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cine- and *tele*-Substitution reactions

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1. Introduction

cine-Substitution is the reaction in which an entering group occupies the position adjacent to that taken up previously by a leaving group. *tele*-Substitution is the reaction where an entering group occupies the position located by more than one atom from the atom to which the leaving group was bonded. Definitions of the title reactions are given in the glossary of terms used in physical organic chemistry.[1] As may be seen from the definitions, the criterion that discriminates between *cine*- and *tele*-substitutions and differentiates them from *ipso*-substitution (which consists of bonding of the entering group to the same atom to which the leaving group was bonded) is a comparison of the structures of the substrates and the final products. To complete the definition of *cine*- and *tele*-substitutions it should be added that in such typical reactions, a hydrogen atom takes the place of a leaving group in the final product. All *cine*- and *tele*-substitutions can formally be considered as reactions of vicarious substitution of hydrogen atoms, where the leaving group departs the substituted system from a position other than that which is attacked. In fact, the term 'vicarious substitution' was sometimes used in the literature to describe nucleophilic aromatic *tele*-substitution of compounds having a nucleofugal group in a side chain. It seems, however, that according to the intention of the authors[2] who first proposed this term, it should be reserved for reactions in which the leaving group is present in a reactant undergoing substitution.

Substitution reactions are the most widespread and useful reactions in organic synthesis. Every year provides new achievements and numerous papers within this field. In the last decade a few books and many reviews have been published which are devoted in particular to nucleophilic substitution reactions of typical nucleofugal groups or the hydrogen atom in aromatic compounds.[3,4] In some of these reviews the *cine*- and *tele*-reactions were neglected or treated marginally.[5] No reviews on *cine*- and *tele*-substitutions have been published recently. This article, which in principle comprises a review of papers within the last 30 years, aims at filling this gap.

The definitions of the title reactions do not introduce any constraints regarding the character of the starting compounds, the leaving and entering groups and in the nature of the substitution mechanisms. *cine*- and *tele*-Substitutions can

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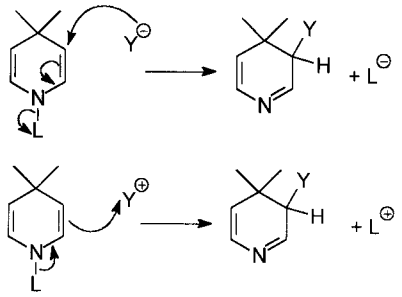


Scheme 1.

therefore refer to reactions of aliphatic as well as aromatic compounds, occurring as ionic, radical–ionic or radical processes. The mechanisms of these reactions can be less or more complex. In a substrate, the leaving group may also be combined with an atom other than carbon. For condensed cyclic compounds, such a group can be present even in a ring that is different from that being substituted.

Even in structurally similar systems, *cine*- or *tele*-substitution can proceed under the action of both nucleophilic and electrophilic reagents (Scheme 1). The latter reactions are much less common.

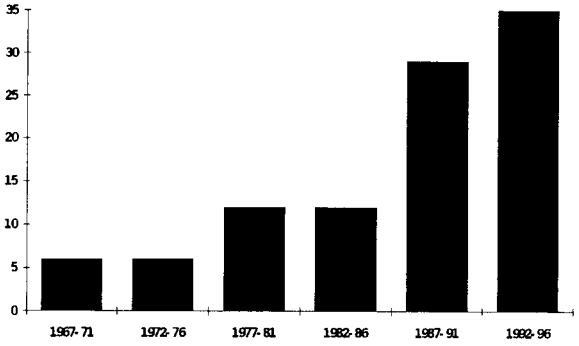


Figure 1. Papers directly or exclusively devoted to the *cine*- and *tele*-substitution reactions (1967–1996).

Although *cine*- and *tele*-substitution reactions are widely distributed in organic chemistry, checking the appropriate keywords in *Chemical Abstracts* shows that the number of works directly or exclusively devoted to these reactions within the 1972–1996 period comprises only about 100 papers. Recently, however, a distinct upward trend in the five-year comparison periods can be observed (Fig. 1).

Most studies concern nucleophilic *cine*- or *tele*-substitution in homoarene derivatives or their complexes with metals, and in heteroarenes. Only a few papers discuss electrophilic aromatic *cine*-substitution. Occasionally examples of *cine*- and *tele*-substitutions in aliphatic systems are described and investigated.

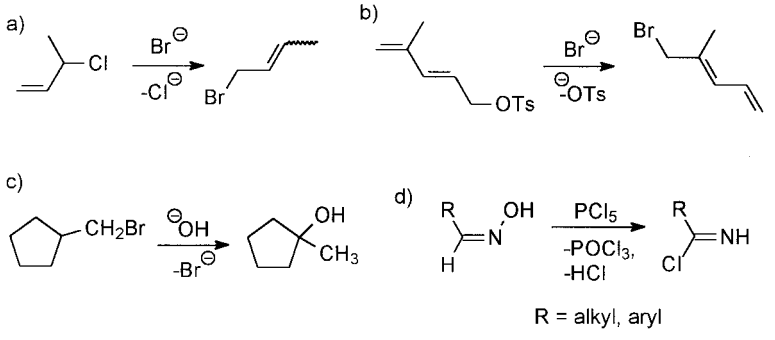
Some of the reactions that satisfy the formal criteria of the definition of *cine*- and *tele*-substitution (Scheme 2) are often depicted otherwise in the literature. These include S_N2' type reactions with π-bond migration in (a) non-cyclic allyl systems or (b) pentadienyl conjugated systems, (c) nucleophilic substitutions accompanied by a 1,2-shift of hydride anion and (d) formation of imidoyl chlorides in the course of Beckmann rearrangement of (*Z*)-aldoximes. In principle, such reactions will not be discussed here, except those examples where the terms *cine*- and *tele*-substitution have been used in the original papers.

In this review, the material found is discussed in Sections 2–5. Three of which refer to nucleophilic and one to electrophilic substitution. In each of the sections the most widely discussed suggestions on the mechanisms of *cine*- and *tele*-substitution reactions are presented.

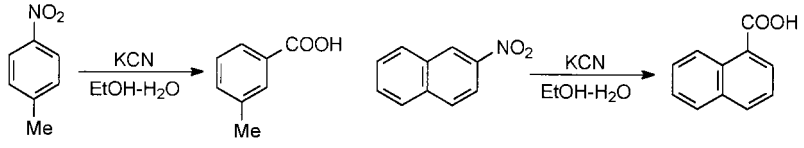
2. Nucleophilic *cine*- and *tele*-substitution of homoarene derivatives

2.1. Nitrohomoarenes

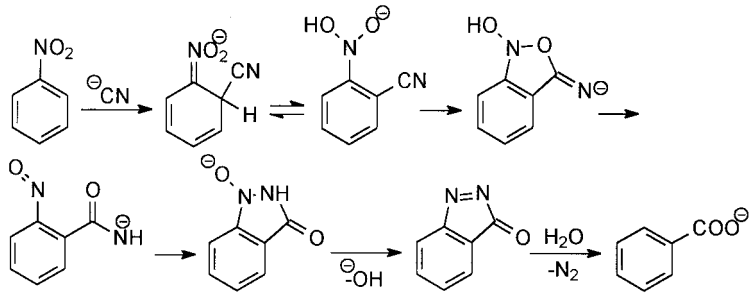
Most nucleophiles do not react with derivatives of alternant



Scheme 2.



Scheme 3.



Scheme 4.

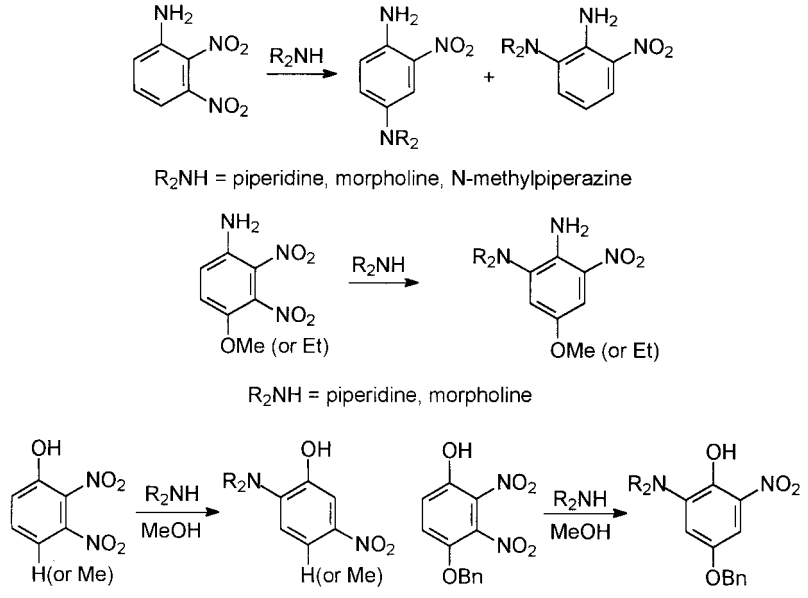
homoarenes without strong electron-withdrawing substituents at the *ortho* or *para* positions to the leaving groups. For this reason a considerable portion of the reactions of nucleophilic aromatic substitution concerns nitroarenes and even polynitroarenes. Long ago, prior to the introduction of the terms *cine*- and *tele*-substitution, it was known that nucleophilic aromatic substitution of benzene or naphthalene derivatives activated in such a manner sometimes leads to the formation of products which contain the entering group in a position other than that formerly occupied by the leaving group. One such example is von Richter's reaction (Scheme 3), which was discovered in the last century, and the mechanism of which was the subject of investigations at least up to the first half of the 1960s[3,4,6] (Scheme 4).

It was later found that a similar phenomenon (consisting of the introduction of a substituent in a position adjacent to the leaving group) occurs in other reactions of arenes activated by the nitro groups. At the same time, in contrast to von Richter's reaction, these reactions can occur under relatively mild conditions, especially in polynitroarenes. *cine*- and *tele*-Substitutions have additionally been described for the replacement of the nitro by the amino group in dinitro derivatives of aniline[7–9] and phenol[10] (Scheme 5).

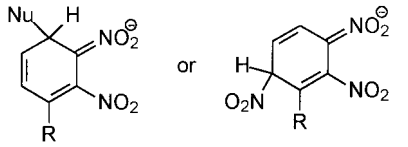
Good yields of the *cine*- and *tele*-substitution products were obtained when strongly basic, cyclic secondary amines were used as nucleophiles and the reaction was performed in methanol, whereas an *ipso*-substitution of the nitro group prevailed in aprotic solvents. The reactions of *cine*- and *tele*-substitution proceeded according to the addition–elimination mechanisms. Nucleophilic attack on an *ortho*- or *para*-substituted carbon atom with respect to the atom combined with the nitro group results in the formation of a σ^H-complex. In a protic solvent the latter is protonated and, due to the basicity of the nucleophile used in excess, nitric(III) acid is eliminated from the addition product leading to regeneration of the aromatic system. For benzene derivatives, the entering substituent always occupies an *ortho* or *para* position with respect to the leaving group. This confirms the mechanisms of nucleophilic addition–elimination unequivocally, since only such *ortho*- and *para*-σ^H-complexes forming as a result of nucleophilic attack can be stabilized by the nitro group (Scheme 6).

