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THE ORTHO-ALKYLATION OF ANILINES VIA [2,3]-SIGMATROPIC REARRANGEMENTS OF AZASULFONIUM YLIDS. A NEW PROCESS FOR THE INTRODUCTION OF ALKYL GROUPS

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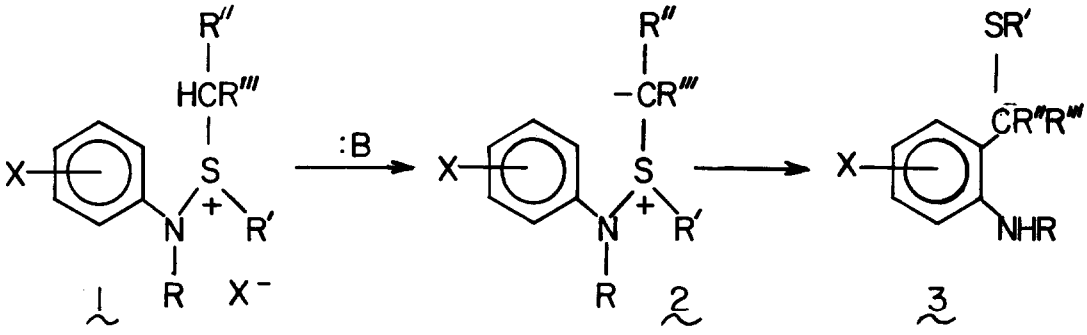
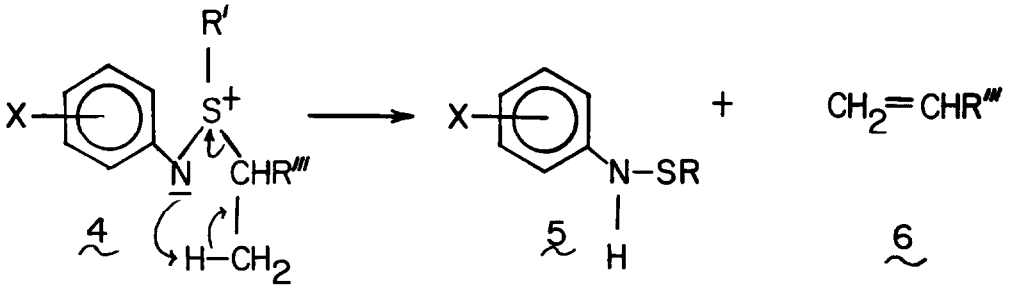
The alkylation of anilines has long been a subject of interest in both academic and industrial laboratories. Recently, we described a process for the specific ortho-alkylation of anilines.[1] This process, which involved the conversion of azasulfonium salts of general formula 1 into ylids of type 2, followed by [2,3]-sigmatropic rearrangement and rearomatization to give 3, was excellent when R was an alkyl group. For instance, when R was methyl a variety of side

