Pergamon

Tetrahedron Letters, Vol. 36, No. 12, pp. 2029-2032, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00229-4

Transfer of Activation from Indoles to Alcohols: A New Method for the Synthesis of Aminoethylindoles.

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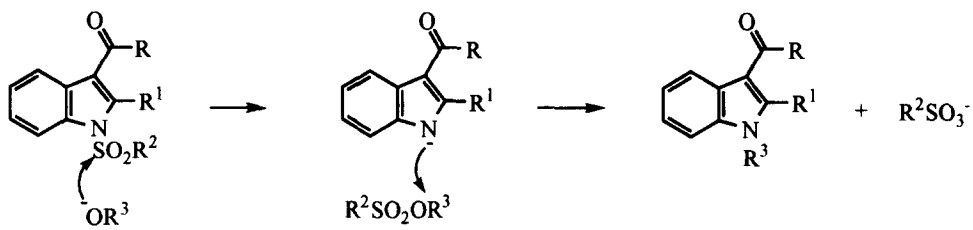
Abstract: Transfer of a sulfonyl group from an indole nitrogen to a β-amino alkoxide generates an indole anion and an aminoethylsulfonate which react to give aminoethylindoles.

We have recently described a series of aminoalkylindoles, one of which, pravadoline was shown to be a clinically effective analgesic.[1-3] In the course of developing the SAR for analogs of pravadoline, we encountered difficulty in synthesizing in a pure state certain alkylating agents which had an amino group beta to the leaving group. Such compounds containing both nucleophilic and nucleofugal groups are understandably unstable. One way to solve this problem would be to generate the alkylating agent in the presence of the indole anion we wished to alkylate.[4] However, common methods of activating an alcohol to provide an alkylating agent would not be compatible with the indole anion. It occurred to us that the anion of an amino alcohol might attack a sulfonylated indole at sulfur, with the net effect of transferring the sulfonyl group from the indole to the alcohol, thus providing the alkylating reagent and the indole anion in the same step (Scheme 1).[5,6] This activation-transfer protocol would utilize readily available and stable sulfonylated indoles as the source of the activating group for the alcohol.[7,8]

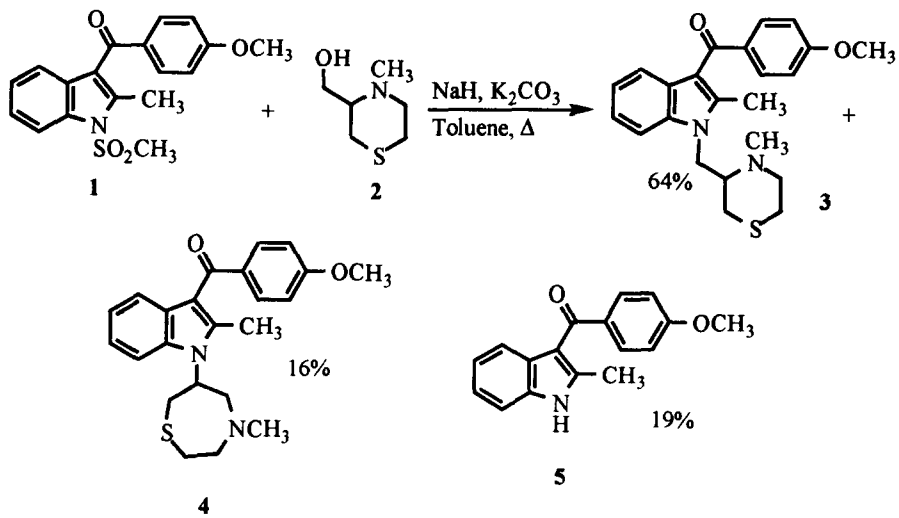
Scheme 1



The sulfonyl group is perhaps the most common protecting group for indoles and as such, many methods for the synthesis of sulfonylated indoles exist. One of the methods used for the deprotection of these compounds is heating in the presence of alkoxide, which should generate the indole anion in the presence of an alkylating agent, however alkylated by-products are not generally observed. For the compounds we were targeting, the sulfonylated alcohol would contain a β-amino functionality which should increase the electrophilicity of the alkylating agent because of the availability of an aziridinium ion intermediate. Along with providing a more reactive substrate the aziridinium ion intermediate allows for nucleophilic attack at a different site than was originally activated, potentially giving a mixture of products.[9]