2,4-Dinitroanisole reacts with sodium borodeuteride in dimethyl sulfoxide to give a mixture, with the *cine*-substitution product predominating[11] (Scheme 7).

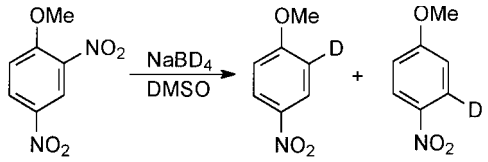
An example of nucleophilic *tele*-substitution of aromatic



Scheme 5.



Scheme 6.



Scheme 7.

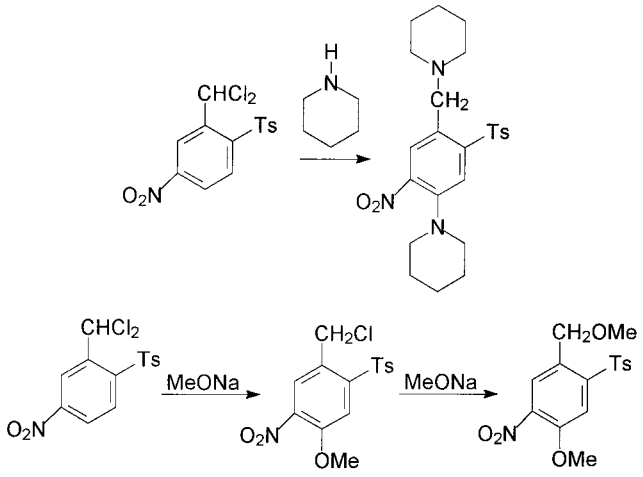
sulfones has also been reported. This involves a benzene derivative activated with two phenylsulfonyl groups, one of which has been substituted by 2,4,6-trimethylthiophenolate anion (Scheme 8). This *tele*-substitution is accompanied by an intramolecular cyclocondensation reaction and by benzenesulfinic acid elimination.[12]

A leaving group may additionally be present in a side chain. For example, 5-nitro-2-tosylbenzylidene chloride when treated with piperidine or alkoxides undergoes substitution both at the ring and at the side chain[13] (Scheme 9).

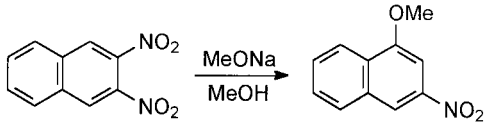
Nitrobenzylidene chlorides react with carbanions in a similar way.[14] 3-Trichloromethylnitrobenzene, 1,3-dinitro-5-trichloromethylbenzene and 3-trichloromethylbenzonitrile react with sodium methoxide to give 4-methoxy-3-nitrobenzaldehyde, 4-methoxy-3,5-dinitrobenzaldehyde and 5-dimethoxymethyl-2-methoxybenzonitrile, respectively. First two compounds react with methyl thioglycolate to afford dichloromethylacetates. All these products are the result of *tele*-substitution.[15]

Similar reactions were observed in naphthalene derivatives as exemplified by 2,3-dinitronaphthalene, which reacts with sodium methoxide in methanol to give 1-methoxy-3-nitronaphthalene (Scheme 10) with a yield exceeding 95%, and only traces of 2-methoxy-3-nitronaphthalene (the *ipso*-substitution product). The reaction of 2,3-dinitronaphthalene with hydroxide ions, however, gave only tars.[16]

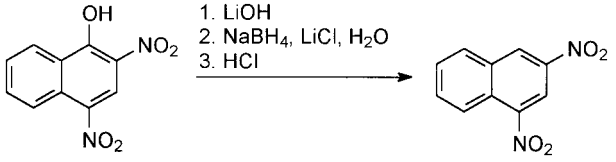
Detailed kinetic studies of the 2,3-dinitronaphthalene and piperidine reactions in benzene solution have shown that the piperidine residue only enters position 1. The yield of the reaction is practically quantitative. The reaction is second order with respect to piperidine and first order with respect to the dinitronaphthalene.[17]



Scheme 9.



Scheme 10.

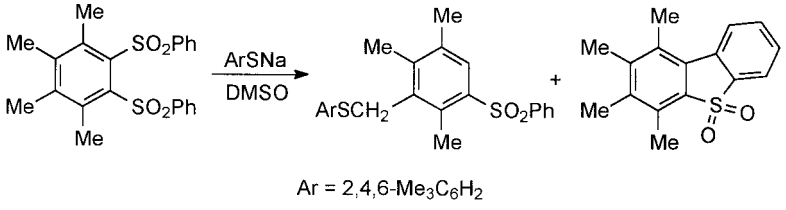


Scheme 11.

In the *cine*-substitution of 2,3-dinitronaphthalene by *N*,*N*-dimethylethylenediamine, its primary amino group serves as a nucleophile, whereas the tertiary amino group plays the role of intramolecular base catalyst. This facilitates the elimination of a nitric(III) acid molecule from an addition product.[18]

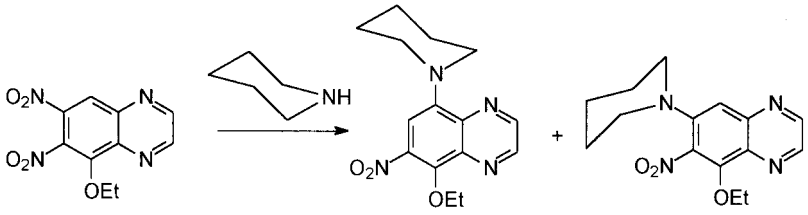
2,3-Dinitronaphthalene reacts in a similar way with carbanions generated from alkyl cyanoacetates in the presence of potassium hydroxide in DMF.[19]

The lithium salt of 2,4-dinitro-1-naphthol undergoes an interesting reaction when treated with sodium borohydride in the presence of lithium chloride (Scheme 11). On acidification of the reaction mixture 2,4-dinitronaphthalene is obtained as a result of *tele*-substitution of the hydroxy group.[20]

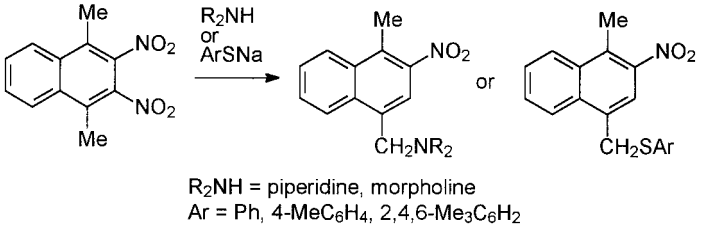


Ar = 2,4,6-$Me_3C_6H_2$

Scheme 8.



Scheme 12.



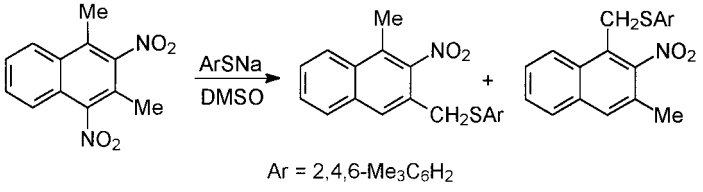
Scheme 13.

Nasielski-Hinkens et al. has described an interesting example of *cine*-substitution of the nitro group by piperidine in 5-ethoxy-6,7-dinitroquinoxaline (Scheme 12), which provides information on the proportion of *cine*- to *ipso*-substitution while increasing the amine concentration.[21]

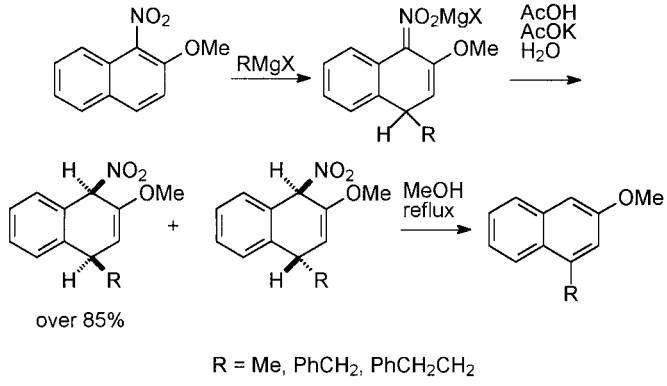
tele-Substitution was observed when 1,4-dimethyl-2,3-dinitronaphthalene reacted with secondary cyclic amines or sodium thiophenolates to yield 1-dialkylaminomethyl- and 1-arylthiomethyl-4-methyl-3-nitronaphthalenes, respectively.[22,23] The nucleophiles did not attack the benzene ring substituted by the nitro groups but attacked the exocyclic methyl group carbon atoms (Scheme 13). The reaction requires fairly severe conditions (110°C) and a highly polar solvent (DMSO). The mechanism of the latter reaction must differ from that described earlier. It should be assumed that the reaction starts with a tautomeric shift of the hydrogen atom from the methyl group to the oxygen of the nitro group, followed by amine or thiophenol addition to the carbon–carbon double bond formed.[24]

1,4-Dimethyl-2-nitro-3-phenylsulfonylnaphthalene reacts in a similar manner with thiophenolates to yield mainly 1-methyl-4-phenylthiomethyl-2-nitronaphthalene (the *tele*-substitution product), apart from some of the *ipso*-substitution product of the nitro group. The use of the larger 2,4,6-trimethylthiophenolate anion results in *tele*-substitution only.[25]

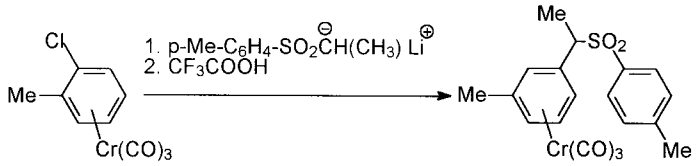
Nucleophilic *tele*-substitution (parallel with nitro group *ipso*-substitution) also occurred if 1,3-dimethyl-2,4-dinitronaphthalene was subjected to sodium thiophenolates in DMSO at elevated temperature (Scheme 14). Both methyl groups were attacked.[24]



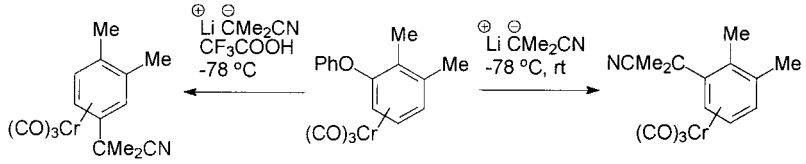
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

Similar *tele*-substitutions were observed in the reactions of thiophenolates with 1,4-dimethyl-2,3-bis-phenylsulfonyl-[25] and 1,3-dimethyl-2-nitro-4-phenylsulfonylnaphthalenes.[24]

2-Methoxy-1-nitronaphthalene reacts with Grignard compounds to form adducts which, after acidification and heating in methanol, eliminate nitric(III) acid to give 1-alkyl-3-methoxynaphthalenes (*tele*-substitution)[26] (Scheme 15).

