Pergamon

Tetrahedron Letters, Vol. 38, No. 39, pp. 6937-6940, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01626-2

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

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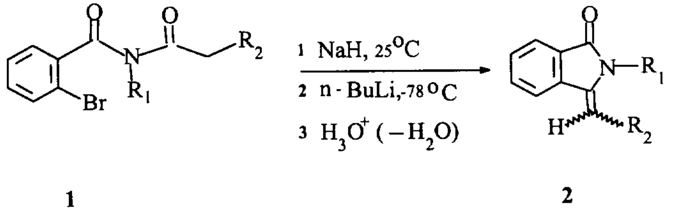
Abstract : N-Aryl(or, alkyl)-2-iodobenzamides underwent palladium-catalysed reaction with (trimethylsilyl)acetylene to form N-substituted-2-(trimethylsilyl)ethynyl benzamides, which on further Friedel-Crafts acylation and cyclisation yielded Z-3-alkylidene isoindolin-1-ones in a completely regio- and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

Isoindolinones (phthalimidines), particularly 3-alkylidine isoindolinones, have drawn considerable interest because of their reported biological activities[2] 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] quinolines[13] and benzodioxans[14] 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.

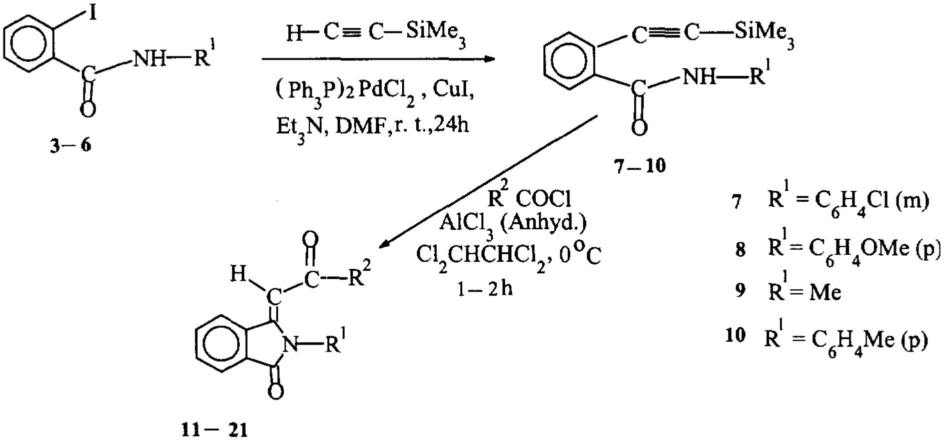
Recently, Wolfe and co-workers[8] have reported a low temperature reaction where N-acyl-2-bromobenzamides **1** underwent metal-halogen exchange with n-BuLi to form N-acyl-2-lithiobenzamides which cyclised under acidic condition to 3-alkylidene phthalimidines **2** (Scheme 1).

Scheme-1



We found that N-alkyl or, N-aryl-2-iodobenzamides **3-6** underwent smooth reaction with (trimethyl silyl)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.

Scheme-2



The reactions were carried out by stirring a mixture of *o*-iodobenzamide **3-6** (1 mmol), (trimethylsilyl) acetylene (2.0 mmol), $(PPh_3)_2PdCl_2$ (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 temperature[5] or low temperature[8] reactions which are generally used for the synthesis of 3-alkylideneisoindolinones, and (iii) relatively good yields. Also, the reaction is highly regio[16] and stereospecific[17] - 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_6H_4Cl-*m*	*p*-MeC_6H_4COCl	*p*-Me-C_6H_4	**11**	84 (74)
2	**4**	C_6H_4OMe-*p*	*p*-MeC_6H_4COCl	*p*-Me-C_6H_4	**12**	66 (59)
3	**5**	Me	*p*-MeC_6H_4COCl	*p*-Me-C_6H_4	**13**	52 (45)
4	**6**	C_6H_4Me-*p*	*p*-$MeOC_6H_4COCl$	*p*-MeO-C_6H_4	**14**	59 (49)
5	**5**	Me	*p*-$MeOC_6H_4COCl$	*p*-MeO-C_6H_4	**15**	50 (44)
6	**4**	C_6H_4OMe-*p*	C_6H_5COCl	C_6H_5	**16**	76 (68)
7	**5**	Me	C_6H_5COCl	C_6H_5	**17**	72 (62)
8	**3**	C_6H_4Cl-*m*	CH_3COCl	Me	**18**	52 (46)
9	**4**	C_6H_4OMe-*p*	CH_3COCl	Me	**19**	56 (50)
10	**4**	C_6H_4OMe-*p*	$(CH_3CO)_2O$	Me	**20**	83 (74)
11	**6**	C_6H_4Me-*p*	$(CH_3CO)_2O$	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.

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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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H, CH_3), 3.88 (s, 3H, OCH_3), 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). ^{13}C NMR (75 MHz, $CDCl_3$) 21.61 (CH_3), 55.51 (OCH_3), 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 (C_1= O), 189.52 ($C_6H_4\underline{C}O$); Anal: Calc. for $C_{24}H_{19}NO_3$: 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; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.36 (s,3H, N-CH_3), 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); ^{13}C NMR (75 MHz, $CDCl_3$) 26.34 (N - CH_3), 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 (C_1= O), 189.53 ($C_6H_5\underline{C}O$); Anal: Calc. for $C_{17}H_{13}NO_2$: 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 C_4-aromatic hydrogens also confirmed the Z-configuration.
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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)