An Improved Process for the *N*-Alkylation of Indoles Using Chiral *N*-Protected 2-Methylaziridines

Paul R. Giles,*,† Mark Rogers-Evans,‡ Milan Soukup,‡ and John Knight†

Vernalis Research Ltd., Oakdene Court, 613 Reading Road, Winnersh, Wokingham RG41 5UA, UK, and F. Hoffmann-La Roche Ltd., CH-4070 Basel, Switzerland

Abstract:

An improved process for the *N*-alkylation of indoles using *N*-protected homochiral aziridines has been developed. This procedure allows reduced quantities of homochiral starting material to be used and leads to improved overall yields and operability.

Introduction

RO 60-0175 **4a** is a selective $5HT_{2C}$ agonist with potential therapeutic utility in the treatment of obsessive compulsive disorder.[1] Its synthesis includes a key step (Scheme 1) involving the reaction of indole **1a** with the *N*-protected alaninyl mesylate **2** to give the *N*-alkylated indole **3a**.[2,3]

In our hands this transformation proved to be less than ideal for several reasons:

(1) The reaction lacked generality, giving inconsistent yields and incomplete conversion in the synthesis of close analogues of indole **3a**.

(2) Incomplete reaction gave a mix of materials, which proved difficult to purify without recourse to chromatography.

(3) Alaninyl mesylate **2** required very slow addition to the reaction mixture, typically 1−2 h.

(4) The reaction conditions resulted in a partial loss of the BOC protecting group to give indoles **4**.

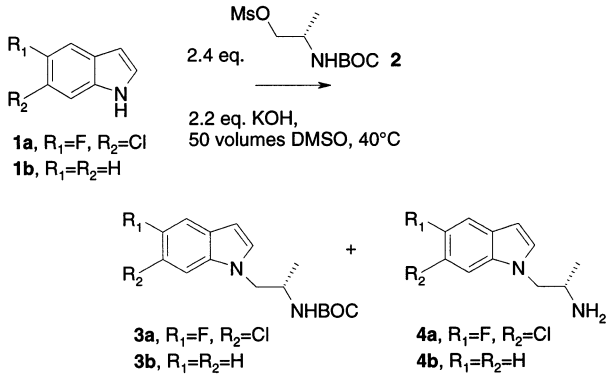
(5) Large solvent volumes, typically 20−50 vols, and thus large aqueous volumes, were required during the workup of indoles **3**.

We sought a method which would circumvent these problems and provide a scaleable, less capricious, and more operable procedure. We therefore carried out a limited amount of process development to improve this transformation.

Results and Discussion

The reaction illustrated in Scheme 1 using indole **1b** and literature conditions[2] was monitored by HPLC to quantify

Scheme 1. **Initial alkylation conditions for the synthesis of indoles 3**



the amounts of indole **1b**, alkylated indole **3b**, and deprotected alkylated indole **4b**. The HPLC method,[4] using 1-methylnaphthalene as internal standard, gave baseline separation of each of these entities.

A number of parameters were independently investigated with the following results:

Temperature. Higher reaction temperatures increased the loss of the BOC group to give amine **4b**.

Base. Replacement of KOH with KO^{t}Bu resulted in increased loss of the BOC group to give amine **4b**. The use of powdered KOH prepared in a blender and KOH ground with a mortar and pestle gave similar results.

Rate and Order of Addition of Compound 2. Slow addition of **2** gave better initial alkylation although, by the end of the reaction, yields of each entity were similar. It was also found that the order of addition of reagents was critical. The desired reaction was only observed when a solution of **2** was added to a suspension of indole and powdered KOH. The KOH could not be added to a solution of compound **2** and the indole.

Reaction Times. Prolonged reaction times decreased the yield of **3b**, mainly by loss of the BOC group to give **4b**. The alkylation reaction was effectively over once the addition of mesylate **2** was complete.

Water Content. The use of dry DMSO and standard grade DMSO gave similar results.

* Corresponding author. E-mail p.giles@vernalis.com. Telephone: + 44 118 977 3133. Fax: + 44 118 989 9300.

† Vernalis Research Ltd.

‡ F. Hoffmann-La Roche Ltd.

(1) Boes, M.; Jenck, F.; Martin, J. R.; Moreau, J.-L.; Sleight, A. J.; Wichmann, J.; Widmer, U. *J. Med. Chem.* **1997**, *40*, 2762−2769.

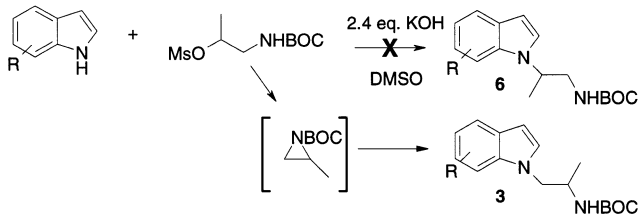
(2) Rogers-Evans, M.; Soukup, M. PCT Int. Appl., WO 9747598 A1, 1997; *Chem. Abstr.* **1998**, *128*, 75296.

