A Highly Regio and Stereoselective Synthesis of (Z)-3- Aryl(alkyl)idene Isoindolin-1-ones via Palladium Catalyzed Annulation of Terminal Alkynes

M. Wahab Khan[1] and Nitya G. Kundu*

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

Fax: (91) (33) 473 2805; e-mail: ocngk@iacs.ernet.in

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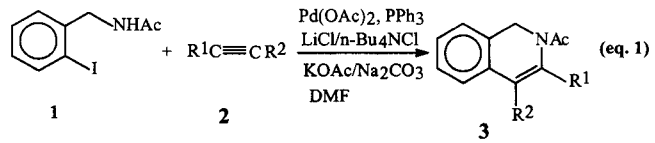
Abstract: *o*-Iodobenzamide or its *N*-substituted derivatives **4-10** and terminal alkynes **11-17** reacted in DMF in the presence of bis(triphenylphosphine)palladium(II)chloride, cuprous iodide and triethylamine leading to (*Z*)-3- arylidene isoindolin-1-ones (**22, 24, 27** and **28**) or *o*-alkynyl *N*-substituted benzamides (**I**). The latter could be cyclised with sodium in ethanol in a completely regio and stereoselective manner to (*Z*)-3-aryl(alkyl)idene isoindolin-1-ones **18-35.**

Although there have been several reports of the synthesis of the isoindolinone (phthalimidine) compounds in the literature,[2] efforts towards the synthesis of these interesting compounds through palladium-catalyzed reactions are lacking.[3] Palladium-catalyzed reactions[4] have been extensively utilised for carboannulation[5] and heteroannulation[6] processes. Larock and others[7-11] have reported the synthesis of various aromatic heterocycles *via* palladium-catalyzed annulation of internal alkynes. Larock and co-workers[7] have shown that *o*-iodo-*N*-acetyl benzylamine **1** reacted with internal alkynes **2** to produce 1,2-dihydroisoquinolines **3**. The palladium-catalyzed cyclisation of *o*-alkynyl benzamides to isocarbostyrils has also been reported.[12]



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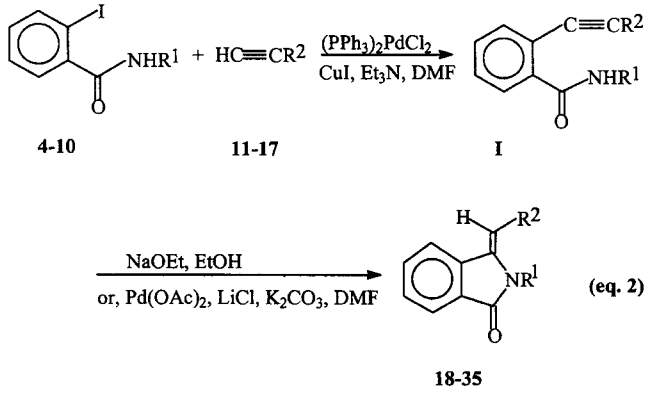
We, however, now report a new strategy for the regio and stereoselective synthesis of isoindolinones **18-35** *via* the palladium-catalyzed condensation of *o*-iodobenzamides **4-10** with terminal alkynes **11-17** and subsequent cyclisation (eq. 2). Our results (Table 1) demonstrate that a number of (*Z*)-3-aryl(alkyl)idene isoindolin-1-ones **18-35** were formed without any formation of the corresponding isoquinolinones.



The reactions were usually carried out by heating a mixture of *o*-iodobenzamide or, its *N*-substituted derivatives **4-10** (1 mmol) and the alkynes **11-15** (1.2 mmol) in DMF (5 mL) at 80°C for 16h in the presence of $(Ph_3P)_2PdCl_2$ (3.5 mol%), CuI (8 mol%)[13] and triethylamine (4 mmol) (entries 1-13, condition **1a**). However, with (trimethylsilyl) acetylene **16** or dimethylpropargyl alcohol **17,** 2.0 equivalents of the alkyne were used and the reactions were carried out at room temperature for a longer period (24h) (condition **1b**). In the case of

