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NUCLEOPHILIC DISPLACEMENT OF AROMATIC NITRO GROUPS

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Abstract—The relative nucleofugicity of the nitro group in many aromatic nucleophilic substitution reactions rivals, and in some cases surpasses, that of the fluorine atom. The use of the nitro function as a leaving group in such reactions facilitates the synthesis of novel substituted benzene derivatives and simplifies the synthesis of a wide variety of heterocycles.

INTRODUCTION

The nitro group is a valuable precursor to a variety of substituents in aromatic systems. The procedure ordinarily involves (1) reduction to an amine function, (2) diazotization and (3) displacement by a nucleophile. A second procedure entails the direct replacement of the nitro group by a nucleophile. In this case activation by at least one other electron-withdrawing function is necessary, and the reaction is analogous to the more commonly encountered nucleophilic displacement of an activated aromatic halogen. The synthetic potential for the second process has been enhanced in recent years due to increased use and availability of dipolar aprotic solvents, such as DMF, DMSO and HMPA.

This review will discuss the literature with respect to direct nucleophilic aromatic nitro group displacement with special attention given to its synthetic utility. Nucleophilic aromatic photosubstitution of the nitro group will not be covered since this subject has been recently reviewed.[1]

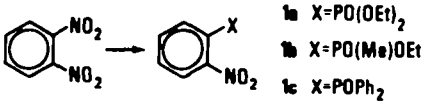
KINETIC STUDIES

The relative nucleofugicity of an activated aromatic nitro group in comparison with other similarly activated functions has been the subject of several kinetic studies. Bunnett *et al.* examined the kinetics involved with the reaction of 1-X-2,4-dinitrobenzenes with piperidine in methanol.[2] The relative rate for displacement of a nitro group ($X=NO_2$) was approximately 200-times that of chlorine or bromine and one-fourth that of fluorine. Bolto and Miller reported kinetic results for the reaction of 1-X-4-nitrobenzenes and methoxide ion in methanol.[3] These authors reported the following order of nucleofugicity: $Me_2S^+ > Me_3N^+ > F \cong NO_2 > Cl$. More recently, Bartoli and Todesco obtained similar results with the reaction of 1-X-2,4-dinitrobenzenes and methoxide ion in methanol.[4] Again the relative rates of nitro and fluorine displacement were essentially equal, and the rate of nitro displacement was 400-times that of chlorine. Parker and Read examined the displacement reaction of 1-X-2,6-dinitrobenzenes and aniline in ethanol.[5] They reported the rate constant for nitro displacement to be considerably higher than that of fluorine, which in turn was higher than chlorine. The authors attributed this unexpected result to steric acceleration in the nitro case. Finally, Suhr reported kinetic data involving the reaction of 1-X-4-nitrobenzenes and piperidine in DMSO.[6] In this case the relative rate of fluorine displacement was 50-times that of the nitro group, and nitro displacement was only 9-times that of chlorine.

INTERMOLECULAR NITRO DISPLACEMENT IN AROMATIC SYSTEMS

Most early examples of aromatic nitro displacement involved the reaction of *o*- or *p*-dinitrobenzene with various nucleophiles, and these have been discussed extensively elsewhere.[7] Since the products of such displacements can ordinarily be obtained from the more readily available *o*- and *p*-halonitrobenzenes, these reactions have little synthetic utility and will not be reviewed here.

An exception is the condensation of *o*-dinitrobenzene with phosphorus nucleophiles reported by Cadogan *et al.*[8] In this case the reaction of triethyl phosphate and *o*-dinitrobenzene in refluxing acetonitrile yielded the phosphonate ester **1a** (78%). The authors presented evi-



1a X=PO(OEt)$_2$
1b X=PO(Me)OEt
1c X=POPh$_2$

dence for a mechanism involving nucleophilic displacement by phosphorus with the formation of a phosphonium nitrite salt intermediate, which was converted by dealkylation, as in the Arbusov reaction, to form **1a** and ethyl nitrite. Surprisingly, the reaction did not occur to a measurable extent with either *p*-dinitrobenzene or *o*-chloronitrobenzene. Similarly prepared were **1b** (78%) and **1c** (57%) when *o*-dinitrobenzene was allowed to react with diethyl methylphosphonate and ethyl diphenylphosphinate, respectively.

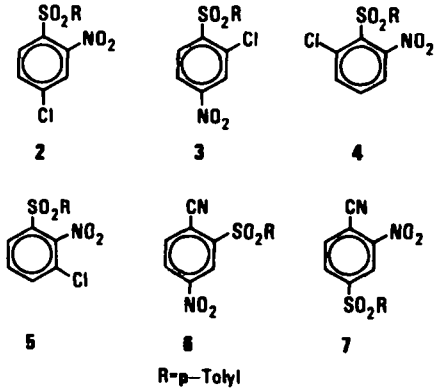
Synthetic utility has also been demonstrated for nucleophilic displacements involving *m*-dinitrobenzenes.

Gold and Rochester reported the synthesis of 3,5-dinitroanisole (90%) from 1,3,5-trinitrobenzene and sodium methoxide in methanol.[9] In similar fashion, 3-methoxy-5-nitrobenzotrifluoride was obtained in high yield from 3,5-dinitrobenzotrifluoride.[10] The conversion of *m*-dinitrobenzene to *m*-nitroanisole (83%) and 1-nitro-3-(phenylthio)benzene (88%) by treatment with the appropriate nucleophile in HMPA at ambient temperature was described by Kornblum *et al.*[11] The reaction of potassium fluoride with *m*-dinitrobenzene in HMPA at 180° for 48 hr gave 1-fluoro-3-nitrobenzene (45%).[12]

Replacement of nitro groups activated by two *meta* electron-withdrawing substituents other than nitro have been reported. 3,5-Bis(trifluoromethyl)anisole[10] and 1,3-bis(trifluoromethyl)-5-(phenylthio)benzene[11] were obtained from 1,3-bis(trifluoromethyl)-5-nitrobenzene in high yield under mild conditions. Similarly prepared were 3,5-bis(trifluoromethylsulfonyl)anisole and 1,3-bis(trifluoromethylsulfonyl)-5-(phenylthio)benzene from the appropriate nitro precursor.[13]

The synthetic utility of nucleophilic displacement of a nitro group activated by an *ortho* or *para* function other than nitro was demonstrated very early in the chemical literature. Tiemann in 1891 described the synthesis of 2-chloro-4-methoxybenzaldehyde from 2-chloro-4-nitrobenzaldehyde and a molar equivalent of sodium methoxide.[14] Ringer in 1899 reported the preparation of *o*- and *p*-methoxybenzonitrile from *o*- and *p*-nitrobenzonitrile, respectively, and sodium methoxide in methanol.[15] Bogert and Boroschak in 1901 synthesized 3-chlorophthalic anhydride by the reaction of 3-nitrophthalic anhydride and phosphorus pentachloride at elevated temperature.[16]

A systematic investigation of the synthetic potential of nucleophilic displacement reactions of this type was described in a series of papers by Loudon *et al.* published between 1935 and 1941. Much of this work involved replacement reactions of substituted benzenes having three different activated leaving groups (nitro, chloro and arylsulfonyl). For example, treatment of the sulfone **2** with either methanolic ammonia or methoxide ion gave isolable products obtained exclusively by nitro displacement.[17] With piperidine two products were identified. One was formed by nitro displacement and the other by loss of chlorine. With sodium *p*-toluenesulfinate the chlorine was selectively replaced, and reaction with *p*-toluenethiol anion resulted in the loss of the sulfonyl function. In the case of the related sulfone **3**, no reaction occurred with ammonia, whereas methoxide ion again selectively replaced the nitro group.



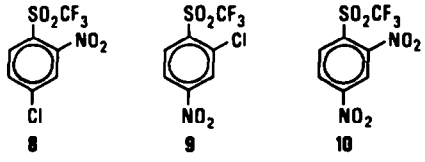
Piperidine reacted as in the case of **2** with both chlorine and nitro displacement. A complex mixture of products was obtained upon treatment of **3** with sodium *p*-toluenesulfinate, whereas *p*-toluenethiol anion again displaced the sulfonyl function. In the case of the sulfone **4**, treatment with ammonia led to nitro replacement, but methoxide ion displaced both chlorine and nitro with a minor product attributed to loss of sulfone.[18] The reaction of **4** with *p*-toluenethiol anion resulted in sulfone displacement as in the case of both **2** and **3**, whereas piperidine selectively replaced chlorine. Finally, in the example of the sulfone **5**, ammonia, methoxide ion, and, unexpectedly, *p*-toluenethiol anion all reacted by exclusive nitro displacement. As in the case of **4**, piperidine selectively replaced chlorine.

Other examples were described by Loudon,[19] although the above illustrate the overall properties of such systems. It is difficult to draw conclusions from Loudon's work since product yields were not reported. Nevertheless, it appears that nitro displacement was the predominant reaction with respect to unhindered nucleophiles, such as methoxide ion and ammonia. In the case of a hindered nucleophile, such as piperidine, chlorine displacement became a factor and actually predominated in two instances (**4** and **5**). With a stronger nucleophile, such as *p*-toluenethiol anion, sulfonyl displacement ordinarily occurred, although in the case of **5** the isolated product was formed by nitro displacement.