The behaviour of a 9-nitroanthracene is similar.[27]

2.2. Complexes of homoarene derivatives with metals

Activation of the benzene ring to the attack of nucleophiles can also be achieved by complexing the aromatic system with some metals. Much attention has been given in particular to the nucleophilic substitution of complexes of benzene derivatives with tricarbonylchromium. Most studies of this subject were carried out by Rose's group in France in the 1980s and 1990s. A recently published review[28] by Rose-Munch et al. contains 119 references on nucleophilic *cine*- and *tele*-substitution of arenetricarbonylchromium and of cyclohexadienyltricarbonylmanganese complexes. For a better description of the position of substitution the authors have introduced the new terms, *tele-ortho*, *tele-meta* and *tele-para* S_NAr.

The *o*-chlorotoluenetricarbonylchromium complex reacts with deprotonated ethyl-*p*-tolyl sulfone to yield *cine* (*tele-ortho*) substitution products[29,30] (Scheme 16).

Depending on the reaction conditions the 1-phenoxy-2,3-dimethoxybenzene-tricarbonylchromium complex gives either *tele-meta* or *ipso* substitution products with 2-lithioisobutyronitrile[31,32] (Scheme 17).

The same nucleophile quantitatively substitutes one of the methoxy groups in the similar 1,2,3-trimethoxybenzene complex, and only *tele-meta* substitution was observed[33,34] (Scheme 18).

Similar *tele*-substitution of the methoxy group was observed in chiral arenetricarbonylchromium complexes as well.[35]

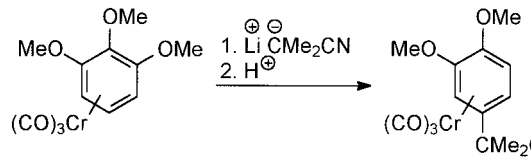
Tricarbonylchromium complexes of arenes are so susceptible to attack of nucleophiles that even the very weak nucleofugal amino group can be substituted[36] (Scheme 19).

Recently Schmalz and Schellhaas have pointed out the possibility of using similar reactions in the syntheses of useful natural products, e.g. (+)-ptilocaulin.[37,38]

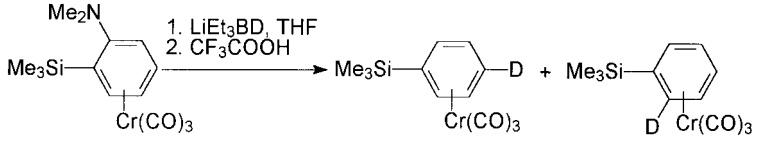
It has been shown that nucleophilic *cine*- and *tele*-substitutions of complexes of benzene derivatives with tricarbonylchromium proceed according to the addition–elimination mechanism by isolating a relatively stable intermediate product of nucleophilic addition[39] (Scheme 20).

The study of the regioselectivity of the addition of a nucleophile to chlorotoluenetricarbonylchromium complexes indicated that stabilized carbanions added predominantly to the carbon eclipsed by a Cr—CO bond of the most stable conformer.[40]

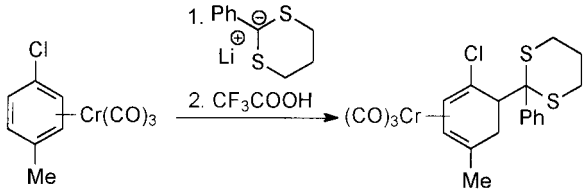
Examples of *tele-para* substitution are also known, such as the reaction of 2,6-dimethylchlorobenzenetricarbonylchro-



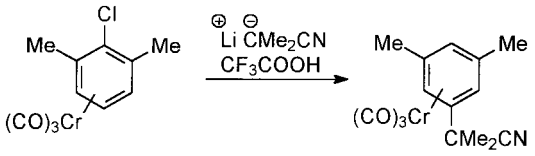
Scheme 18.



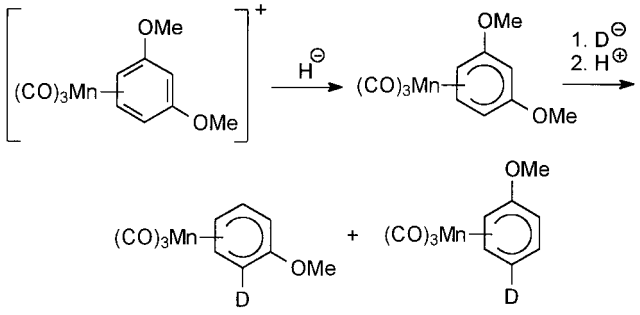
Scheme 19.



Scheme 20.



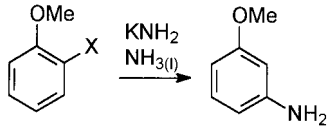
Scheme 21.



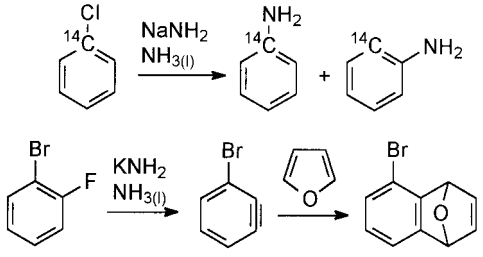
Scheme 22.

mium with 2-lithio-2-methylpropionitrile (Scheme 21) or 2-lithio-2-phenyl-1,3-dithiane.[41,42]

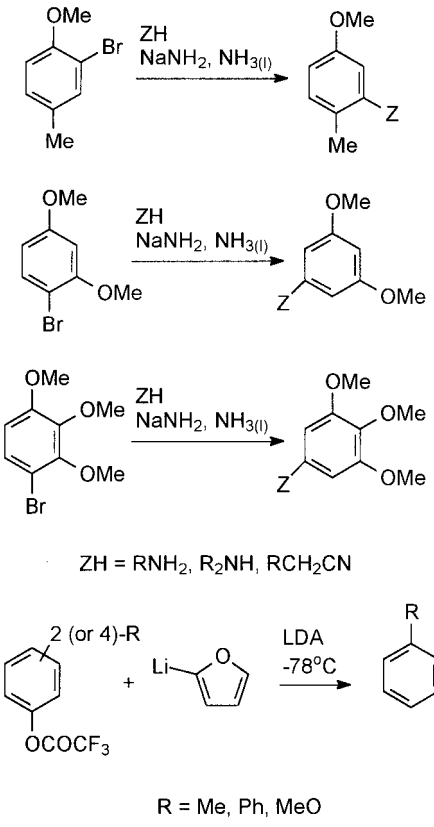
The reactions of neutral (η^5-cyclohexadienyl)tricarbonylmanganese complexes are actually substitutions of non-aromatic compounds. The complexes are usually formed by addition of a nucleophile to cationic (η^6-arene)tricarbonylmanganese complexes, hence the reason for a description of the reaction in this section. An example of *cine*- and *tele*-substitution in cyclohexadienyltricarbonylmanganese complexes is shown in Scheme 22.[43]



Scheme 23.



Scheme 24.



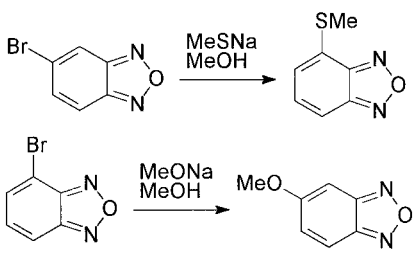
Scheme 25.

2.3. Other compounds—nucleophilic attack on homoarenes

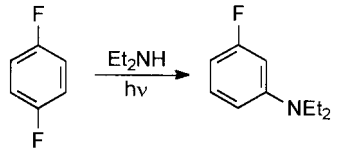
cine-Substitution was often observed and examined when the starting arene was a non-activated aryl bromide or aryl chloride and the reaction was performed in the presence of exceptionally strong bases. An example of such a reaction is the formation of *m*-anisidine from *o*-halogenoanisoles and potassium amide in liquid ammonia[44] (Scheme 23).

The mechanism of these reactions has been examined with great care and a detailed description is given in many monographs and handbooks. Only the most important facts are therefore described below.

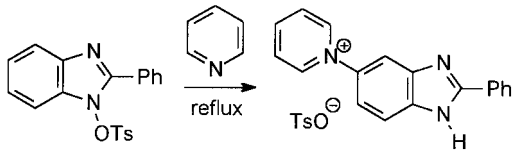
It has been demonstrated that benzynes are intermediate products in these reactions, trapping the latter in the cycloaddition reaction with furan.[45] ^{14}C-1 labelled chlorobenzene[46] (Scheme 24) and MS techniques were used in the investigations. In subsequent years, papers occasionally



Scheme 26.



Scheme 27.



Scheme 28.

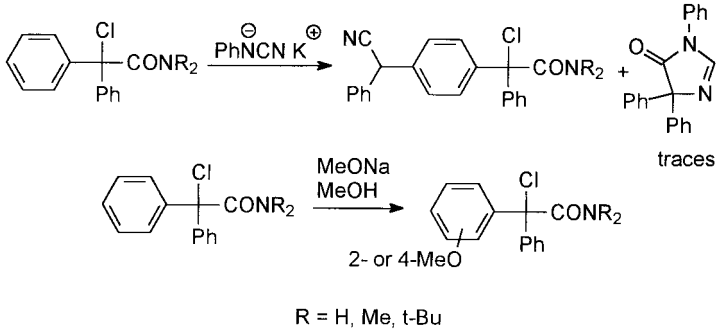
appeared on the mechanistic details of this type of reaction to show that halogen departure is preceded by carbon to hydrogen bond breaking.[47]

A few examples are summarized in Scheme 25 for *cine*-substitutions that probably proceed according to an aryne mechanism and which have been described in the last 12 or so years.[48,49]

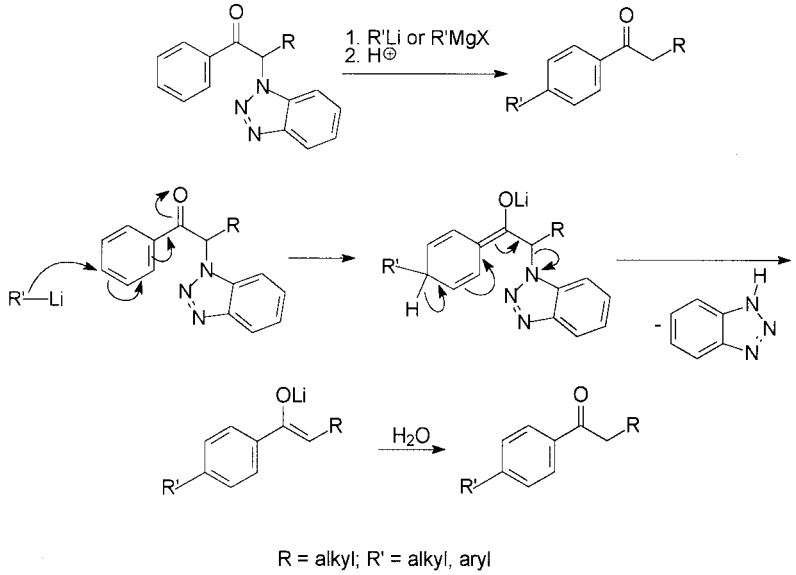
In the literature, nitrofurazone reactions have also been considered as *cine*-substitution that proceeds according to the elimination–addition mechanism[50–53] (Scheme 26). This would appear to require a reinvestigation.