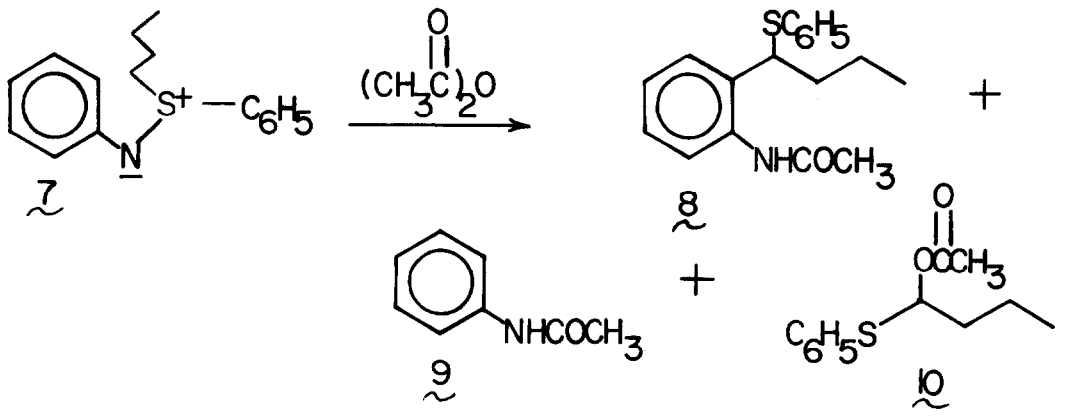


chains could be introduced. Desulfurization of 3 would then provide the desired ortho-alkylated aniline.[1] Unfortunately, the generality of this process was limited if R was hydrogen and R', R", or R''' bore hydrogens which were β to the sulfonium cation.[2] When β-hydrogens were present and R was hydrogen, treatment of 1 with base gave the sulfilimine 4, which on warming



gave 5 and 6 through transfer of the β-hydrogen. We now wish to report a major modification of our general procedure which circumvents the serious problems associated with the elimination re-

action normally observed for 4. The modification, which involves *in situ* acylation of 4, allows a wide variety of ortho-alkylations of aniline and of its derivatives. For example, treatment of the sulfilimine 7 with acetic anhydride at 0° gave 55% of 8 and 30% each of 9 and 10.[3]



7 8 9 10

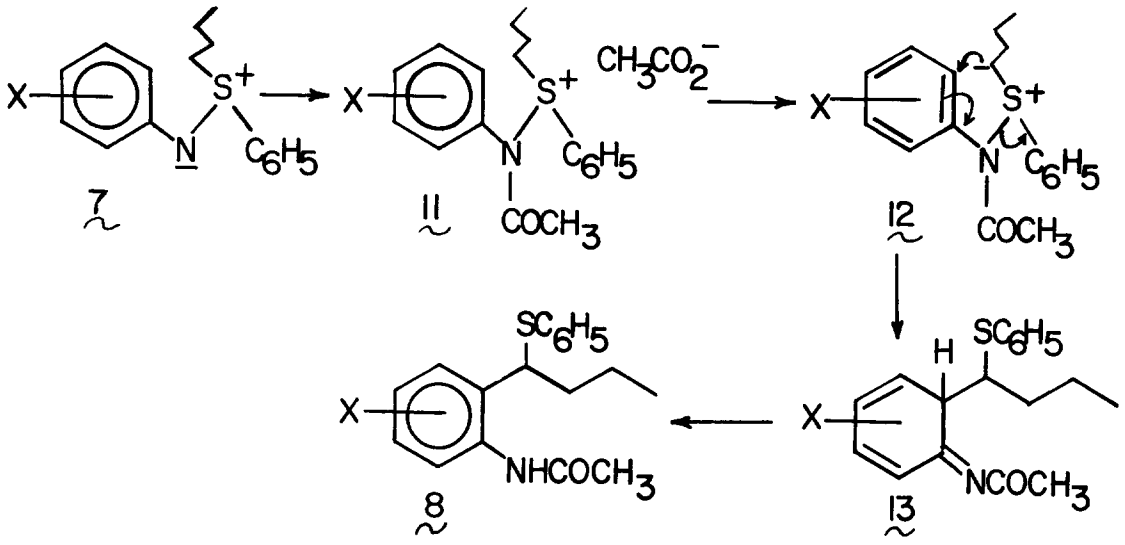
In a typical procedure, a methylene chloride solution of 1.0 equiv. of an aniline and 1.2 equiv. of a phenyl alkyl sulfide was treated with 1.0 equiv. of *tert.*-butyl hypochlorite at -40° and the reaction mixture was stirred at that temperature for 3 hr. One equiv. of triethylamine was added and the reaction mixture was stirred at -40° for 0.5 hr and then allowed to warm to 0°. Two equiv. of acetic anhydride was then added and the reaction mixture was allowed to warm to room temperature over a 1-hr period. Table 1 lists the yields of products obtained

Table 1. Yields of 2-(1-Thiophenoxybutyl)acetanilides (8) and Acetanilides (9) from Anilines.