Loudon also examined competitive reactions in a series of nitro- and chloro-substituted benzonitriles and results were obtained similar to those described above.[20] For example, the reaction of 4-chloro-2-nitrobenzonitrile and piperidine resulted in replacement of both nitro and chlorine, whereas *p*-toluenethiol anion selectively displaced the nitro group. When 2-chloro-4-nitrobenzonitrile was utilized as the substrate, piperidine selectively replaced chlorine and *p*-toluenethiol anion displaced both nitro and chlorine groups to give a mixture of products.

In the same paper Loudon reported the reaction of 2,4-dinitrobenzonitrile and piperidine, which yielded 2-nitro-4-piperidinobenzonitrile as the sole product isolated. With *p*-toluenethiol anion a mixture was obtained, which involved both *o*- and *p*-nitro displacement. Also discussed was the reaction of the sulfones **6** and **7** with piperidine and *p*-toluenethiol anion. In each case the products obtained were formed by exclusive nitro group displacement.

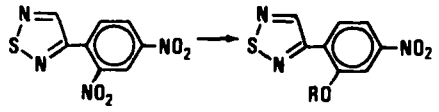
Competitive substitution reactions of a more refined nature were recently reported by Boiko and Yagupolskii utilizing the sulfones **8**, **9** and **10**.[21] Treatment of **8** with



methoxide ion gave 61% of methyl ether formed by nitro displacement and 34% formed by loss of chlorine. Only the 4-methoxy derivative (96%), which resulted from nitro displacement, was obtained by similar treatment of **9**. In the case of **10**, 70% of methyl ether was formed by displacement of the *p*-nitro group and 30% was formed by replacement of the trifluoromethylsulfonyl function.

Further examples of activated nitro group displace-

ment are found throughout the chemical literature, although they are often reported as unexpected or isolated results rather than as general synthetic procedures. For instance, Cortes and Walls obtained 2-benzyloxy-6-ethoxybenzonitrile from 2-benzyloxy-6-nitrobenzonitrile and sodium ethoxide.[22] De Munno *et al.* reported the synthesis of **12a** (80%) and **12b** (90%) by treatment of **11**



11 **12a** R=Me **12b** R=Et

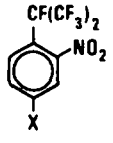
with potassium hydroxide in the appropriate aqueous alcohol solvent.[23] The products were identified by permanganate oxidation to the corresponding known benzoic acids. Soti *et al.* obtained 2-bromo-4,6-dimethoxybenzonitrile (95%) from 2-bromo-4,6-dinitrobenzonitrile and methoxide ion.[24] Baumann described several nitro displacement reactions utilizing sulfur nucleophiles.[25] For example, methyl *p*-nitrobenzoate and *p*-nitrobenzophenone were treated with benzylmercaptan anion in DMF to form the corresponding benzyl thioethers by nitro displacement. Also reported were displacements involving dodecylthiol anion and methyl *p*-nitrobenzoate, *p*-nitrobenzonitrile, *p*-nitrobenzaldehyde, and *p*-nitrobenzophenone. The yields in all cases were rather low (30–50%).

Radlmann *et al.* obtained useful polymers by the polycondensation of 4,4'-dinitrobenzophenone and bisphenol A salts.[26] Heath and Wirth reported nitro displacement reactions when phenoxide salts were allowed to react with ethyl *p*-nitrobenzoate, *o*- and *p*-nitrobenzonitriles, or phenyl *o*-nitrobenzoate in DMF or DMSO.[27] The same authors described the reaction of various phenoxide salts with diethyl 4-nitrophthalate, diethyl nitroterephthalate, and diethyl 2-nitroisophthalate in DMSO.[28] Nitro displacement resulted in all cases, and the yields were in the range of 65–95%.

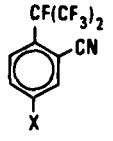
Marburg and Grieco described the synthesis of 3-azidophthalic acid by treatment of 3-nitrophthalic anhydride with azide ion.[29] Caswell and Kao obtained N-substituted 3-methoxyphthalimides by the reaction of methoxide ion and the corresponding 3-nitrophthalimides.[30] Fusion of 3-nitrophthalic anhydride with potassium fluoride at 180–190° yielded 3-fluorophthalic anhydride (65%).[31] Similarly prepared at slightly higher temperature was the analogous 4-fluoro derivative (56%) from 4-nitrophthalic anhydride. When either reaction was carried out in DMSO or DMF at lower temperature, the yields were somewhat lowered. Attempted reaction of 3- and 4-nitrophthalic anhydride with sodium phenoxide in DMF at room temperature led to anhydride ring-opening with no detectable nitro displacement.[32] In this case the problem could be overcome by utilizing the corresponding 3- and 4-fluoro derivatives and higher temperature. Treatment of 3- and 4-nitro-N-substituted phthalimides with sodium phenoxide in DMF or DMSO gave quantitative yields of the corresponding phenyl ethers by nitro displacement.[33] Markezich and Zamek reported the reaction of N-methyl-4-nitrophthalimide and potassium fluoride in DMF or DMSO to yield 4,4'-oxybis-(N-methylphthalimide) as the major product.[34] Similar results were obtained with the use of potassium nitrite as the nucleophile. The same authors described the condensation of N-methyl-4-nitrophthalimide with methanethiol anion in DMF and the product obtained was the methylthio derivative (76%) formed by nitro displacement. Useful polymers were obtained by the polycondensation of bis(nitrophthalimides) and bisphenols in DMSO.[35]

Extensively studied was the mobility of activated nitro groups in benzophenones and xanthones. Gorvin reported that treatment of 4-nitrobenzophenone with either methoxide or ethoxide ion in DMF, DMSO or HMPA at 20° for 24 hr afforded almost quantitative yields of the corresponding 4-alkoxybenzophenones.[36] Under the same conditions, only a trace of displacement product was obtained from 4-chlorobenzophenone, and none was isolated from 3-nitrobenzophenone. Also synthesized were 4,4'-dialkoxybenzophenones from 4,4'-dinitrobenzophenone and alkoxide ions. The reaction of 2,2'-dibromo-4,4'-dinitrobenzophenone and methoxide ion yielded 2,2'-dibromo-4,4'-dimethoxybenzophenone (90%) with little or no bromine displacement. No detectable reaction was noted with 2-nitrobenzophenone and alkoxides under the mild conditions utilized, and this was attributed to steric inhibition. Nevertheless, 2,2'-dinitrobenzophenone readily underwent displacement of one nitro group to yield 2-methoxy-2'-nitrobenzophenone (93%). The formation of 1-methoxyxanthone from 1-nitroxanthone was complete in only 3 hr, and 3-methoxyxanthone was formed even faster from 3-nitroxanthone. As in the case of the benzophenones, 1-chloroxanthone and 3-chloroxanthone were found to undergo replacement at a much reduced rate.

The displacement of a nitro group which was activated by a perfluoroisopropyl function was reported by Ishikawa *et al.*[37] Treatment of **13a** with methoxide ion in methanol gave the methyl ether **13b** in high yield. The phenyl ether **13c** (50%) was obtained from **13a** and phenoxide ion in DMF. Similarly prepared was the amine **13d** (90%) from **13a** and dimethylamine in DMF. It is interesting to note the selectivity of *p*-nitro displacement in all of the above examples. This is in contrast to the *o*-nitro displacement observed with the formation of **12a**



13a X=NO_2
13b X=OMe
13c X=OPh
13d X=NMe_2



14a X=NO_2
14b X=OMe

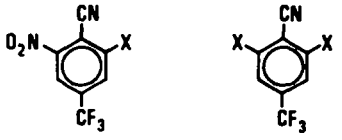
and **12b** above, but in agreement with the finding of Loudon with respect to the reaction of 2,4-dinitrobenzonitrile and piperidine (Ref. 20 above). Ishikawa also reported the formation of the methyl ether **14b** from the reaction of **14a** and methoxide ion.

An investigation of replacement reactions involving 2,6-dinitrobenzonitriles was recently reported from our laboratory.[38] For example, the reaction of 2,6-dinitrobenzonitrile and methoxide ion in methanol yielded 2,6-dimethoxybenzonitrile (81%). In similar fashion, methanethiol anion in aqueous DMF at ice bath temperature gave 2,6-bis(methylthio)benzonitrile (75%). Treatment with a molar equivalent of methoxide ion in

methanol–DMF at room temperature yielded 6-nitro-*o*-anisonitrile (80%), which was converted to 6-(methylthio)-*o*-anisonitrile (85%) by reaction with methanethiol anion in aqueous DMF. In competitive displacement experiments utilizing 2-chloro-6-nitrobenzonitrile and methanethiol anion, azide ion, or methoxide ion, the product isolated in each case was formed by nitro displacement only. For instance, 2-chloro-6-nitrobenzonitrile and methanethiol anion in aqueous DMF gave 2-chloro-6-(methylthio)benzonitrile (83%).

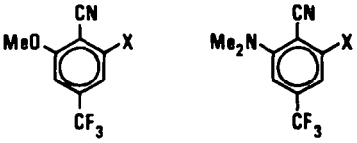
A majority of the reported examples utilized α,α,α - trifluoro - 2,6 - dinitro - *p* - tolunitrile (**15a**) as the substrate, and the displacements were even more facile due to the presence of the trifluoromethyl function. The reaction of methoxide ion and **15a** in methanol yielded **15b** (83%) after only 5 min at ice bath temperature. The reactions of **15a** with azide ion, methylamine, and dimethylamine were carried out in DMF at ice bath temperature and gave **15c** (50%), **15d** (63%), and **15e** (78%), respectively. The chloro derivative **15f** (74%) was obtained from **15a** by the action of hydrogen chloride gas in hot DMF for 10 min. Finally, the phenol **15g** (65%) was isolated after treatment of **15a** with moist potassium fluoride in refluxing DMF.

