

Review

Tele-substitutions in Heterocyclic Chemistry

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Abstract

Particular and rare examples of aromatic nucleophilic substitution are described as *tele*-substitution. Usually strong nucleophiles are involved and the entering group is introduced at a position distant from the expected leaving group. Examples of *tele*-substitution in various heteroaromatic systems are presented.

Keywords: *Tele*-substitution, heteroaromatic five-, six-membered, bicyclic and polycyclic systems.

1. Introduction

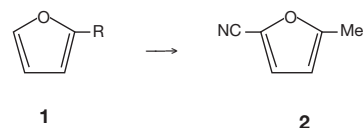
In general, nucleophilic substitution reactions of aromatic or heteroaromatic compounds occur at the same position of the leaving group (*ipso*-substitution). However, there are some exceptions – a substitution reaction can take place at a position more than one atom away from the atom in which the leaving group was attached and is called a *tele*-substitution. On the other hand, when the entering group takes up a position adjacent to that occupied by the leaving group, this is called a *cine*-substitution (IUPAC Gold Book).¹ Previously, in the 1980s, such substitutions were designed as “abnormal” substitutions. Moreover, a nucleophilic aromatic substitution can occur in special cases with replacement of a hydrogen atom and not a halogen atom or other leaving group and this kind of reaction is called *vicarious nucleophilic substitution* (VNS). A more complicated mechanism occurs under the action of a strong nucleophile (e.g. amide anion); ring opening of the heterocyclic ring with subsequent cyclization, representing the ANRORC mechanism (Addition of the Nucleophile, Ring Opening, and Ring Closure).

In this article we like to deal only with *tele*-substitution involving heterocyclic systems.

2. Five-membered Heterocycles

In the five-membered heterocycles several *tele*-substitutions were recorded. In an earlier described reaction between α -furfuryl chloride (**1**, R = CH₂Cl) with an aqueous solution of cyanide ion the reaction product was assigned

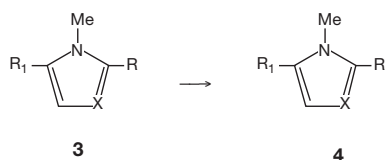
to be an *ipso*-substitution product. Later, however, it was established that the product was actually 5-cyano-2-methylfuran (= 2-cyano-5-methylfuran) (**2**). Its structure was established after hydrolysis into 5-methylfuroic acid. The reaction with the cyanide is thus an early example of *tele*-substitution.² The same compound (**2**) was obtained as the major product when 2-furfuryltrimethylammonium iodide (**1**, R = CH₂NMe₃⁺I⁻) was treated with sodium cyanide in the absence of solvent at 180–200 °C.³ For this *tele*-substitution a tentative mechanism was proposed. It was also established that related 2-chloromethylthiophene or benzyl chloride are not transformed in this way.⁴



2-(*N*-methylpyrrolyl)trimethylammonium salts (**3**, X = CH, R = CH₂NMe₃⁺, R₁ = H) when treated with sodium cyanide at elevated temperature afforded among other products also 1,2-dimethyl-5-cyanopyrrole (**4**, X = CH, R = Me, R₁ = CN), a product of *tele*-substitution. With variation of temperature and solvent it could be observed that *tele*-substitution is greatly dependent on the reaction medium and yields were in the range of 10–40%.⁵

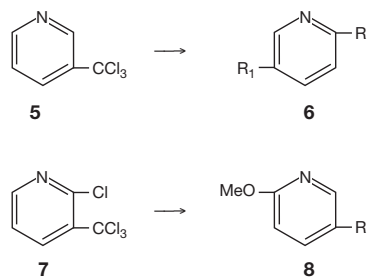
When 5-bromo-1-methylimidazole (**3**, X = N, R = H, R₁ = Br) was treated with lithium piperidide and piperidine in boiling ether among other products also 1-methyl-2-piperidinoimidazole (**4**, X = N, R = NC₅H₁₀, R₁ = H), a *tele*-substitution product, was formed in 16% yield. The

