



An Expedient Synthesis of Z-3-Alkylidene Isoindolinones via Combined Palladium Catalysed and Friedel-Crafts Reactions

Nitya G. Kundu* and M. Wahab Khan[†]

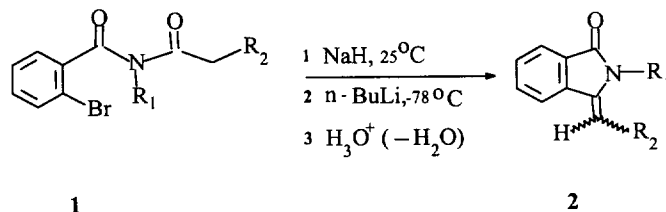
Department of Organic Chemistry, Indian Association for the
Cultivation of Science, Jadavpur, Calcutta - 700 032, India.

Abstract : N-Aryl(or, alkyl)-2-iodobenzamides underwent palladium-catalysed reaction with (trimethylsilyl)acetylene to form N-substituted-2-(trimethylsilyl)ethynyl benzamides, which on further Friedel-Crafts acylation and cyclisation yielded Z-3-alkylidene isoindolin-1-ones in a completely regio- and stereoselective manner. © 1997 Elsevier Science Ltd.

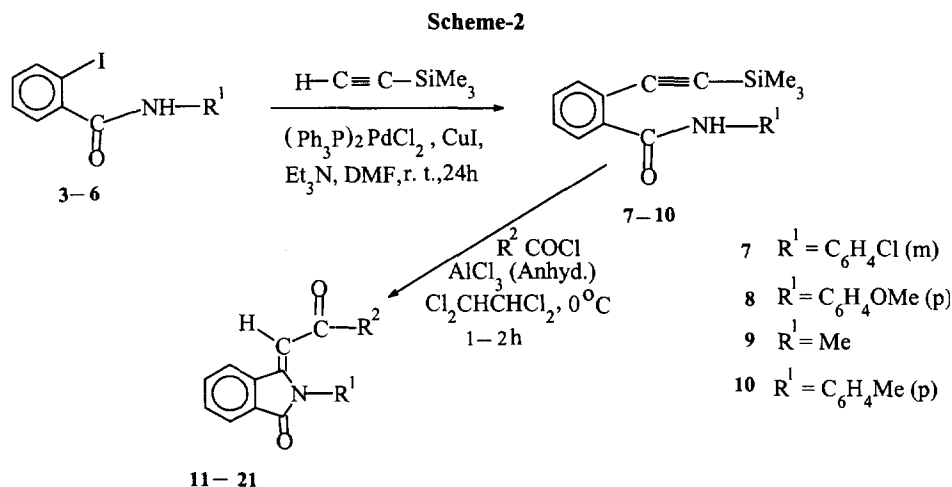
Isoindolinones (phthalimidines), particularly 3-alkylidene isoindolinones, have drawn considerable interest because of their reported biological activities² and close similarities in structures between the isoindolinones and the indoles, many of which are of biological importance.³ Although a few synthesis of these compounds have been reported,⁴⁻⁹ palladium-catalysed reactions for the synthesis of 3-alkylidene isoindolinones are limited.¹⁰ Recently we have developed several heterocyclic nuclei, e.g., benzofurans,¹¹ phthalides,¹² quinolines¹³ and benzodioxans¹⁴ through the palladium-catalysed heteroannulation of terminal alkynes. In continuation of these studies, we now report a novel approach where a palladium-catalysed reaction has been combined with Friedel-Crafts acylation and cyclisation to obtain Z-3-alkylidene isoindolinones in good to excellent yields in a completely regio- and stereoselective manner.

Recently, Wolfe and co-workers⁸ have reported a low temperature reaction where N-acyl-2-bromobenzamides **1** underwent metal-halogen exchange with n-BuLi to form N-acyl-2-lithiobenzamides which cyclised under acidic condition to 3-alkylidene phthalimidines **2** (Scheme 1).

Scheme-1



We found that N-alkyl or, N-aryl-2-iodobenzamides **3-6** underwent smooth reaction with (trimethylsilyl)acetylene in the presence of bis(triphenylphosphine)palladium(II)chloride and cuprous iodide at room temperature to yield 2-(trimethylsilyl)ethynyl benzamides **7-10** in excellent yields (86-89%). The latter on Friedel-Crafts reaction with acid chlorides or anhydrides afforded the 3-alkylidene isoindolin-1-ones **11-21** (Scheme 2) in good yields.



The reactions were carried out by stirring a mixture of *o*-iodobenzamide **3-6** (1 mmol), (trimethylsilyl)acetylene (2.0 mmol), $(\text{PPh}_3)_2\text{PdCl}_2$ (3.5 mol%), cuprous iodide (8 mol%) and triethylamine (4 mmol) in DMF at room temperature under nitrogen atmosphere for 24 hours to yield the 2-(trimethylsilyl) ethynyl benzamides **7-10** which were purified by column chromatography on silica gel (60-120 mesh). A mixture of the acyclic product **7-10** (1 mmol), anhydrous aluminium chloride (4 mmol) and acid chloride or anhydride (1.2 mmol) in tetrachloroethane was stirred at 0°C for 1-2 h (acid chloride) or 3 - 4 h (acid anhydride) when the 3-alkylidene isoindolinones **11-21** were obtained in good yields (Table I), purified by chromatography over neutral alumina.