Both nitro groups of **15a** could be replaced by the same nucleophile and this was illustrated by the preparation of **16a** (78%), **16b** (85%), and **16c** (58%) under



15a X=NO_2 **15e** X=NMe_2 **16a** X=OMe
15b X=OMe **15f** X=Cl **16b** X=SMe
15c X=N_3 **15g** X=OH **16c** X=N_3
15d X=NHMe

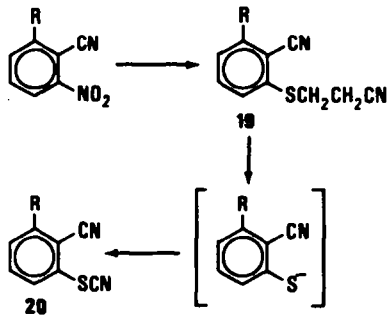
relatively mild conditions. Alternatively, the nitro groups of **15a** could be sequentially displaced. For example, nitriles **17a** (77%), **17b** (92%), **17c** (73%), and **17d** (72%) were obtained from the methyl ether **15b** and the appropriate nucleophile. Similarly prepared were **18a** (74%), **18b** (76%), **18c** (90%), and **18d** (66%) from the amine **15e**. Other examples of the reaction of **15a** with



17a X=SMe **18a** X=OMe
17b X=OEt **18b** X=SMe
17c X=N_3 **18c** X=N_3
17d X=NHMe **18d** X=NMe_2

various sulfur nucleophiles have been reported in several U.S. patents.[39]

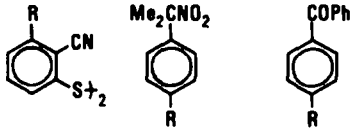
Displacement products were not obtained with **15a** and hindered amines or alkoxides, ammonia, and thiocyanate ion. The latter problem was overcome with the use of a more potent nucleophile, 3-mercaptopropionitrile, in order to facilitate the initial displacement (Scheme 1).[40] For example, *o*-nitrobenzonitrile was allowed to react with 3-mercaptopropionitrile in aqueous DMF containing



Scheme 1.

potassium hydroxide at ice bath temperature. The intermediate **19** (R = H) rapidly underwent β-elimination in the basic medium and gave the arylthiol anion and acrylonitrile. Excess cyanogen chloride was added and the product **20** (R = H) was isolated in 72% yield. The entire 3-step procedure required approximately one hr, and the reaction was applied to the synthesis of a number of thiocyanic acid, 2-cyanophenyl esters. The intermediate thioether **19** (R = Cl) had been isolated and characterized in an earlier report.[41] Acidification of the reaction mixture shortly after the initial addition yielded the corresponding disulfides **21** (60–80%), apparently formed by oxidation of the aryl thiols by the nitrous acid generated.[40]

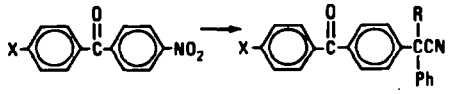
Kornblum *et al.* examined the displacement of activated *p*-nitro groups by a variety of nucleophiles.[11] The substituted derivatives **22a** (78%), **22b** (60%), **22c** (82%) and **22d** (76%) were obtained by treatment of the appropriate *p*-nitro precursor with 2-nitropropane (lithium salt) in HMPA at room temperature. Similarly prepared were **23a** (83%) and **23b** (82%) from 4-nitrobenzophenone and the appropriate nucleophile. The



21 **22a** R=PhCO **23a** R=PhO
22b R=COOMe **23b** R=$PhCH_2S$
22c R=CN
22d R=$PhSO_2$

reaction of 1-nitro-4-phenylsulfonylbenzene and methanethiol anion gave 61% of product by nitro displacement and 17% with loss of the phenylsulfonyl function. Finally, treatment of *p*-nitrobenzonitrile with sodium benzenesulfinate yielded 4-phenylsulfonylbenzonitrile (67%). The solvent utilized in the latter reaction was DMSO instead of HMPA.

Makosza *et al.* reported the displacement of activated nitro groups in substituted 4-nitrobenzophenones by carbanions of α-substituted benzyl cyanides (Scheme 2).[42] A two-phase system was utilized



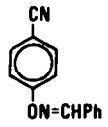
X=Cl, Br, OMe, Me, H R=Methyl, ethyl, benzyl

Scheme 2.

consisting of 50% sodium hydroxide solution and the reactants (with or without added organic solvents) in the presence of a catalytic amount of benzyltriethylammonium chloride. The conditions were mild and the yields were in the range of 65–90%. In the case of R = isopropyl, the only product isolated was the azoxy derivative corresponding to the starting nitro compound.

A novel conversion of an activated nitro group to a phenol was reported by Knudsen and Snyder.[43] When *p*-nitrobenzonitrile was allowed to react with two molar equivalents of the sodium salt of benzaldoxime in DMSO at ambient temperature, the product obtained was 4-hydroxybenzonitrile (94%). The reaction apparently occurred through the intermediacy of the O-aryl aldoxime **24**, which on reaction with a second equivalent of sodium benzaldoximate gave the product and benzonitrile, which was also isolated. Lower yields of the corresponding phenols were reported from *o*-nitrobenzonitrile, ethyl *o*- and *p*-nitrobenzoates, *p*-nitrobenzamide, and *p*-nitrobenzophenone. No product was isolated from either *p*-nitrobenzaldehyde or *p*-nitroacetophenone as the substrate in the reaction.

Baumann described a similar displacement of activated aryl nitro groups utilizing salts of ketoximes.[44] Examples included the formation of O-aryl ketoximes **25a** (61%), **25b** (66%), and **25c** (59%) from the corresponding nitro precursors. Other substrates included methyl *p*-nitro-



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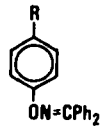


25a R=CN
25b R=COPh
25c R=CHO

benzoate and *p*-nitroacetophenone. Other oximate salts utilized were those obtained from cyclohexanone, acetophenone, and fluorenone. The products were reported to be useful in the synthesis of benzofurans.

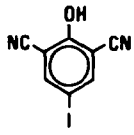
An unusual transformation of an activated nitro group leading to the formation of an *o*-cyanophenol was reported by Gorvin.[45] Treatment of 4-nitrobenzophenone with three molar equivalents of cyanide ion in DMSO at 100° for 3 hr afforded 5-benzoylsalicylonitrile (Scheme 3) in

Scheme 3.

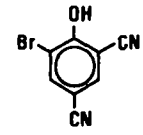
55–60% yield. The reaction also occurred in either DMF or HMPA but at a slower rate. Similar conversions and yields were reported for *p*-nitrobenzonitrile, ethyl *p*-nitrobenzoate, and 1-nitro-4-phenylsulfonylbenzene. 3-Nitroxanthone was converted to 4-cyano-3-hydroxyxanthone (60–70%), whereas 1-nitroxanthone yielded 1-cyanoxanthone (75%) formed by direct nitro displacement. Snyder *et al.* examined the same reaction using *o*-nitrobenzonitrile as the substrate.[46] Treatment with two molar equivalents of sodium cyanide in DMSO at 120° for 1 hr gave a 60% yield of 2-hydroxyisophthalonitrile (Scheme 4). The other product of the reaction was identified as nitrous oxide. The authors proposed a mechanism involving *ortho*-addition of cyanide ion to give an adduct, as in the case of the related von Richter reaction,[47] which then underwent a Nef-type rearrangement to form the product. Further studies by Gorvin expanded the scope of the reaction and added support for the proposed mechanism.[48] He

Scheme 4.

found that 2-nitroisophthalonitrile in which case both *ortho*-positions were blocked did not undergo attack at the *para*- or 5-position, but gave instead 2-hydroxyisophthalonitrile (65–75%) and 1,2,3-tricyanobenzene (15%) as the only isolable products. Furthermore, treatment of 2-nitroisophthalonitrile with lithium chloride or phenolate salts in DMSO resulted in ordinary nucleophilic displacement of the nitro group.[49] However, reaction with potassium iodide in DMSO yielded the phenol **26** (60%) formed by initial *para*-attack. Reaction with sodium bromide gave a mixture involving both direct nitro displacement and phenol formation. Treat-



26

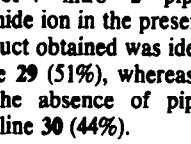


27

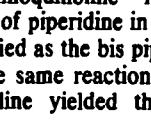
ment of 4-nitroisophthalonitrile with sodium cyanide under similar conditions yielded only 4-hydroxyisophthalonitrile (70–80%) even though a position *ortho* to the nitro group was vacant. With sodium bromide in DMSO, the same compound gave the phenol **27** (65%) as the main product.

INTERMOLECULAR NITRO DISPLACEMENT IN HETEROAROMATIC SYSTEMS

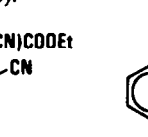
Displacement reactions related to those described above have been reported by Himeno *et al.* in the case of a series of quinoline N-oxides.[50] Treatment of 4-nitroquinoline-1-oxide with potassium cyanide (two molar excess) and ethyl cyanoacetate (four molar excess) in DMSO at room temperature yielded the cyanoquinoline **28**, but only in 27% yield. Another reaction investigated was that of 4 - nitro - 2 - piperidinoquinoline - 1 - oxide with cyanide ion in the presence of piperidine in DMSO. The product obtained was identified as the bis piperidino derivative **29** (51%), whereas the same reaction carried out in the absence of piperidine yielded the dicyanoquinoline **30** (44%).



