Pergamon

Tetrahedron Letters, Vol. 35, No. 12, pp. 1847-1850, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0192-Z

N-Alkylation of Indole Ring using Mitsunobu Reaction.[1]

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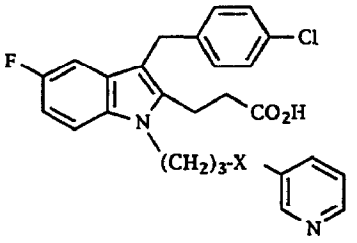
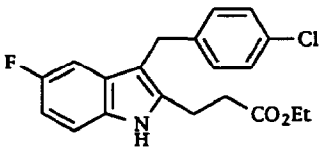
Abstract: Indole rings substituted with two electron withdrawing groups were alkylated on the nitrogen under Mitsunobu reaction conditions.

As part of our program for the development of bimodal antithrombotic agents which antagonize the receptors of thromboxane A_2 and simultaneously inhibit thromboxane synthase, we were interested in preparing indole carboxylic acids **1a** and **1b** shown below. Our synthetic plan included an alkylation of the nitrogen of the indole ring of **2**. However, the attempted alkylation under different conditions of the indole anion derived from **2** gave low and variable yields of the alkylated product. Analysis of the product mixture indicated that the unalkylated indole carboxylic acid was the major component. The formation of this product could be explained if the ester group interacted with the indole anion resulting in the blockade of N-alkylation. The reaction mixture in this case would give the unalkylated indole carboxylic acid upon workup. The alkylation of the dianion of the corresponding indole carboxylic acid gave a mixture of N- and/or O-alkylated products. This result was undesirable especially when the electrophile was a valuable material that had to be prepared. Therefore, we decided to try Mitsunobu reaction conditions for indole N-alkylation.[2]





2

1a X = O

1b X = CH_2

An unsubstituted indole ring does not participate in a Mitsunobu reaction. However, compound **3**, with an ester group at the 2-position gave 20% yield of the desired product **5** in the Mitsunobu reaction with **4**.[3]

Under identical reaction condtions, 6[4] with an electron withdrawing group at the 3-position was alkylated with **4** to give **7** in 18% yield. Compound **8** with two activating groups reacted with **4** to give a 98% yield of **9**. This result implies that one needs two electron withdrawing groups to activate an indole ring so that it participates in the Mitsunobu reaction satisfactorily.

The procedure given below for the conversion of **8** to **9** is typical. To a solution of **8** (2 g, 5.8 mmol) in 54 mL CH_2Cl_2 under nitrogen atmosphere was added **4** (1.1 g, 7.4 mmol) followed by triphenylphosphine (2.5 g, 9.4 mmol). The mixture was allowed to stir at room temperature for 10 min and then cooled in an ice-bath before adding diethyl azodicarboxylate (DEAD, 1 mL, 6.4 mmol) slowly in a dropwise manner to avoid an exotherm. The ice-bath was removed after the addition of DEAD and the reaction mixture was allowed to stir for 2.5 h. The solvent was evaporated and the residue was purified by column chromatography on silica gel to obtain 2.7 g (98%) of **9** as a thick oil. IR (CH_2Cl_2) 1717, 1646, 1240, 1178 cm^{-1}; 300 MHz ^1H NMR ($CDCl_3$) d 8.3 (d, J = 1 Hz, 1H), 8.23 (br d, J = 4.5 Hz, 1H), 7.75 (d, J = 8 Hz, 2H), 7.42 (m, 4H), 7.17 (m, 3H), 4.78 (t, J = 7 Hz, 2H), 3.98 (t, J = 7 Hz, 2H), 3.82 (q, J = 7 Hz, 2H), 2.39 (qn, J = 7 Hz, 2H), 0.86 (t, J = 7 Hz, 3H).