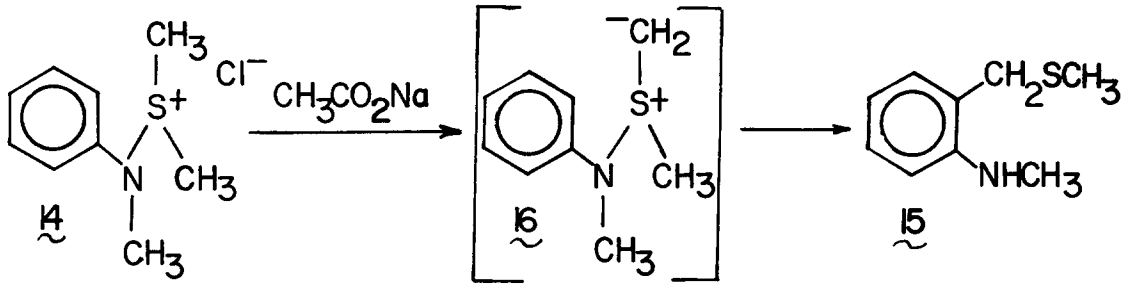
Substituent on aniline	% Yield of substituted 8	% Yield of substituted 9
p-OCH_3	40	18
H	55	30
p-Cl	61	35
p-$CO_2C_2H_5$	54	39

with phenyl *n*-butyl sulfide and a series of substituted anilines.[4] As shown, the process offers an attractive method for the introduction of an alkyl side chain, since Raney-nickel desulfurization can readily remove the thiophenoxyl moiety.

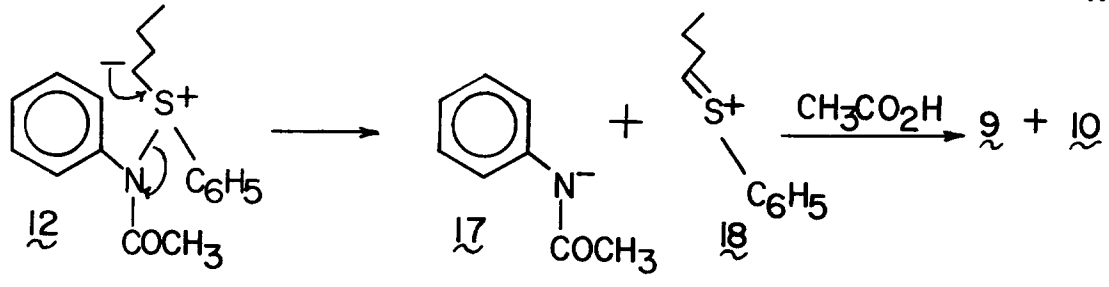
The most plausible mechanism for the formation of 8 involves acylation of the sulfilimine 7 to produce 11, which reacts in turn with the generated acetate ion to produce the ylid 12. [2,3]-Sigmatropic rearrangement of 12, in a typical Sommelet-Hauser manner,[1,5] would be expected to yield 13, which on hydrogen shift and accompanying rearomatization would produce 8. A surprising feature of this mechanism is that it requires acetate ion to be a base which is strong



enough to generate the ylid 12. In order to test this assumption, we prepared 14 by standard procedures[1] and treated it with a methanolic solution of sodium acetate. We found that these



