Synthesis of 3-Alkoxy- and 3-Alkylamino-2-alkyl-3-arylisoindolinones

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Received 16 February 1999

Abstract: Solvent-controlled regioselectivity in the reactions of 3-chloroisoindolinones with primary amines allows the rational synthesis of isoindolinones by a route suitable for parallel combinatorial chemistry.

Key words: isoindolinones, regioselectivity, solvent effect, combinatorial synthesis

The molecular diversity offered by isoindolinones **1** is attractive in the context of the synthesis of combinatorial libraries for evaluation against targets implicated in the molecular pathology of cancer.

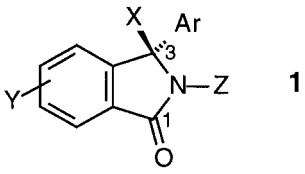

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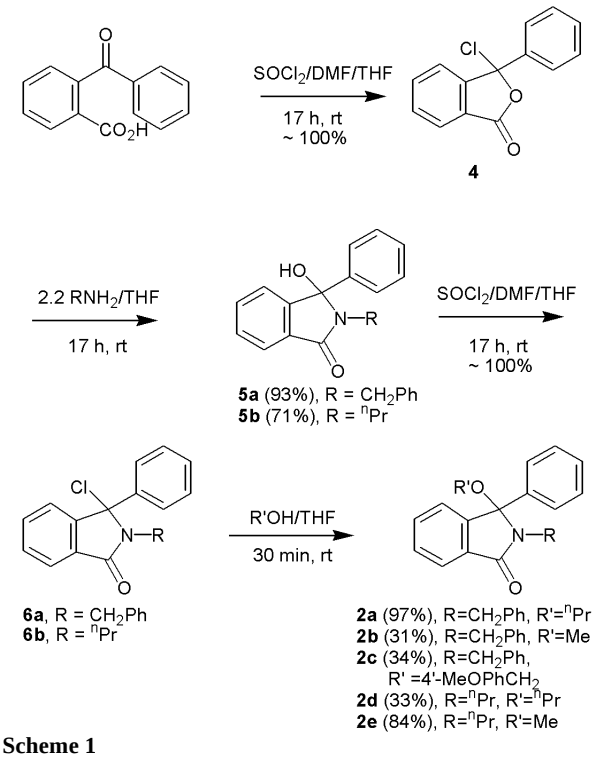
Figure 1

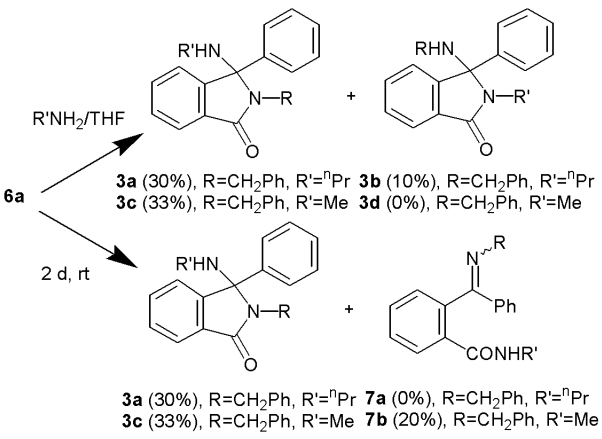
The literature on the synthesis of such isoindolinones is confusing because the common route from 2-benzoylbenzoic acids provides numerous opportunities for the generation of isomeric structures.[1] We have found that 3-alkoxy- and 3-alkylamino-2-alkyl-3-arylisoindolinones (**2a-e** and **3a-c**, respectively) can be rationally synthesized from 2-benzoylbenzoic acid by a sequence in which each intermediate and the end-products have been structurally defined.

Reaction of 2-benzoylbenzoic acid with 1 equiv. of thionyl chloride in tetrahydrofuran, containing a catalytic quantity of dimethylformamide, gave 3-chloro-3-phenylisobenzofuranone (**4**)[2] as an unstable oil (~ 100%),[3] which was obtained by removal of the reaction solvent in vacuo. Immediate reaction of **4** with 2.2 equiv. of either benzylamine or propylamine in tetrahydrofuran gave 3-hydroxy-3-phenylisoindolinones[4,5] **5a/b** in good yield (71 and 93% respectively). Functionalisation of **5a** or **5b** was achieved via conversion into 3-chloroisoindolinones **6a/b** (~ 100%),[2] compounds which have previously been described as highly reactive and not isolable.[6] We obtained crystals of 2-benzyl-3-chloro-3-phenylisoindolinone (**6a**) by refrigerating the initially formed oil under petroleum ether.[7] 3-Alkoxyisoindolinones **2a-e** (31-97%) were obtained by quenching **6a/b** with dry alcohols (Scheme 1).[5,8]

