $NaHCO_3$ instead of Et_3N under the same reaction conditions afforded a poorer yield (20%) while in the presence of K_2CO_3 no reaction occurred under the same conditions (condition A).

Effects of substituents in the acetylenic compounds and 2-iodobenzamides

In order to explore the effects of substituents on the iodobenzamide moiety we have used 2-iodobenzamide, *N*-substituted benzamides and also substituents on the benzene ring of benzamides **1**–**10** and obtained different results under the same reaction conditions. For example the reaction of phenylacetylene with *N*-*p*-methylphenyl-2-iodobenzamide **5** and *N*-*m*-chlorophenyl-2-iodobenzamide **7** afforded isoindolinones **50**, and **52** directly but 2-iodobenzamide **1**, *N*-methyl-2-iodobenzamide **2** and *N*-benzyl-2-iodobenzamide **3** gave only the open chain condensation products **20**–**22** (Table 1, entries 5, 7, vs. entries 1,2,3) under the same reaction conditions. Treatment of *p*-methoxyphenylacetylene with *N*-*p*-methoxyphenyl-2-iodobenzamide **6** yielded isoindolinone **56** in one step but 2-iodobenzamide **1** and *N*-benzyl-2-iodobenzamide **3** afforded only the acyclic products **27**, and **28** respectively (Table 1, entry 11 vs. entries 9, 10). It appears that in order to get the isoindolinones in one step, the presence of an aryl substituent on the nitrogen atom of the benzamide moiety and in the terminal alkyne is an essential requirement.

The substituents on the benzene ring of 2-iodobenzamide have an effect. *N*-Methyl-2-iodo-4,5-dimethoxybenzamide **9** and *N*-*p*-methylphenyl-2-iodo-5-hydroxybenzamide **10** on reaction with trimethylsilylacetylene yielded the acyclic products in 91% and 86% yield respectively (Table 1, entries 24, 25). Treatment of *p*-anisyl acetylene with *N*-methyl-2-iodo-4,5-dimethoxybenzamide **9** afforded an excellent yield of **29** (91%) (Table 1, entry 12). However, the reaction of *N*-*p*-methoxyphenyl-2-iodo-5-hydroxybenzamide **10** with phenylacetylene gave very poor yield (43%) (Table 1, entry 8) under the same reaction conditions. The reaction of *N*-*p*-anisyl-2-iodo-5-nitrobenzamide **8** with



46,48,49,51,52,55, 63,65-67,70

78-88

Compound	R^1	Compound	R^2
63, 65-67, 78-81	H	**46, 83**	H
46, 48, 49, 51, 52, 83-87	Ph	**48, 55, 63, 78, 84, 88**	CH_2Ph
55, 88	C_6H_4OMe-*p*	**49, 85**	Ph
70, 82	CMe_2OH	**65, 70, 79, 82**	$C_6H_4CH_3$-*p*
		51, 66, 80, 86	$C_6H_4OCH_3$-*p*
		52, 67, 81, 87	C_6H_4Cl-*m*

Scheme 3.

trimethylsilyl acetylene gave only the de-iodinated product **39** (Table 1, entry 23).

Similarly, we have observed the effect of substituents in the acetylenic compounds on these. For example, the reaction of 2-iodobenzamides with *p*-methoxy phenylacetylene was found to be slightly better than the reaction with phenyl acetylene (Table 1, entry 9 vs. entry 1) and the reaction of *N*-benzyl 2-iodobenzamide with *p*-methoxyphenylacetylene afforded a better yield than with phenylacetylene (Table 1, entry 10 vs. entry 3). The heteroannulation reaction of *N*-*p*-anisyl-2-iodobenzamide with *p*-methoxyphenyl acetylene gave isoindolinone **56** but with phenylacetylene yielded the acyclic product **25** (Table 1, entry 11 vs. entry 6). *N*-*m*-Chlorophenyl-2-iodobenzamide underwent the heteroannulation reaction with 2,4-dimethoxy pyrimidin-5-ylacetylene affording isoindolinone **58** directly but with trimethylsilylacetylene gave the acyclic product **38** (Table 1, entry 13 vs. entry 22). Aromatic substituents on the alkyne moiety help in the palladium catalysed condensation reactions, further substitution (methoxy) on the aromatic rings augmenting the yields considerably.

It was also observed that the reactive alkynes e.g. phenylacetylene **11**, *m*-chlorophenylacetylene **14** and 1-naphthyl acetylene **15** underwent considerable dimerisation[45] during the heteroannulation reaction which led to somewhat reduced yields of products in some cases (Table 1, entries 1, 2, 14, 15).

Formation of isoquinolinones

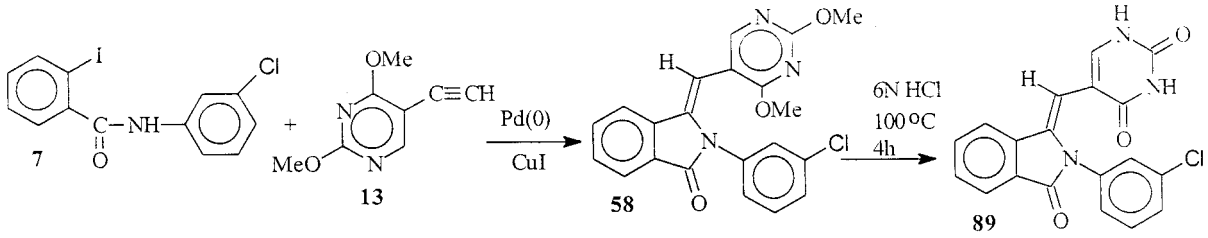
The reaction of 2-iodo-*N*-*p*-tolyl benzamide **5** with propargyl alcohol **18** under palladium-catalysis followed by cyclisation with $Pd(OAc)_2$ and LiCl (condition E) yielded isoindolinone **71** and isoquinolinone **72** (Table 1, entry 27). The reactions of 2-iodo-*N*-substituted benzamides **2** and **6** with 1-hexyne **19** under palladium-catalysis followed by refluxing with NaOEt in ethanol afforded isoindolinones **73** and **75** and isoquinolinones **74** and **76** (Table 1, entries 28 and 29). In other cases no isoquinolinones were obtained. Thus 2-iodobenzamides and aliphatic alkynes react to afford a mixture of isoindolinone and isoquinolinone but with aromatic alkynes and trimethylsilyl acetylene isoindolinones are obtained in a highly regioselective manner.

Characterization of products

The isoindolinones and open chain condensation products gave satisfactory spectroscopic (IR, UV and ^{1}H NMR) and analytical data. The structures of the cyclised products (isoindolinones) and acyclic products (2-alkynyl benzamides) were established on the basis of the following observations: (i) 2-phenylethynyl *N*-substituted benzamides **20**, **21**, **23**–**25** and 2-*p*-anisylethynyl *N*-*p*-anisyl benzamide **77** exhibited an NH proton signal in their ^{1}H NMR spectra at δ 9.15–9.3 (br s) and no olefinic proton signal; in the IR spectra C≡C stretching frequencies appeared at 2220–2210 cm^{-1}, NH stretching vibration at 3340–3280 cm^{-1} and C=O stretching vibration at 1650 cm^{-1}; UV absorption was found in the region λ_{max} 301–302 nm and 282–284 nm. (ii) 2-trimethylsilylethynyl *N*-substituted benzamides **35**–**38** displayed the following data: ^{1}H NMR spectra—NH proton signal at δ 8.0–9.2 (br s) and no olefinic proton signal; IR C≡C stretching frequency at 2150–2160 cm^{-1}, C=O streching vibration at 1660 cm^{-1} and NH stretching vibration at 3310–3340 cm^{-1} and UV absorption in the region 206–208 nm and 249 nm. The above data were absent in case of the corresponding cyclised products (e.g. isoindolinones) exhibited characteristic vinylic proton signals in the ^{1}H NMR at δ 6.40–7.05, exomethylenic proton signals as double doublets at δ 4.67–5.00 and δ 5.03–5.20 and characteristic γ—lactam IR absorption at 1700–1720 cm^{-1}.

The isoindolinones and isoquinolinones were differentiated on the basis that the physical data of our synthesized isoindolinones **46**–**48**, **54**, **55**, **71**, **73**, **75** were different from those of the corresponding known isoquinolinones[45–50] and our synthesised isoquinolinones **72**, **74**, **76**. In particular:

(i) In ^{1}H NMR spectra, 3-arylidene isoindolinones **46**–**60** exhibited a vinylic proton signal at δ 6.40–7.05 (singlet). 3-Methylene isoindolinones **61**–**69** showed characteristic exo-methylene double doublets at δ 4.67–5.00 and



Scheme 4.

5.03–5.20 (J=2 Hz); 3-(2-hydroxyethylidene)-*N*-*p*-tolyl-isoindolinone **71**, 3-pentylidene *N*-*p*-anisyl isoindolinone **73** and 3-pentylidene *N*-methyl isoindolinone **75** gave vinylic proton signals at 5.72, 5.18 and 5.30 (triplet, J=6.6 an 8.0 Hz), respectively. The corresponding isoquinolinones **72**, **74**, **76**, however showed signals for vinylic protons at δ 6.15, 5.85 and 6.36, respectively (singlet).

(ii) The carbonyl stretching frequencies of isoindolinones occur at 1700–1720 cm^{-1} (γ-lactams) but the corresponding frequencies for the isoquinolinones are at 1640–1660 cm^{-1} (δ-lactams). These observations are in accord with those reported by other workers.[7,21,22b]

(iii) Hydrogenation of 3-methylene isoindolinones **63**, **65**–**67**, afforded 3-methyl isoindolinones **78**–**81** (Scheme 3) which were also characterized by ^{1}H NMR, IR, UV and analytical data. 3-Methyl isoindolinones **78**–**81** showed characteristic signals for methyl groups in their ^{1}H NMR at δ 1.43–1.48 (d, 3H, J=6 Hz) and for the C-3H of the isoindolinone ring at δ 5.05–5.20 (q, 1H, J=6 Hz).

Hydrogenation of 3-arylidene isoindolinones **46**, **48**, **49**, **51**, **52**, **55**, gave 3-benzylisoindolinones **83**–**88** in which the chemical shift of C-3H and CH_2 of compound **84** occurred at δ 4.58 (dd, 1H, J=4.8, 7.8 Hz, C-3H), 2.84 (dd, 1H, J=7.8, 13.8 Hz, CH_2), 3.38 (dd, ^{1}H, J=4.8, 13.8 Hz, CH_2), respectively. IR absorption frequencies for C=O of the saturated isoindolinones appeared at 1690–1680 cm^{-1}. These data would not be observed for the corresponding 3,4-dihydroisoquinolinones.[51]

We have synthesised isoindolinones **46**, **47**, **49**, **51** according to the Gabriel method[19] and found their physical and chemical data are compatible with the data of the compounds synthesised by us through palladium catalysis. We have also prepared the isoindolinone **46** from the corresponding phthalide through known procedures[41b] and shown it to be identical with the compound prepared above.