28



R=piperidino
29

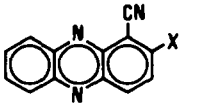


R=piperidino
30

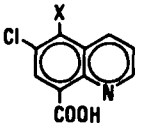
As in the above three examples, nitro displacement in heteroaromatic systems is usually related to reactions ordinarily observed in similarly substituted nitrobenzenes. Exceptions are the displacements at so-called activated positions in certain nitrogen heterocycles. For example, leaving group activation at the 2- and 4-positions in pyridine is nearly as strong as that for the 2- and 4-positions of nitrobenzene.[47] Since halogens are ordinarily utilized as leaving groups in such reactions, a thorough review of nitro displacement of this type will not be attempted. Recent reports include examples of activated nitro replacement in pyridine,[51] quinoline,[52] thiazole,[53] 1,3,4-thiadiazole,[54] 1,2,4-triazole,[55] and furazan-N-oxide[56] derivatives. Another type of heteroaromatic nitro displacement involves activation by a second nitro group, as already briefly discussed in the analogous case of *o*- or *p*-dinitrobenzene. This type of reaction will not be thoroughly reviewed because of lack of synthetic utility. Recent examples reported displacements involving dinitro derivatives of thiophene,[57] pyrrole,[58] and imidazole.[59]

There are only a few examples in heterocyclic chemistry dealing with the intermolecular displacement of nitro groups activated by substituents other than nitro. Pietra *et al.* described the reaction of 1-cyano-2-nitrophenazine (**31a**) with methylamine, and the major product isolated was **31b**, but two side reactions were also noted.[60] The first was displacement of the cyano function and the second involved substitution at the 4-position with or without concurrent nitro displacement. The latter reaction became the predominating pathway as the steric bulk of the amine increased (for example, in the case of *t*-butylamine). The reaction of **31a** with azide ion in aqueous pyridine yielded **31c**. Pietra and Casiraghi also investigated the reaction of nucleophiles with 1-(1-pyrazolyl)-2-nitrophenazine (**32**).[61] Azide ion exclusively replaced the nitro group, while ammonia and primary amines displaced the activated pyrazolyl function.

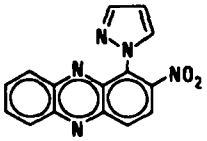
Bailey and Wood described the preparation of the dichloroquinoline **33b** (70%) by the reaction of **33a** with hydrogen chloride gas in DMF at 115–120°.[62] Similarly, **33a** on treatment with hydrogen bromide in DMF at 120–125°, afforded **33c** (88%).



31a X=NO_2
31b X=NHMe
31c X=N_3



33a X=NO_2
33b X=Cl
33c X=Br



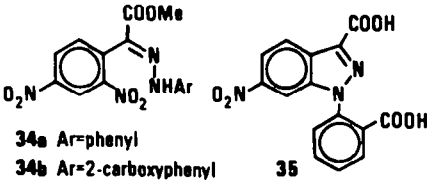
32

Several workers reported displacement reactions involving 5-nitro-2-furaldehyde although the yields were low in most cases. Treatment with methoxide ion in methanol afforded 5-methoxy-2-furaldehyde (45%), which was isolated as its oxime derivative.[63] The related reaction with azide ion yielded 5-azido-2-furaldehyde (43%), and displacement by benzenethiol anion in methanol gave 5-phenylthio-2-furaldehyde (58%).[64] Finally, treatment with 48% hydrobromic acid or concentrated hydrochloric acid produced the corresponding 5-bromo and 5-chloro derivatives.[65]

In the pyrimidine series Clark and Pendergast reported a 30% yield of 2,4,5-trichloro-6-cyanopyrimidine by the reaction of 2,4-dihydroxy-5-nitropyrimidine-6-carboxamide and phosphoryl chloride.[66]

INTRAMOLECULAR NITRO DISPLACEMENT

The intramolecular displacement of activated nitro groups has been a valuable tool for the synthesis of numerous heterocyclic ring systems. Among the early examples, many involved the condensation of picryl chloride with an aromatic compound, which contained two nucleophilic centers situated *ortho* to one another, such as *o*-mercaptoaniline. These have little synthetic utility and will not be discussed in detail.[67] One of the recognized procedures for the synthesis of indazoles does, however, involve nitro displacement.[68] Meyer in 1889 reported the preparation of 6-nitro-1-phenylindazole-3-carboxylic acid by cyclization of the potassium salt of the hydrazone **34a**.[69] More recently, Schim-

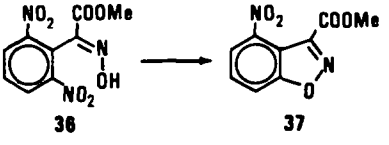


34a Ar=phenyl
34b Ar=2-carboxyphenyl

35

melschmidt and Hoffmann obtained the indazole **35** (96%) by the reaction of the hydrazone **34b** with potassium hydroxide in methanol–DMSO at 70° for 15 min.[70]

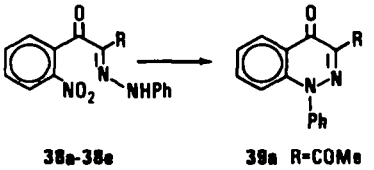
Substitution of an oxime function for the hydrazone in the indazole synthesis leads to the formation of benzisoxazole derivatives, and this subject has been reviewed.[71] Again most examples required the presence of a second nitro group *meta* to the one being displaced. A recent report involved the synthesis of methyl 4-nitrobenzisoxazole-3-carboxylate (**37**) in 78% yield by the



36 **37**

reaction of the oxime **36** and sodium hydride in dimethoxyethane.[72]

A related procedure for the synthesis of 1-phenylcinnolin-4(1H)-ones was reported by Sandison and Tennant.[73] The hydrazone precursors **38a–e** were readily prepared from aryl diazonium salts and the appropriate active methylene compounds, as also in the case of the indazole precursors above. Cyclization of **38a–d** occur-

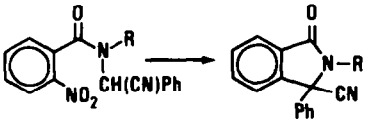


38a-38e

39a R=COMe
39b R=COPh
39c R=$CONH_2$
39d R=COOEt
39e R=CN

red in alcohol and aqueous sodium carbonate and yielded the corresponding cinnolinones **39a** (92%), **39b** (81%), **39c** (98%), and **39d** (71%), respectively. The cyclization of **38e** to form cinnolinone **39e** (91%) was carried out in aqueous alcohol containing sodium acetate.

A recent report by Spence and Tennant described the intramolecular displacement of nitro groups by carbonions.[74] For instance, treatment of the *o*-nitrobenzamides **40** (Scheme 5) with sodium carbonate in alcohol yielded the isoindolinones **41** in high yields. Under the

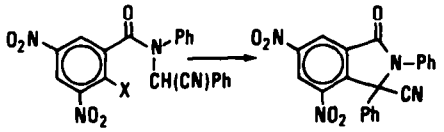


40 **41**

R=Me, Ph, CH_2Ph

Scheme 5.

same conditions no reaction was noted when the nitro group in the starting amide was replaced with bromine or methoxyl. In a second paper the authors reported what is formally an intramolecular displacement of hydride ion.[75] By warming a solution of the dinitrobenzamide **42a** in aqueous potassium carbonate solution, the authors obtained a mixture, from which was isolated by chromatography the isoindolinone **43** (20%). The latter was

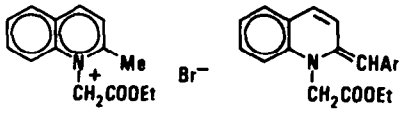


42a X=H
42b X=Cl

43

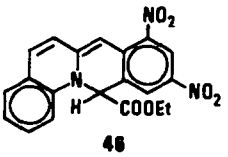
identical with the product obtained under similar conditions from **42b** involving activated chlorine displacement. Compound **43** was formed in quantitative yield from **42a** when benzoquinone was present in the reaction mixture. Benzoquinone apparently served as a scavenger for hydride ion, or more likely, as an oxidizing agent of the addition intermediate in the reaction. Similar results were obtained when only the nitro group *para* to X in **42a** was present.

Another example involving intramolecular displacement of a nitro group by a carbon nucleophile was reported by Reuschling and Kröhnke.[76] Treatment of the quaternary salt **44** with picryl chloride in DMSO containing triethylamine afforded the dihydroquinoline derivative **45**. Further treatment of **45** with piperidine in



44 **45**

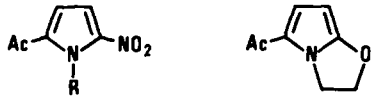
Ar=2,4,6-trinitrophenyl



46

DMSO gave the fused quinoline **46** (94%) by nucleophilic nitro displacement. Corresponding fused heterocycles were also reported for similar reactions involving 2 - methyl - 3 - (ethoxycarbonylmethyl)benzothiazolium bromide and 2,4 - dimethyl - 3 - (ethoxycarbonylmethyl)thiazolium bromide as precursors. The yields were 86 and 80%, respectively.