The palladium-catalysed reactions between the *o*-iodobenzamides and (trimethylsilyl)acetylene proceeded in good yields (86-89%). However, the Friedel-Crafts reactions between the silyl derivatives **7-10** and the acid chlorides proceeded in variable yields (50 - 84%). It was observed that both aromatic and aliphatic acid chlorides underwent the reaction, to yield the 3-alkylidene isoindolinones, the aromatic acid chlorides giving better yields than the aliphatic acid chloride, e.g., acetyl chloride (entries 1 vs. 8 or entry 6 vs 9). Also acetic anhydride gave better yield than acetyl chloride (entry 10 vs 9). Furthermore, it was noticed that substitution on the nitrogen atom affected the yields of the isoindolinones. A *m*-chlorophenyl or *p*-anisyl substitution on the nitrogen atom gave better yields than the corresponding N-methyl derivative (entries 1 and 2 vs 3).

In conclusion, we have described for the first time a highly convenient and general procedure for the synthesis of a number of novel 3-alkylidene isoindolinones (e.g. 3-acylmethylene isoindolinones). The method is characterised by (i) ready availability of starting materials,¹⁵ (ii) relatively mild reaction conditions in contrast to the high temperature⁵ or low temperature⁸ reactions which are generally used for the synthesis of 3-alkylideneisoindolinones, and (iii) relatively good yields. Also, the reaction is highly regio¹⁶ and stereospecific¹⁷ - Z-3-alkylidene isoindolinones were obtained as the exclusive products.

Table 1: Z - 3 - Alkylidene Isoindolin -1- ones from o - Iodo - N - Substituted Benzamides (Scheme 2)

Entry	2 - Iodo benzamides ¹⁵	R ¹	Acid Chlorides or, Anhydrides	R ²	3 - Alkylidene isoindolinones ^{16,17}	Yields(%) ¹⁹
1	3	C ₆ H ₄ Cl- <i>m</i>	<i>p</i> -MeC ₆ H ₄ COCl	<i>p</i> -Me-C ₆ H ₄	11	84 (74)
2	4	C ₆ H ₄ OMe- <i>p</i>	<i>p</i> -MeC ₆ H ₄ COCl	<i>p</i> -Me-C ₆ H ₄	12	66 (59)
3	5	Me	<i>p</i> -MeC ₆ H ₄ COCl	<i>p</i> -Me-C ₆ H ₄	13	52 (45)
4	6	C ₆ H ₄ Me- <i>p</i>	<i>p</i> -MeOC ₆ H ₄ COCl	<i>p</i> -MeO-C ₆ H ₄	14	59 (49)
5	5	Me	<i>p</i> -MeOC ₆ H ₄ COCl	<i>p</i> -MeO-C ₆ H ₄	15	50 (44)
6	4	C ₆ H ₄ OMe- <i>p</i>	C ₆ H ₅ COCl	C ₆ H ₅	16	76 (68)
7	5	Me	C ₆ H ₅ COCl	C ₆ H ₅	17	72 (62)
8	3	C ₆ H ₄ Cl- <i>m</i>	CH ₃ COCl	Me	18	52 (46)
9	4	C ₆ H ₄ OMe- <i>p</i>	CH ₃ COCl	Me	19	56 (50)
10	4	C ₆ H ₄ OMe- <i>p</i>	(CH ₃ CO) ₂ O	Me	20	83 (74)
11	6	C ₆ H ₄ Me- <i>p</i>	(CH ₃ CO) ₂ O	Me	21	67 (59)

Acknowledgement

Financial assistance [Project No. 01 (1385)/ 95 / EMR-II] from the Council of Scientific and Industrial Research, Government of India, New Delhi, is gratefully acknowledged.

REFERENCES AND NOTES

- On study leave from Bangladesh University of Engineering and Technology, Dhaka, Bangladesh.
- Fuska, J.; Fuskova, A.; Proksa, B. *Neoplasms*, **1985**, 32(4), 407.
- Sundberg, R. J. "Pyrroles and their Benzo Derivatives - Synthesis and Applications" in *Comprehensive Heterocyclic Chemistry*, vol. 4, pp. 370-376, ed. Katrizky, A. R.; Rees, C.W., Pergamon Press, Oxford, 1984.
- White, J. D.; Mann, M.E. *Adv. Heterocycl. Chem.*, **1969**, 10, 113.
- Perjessy, A.; Lacova, M.; Hrniciar, P. *Coll. Czechoslov. Chem. Commun.*, **1971**, 36, 2775.
- Ang, W. S.; Halton, B. *Aust. J. Chem.*, **1971**, 24, 851.
- Marsili, A.; Scartini, V. *Gazz Chim. Ital.*, **1972**, 102, 806.
- Hendi, M. S.; Natalie, Jr., K. J.; Hendi, S. B.; Campbell, J. A.; Greenwood, T. D.; Wolfe, J. F. *Tetrahedron Lett.*, **1989**, 30, 275.
- Freccero, M.; Fasani, E.; Albini, A. *J. Org. Chem.*, **1993**, 58, 1740.