corresponding 5-chloro analog yielded the same product in low yield (3–5%).⁶

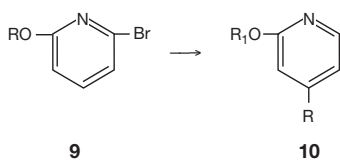


3. Six-membered Heterocycles

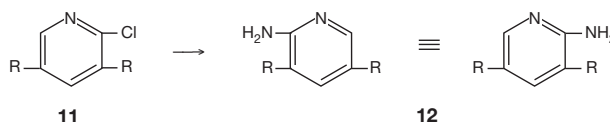
There are several examples of *tele*-substitution in the pyridine series. 3-Trichloromethylpyridine (**5**) reacted with various nucleophiles by an attack at position 5 to give 5-substituted pyridines. With sodium phenoxide at elevated temperature a mixture of 2-phenoxy-5-carbaldehyde (**6**, R = OPh, R₁ = CHO) and the corresponding 5-diphenoxymethyl analogue [**6**, R = OPh, R₁ = CH(OPh)₂] were formed in low yield. A similar *tele*-substitution occurred with thiophenol and methyl thioglycolate to give **6** (R = SPh or SCH₂COOMe, R₁ = CHCl₂) in high yield. Similarly, the reaction with morpholine in acetonitrile under reflux afforded **6** [R = N(CH₂)₄O, R₁ = CHO] whereas at room temperature the trichloromethyl group was attacked. Analogous reactions at position 6 were observed in the case of 3-trichloromethylpyridine-*N*-oxide with the *N*-oxide group remaining unaffected.⁷ When 2-chloro-3-trichloromethylpyridine (**7**) was treated with methoxide ion the methoxy group entered at position 6 and the trichloromethyl group was converted either into an acetal or aldehyde [**8**, R = CH(OMe)₂ or CHO].^{8,9}



2-Bromo-6-alkoxy-pyridines (**9**, R = Me, Et) reacted in a solution of the potassium salt of pentanone-3 in liquid ammonia to give among other products also *tele*-substitution products such as the 4-amino (**10**, R = NH₂, R₁ = Et) and 4-pentanone substituted derivatives [**10**, R = CH(Me)COEt, R₁ = Et].¹⁰ Moreover, 2-bromo-6-ethoxypyridine (**9**, R = Et) when treated with KNH₂/NH₃ yielded as by-product in 14% yield the corresponding *tele*-product, 4-amino-6-ethoxypyridine (**10**, R = NH₂, R₁ = Et).¹¹

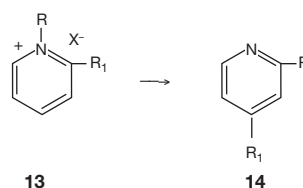


Amination of 2-chloro-3,5-dinitropyridine (**11**, R = NO₂) in liquid ammonia containing potassium permanganate, followed by ¹³C NMR spectra measurements revealed that at –40 °C addition at C-6 has occurred to give a thermodynamically stable *tele*-addition intermediate and then **12** (R = NO₂) as the end product. At lower temperature (–60 °C) the addition occurred at C-4 to give a kinetically controlled *tele*-adduct.¹²

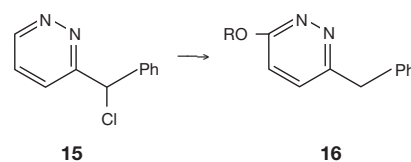


N-fluoropyridinium tetrafluoroborate (**13**, R = F, R₁ = H, X = BF₄) reacted with weakly-basic C-nucleophiles at position 4. Examples of *tele*-substitution, which is influenced by the nature of the carbanion and reaction conditions, involve anions of trinitromethane and ethyl nitroacetate [**14**, R = H, R₁ = C(NO₂)₃CH(NO₂)COOEt]. A reaction mechanism was proposed.¹³ Although *N*-fluoropyridinium salts are used as fluorinating agents they display also other reactivities, among them nucleophilic aromatic *tele*-substitution.¹⁴

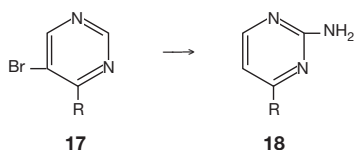
Cyanation of 1-(*N*-methylacetamido)-2-methylpyridinium iodide [**13**, R = N(Me)COMe, X = I] in aqueous solution afforded 4-cyano-2-methylpyridine in 88% yield (**14**, R = Me, R₁ = CN).¹⁵