Nucleophilic photosubstitution of fluoroarenes by primary and secondary amines was investigated while observing *cine*-substitution that proceeded in agreement with the addition–elimination mechanism[54,55] (Scheme 27).

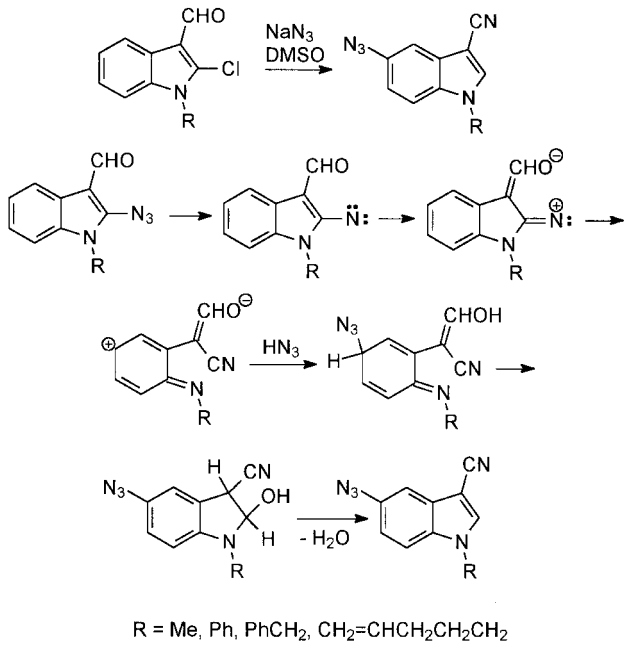
Numerous examples of nucleophilic *tele*-substitution are also known, in which the leaving group is not located directly at the benzene ring, but is combined either with an exocyclic carbon atom or with a nitrogen atom of a heterocyclic ring condensed with the benzene ring. It is interesting to note that both benzoimidazole and benzopyrazole derivatives with leaving groups at the heterocyclic rings (lacking a free position at the azole) undergo *tele*-substitution in a similar way (Scheme 28). The entering group substitutes the hydrogen atom at position 5 of the benzene ring.[56,57] The mechanisms of these reactions have not been investigated in detail, but it can be assumed that the reactions proceed as a result of nucleophile attack associated with departure of the nucleofugal group and formation of a neutral σ^H-complex, followed by a tautomeric shift of the hydrogen atom and rearomatization of the system.[57]



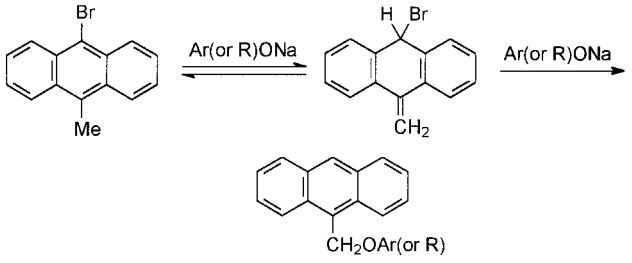
Scheme 29.



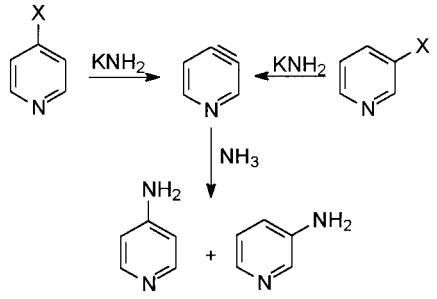
Scheme 30.



Scheme 31.



Scheme 32.



Scheme 33.

It has been shown that the products of *cine*- and *tele*-substitution of non-nitro derivatives are not formed according to the $S_{NR}1$ mechanism[58,59] (Scheme 29).

For practical reasons, out of the *tele*-substitutions discussed in this section, attention should be paid to the recently developed Katritzky method for introducing alkyl groups at the *para* position in alkylphenylketones. The nucleofugacity of the benzotriazole anion is utilized in this method (Scheme 30)and it may be assumed that the reaction occurs according to the addition–elimination mechanism via a neutral σ^H-complex.[60]

The mechanism of the *tele*-substitution reaction described in Pluta et al.[61] is more complex, and assumes that a nitrene may be formed, followed by opening–closure of the pyrrole ring. One of the probable intermediate products is a neutral σ^H-complex (Scheme 31).

tele-Substitution reactions in which the nucleophile attacks an exocyclic carbon atom are less frequent. These reactions may be exemplified by the synthesis of 9-aryloxymethylanthracenes from 9-bromo-10-methylanthracene.[62,63] The probable mechanism of the reaction is shown in Scheme 32.

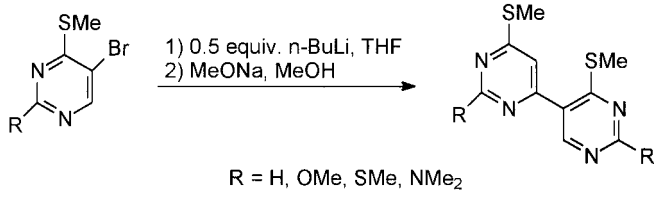
Reactions of triphenylmethyl chloride or bromide with tributyl-[64] or triphenylphosphine[65] furnish mixtures of triphenylmethane and *tele*-substitution products: 4-(diphenylmethyl)phenyl phosphonium chloride or bromide, respectively.

3. Nucleophilic *cine*- and *tele*-substitution of heterocycles

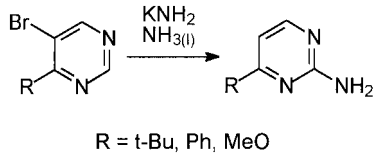
3.1. Six-membered heterocycles with a leaving group at a carbon atom

A very well documented example of a heteroaryne mechanism is the amination of 3- and 4-halopyridines using potassium amide in liquid ammonia[66] (Scheme 33).

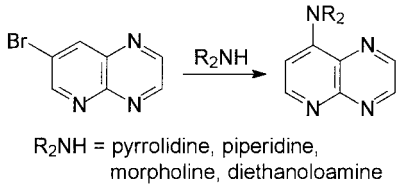
Nevertheless, most of the reactions of diazines with nucleophiles probably occur according to the addition–elimination (or ANRORC—addition of the nucleophile–ring opening–ring closure[67]) mechanism even if there are no electron-withdrawing groups in the molecule. This results from a relatively high susceptibility of diazines to nucleophilic attack and from the possibility of anionic σ-adduct stabilization through electron pair acceptance by the annular nitrogen atom. For example, lithium reagent generated *in situ* from 5-bromo-4-(methylthio)pyrimidine binds to a second pyrimidine molecule yielding σ-complex which, by protonation and subsequent loss of hydrogen bromide, yields a substituted pyrimidine[68] (Scheme 34).



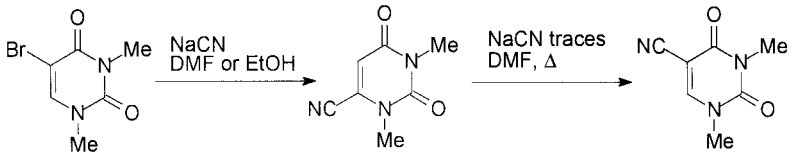
Scheme 34.



Scheme 35.



Scheme 36.



Scheme 37.

This reaction has been applied in the preparation of a series of biologically important 4,5′-bipyrimidines.[69]

tele-Amination of 4-substituted-5-bromopyrimidines by potassium amide in liquid ammonia (Scheme 35) does not proceed according to the S_N(ANRORC) mechanism. The latter mechanism, which is common for most amination reactions of haloazines, has been demonstrated using ^{15}N labelled compounds in the reaction.[70]

5-Chloro- and 5-bromopyrimidines react with piperidine or diethylamine to give *cine*-substitution products 4-piperidino- and 4-diethylaminopyrimidines, respectively.[71]

The bromine atom in bromotriazolopyrimidine undergoes *cine*-substitution by indoles to form (3-indoyl)triazolopyrimidines.[72]

7-Bromo-5-azaquinoxaline reacts with secondary amines to give *cine*-substitution products[73] (Scheme 36).

Heteroaromatic systems with an exocyclic conjugation (e.g. pyridone systems) are characterized by a high susceptibility to nucleophilic attack and nucleophilic *cine*-substitution is often observed in systems of this type. It has been demonstrated that the originally formed *cine*-substitution product can rearrange to a more stable *ipso*-substitution product[74] (Scheme 37).

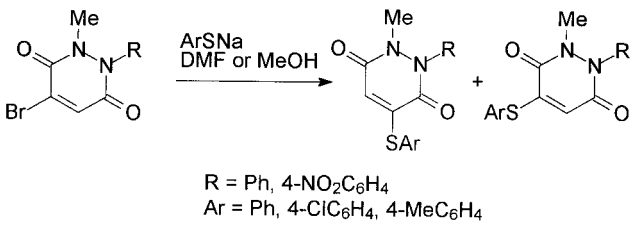
Inter- and intramolecular *cine*-substitution of the bromine atom by the amino group in *N*-[2-(bromouracil-1-yl)ethyl]-alkylamines are possible as well.[75]

Investigations on *N*,*N*-disubstituted 5-bromopyridazino-3,6-diones have revealed that the *cine*-substitution product is predominant due to higher susceptibility of position 4 than 5 to nucleophilic attack[76,77] (Scheme 38).

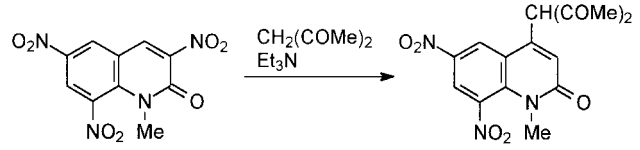
5-Chloro- and 5-bromopyridazine-3,6-diones react with alkoxides or amines in a similar way.[78]

It has also been found that the susceptibility of the hetero-cyclic ring in 1-methyl-3,6,8-trinitro-2-quinolone to attack by carbanions exceeds that of the homoarene system. Reaction of the quinolone with 2,4-pentanedione, performed in the presence of triethylamine, led to the separation of an adduct which, on treatment with protic acid, gave the product of *cine*-substitution. This showed that the substitution proceeds according to the addition–elimination mechanism[79] (Scheme 39) and moreover, the 8-nitro group seems to activate the 2-quinolone ring sterically rather than by electronic effects.[80]

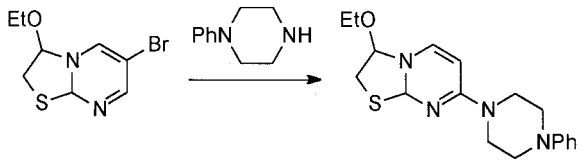
Reports are also known on nucleophilic *cine*-substitution reactions of dihydropyrimidine derivatives, thus diazines with incomplete aromaticity[81] (Scheme 40).



