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SELECTIVE *N*-ALKYLATION OF PYRROLOPYRIMIDINES AND INDOLES BY "TRANSFER OF ACTIVATION"

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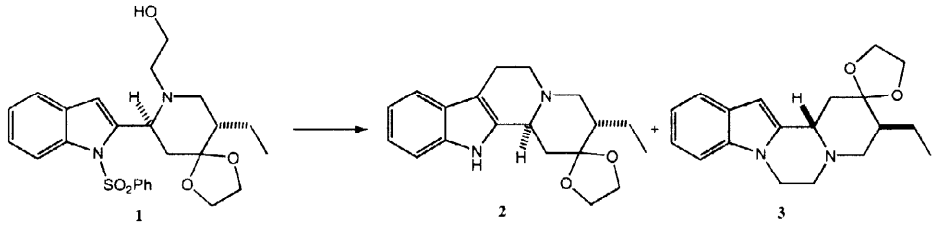
Abstract: The benzene sulfonyl group is used as a "transfer of activation" reagent to alkylate selectively the *N*-H of both pyrrolopyrimidines and 5-aminoindoles substituted on thienopyrimidines. A variety of primary and secondary alcohols are utilized as alkylating substrates.

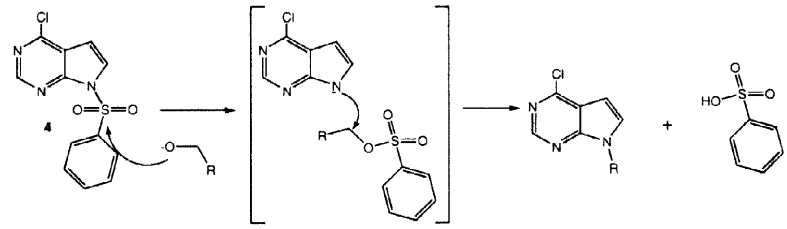
In the course of studies of pyrrolo-[2,3-d]-pyrimidines, we encountered difficulties in controlling the regioselectivity in alkylation of the pyrrole nitrogen. Poor selectivity for *N*-alkylation versus C-3 alkylation of the pyrrole and related heterocycles, including 3-unsubstituted indoles, is not uncommon.[1] In our initial attempts to alkylate specifically at the nitrogen, we used several activated electrophiles, such as methyl iodide or allyl bromide, ran the reactions in polar solvents ranging from THF to DMF, and reactions were attempted both in the presence and absence of base. In all cases, we obtained mixtures of C-alkylation and *N*-alkylation products in low yield.

Bosch and coworkers found an unexpected result when trying to deprotect a C-2 substituted *N*-benzene sulfonylindole with potasium t-butoxide in THF.[2] The 2-*N*-ethyl hydroxy-piperdine-subsituent underwent cyclization to a 1:1 mixture of 2 indoloquinolizidine regioisomers **2** and **3** (Scheme 1). One arising from C-3 alkylation and one from *N*-1 alkylation. They propose that this occurs by intermolecular sulfonylation of ethoxide followed by displacement of the ambident indole anion. They propose that *t*-butyl benzenesulfonate,



Scheme 1. Reagents: *t*-BuOK in THF

formed by deprotection of the indole nitrogen by *t*-BuOK, is the intermolecular sulfonylation agent. Katritzky[3] and Eissentstat[4] in independent reports, showed that this reaction can occur in a bimolecular fashion. Katritzky[3]



Scheme 2. Proposed mechanism of transfer

showed that the benzenesulfonyl group could be transferred from the *N*-1 of 1,2,4-triazoles to sodium alkoxide[5] to produce *N*-1 alkylated products. Eissenstat and Weaver[4] used a similar reaction which they term "transfer of

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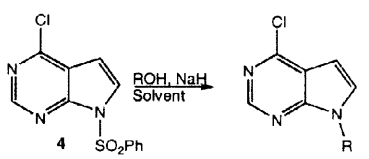
activation" for synthesizing analogues of the indole natural product pravadoline. In the bimolecular reaction, the mechanism for this transformation involves, first , attack of the pre-formed alkoxide on the sulfonamide to give an alkyl sulfonate and nitrogen anion. Then the newly formed nitrogen anion affects a nucleophilic displacement on the alkyl sulfonate. This transfer results in the overall alkylation of the previously sulfonylated nitrogen (Scheme 2).