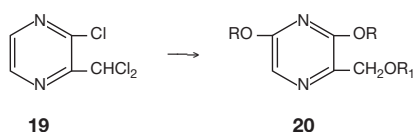
In the case of pyridazines, 3- α -chlorobenzylpyridazine (**15**) when heated with different sodium alkoxides afforded *tele*-substituted 3-benzyl-6-alkoxy-pyridazines [**16**, R = Me, Et, (CH₂)₂NMe₂] with simultaneous dehalogenation. Alkoxides were prepared from methanol, ethanol, and dimethylaminoethanol and yields were in the range of 11–77%.¹⁶



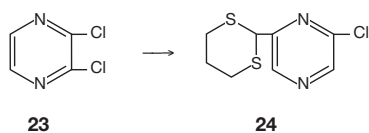
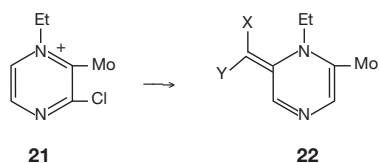
Several 4-substituted-5-bromopyrimidines were investigated and treated with strong nucleophiles, but only 5-bromo-4-piperidinopyrimidine [**17**, R = N(CH₂)₅] afforded with KNH₂/NH₃ a *tele*-substitution product, namely 2-amino-4-piperidinopyrimidine [**18**, R = N(CH₂)₅] in low yield (4–6%).¹⁷



Tele-substitutions were reported also in the pyrazine series. Treatment of 2-chloro-3-dichloromethyl pyrazine (**19**) with three equivalents of methoxide ion afforded 2,6-dimethoxy-3-methoxymethylpyrazine (**20**, R, R₁ = Me, referred also as 3,5-dimethoxy-2-methoxymethylpyrazine), the methoxy group entering at position 6. Similarly, the reaction with one equivalent of ethoxide ion afforded as the principal product 2-chloro-3-chloromethyl-6-ethoxypyrazine.

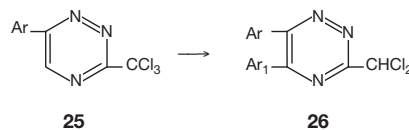


Tele-substitution occurred also in the case of 2-trichloromethylpyrazine with methoxide ion to give a mixture of di-, tri- and tetrasubstituted products.¹⁸ 3-Chloro-1-ethyl-2-morpholinopyrazinium salts [**21**, Mo = N(CH₂)₄O] were treated with various C-nucleophiles of the type X-CH₂-Y (X, Y = CN, COOEt, COMe) to give 6-substituted derivatives with an alkylidene side chain [**22**, Mo = N(CH₂)₄O; X, Y = CN, COOEt, COMe].¹⁹ In another case, 2,3-dichloropyrazine (**23**) when treated with lithio-1,3-dithiane at -70 °C produced *tele*-substituted product 2-chloro-6-(1',3'-dithian-2'-yl)pyrazine (**24**). Its structure was confirmed by deuterium labeling and X-ray determination.²⁰



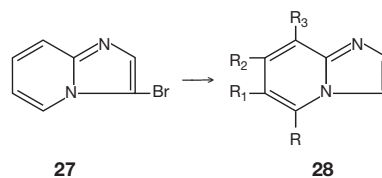
6-Aryl-3-trichloromethyl-1,2,4-triazines (**25**, Ar = phenyl, 4-chlorophenyl or 4-methylphenyl) were transformed with indole or 1-methylindole in the presence of a catalytic amount of hydrochloric or trifluoroacetic acid into 6-aryl-3-dichloromethyl-5-(indol-3-yl or 1-methylindol-3-yl)-1,2,4-triazines [**26**, Ar₁ = 3-indolyl or 3-(1-methylindolyl)] in 60–70% yield. *Tele*-substitution is accompanied by elimination of one of the chlorine atoms in the trichlo-

romethyl group. It was further reported that phenols reacted in an analogous manner as C-nucleophiles (2,6-dimethylphenol, resorcinol or 4-hexylresorcinol). Phenols reacted at their *ortho*- or *para*-positions in the C-C bond formation with triazines.^{21, 22}