Vecchietti *et al.* described the preparation of 5 - acyl - 2,3 - dihydropyrrolo[2,1-b]oxazoles from 2 - acyl - 5 - nitropyrroles and ethylene oxide.[77] For example, the thermolysis of **47a** and ethylene oxide at 120° gave the fused derivative **48**, although the yield was rather low. The same compound was obtained in higher yield by the

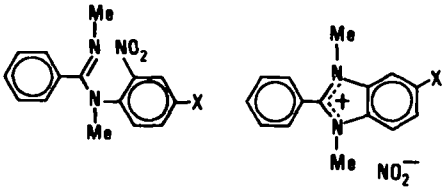


47a R=H
47b $R=CH_2CH_2OH$
47c $R=CH_2CH_2OAc$

48

reaction of the hydroxyethyl derivative **47b** and sodium hydride in THF. Treatment of the ester derivative **47c** with one molar equivalent of sodium methoxide also gave **48**.

Wolff and Hartke reported the thermal cyclization of *o*-nitrobenzamidines to form benzimidazolium salts by nitro displacement.[78] Treatment of the benzamidine **49a** in refluxing bromobenzene for 10 min led to the formation of the benzimidazolium nitrite salt **50a** (100%). Also

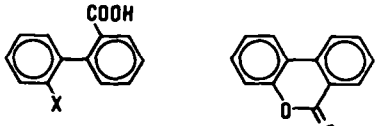


49a $X=NO_2$
49b X=H

50a $X=NO_2$
50b X=H

described was the cyclization of **49b** in refluxing bromobenzene for 1 hr to yield **50b** (60%). The corresponding *o*-chloro derivative gave only a 25% yield of **50b** even after 20 hr in refluxing bromobenzene.

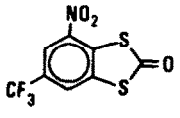
The preparation of 3,4-benzocoumarin (**52**) in 89% yield was reported by Rees *et al.* by thermolysis of the potassium salt of 2'-nitrobiphenyl-2-carboxylic acid (**51a**).[79] Similar treatment of the potassium salts of **51b**



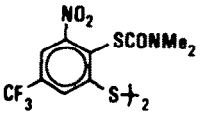
51a $X=NO_2$
51b X=F
51c X=Br

52

and **51c** yielded **52** in only 13 and 20% yield, respectively. Rasheed and Warkentin recently described the synthesis of the 1,3-benzodithiol-2-one **53** by the reaction of 4-chloro-3,5-dinitrobenzotrifluoride and the sodium salt of dimethyldithiocarbamic acid.[80] The yield was only 43% and the disulfide **54** was also formed in 40% yield. There are other recent examples of intramolecular nitro displacement, but all are related to the picryl chloride



53



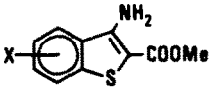
54

reactions discussed at the beginning of this section and will not be discussed in detail.[81]

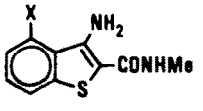
SYNTHESIS OF BENZO[B]THIOPHENE AND BENZOFURAN DERIVATIVES

The synthesis of 3-aminobenzo[b]thiophene-2-carboxylic acid was first described by Friedländer and Laske.[82] The precursor used was *o*-mercaptoaniline, and alkylation with chloroacetic acid, diazotization, cyanide displacement, and, finally, alkali fusion yielded the desired product. There are many variations of this general procedure, but all of them suffer from the inaccessibility of the starting aniline and the number of steps involved.[83] Carrington and co-workers reported the synthesis of ethyl 3 - aminobenzo[b]thiophene - 2 - carboxylate utilizing a rearrangement of 3 - chloro - 1,2 - benzisothiazole, but again the process deals with relatively inaccessible precursors.[84]

More recently, we described a one-flask synthesis of 3 - aminobenzo[b]thiophene - 2 - carboxylate esters from readily available *o*-nitrobenzonitriles.[85] For example, methyl 3 - aminobenzo[b]thiophene - 2 - carboxylate (**55a**) was obtained in 72% yield from the reaction of *o*-nitrobenzonitrile and methyl thioglycolate anion in aqueous DMF (30 min at ice bath temperature). The process involved nitro displacement by the thiol anion and subsequent base-catalyzed ring closure (excess potassium hydroxide was present). No reaction occurred when *o*-chlorobenzonitrile was treated under the same reaction conditions even after 2 days at room temperature. Other activated functions present in the *o*-nitrobenzonitrile precursor did not interfere as was illustrated by the synthesis of **55b** (84%) from 2-chloro-6-nitrobenzonitrile, **55c** (72%) from 4-chloro-2-nitrobenzonitrile, and **55d** (67%) from 2,6-dinitrobenzonitrile. The reaction was also investigated using an amide of thioglycolic acid as the nucleophile substrate.[86] For instance, the amide



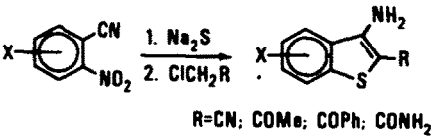
55a X=H
55b X=4-Cl
55c X=6-Cl
55d X=4-NO_2



56a X=Cl
56b X=H

56a (78%) was prepared from 2-chloro-6-nitrobenzonitrile and mercapto-N-methylacetamide under conditions similar to those used in the ester synthesis. In a related case, however, the amide **56b** was obtained from *o*-nitrobenzonitrile in only 8% yield.

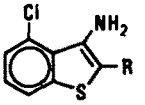
A more general synthesis of 3-aminobenzo-[b]thiophenes substituted at the 2-position with a variety of electron-withdrawing functions was also reported from our laboratory.[41] In this procedure the *o*-nitrobenzonitrile was first treated with sodium sulfide in aqueous DMF to give a benzenethiol salt by nitro displacement (Scheme 6). The salt was then alkylated *in situ* to yield a thioether, which underwent ring closure catalyzed by the



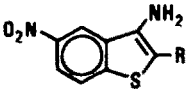
R=CN; COMe; COPh; $CONH_2$

Scheme 6.

excess sodium sulfide present. Utilizing this method we were able to prepare the 4-chloro derivatives **57a** (66%), **57b** (68%), **57c** (60%), and **57d** (69%) from 2-chloro-6-nitrobenzonitrile, sodium sulfide, and the appropriate alkylating agent. The corresponding 4-nitro derivatives were obtained from 2,6-dinitrobenzonitrile in 84, 83, 60, and 65%, respectively. In all cases, the reaction was complete in approximately 1 hr at room temperature.



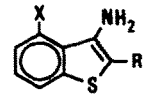
57a R=CN
57b R=COMe
57c R=COPh
57d R=$CONH_2$



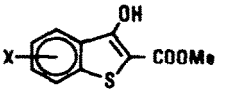
58a R=CN
58b R=COPh

Also synthesized by this procedure were the 5-nitro derivatives **58a** (87%) and **58b** (90%) from 2-chloro-5-nitrobenzonitrile by a similar process involving activated chlorine replacement.

The disadvantage of the sulfide ion nitro displacement reaction was the requirement for a second electron-withdrawing substituent (chloro or nitro) in the *o*-nitrobenzonitrile precursor. For example, 6-nitro-*o*-anisonitrile did not undergo nitro displacement by sulfide ion even at 100° for an extended period of time. This problem was overcome with the use of 3-mercaptopropionitrile and aqueous potassium hydroxide in place of the aqueous sodium sulfide used in Scheme 6. The more nucleophilic thiol anion rapidly displaced the nitro group and yielded a thioether **19** of the type previously described in Scheme 1. In the basic reaction medium this intermediate rapidly underwent β-elimination with loss of acrylonitrile and afforded the same benzenethiol anion formed in Scheme 6. Addition of the alkylating agent and base-catalyzed ring closure yielded the desired substituted 3-aminobenzo[b]thiophene. The entire procedure was carried out at ice bath temperature. In this fashion the amino derivatives **59a** (70%), **59b** (67%), and **59c** (50%) were prepared by a one-flask process.



59a X=H; R=CN
59b X=H; R=COMe
59c X=OMe; R=CN



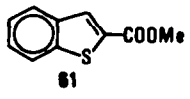
60a X=H
60b X=7-Cl
60c X=4-NO_2
60d X=7-NO_2
60e X=6-Cl

Friedländer first synthesized methyl 3-hydroxybenzo[b]thiophene-2-carboxylate(**60a**) by base-catalyzed cyclization of the bis methyl ester of *o*-[(carboxymethyl)thio]benzoic acid, which was obtained in three steps from *o*-mercaptobenzoic acid.[87] We

recently reported a facile one-flask preparation of **60a** from methyl *o*-nitrobenzoate and methyl thioglycolate involving a nitro displacement reaction similar to the one described above for the synthesis of the amino esters **55a–d**.[88] The main difference was the use of relatively anhydrous conditions (lithium hydroxide in DMF), since the major side reaction appeared to be hydrolysis of the activated methyl ester function. When this procedure was used, the hydroxy ester **60a** was obtained in 61% yield in 2.5 hr at room temperature. The reaction was remarkably insensitive to the presence of other activated functions as was illustrated by the synthesis of **60b** (80%) from methyl 3-chloro-2-nitrobenzoate, **60c** (85%) from methyl 2,6-dinitrobenzoate, **60d** (73%) from methyl 2,3-dinitrobenzoate, and **60e** (75%) from methyl 4-chloro-2-nitrobenzoate.

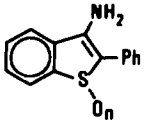
Utilizing a similar procedure, we also obtained methyl benzo[b]thiophene-2-carboxylate (**61**) from *o*-nitrobenzaldehyde and methyl thioglycolate anion.[85] The base used in this instance was anhydrous potassium carbonate. The reaction was carried out at room temperature for 20 hr and the yield of **61** was 52%.