(3) Adams, D. R.; Bentley, J. M.; Roffey, J. R. A.; Hamlyn, R. J.; Gaur, S.; Duncton, M. A.; Bebbington, D.; Monck, N. J.; Dawson, C. E.; Pratt, R. M.; George, A. R. PCT Int. Appl. WO 0012475, 2000; *Chem. Abstr.* **2000**, *132*, 194289.

(4) The internal standard was weighed into the reaction vessel prior to addition of the solvent and base. Samples (0.5 mL) of the reaction mixture were taken for analysis and diluted with 10% aqueous acetic acid and methanol prior to injection onto HPLC using the Vernalis conditions as described in the Experimental Section. Typical retention times of the species are indole **1b**, 3.76 min; alkylated product **3b**, 5.78 min; internal standard 9.8 min; deprotected amine **4b**, 2.85 min.

10.1021/op020078v CCC: $25.00
Published on Web 00/00/0000

Scheme 2. **Unexpected reaction**



Stirring Efficiency. The use of either a mechanical stirrer or a magnetic follower to mix the resulting suspension gave similar results on a small scale (up to 5 g).

*Protecting Group in Compound **2***. Changing the *N*-BOC protecting group to *N*-tosyl, *N*-benzylidine imine, or *N*-CBz resulted in no improvement in the overall alkylation.

*Leaving Group in Compound **2***. Similarly, the use of *O*-tosyl, *O*-nosyl, and iodo gave no improvement in the overall alkylation process.

The identification by proton NMR of the chiral *N*-BOC aziridine **5** as a byproduct in the crude reaction product mixtures from many of the above investigations led to a suspicion that *N*-BOC alaninyl mesylate **2** may be unstable under the reaction conditions. Indeed, compound **2** is completely and rapidly (less than 5 min) converted to aziridine **5** on treatment with KO^{t}Bu in d_6-DMSO at ambient temperatures. The use of powdered KOH resulted in a slower transformation unless D_2O was added to the solution, in which case conversion was more rapid presumably as a result of homogenising the reaction mixture. Aziridine **5** was prepared by treatment of mesylate **2** (5 g) with KO^{t}Bu (1.5 g) in THF (83% yield, 95% purity by NMR).[5]

These observations led us to suspect that aziridine **5** might be useful as an alternative, more stable alkylating agent in this reaction. Various *N*-protected aziridines have been reacted with *N*-lithiated indoles to afford *N*-alkylated and 3-alkylated products, the exact ratios depending on the reaction solvent and the nature of the *N*-protecting group.[6] Indoles and *N*-alkyl indoles afford tryptamine derivatives on reaction of aziridines under Lewis acid catalysis.[7]

This evidence was further supported by the observation that alkylation with a regioisomer of **2** did not give the desired alkylation product **6**, but the unexpected regioisomer **3** (Scheme 2), derived from the ring-opening of the intermediate aziridine.[8]

Instead of direct displacement of the mesylate group, the replacement of mesylate **2** with aziridine **5** using the literature conditions (2.4 equiv of alkylating agent added to indole−KOH slurry in DMSO) resulted in efficient alkylation of indole **1b**. It was noted that using only 1.2 equiv of aziridine also gave the same outcome, as determined by HPLC analysis.

Scheme 3. **Improved process for the alkylation of indoles 1**

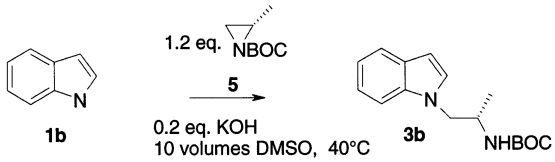


Table 1. **Comparison of improved yields and reaction conditions for indole alkylations**

entry	indole **1**	yield %[a]	% purity NMR[b]	% area purity HPLC[b]	previous yield[c]
1	indole	80	85	85	not reported
2	6-bromoindole	79	85	82	56
3	5-chloroindole	86	92	93	29
4	6-trifluoromethylindole	89	85	88	11
5	5-methoxyindole	85	90	75	not reported
6	5-fluoro-6-chloroindole	82	90	88	59

[a] All figures are for crude reaction products. [b] The major impurity in each case was the unreacted starting indole. [c] Yields previously obtained in-house after chromatography using initial general procedure.[9]

Observations during our initial investigations also led us to suspect that the BOC protected indole **3b** may also be unstable to the reaction conditions. Examination of a sample of indole **3b** treated with K^{t}OBu in d_6-DMSO by proton NMR demonstrated a slow conversion to the deprotected indole **4b** (1:1 mixture of **3b** and **4b** after 24 h). We therefore investigated the reduction or omission of base in this procedure.

Treatment of indole **3b** with aziridine **5** in DMSO at 40 °C in the absence of base resulted in no reaction. However, alkylation was observed after adding a small quantity of powdered KOH to the aziridine−indole solution. This demonstrated that not only could substoichiometric quantities of base be used but, more importantly, the order of the addition of reagents in this modified procedure was no longer key to the outcome (Scheme 3).