We have established that all the isoindolinones have the (*Z*)-configuration by comparing them with known compounds[22b,23d] **46**, **47**, **54**. The configuration of which were established through NOE NMR experiments.[23d] Finally, the stereochemistry of the isoindolinones was confirmed by X-ray analyses of single crystals of the isoindolinones **48**, **49**, **51**, **54**, **70** which unequivocally established the *Z*-configuration.[52]

Application and prospect of our approach

Synthesis of a novel 5-substituted uracil derivative. Recently in our laboratory a number of 5-substituted uracil derivatives e.g. 5-(2-acylethynyl)uracils, 5-(2-acylvinyl)-uracils have been synthesised and found to be potent inhibitors of thymidylate synthase (TS), a crucial enzyme required for cellular multiplication processes, and also found to be effective against CCRF-CEM human lymphoblastoid cells, HT-29 colon carcinoma cells and L1210/0 mouse leukemia cells.[53] From this point of view, we have synthesised (*Z*)-3-(2,4-dimethoxypyrimidin-5-ylmethylidene)-*N*-*m*-chlorophenyl isoindolinone **58** by applying our condition A. The pyrimidine derivative **58** was demethylated in 6 N HCl at 100°C for 4 h to afford 3-(5-uracilyl)methylidene-*N*-*m*-chlorophenyl isoindolinone **89** (Scheme 4).

Scope of our methodology for the synthesis of isoindolinone of medicinal interest. Isoindolinones **90** and **91** are vasodilators,[12] 1,3-dihydro-3-(2-hydroxy-2-methylpropyl)-*2H*-isoindol-1-one **92** inhibits gastric acid secretion,[11] and 3-benzylidene isoindolinone **46** is a cytotoxic agent (Fig. 2).[14b]

These compounds can be easily synthesised by our procedures as can isoindolinones **46**, **48**, **51** and **70** (Table 1) which are very similar to these active compounds.

Thus, biologically and medicinally important isoindolinones can be synthesised in a facile manner through proper choice of terminal alkyne and *N*-substituted 2-iodobenzamide utilising our palladium mediated procedure.

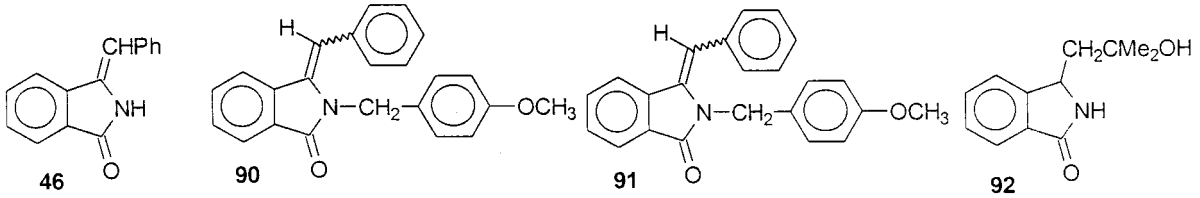


Figure 2.

Conclusion

In this paper, we have demonstrated for the first time a convenient, general, and facile method for the synthesis of 3-substituted isoindolin-1-ones from the reaction of 2-iodobenzamides with terminal alkynes by a $(PPh_3)_2PdCl_2$-CuI-Et_3N system. The most important features of the synthesis are that readily available, inexpensive starting materials are used under relatively mild reaction conditions. Also, no toxic and hazardous compounds are produced by this procedure. The reaction is highly regio- and stereoselective in case of the aromatic alkynes. By using aliphatic alkynes both isoindolinones and isoquinolinones can be synthesised in good yields. A variety of functional groups can be introduced at the 2 and 3 positions of the isoindolinone moiety by this procedure.

Experimental

General

Melting points were determined in open capillary tubes on Gallenkamp (England) apparatus and on a 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 taken 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 for samples as indicated with tetramethylsilane as internal reference. ^{13}C Spectra (75.5 MHz) were obtained on a Bruker DPX-300 spectrometer. Chemical sifts are reported in δ unit (parts per milion); J values given in Hz; 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 visualised with UV light. Column chromatography was done on silica gel (60–120 mesh) or neutral alumina. Elemental analyses (C, H, N) were carried out on Perkin-Elmer 240C Analyser. Phenyl acetylene **11**, trimethylsilyl acetylene **16**, propargyl alcohol **18** and *n*-hexyne **19** were commercially available (Aldrich Chem. Co.). Bis(triphenylphosphine)palladium(II) chloride, $Pd(OAc)_2$, and $(PPh_3)_4Pd$ were purchased from Aldrich Chemical Co., Milwaukee, Wisconsin, USA.

Preparation of 2-iodobenzamides 1–10: general procedure

2-Iodobenzamides **1**–**10** were prepared from 2-iodobenzoic acids which were synthesised from anthranilic acids via Sandmeyer iodination with potassium iodide.[54a,b] 2-Iodobenzoic acid was converted to 2-iodobenzoyl chloride by heating with PCl_5 at 80°C for 2 h. 2-Iodobenzoyl chloride (3.15 g, 11.15 mmol) was dissolved in dry benzene (30 mL) under a nitrogen atmosphere. To the resulting solution cooled in an ice bath was added a solution of the primary amine (2.02 equiv.) in benzene (10 mL) slowly with stirring. The precipitate, obtained by filtration, was washed with dilute HCl (3×50 mL), saturated sodium bicarbonate solution (3×50 mL), water (3×50 mL) and, finally, with ether (2×25 mL). The colourless crystalline powder obtained was crystallised from EtOH to yield the benzamides **1**–**10** in excellent yields.

2-Iodobenzamide 1. Small colourless needles (EtOH); mp 188–189°C; 184°C (lit).[55]

2-Iodo-*N*-methylbenzamide 2. Colourless amorphous powder (EtOH); mp 145–147°C; IR: ν_{max} (KBr) 3290, 1640, 1590, 1540 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.00 (d, 3H, J=4 Hz), 6.10 (br s, 1H), 6.98–7.40 (m, 3H), 7.88 (d, 1H, J=8 Hz). Anal. Calcd for C_8H_8INO: C, 36.8; H, 3.1; N, 5.35. Found: C, 36.55; H, 3.1; N, 5.6.

2-Iodo-*N*-benzylbenzamide 3. Colourless needles (EtOH); mp 124–125°C; IR: ν_{max} (KBr) 3275, 1640, 1585, 1550 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 4.60 (d, 2H, J=5 Hz), 6.28 (br s, 1H), 6.97–7.52 (m, 8H), 7.95 (m, 1H). Anal. Calcd for $C_{14}H_{12}INO$: C, 49.75; H, 3.6; N, 4.0. Found: C, 49.85; H, 3.6; N, 4.15.

2-Iodo-*N*-phenylbenzamide 4. Coloourless needles (EtOH); mp 143–144°C; IR: ν_{max} (KBr) 3230, 1650, 1600, 1540 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.85–7.92 (m, 9H). Anal. Calcd for: $C_{13}H_{10}INO$: C, 48.15; H, 3.05; N, 4.1. Found: C, 48.3; H, 3.1; N, 4.3.

2-Iodo-*N*-*p*-tolylbenzamide 5. Colourless needles (EtOH); mp 171–173°C; IR: ν_{max} (KBr) 3260, 1650, 1600, 1540 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.10–8.05 (m, 9H). Anal. Calcd for $C_{14}H_{12}INO$: C, 49.85; H, 3.6; N, 4.15. Found: C, 50.1; H, 3.7; N, 4.4.

2-Iodo-*N*-*p*-anisyl benzamide 6. Colourless needles (EtOH); mp 174–176°C; IR: ν_{max} (KBr) 3310, 1650, 1600, 1515 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.83–7.97 (m, 9H). Anal. Calcd for $C_{14}H_{12}INO_2$: C, 47.6; H, 3.4; N, 3.95. Found: C, 47.35; H, 3.5; N, 4.1.

2-Iodo-*N*-*m*-chlorophenyl benzamide 7. Colourless needles (EtOH); mp 148–150°C; IR: ν_{max} (KBr) 3230, 1650, 1600, 1535 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$), 7.00–8.00 (m, 9H). Anal. Calcd for $C_{13}H_9ClNO$: C, 43.65; H, 2.55; N, 3.9. Found: C, 43.7; H, 2.8; N, 4.15.

2-Iodo-5-nitro-*N*-*p*-anisyl benzamide 8. Small colourless needles ($CHCl_3$+light petroleum 60–80°C 1:1); mp 213–214°C; IR: ν_{max} (KBr) 3270, 1650, 1595, 1530, 1510 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$+DMSO-d_6) δ 3.78 (s, 3H), 6.88 (d, 2H, J=9 Hz), 7.43–7.82 (m, 6H). Anal. Calcd for $C_{14}H_{11}IN_2O_4$: C, 42.2; H, 2.8; N, 7.0. Found: C, 41.85; H, 2.8; N, 6.7.

2-Iodo-4,5-dimethoxy-*N*-methyl benzamide 9. Colourless amorphous powder (EtOH); mp 149–151°C; IR ν_{max} (KBr) 3300, 1640, 1590, 1550 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.00 (d, 3H, J=5 Hz), 3.92 (s, 3H), 3.95 (s, 3H), 6.02 (br s, 1H), 7.00 (s, 1H), 7.20 (s, 1H, Ar-H). Anal. Calcd for $C_{10}H_{12}INO_2$: C, 37.4; H, 3.75; N, 4.35. Found: C, 35.13; H, 3.6; N, 4.55.

2-Iodo-5-hydroxy-*N*-*p*-tolyl benzamide 10. Colourless amorphous powder ($CHCl_3$+light petroleum); mp 153–

154°C; IR: ν_{max} (KBr) 3300, 3260, 1640, 1600, 1530 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$+DMSO-d_6), 2.23 (s, 3H), 6.52–7.67 (m, 7H), 10.15 (s, 1H). Anal. Calcd for $C_{14}H_{13}INO_2$: C, 47.5; H, 3.7; N, 3.95. Found: C, 47.2; H, 3.6; N, 4.1.

Synthesis of acetylenic compounds 12–15: a typical procedure

Aromatic halides were prepared by the literature[54c] procedure. 5-Iodo-2,4-dimethoxypyrimidine was prepared by heating 5-iodouracil with phosphorus oxychloride in the presence of *N*,*N*-dimethylaniline followed by treatment of the resulting 5-iodo-2,4-dichloropyrimidine with sodium methoxide in methanol.[56] The terminal alkynes **12**–**15** were prepared from aromatic halides according to the procedure of Bumagin and co-workers[57] which involved palladium catalysed coupling of propargyl alcohol followed by oxidative decarbonylation using active MnO_2 in dichloromethane in the presence of potassium hydroxide. Dimethylpropargyl alcohol **17** was prepared by the procedure of Jones et al.[58]

***p*-Methoxy phenyl acetylene 12.** Light yellow oil; bp 92–96°C (10 mm) [lit.[59] 90–95°C (10 mm)]; IR: ν_{max} (neat) 2110 (C≡C) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$+CCl_4) δ 2.85 (s, 1H, –C≡CH), 3.76 (s, 3H, OCH_3), 6.78 (d, 2H, J=9.0 Hz), 7.40 (d, 2H, J=9.0 Hz, Ar-H).

(2,4-Dimethoxy-5-pyrimidinyl) acetylene 13. Colourless amorphous powder (EtOH); mp 75–77°C (lit.[60] 78–80°C); IR: ν_{max} (KBr) 2105 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$+CCl_4) δ 3.30 (s, 1H), 4.00 (s, 3H), 4.06 (s, 3H, OCH_3), 8.37 (s, 1H).