Also recently reported from our laboratory was the synthesis of 3 - amino - 2 - phenylbenzo[b]thiophene (**63a**) and the corresponding S-oxide **63b** and S,S-dioxide **63c** from *o*-nitrobenzonitrile.[89] Treatment of the latter compound with benzylmercaptan anion in DMF gave the thioether **62a** (64%) by nitro displacement. The thioether was then oxidized to the sulfoxide **62b** (80%) and the sulfone **62c** (88%) with *m*-chloroperoxybenzoic acid. Cyclization of **62a** with potassium *t*-butoxide in benzene yielded **63a** (78%). Treatment of the sulfoxide **62b** with



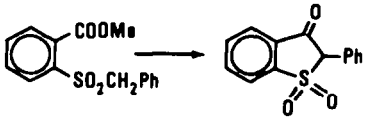
61

62a n=0
62b n=1
62c n=2



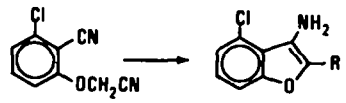
63a n=0
63b n=1
63c n=2

sodium methoxide in methanol gave the S-oxide derivative **63b** (72%), and in similar fashion, the sulfone **62c** was converted to the S,S-dioxide derivative **63c** (91%). The reaction of benzylmercaptan anion with methyl *o*-nitrobenzoate gave the corresponding thioether by nitro displacement, and the thioether was readily oxidized to the sulfone derivative **64** (73%). Cyclization of **64** with sodium methoxide in methanol yielded the S,S-dioxide derivative **65** (92%).



64 **65**

Also reported was the synthesis of related 3-aminobenzofurans by a process involving nitro displacement.[90] The cyanomethyl ether **66** (74%) was obtained by the reaction of 2-chloro-6-nitrobenzonitrile and glycolonitrile anion in aqueous DMF. Cyclization of **66** with potassium carbonate in DMF yielded the amino



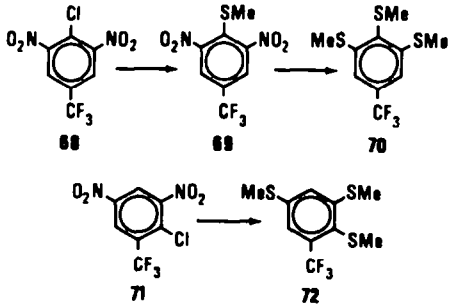
66 **67a** R=CN
67b R=CONH$_2$

derivative **67a** (50%), whereas treatment with alcoholic potassium hydroxide gave the carboxamide **67b** (70%).

NITRO DISPLACEMENT BY THIOL ANIONS

Benzenethiol anion has long been recognized as a strong nucleophile in aromatic displacement reactions.[7] It was also demonstrated that the nucleofugicity of an activated aromatic nitro group was unexpectedly high when the nucleophile was benzenethiol anion. For instance, Bunnett and Merritt examined the kinetics of the reaction of 1-X-2,4-dinitrobenzenes and benzenethiol anion in methanol at 0° and found that nitro displacement (X = NO_2) was too fast for measurement, even though fluorine and chlorine displacement rates were readily obtained.[91] More recently, Bartoli and Todesco measured the rate of the same reaction at 25° and reported the relative rate of nitro displacement to be 2000-times that of chlorine and 50-times that of fluorine.[4] Similar results were obtained with methanethiol anion. These are much larger differences than those previously noted with other nucleophiles discussed near the beginning of this review.[2-6] The authors also reported a k_{PhS^-}/k_{MeO^-} factor of 2600 for the nitro group, whereas fluorine showed a ratio of only 43. The high reactivity of the nitro group was attributed to the polarizability of the thiol anion, which minimized zone repulsion in the transition state of the rate-limiting or addition step of the displacement reaction.

The synthetic potential for the high reactivity of the nitro group with regard to thiol anion displacement was the subject of a recent report from our laboratory.[92] 4 - Chloro - 3,5 - dinitrobenzotrifluoride (**68**) was allowed to react with methanethiol anion in aqueous ethanol and gave the expected thioether **69** (Scheme 7). When **69** was allowed to react further with excess methanethiol anion (lithium salt) in DMF for 1 hr at ice bath temperature, the product obtained was identified as the tris thioether **70** (95%). Alternatively, **70** was formed in 74% yield directly from **68** under similar conditions. In the same fashion the



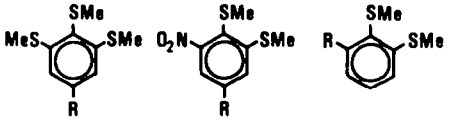
68 **69** **70**

Scheme 7.

tris thioether **72** (70%) was obtained from 2 - chloro - 3,5 - dinitrobenzotrifluoride (**71**). The activation of the first nitro displacement involved in the formation of either **70**

or 72 could be attributed to the second nitro group. For example, it was noted earlier that treatment of *m*-dinitrobenzene with benzenethiol anion in HMPA at ambient temperature yielded 1 - nitro - 3 - (phenylthio)benzene (88%).[11] It could also be argued that the activation of the second nitro group displaced was due to the trifluoromethyl function present in both examples. As was noted earlier, 1,3 - bis(trifluoromethyl) - 5 - (phenylthio)benzene was obtained in 92% yield from the corresponding nitro precursor in HMPA.[11]

We therefore investigated examples in which nitro displacement could only be attributed to activation by a methylthio function. Treatment of 1 - chloro - 2,6 - dinitrobenzene with methanethiol anion in DMF for 4.5 hr at room temperature yielded the tris thioether **73a** (75%). Under similar conditions 4 - chloro - 3,5 - dinitrotoluene gave the tris thioether **73b** (60%). Quenching of the reaction in each of the above examples after 15 min at ice bath temperature yielded the bis thioethers **74a** (79%) and **74b** (78%), respectively. When 1,2 - dichloro -

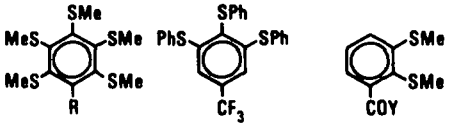


73a R=H **74a** R=H **75a** R=Cl
73b R=Me **74b** R=Me **75b** R=OMe

3 - nitrobenzene was subjected to the usual reaction conditions for 30 min at room temperature, the bis thioether **75a** (73%) was isolated. Similar treatment of 2 - chloro - 3 - nitroanisole for 30 hr at room temperature yielded the bis thioether **75b** (55%). The synthesis of **73a–b** and **75a–b** indicated a degree of nitro group activation by the *o*-methylthio function, although this effect may have been magnified by the unusually high nucleofugicity of the nitro group with respect to displacement by methanethiol anion previously discussed. In fact, Miller examined the kinetics of chlorine displacement in *p*-substituted *o*-nitrochlorobenzenes by methoxide ion and concluded that a *p*-methylthio function produced only weak activation, which was similar to the effect seen with the heavier halogens.[93] In addition, Bordwell and Boutan, utilizing acidity constants and spectral data, predicted only slight electron pair stabilization for an aromatic methylthio function.[94]

We next examined the scope of the reaction with other simple nitro precursors and found that the process was not general. For instance, *o*- and *p*-chloronitrobenzenes gave chlorine displacement products at ice bath temperature, but nitro displacement was not detected. Attempts to replace the nitro group at room temperature resulted in the formation of complex mixtures, which involved reduction of the nitro group by methanethiol anion. Similar mixtures were obtained with 2,4 - dichloro - 1 - nitro- and 1 - chloro - 2,4 - dinitrobenzenes, 2 - chloro - 3 - nitrotoluene, 2 - chloro - 5 - nitrobenzotrifluoride, and 4 - chloro - 3 - nitrobenzamide. Picryl chloride gave a complex mixture even at −70°. In all of the successful examples the nitro group which was displaced was *ortho* (2-position) to a methylthio function and *meta* (3-position) to an electronegative substituent, such as nitro, methylthio, trifluoromethyl, chlorine, or methoxyl. Although an explanation of this phenomenon must be speculative, the effect seen with *meta* electronegative functions might involve stabilization of the transition state through *sigma*-bond interactions or perhaps influence the reduction potential of the nitro group, thus eliminating the observed side reaction.

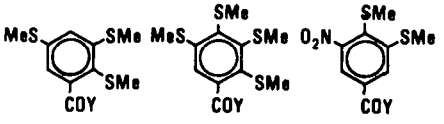
Another successful application of the procedure involved the synthesis of pentakis(methylthio)benzene (**76a**) in 63% yield from 1,3,5 - trichloro - 2,4 - dinitrobenzene. Hexakis(methylthio)benzene (**76b**) was readily obtained from a number of precursors including 1,3,4,5 - tetrachloro - 2,6 - dinitrobenzene, 1,2,3,4 - tetrachloro - 5,6 - dinitrobenzene, pentachloronitrobenzene, and hexachlorobenzene and the yields were 71, 57, 76, and



76a R=H **77** **78a** Y=SMe
76b R=SMe **78b** Y=OH

75%, respectively. Treatment of 4 - chloro - 3,5 - dinitrobenzotrifluoride (**68**) with benzenethiol anion in DMF at room temperature for 24 hr yielded the tris thioether **77** (50%). Other phenylthio derivatives were not investigated.