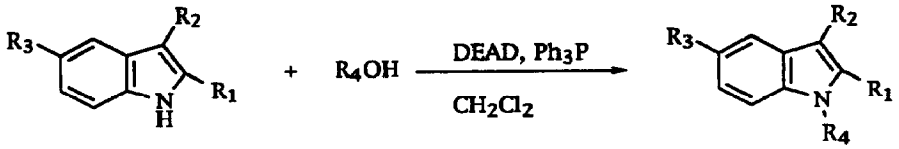
Several other primary alcohols such as methanol, n-butanol, **10** and **11** also reacted with **8** under these conditions and gave good yields of the corresponding alkylated products. It is important to note that **14** could be obtained in 64% yield using the Mitsunobu reaction conditions. This product with a pyridinylethyl group could not be prepared using the anion alkylation method. Attempted alkylation of the anion of **2** with pyridinylethyl bromide did not give any significant amount of the desired product probably because the elimination of HBr was faster than the alkylation. Therefore, this method appears to be extremely useful for introducing an alkyl residue which, when used as an alkylating agent, would undergo competive elimination faster than alkylation. Additionally, this method offers the convenience of not having to prepare and use the corresponding alkyl halides. We have experienced that this reaction provides a solution to the inconvenience (generation of free base) and/or problems (need to use more than one equivalent, low yields) associated with the use of the acid salts of the pyridinylalkyl halides in such anion alkylation reactions. Even isopropanol participated in this reaction to give a modest 41% yield of **16** indicating that the potential problems of such alkylations, viz., steric hindrance and elimination could be avoided using the Mitsunobu reaction conditions.

The substituent at the 5-position of **8** could be changed from flourine to either bromine (**17**) or hydrogen (**19**) with very little effect on the outcome of the reaction. Thus, the products **18** and **20** were obtained in 75 and 55% yield from **17** and **19** respectively (see Table I).

The compounds described so far have two electron withdrawing groups at the 2- and 3-position of the indole ring. We decided to test the effect of placing electron withdrawing groups at the 2- and 5-positon. It was found that the commercially available compound **21**, with a nitro group at the 5-position as the second electron withdrawing group also participated in this reaction. Thus, reaction of **21** with methanol and **10** under the Mitsunobu reaction conditions gave **22** and **23** in 68 and 54% yield, respectively. It is interesting to note that 5-nitroindole (**24**) which has only one activating group reacted with **10** to give **25** in 10% yield.

The scope of this method of alkylation of the indole ring was further demonstrated by allowing the chiral secondary alcohol **26** to react with **17** under the Mitsunobu reaction conditions to give **27** in 53% yield

Table I. Mitsunobu Alkylation of Indole Ring.



Compound	R_1	R_2	R_3	R_4	Product[a]	% Yield
3	CO_2Et	H	F	Py-O$(CH_2)_3$[b] (4)	5	20
6	$(CH_2)_2CO_2Et$	COC_6H_4Cl	"	"	7	18
8	CO_2Et	"	"	"	9	98
"	"	"	"	Me	12	77
"	"	"	"	nBu	13	50
"	"	"	"	Py$(CH_2)_2$ (10)	14	64
"	"	"	"	Py$(CH_2)_4$ (11)	15	91
"	"	"	"	iPr	16	41
17	"	"	Br	nBu	18	75
19	"	"	H	"	20	55
21	"	C_6H_5	NO_2	Me	22	68
"	"	"	"	Py$(CH_2)_2$ (10)	23	54
24	H	H	"	"	25	10
17	CO_2Et	COC_6H_4Cl	Br	(R)-Ethyl-2-hydroxy-4-phenylbutyrate (26)	27	53

[a] All of the products were characterized by FT-IR and 300 MHz ^1H NMR. [b] Py = a pyridine ring substituted at the 3-position.

[α_D=+1.8°, c=0.91, MeOH]. This result was very satisfying in view of the fact that alkylation of the sodium salt of **17** with the triflate derived from **26** in CH_2Cl_2 gave **27** in only 20% yield [α_D=+1.8°, c=1.24, MeOH], with the unreacted triflate being recovered. The product derived from the Mitsunobu reaction was identical in all respects with that derived from the anion alkylation. Since the reaction proceeds with inversion under both conditions, the Mitsunobu alkylation described here is the method of choice for introducing a chiral secondary alkyl group on to the indole nitrogen.