***m*-Chlorophenyl acetylene 14.** Light yellow oil; IR: ν_{max} (neat) 2110 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.01 (s, 1H), 7.14–7.50 (m, 4H).

1-Naphthylacetylene 15. Colourless oil; bp 131–133°C (20 mm) [lit.[61] 135°C (20 mm)]; IR: ν_{max} (neat) 2105 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 3.28 (s, 1H), 7.10–7.70 (m, 6H), 8.13–8.34 (m, 1H).

1,1-Dimethylpropargyl alcohol 17. It was synthesised according to literature procedure.[58] IR: ν_{max} (neat) 3300 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 1.40 (s, 6H); 2.34 (s, 1H), 3.89 (br s, 1H).

Synthesis of 3-Aryl(alkyl)idene isoindolin-1-ones: general procedure for 3-arylidene isoindolin-1-ones 50, 52, 56, 58

(Condition A). A mixture of 2-iodobenzamide **5**, **6** or **7** (1 mmol), bis(triphenylphosphine) palladium(II)chloride (3.5 mol%), copper(I)iodide (8 mol%), and triethylamine (4 mmol) was stirred in DMF (5 mL) under nitrogen atmosphere for 1 h. Then the alkyne **11**, **12**, or **13** (1.2 mmol) was added and the solution heated at 80–85°C for 15 h. The mixture was then evaporated to dryness under reduced pressure, the residue extracted with chloroform (3×50 mL), the combined chloroform extracts washed with distilled water (3×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel and crystallised to afford the pure products **50**, **52**, **56** and **58**.

(*Z*)-3-Benzylidene-*N*-*p*-tolyl isoindolin-1-one 50. Colourless small needles (EtOH); mp 92–93°C; IR: ν_{max} (KBr) 3060, 1700, 1640, 1600, 1490, 1070, 840, 760, 690 cm^{-1}; UV: λ_{max}/nm 301.2 (log ϵ 4.31), 269 (4.33), 261.4 (4.31), 232.4 (4.25); ^1H NMR (60 MHz, CCl_4) δ 2.36 (s, 3H, CH_3), 6.60 (s, 1H, =CH–), 7.10–7.66 (m, 12H), 8.20–8.40 (m, 1H, Ar-H). Anal. Calcd for $C_{22}H_{17}NO$: C, 84.85; H, 5.5; N, 4.5. Found: C, 84.65; H, 5.5; N, 4.15.

(*Z*)-3-Benzylidene-*N*-*m*-chlorophenyl isoindolin-1-one 52. Colourless small needles (EtOH); mp 147–151°C; IR: ν_{max} (KBr) 3080, 1710, 1630, 1590, 1470, 1400, 1350, 1300, 1130, 1010, 910, 800, 770, 700, 690 cm^{-1}; UV: λ_{max}/nm 332.8 (log ϵ 4.17), 274.8 (4.02), 243.8 (4.24); ^1H NMR (60 MHz, $CDCl_3$) δ 6.8 (s, 1H, =CH–), 6.9–7.16 (m, 7H), 7.36–8.03 (m, 6H, Ar-H). Anal. Calcd for $C_{21}H_{14}ClNO$: C, 76.0; H, 4.25; N, 4.2. Found: C, 75.8; H, 4.5; N, 4.0.

(*Z*)-3-(*p*-Methoxyphenyl)methylidene-*N*-*p*-anisyl isoindolin-1-one 56. Colourless small needles (EtOH); mp 177–179°C; IR: ν_{max} (KBr) 3000, 1705, 1650, 1610, 1501, 1300, 1250, 1130, 830, 770, 700, 620 cm^{-1}; UV: λ_{max}/nm 348.4 (log ϵ 4.22), 242.6 (4.10); ^1H NMR (60 MHz, $CDCl_3$) δ 3.69 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 6.54 (s, 1H, =CH–), 6.58–7.10 (m, 8H), 7.49–8.00 (m, 4H, Ar-H). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.3; H, 5.35; N, 3.9. Found: C, 77.7; H, 5.5; N, 3.45.

(*Z*)-3-(2′,4′–Dimethoxypyrimidin-5′-yl)methylidene-*N*-*m*-chlorophenyl isoindolin-1-one 58. Colurless powder (EtOH); mp 140–141°C; IR: ν_{max} (KBr) 3000, 1710, 1590, 1550, 1440, 1020, 760, 690 cm^{-1}; UV: λ_{max}/nm 330.5 (log ϵ 4.17), 274.4 (4.07), 228 (4.49); ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.50 (s, 1H, =CH–), 7.04–7.26 (m, 4H), 7.55–7.72 (m, 3H), 7.85 (d, J=9 Hz, 1H), 7.94 (d, J=6 Hz, 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) 54.13, 54.91, 97.89, 108.96, 119.78, 124.04, 125.78, 127.37, 127.62, 127.71, 129.42, 129.78, 132.82, 133.94, 136.23, 136.27, 137.84, 157.59, 164.30, 167.50, 167.54; DEPT-135: 98.00, 119.89, 124.14, 125.89, 127.49, 127.81, 129.54, 129.81, 132.94, 157.67. Anal. Calcd for $C_{21}H_{16}ClN_3O_3$: C, 64.05; H, 4.1; N, 10.65. Found: C, 63.95; H, 4.3; N, 10.6.

Synthesis of 2-alkynyl benzamide 20–31 and 3-arylidene isoindolin-1-ones 46–49, 51, 53–55, 57, 59, 60

2-Alkynyl benzamide **20**–**31** and **77** were synthesised using the condition A.

Condition D. To the 2-alkynyl benzamide (1 mmol) was added sodium ethoxide (1.2–1.5 mmol) in ethanol (20 mL) and the mixture was stirred under a nitrogen atmosphere for 4 h at 80°C (bath temp.). At the end of the reaction the mixture was evaporated to dryness under reduced pressure. Distilled water (200 mL) was added to the residue and it was neutralised with dilute 6N HCl, extracted with chloroform (3×50 mL), the organic layer

washed with distilled water (3×50 mL), dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to yield the pure 3-arylidene isoindolin-1-ones **46**–**49**, **51**, **53**–**55**, **57**, **59**–**60**.

2-(2′-Phenylethynyl)benzamide 20. Colourless amorphous powder (EtOH), mp 158–160°C; IR: ν_{max} (KBr) 3500, 3200, 2210, 1650, 1620, 1490, 1400, 1110, 760, 690 cm^{-1}; UV: λ_{max}/nm 301.2 (log ϵ 4.21), 284.4 (4.30); ^{1}H NMR (60 MHz, $CDCl_3$+CCl_4) δ 7.30–8.02 (m, 9H, Ar-H), 8.20 (br, s, NH_2). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.4; H, 5.0; N, 6.3. Found: C, 81.15; H, 5.25; N, 6.6.

2-(2′-Phenylethynyl)-*N*-methyl benzamide 21. Colourless amorphous powder, mp 103–105°C; IR: ν_{max} (KBr) 3300, 3000, 2215, 1650, 1540, 1410, 1410, 1320, 760, 690 cm^{-1}; UV: λ_{max}/nm 301.2 (log ϵ 4.29), 283.6 (4.37); ^{1}H NMR (60 MHz, CCl_4) δ 2.93 (d, 3H, J=5 Hz, CH_3), 7.18–7.94 (m, 9H, Ar-H and 1H, NH). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.65; H, 5.55; N, 5.95. Found: C, 81.45; H, 5.75; N, 6.35.

2-(2′-Phenylethynyl)-*N*-phenyl benzamide 23. Colourless amorphous powder (EtOH), mp 151–153°C; IR: ν_{max} (KBr) 3300, 3020, 2210, 1600, 1525, 1500, 1440, 1320, 760, 690 cm^{-1}; UV: λ_{max}/nm 301.8 (log ϵ 4.29), 282.8 (4.40), 274.6 (4.40), 268.4 (4.41); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.20–8.20 (m, 14H, Ar-H), 9.20 (br s, 1H, NH). Anal. Calcd for $C_{21}H_{15}NO$: C, 84.8; H, 5.1; N, 4.7. Found: C, 84.6; H, 5.1; N, 4.85.

2(2′-Phenylethynyl)-*N*-*p*-tolyl benzamide 24. Light yellow small needles (EtOH), mp 125–127°C; IR: ν_{max} (KBr) 3280, 3050, 2220, 1650, 1590, 1520, 1400, 1320, 810, 760, 690 cm^{-1}; UV: λ_{max}/nm 302 (log ϵ 4.29), 282.8 (3.90), 268.4 (4.41), 239.6 (4.30); ^{1}H NMR (60 MHz, CCl_4) δ 2.30 (s, 3H, CH_3), 7.0–8.30 (m, 13H, Ar-H), 9.30 (br s, 1H, NH). Anal. Calcd for $C_{22}H_{17}NO$: C, 84.85; H, 5.5; N, 4.5. Found: C, 85.0; H, 5.55; N, 4.2.

2-(2′-Phenylethynyl)-*N*-*p*-anisyl benzamide 25. Colourless needles (EtOH), mp 154–156°C; IR: ν_{max} (KBr) 3280, 3050, 2840, 2220, 1650, 1600, 1500, 1415, 1320, 1030, 830, 750, 690 cm^{-1}; UV: λ_{max}/nm 301.2 (log ϵ 4.27), 283.4 (4.41), 270.22 (4.38); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 7.30–8.20 (m, 13H, Ar-H), 9.15 (br s, 1H, NH). Anal. Calcd for $C_{21}H_{17}NO_2$: C, 80.7; H, 5.2; N, 4.25; Found: C, 80.9; H, 5.5; N, 4.3.

2-(2′-*p*-Anisylethynyl)-*N*-*p*-anisyl benzamide 77. The compound **77** was synthesised from 2-iodo-*N*-*p*-anisylbenzamide **6** and *p*-methoxyphenyl acetylene **12** using condition A at room temperature. Colourless powder, mp 135–137°C; IR: ν_{max} (KBr) 3300, 3030, 2210, 1650, 1600, 1510, 1410, 1250, 1030, 830, 760 cm^{-1}; UV: λ_{max}/nm 310 (log ϵ 4.28), 291.2 (4.41), 256 (4.38); ^{1}H Nmr (60 MHz, $CDCl_3$) δ 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.78–8.03 (m, 12H, Ar-H), 9.20 (br s, 1H, NH). Anal. Calcd for $C_{23}H_{19}NO_3$: C, 77.3; H, 5.35; N, 3.95. Found: C, 76.9; H, 5.45; N, 3.95.

(*Z*)-3-Benzylidene isoindolin-1-one 46. Colourless small needles (EtOH); mp 183–184°C; IR: ν_{max} (KBr) 3250, 3020, 1710, 1640, 1610, 1450, 1310, 1150, 770, 700, 640 cm^{-1}, UV: λ_{max}/nm 339.2 (log ϵ 4.30), 241.4 (3.88); ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.58 (s, 1H, =CH–), 7.3–8.05 (m, 9H, Ar-H), 9.15 (br s, 1H, NH). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.4; H, 5.0; N, 6.3. Found: C, 81.4; H, 5.15; N, 5.9.