The displacement reaction was also investigated in a series of benzoic acid derivatives.[95] For example, 2 - chloro - 3 - nitrobenzoic acid was treated with 1,1'-carbonyldiimidazole in DMF and the resulting intermediate was allowed to react *in situ* with an excess of methanethiol anion. After 1 hr at ice bath temperature, the bis methylthio thioester **78a** (64%) was isolated. Similarly prepared were the thioesters **79a** (64%) from 2 - chloro - 3,5 - dinitrobenzoic acid and **80a** (56%) from 2,4 -

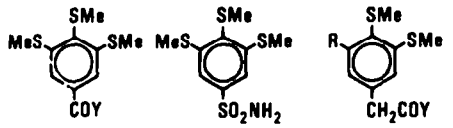


79a Y=SMe **80a** Y=SMe **81a** Y=OH
79b Y=OH **80b** Y=OH **81b** Y=morpholino

dichloro - 3,5 - dinitrobenzoic acid. The thioesters were readily hydrolyzed to the corresponding benzoic acids, **78b**, **79b**, and **80b** in 85–95% yield.

Treatment of 4 - chloro - 3,5 - dinitrobenzoic acid under the ordinary reaction conditions yielded the bis thioether **81a** (80%). Attempts to displace the second nitro group were unsuccessful. The acid was converted to its morpholine amide **81b**, which reacted rapidly (1 hr at room temperature) with methanethiol anion to give the tris thioether **82a** (90%). In a similar fashion 4 - chloro - 3,5 - dinitrobenzamide was converted directly (1.5 hr at room temperature) to the tris thioether **82b** (76%). Hydrolysis of **82b** yielded 3,4,5 - tris(methylthio)benzoic acid (**82c**) in 76% yield. Alternately **82c** was synthesized by hydrolysis of the thioester **82d**, which was prepared from 4 - chloro - 3,5 - dinitrobenzoic acid in 71% yield utilizing the procedure described above for the preparation of **78a**, **79a**, and **80a**.

Other examples included the synthesis of the sulfonamide **83** (71%) from 4 - chloro - 3,5 - dinitrobenzenesulfonamide (2 hr at room temperature). Treatment of 4 - chloro - 3,5 - dinitrophenylacetic acid



82a Y=morpholino **83** **84a** R=NO_2; Y=OH
82b Y=NH_2 **84b** R=NO_2; Y=NH_2
82c Y=OH **84c** R=SMe; Y=NH_2
82d Y=SMe

under the ordinary conditions gave the bis thioether **84a** (85%). As in the case of the related benzoic acid **81a**, conditions for the displacement of the second nitro group could not be found. Conversion of **84a** to the corresponding carboxamide **84b**, followed by reaction with methanethiol anion (7 hr at room temperature), yielded the tris thioether **84c** (57%).

A related example of nitro displacement was reported by Takikawa and Takizawa, who obtained 2,3,5,6 - tetrachlorobenzenethiol from the reaction of 2,3,5,6 - tetrachloro - 1 - nitrobenzene and sodium hydrosulfide in liquid ammonia.[96] The same reaction with pentachloronitrobenzene gave a mixture of pentachlorobenzenethiol and 2,3,4,5 - tetrachloro - 6 - nitrobenzenethiol. Several trichloronitro- and dichloronitrobenzene derivatives reacted exclusively by activated chlorine displacement. Musial and Peach examined the reaction of pentafluoronitrobenzene and methanethiol anion in ethylene glycol–pyridine and reported only mono-, di-, and tri-substituted products, which were all formed by activated fluorine displacement.[97]

SUMMARY

The nucleofugicity of the activated nitro group in most aromatic nucleophilic substitution reactions has been demonstrated by both kinetic and synthetic studies to be superior to that of similarly activated halogens except for fluorine. In some instances, namely intramolecular and thiol anion displacements, its nucleofugicity is often considerably greater than that of even fluorine. The nitro group also has the advantage over fluorine in that it can usually be designed into an aromatic system with greater facility.

The major disadvantage of the activated nitro function as a leaving group in aromatic substitution reactions involves its relatively large size. One is ordinarily limited to the use of unhindered nucleophiles in intermolecular nitro displacements. This is not as much of a problem in intramolecular substitution or in thiol anion displacements, where the polarizability of the nucleophile usually overcomes the steric hindrance. A second disadvantage of the nitro group involves its ease of reduction in basic media. The use of dipolar aprotic solvents, such as DMF, DMSO, and HMPA, seems to minimize this problem.

REFERENCES

[1]J. Cornelisse and E. Havinga, *Chem. Rev.* **75**, 353 (1975).
[2]J. F. Bunnett, E. W. Garbisch, Jr. and K. M. Pruitt, *J. Am. Chem. Soc.* **79**, 385 (1957).
[3]B. A. Bolto and J. Miller, *Aust. J. Chem.* **9**, 74 (1956).
[4]G. Bartoli and P. E. Todesco, *Accounts Chem. Res.* **10**, 125 (1977).
[5]R. E. Parker and T. O. Read, *J. Chem. Soc.* 3149 (1962).
[6]H. Suhr, *Chem. Ber.* **97**, 3268 (1964).
[7]J. F. Bunnett and R. E. Zahler, *Chem. Rev.* **49**, 273 (1951); F. Pietra and D. Vitali, *J. Chem. Soc.* Perkin II, 385 (1972).
[8]J. I. G. Cadogan, D. J. Sears and D. M. Smith, *Ibid.* C, 1314 (1969); J. I. G. Cadogan and D. T. Eastlick, *Ibid.* B, 1314 (1970).
[9]V. Gold and C. H. Rochester, *Ibid.* 1692 (1964).
[10]S. S. Gitis and I. G. L'vovich, *Zh. Obshch. Khim.* **34**, 2250 (1964).
[11]N. Kornblum, L. Cheng, R. C. Kerber, M. M. Kestner, B. N. Newton, H. W. Pinnick, R. G. Smith and P. A. Wade, *J. Org. Chem.* **41**, 1560 (1976).
[12]G. Bartoli, A. Latrofa, F. Naso and P. E. Todesco, *J. Chem. Soc.* Perkin I, 2671 (1972).
[13]V. N. Boiko and G. M. Shchupak, *Zh. Org. Khim.* **13**, 1042 (1977).
[14]F. Tiemann, *Ber. Dtsch. Chem. Ges.* **24**, 699 (1891).
[15]W. Reinders and W. E. Ringer, *Rec. Trav. Chim. Pays-Bas*, **18**, 326 (1899); W. E. Ringer, *Ibid.* 330 (1899).
[16]M. T. Bogert and L. Boroschak, *J. Am. Chem. Soc.* **23**, 740 (1901). See also: J. C. Smith, *J. Chem. Soc.* 1643 (1933).
[17]J. D. Loudon and T. D. Robson, *Ibid.* 242 (1937).
[18]J. D. Loudon and N. Shulman, *Ibid.* 722 (1941).
[19]J. D. Loudon, *Ibid.* 218 (1936); A. Livingston and J. D. Loudon, *Ibid.* 246 (1937); J. D. Loudon and N. Shulman, *Ibid.* 1618 (1938); J. D. Loudon, *Ibid.* 902 (1939).
[20]C. W. N. Holmes and J. D. Loudon, *Ibid.* 1521 (1940).
[21]V. N. Boiko and L. M. Yagupolskii, *Zh. Org. Khim.* **6**, 1874 (1970).
[22]E. Cortes and F. Walls, *Bol. Inst. Quim. Univ. Nacl. Auton. Mex.* **16**, 71 (1964).
[23]A. De Munno, V. Bertini and G. Denti, *Int. J. Sulfur Chem.* A, **2**, 25 (1972).
[24]F. Soti, M. Incze, M. Kajtar-Peredy, E. Baitz-Gacs, L. Imre and L. Farkas, *Chem. Ber.* **110**, 979 (1977).
[25]J. B. Baumann, *J. Org. Chem.* **36**, 396 (1971).
[26]E. Radlmann, W. Schmidt and E. G. Nischk, *Makromol. Chem.* **130**, 45 (1969).
[27]D. R. Heath and J. G. Wirth, *U.S. Pat.* 3,763,210.
[28]D. R. Heath and J. G. Wirth, *U.S. Pat.* 3,787,475. See also: F. J. Williams, H. M. Relles, J. S. Manello and P. E. Donahue, *J. Org. Chem.* **42**, 3419 (1977).
[29]S. Marburg and P. A. Grieco, *Tetrahedron Letters* 1305 (1966).
[30]L. R. Caswell and T. L. Kao, *J. Heterocycl. Chem.* **3**, 333 (1966).
[31]N. Ishikawa, T. Tanabe and D. Hayashi, *Bull. Soc. Chem. Japan* **48**, 359 (1975). See also: R. L. Markezich, O. S. Zamek, P. E. Donahue and F. J. Williams, *J. Org. Chem.* **42**, 3435 (1977).
[32]F. J. Williams, H. M. Relles, P. E. Donahue and J. S. Manello, *Ibid.* **42**, 3425 (1977).
[33]F. J. Williams and P. E. Donahue, *Ibid.* **42**, 3414 (1977). See also: H. M. Relles, D. S. Johnson and J. S. Manello, *J. Am. Chem. Soc.* **99**, 6677 (1977).
[34]R. L. Markezich and O. S. Zamak, *J. Org. Chem.* **42**, 3431 (1977).
[35]J. G. Wirth and D. R. Heath, *U.S. Pat.* 3,838,097.
[36]J. H. Gorvin, *Chem. & Ind.* 1525 (1967).
[37]N. Ishikawa, Y. Inoue and K. Kitagawa, *Nippon Kagaku Zasshi* **91**, 742 (1970).
[38]J. R. Beck, R. L. Sobczak, R. G. Suhr and J. A. Yahner, *J. Org. Chem.* **39**, 1839 (1974).
[39]J. R. Beck and R. G. Suhr, *U.S. Pats.* 3,857,862, 3,890,337, and 3,897,440.
[40]J. R. Beck and J. A. Yahner, *J. Org. Chem.* **43**, 1604 (1978).
[41]J. R. Beck and J. A. Yahner, *Ibid.* **39**, 3440 (1974).
[42]M. Makosza, M. Jagusztyn-Grochowska, M. Ludwikow and M. Jawdosiuk, *Tetrahedron* **30**, 3723 (1974).
[43]R. D. Knudsen and H. R. Snyder, *J. Org. Chem.* **39**, 3343 (1974).
[44]J. B. Baumann, *Synthesis* 782 (1975).
[45]J. H. Gorvin, *J. Chem. Soc.* Chem. Commun. 1120 (1971).
[46]R. B. Chapas, R. D. Knudsen, R. F. Nystrom and H. R. Snyder, *J. Org. Chem.* **40**, 3746 (1975).
[47]J. F. Bunnett, *Quart. Revs.* **12**, 1 (1958).
[48]J. H. Gorvin, *J. Chem. Soc.* Chem. Commun. 972 (1976).
[49]J. H. Gorvin, *U.S. Pat.* 3,950,342.
[50]J. Himeno, K. Noda and M. Yamazaki, *Chem. Pharm. Bull. Japan* **18**, 2138 (1970).
[51]R. J. Dummel and H. S. Mosher, *J. Org. Chem.* **24**, 1007 (1959).
[52]K. M. Dyumaev and E. P. Popova, *Khim. Geterotsikl. Soedin* 382 (1975).
[53]R. J. A. Walsh and K. R. H. Wooldridge, *Chim. Ther.* 199 (1973); A. D. Borthwick, W. W. Foxton, B. V. Gray, G. I. Gregory, P. W. Seale and W. K. Warburton, *J. Chem. Soc.* Perkin I, 2769 (1973).