We were utilizing the benzenesulfonyl group as a protecting group to obtain specific C-3 alkylation and with this procedure we could now effect a one pot transformation from protecting group to a specific *N*-alkyl group. This procedure allows us to start with alcohols as the ultimate alkyl group, which provides a large pool of readily available and stable reactants. We have found this in situ deprotection/activation/alkylation reaction very useful for the preparation of a variety of *N*-alkylated products both in the pyrrolopyrimidine ring system (Table 1) and the indole thienopyrimidine system (Table 2) in satisfactory to excellent yields (17%-86%). This in situ deprotection/activation/alkylation sequence not only simplifies and economizes the overall transformation, it serves to control the regiochemical outcome affording ready access to *N*-alkylated products.

Benzenesulfonamide **4** was synthesized in quantitative yield by deprotonation of the pyrrolopyrimidine[6] *N*-H with nBuLi or NaH in THF followed by the addition of benzene sulfonylchloride. We began our study with the transformation of benzenesulfonamide **4** and hydroxymethyl morpholine, utilizing published conditions[4] (NaH in toluene at 110°C with K_2CO_3 to neutralize the sulfonic acid formed) to obtain an 83% yield of the desired product (Table I, entry 1). Eissentstat and co-workers propose that a β-amino functionality was necessary to increase the electrophilicity of the alkylsufonate and we began our study with activated alcohols



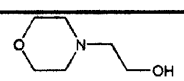
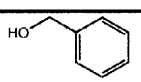
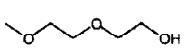
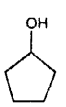
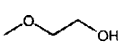
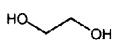
Entry	ROH	Conditions	Yield	Entry	ROH	Conditions	Yield
1		A	83	4		A	62
2		A	90	5		A	17
3		A	56	6		A	46

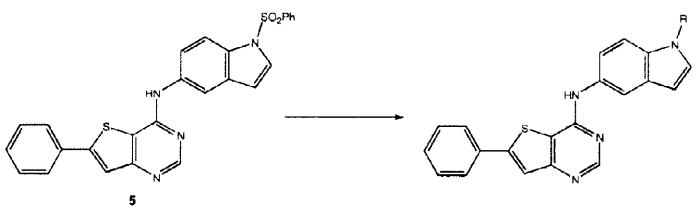
Table 1. Reagents A: NaH (2.0 eq.), toluene, K_2CO_3(2.0 eq.),110°C, 24h

but we found that alcohols without this activation could act as alkylating agents. In fact the reaction worked in the presence of excess protons, as seen with ethylene glycol (table 1, entry 6). In the reaction with ethylene

glycol, we examined the effect of varying the stoichiometry of the base and found in a range of 0.5 to 3 equivalents, all ratios worked, but one equivalent of base in ethylene glycol as the solvent gave highest yield. This indicated that the intermediate nitrogen anion formed must displace the incipient sulfonate formed faster than it is quenched by a proton (Scheme 2).

The 4-chloro pyrrolopyrimidine **4** was not an ideal substrate due to the competing electrophilic nature of the 4-chloro moiety with the benzenesulfonyl group. This poses a selectivity problem and led to lower yields of less reactive alcohols (entries 5 and 6, Table 1). In cases where yields are low, the side products seen were alkoxide replacement of the 4-chloro substituent, and product from *N*-alkylation and chloride displacement. Replacement of the 4-chloro group with 3-methyl-anilino group prior to reaction with cyclopentanol or ethylene glycol provided 56% and 72% yield of desired product, respectively. This procedure provided us with a one step reaction that produces the target molecules in quantities necessary for biological testing.

We have studied this chemical sequence on 5-aminoindole substituted thienopyrimidines. Here, selective modification of the indole nitrogen presents an additional challenge due to the presence of a secondary aniline at the 4-position of the pyrimidine ring (Table 2). Sulfonamide **5** was synthesized starting from 5- nitroindole



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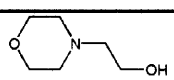
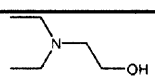
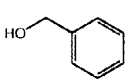
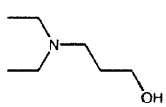
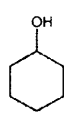
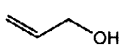
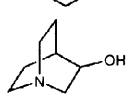
Entry	ROH	Conditions	Yield	Entry	ROH	Conditions	Yield
1		B	86	5		C	62
2		A	67	6		C	44
3	MeOH	B	79	7		B	37
4		C	66	8		C	15