(*Z*)-3-Benzylidene-*N*-methyl isoindolin-1-one 47. Colourless small needles (EtOH); mp 110–111°C; IR: ν_{max} (KBr) 3000, 1700, 1640, 1610, 1470, 1430, 1345, 1330, 1100, 1030, 1010, 770, 760, 720, 690; UV: λ_{max}/nm 324.8 (log ϵ 4.21), 272.4 (4.05), 221.8 (4.37); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.05 (s, 3H, N-CH_3), 6.78 (s, 1H, =CH–), 7.25–8.00 (m, 9H, Ar-H). Anal. Calcd for $C_{16}H_{13}NO$: C, 81.65; H, 5.55; N, 5.95. Found: C, 81.3; H, 5.65; N, 6.2.

(*Z*)-3-Benzylidene-*N*-benzyl isoindolin-1-one 48. Colourless prisms (CCl_4); mp 122–123°C; IR: ν_{max} (KBr) 3020, 1705, 1655, 1495, 1450, 1400, 1350, 1120, 950, 760, 700, 630 cm^{-1}; UV: λ_{max}/nm 323.8 (log ϵ 4.21), 271.22 (4.07), 221.4 (4.48); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 2H, N-CH_2), 6.52 (dd, 2H, J=0.9, 7.5 Hz, Ar-H), 6.73 (s, 1H, =CH–), 7.05–7.09 (m, 5H), 7.25–7.29 (m, 3H), 7.53 (td, 1H, J=0.9 Hz, 7.5H), 7.63 (td, 1H, J=1.2, 7.5 Hz), 7.75 (d, 1H, J=7.5 Hz), 7.94 (d, 1H, J=7.5 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 44.84, 107.5 119.43, 123.51, 126.32, 126.68, 127.39, 127.88, 127.98, 128.06, 129.03, 129.64, 132.10, 134.32, 134.53, 136.77, 138.46, 169.04. Anal. Calcd for $C_{22}H_{17}NO$: C, 84.85; H, 5.5; N, 4.5. Found: C, 84.7; H, 5.75; N, 4.9.

(*Z*)-3-Benzylidene-*N*-phenyl isoindolin-1-one 49. Colourless small needles (EtOH) mp 197–198°C; IR: ν_{max} (KBr) 3020, 1710, 1650, 1610, 1600, 1500, 1470, 1390, 1300, 1130, 995, 760, 700, 630 cm^{-1}; UV: λ_{max}/nm 332.8 (log ϵ 4.23), 275.8 (4, 03), 233.6 (4,41); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 1H, =CH–), 6.84–6.96 (m, 5H), 7.03–7.08 (m, 5H), 7.50 (t, 1H, J=7.2 Hz), 7.67 (t, 1H, J=7.2 Hz), 7.85 (d, 1H, J=7.8 Hz), 7.95 (d, 1H, J=7.5 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 107.61, 119.32, 123.82, 126.51, 126.66, 127.72, 127.72, 128.11, 129.03, 132.39, 133.47, 134.26, 135.78, 138.58, 167.94. Anal. Calcd for $C_{21}H_{15}NO$: C, 84.8; H, 5.1; N, 4.7. Found: C, 84.4H, 5.1; N, 4.6.

(*Z*)-3-Benzylidene-*N*-*p*-anisyl isoindolin-1-one 51. Light yellow needles (EtOH); mp 171–173°C; IR: ν_{max} (KBr) 3000, 1710, 1640, 1610, 1510, 1390, 1300, 1250, 1120, 1020, 830, 770, 710, 700, 630 cm^{-1}; UV: λ_{max}/nm 332.2 (log ϵ 4.21), 274.4 (4.13), 240.0 (4.36); ^{1}H NMR (200 MHz, $CDCl_3$), δ 3.7 (s, 3H, OCH_3), 6.8 (s, 1H, =CH–), 6.9–8.1 (m, 13H, Ar-H). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.9; H, 5.2; N, 4.25. Found: C, 80.9; H, 5.35; N, 4.1.

(*Z*)-3-Benzylidene-*N*-*p*-tolyl-6-hydroxy isoindolin-1-one 53. Colourless needles (EtOH); mp 207–210°C; IR: ν_{max} (KBr) 3360, 3000, 1685, 1645, 1600, 1510, 1390, 1320, 1140, 840, 810, 780, 700 cm^{-1}, ^{1}H NMR (60 MHz, $CDCl_3$+DMSO-d_6) δ 2.23 (2, 3H, CH_3), 6.73 (s, 1H, =CH–), 6.85–7.90 (m, 12H, Ar-H), 9.90 (br s, 1H, OH). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.7; H, 5.2; 4.25. Found: C, 80.45; H, 5.1; N, 4.5.

(*Z*)-3-(*p*-Methoxyphenyl)methylidene isoindolin-1-one 54. Colourless prisms (EtOH+H_2O); mp 200–201°C; IR: ν_{max} (KBr) 3215, 2990, 1705, 1660, 1580, 1520, 1480, 1310, 1260, 1190, 1150, 1040, 850, 820, 760, 700, 610 cm^{-1}; UV: λ_{max}/nm 355.6 (log ϵ 4.41); ^{1}H NMR (300 MHz, $CDCl_3$-DMSO-d_6) δ 3.68 (s, 3H, OMe), 6.41 (s, 1H, =CH–), 6.79 (d, 2H, *J*=9 Hz), 7.34 (t, 1H, *J*=7.5 Hz), 7.43 (d, 2H, *J*=9 Hz), 7.48 (t, 1H, *J*=7.2 Hz), 7.62 (d, 1H, *J*=7.5 Hz), 7.74 (d., 1H, *J*=7.8 Hz, Ar-H), 10.34 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$−DMSO-d_6) δ 55.49, 106.26, 114.54, 120.11, 123.04, 127.59, 128.74, 130.91, 131.28, 132.20, 139.23, 159.06, 169.68, DEPT-135: 55.21, 105.97, 114.25, 119.79, 125.75, 128.46, 130.61 131.91. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.45; H, 5.2; N, 5.55. Found: C, 76.65; H, 5.4; N, 5.6.

(*Z*)-3-(*p*-Methoxyphenyl)methylidene-*N*-benzyl isoindolin-1-one 55. Colourless needles (EtOH). mp 125–126°C, IR: ν_{max} (KBr) 3000, 1700, 1650, 1610, 1510, 1450, 1400, 1360, 1300, 1250, 1180, 1110, 1040, 765, 740, 700 cm^{-1}; UV: λ_{max}/nm 334.22 (log ϵ 4.20), 254 (4.03), 221.22 (4.48); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 4.96 (s, 2H, N-CH_2), 6.59–6.62 (m, 2H), 6.68 (s, 1H, =CH–), 6.79 (d, 2H, *J*=8.7 Hz), 7.01 (d, 2H, *J*=8.5 Hz), 7.02–7.09 (m, 3H), 7.51–7.61 (m, 2H), 7.73 (d, 1H, *J*=7.8 Hz), 7.92 (d, 1H, *J*=8 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 45.33, 55.78, 108.01, 113.84, 119.76, 123.90, 126.85, 127.15, 127.19, 1280.40, 128.44, 129.25, 131.31, 132.46, 134.32, 137.38, 139.01, 159,42, 169.55; DEPT-135: 45.04, 55.48, 107.71, 113.55, 119.47, 123.61, 126.56, 126.86, 128.11, 128.96, 131.02, 132.17. Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6; N, 4.1. Found: C, 80.6; H, 5.75; N, 4.0.

(*Z*)-3-(*p*-Methoxyphenyl)methylidene-*N*-methyl-5,6-dimethoxy isoindolin-1-one 57. Colourless needles (EtOH); mp 155–156°C; IR: ν_{max} (KBr) 2960, 1710, 1690, 1645, 1604, 1510, 1300, 1030 cm^{-1}; UV: λ_{max}/nm 333.8 (log ϵ 4.31), 300 (4.09), 242.6 (4.48); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.03 (s, 3H, N-CH_3), 3.83 (S, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.62 (s, 1H, =CH–), 6.86–7.40 (m, 6H, Ar-H). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.1, H, 5.85; N, 4.3. Found: C, 69.7; H, 5.7; N, 4.4.

(*Z*)-3-(*m*-Chlorophenyl)methylidene isoindolin-1-one 59. Light yellow small needles (EtOH); mp 202–203°C; IR: ν_{max}(KBr) 3215, 1700, 1680, 1650, 1480, 1440, 1310, 1140, 865, 760, 700 cm^{-1}; UV: λ_{max}/nm 339.8 (log ϵ 4.40), 297.8 (4.12), 248.8 (3.99), 223.0 (4.38); ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 6.51 (s, 1H, =CH–), 7.24 (d, 1H, *J*=7.9 Hz), 7.36 (t, 1H, *J*=7.8 Hz), 7.49 (d, 1H, *J*=6.6 Hz), 7.54 (d, 1H, *J*=7.5 Hz), 7.62–7.67 (m, 2H), 7.78 (d, 1H, *J*=7.5 Hz), 7.86–7.88 (m, 1H, Ar-H), 10.64 (s, 1H, NH). Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.95; N, 5.45. Found: C, 70.5; H, 4.05; N, 5.45.

(*Z*)-3-(1′-Naphthyl)methylidene-*N*-methyl isoindolin-1-one 60. Colourless needles (EtOH); mp 150–151°C; IR: ν_{max} (KBr) 3000, 1705, 1660, 1505, 1470, 1430, 1340, 1310, 1010, 780, 760, 690 cm^{-1}; UV: λ_{max}/nm 328.4 (log ϵ 4.28), 220.4 (4.87); ^{1}H NMR (300 MHz, $CDCl_3$) δ 280 (s, 3H, N-CH_2), 7.06 (s, 1H, =CH–), 7.41–755 (m, 5H), 7.61–7.63 (m, 1H), 7.81–7.92 (m, 4H), 7.97–8.02 (m, 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 30.06, 104.71, 119.88, 123.63, 125.46, 126.01, 126.68, 126.95, 128.32, 128.67, 128.99, 129.08, 129.55, 132.35, 132.51, 132.84, 133.79, 137.95, 138.07, 169.07. Anal. Calcd for $C_{20}H_{15}NO$: C, 84.2; H, 5.3; N, 4.9. Found: C, 84.2; H, 5.4; N, 4.85.

Synthesis of 2-trimethylsilylethynyl benzamides 32–38, 40, 41 and 3-methylene isoindolinones 61–69

Condition B. Bis(triphenylphosphine)palladium(II) chloride (3.5 mol%), copper(I) iodide (8 mol%), and triethylamine (4 mmol) were added to a solution of 2-iodobenzamide **1**–**10** (1 mmol) in DMF (5 mL). The mixture was stirred for 1 h under a nitrogen atmosphere at room temperature. Then trimethylsilyl acetylene **16** (2 mmol) was added dropwise to the mixture, stirring continued for 23 h at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, the residue extracted with chloroform (3×5 mL), the organic extracts washed with distilled water (3×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to afford the 2-trimethylsilyl ethynyl benzamides **32**–**38**, **40**, **41**.

Condition D. 2-Trimethylsilylethynyl benzamide **32**–**38**, **40**, **41** were cyclised according to the condition D to afford isoindolinones **61**–**69**.

2(2′-Trimethylsilylethynyl)-*N*-phenyl benzamide 35. Colourless small needless (EtOH), mp 95–96°C; IR: ν_{max} (KBr) 3330, 2160, 1660 cm^{-1}; UV: λ_{max}/nm 248.6 (log ϵ 4.36); ^{1}H NMR (60 MHz, CCl_4) δ 0.15 (s, 9H, TMS-H), 6.90–8.20 (m, 9H, Ar-H), 9.00–9.20 (br s, 1H, NH). Anal. Calcd for $C_{18}H_{19}SiNO$: C, 73.65; H, 6.5; N, 4.75. Found: C, 73.55; H, 6.55; N, 4.5.