10. Cho, C. S.; Lee, J. W.; Lee, D. Y.; Shim, S. C.; Kim, T. J. *J. Chem. Soc., Chem. Commun.*, **1996**, 2115.
11. Kundu, N. G.; Pal, M.; Mahanty, J. S.; Dasgupta, S. K. *J. Chem. Soc., Chem. Commun.*, **1992**, 41.
12. Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.*, **1993**, 86.
13. Kundu, N. G.; Mahanty, J. S.; Das, P.; Das, B. *Tetrahedron Lett.*, **1993**, 34, 1625.
14. Chowdhury, C.; Kundu, N. G. *J. Chem. Soc., Chem. Commun.*, **1996**, 1067.
15. The 2-iodobenzamides were synthesised from the corresponding acid chlorides and the amines.
16. The structures of the compounds were established from IR, UV and NMR data. Only Z-3-alkylidene)isoindolin-1-ones were obtained. Some typical spectral data : N-*p*-methoxyphenyl-3-(2'-oxo-2'-*p*-tolyl)ethylidene isoindolin-1-one, **12**, m.p. 175-176°C; ν_{\max} (KBr)/cm⁻¹ 1720 (γ -lactam), 1650, 1610, 1515; λ_{\max} (EtOH) 335, 302, 230 nm; ¹H NMR (300 MHz, CDCl₃) δ 2.39 (s, 3H, CH₃), 3.88 (s, 3H, OCH₃), 6.52 (s, 1H, vinylic-H), 7.07-7.10 (m, 2H, Ar-H), 7.22 (d, 2H, *J*=7.8 Hz, Ar-H), 7.30-7.33 (m, 2H, Ar-H), 7.64-7.75 (m, 4H, Ar-H), 7.93 (dd, 1H, *J* = 1 Hz, *J* = 7.8 Hz, Ar-H), 8.93 (d, 1H, *J* = 7.5 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃) 21.61 (CH₃), 55.51 (OCH₃), 105.55, 113.94, 115.08, 123.49, 126.27, 127.29, 128.34, 128.59, 128.62, 128.87, 129.27, 129.79, 129.91, 131.68, 133.43, 133.88, 136.49, 143.68, 149.71, 159.82 (Ar-C), 167.32 (C₁=O), 189.52 (C₆H₄CO); Anal: Calc. for C₂₄H₁₉NO₃: C, 78.03; H, 5.18; N, 3.79. Found: C, 77.95; H, 5.16; N, 3.73.
N-Methyl-3-(2'-oxo-2'-phenyl)ethylidene isoindolin-1-one, **17**, m.p. 115-116°C; ν_{\max} (KBr)/cm⁻¹ 1700 (γ -lactam), 1665, 1610, 1585; λ_{\max} (EtOH) 349, 300, 229 nm; ¹H NMR (300 MHz, CDCl₃) δ 3.36 (s, 3H, N-CH₃), 6.66 (s, 1H, vinylic-H), 7.48-7.62 (m, 5H, Ar-H), 7.82-7.85 (m, 1H, Ar-H), 8.01-8.04 (m, 2H, Ar-H), 8.88 (d, 1H, *J* = 6 Hz, Ar-H); ¹³C NMR (75 MHz, CDCl₃) 26.34 (N-CH₃), 103.29, 123.11, 127.24, 128.22, 128.63, 130.10, 131.44, 132.79, 133.24, 133.80, 139.27, 149.27 (Ar-C), 167.35 (C₁=O), 189.53 (C₆H₅CO); Anal: Calc. for C₁₇H₁₃NO₂: C, 77.55; H, 4.97; N, 5.32. Found: C, 77.29; H, 5.10; N, 5.63.
17. The Z-configuration was assigned from mechanistic consideration and comparison of the chemical shifts of the vinylic protons with those reported for similar compounds.^{6,7} Also the vinylic proton chemical shifts for compounds **11-17** agreed with those (δ 6.80-5.94) reported for the corresponding phthalide of Z-configuration.¹⁸ The absence of down field shifting of C₄-aromatic hydrogens also confirmed the Z-configuration.
18. Ingham, C. F.; Massy-Westropp, R. A.; Reynolds, G. D.; Thorpe, W. D. *Aust. J. Chem.*, **1975**, 28, 2499.
19. Yields are based on the 2-(trimethylsilyl)ethynyl benzamides **7-10**; yields in bracket are based on the 2-iodobenzamides **3-6**.

(Received in UK 23 June 1997; revised 1 August 1997; accepted 8 August 1997)