Table 1. Palladium-Catalyzed Heteroannulation of Terminal Alkynes to Isoindolinones (eq. 2)

Entry	2-Iodo-benzamides	R^1	Alkynes[a]	R^2	Conditions[b]	Iso-indolinones[c]	Overall Yields[d] (%)
1	**4**	H	**11**	Ph	**1a, 2a**	**18**	50
2	**5**	Me	**11**	Ph	**1a, 2a**	**19**	52
3	**6**	CH_2Ph	**11**	Ph	**1a, 2a**	**20**	60
4	**7**	Ph	**11**	Ph	**1a, 2a**	**21**	41
5	**8**	C_6H_4Me-p	**11**	Ph	**1a**	**22**	34
6	**9**	C_6H_4OME-*p*	**11**	Ph	**1a, 2a**	**23**	77
7	**10**	C_6H_4Cl-*m*	**11**	Ph	**1a**	**24**	86
8	**4**	H	**12**	C_6H_4OMe-*p*	**1a, 2a**	**25**	75
9	**6**	CH_2Ph	**12**	C_6H_4OMe-*p*	**1a, 2a**	**26**	65
10	**9**	C_6H_4OMe-*p*	**12**	C_6H_4OMe-*p*	**1a**	**27**	82
11	**10**	C_6H_4Cl-*m*	**13**	2,4-dimethoxy-pyrimidin-5-yl	**1a**	**28**	81
12	**4**	H	**14**	C_6H_4Cl-*m*	**1a, 2a**	**29**	50
13	**5**	Me	**15**	1-naphthyl	**1a, 2a**	**30**	41
14	**4**	H	**16**	$SiMe_3$	**1b, 2a**	**31**	65
15	**5**	Me	**16**	$SiMe_3$	**1b, 2a**	**32**	66
16	**6**	CH_2Ph	**16**	$SiMe_3$	**1b, 2a**	**33**	61
17	**8**	C_6H_4Me-*p*	**16**	$SiMe_3$	**1b, 2a**	**34**	71
18	**8**	C_6H_4Me-*p*	**17**	CMe_2OH	**1b, 2b**	**35**	60

[a]Alkynes (**11-15**). 1.2 mmol; alkynes (**16,17**) 2 mmol/1 mmol of **4-10**

[b]**1a**, $(PPh_3)_2PdCl_2$ (3.5 mol %), CuI (8 mol %), Et_3N(4 mmol.), DMF (5 mL), 80°C, 16h; **1b**, $(PPh_3)_2PdCl_2$ (3.5 mol %), CuI (8 mol %), Et_3N (4 mmol), DMF (5 mL), rt., 24h; **2a**, NaOEt (1.2 mmol) in EtOH, reflux, 4h; **2b**, $Pd(OAc)_2$ (5 mol %), LiCl (1 mmol), K_2CO_3 (2.5 mmol), DMF (5 mL), 100°C, 16h; For compounds **31-34**, R^2 = H; satisfactory spectroscopic data were obtained for all the compounds reported. [d]Yields are based on the 2-iodobenzamides and of chromatographically pure isoindolinones

entries 5, 7 10 and 11 the cyclised products (isoindolinones **22, 24, 27** and **28** respectively) were directly obtained usually in excellent yields. In the case of entry 5, the yield was lower due to the concurrent formation of some open chain condensation product (**I**). In other cases (entries 1-4, 6, 8, 9, 12-17), however the open chain condensation products (**I**) were the major products which could then be cyclised in the same pot, after removal of solvent, by refluxing with sodium ethoxide in ethanol (condition **2a**) for 4h to yield isoindolinones **18-21, 23, 25, 26, 29-34** respectively. Cyclisation could also be performed with pure condensation products (**I**) which were isolated and characterised completely. The yields were almost the same in both the cases. Where (trimethylsilyl)acetylene **16** was used as the starting alkyne (entries 14-17), the *N*-substituted 3-methylene isoindolinones **31-34** were obtained as the final products exclusively. The trimethylsilyl group was completely removed under the cyclisation conditions. The cyclisation could also be carried out by heating the open chain product (I, entry 18) with $Pd(OAc)_2$ (5 mol%), LiCl (1 mmol) and K_2CO_3 (2.5 mmol) in DMF (5 mL) for 16h at 100°C.[11] The cyclisation of other acyclic intermediates could also be achieved under Larock's condition[11], however, somewhat lower yields were obtained.