2-(2′-Trimethylsilylethynyl)-*N*-*p*-tolylbenzamide 36. Colourless amorphous powder (CCl_4), mp 85–87°C; IR: ν_{max} (KBr) 3340, 3000, 2160, 1665 cm^{-1}; UV: λ_{max}/nm 249.4 (log ϵ 4.26); ^{1}H NMR (60 MHz, CCl_4) δ 0.15 (s, 9H, TMS-H), 2.10 (s, 3H, CH_3), 6.80–8.10 (m, 8H, Ar-H), 8.90–9.10 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{21}SiNO$: C, 74.2; H, 6.9; N, 4.55. Found: C, 74.05; H, 6.75; N, 44.

2-(2′-Trimethylsilylethynyl)-*N*-*p*-anisyl benzamide 37. Colourless small needles (EtOH), mp 116–117°C; IR: ν_{max} (KBr) 3330, 3000, 2150, 1660 cm^{-1}; UV: λ_{max}/nm 249.8 (log ϵ 4.44); ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.30 (s, 9H, TMS-H), 3.50 (s, 3H, OCH_3); 6.80–8.00 (m, 8H, Ar-H), 8.90 (br s, 1H, NH). Anal. Calcd for $C_{19}H_{21}SiNO_2$: C, 70.55; H, 6.55; N, 4.3. Found: C, 70.85; H, 6.8; N, 4.3.

2-(2′-Trimethylsilylethynyl)-*N*-*m*-chlorophenyl benzamide 38. Colourless small needles (CCl_4), mp 70–71°C; IR: ν_{max} (KBr) 3310, 2970, 2160, 1660, 1600 cm^{-1}; UV: λ_{max}/nm 249.0 (log ϵ 4.46) nm; ^{1}H NMR (60 MHz, CCl_4) δ 0.20 (s, 9H, TMS-H), 6.90–8.20 (m, 8H, Ar-H), 9.40–9.50 (br s, 1H, NH). Anal. Calcd for $C_{18}H_{18}ClSiNO$: C, 65.9; H, 5.5; N, 4.25. Found: C, 66.15; H, 5.7; N, 4.0.

3-Methylene isoindolin-1-one 61. Unstable colourless oil; IR: ν_{max} (film) 3200, 1720, 1670, 1650, 1470, 1310, 1010, 770, 710 cm^{-1}; UV; λ_{max}/nm 304 (log ϵ 3.62), 254.2 (3.95),

222.4 (4.22); ^{1}H NMR (60 MHz, $CDCl_3$) δ 5.03 (d, 1H, J=2 Hz,=CH_2), 5.23 (d, 1H, J=2 Hz, =CH_2), 7.33 (br s, 1H, NH).

3-Methylene-*N*-methyl isoindolin-1-one 62. Unstable colourless oil: IR: ν_{max} (film) 3000, 1710, 1650, 1600, 1450, 720, 700 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.26 (s, 3H, N-CH_3), 4.80 (d, 1H, J=2 Hz, =CH_2), 5.20 (d, 1H, J=2 Hz, CH_2); 7.32–7.92 (m, 4H, Ar-H).

3-Methylene-*N*-benzyl isoindolin-1-one 63. Colourless needles, mp 118–119°C; IR: ν_{max} (KBr) 3010, 1710, 1645, 1600, 1470, 1455, 1400, 1360, 1335, 1290, 1200, 1130, 980, 830, 780, 740, 700, 640 cm^{-1}; uv: λ_{max}/nm 306.8 (log ϵ 3.87), 255.6 (4.13), 224.2 (4.48); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, J=2.4 Hz, 1H, =CH_2), 5.02 (s, 2H, N-CH_2), 5.15 (d, 1H, J=2.4 Hz, =CH_2), 7.25–7.34 (m, 5H), 7.50–7.62 (m, 2H), 7.67 (d, J=7.5 Hz, 1H), 7.89 (d, J=7.5 Hz, 1H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 43.05, 89.89, 119.28, 123.23, 127.03, 127.28, 127.49, 128.55, 129.10, 129.41, 131.97, 136.33, 136.75, 141.47, 168.00; DEPT-135: δ 43.26, 90.13, 120.03 123.45, 127.24, 127.49, 128.77, 129.62, 132.18 Anal. Calcd for $C_{16}H_{13}NO$: C, 81.65; H, 5.55; N, 5.95 Found: C, 81.45; H, 5.65; N, 5.8.

3-Methylene-*N*-phenyl isoindolin-1-one 64. Colourless small needless (EtOH); mp 98–99°C; IR: ν_{max} (KBr) 3000, 1700, 1650, 1595, 1495, 1390, 1180, 890, 760, 720, 700 cm^{-1}; UV: λ_{max}/nm 309.4 (log ϵ 3.87), 255.2 (4.48), 223.4 (4.52); ^{1}H NMR (60 MHz, $CDCl_3$); 4.76 (d, 1H, J=2 Hz,=CH_2), 5.20 (d, 1H, J=2 Hz, =CH_2), 7.35–7.98 (m, 9H, Ar-H). Anal. Calcd for $C_{15}H_{11}NO$: C, 81.4; H, 5.0; N, 6.3. Found: C, 80.9; H, 5.3; N, 6.3.

3-Methylene-*N*-tolyl isoindolin-1-one 65. Colourless small needles (EtOH); mp 126–127°C; IR: ν_{max} (KBr) 3000, 1710, 1640, 1510, 1380, 1300, 1145, 770, 690 cm^{-1}; UV: λ_{max}/nm 310.4 (log ϵ 3.89), 255.6 (4.21), 224.2 (4.56); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3), 4.70 (d, 1H, J=2 Hz, =CH_2), 7.20–7.80 (m, 8H, Ar-H). Anal. Calcd for $C_{16}H_{13}NO$; C, 81.65; H, 5.55; N, 5.95. Found: C, 81.7; H, 5.6; N, 6.1.

3-Methylene-*N*-*p*-anisyl isoindolin-1-one 66. Colourless powder ((EtOH); IR: ν_{max} (KBr) 3000, 1710, 1640, 1510, 1390, 1300, 1260, 1140, 1030, 830, 780, 700 cm^{-1}; UV: λ_{max}/nm 310.6 (log ϵ 3.78), 255.6 (4.15), 225.2 (4.43); ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.85 (s, 3H, Ar-OCH_3), 4.72 (d, 1H, J=2 Hz, =CH_2), 5.16 (d, 1H, J=2 Hz, CH_2), 6.90–8.00 (m, 8H, Ar-H). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.45; H, 5.2; N, 5.55. Found: C, 76.3; H, 5.1; N, 5.4.

3-Methylene-*N*-*m*-chlorophenyl isoindolin-1-one 67. Colourless powder (EtOH); mp 88–90°C; IR: ν_{max} (KBr) 3000, 1700, 1640, 1510, 1375, 825, 860, 720, 690 cm^{-1}; UV: λ_{max}/nm 309.8 (log ϵ 3.84), 255.4 (4.43), 223.4 (4.57) nm; ^{1}H NMR (60 MHz, CCl_4) δ 5.02 (d, 1H, J=2 Hz, =CH_2), 5.35 (d, 1H, J=2 Hz, =CH_2), 7.32–8.15 (m, 8H, Ar-H). Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.45; H, 3.95; N, 5.45. Found: C, 70.4; H, 4.1; N, 5.25.

3-Methylene-*N*-methyl-5,6-dimethoxy isoindolin-1-one 68. Colourless powder (EtOH); mp 225–227°C; IR: ν_{max} (KBr) 1700, 1660, 1615, 1500, 1430, 1380, 1310, 1030, 780 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 3.26 (s, 3H, N-CH_3), 4.00 (s, 3H, Ar-OCH_3), 4.03 (s, 3H, Ar-OCH_3), 4.76 (d, 1H, J=2 Hz, =CH_2), 5.06 (d, 1H, J=2 Hz, =CH_2), 7.07 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.95; N, 6.4. Found: C, 65.65; H, 5.95; N, 6.6.

3-Methylene-*N*-tolyl-6-hydroxy isoindolin-1-one 69. Colourless powder (EtOH); mp 162–164°C; IR: ν_{max} (KBr) 3320, 3000, 1700, 1640, 1620, 1520, 1500, 1385, 1220, 1135, 810, 760 cm^{-1}; UV: λ_{max}/nm 233 (log ϵ 4.46), 267.6 (4.28), 321.2 (3.82); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.40 (s, 3H, Ar-CH_3), 4.64 (d, 1H, J=2 Hz, =CH_2), 5.08 (d, 1H, J=2 Hz, =CH_2), 6.93–7.58 (m, 7H, Ar-H). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 74.45; H, 5.2; N, 5.55. Found: C, 76.75; H, 5.3; N, 5.6.

3-Nitro-*N*-*p*-anisyl benzamide 39. 3-Nitro-*N*-*p*-anisyl benzamide **39** was obtained from the reaction of 2-iodo-5-nitro-*N*-*p*-anisylbenzamide **8** with trimethylsilyl acetylene using condition A. Colourless small needles (EtOH); mp 161–163°C, ^{1}H NMR (60 MHz, $CDCl_3$+DMSO-d_6) δ 3.80 (s, 3H, OCH_3), 6.88 (d, 2H, J=9.0 Hz, Ar-H), 7.60–7.88 (m, 3H, Ar-H), 8.28–8.52 (m, 2H, Ar-H), 8.92 (t, 1H, J=1 Hz, Ar-H). Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.75; H, 4.45; N, 10.3. Found: C, 61.4; H, 4.6; N, 10.3.

Synthesis of 3-(2′-hydroxy-2′ methyl)propylidene-*N*-*p*-tolyl isoindolinone 70

2-(2′-Hydroxy-2′-methylpropynyl)-*N*-*p*-tolyl benzamide **42** was synthesised from *2*-iodo-*N*-*p*-tolyl benzamide **5** and dimethyl propargyl alcohol **17** according to condition B.

Condition E. Palladium(II) acetate (5 mol%), LiCl (1 mmol), and K_2CO_3 (2.5 mmol) were added to a solution of 2-(2′-hydroxy-2′-methylpropynyl)-*N*-*p*-tolyl benzamide **42** (1 mmol) in DMF (5 mL), and the mixture was stirred for 16 h at 100°C (bath temperature). The reaction mixture was evaporated under reduced pressure, the residue extracted with chloroform (3×50 mL), the combined organic extracts washed with distilled water (3×50 mL), dried over anhydrous Na_2SO_4 and filtered. The residue obtained after removal of solvent was purified by column chromatography on silica gel to yield 3-(2′-hydroxy-2′-methylpropylidene)-*N*-(*p*-tolyl)isoindolin-1-one **70**. Single crystals suitable for X-ray analysis were obtained by slow crystallisation from a dilute solution of **70** in ethanol.