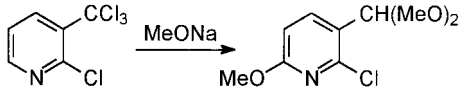
Scheme 38.



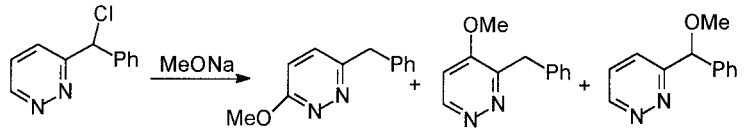
Scheme 39.



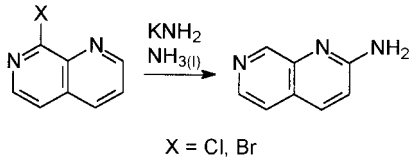
Scheme 40.



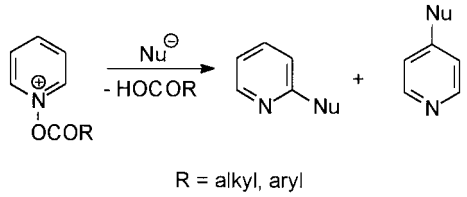
Scheme 41.



Scheme 42.



Scheme 43.



Scheme 44.

An interesting example of *tele*-substitution of pyridine derivatives has been described Suschitzky and co-workers[82] in which 2-chloro-3-trichloromethylpyridine reacts, in methanol, with sodium methoxide to form 2-chloro-3-dichloromethyl-6-methoxypyridine. In this reaction, a chlorine atom from the trichloromethyl group plays the role of a leaving group and not the chlorine atom that is directly bound to the pyridine ring at the 2 position (Scheme 41).

Similar reactions have been reported for pyridazine derivatives[83] (Scheme 42).

For further examples of *tele*-substitution in pyridazines see also Heinisch.[84]

8-Halo-1,7-naphthyridines also undergo *tele*-substitution[85,86] (Scheme 43).

According to van den Haak and van der Plas two types of *tele*-substitutions in naphtyridines can be discerned, namely, *even*[87] and *odd*.[88] Even or odd *tele*-substitution comprise a substitution reaction in which there is an even or an odd number of atoms lying between the carbon atom on which the nucleophile attacks and that from which the leaving group departs.

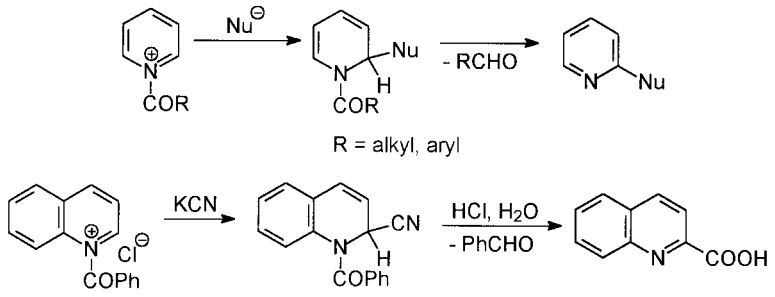
8-Chloropurine with potassium amide in liquid ammonia gave adenine as main product via *tele*-substitution reaction.[89]

4-Aza-6-bromobenzo-2,1,3-thiadiazole and 4-aza-6-bromobenzo-2,1,3-selenadiazole gives *cine*-substitution products with nucleophiles.[90]

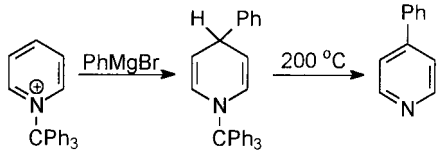
3.2. Six-membered heterocycles with a leaving group at a nitrogen atom

The first examples of the title conversion in pyridine chemistry (known as early as the 1930s) were most likely the reactions of *O*-acyl derivatives of pyridine *N*-oxides (or other azines) with nucleophiles, leading to mixtures of the 2- and 4-substituted pyridine derivatives (Scheme 44). The *O*-acyl derivatives are usually not isolated, but form *in situ* during the course of the reaction. Stable *N*-alkoxypyridinium salts react with nucleophiles in a similar manner. It is very probable that these conversions follow the addition–elimination mechanism. The reactions have not found wider applications in synthesis due to formation of mixtures.

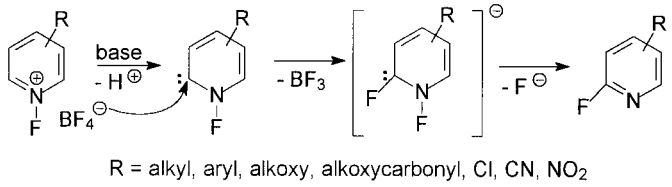
In many reactions *N*-acylazinium salts are attacked by nucleophiles in position 2 or, if this is occupied, in position 4. In these reactions, due the effect of the *N*-acyl group, the product of nucleophilic addition is, on the whole, relatively stable and can be isolated. Aromatization of the system does not usually occur before isolation of the product that requires acidification of the reaction mixture. A typical example of such a reaction is the formation of Reissert's compounds from naphthyridine, acridine, phthalazine or isoquinoline derivatives by reacting with metal cyanides (Scheme 45). It is noteworthy that the reactions discussed in this section are not commonly classified in the literature as *cine*- or *tele*-substitutions.



Scheme 45.



Scheme 46.



Scheme 47.

Details of the behaviour of *N*-oxides, compounds derived from them, and *N*-acyl derivatives of azines in the reactions with *C*-, *N*-, *O*-, *P*- and *S*-nucleophiles can be found in two monographs.[4,91] There are also some more interesting examples described in a review paper on pyridine functionalization.[92]

The reaction of 3-pyrrolidino-1,2,4-triazine-4-oxide with ammonia leads to the product of *tele*-substitution of pyrrolidine namely 5-amino-1,2,4-triazine-4-oxide. A sigmatropic shift of hydrogen postulated for such reactions has been proved by the isolation of key intermediates.[93]

For the reaction of pyridine *N*-oxide with phenyl isocyanate leading to 2-phenylaminopyridine, a mechanism involving initial 1,3-dipolar cycloaddition has been proposed.[94] Pyridine *N*-oxide reacts with *N*-phenylbenzimidoyl chloride by a similar mechanism to give 3-chloropyridine.[95]

N-alkylpyridinium salts can also undergo *tele*-substitution reactions[96] (Scheme 46).

2-Nitro-10-oxyphenazine reacts with many nucleophiles (primary and secondary amines, carbanions) to give *tele*-substitution products lacking an *N*-oxide function.[97,98] The nucleophiles substitute the hydrogen atom in position 1. The behaviour of the 10-oxy group in 5,10-dioxy-2-nitrophenazine is similar.[99]

The reactions of various nucleophiles with tetrafluoroboranes, trifluoromethanesulfonates and other stable *N*-fluoropyridinium salts are relatively rare although they have been well investigated. The 2-substituted azine derivatives are generated as a result of fluorine *cine*-substitution. Such reactions have found practical application, for example, in the synthesis of 2-fluoropyridines, which are additionally substituted by an electron-donating or electron-withdrawing group. No *tele*-substitution was observed in these reactions. The nucleophilic fluorination probably involves the formation of singlet carbene in position 2[100] (Scheme 47).

A review with an exhaustive and detailed description of fluoroazinium salts (fluoroborates, triflates and acetates) with various nucleophiles (methylene halides, nitriles, benzene, alcohols, carboxylic acids, phosphines, arsines, phosphites) is given in a monograph.[4]

Fluoropyridinium tetrafluoroborates or triflates give 2-substituted pyridines with anions derived from benzenethiols, phenols, azoles, cyanamide and azide.[101]

Unlike the above-mentioned reaction, an *N*-fluoropyridinium tetrafluoroborate is subject both to carbanion *cine*- and *tele*-substitution to give high yields of substitution products in positions 2 and 4.[102] It has been suggested that the reaction can proceed through addition products and carbenes. The $S_{RN}1Ar$ mechanism is also proposed for these reactions.[103]

Many of the reactions of *N*-fluoropyridinium salts with nucleophiles different from fluoride anion have, unfortunately, not found practical use because of low yields or the formation of product mixtures.

A few examples of *cine*- and *tele*-substitution in *N*-aminoazinium salts are known. *N*-acetylaminopyridinium salts react with potassium cyanide to yield mainly 4-cyanopyridine. The elimination of an *N*-methylacetamide molecule from transition state adduct accompanies hydrogen substitution[104] (Scheme 48).

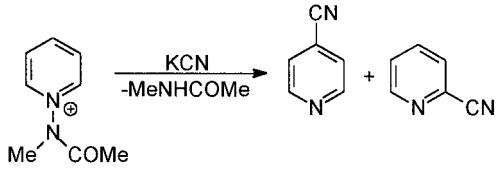
N-pyridinio-4-pyridine reacts similarly, to give a mixture of cyanation products at C-2 and C-4 and 4-pyridone as the by-product.[105]

A reaction of this type was used to prepare *N*-(4-pyridyl)-anilines[106] (Scheme 49).

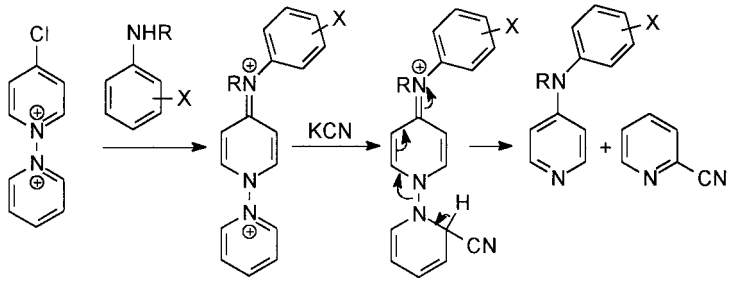
3.3. Five-membered heterocycles with a leaving group at a carbon atom

As early as 1968, Reinecke and Adickes described the reaction of 2-bromothiophene with potassium amide in liquid ammonia, which led to a mixture of 3-bromo- and 3-aminothiophene[107] (Scheme 50).

A more careful study showed that this reaction does not

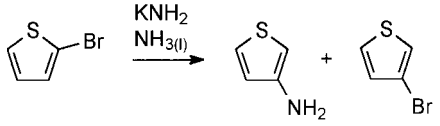


Scheme 48.