It is to be observed that reactive alkynes, e. g. phenylacetylene **11** and *m*-chlorophenylacetylene **14** underwent considerable dimerisation[14] under the reaction conditions lowering the yields of the intermediates (**I**) which led to poorer yields (entries 1-5, 12). However, less reactive alkynes, e. g. **12, 13** and **16**, led to good yields of the isoindolinones (entries 8-11, 14-17). Also *m*-chlorophenyl or *p*-anisyl substitution on the nitrogen of the *o*-iodobenzamide group led to a very fast cyclisation of the intermediate condensation products (**I**) thus giving rise to excellent overall yields of the isoindolinones (entries 6, 7, 10 and 11).

The structures of the isoindolinones followed from their analytical and spectroscopic data[15]. The *Z*-configuration was assigned from mechanistic considerations and comparison of the chemical shifts of the vinylic protons with those reported for similar compounds[2c]. The vinylic proton chemical shift for **35** also agreed with that reported for the corresponding phthalide of *Z*-configuration[16]. Lastly, single crystal X ray structure determinations[17] for **20** and **25** unequivocally established the (*Z*)-3 arylidene isoindolin-1-one structures for them. Thus, the regio and stereochemistry of the annulation process leading to the isoindolinones followed the major pattern which we observed in the case of heteroannulation of terminal alkynes to phthalides[18] and is in contrast to the observations of Larock[7] in the annulation of internal alkynes to isoquinolines.

In conclusion, we report for the first time a palladium-catalyzed procedure for an exceedingly efficient regio and stereoselective synthesis of (*Z*)-3-aryl(alkyl)idene isoindolin-1-ones. The method because of its milder reaction conditions, ready availability of starting materials and good yields compares well with the high temperature[2b,19] or multi-step procedures[2,20] available for the synthesis of isoindolinones. Particularly in view of the reported biological activities[21] of 3-benzylidene isoindolinones and the close similarities in structures between the isoindolinones and the indoles, many of which are of biological importance,[22] our method will open up an extensive investigation of isoindolinones for biological studies.

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15. For compounds **18-35,** ν_{max} 1700-1720 cm^{-1} (C=O of the γ-lactam). The ^1H NMR signal for the vinylic protons of compounds **18-30** was observed at δ 6.40-7.05; **30-34** had double doublets at δ 4.67-5.00 and δ 5.03-5.20 characteristic of the exo-methylene protons; hydrogenated products for **33** and **34** showed the characteristic methyl groups at δ 1.43-1.48 (d, 3H, J = 6 Hz); and the C_3-H of the isoindolinone ring at 5.05-5.20 (q, 1H, J = 6 Hz); **18**, mp. 183-184°C (lit[2e] mp. 178-181°C); **25** , mp. 200-201°C (lit[2b] mp. 202-203°C); **31** and **32**, unstable colorless oil;[2e] the ^{13}C NMR signal of the carbon in the carbonyl group in lactam