The products obtained using this Mitsunobu alkylation of indole rings substituted with two electron withdrawing groups could be synthetically useful. The products shown in Table I could be selectively manipulated at the carbonyl carbon to give synthetically useful compounds. Compounds **9** and **15**, for

example, have been converted to **1a** and **1b**[5] respectively by first reducing the carbonyl group at the 3-position ($NaBH_3CN$, ZnI_2, dichloroethane, reflux, 24 h, >60% yield) followed by homologation of the ester group by reduction to alcohol (DIBAL, CH_2Cl_2, -78 °C, quantitative), oxidation to aldehyde (MnO_2, acetone, room temperature, >85% yield), Wittig reaction ($Ph_3P{=}CHCO_2Me$, CH_2Cl_2, room temperature, >90% yield), reduction of the double bond ($NaBH_4$, $CoCl_2.6H_2O$, MeOH, 0 °C, >70% yield) and saponification of the ester.

In conclusion, we have demonstrated that an indole ring substituted with two electron withdrawing groups at 2,3- or 2,5-positions undergoes alkylation with a variety of hydroxy compounds under Mitsunobu reaction conditions to produce N-alkylated products. This reaction provided a solution to the problem of alkylating an indole ring substituted with an ester of propionic acid at the 2-position. It was the method of choice for introducing a chiral secondary alkyl group and an alkyl residue which, when used as an alkylating agent in an anion alkylation reaction, underwent elimination faster than alkylation. The method also provided us a solution to the problems associated with the use of the acid salts of pyridinylalkyl halides in the indole anion alkylation reactions. We have elaborated the two electron withdrawing groups of some of these alkylated products into compounds which possess both thromboxane synthase inhibitory and thromboxane receptor antagonizing activities.

Acknowledgment: We thank Dr. Benjamin Mugrage for helpful discussions and Mr. Mike Hatolski for the IR spectra.

References

(1) This paper is part 8 in the series: "Thromboxane Receptor Antagonism Combined with Thromboxane Synthase Inhibition." For part 7 see: Bhagwat S. S.; Roland, D. M.; Main, A. J.; Gude, C.; Grim, K; Goldstein, R.; Cohen, D. S.; Dotson, R.; Mathis, J. and Lee, W. *Bio. Med. Chem. Lett.* **1992**, *2*, 1623-1626.

(2) Two cases of intramolecular Mitsunobu reaction involving indole N- and C-alkylation have been reported. Although the indole rings in these cases are unactivated, the reactions proceeded probably due to the intramolecular nature of the alkylation: see: (a) Danishefsky, S.; Regan, J. *Tetrahedron Lett.* **1981**, 3919-3922. (b) Magnus, P.; Mugrage, B. ; DeLuca, M. R.; Cain, G. A. *J. Am. Chem. Soc.* **1990**, *112*, 5220-5230.

(3) Compound **4** was prepared by the Mitsunobu reaction of 1,3-propanediol with 3-hydroxy-pyridine (27% yield).

(4) Compound **6** was prepared by acylation of ethyl 3-(5-fluoroindol-2-yl)propionate which in turn was prepared by homologation of **3** under standard conditions.

(5) Compounds **1a** and **1b** inhibited thromboxane synthase in a microsomal platelet preparation with IC_{50} values of 0.026 μM and 0.042 μM respectively. These compounds also inhibited the U 46619 induced aggregation of washed human platelets with IC_{50} values of 0.01 μM and 0.046 μM respectively. For details of the assay see: Bhagwat S. S.; Gude, C.; Cohen, D. S.; Lee, W.; Furness, P. and Clarke, F. H. *J. Med. Chem.*, **1991**, *34*, 1790-1797. We thank Mr. Warren Lee and Mr. David Cohen for determining in vitro activities of **1a** and **1b**.

(*Received in USA* 16 *August* 1993; *revised* 17 *November* 1993; *accepted* 18 *January* 1994)