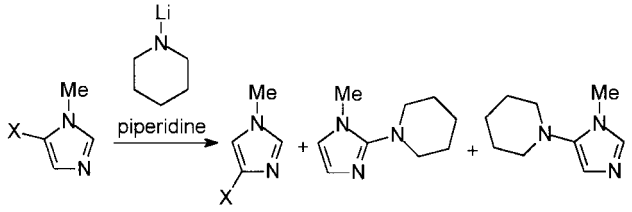


R = H, Me, Et, Ph
X = H, OH, Me, MeO, Ac, COOH, COOMe, NO_2, F, Cl, Br

Scheme 49.

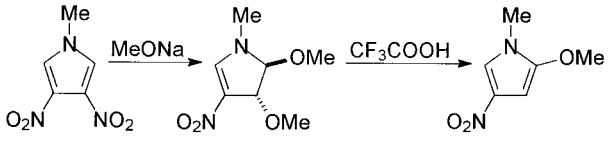


Scheme 50.



X = Cl, Br

Scheme 51.



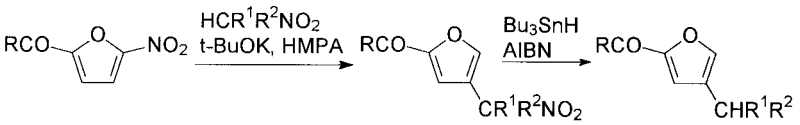
Scheme 52.

proceed via a heteroaryne or addition–elimination but unexpectedly via an interesting mechanism called 'base-catalysed halogen dance' (BCHD).[108] As a result of this process, a mixture of di- and tribromothiophenes is formed which, under the influence of the amide anion, is subsequently converted to 3-aminothiophene. Similar trans-halogenation reactions with amides (but without amination) were observed for haloimidazoles[109] and haloisothiazoles.[110]

In the reaction of 5-chloro- or 5-bromo-1-methylimidazole with lithium piperidide in piperidine, 1-methyl-2-piperidineimidazole is produced as one of the products due to halogen atom *tele*-substitution[111] (Scheme 51).

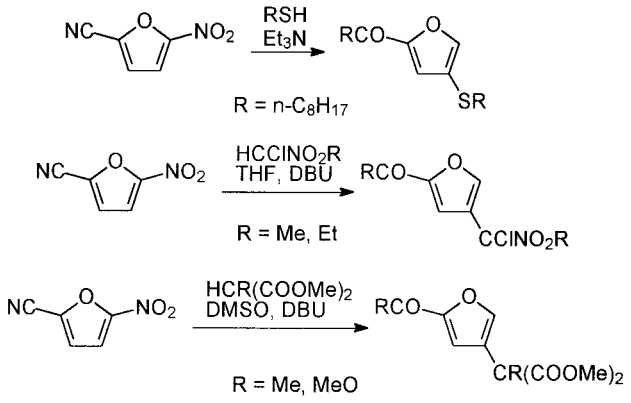
In the 1970s and 1980s, papers appeared on *cine*- and *tele*-substitutions of imidazole, furan, pyrrole and thiophene derivatives activated to nucleophile attack by strongly electron-withdrawing substituents such as cyanide, carbonyl, arenesulfonyl and nitro groups. The starting material mostly contained two substituents of this type. Similar reactions were additionally described for pyrazole salts. Thioles, thiolate ions, alkoxide ions, secondary amines, tertiary stabilized carbanions, azide ions and even hydroxyl ions were used as nucleophiles and nitric(III) acid anions were most frequently the leaving groups. The reaction mixtures sometimes required strong acidification to obtain the final reaction products. Reactions of this type usually take place according to the addition–elimination mechanism. In some cases the addition products are stable just enough to be isolated with satisfactory yields.

It has been found that 1-methyl-3,4-dinitropyrrole reacts with sodium methoxide in methanol to produce *trans*-1-methyl-4,5-dimethoxy-3-nitro-2-pyrroline which can be isolated and then converted into the *cine*-substitution product using the appropriate acids (Scheme 52). Methanol replacement by the non-polar benzene or hexane leads to *ipso*-substitution of the nitro group.[112,113] The reaction between 1-methyl-3,4-dinitropyrrole and piperidine takes place in a very similar manner, with the *cine*-substitution product being formed, and an intermediate cyclic product from the addition of two amine molecules to the ring could also be separated.[114–116] With primary amines mixtures of various 1-alkyl-3-alkylamine-4-nitropyrroles are formed,[114,115] and the reaction mechanism is unclear.

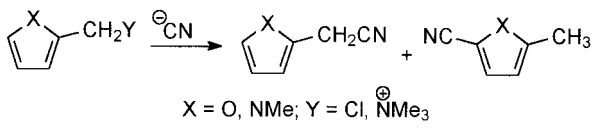


R = Me, i-Pr, t-Bu, MeO
R^1 = Me; R^2 = Me, CH_2CH_2COOMe, n-C_6H_{13}, n- C_8H_{17}, $PhCH_2$
R^1R^2 = -$(CH_2)_4$-

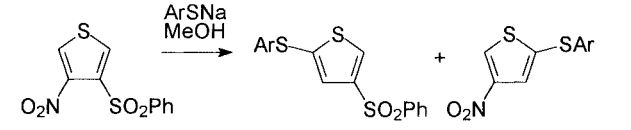
Scheme 53.



Scheme 54.



Scheme 55.



Scheme 56.

High yields of *cine*-substitution products were obtained when 5-acyl- or 5-alkoxycarbonyl-2-nitrofurans were treated with anions of secondary nitroalkanes[117,118] (Scheme 53). If a primary nitro compound was used for the reaction, the nitroalkyl derivative could not be isolated, but only ketones which resulted from the Neff reaction.[118] With other nucleophiles, *ipso*-substitution of the nitro group proceeded.[117]

The nitro group in nitroalkyl derivatives of furan could be changed with high yields of hydrogen during heating in benzene solution with tributyltin hydride and azobisisobutyronitrile (AIBN). So, two above reaction combination is a very useful method for the preparation of 2-acyl- or 2-alkoxycarbonyl-3-alkylfurans.[118]

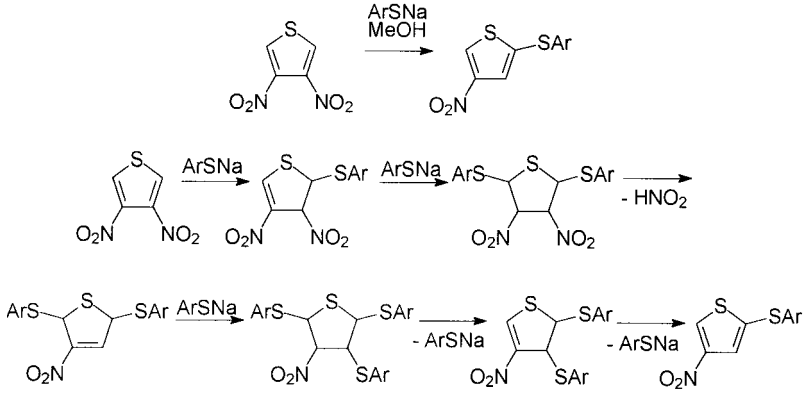
2-Cyano-5-nitrofurans are also subject to nucleophilic *cine*-substitution. They react in this manner not only with carbanions[119] but also with thiols[119,120] (Scheme 54). It is interesting to note that the adducts that are formed after attack of the chloronitrocarbanion are not stabilized, in compliance with the nucleophilic vicarious substitution mechanism.

In the reaction of 5-cyano or 5-methoxycarbonyl-2-nitrofuran with 1,3-dicarbonyl compounds, after the stage of the nitro group *cine*-substitution, intramolecular Michael addition takes place and derivatives of dihydrofurofuran are formed.[121]

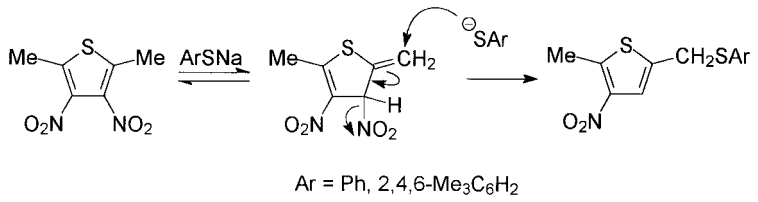
It has been known for a long time that, in the reaction between 2-(chloromethyl)furan and cyanide anion, apart from chlorine atom *ipso*-substitution, the product of *tele*-substitution is also formed, i.e. 2-cyano-5-methylfuran.[122,123] 2-Furylmethyltrimethylammonium iodide reacts in a similar manner.[124] In addition 2-(*N*-methylpyrrolyl)methyltrimethylammonium salts yield with cyanides, besides other products, some 2-cyano-1,5-dimethylpyrrole[125] (Scheme 55).

4-(Phenylsulfonyl)-3-nitrothiophene reacts with arenethiolates in boiling methanol to give a mixture of two *cine*-substitution products containing nitro or phenylsulfonyl groups. The nitro group is a much better nucleofuge[126] (Scheme 56).

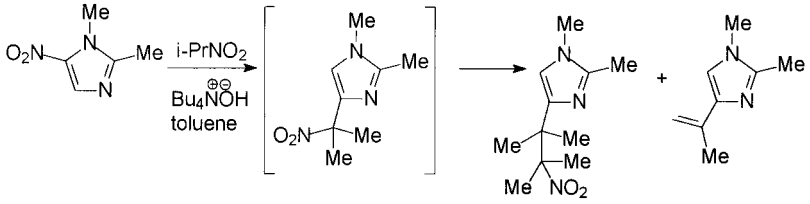
In the reaction of 3,4-dinitrothiophene with thiophenolate anions in methanol, not only was *cine*-substitution observed but some of the intermediate products also separated (Scheme 57) and their structures were confirmed by X-ray crystallography. It has been shown that 3,4-dinitrothiophene does not behave as an aromatic system but as a compound that contains two unconjugated nitroalkene moieties, each of which is capable of independent thiophenol addition.[127,128] This mechanism was then modified by



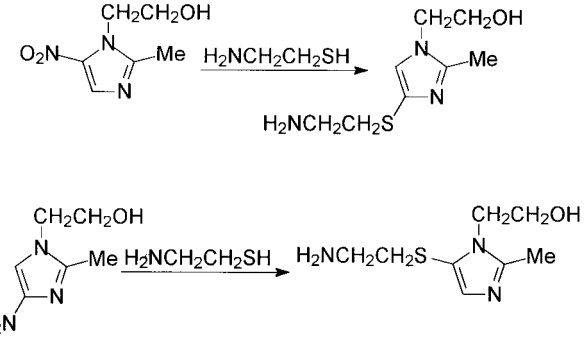
Scheme 57.



Scheme 58.



Scheme 59.

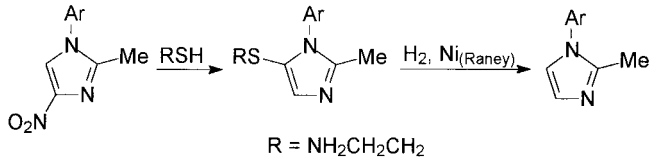


Scheme 60.