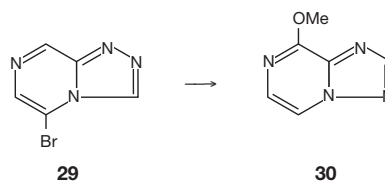


4. Bi- and Polycyclic Heterocyclic Compounds

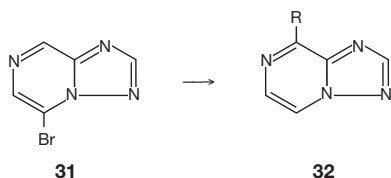
There are also several cases reported for bicyclic heterocyclic compounds. For 3-bromoimidazo[1,2-a]pyridine (**27**) *tele*-substitutions were observed. With ethylamine anion as a minor product 6-bromo-7-ethylaminoimidazo[1,2-a]pyridine (**28**, R₁ = Br, R₂ = EtNH, R, R₃ = H, 2.5 %) was identified. Its formation is explained by postulating electrophilic substitution at position 6 followed by *tele*-substitution of the bromine atom at position 3. In a similar reaction with lithium diethylamide several *tele*-substituted products were obtained: the 5- (**28**, R = NEt₂, R₁, R₂, R₃ = H, 4%), 7- (**28**, R₂ = NEt₂, R, R₁, R₃ = H, 13%), 8-diethylamino compound (**28**, R₃ = NEt₂, R, R₁, R₂ = H, 9%), and the 5,7-bis(diethylamino) compound (**28**, R = R₂ = NEt₂, R₁, R₃ = H, 1%). With KNH₂ compound **27** yielded among other products 6-aminoimidazo[1,2-a]pyridine (**28**, R₁ = NH₂, R, R₂, R₃ = H) in 50% yield.²³



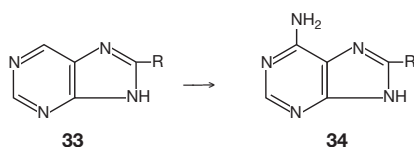
5-Bromo-*s*-triazolo[4,3-*a*]pyrazine (**29**) reacted with sodium methoxide at room temperature to give a mixture of the *ipso*-substitution product and the 8-methoxy derivative (**30**) as an example of *tele*-substituted product.²⁴



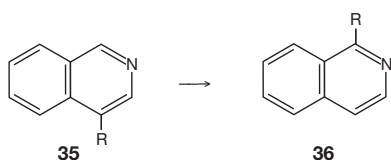
Also 5-bromo-*s*-triazolo[1,5-*a*]pyrazine (**31**) when treated with hydrazine, hydroxylamine or liquid ammonia afforded the corresponding 8-substituted derivatives (**32**, R = NH₂, NHOH, NHNH₂) as a result of *tele*-substitution.²⁵



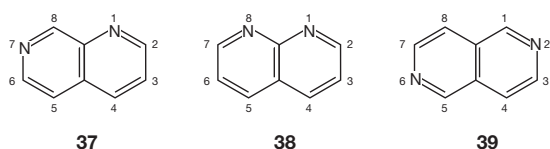
8-Chloropurine (**33**, R = Cl) when treated with potassium amide in liquid ammonia yielded adenine (**34**, R = H) as the main product (30%) together with 8-chloroadenine (**34**, R = Cl, 10%). In a similar manner 8-(methylthio)purine (**33**, R = SMe) afforded 8-methylthioadenine (**34**, R = SMe) in 80% yield.²⁶



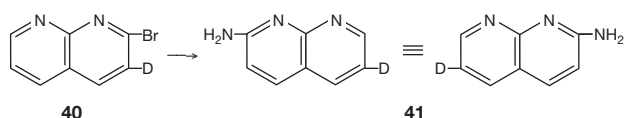
4-Halogenoisoquinolines (**35**, R = Cl, Br, I) after treatment with KNH_2 in liquid ammonia were transformed into 1-aminoisoquinoline (**36**, R = NH_2) in 4–17% yield. In an analogous transformation with piperidine 1-piperidinoisoquinoline [**36**, R = $\text{N}(\text{CH}_2)_5$] was obtained in 3–17% yield.²⁷



