

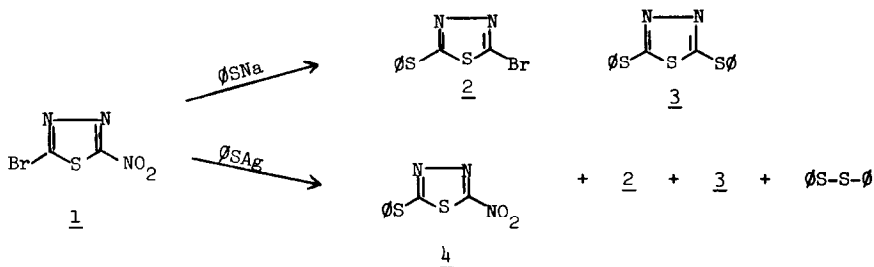
Counter-ion Dependency of Leaving Group Potential in Nucleophilic Displacement

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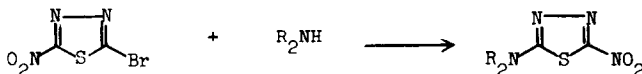
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We would like to report what we believe to be the first case of leaving group potential dependency on the cation associated with an anionic nucleophile. Thus we have found that whereas sodium thiophenolate reacts with an equivalent of 2-bromo-5-nitro-1,3,4-thiadiazole (1)¹ in ethanol to give 2-bromo-5-phenylthio-1,3,4-thiadiazole (2)² (m.p. 56-58°) as the sole monosubstitution product (39%) along with 2,5-bis(phenylthio)-1,3,4-thiadiazole^{2,3a} (3) (40%) (m.p. 107-108°), silver thiophenolate reacts in the same solvent⁴ with 1 (equimolar quantities) to give predominantly (ca. 50%) 2-nitro-5-phenylthio-1,3,4-thiadiazole (4)² (m.p. 92-94°) along with minor amounts of 2, 3 and diphenyldisulfide (ca. 4% of each).^{3b}



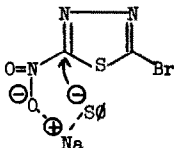
We were led to this finding as a result of earlier studies by A. S. Tomcufock and A. Hoffman of these laboratories⁵ on the behavior of amine nucleophiles towards 1. These workers found that 1 reacted with a variety of amines (e.g. morpholine, dimethylamine, ammonia) to give exclusively the product of bromide ion displacement.



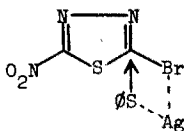
In an attempt to extend this observation to sulfur nucleophiles we investigated the reaction of 1 and sodium thiophenolate, but contrary to expectation we obtained 2 as the only monosubsti-

tution product.

The HASB (Hard Acid Soft Base) concept recently introduced by Pearson⁶ appeared to offer a satisfactory explanation for this rather dramatic difference in behavior between amines and mercaptide ion. Thus, the preferential displacement of bromide ion vs nitrite observed in the reaction of 1 with amines could have been reversed in its reaction with sodium thiophenolate because of the enhancement of the leaving group potential of nitrite owing to the interaction of the negatively charged oxygen of the nitro group in 1 (a hard base)⁶ with the associated sodium cation (a hard acid).⁶



It was further anticipated that the formation of 1, the product of bromide ion displacement, would be favored from the reaction of silver thiophenolate and 1, since the silver cation, a soft acid,⁶ would be expected to interact preferentially with the bromo substituent of 1, a soft base center.⁶ This result was, in fact, realized.



(The sulfur atom in the thiadiazole ring represents another soft base center for interaction with the soft silver cation. The same result, i.e. preferential bromide ion displacement, would also be anticipated should this be the site of interaction, since it has already been established from the reaction of 1 with amines that in the absence of external activation the bromo substituent in 1 is preferentially displaced.)

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References

1. First prepared by A. S. Tomcufoik and A. Hoffman of these laboratories by nitrite ion displacement of the nitrogen from the diazonium salt of 2-amino-5-bromo-1,3,4-thiadiazole.
2. Satisfactory analytical data were obtained for all new compounds.

3. a) 2 and 3 are most conveniently separated by partition chromatography on Celite 545 using heptane-methyl cellosolve. b) After isolating the bulk (43%) of 4 by triturating the crude reaction mixture with ether, the other components were separated by partition chromatography (Celite 545, heptane-methyl cellosolve).
4. The rate of reaction of the two salts with 1 differed considerably. The sodium salt reacted with 2 at room temperature overnight, whereas the silver salt required heating under reflux for 48 hr. The homogeneity of the reaction mixture in the case of the sodium salt but not in that of the silver salt could be a contributing factor to the observed rate difference. (The sodium salt was prepared in situ from thiophenol and sodium ethoxide; the Ag salt was separately prepared from thiophenol and aqueous silver nitrate-sodium acetate.)
5. Unpublished.
6. R. G. Pearson, J. Am. Chem. Soc., 85, 3533 (1963); Science, 151, 172 (1966).