The high reduction potential of most five-membered nitroarenes allows oxidation of nucleophiles. Many of the reactions just described are therefore probably proceeding via anionoradicals. Such an $S_{RN}1$ mechanism was postulated, among others, for nucleophilic *cine*-substitution in 5-nitroimidazoles[134,135] (Scheme 59).

The lower the reduction potential of a nitro compound the more drastic the reaction conditions that are required. This may be exemplified by the *C*-denitration of nitroimidazoles using thiolanes, where the 5-nitro derivatives react much easier than their 4-isomers[136] (Scheme 60).

The reaction of nitroimidazoles and thiols can be used for



Scheme 61.

introducing the *S*-arylepisulfonium cation as an intermediate product.[129]

It is of interest to note that 2,5-dimethyl-3,4-dinitrothiophene, in which *cine*-type substitution is already impossible, does not yield an *ipso*-substitution product with thiophenolate, but a derivative of *tele*-substitution[130] (Scheme 58).

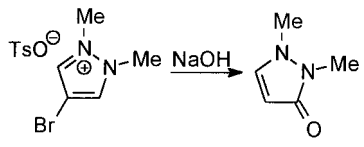
2,5-Diethyl-3,4-dinitrothiophene reacts in the same manner but much faster,[131] while 2-methyl-3,4-dinitrothiophene gives only a *cine*-substitution product.[132]

2,5-Dimethyl-3,4-dinitrothiophene reacts with piperidine and morpholine to give products with structures which are analogous to those formed from 1-methyl-3,4-dinitropyrrole (see above). These addition products are not subject to rearomatization.[133]

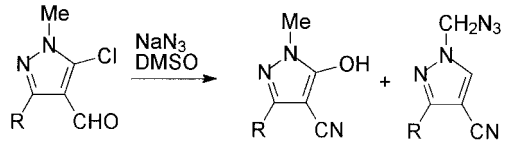
removing the nitro group in the reaction sequence shown below[137] (Scheme 61).

cine-Substitutions of 4-bromopyrazolium salts with hydroxyl ions were described almost 30 years ago by Begtrup[138,139] (Scheme 62).

Many years later, Becher et al. reported nucleophilic *ipso*- and *tele*-substitution reactions by azide ions in relation to neutral chloropyrazole derivatives activated with an



Scheme 62.



Scheme 63.

aldehyde group that undergoes conversion into a cyanide group in the course of the reaction[140,141] (Scheme 63).

The hypothetical mechanism of *tele*-substitution product formation is similar to that previously described for the reaction of 2-chloro-3-formylindole with azide anion.

4-Nitro-3-phenylisoxazole reacts with 1,3-dimethyluracil to give 1,3-dimethyl-5-(3-phenylisoxazol-5-yl)uracil as the product of nitro group *cine*-substitution.[142]

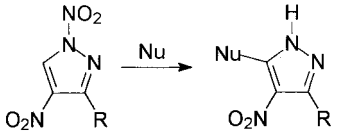
3.4. Five-membered heterocycles with a leaving group at a nitrogen atom

As observed with certain azines *N*-substituted with nucleofugal groups, azole derivatives that contain a nucleofugal group on the pyrrole-type nitrogen atom can also be *cine*-substituted. Such reactions are known for 1,4-dinitropyrazoles, 1,4-dinitroimidazoles and for 1-nitro-1,2,4-triazole derivatives. They resemble S'_N reactions in aliphatic systems. As a result of the reaction, an entering group usually occupies the 5-position of the azole. Introduction of a substituent into the 3-position can be effected only when the 5-position is already occupied in the pyrazole.

1,4-Dinitropyrazoles react with a number of phosphoric, carbonic, sulfuric, oxygen and nitrogen nucleophiles under mild conditions[143–145] (Scheme 64).

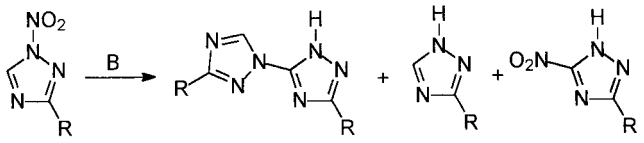
This allowed their use in the syntheses of tripyrazoles by Habraken and co-workers[146,147] and of *C*-nucleosides (formycine and pyrazofuryne) by Buchanan et al.[144,148–151] The reactions proceed with good yields in alcohols. *N*-Denitration predominates in aprotic solvents. Treatment of isopropyl 1,4-dinitropyrazole-5-carboxylate with alcoholic potassium hydroxide gives 3(5)-alkoxy-4-nitropyrazole-5(3)-carboxylic acids resulting in *cine*-substitution.[152] 1,3-Dinitropyrazole does not undergo *cine*-substitution.[143]

1-Nitro-1,2,4-triazoles, with a chlorine atom or a nitro group at the 3 position, under the influence of various nucleophiles



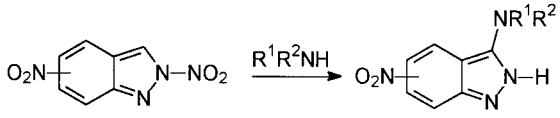
R = H, Me
Nu = NH_3, R_2NH, H_2NCH_2COOMe, $MeHNCH_2COOEt$, EtONa, EtSNa, PhSNa, $EtOOCCH_2SNa$, $P(OMe)_3$, $CH_2(COMe)_2$, $CH_2(COMe)COOMe$, $CH_2(COOMe)_2$ KCN

Scheme 64.



R = Cl, Br, NO_2; B = $\overset{\ominus}{O}H$, $\overset{\ominus}{I}$, Et_3N, $H_2PO_2^{\ominus}$, $Fe^{2\oplus}$

Scheme 65.



R^1R^2NH = piperidine, pyrrolidine, morpholine, $MeNH_2$, $EtNH_2$, $PrNH_2$, Me_2NH, Et_2NH, Pr_2NH

Scheme 66.

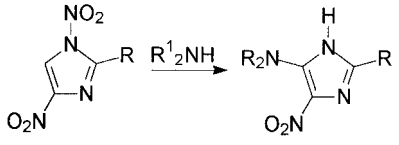
and reducing agents give a post-reaction mixture containing a *cine*-substitution product of the 1-nitro group by the 1,2,4-triazole (which is formed during substrate denitration)[153] (Scheme 65).

Studies on *cine*-substitutions of derivatives of *C*,*N*-dinitroindazoles are relatively rare. 2,5-Dinitro- and 2,6-dinitroindazoles react at a low or room temperature with primary and secondary amines, which attack the 3 position. As a consequence of *cine*-substitution, 3-amino-1*H*-5(or 6)-nitroindazoles are produced, respectively[154,155] (Scheme 66).

7,7′-Dinitro-5,5′-dimethyl-2,2′-biindazole reacts with sodium methoxide to give a complicated mixture as a result of N—N′ bond cleavage. One of the indazoyl moieties acts as a leaving group while the nucleophile enters at position 3 of the other ring.[156] Previous examples of such *cine*-substitution have been observed in *N*,*N*′-linked biheteroaryl quaternary salts. For instance, *N*-pyridinium-substituted pyrazolium quaternary salts are transformed by nucleophiles into 1,5-disubstituted pyrazoles.[157,158]

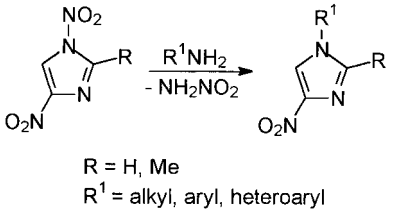
1,4-Dinitroimidazoles are also susceptible to much the same reactions as dinitropyrazoles and dinitroindazoles. The reaction with nitrogen nucleophiles is, however, limited to that of secondary amines, azoles or other compounds containing an NH arrangement[159] (Scheme 67).

1,4-Dinitroimidazoles react similarly with alcohols to give 5(4)-alkoxy-4(5)-nitroimidazoles.[160–162]



R = H, Me
$R^1{}_2NH$ = piperidine, N-methylaniline, imidazole, triazole

Scheme 67.



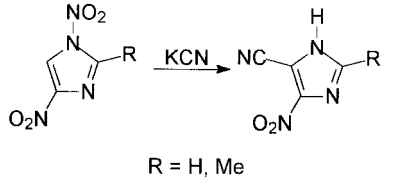
Scheme 68.

2-Methyl-1,4-dinitroimidazole reacts with iodide or azide anions to form 2-methyl-5(4)-(2-methyl-4-nitro-1-imidazoyl)-4(5)-nitroimidazole by *cine*-substitution of the 1-nitro group by 2-methyl-4(5)-nitroimidazole (which is formed during substrate denitration).[137]

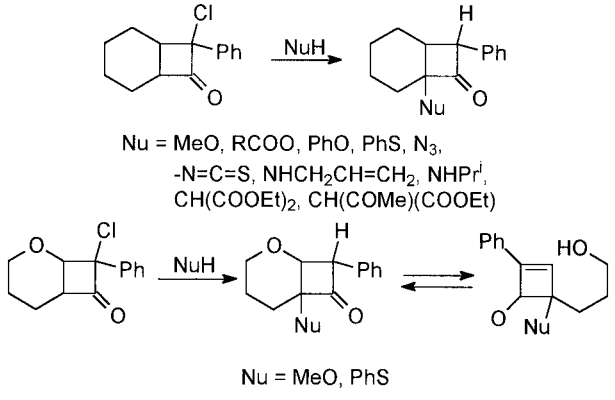
cine-Substitution is not observed if a nucleophilic reagent with a primary amino group is used, but then a reaction of degenerated transformation of the imidazole ring occurs which leads to the 1-substituted 4-nitroimidazole and nitroamide[163–166] (Scheme 68), but with 4-aminopyridine *cine*-substitution product was obtained.[166]

The recently described *cine*-substitution of 1,4-dinitroimidazoles by cyanide ion is the only method known so far for the preparation of 1-*H*-4(5)-cyanoimidazole (with labelled ^{13}C or ^{15}N cyano group, as well[137]), which is a convenient starting material in purine nucleoside synthesis. Good yields for the *cine*-substitution of 1,4-dinitroimidazole can be obtained in aqueous methanol in the presence of sodium bicarbonate[167] (Scheme 69).

A multistep *cine*-substitution of nitroporphyrins by sodium methoxide or phenyl methoxide was used in a highly unconventional but efficient synthesis of alkoxytetraphenylporphyrins.[168]



Scheme 69.



Scheme 70.