Compound 70. Colourless prisms (EtOH); mp 139–140°C; IR: ν_{max} (KBr) 3420, 3000, 1700, 1655, 1610, 1510, 1475, 1400, 1380, 1120, 1020, 910, 790, 765, 700, 640 cm^{-1}; UV: λ_{max}/nm 314.6 (log ϵ 4.06), 260.2 (4.24), 222.4 (4.57); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (s, 6H, 2×CH_3), 2.42 (s, 3H, Ar-CH_3), 5.78 (s, 1H, =CH–), 7.29–7.36 (m, 4H), 7.50 (td, 1H, J=1.2, 7.5 Hz), 7.62 (td, 1H, J=1.2, 7.2 Hz, Ar-H), 769 (d, 1H, J=7.8 Hz), 7.88 (d, 1H, J=7.5 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.32, 31.54, 70.18, 115.91, 119.10, 123.69, 127.19, 128.92, 130.24, 134.17, 135.62, 139.05, 139.47, 168.82. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.8; H, 6.5; N, 4.75. Found: C, 77.65; H, 6.6; N, 4.8.

Condition C. Bis(triphenylphosphine) palladium(II) chloride (3.5 mol%) copper(I) iodide and triethylamine (4 mmol) were added to a solution of *N*-*p*-tolyl-2-iodobenzamide **5** (1 mmol) in DMF (5 mL). The mixture was stirred for 1 h under a N_2 atmosphere at room temperature. Then propargyl alcohol **18** (2 mmol) was added with continued stirring at 60°C (bath temperature) for 5 h. The reaction mixture was evaporated under vacuum, the residue extracted with chloroform (3×50 mL), the organic combined layers washed with distilled water, dried over anhydrous Na_2SO_4 and filtered. The residue obtained after removal of solvent was purified by column chromatography on silica gel to yield 2-(2′-hydroxyethylidene)-*N*-*p*-tolyl benzamide **43**, which was cyclised using condition E to afford a 3:7 mixture of isoindolinone **71** and the isoquinolinone **72**.

3-(2′-Hydroxyethylidene)-*N*-*p*-tolyl isoindolin-1-one 71. Colourless powder (EtOH); mp 88–90°C; IR: ν_{max} (KBr) 3460, 2980, 1690, 1660, 1510, 1390, 1140, 1020, 820, 760, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, CH_3), 3.75 (d, 2H, J=6.6 Hz, CH_2OH), 5.72 (t, 1H, J=6.6 Hz, =CH–), 7.06–7.60 (m, 8H, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.97, 57.46, 108.31, 119.71, 123.47, 127.94, 129.03, 129.30, 130.03, 132.01, 133.77, 138.66, 142.16, 149.36, 167.96, DEPT-135: δ 21.19, 57.67, 108.54, 119.49, 123.68, 128.24, 129.51, 130.08, 132.42. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.7; N, 5.3. Found: C, 77.1; H, 5.45; N, 5.5.

3-Hydroxymethyl-*N*-*p*-tolyl-1(2*H*) isoquinolinone 72. Colourless powder (EtOH); mp 107–108°C; IR: ν_{max} (KBr) 3210, 3000, 1670, 1640, 1610, 1510, 1460, 1610, 1510, 1460, 1320, 1250, 1200, 1100, 840, 760, 680 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.3 (s, 3H, CH_3), 2.85 (br s, 1H, OH), 4.15 (s, 2H, CH_2), 6.15 (s, 1H, C4-H), 7.06–7.12 (m, 3H), 7.18 (d, 2H, J=7.8 Hz), 7.38 (t, 1H, J=7.5 Hz), 7.49 (t, 1H, J=7.5 Hz), 8.32 (d, 1H, J=7.8 Hz, ArH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.39, 61.72, 102.52, 123.15, 124.26, 125.69, 127.81, 128.61, 129.75, 132.72, 133.59, 133.67, 143.84, 150.00, 154.27; DEPT-135: δ 21.10, 61.41, 102.23, 122.87, 125.41, 127.52, 128.32, 129.47, 132.43. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.95; H, 5.7; N, 5.3. Found: 76.8; H, 6.0; N, 5.85.

3-Pentylidene *N*-*p*-anisyl isoindolinone 73 and 3-pentylidene *N*-methyl isoindolinone 75. 2-Hexynylbenzamides **44**, and **45** were synthesised according to condition B using *n*-hexyne **19** as a terminal alkyne and cyclised by condition D to yield the isoindolinones **73**, **75** and the isoquinolinones **74**, **76**.

(*Z*)-3-Pentylidene-*N*-*p*-anisyl isoindolin-1-one 73. Colourless amorphous powder (EtOH); mp 159–160°C; IR: ν_{max} (KBr) 2985, 1705, 1640, 1610, 1590, 1510, 1400, 1250, 1040, 830, 780, 700 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.68–1.12 (m, 3H, CH_3), 1.18–1.66 (m, 4H, $-(CH_2)_2-$), 2.32–2.90 (m, 2H, $-CH_2-$), 3.82 (s, 3H, OCH_3), 5.18 (t, 1H, J=8 Hz, =CH–), 6.78–7.98 (m, 8H, Ar-H). Anal. Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.9; N, 4.55. Found: C, 78.3; H, 6.8; N, 4.65.

3-Butyl-*N*-*p*-anisyl-1(2*H*)-isoquinolinone 74. Light yellow gum, IR: ν_{max} (KBr) 3000, 1650, 1630, 1600, 1510, 1430, 1350, 1030, 840, 760, 700 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.67–1.15 (m, 3H, CH_3), 1.18–1.68 (m, 4H, $-(CH_2)_2-$), 2.16–2.58 (m, 2H, $-CH_2-$), 3.78 (s, 3H, OCH_3), 5.85 (s, 1H, =CH–), 6.74–7.61 (m, 7H), 8.22–8.48 (m, 1H, Ar-H).

(*Z*)-3-Pentylidene-*N*-methyl isoindolinone 75. Colourless small needles (EtOH); mp 84–85°C; IR: ν_{max} (KBr) 3000, 1705, 1640, 1615, 1585, 1510, 1400, 1240, 1030, 820, 760, 700 cm^{-1}; ^1H NMR (60 MHz, CCl_4) δ 0.70–1.20 (m, 3H, CH_3), 1.25–1.72 (m, 4H, $-(CH_2)_2-$), 2.40–2.70 (m, 2H, $-CH_2-$), 3.15 (s, 3H, N-CH_3), 5.30 (t, 1H, J=8 Hz, =CH–), 7.10–7.90 (m, 4H, Ar-H). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.1; H, 7.95; N, 6.5. Found: C, 78.4; H, 8.1; N, 6.65.

3-Butyl-*N*-methyl-1(2*H*)-isoquinolinone 76. Light yellow gum, IR: ν_{max} (KBr) 3000, 1650, 1630, 1610, 1515, 1440, 1350, 1020, 830, 760, 700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 0.82–1.12 (m, 3H, CH_3), 1.45–1.84 (m, 4H, $-(CH_2)_2-$), 2.52–2.82 (m, 2H, $-CH_2$-), 6.36 (s, 1H, =CH–), 7.35–7.68 (m, 3H), 8.30–8.52 (m, 1H, Ar-H).

Synthesis of 3-alkyl isoindolinones 78–88 via hydrogenation of isoindolinones 46, 48, 49, 51, 52, 55, 63, 65–67, 70: typical procedure

A mixture of 3-benzylidene-*N*-*p*-anisyl isoindolin-1-one **51** (100 mg, 0.305 mmol) was hydrogenated in glacial acetic acid (10 mL) in the presence of Pd–C (10%, 30 mg) at room temperature under atmospheric pressure for 24 h. The reaction mixture was filtered through celite. The residue obtained after removal of solvent was dissolved in $CHCl_3$ and washed with a saturated solution of $NaHCO_3$, and distilled water then dried over Na_2SO_4 (anhyd.). The residue obtained after removal of solvent was purified by column chromatography on silica gel to yield 3-benzyl-*N*-*p*-anisyl isoindolin-1-one. In the case of compounds **78**–**88** glacial acetic acid was used as solvent and in the other cases EtOH was used as solvent.

3-Methyl-*N*-benzyl isoindolin-1-one 78. Colourless amorphous powder (EtOH); mp 143–146°C; IR: ν_{max} (KBr) 3000, 1680, 1610, 1515, 1460, 1390, 1300, 1250, 1040, 840, 760 cm^{-1}; UV: λ_{max}/nm 275.01 ($\log \epsilon$ 4.03), 227.3 (4.20); ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (d, 3H, J=9 Hz, CH_3), 4.24 (d, 1H, J=15 Hz, N-CH_2), 4.35 (q, 1H, J=9 Hz, C-3H), 5.32 (d, 1H, J=15 Hz, N-CH_2), 7.23–7.53 (m, 8H), 7.87 (d, 1H, J=9 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 18.44, 43.79, 55.35, 122.40, 124.19, 127.96, 128.45, 128.53, 129.15, 132.05, 137.67, 147.41, 168.50; DEPT: 18.15, 43.79, 55.06, 122.11, 123.91, 127.67, 128.16, 128.24, 128.87, 131.68. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.95; H, 6.35; N, 5.9. Found: C, 80.7; H, 6.1; N, 6.2.

3-Methyl-*N*-*p*-tolyl isoindolin-1-one 79. Colourless powder (EtOH); mp 80–82°C; IR: ν_{max} (KBr) 3000, 1680, 1615, 1510, 1450, 1370, 1300, 1110, 830, 760, 720, 690 cm^{-1}; UV: λ_{max}/nm 274.8 ($\log \epsilon$ 4.06), 227.6 (4.21) nm; ^1H NMR (60 MHz, CCl_4) δ 1.42 (d, 3H, CH_3, J=6 Hz), 2.35 (s, 3H, CH_3), 5.13 (q, 1H, J=6 Hz, C-3H), 7.10–7.95 (m, 8H, Ar-H). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.95; H, 6.35; N, 5.9. Found: C, 81.15; H, 6.4; N, 5.6.

3-Methyl-*N*-*p*-anisyl isoindolin-1-one 80. Colourless powder (EtOH); mp 88–90°C; IR: ν_{max} (KBr) 3000, 1680, 1640, 1515, 1470, 1440, 1390, 1300, 1230, 1180, 1040, 840, 760 cm^{-1}; λ_{max}/nm 281.6 (log ϵ 3.98), 227.4 (4.24); ^1H NMR (60 MHz, $CDCl_3$) δ 1.42 (d, 3H, CH_3, J=6 Hz), 3.85 (s, 3H, OCH_3), 5.08 (q, 1H, J=6 Hz, C-3H), 6.95–8.00 (m, 8H, Ar-H). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.85; H, 5.95; N, 5.5. Found: C, 75.75; H, 6.0; N, 5.25.

3-Methyl-*N*-*m*-chlorophenyl isoindolin-1-one 81. Colourless powder (EtOH); mp 108–110°C; IR: ν_{max} (KBr) 3000, 1690, 1600, 1485, 1360, 1150, 860, 780, 760, 700, 690 cm^{-1}; UV: λ_{max}/nm 274.8 (log ϵ 4.13); ^1H NMR (60 MHz, $CDCl_3$) δ 1.50 (d, 3H, J=6 Hz, CH_3), 5.20 (q, 1H, J=6 Hz, C-3H), 7.20–8.05 (m, 8H, Ar-H). Anal. Calcd for $C_{15}H_{12}ClNO$: C, 69.9; H, 4.7; N, 5.4. Found: C, 70.2; H, 5.0; N, 5.55.