ring was found at δ 167-174; **18, 19**, and **21** were identical with samples synthesized by alternative procedure[2b] from mp., IR, U.V., and N.M.R. comparison. Physical data of compound **20:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 2H, N-CH_2), 6.52 (dd, *J* = 0.9 Hz, *J* = 7.5 Hz , 2H, aromatic-H), 6.73 (s, 1H, =CH-). 7.05-7.09 (m, 5H, aromatic-H), 7.25-7.29 (m, 3H, aromatic-H), 7.53 (td, *J* = 0.9 Hz, *J* = 7.5 Hz, 1H, aromatic-H), 7.63 (td, *J* = 1.2 Hz, *J* = 7.5 Hz, 1H, aromatic-H),. 7.75 (d, *J* = 7.5 Hz, 1H, aromatic-H), 7.94 (d, *J* = 7.5 Hz, 1H, aromatic-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.84(N-$\underline{C}H_2$), 107.54(=$\underline{C}$H-), 119.43($\underline{C}$H aromatic), 123.51($\underline{C}$H aromatic), 126.32($\underline{C}$H aromatic), 126.68($\underline{C}$H aromatic), 127.39($\underline{C}$H aromatic), 127.88($\underline{C}$ -3), 127.98($\underline{C}$H aromatic), 128.06($\underline{C}$H aromatic), 129.03($\underline{C}$H aromatic), 129.64($\underline{C}$H aromatic), 132.10($\underline{C}$H aromatic), 134.32($\underline{C}$ aromatic), 134.53($\underline{C}$ aromatic), 136.77($\underline{C}$ aromatic), 138.46($\underline{C}$ aromatic), 169.04($\underline{C}$=O); mp. 122-123°C; IR (KBr) 1705, 1650, 1495 cm^{-1}; UV(EtOH): 323.8, 271.2, 221.4 nm; Anal. Calcd. for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.49. Found :, 84.72; H, 5.74; N, 4.93. Compound **28** : ^{1}H 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. aromatic-H), 7.55-7.72 (m, 3H, aromatic-H), 7.85 (d, *J* = 9 Hz, 1H, aromatic-H), 7.94 (d, *J* = 6 Hz, 1H, aromatic-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.13(O$\underline{C}H_3$), 54.91(O$\underline{C}H_3$), 97.89(=$\underline{C}$H-), 108.96($\underline{C}$ pyrimidine), 119.78($\underline{C}$H aromatic), 124.04($\underline{C}$H aromatic), 125.78($\underline{C}$H aromatic), 127.37($\underline{C}$H aromatic), 127.62($\underline{C}$-3), 127.71($\underline{C}$H aromatic), 129.42($\underline{C}$H aromatic), 129.78($\underline{C}$H aromatic), 132.82($\underline{C}$H aromatic), 133.94($\underline{C}$ aromatic), 136.23($\underline{C}$ aromatic), 136.27($\underline{C}$ aromatic), 137.84($\underline{C}$ aromatic), 157.59($\underline{C}$H pyrimidine), 164.30($\underline{C}$ pyrimidine), 167.50($\underline{C}$ pyrimidine), 167.54($\underline{C}$=O); mp. 140-141°C; IR(KBr) 1710, 1590, 1550, 1400 cm^{-1}; UV(EtOH): 330.5, 274, 222.8 nm; Anal. Calcd. for $C_{21}H_{16}N_3O_3Cl$: C, 64.04; H, 4.09; N; 10.66. Found : C, 63.94; H, 4.31; N, 10.62. Compound **33** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.80 (d, *J* = 2.4 Hz, 1H, =CH-), 5.02 (s, 2H, N-CH_2), 5.15 (d, *J* = 2.4 Hz, 1H, =CH-), 7.25-7.91 (m, 9H, aromatic-H); ^{13} C NMR (75 MHz, $CDCl_3$) δ 43.05(N-$\underline{C}H_2$), 89.89(=$\underline{C}$H-), 119.82($\underline{C}$H aromatic), 123.23($\underline{C}$H aromatic), 127.03($\underline{C}$-3), 127.28($\underline{C}$H aromatic),127.49($\underline{C}$H aromatic), 128.55($\underline{C}$H aromatic), 129.10($\underline{C}$H aromatic), 129.41($\underline{C}$H aromatic), 131.97($\underline{C}$H aromatic), 136.33($\underline{C}$ aromatic), 136.75($\underline{C}$ aromatic), 141.47($\underline{C}$ aromatic), 168.00($\underline{C}$=O); mp. 118-119°C; IR(KBr) 1710, 1645, 1600, 1470 cm^{-1}; UV(EtOH): 306.8, 255.6, 224.2, 219.4 nm; Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.67; H, 5.56; N, 5.95. Found : C, 81.44; H, 5.67; N, 5.78.

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