Examples of the title reactions are also known for azoles with leaving groups other than nitro. 1-Oxy-2-phenyltriazoles and 1-methoxy-2-phenyltriazolium salts with nucleophiles undergo *cine*-substitution in which the 1-oxy or 1-methoxy group, respectively, play the role of leaving groups.[169]

4. Nucleophilic *cine*- and *tele*-substitution in nonaromatic systems

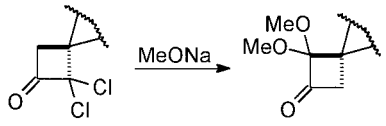
Theoretical calculations of nucleophilic substitution of, e.g. allyl chloride by chloride anion have been carried out using various ab initio methods. The mechanisms of possible processes and their probability have been discussed in comparison to potential barriers.[170]

The largest number of reactions of nonaromatic compounds described (in contradiction with IUPAC terminology[1]) as *cine*-substitution in the literature concerns the 2-haloketones. In particular much attention has been devoted to reactions between 2-chlorocyclobutanones and nucleophiles, which lead to 4-substituted cycloalkanones.[171–176] A typical example of these *tele*-substitution reactions is given below. In bicyclic systems, rearrangement reactions often accompanied *tele*-substitution[177] (Scheme 70).

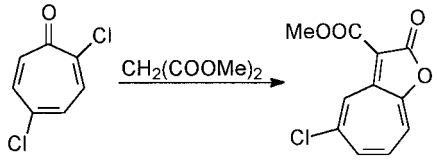
A review of their own studies on *tele*-substitution of 2-chlorocyclobutanones containing 5-, 6- and 7-membered rings has recently been published by Hassner and Naidorf-Meir.[178] See also review about cyclobutanones and cyclobutenones.[179]

A double nucleophilic *tele*-replacement of both chlorine atoms by methoxy groups was observed for some 2,2-dichlorocyclobutanones[180,181] (Scheme 71).

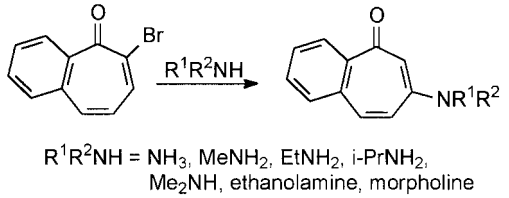
Similar reactions have been applied in the preparation of



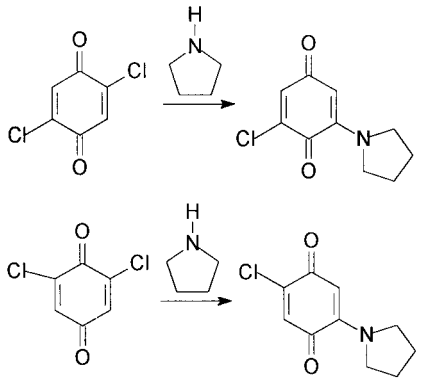
Scheme 71.



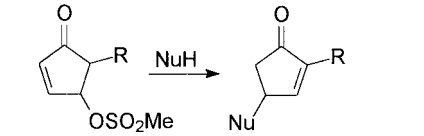
Scheme 72.



Scheme 73.

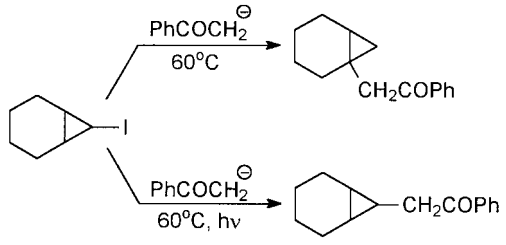


Scheme 74.

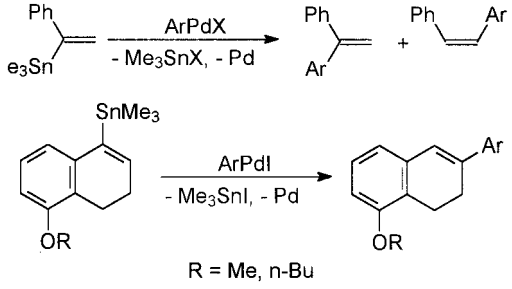


R = Me, i-Pr, $PhCH_2$, $PhCH_2CH_2$,
Nu = Br, PhS, $PhCH_2NH$, N_3, $CH(COOMe)_2$

Scheme 75.



Scheme 76.



Scheme 77.

derivatives of a series of naturally occurring compounds, e.g. steroids.[182,183]

2,5-Dichlorotropone when treated with dimethyl malonate in methanol in the presence of bases, undergoes the *tele*-substitution followed by an intramolecular condensation reaction shown in Scheme 72.[184]

The tropone derivatives treated with primary or secondary amines undergo *cine*-substitution[185,186] (Scheme 73).

The behaviour of bromotropone condensed with furan ring towards amines is similar.[187] There are many other reactions of troponoids with various nucleophiles.[188,189] Some of these reactions were utilized in the synthesis of derivatives of natural products,[190] e.g. colchicinoids and isocolchicinoids.[191–195]

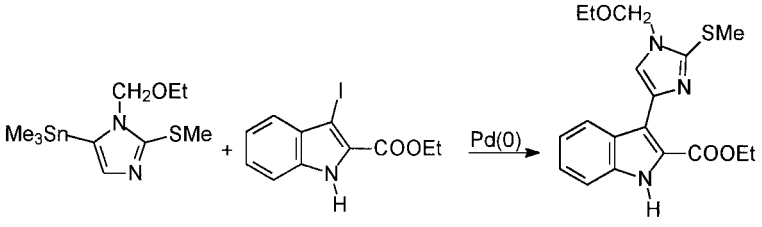
2,5-Dichloro- and 2,6-dichloro-1,4-benzoquinones react with the highly basic pyrrolidine to give products of *cine*-substitution of one chlorine atom[196] (Scheme 74).

Acyclic α-chloroketones could undergo such reactions, e.g. 1-chloro-3-phenoxy-1-phenylthio-2-propanone reacts with potassium acetate in acetic acid to give not only *ipso*-, but also *tele*-substitution product, 1-acetoxy-1-phenoxy-3-phenylthio-2-propanone.[197]

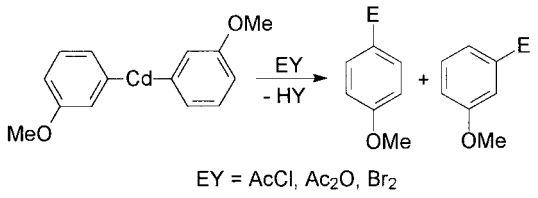
Pseudocine-substitution was used to describe the formation of 4-substituted 2-alkyl-2-cyclopentenones from 5-alkyl-4-mesitylenesulfonyl-2-cyclopentenones. Several nucleophiles have been used for substitution of the mesitylenesulfonyl group in this reaction[198] (Scheme 75).

A mixture (1:1) of isomeric *exo–endo* 7-iodobicyclo[4.1.0]-heptanes, in a reaction with the enolate anion of acetophenone, performed in the dark, gave also the *cine*-substitution product. The product of *ipso*-substitution was formed however as the result of a similar photostimulated transformation[199] (Scheme 76).

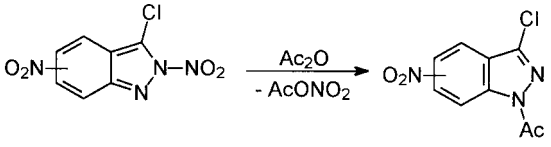
In recent years, many papers have been published on the Stille reaction which provides a convenient method for the stereoselective formation of a carbon–carbon bond.[200] In this reaction trialkylstannyl derivatives of α-substituted olefins, both in the open[201] and cyclic systems,[202] tend to undergo *cine*-substitution reaction[203] (Scheme 77). The appropriate choice of conditions however sometimes allows the regio- and stereoselectivity of the reaction to be controlled.[204] A reaction mechanism via Pd(0) carbenes is proposed, which excludes thermal anti β-elimination of PdH.[203,205]



Scheme 78.

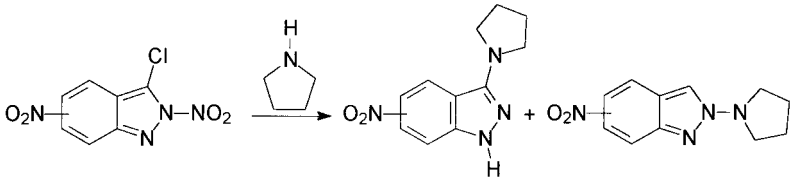


Scheme 79.



Scheme 80.

The behaviour of 3-chloro-2,5(or 6)-dinitroindazoles in the presence of cyclic amines at low temperatures (0–20°C) is also interesting. Under these conditions, the chlorine atom is *ipso*-substituted, and the *N*-nitro group is replaced by the hydrogen atom, which combines with the nitrogen atom in position 1. The latter reaction step can be considered as electrophilic *cine*-substitution of the nitro group by the hydrogen atom. Apart from the above-mentioned reaction, nitro group replacement was observed in position 2 by amine residual. From the reactions also 2-(*N*,*N*-dialkylamino)-5(or 6)-nitroindazoles were obtained as by-products (Scheme 81). At 90°C the product containing the N—N bond rearranged to the 3-amino derivative.[209] The mechanism of the reactions is not clear.



Scheme 81.

It is of interest to note that *cine*-substitution in the Stille reaction has also been observed in heterocyclic systems. The reaction of the trimethylstannyl derivative of imidazole with the iodoindole shown in Scheme 78 is of this type.[206]

The cross-coupling reaction 1-(fluorodimethylsilyl)-1-phenylethene with aryl iodides promoted by a palladium catalyst gives not only normal *ipso*- but also *cine*-substitution product 1-aryl-2-phenylethenes.[207]

5. Electrophilic *cine*- and *tele*-substitution

It was reported 21 years ago that *cine*-substitution of di-(3-methoxyphenyl)cadmium took place under the influence of typical electrophilic reagents, such as molecular bromine, acetyl chloride or acetic anhydride, and that good yields of *p*-substituted anisole derivatives were obtained[208] (Scheme 79).

3-Chloro-2,5(or 6)-dinitro-2*H*-indazole treated with acetic anhydride undergoes acetylation on the nitrogen atom in position 1. This is accompanied by departure of the nitronium cation from position 2. Electron pairs are then shifted to reproduce a π aromatic sextet in the benzene ring condensed with pyrazole[209] (Scheme 80).

Scheme 82.

As electrophilic *tele*-substitution in aliphatic system the formation of 1-alkyl-2-methoxymethyloxirane from 2-hydroxyalkyloxirane and alkylating agent was described[210] (Scheme 82). According to criteria assumed in our study, it would not be a *tele*-substitution but rather *O*-alkylation involving oxirane ring opening–ring closure reactions.

6. Conclusions

cine- and *tele*-Substitution reactions are well widespread in organic chemistry though only in some cases they are sole reactions not accompanied by other processes. Most studies decidedly concern nucleophilic *cine*- or *tele*-substitution in homoarene derivatives or their complexes with metals, and in heteroarenes. These reactions have found interesting applications in syntheses of lesser available derivatives of the starting materials. Occasionally examples of *cine*- and *tele*-substitutions in aliphatic systems are described and investigated, being more common and useful in syntheses of bicyclic compounds. A few papers only discuss electrophilic aromatic *cine*-substitution. This field requires further investigations. Some of the reactions, which satisfy formal criteria of *cine*- and *tele*-substitution definition, are otherwise depicted in the literature.

Acknowledgements

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