Table 2. A: NaH, toluene, 110^{0}C, 24h; B: Na (2.0 eq.) in alcohol, sealed tube, 100^{0}C, 4h, C: NaH, dioxane, 110^{0}C, 24h

and protecting the indole nitrogen with benzenesulfonyl chloride as described above. The nitro group is reduced with hydrazine and palladium[7] and then the amino indole is coupled with 4-chloro-thienopyrimidine in t-BuOH and dichloroethane.[8] We found that when the requisite alcohols were readily available liquids, the highest yields were obtained by preforming the alkoxide with sodium metal in the alcohol as solvent (entries 1,3,and 7, Table 2), then adding the sulfonamide **5**. All other alcohols were deprotonated with sodium hydride in either toluene

or dioxane, depending on solubility. The only byproduct identified was that from loss of the benzenesulfonyl group which was easily separable by column chromatography.

Moderate to good yield were obtained with all primary alcohols utilized. We were surprised by the good yield seen when methanol was employed since sodium methoxide has been used for deprotection of aromatic nitrogens protected with a sulfonyl group. Closer inspection of the literature revealed that deprotected is usually effected by reduction or acid hydrolysis and more recently F⁻.[9] For comparison of this procedure to the use of standard nitrogen alkylation, the unsubstituted indolyl-thienopyrimidine was treated with NaH and one equivalent of methyl iodide in DMF. At room temperature no methylation was seen but at 90°C a mixture of three different monoalkylated and bisalkylated products were identified. This in situ deprotection/activation/alkylation sequence allowed for selective alkylation of the sulfonated nitrogen.

In conclusion, both sulfonamide **4** and sulfonamide **5** react with a variety of sodium alkoxides to give *N*-alkyl derivatives. The only side products obtained were desulfonylated products, which were seen with less electrophilic or sterically hindered sulfonate intermediates. This method is particularly useful for selective *N*-alkylation over C-alkylation in unsubstituted indoles and pyrrolopyrimidines, and specific alkylation of an *N*-sulfonyl moiety in a molecule with more than one reactive nitrogen.

References and Notes

1. Pudlo, J.S.; Nassiri, M.R.,; Kern, E.R.; Wotring, L.L.; Drach, J.C.; Townsend, L.B. *J. Med. Chem.* **1990,** *33,* 1984. Zhou, J.; Bouhadir, K.; Webb, T. R.; Shelvin, P.B. *Tetrahedron Lett.* **1997,** *38,* 4037. Coe, J. W.; Vetelino, M. G.; and Bradlee, M.J. *Tetrahedron Lett.* **1996,** *37,* 6045 and references cited there in.
2. Rubiralta, M.; Diez, A.; Bosch, J.; Solans, X. *J. Org. Chem.* **1989,** *54,* 5591.
3. Katritzky, A.R., Zhang, G.-F.; Pernak, J.; Fan, W-Q. *Heterocycles.* **1993,** *36,* 1253.
4. Eissenstat, M.A.; Weaver, J.D. *Tetrahedron Lett.* **1995,** *36,* 2029.
5. The use of the sodium alkoxide in this reaction can also be referred to as a *counter attack reagent*: Hwu, J.R. and Gilbert, B.A. *Tetrahedron* **1989,** *45,* 1233.
6. Davoll, J. *J. Am. Chem. Soc.* **1960,** 131.
7. Adger, B. M.; Young, R. G.; *Tetrahedron Lett.* **1984,** *25,* 5219.
8. Ren, W. Y.; Rao, K.V. B.; Klein, R. S. *J. Heterocycl. Chem.* **1986,** *23,* 1757. Yauhara, A.; Sakamoto, T. *Tetrahedron Lett.* **1998,** *39,* 595.
9. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis* John Wiley and Sons, Inc.: New York, 1991; p.383. Muratake, H. and Natsume, M. *Heterocyles* **1989,** *29,* 783. Carter, P.; Fitzjohn, S.; Magnus, P. *J. Am. Chem.Soc.* **1987,** *109,* 2711. Itahara, T.; Kawasaki, K., Ouseto, F. *Synthesis* **1984,** *3,* 236.