[54]H. Newman, E. L. Evans and R. B. Angier, *Tetrahedron Letters* 5829 (1968).
[55]L. I. Bagal, M. S. Pevzner, V. Y. Samarenko and A. P. Egorov, *Khim. Geterotsikl. Soedin* 1701 (1970).
[56]R. Calvino, V. Mortarini, A. Gasco, M. A. Bianco and M. L. Ricciardi, *Eur. J. Med. Chem.-Chim. Ther.* **12**, 157 (1977).
[57]C. Dell'Erba and D. Spinelli, *Boll. Sci. Fac. Chim. Ind. Bologna* **26**, 97 (1968); C. Dell'Erba and G. Guanti, *Gazz. Chim. Ital.* **100**, 223 (1970).
[58]G. Doddi, P. Mencarelli and F. Stegel, *J. Chem. Soc.* Chem. Commun. 273 (1975); P. Mencarelli and F. Stegel, *J. Org. Chem.* **42**, 3550 (1977).
[59]G. P. Sharnin, R. K. Fassakhov, T. A. Eneikina and P. P. Orlov, *Khim. Geterotsikl. Soedin* 653 (1977).
[60]S. Pietra, G. Casiraghi and F. Rolla, *Gazz. Chim. Ital.* **99**, 665 (1969). See also: S. Pietra and G. Casiraghi, *Ibid.* **97**, 1817 (1967) and Ref. 61.
[61]S. Pietra and G. Casiraghi, *Ibid.* **100**, 119 (1970).
[62]D. M. Bailey and D. Wood, *J. Heterocycl. Chem.* **11**, 229 (1974).
[63]J. Olivard and J. P. Heotis, *J. Org. Chem.* **33**, 2552 (1968).
[64]F. Lieb and K. Eiter, *Justus Liebigs Ann. Chem.* **761**, 130 (1972).
[65]H. R. Snyder, Jr. and P. H. Seehausen, *J. Heterocycl. Chem.* **10**, 385 (1973).
[66]J. Clark and W. Pendergast, *J. Chem. Soc.* C, 2780 (1969).
[67]For early examples see: G. S. Turpin, *Ibid.* **59**, 714 (1891); L. Schild, *Ber. Dtsch. Chem. Ges.* **32**, 2605 (1899); F. Ullmann, *Justus Liebigs Ann. Chem.* **366**, 79 (1909); F. Kehrmann and J. Steinberg, *Ber. Dtsch. Chem. Ges.* **44**, 3011 (1911); A. Werner and T. Herberger, *Ibid.* **32**, 2686 (1899).
[68]R. C. Elderfield, *Heterocyclic Compounds* (Edited by R. C. Elderfield), Vol. 5, p. 162. Wiley, New York (1957).
[69]V. Meyer, *Ber. Dtsch. Chem. Ges.* **22**, 319 (1889).
[70]K. Schimmelschmidt and H. Hoffmann, *Justus Liebigs Ann. Chem.* **677**, 157 (1964).
[71]K. H. Wünsch and A. J. Boulton, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky and A. J. Boulton), Vol. 8, p. 277. Academic Press, New York (1967).
[72]D. S. Kemp, D. D. Cox and K. G. Paul, *J. Am. Chem. Soc.* **97**, 7312 (1975).
[73]A. A. Sandison and G. Tennant, *J. Chem. Soc.* Chem. Commun. 752 (1974).
[74]T. W. M. Spence and G. Tennant, *Ibid.* Perkin I, 835 (1972).
[75]D. W. Bayne, G. Tennant and T. W. M. Spence, *Ibid.* Chem. Commun. 849 (1972).
[76]D. B. Reuschling and F. Kröhnke, *Chem. Ber.* **104**, 2110 (1971).
[77]V. Vecchietti, E. Dradi and F. Lauria, *J. Chem. Soc.* C, 2554 (1971).
[78]H. M. Wolff and K. Hartke, *Tetrahedron Letters* 3453 (1977).
[79]D. M. Collington, D. H. Hey and C. W. Rees, *J. Chem. Soc.* C, 1030 (1968); D. H. Hey, J. A. Leonard and C. W. Rees, *Ibid.* 4579 (1962). For related examples see: K. B. L. Mathur and K. P. Sarbhai, *Tetrahedron Letters* 1743 (1964); G. I. Migachev, A. M. Andrievskii and N. S. Dokunikhin, *Zh. Org. Khim.* **13**, 463 (1977).
[80]K. Rasheed and J. D. Warkentin, *J. Org. Chem.* **42**, 1265 (1977). See also: J. J. D'Amico, C. C. Tung and W. E. Dahl, *Ibid.* **41**, 3564 (1976); J. J. D'Amico, C. C. Tung, W. E. Dahl and D. J. Dahm, *Ibid.* **42**, 2896 (1977).
[81]M. W. Partridge, J. M. Sprake and H. J. Vipond, *J. Chem. Soc.* C, 1245 (1966); V. N. Drozd, V. N. Knyazev and A. A. Klimov, *Zh. Org. Khim.* **10**, 826 (1974); V. N. Knyazev, V. M. Minov and V. N. Drozd, *Ibid.* **12**, 844 (1976); G. I. Migachev, A. M. Andrievskii and N. S. Dokunikhin, *Ibid.* **13**, 463 (1977); M. Muraoka, T. Yamamoto, S. Yamaguchi, F. Tonosaki, T. Takeshima and N. Fukada, *J. Chem. Soc.* Perkin I, 1273 (1977); G. E. Martin, J. C. Turley, L. Williams, M. L. Steenberg and J. P. Buckley, *J. Heterocycl. Chem.* **14**, 1067 (1977).
[82]P. Friedländer and A. Laske, *Justus Liebigs ANN. Chem.* **351**, 412 (1907).
[83]For two reviews on benzo[b]thiophene chemistry see: H. D. Hartough and S. L. Meisel, *The Chemistry of Heterocyclic Compounds* (Edited by A. Weissberger). Interscience, New York (1954); B. Iddon and R. M. Scrowston, *Advan. Heterocycl. Chem.* **11**, 177 (1970).
[84]D. E. L. Carrington, K. Clarke and R. M. Scrowston, *Tetrahedron Letters* 1075 (1971).
[85]J. R. Beck, *J. Org. Chem.* **37**, 3224 (1972).
[86]J. R. Beck and J. A. Yahner, *Ibid.* **38**, 2450 (1973).
[87]P. Friedländer, *Justus Liebigs Ann. Chem.* **351**, 390 (1907).
[88]J. R. Beck, *J. Org. Chem.* **38**, 4086 (1973).
[89]J. R. Beck, *J. Heterocycl. Chem.* **15**, 513 (1978).
[90]J. R. Beck and R. G. Suhr, *Ibid.* **11**, 227 (1974).
[91]J. F. Bunnett and W. D. Merritt, Jr., *J. Am. Chem. Soc.* **79**, 5967 (1957).
[92]J. R. Beck and J. A. Yahner, *J. Org. Chem.* **43**, 2048 (1978).
[93]J. Miller, *Aromatic Nucleophilic Substitution*, p. 87. Elsevier, New York (1968).
[94]F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.* **78**, 854 (1956).
[95]J. R. Beck and J. A. Yahner, *J. Org. Chem.* **43**, 2052 (1978).
[96]Y. Takikawa and S. Takizawa, *Nippon Kagaku Kaishi* 756 (1972).
[97]B. C. Musial and M. E. Peach, *J. Fluorine Chem.* **7**, 459 (1976).