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Reactions of Halodiazirines with Potassium Ethyl Xanthate

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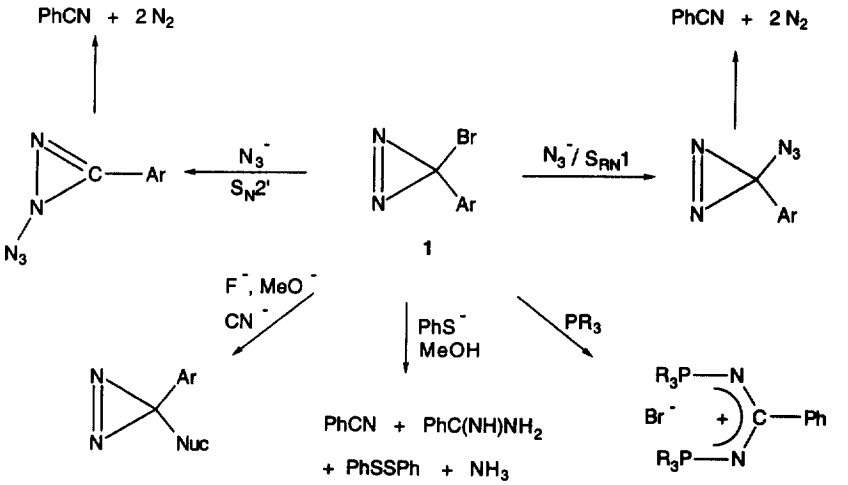
Abstract: Aryl halodiazarines are reduced by potassium ethyl xanthate to give benzonitrile as the major product along with significant amounts of a novel heterocyclic product, 3-phenyl-5-ethoxy-1,2,4-thiadiazole. A mechanism involving fragmentation of an *N*-substituted diazirine is considered.

The mechanisms by which halodiazirines of general type **1** react with nucleophiles remains an area of fascination.[1,2] The S_N2' mechanism for reaction of **1** with azide ion is now well documented,[3] as is the $S_{RN}1$ mechanism.[4] Recently, Moss has found an unusual variation of the $S_{RN}1$ mechanism using acetate ion.[5] Bertrand has found that phosphines react to give an unusual delocalized phosphonium salt.[6] In other words, azide, fluoride, acetate, phosphines, thiophenoxide, and organometallic reagents give, in many instances, very different types of products by a number of mechanistic processes which are still not completely understood. Some of these processes studied by us and others are summarized below.



With the goal of better understanding the reaction of sulfur containing nucleophiles with **1**, we have now carried out a study of the reaction of phenylbromodiazirine, **2**, with potassium ethyl xanthate, **3**. A fascinating series of color changes accompany this reaction which occurs readily at room temperature. Over the course of the reaction, the mixture changes from light yellow to green, to blue, to violet, and finally, to red. Benzonitrile is the major product formed in this reaction (87%), along with a significant amount (13%) of the heterocycle **5**.[7] The structure of this product was assigned by standard spectroscopic methods.[8] The