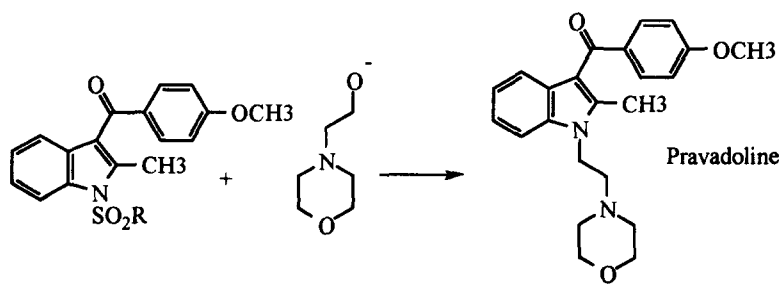
In the event, we found that when alcohol **2** was treated with sodium hydride and the resulting alkoxide heated with sulfonylated indole **1**, target **3** was obtained in 64% yield as well as the expected (*vide supra*) rearrangement product **4** (Scheme 2). Previous attempts to derivatize alcohol **2** and react it with the indole anion using standard procedures were unsuccessful.

Scheme 2



We used commercially available morpholinoethanol to explore variations of the sulfonyl substituent (Table 1). The benzenesulfonyl analog was somewhat less reactive than the methanesulfonyl derivative and also gave a lower yield. When the methanesulfonyl group was replaced by a trifluoromethanesulfonyl group, both the transfer to the alkoxide and the alkylation of the indole proceeded at lower temperature, but the yield of product was lower, probably because of the extreme instability of the morpholinoethyltriflate intermediate. This indole derivative might find application for less reactive alcohols.

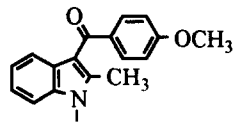
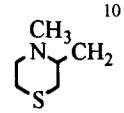
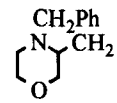
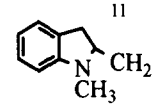
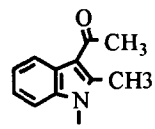
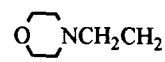
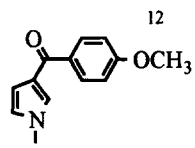
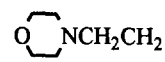
Table 1. Effect of Sulfonyl Group on Reactivity



R	Rxn Temp (°C)	Rxn Time (min)	% Yield
CH_3	70-100	120	90
CF_3	30	20	42
Ph	110	30	54

Table 2. Variations of the heteroaromatic and the alcohol

Heterocyclic-SO_2CH_3 $\xrightarrow{RO^-}$ Heterocyclic-R

Entry	Heterocyclic	R	% Yield
1	 **1**		90
2	**1**	 [10]	64
3	**1**	 [9]	80
4	**1**	 [11]	50
5	**1**		11
6			60
7			51
8			85
9	 [12]		80

The reaction worked well for the aminoethanol derivatives tried. However an aminopropyl analog was far less successful. Clearly the reactivity of the aziridinium pathway is required to avoid alternate degradation manifolds. In exploring the generality of the indole component it appears that a less activated indole may give a somewhat lower yield. The fact that benzimidazole and pyrrole work well presages promise for this reaction with other acidic heterocycles.[13]

A representative experimental procedure is as follows. To a solution of 184 mg (1.4 mmol) of 4-(2-hydroxyethyl)morpholine in 10 ml toluene is added 276 mg (2.0 mmol) of anhydrous K_2CO_3 and then 32 mg (1.3 mmol) of 97% NaH. After 30 min 343 mg (1.0 mmol) of sulfonyated indole **1** is added and the reaction is heated at 100^0 C for 2h. The reaction is then partitioned between ethyl acetate and water and the aqueous layer extracted with two additional portions of ethyl acetate. The combined organic phase is washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel using 50% ethyl acetate/hexane to give 340 mg (90%) of pravadoline.[14] The rest of the material is predominantly desulfonylated indole **5**.

If the reaction is not kept anhydrous the proportion of desulfonyated indole increases. The K_2CO_3 is present to help keep the reaction dry, although ion exchange with the sodium salt has not been ruled out. More polar solvents were less effective.

In conclusion, an activation-transfer method has been developed in which an alkoxide reacts with a sulfonylated indole to generate the indole anion and the sulfonate of the alcohol which subsequently react to provide an aminoethylindole. This method can be applied to other heterocycles such as pyrroles and benzimidazoles.

Acknowledgements: We would like to thank Richard Philion and George Monsour for preparing some of the intermediates used in this work.

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(*Received in USA* 11 *November* 1994; *revised* 24 *January* 1995; *accepted* 31 *January* 1995)