Further investigation led to an optimised procedure (see Experimental Section) with only 0.2 equiv of KOH being necessary. The generality of the procedure was demonstrated by the conversion of a number of substituted indoles, some of which had previously proved problematic using the literature procedure, to the corresponding alkylated indoles **3**. The yields and product purities were superior to those obtained by the initial general procedure (see Table 1, entries 1−6).

Conclusions

We have developed an improved technical process for the efficient *N*-alkylation of indoles using the *N*-protected homochiral aziridine **5**. The optimised procedure minimises the required number of equivalents of homochiral reagent, the volumes of solvent and thus the quantity of waste products. The reduced quantity of base used also reduces unwanted side reactions. The new procedure also has improved operability, yields, and conversions over a range of indole substrates.

(5) Conversion of (*S*)-BOC-alaninyl mesylate **2** to the corresponding aziridine **5** has been reported using 4 equiv of KOH and 1.2 equiv TsCl in ether; see Wessig, P.; Schwarz, J. *Synlett* **1997**, 893.
(6) Onistschenko, A.; Stamm, H. *Chem. Ber.* **1989**, *122*, 2397.
(7) For an example using $BF_3.Et_2O$: Shima, I.; Shimazaki, N.; Imai, K.; Hemmi, K.; Hasimoto, M. *Chem. Pharm. Bull.* **1990**, *38*, 564; using scandium triflate: Bennani, Y. L.; Zhu, G.-D.; Freeman, J. C. *Synlett* **1998**, 754.
(8) Mansell, H. L. Unpublished results.
(9) Roffey, J. R. A.; Duncton, M. A.; Dawson, C. E.; Hamlyn, R. J. Unpublished results.

Experimental Section

Reagents and solvents were used as received from commercial suppliers. All equipment was inspected visually for cleanliness and integrity before use.

Analytical HPLC was performed on a Hewlett-Packard 1050 or 1100 system with UV detection at a wavelength of 210 nm using a LiChrospher 100 RP18 endcapped (5 μm) 250 mm $\times$ 4 mm column (Merck) and gradient elution with H_2O−MeCN (Roche) or a Perkin-Elmer series 200 system with UV detection at a wavelength of 210 nm using a Supercosil ABZ$^+$ 150 mm $\times$ 6 mm column and isocratic elution with MeOH−ammonium acetate buffer (70/30 ratio) (Vernalis). TLCs were perfomed either with (a) isohexanes−ethyl acetate (1:1) and developed using $KMnO_4$ dip or (b) in DIPE and developed using Ninhydrin spray.

Initial General Procedure Using 5-Fluoro-6-chloroindole (1a). To a suspension of ground potassium hydroxide (0.58 g, 10.3 mmol) in DMSO (20 mL) was added indole **1a** (0.44 g, 2.6 mmol) and the resulting suspension was stirred at 40 °C. An inert atmosphere was not used. After 30 min, a solution of alaninyl mesylate **2** (1.64 g, 6.5 mmol) in DMSO (20 mL) was added slowly over a period of 2 h, and the resulting mixture was stirred overnight at 40 °C. The viscous gel-like suspension was poured into ice−water, extracted with diethyl ether (2 $\times$ 20 mL), washed with water and brine, dried ($MgSO_4$), and evaporated to afford the alkylated indole **3a**, 0.5 g, 59% yield after purification).

Synthesis of Aziridine (5). To a solution of alaninyl mesylate **2** (5.2 g, 20.5 mmol) in THF (100 mL) was added solid potassium *tert*-butoxide (2.5 g, 22.3 mmol) portionwise over 5 min. The reaction mixture was stirred for 10 min, checked by TLC to ensure complete reaction (condition a; R_f product 0.7, starting material, R_f 0.2) then diluted with water (100 mL), washed with diethyl ether (1 $\times$ 100 mL, 1 $\times$ 50 mL) and brine, dried ($MgSO_4$), and evaporated to afford the aziridine **5** (2.7 g, 83% crude yield).

Improved General Procedure starting from 5-Fluoro-6-chloroindole (1a). To a solution of aziridine **5** (0.566 g, 3.54 mmol) and indole **1a** (0.5 g, 2.90 mmol) in DMSO (5 mL) was added ground potassium hydroxide (34 mg, 0.2 equiv) and the resulting solution was stirred at 25−40 °C and monitored by either TLC (condition b) or HPLC. When judged to be complete, typically 1−8 h, the reaction mixture was poured into ice−water (20 vols) and allowed to solidify; the solid was filtered off and dried to give alkylated indole **3a**, crude yield 82%, 88% purity by HPLC.

Acknowledgment

We thank Dr. Ken Heatherington (Vernalis) for his help during this investigation and Antoine Ritter and Gerd Schaffner (Roche) for skillful synthetic assistance.

Received for review September 6, 2002.

OP020078V