3-(2′-Hydroxy-2′-methylpropyl)-*N*-*p*-tolyl isoindolin-1-one 82. Light yellow powder (EtOH); mp 160–163°C; IR: ν_{max} (KBr) 3480, 2980, 1690, 1610, 1510, 1470, 1400, 1150, 810 cm^{-1}; UV: λ_{max}/nm 273.4 (log ϵ 4.00); 225.8 (4.15); ^1H NMR (60 MHz, $CDCl_3$+CCl_4) δ 1.23 (s, 6H, 2×CH_3), 1.97 (d, 2H, J=4 Hz, CH_2), 2.39 (s, 3H, CH_3), 5.33 (t, J=4 Hz, 1H, C-3H), 7.16–8.03 (m, 8H, Ar-H). Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.25; H, 7.15; N, 4.75. Found: C, 77.6; H, 7.3; N, 4.7.

3-Benzyl isoindolin-1-one 83. Colourless small needles (EtOH); mp 126–128°C; IR: ν_{max} (KBr) 3200, 3000, 1680, 1610, 1510, 1470, 1395, 1150, 830, 760, 700 cm^{-1}; UV: λ_{max}/nm 282.5 (log ϵ 4.01), 225.3 (4.11); ^1H NMR (300 MHz, $CDCl_3$) δ 2.88 (dd, 1H, J=9, 12 Hz, CH_2), 3.16 (dd, 1H, J=6, 12 Hz, CH_2), 4.80 (dd, 1H, J=6, 9 Hz, C-3H), 7.18–7.31 (m, 6H), 7.42–7.53 (m, 2H), 7.82 (d, 1H, J=9 Hz, Ar-H), 10.35 (s, 1H, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 41.63, 58.47, 123.20, 124.25, 127.51, 128.74, 129.17, 129.74, 132.11, 132.40, 137.26, 147.26, 171.10. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.7; H, 5.85; N, 6.25. Found: C, 80.35; H, 5.8; N, 6.35.

***N*,3-Dibenzyl isoindolin-1-one 84.** Colourless powder (EtOH); mp 83–84°C; IR: ν_{max} (KBr) 3000, 1670, 1600, 1420, 1290, 1160, 750, 740, 700 cm^{-1}; UV: λ_{max}/nm 281.7 (log ϵ 4.02), 224.3 (4.15); ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 (dd, 1H, J=7.8, 13.8 Hz, CH_2), 3.38 (dd, 1H, J=4.8, 13.8 Hz, CH_2), 4.23 (d, 1H, J=15 Hz, N-CH_2), 4.58 (dd, 1H, J=4.8, 7.8 Hz, C-3H), 5.47 (d, 1H, J=15 Hz, N-CH_2), 6.88 (d, 1H, J=6.6 Hz), 7.86 (d, 1H, J=2.1 Hz, Ar-H); ^{13}C NMR (300 MHz, $CDCl_3$) δ.38.31, 44.17, 59.52, 122.87, 123.72, 126.92, 127.57, 128.07, 128.64, 128.70, 129.59, 131.02, 131.90, 135.97, 136.97, 145.01, 168.36, DEPT: 38.51, 44.37, 59.72, 123.07, 123.93, 127.14, 127.79, 128.28, 128.69, 128.92, 129.59, 131.24. Anal. Calcd for $C_{22}H_{19}NO$: C, 84.3; H, 6.1; N, 4.45. Found: C, 84.25; H, 6.35; N, 4.15.

3-Benzyl-*N*-phenyl isoindolin-1-one 85. Colourless small needles (EtOH); mp 122–123°C; IR: ν_{max} (KBr) 3000, 1680, 1600, 1500, 1390, 1150, 700, 7220, 760 cm^{-1}; UV: λ_{max}/nm 281.3 (log ϵ 4.00), 224.6 (4.02); ^1H NMR (60 MHz, $CDCl_3$) δ 2.76 (dd, 1H, J=8, 14 Hz, CH_2), 3.28 (dd, 1H, J=4, 14 Hz, CH_2), 5.33 (dd, 1H, J=4, 8 Hz, C-3H), 6.68–7.85 (m, 14H, Ar-H). Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.7; N, 4.65. Found: C, 84.1; H, 5.9; N, 4.65.

3-Benzyl-*N*-*p*-anisyl isoindolin-1-one 86. Colourless small needles (EtOH); mp 130–133°C; IR: ν_{max} (KBr) 3000, 1680, 1580, 1510, 1395, 1300, 1220, 1020, 830, 760, 725, 700, 630 cm^{-1}; UV: λ_{max}/nm 283.4 (log ϵ 4.01), 224.2 (4.01); ^1H NMR (200 MHz, $CDCl_3$) δ 2.79 (dd, 1H, J=8.4 Hz, J=13.7 Hz, CH_2), 3.37 (dd, 1H, J=3.6, 13.7 Hz, CH_2), 3.86 (s, 3H, OCH_3), 5.35 (dd, 1H, J=3.6, 8.4 Hz, C-3H) 6.88–7.49 (m, 12H), 7.81–7.86 (m, 1H, Ar-H) Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.2; H, 5.8; N, 4.25. Found: C, 80.35; H, 6.1; N, 3.9.

3-Benzyl-*N*-*m*-chlorophenyl isoindolinone 87. Small colourless needles (EtOH); mp 108–109°C; IR: ν_{max} (KBr) 3000, 1680, 1600, 1590, 1570, 1380, 1260, 1180, 800, 750, 690 cm^{-1}; UV: λ_{max}/nm 276.2 (log ϵ 4.09), ^1H NMR (60 MHz, CCl_4) δ 2.73 (dd, 1H, J=8, 14 Hz, CH_2), 3.29 (dd, 1H, J=4, 14 Hz, CH_2), 5.26 (dd, 1H, J=4, 8 Hz, C-3H), 6.82–7.75 (m, 13H, Ar-H). Anal. Calcd for $C_{21}H_{16}ClNO$: C, 75.55; H, 4.8; N, 4.2. Found: C, 75.2; H, 4.8; N, 4.3.

3-*p*-Methoxybenzyl-*N*-benzyl isoindolin-1-one 88. Colourless small needles (EtOH); mp 112–114°C; IR: ν_{max} (KBr) 3000, 1670, 1600, 1420, 1290, 1160, 1750, 740, 700 cm^{-1}; UV: λ_{max}/nm 283.3 (log ϵ 4.00), 225.1 (4.02); ^1H NMR (300 MHz, $CDCl_3$) 2.78 (dd, 1H, J=7.8, 13.8 Hz, CH_2), 3.32 (dd, 1H, J=4.8 Hz, 13.8 Hz, CH_2), 3.77 (s, 3H, OCH_3), 4.18 (d, 1H, J=15 Hz, N-CH_2), 4.53 (dd, 1H, J=4.8, 7.8 Hz, C-3H), 5.47 (d, 1H, J=15 Hz, N-CH_2), 6.81 (d, 2H, J=8.7 Hz, Ar-H), 6.87–6.93 (m, 3H), 7.24–7.42 (m, 7H), 7.83–7.85 (m, 1H, Ar-H); ^{13}C NMR (85.5 MHz, $CDCl_3$) δ 37.73, 44.61, 55.63, 60.08, 114.28, 123.41, 124.18, 128.22, 128.32, 128.96, 129.21, 130.84, 131.49, 132.43, 137.50, 145.56, 158.95, 168.87; DEPT: 37.42, 44.32, 55.34, 59.79, 113.97, 123.13, 123.89, 127.80, 128.29, 128.93, 130.56, 131.21. Anal. Calcd for $C_{23}H_{21}NO$: C, 80.45; H, 6.15; N, 4.1. Found: C, 80.7; H, 5.9; N, 4.35.

Synthesis of 3-(5′-uracilyl)methylidene-*N*-*m*-chlorophenyl isoindolinone 89. (*Z*)-3-(2′,4′-Dimethoxypyrimidin-5′-yl)methylidene-*N*-*m*-chlorophenyl isoindolin-1-one **58** (110 mg, 0.27 mmol) was refluxed in 6 N HCl (4 mL) at 100°C for 4 h. The reaction mixture was cooled and filtered. The residue obtained was washed with H_2O (3×10 mL) and dried at room temperature. Crystallisation from methanol and few drops of DMF afforded a colourless powder (methanol-DMF) in quantitative yield, mp >250°C decomp; IR: ν_{max} (KBr) 3210, 3040, 1720, 1680 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$+DMSO-d_6) δ 6.50 (s, 1H, =CH–), 6.63 (s, 1H, =CH), 7.28–8.10 (m, 8H, Ar-H). Anal. Calcd for $C_{19}H_{12}ClN_3O_3$: C, 62.4; H, 33; N, 11.5. Found: 62.02; H, 3.35; N, 11.1.

Acknowledgements

We gratefully acknowledge CSIR, Government of India (Project No. 01(1385)/95-EMR-II) for financial support.