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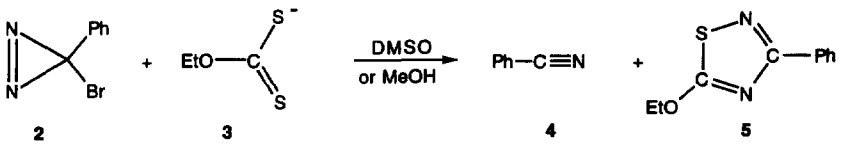
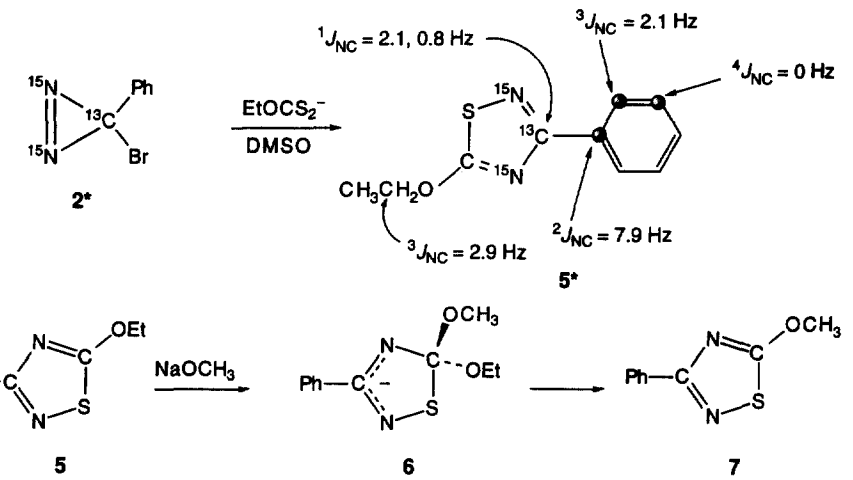


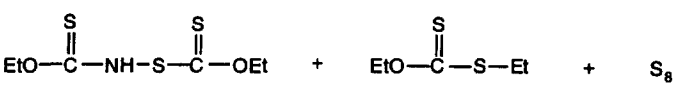
2 3 4 5

atom connectivity was established using ^{15}N NMR and ^{13}C NMR on a sample of the heterocycle prepared from the triply labeled substrate **2***, which gives a product **5***. The ^{15}N-^{15}N coupling in **5*** is relatively small (1.3 Hz; two bond coupling) and the ^{15}N atoms are both coupled in expected fashion to the additional ^{13}C atoms in both rings.[9,10] Additionally, **5** undergoes a facile substitution reaction with methoxide ion at room temperature to form the analogous methoxy derivative **7**. This substitution reaction presumably proceeds via the conjugated sulfur stabilized anionic intermediate **6**.



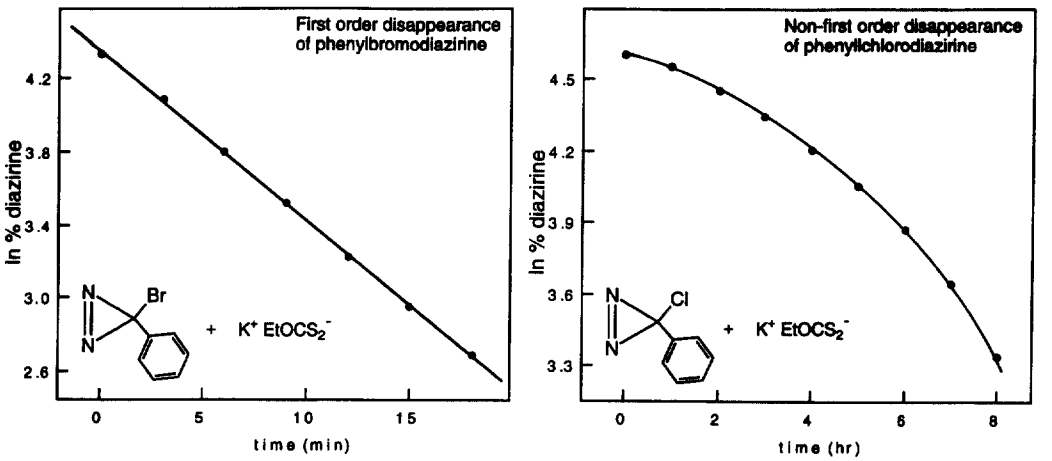
2* **5*** **5** **6** **7**

The fate of the second nitrogen atom in the benzonitrile forming reaction, as well as the sulfur atom in the process that leads to **5** is also of interest. The second nitrogen atom ends up partially as the thioamide, **8** (20%). Monitoring the reaction by ^{15}N NMR in DMSO-d_6 shows that **8** is not a primary product, but is formed during the aqueous workup. Also formed is a small amount of the ethylated xanthate **9**. Finally, elemental sulfur is also formed in high yield.