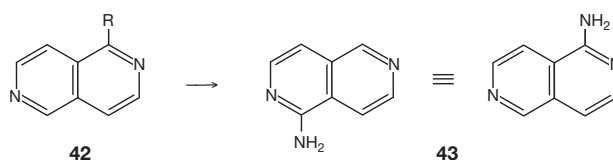
Extensive investigations were performed with 1,7- (**37**), 1,8- (**38**) and 2,6-naphthyridines (**39**). 8-Chloro-1,7-naphthyridine afforded after treatment with KNH_2/NH_3 a small amount of the *tele*-substituted 2-amino-1,7-naphthyridine in low yield (5%).^{28, 29} On the other hand, 2-chloro- or 2-bromo-1,7-naphthyridine upon treatment with KNH_2/NH_3 yielded two *tele*-substitution products, 4-amino-1,7-naphthyridine (1,2% from the chloro and 3.6% from the bromo starting compound) and 8-amino-1,7-naphthyridine (9.4% from the chloro and 1.0% from the bromo starting compound).³⁰ 5-Bromo- or 5-chloro-1,7-naphthyridine underwent *tele*-amination with KNH_2 in liquid ammonia to give 8-amino-1,7-naphthyridine (42% from the bromo and 1% from the chloro starting compound) and 2-amino-1,7-naphthyridine (17% from the bromo starting compound) as well as 8-amino-5-chloro-1,7-naphthyridine (4% from the chloro starting compound). The reaction with the chloro analogue proceeded very slowly.³¹



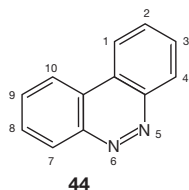
An interesting example provided the reaction at position 3 deuterated 2-bromo-1,8-naphthyridine (**40**) which was after treatment with KNH_2/NH_3 transformed in 40% yield into 7-amino-3-deuterio- (actually 2-amino-6-deuterio) -1,8-naphthyridine (**41**) thus presenting a clear evidence for *tele*-substitution.³² From NMR evidence it became clear that the intermediate δ -adduct occurred at position 7 giving the *tele*-substituted product. Also in the case of the related deuterated 2-chloro derivative it was established that replacement of the chlorine atom with the amino group occurred partly (~8%) via a *tele*-substitution process.³³ In the last mentioned publication (ref. 7) it was stated that upon amination of 2-bromo-7-deuterio-1,8-naphthyridine *tele*-substitution proceeded with 27%. However, more exact method of calculation revealed later that the extent of this transformation was 45%.³²



1-Bromo- (**42**, R = Br) or 1-chloro-2,6-naphthyridine (**42**, R = Cl) when treated with KNH_2 in liquid ammonia afforded among other products also 5-amino-2,6-naphthyridine (= 1-amino-2,6-naphthyridine (**43**) as a *tele*-substitution product in 28% or 20% yield. From NMR evidence it was suggested that as intermediate adduct at position 5 is formed. Without this evidence the reaction would formally appear as normal *ipso*-substitution. Experiments involving deuterated and undeuterated starting 1-chloro compound revealed from the kinetic isotope effect that *tele*-amination of the undeuterated compound proceeded about 13 times faster than the normal *ipso*-substitution. In both cases also the 1,5-diamino compound was formed (17% or 14% yield).³⁴



Investigations of *tele*-substitution were performed also with the tricyclic benzo[c]cinnoline system (**44**). 1-Chlorobenzo[c]cinnoline when treated with lithiated dimethylamine afforded a mixture of 1-chloro-4-dimethylamino- and 1-chloro-7-dimethylamino derivatives together in 72% yield. Similarly, *tele*-substitution was observed with 2-chlorobenzo[c]cinnoline to give 2,4,7-tris(dimethylamino)benzo[c]cinnoline in 33% yield.^{35,36} Also 4-chlorobenzo[c]cinnoline afforded with KNH_2/NH_3 as *tele*-product 2-aminobenzo[c]cinnoline in low yield (5%).³⁷



5. Conclusion

Increasing knowledge and detailed investigations concerning (hetero)aromatic nucleophilic substitutions have lead to discovery of several kinds of unusual reaction paths. Among them, *tele*-substitution has been found to occur with several heterocyclic systems and a summary of them is presented in the present review article.

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Povzetek

Posebne in redke primere aromatske nukleofilne substitucije predstavljajo reakcije *tele*-substitucije. Običajno potekajo pri uporabi jakih nukleofilov tako, da se ne zamenja pričakovana izstopajoča skupina, ampak se veže nukleofil na bolj oddaljeno mesto. Prikazani so znani primeri *tele*-substitucije na heteroaromatskih sistemih.