The reaction of **6a** with redistilled propylamine in tetrahydrofuran gave two products. Separation of these by column chromatography, and subsequent analysis by ^{1}H NMR spectroscopy, indicated that they were the isomeric 3-alkylaminoisoindolinones **3a** (30%) and **3b** (10%) (Scheme 2).[5,9]



Scheme 1

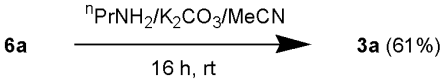


Scheme 2

These isomeric products were also obtained with 1,4-dioxane as reaction solvent. The literature suggested that only one of the products would be an isoindolinone.[10] In our case iminoamide **7a**, resulting from the attack of the amine on the 1-position of **6a**, has evidently undergone cyclization to give **3b** in addition to **3a**, which arises from amine attack at the 3-position.

^{1}H NMR spectroscopy allowed conclusive identification of the isomeric isoindolinones. The diastereotopic benzylic methylene protons of **5** exhibit a large chemical shift difference.[11] The chemical shifts of the protons in the *N*-methylene groups of compounds **3** provide a useful ^{1}H NMR chemical marker. We compared the spectra of compounds **3** with the ^{1}H NMR spectrum of **5a**, to identify which compound has a benzyl substituent attached to the 5-ring nitrogen and which has a pendant benzylamino moiety. The identifications were supported by adding a drop of deuterium oxide to the ^{1}H NMR sample and recording another spectrum. This allowed determination of which protons were coupled to the exchangeable amino proton, and hence which moiety was pendant, and which was attached to the 5-ring nitrogen. These structural assignments were subsequently shown to be correct by crystal structure analysis.[12,13]

The use of acetonitrile as the solvent in the reaction of **6a** with propylamine was found to lead to only one product, 2-benzyl-3-phenyl-3-propylaminoisoindolinone **3a** (61%). An identical result was obtained when the reaction solvent was changed to dichloromethane.



This solvent effect was verified by synthesizing 3-hydroxy-3-phenyl-2-propylisoindolinone (**5b)** (71%), converting it into the chloride **6b** (~ 100%) in the usual manner, and then reacting **6b** with benzylamine in either tetrahydrofuran or acetonitrile. Similar results were obtained as in the reaction of **6a** with propylamine, i.e. two isomeric isoindolinones **3a** (7%) and **3b** (35%) were formed in tetrahydrofuran, whereas only one isoindolinone **3b** (36%) was formed in acetonitrile.

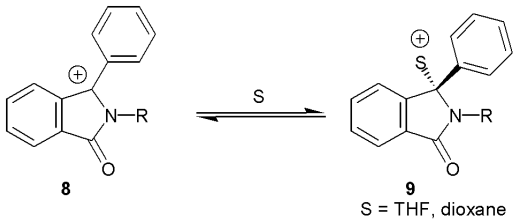
Table 1. Reaction of 3-Chloroisoindolinones with Primary Amines

Chloride	Amine	Solvent	Ratio **3a**:**3b**[a]	Yield (%) **3a**:**3b**
6a	$PrNH_2$	THF	3.2 : 1	30 : 10
6a	$PrNH_2$	MeCN	1 : 0	61 : 0
6b	$BnNH_2$	THF	1 : 2.4	7 : 35
6b	$BnNH_2$	MeCN	0 : 1	0 : 36

[a] Determined by ^{1}H NMR of the crude mixture

The literature suggested that reaction of **6a** with methylamine would proceed via attack on the 1-position of **6a** leading to the formation of 3-benzylamino-2-methyl-3-phenylisoindolinone (**3d)** as the sole product.[14] When tetrahydrofuran was used as the reaction solvent we obtained two products, 2-benzyl-3-methylamino-3-phenylisoindolinone (**3c)** (33%) and a non-isoindolinone product, probably **7b** (20%) (Scheme 2). In acetonitrile we obtained only **3c** (66%). Assignment of the isoindolinone structures was again based on ^{1}H NMR spectroscopy.

We believe that the reactions of **6** described for relatively polar solvents (i.e. acetonitrile and dichloromethane) involve the isoindolinone carbocation **8**,[15] which reacts selectively at C-3. In the less polar, but nucleophilic tetrahydrofuran or dioxane, the carbocation may be in equilibrium with the adduct **9**, by analogy with trityl cations.[16] The presence of this species may influence the regioselectivity of amine attack.



Acknowledgement

We are grateful to the EPSRC and the Cancer Research Campaign for support of M.S.K. and we thank the EPSRC for funding the diffractometer. Many thanks are due to Dr. L. Horsburgh for crystal structure analysis.