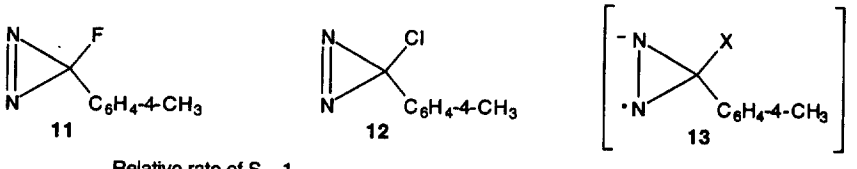


8 **9** **10**

Since benzonitrile is the major aromatic product formed, at first glance, the process might seem to be analogous to the reaction of thiophenoxide with halodiazirines.[11] However, the kinetic behavior is substantially different from any behavior that we have previously observed. Typical phenylbromodiazirine rate data are shown below. Phenylbromodiazirine disappears in a first order process when an excess of xanthate is used. However, phenylchlorodiazirine, which gives the same products as phenylbromodiazirine, does not disappear in a first order process. The reaction of phenylchlorodiazirine and other arylchlorodiazirines appears to be autocatalytic, and a typical plot is shown below for phenylchlorodiazirine. The xanthate reaction therefore contrasts with the thiophenoxide reaction, which is first order in chlorodiazirine.[10] It also contrasts with the reaction of azide ion, which is first order in chlorodiazirine in the S_N2' process,[3] and shows an induction period under photoinitiated $S_{RN}1$ conditions.[4]



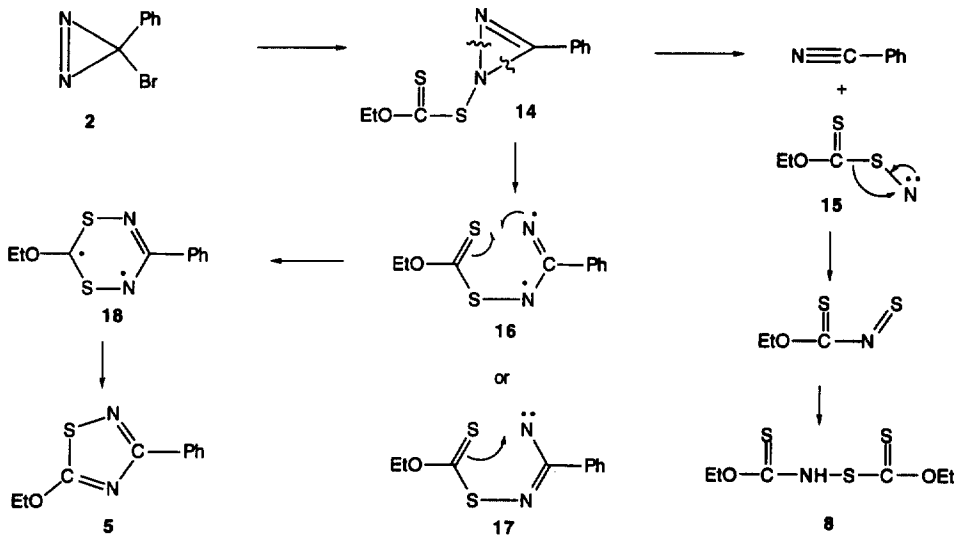
The mechanism of the reaction of xanthate ion with halodiazirines warrants some comment. Electron-withdrawing substituents on the aryl group speed up the reaction but the effect is not large. With respect to the leaving group, the reactivity of phenylfluorodiazirine has been compared to that of *p*-tolylchlorodiazirine, **12**, by means of a direct competition experiment. During the time required for *p*-tolylchlorodiazirine to react completely with potassium ethyl xanthate (40 hours), phenylfluorodiazirine present in the mixture is completely unreacted. In a separate competition experiment, phenylchlorodiazirine reacts completely with xanthate leaving p-tolylfluorodiazirine, **11**, untouched. By way of contrast, relative rates of the electron transfer initiated $S_{RN}1$ reaction of azide ion with the fluoro and chloroodiazirines **11** and **12** have been determined by cross competition experiments and the fluorodiazirine **11** is only 2.6 times less reactive than the chlorodiazirine **12**. The step that determines relative reactivity in the $S_{RN}1$ reaction involves an electron transfer to the competing halodiazirines to give intermediates such as **13**. Since the carbon-halogen bond is not being broken in the formation of **11**, electron transfer to fluorodiazirines vs. chlorodiazirines is a relatively unselective reaction. This contrasts with the very selective reaction of xanthate with chlorodiazirines at the exclusion of fluorodiazirines. Hence the xanthate reaction does not appear to be an electron transfer initiated process.