References

1. A preliminary account has appeared: Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435–1437.
2. On study leave from Bangladesh University of Engineering and Technology, Dhaka, Bangladesh.
3. (a) Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 39–42. (b) Valencia, E.; Freyer, J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599–602. (c) Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M. *Tetrahedron* **1984**, *40*, 3957–3962. (d) Valencia, E.; Fajardo, V.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993–996.
4. (a) Omura, S.; Iwai, Y.; Hirano, A.; Nakagawa, A.; Awaya, J.; Tsuchiya, H.; Takahashi, Y.; Masuma, R. *J. Antibiot.* **1977**, *30*, 275. (b) Omura, S.; Iwai, Y.; Hirano, A. *Japan Kokai* 7873, 501; *Chem. Abstr.* **1978**, *89*, 178086b. (c) Tamaoki, T.; Nomoto, H.; Takahashi, I.; Kato, Y.; Morimoto, M.; Tomita, F. *Biochem. Biophys. Res. Commun.* **1986**, *135*, 397–398. (d) Oka, S.; Kodama, M.; Takeda, H.; Tomizuka, N.; Suzuki, H. *Agric. Biol. Chem.* **1986**, *50*, 2723.
5. Rothweiter, W.; Tamm, Ch. *Experientia*, **1966**, *22*, 750; Aldridge, D. C.; Armstrong, J. J.; Speake, R. N.; Turner, W. B. *J. Chem. Soc., Chem. Commun.* **1967**, 26–27.
6. (a) Binder, M.; Tamm, C. *Angew. Chem., Int. Ed.*, **1973**, *12*, 370–380. (b) Tanenbaum, S. W.; Ed. *Frontiers of Biology*; North-Holland Publishing Co: New York, 1980; Vol. 46.
7. Ferland, J.-M.; Demerson, C. A.; Humber, L. G. *Can. J. Chem.* **1985**, *63*, 361–365.
8. (a) Linden, M.; Hadler, D.; Hofmann, S. *Hum. Psychopharmacol.* **1997**, *12*, 445–452. (b) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499–1502. (c) Zhuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157–166. (d) Norman, M. H.; Minick, D. J.; Rigdon, G. C. *J. Med. Chem.* **1998**, *39*, 149–157.
9. Li, S.; Wang, X.; Guo, H.; Chen, L. *Yiyano Gongye* **1985**, *16*, 543; *Chem. Abstr.* **1986**, *105*, 6378n.
10. Laboratori Baldacci, S. P. A. Jpn. Patent JP 59 46 268, 1984; *Chem. Abstr.* **1984**, *101*, 54922.
11. Lippmann, W. US Patent 4, 1981, 267, 189; *Chem. Abstr.* **1981**, *95*, 61988m.
12. Achinami, K.; Ashizawa, N.; Kobayasui, F. Jpn. Patent JP *03*, **1991**, *133*, 955., *Chem. Abstr.* **1991**, *115*, 255977j.
13. (a) Govindachari, T. R.; Ravindranath, K. R.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1215–1218. (b) Pendrak, I.; Barney, S.; Wittrock, R.; Lambert, D. M.; Kingsbury, W. D. *J. Org. Chem.* **1994**, *59*, 2623–2625. (c) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491–2517.
14. (a) Taylor, E. C.; Zhou, P.; Jenning, L. D.; Mao, Z.; Hu, B.; Jun, J.-G. *Tetrahedron Lett.* **1997**, *38*, 521–524. (b) Fuska, J.; Fuskova, A.; Proksa, B. *Zb. Pr. Chemickotechnol Fak, SVST*, 1979–1981 (pub. 1986), 285–291; *Chem. Abstr.* **1987** *106*, 95582k.
15. (a) Kim, J. N.; Ryu, E. K. *Synth. Commun.* **1996**, *26* (1), 67–74. (b) Takeda Chemical Industries Ltd., Jpn., Kokoi Tokkyo Koho JP, 58, 174, 362; *Chem. Abstr.* **1984**, *100*, 51452q.
16. Brever, E.; Zbaida, Z. *Tetrahedron Lett.* **1975**, *31*, 499–504.
17. Inubushi, Y.; Tsuda, Y.; Konita, T.; Matsumoto, S. *Chem. Pharm. Bull., Tokyo* **1964**, *12*, 749; **1968**, *16*, 1014; *Chem. Abstr.* **1964**, *61*, 9541d; **1968**, *69*, 87256j.
18. Vedejs, E.; Campbell, J. B.; Jr.; Gadwood, R. C.; Rodger, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534–1546. (b) Marsili, A.; Scartoni, V.; Morelli, I.; Pierangeli, P. *J. Chem. Soc, Perkin Trans. 1* **1977**, 959–965. (c) Othman, M; Pigeon, P.; Decroix, B. *Tetrahedron* **1997**, *53*, 2495–2504.
19. Gabriel, S. *Ber* **1885**, *18*, 3470–3480.
20. Honzl *J. Coll. Czech. Chem. Commun.* **1956**, *21*, 725–742.
21. Perjessy, A.; Lacova, M.; Hrnciar, P. *Coll. Czech. Chem. Commun.* **1971**, *35*, 2775–2784.
22. (a) Heidenbluth, V. K.; Tonjes, H.; Scheffier, R. *J. Prakt. Chem.* **1965**, *30* (4)., 204–217. (b) Ang, W. S.; Halton, B. B. *Aust. J. Chem.* **1971**, *24*, 851–856.
23. (a) Watanabe, H.; Mao, C.-L.; Barnish, I. T.; Hauser, C. R. *J. Org. Chem.* **1969**, *34*, 919–926. (b) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1188–1191. (c) Hendi, M. S.; Natalie, K. J.; Hendi Jr., S. B.; Campbell, J. A.; Greenwood, T. D.; Wolfe, J. F. *Tetrahedron Lett.* **1989**, *30*, 275–278. (d) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313–10330. (e) Couture, A.; Deniau, E.; Ionescu, D.; Grandclaudon, P. *Tetrahedron Lett.* **1998**, *39*, 2319–2320.
24. (a) Flitsch, W.; Peters, H. *Tetrahedron Lett.* **1969**, 1161–1162. (b) Mali, R. S.; Yeola, S. *Synthesis* **1986**, 755. (c) Epsztajn, J.; Grzelak, R.; Jozwiak, A. *Synthesis* **1996**, 1212–1216.
25. Gutierrez, A. J.; Shea, K. J.; Svoboda, J. J. *J. Org. Chem.* **1989**, *54*, 4335–4344.
26. (a) Brewster, J. H.; Fusco, A. M.; Carosino, L. E.; Corman, B. G., *J. Org. Chem.* **1963**, *28*, 498–501. (b) Milewska, M. J.; Bytner, T.; Polonski, T. *Synthesis* **1996**, 1485–1488.
27. (a) Yamamoto, I.; Tabo, Y.; Gotoh, H. *Tetrahedron Lett.* **1971**, 2295–2296. (b) Dominh, T.; Johnson, A. L.; Jones, J. E.; Senise, P. P.; Jr. *J. Org. Chem.* **1977**, *42*, 4217–4221. (c) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *Chem. Soc., Chem. Commun.* **1985**, 1183–1184. (d) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353–355.
28. Nefkens, G. H. L.; Zwanenburg, B. *Tetrahedron* **1985**, *41*, 6063–6066.
29. Aubert, T.; Farnier, M.; Guilard, R.; Can *J. Chem.* **1990**, *68*, 842–851.
30. Guillaumel, J.; Boccara, N.; Demersemann, P.; Royer, R. *J. Chem. Soc., Chem. Commun.* **1988**, 1604–1605.
31. (a) Freccero, M.; Fasani, E.; Albini, A. *J. Org. Chem.* **1993**, *58*, 1740–1745. (b) Weidner-Wells, M. A.; Oda, K.; Mazzocchi, P. H. *Tetrahedron* **1997**, *53*, 3475–3486.
32. Rowe, F. M.; McFadyen, W. T.; Peters, A. T. *J. Chem. Soc.* **1947**, 468–473.
33. (a) Pojer, P. M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1968**, *21*, 1375–1379. (b) Camilleri, P.; Cassola, A. *J. Chem. Soc., Chem. Commun.* **1978**, 807–808. (c) Rowe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603–4607. (d) Takeuchi, H.; Eguchi, S. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2149–2154.
34. Wilkinson, G.; Stone, F. G. A.; Abel, E. W. 1st ed.; *Comprehensive Organometallic Chemistry*; Pergamon: Oxford, 1982; Vol. 1.
35. (a) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* **1978**, *43*, 1684–1687. (b) Larock, R. C.; Liu, C.-L.; Lau, H. H.; Varaprath, S. *Tetrahedron Lett.* **1984**, *25*, 4459–4462. (c) Burns, B.; Grigg, R.; Santhakumar, V; Sridharan, V.; Stevenson, P.; Worakun, T. *Tetrahedron* **1992**, *48*, 7297–7320. (e) Cho, C. S.; Jiang, L. H. Shim, S. C. *Synth. Commun.*, **1998**, *28* (5), 849–857.
36. Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: London, 1985; Heck, R. F. *Org. React.* **1982**, *27*, 345–390; Heck, R. F. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Malleron, J. L.; Fiaud, J. C..; Legos, J. Y. *Handbook of Palladium-catalysed Organic Reactions*; Academic: London, 1997.

37. (a) Zhang, Y.; Negishi, E.-I. *J. Am. Chem. Soc.*, **1989**, *11*, 3454 Oxford 3456. (b) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 12491–12509. (c) Ma, S.; Negishi, E.-I. *J. Am. Chem. Soc.* **1995**, *117*, 6345–6357.
38. (a) Hegedus, L. S. *Angew Chem. Int., Ed. Engl.* **1988**, *27*, 1113–1126. (b) Larock, R. C.; Berrios-Pena, N. G.; Fried, C. A.; Yum, E. K.; Tu, C.; Leong, W. *J. Org. Chem.* **1993**, *58*, 4509–4510. (c) Negishi, E.-I; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393.
39. (a) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271. (b) Jeschke, T.; Wensbo, D.; Annby, U.; Gronowitz, S.; Cohen, L. A. *Tetrahedron Lett.* **1993**, *34*, 6471–6474.
40. (a) Larock, R. C.; Berrios-Pena, N.; Fried, C. A. *J. Org. Chem.* **1991**, *56*, 2615–2617; (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Pace, P. *Synlett* **1996**, 568–570.
41. (a) Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.* **1992**, 41–42; Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815–2820. (b) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.*, **1993**, 86–88; Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561–568.
42. Kundu, N. G.; Khan, M. W. *Tetrahedron Lett.* **1997**, *38*, 6937–6940.
43. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4469.
44. Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3711–3716.
45. Rossi, R.; Carpita, A.; Bigelli, G. *Tetrahedron Lett.* **1985**, *226*, 523–526. (b) Kundu, N. G.; Pal, M.; Chowdhury, C. *J. Chem. Res. (Synop.)* **1993**, 432–433.
46. Wilson, J. W.; Anderson, E. L.; Ullyot, G. E. *J. Org. Chem.* **1951**, 800–805.
47. Boyce, W. T.; Levine, R. *J. Org. Chem.* **1966**, 3807–3809.
48. Beugelmans, R.; Bois-Choussy, M. *Synthesis* **1981**, 729–731.
49. Couture, A.; Cornet, H.; Grandclaudon, P. *Tetrahedron* **1992**, *49*, 3857–3866.
50. Haimova, M. A.; Ognyanov, V. I.; Mollov, N. M. *Synthesis* **1980**, 845–847.
51. Couture, A.; Grandclaudon, P. *Synthesis* **1986**, 576–578.
52. (a) Khan, M. W.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *Acta Cryst. C* **1998**, *54*, 119–120. (b) Kundu, N. G.; Khan, M. W.; Guha, S.; Mukherjee, A. K. *Acta Cryst. C* **1999**, *55*, 239–241.
53. (a) Kundu, N. G.; Das, B.; Spears, C. R.; Majumder, A.; Kang, S.-I. *J. Med. Chem.* **1990**, *33*, 1975–1979. (b) Kundu, N. G.; Chaudhuri, L. N. *J. Chem. Res. (Synop.)* **1992**, 64–65; *J. Chem. Res. (Miniprint)* **1992**, 631–655. (c) Kundu, N. G.; Dasgupta, S. K.; Chaudhuri, L. N.; Mahanty, J. S.; Spears, C. P.; Shahinian, A. H. *Eur. J. Med. Chem.* **1993**, *228*, 473–479.
54. *Vogel's Text Book of Practical Organic Chemistry*, 5th ed.; ELBS, Longman Group Limited: London, 1989; p 931. (b) *Vogel's Text Book of Practical Organic Chemistry*, 5th ed.; ELBS, Longman Group Limited: London, 1989, p 1073. (c) *Vogel's Text Book of Practical Organic Chemistry*, 5th ed.; ELBS, Longman Group Limited: London, 1989; p 928.
55. *Vogel's Text Book of Practical Chemistry*, 5th ed.; ELBS, Longman, London, 1989, p 1363.
56. Prystas, M.; Sorm, F. *Coll. Czech. Chem. Commun.* **1964**, *29*, 121–129.
57. Bumagin, N. A.; Ponomaryov, A. B.; Beletskaya, I. P. *Synthesis* **1984**, 728–729.
58. (a) Jones, E. R. H.; McCombie, J. T. *J. Chem. Soc.* **1942**, 733–735. (b) Campbell, K. N.; Campbell, B. K.; Eby, L. T. *J. Am. Chem. Soc.* **1938**, *60*, 2882–2884.
59. King, A. O.; Negishi, E.-I. *J. Org. Chem.* **1978**, *43*, 358–360.
60. Kundu, N. G.; Schmitz, S. A. *J. Heterocycl. Chem.* **1982**, *19*, 463–465.
61. Villemin, D.; Goussu, D. *Heterocycles* **1989**, *29*, 1255–1257.