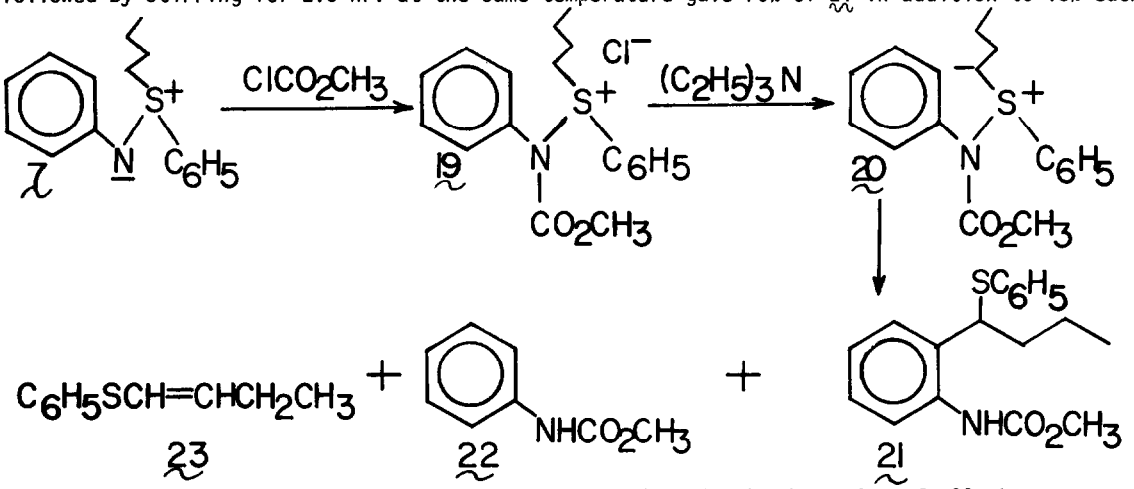
conditions were sufficient to promote the rapid rearrangement of 14 into 15, presumably via the intermediacy of 16. The formation of 9 and 10 as side products in the reaction of 7 with acetic anhydride can be explained in terms of a simple cleavage of 12 to produce the amide anion 17



and the sulfonium cation 18. Protonation of 17 and addition of acetate anion to 18 would then produce 9 and 10, respectively.

In an alternate approach to the problem, 7 was treated with 2.0 equiv. of methyl chloro-

formate at -15°, which gave 19 after 0.5 hr. Addition of 2.5 equiv of triethylamine at -15° followed by stirring for 2.5 hr. at the same temperature gave 76% of 21 in addition to 18% each



of 22 and 23. It is presumed that 20 was an intermediate in the formation of all three products.

In summary, we have developed a general, "one-pot" set of reactions for the specific ortho-alkylation of aromatic amines which should be applicable to the introduction of a wide variety of alkyl groups.[6] The use of methyl chloroformate in the procedure provides substituted anilines with readily removed protecting groups.

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References and Footnotes

1. P.G. Gassman and G.D. Gruetzmacher, *J. Am. Chem. Soc.*, 96, 5495 (1974); P.G. Gassman, G.D. Gruetzmacher, and T.J. van Bergen, *ibid.*, 96, 5512 (1974); P.G. Gassman and C.T. Huang, *ibid.*, 95, 4453 (1973).

2. A major exception to this generality was noted when R' and R" formed part of a sulfur contained ring (e.g. tetrahydrothiophene). In these cases, spatial restrictions prevented concerted eliminations via transfer of a β-hydrogen to nitrogen.[1]

3. Satisfactory elemental analyses and/or exact mass molecular weights were obtained on all new compounds.

4. In the case of *p*-methoxyl derivative, the intermediate azasulfonium salt was prepared through the reaction of *p*-anisidine with the appropriate chlorosulfonium chloride.[1]

5. M. Sommelet, *Compt. Rend.*, 205, 56 (1937); S.W. Kantor and C.R. Hauser, *J. Am. Chem. Soc.*, 73, 4122 (1951); G.C. Jones and C.R. Hauser, *J. Org. Chem.*, 27, 3572 (1962); G.C. Jones, W.Q. Beard, and C.R. Hauser, *ibid.*, 28, 199 (1963). See also L.P.A. Fery, *Bull. soc. chim. Belges*, 71, 376 (1962). C.R. Hauser, S.W. Kantor, and W.R. Brasen, *J. Am. Chem. Soc.*, 75, 2660 (1953).

6. Subsequent to the completion of this work, we learned that a related procedure had been used for the ortho-methylation of *p*-chloroaniline [P.K. Claus, H.A. Schwarz, W. Rieder, and W. Vycudilik, *Phosphorous and Sulfur*, 1, 11 (1976)].