1.0 Relative rate of $S_{RN}1$ reaction with N_3^- 2.6

While the complete mechanism of the xanthate reaction is uncertain, the partial mechanism presented below merits consideration. Formation of the substitution product **14** by some mechanism could be followed by fragmentation of the weak N-N bond of this formally antiaromatic compound. Further N-C bond fragmentation would give benzonitrile and the sulfur stabilized nitrene **15**. While, at first glance, this fragmentation to a nitrene intermediate might seem to be unreasonable, computational studies (HF/6-31G*) suggest that fragmentation of the methyl analog of **14** to CH_3CN and the nitrene **15** is not an unfavorable process; it is essentially thermoneutral. Rearrangement of this nitrene forms the necessary N-C bond required in the nitrogen containing product **8**. Cyclization of a biradical **16** (or the nitrene **17**) would result

in **18** (or the zwitterionic analog). Further cyclization and sulfur extrusion would generate the heterocyclic compound **5**.



There are a number of other questions that need to be answered. What is the origin of the ethylated xanthate **9**? Why do arylchlorodiazirines show non-first order behavior? What is responsible for the color changes that accompany the reaction? These questions, which are currently under investigation, suggest that a variety of fascinating reactive intermediates and products are derived from reaction of xanthate ion with halodiazirines.

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References and Notes

[1] For a summary of reactions of **1** with nucleophiles, see (a) Moss, R. A. *Acc. Chem. Res.* **1989**, *22*, 15. (b) Moss, R. A.; Shen, S.; Hadel, L. M.; Kmiecik-Lawrynowicz, G.; Wlostowska, J.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1987**, *109*, 4341. (c) Moss, R. A.; Terpinski, J.; Cox, D. P.; Denney, D. Z.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1985**, *107*, 2743. (d) Padwa, A.; Eastman, D. *J. Org. Chem.* **1969**, *34*, 2728.

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[6] Alcaraz, G.; Baceiredo, A.; Neiger, M.; Bertrand, G. *J. Am. Chem. Soc.* **1994**, *116*, 2159.

[7] For a review of this heterocyclic system, see Franz, J. E.; Dhingra, O. P. *Comprehensive Heterocyclic Chemistry*, Volume 6, Pergamon Press, New York, **1984**, 463-511.

[8] ^{1}H NMR of **5** ($CDCl_3$) δ 8.25-8.15 (2 H, m), 7.50-7.38 (3 H, m), 4.618 (2 H, q, J = 7.1 Hz), 1.521 (3 H, t, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 190.85, 168.39, 133.06, 130.15, 128.52, 127.80, 69.96, 14.45. Exact Mass calcd for $C_{10}H_{10}N_2OS$: 206.0514, found 206.0527.

[9] For a discussion of ^{13}C-^{15}N and ^{15}N-^{15}N coupling constants, see Levy, G. C.; Lichter, R. L. *Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy*; Wiley: New York, 1979.

[10] Isomeric thiadiazoles can be ruled out by these coupling patterns.

[11] Creary, X.; Sky, A. F.; Phillips, G.; Alonso, D. E. *J. Am. Chem. Soc.* **1993**, *115*, 7584.