References and Notes

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(2) 3-Chloroisobenzofuranone **4** and 3-chloroisoindolinone **6**. 2-Benzoylbenzoic Acid (500 mg, 2.21 mmol) or 3-hydroxyisoindolinone **5** (1.59 mmol) was dissolved in dry THF (20 mL). Thionyl chloride (2.21 mmol or 1.59 mmol respectively) and DMF (1 drop) were added. The mixture was stirred overnight. The reaction was monitored by heating a sample of the reaction mixture with dry methanol before TLC analysis. Removal of the solvent in vacuo gave a pale yellow oil **4** (~ 100%) or **6** (~ 100%) which was used without further purification.

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(4) To a stirred solution of 3-chloroisobenzofuranone **4** (2.21 mmol) in dry THF (20 mL) was added the primary amine (4.86 mmol). In all cases a precipitate appeared almost immediately. After completion (overnight unless otherwise stated) the reaction was filtered and the solvent was removed in vacuo. The residue was taken up into ethyl acetate (30 mL) and washed with water (3 x 30 mL). After drying (Na_2SO_4) the ethyl acetate was removed in vacuo leaving a solid residue,

which was dissolved in a minimum of boiling ethyl acetate and recrystallised by the dropwise addition of petrol to give 3-hydroxyisoindolinone **5** (71-93%).[17, 18]

(5) All yields in this paper, with the exception of **4** and **6a/b**, are for isolated, analytically pure racemates.

(6) Armarego, W. L. F.; Sharma, S. C. *J. Chem. Soc. (C).* **1970**, 1600.

(7) Crystal of **6a** was colourless, monoclinic, $P2_1/c$, a = 11.9175(10), b = 10.0768(9), c = 14.2218(12) Å, β = 102.826(3)°, $C_{21}H_{16}ClNO$, M = 333.80, T = 160 K, Bruker SMART CCD diffractometer, MoKα radiation. R = 0.0352, 3922 reflections, 218 parameters. CCDC reference 114164.

(8) 3-Chloroisoindolinone **6** was dissolved in the dry alcohol (10 mL, large excess) and the resulting solution stirred at room temperature for 30 min. Removal of the solvent in vacuo gave a translucent oil which was dissolved in ethyl acetate (30 mL) and washed with water (3 x 30 mL). The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. The residual oil crystallised when overlayed with petrol and refrigerated, to give 3-alkoxy-3-arylisoindolinone **2** (31-97%). All analytical data obtained (^{1}H NMR, ^{13}C NMR, IR, MS, CHN) supported the assigned structures.

(9) 2-Benzyl-3-phenyl-3-propylaminoisoindolinone (**3a)** and 3-benzylamino-3-phenyl-2-propylisoindolinone (**3b)**. 2-Benzyl-3-chloro-3-phenylisoindolinone (**6a)** (1.05 g, 3.17 mmol) was dissolved in dry THF (20 mL) and redistilled propylamine (3 mL) was added. A white precipitate formed immediately and the mixture was stirred at room temperature for 2 weeks. After removal of the solvent in vacuo the solids were taken into ethyl acetate (30 mL) and washed with water (3 x 30 mL). The organic layer was dried (Na_2SO_4), absorbed onto silica gel, and the isomeric products were separated by column chromatography with (20% EtOAC/petrol) as eluent. After removal of the eluent each compound was obtained as an oil which crystallised when overlayed with petrol and refrigerated. **3a** (334 mg, 0.94 mmol, 30%): white solid; mp. 102-103°C [R_f 0.77 (3:2 petrol:ethyl acetate)] and **3b** (112 mg, 0.31 mmol, 10%): white solid; mp. 139-141°C (lit. 137-138°C)[10] [R_f 0.68 (3:2 petrol:ethyl acetate)].

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(11) Lewin, A. H.; Lipowitz, J.; Cohen, T. *Tetrahedron Lett.* **1965**, 1241.

(12) Crystal of **3a** was colourless, triclinic, $P\bar{1}$, a = 7.1991(9), b = 8.6242(10), c = 16.1894(19) Å, α = 87.743(3), β = 83.227(3) γ = 75.242(3)°, $C_{24}H_{24}N_2O$, M = 356.45, T = 160 K, R = 0.0419, 4408 reflections, 248 parameters. CCDC reference 114165.

(13) Crystal of **3b** was colourless, monoclinic, $P2_1/n$, a = 10.3147(2), b = 14.1360(14), c = 13.3327(13) Å, β = 93.897(3)°, $C_{24}H_{24}N_2O$, M = 356.45, T = 190 K, R = 0.0434, 4560 reflections, 249 parameters. CCDC reference 114166.

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(16) Bleasdale, C.; Ellwood, S. B.; Golding, B. T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 803.

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Article Identifier:
1437-2096,E;1999,0,S1,0997,0999,ftx,en;W07899ST.pdf