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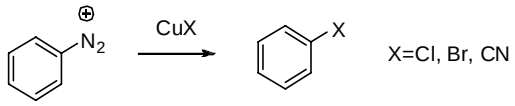
Transformation of Primary Amines into Alternative Functional Groups

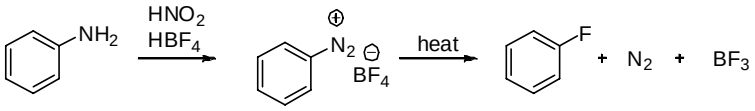
The transformation of an alcohol into an alternative functional group is relatively facile and common in organic synthesis (*via* e.g. Mitsunobu reaction, or conversion to the sulfonic ester and displacing with a nucleophile).[1]

Scheme 1: *transformation of hydroxyl group*

When the group to be converted is a primary amine rather than a hydroxyl, the transformation is not as straightforward. For aromatic amines, it is possible to diazotise and then perform e.g. a Sandmeyer (Scheme 2) or Balz-Schiemann (Scheme 3) reaction to install a halide.[2]



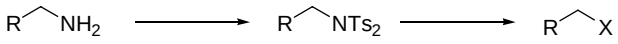
Scheme 2: *Sandmeyer reaction*



Scheme 3: *Balz-Schiemann reaction*

It is also possible to heat with water to form the phenol or with sulfur-containing groups to generate the thiophenol derivatives. However, diazonium ions generated from primary aliphatic amines are generally of little preparative use due to their tendency not only to react with any nucleophile present, but also to undergo any possible rearrangements and eliminations to give a mixture of products.

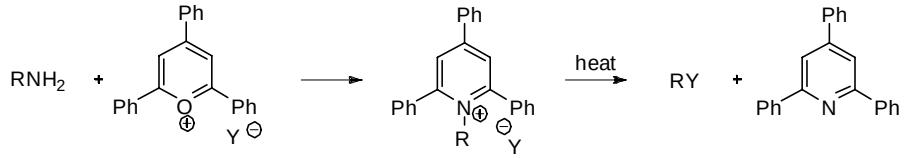
An alternative method is to convert the amine into a ditosylate to enhance its leaving group ability.[3]



Scheme 4: *substitution of ditosylate derivatives of amines*

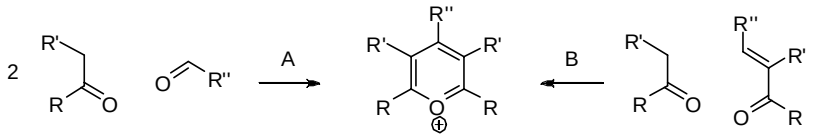
Nucleophiles used here have mainly been NaSPh, NaSePh and halides,[4] and the reaction generally requires heating to >140 ºC. Attempts to use hydroxide or cyanide as nucleophiles led to *N-S* bond cleavage rather than the desired *N-C*, so alternative methods for installation of a hydroxyl were developed. The first employed 85% aqueous HI in DMF at 100 ºC for several days, but these conditions were harsh and led to complications. A slightly milder method involved conversion of the sulfonimide to either the 3,5-dinitrobenzoate or tosylate ester by heating to 140 ºC in DMF with lithium dinitrobenzoate or lithium tosylate for 24h; however, the yields were still somewhat variable and some alkene formation was observed.[5]

However, an ingenious method developed by Katritzky and co-workers allows conversion to a wide variety of functional groups, this time going through the pyridinium salt, mediated by the pyrilium, Scheme 5.[6] A variety of pyrilium salts have been screened, but the most commonly used is the 2,4,6-triphenyl species. The 2- and 6-phenyl substituents are found to be important in steric acceleration of the N-C bond heterolysis and the high stability and leaving group ability of 2,4,6-triphenyl pyridine acts as a driving force for the substitution reaction. If the counteranion Y is nucleophilic, this does the substitution. If it is non-nucleophilic, e.g. tetrafluoroborate or perchlorate, then an external nucleophile may be used.



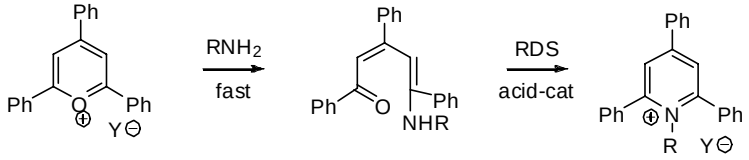
Scheme 5: *conversion of a primary amine into another functional group mediated by a pyrilium species*

The pyrilium salts are generally made by one of the following methods:



Scheme 6: *pyrilium syntheses*

Method A can only be used for symmetrical species, whereas B is for either symmetrical or unsymmetrical cases. The procedure is catalysed by acid, generally perchloric acid or boron trifluoride etherate.[7] The chalcone intermediate functions as a hydride abstracting agent. If an alternative counterion is required, the readily available pyrilium tetrafluoroborate or perchlorate is reacted with weak base to form the unsaturated 1,5-diketone, which is then treated with the relevant acid to give the pyrilium cation in association with the desired anion. The 2,4,6-triphenyl pyridinium species is formed by treating a slight excess of the amine at room temperature with the pyrilium salt in ether or dichloromethane, Scheme 7.



Scheme 7: *formation of the pyridinium species*

The reaction typically takes 3-12 hours, and if carried out in ether, the product separates out as it is formed. Sluggish reactions may be accelerated by addition of acetic acid.

Scope of Nucleophiles Used[6]

1. Counterion acts as nucleophile

- Used in formation of halides, trifluoroacetate, nitrate ester and thiocyanate species.
- Yields of halides are particularly good, RI and RBr typically being formed in ~80% yield.
- Formation of fluorides and chlorides requires azeotropic distillation of water away from the pyrilium salt to allow crystallisation; however, this then allows almost quantitative formation of chlorides and high yields of fluorides, when there had previously been no convenient method to carry out this transformation.
- Procedure may also be carried out on neopentyl substrates to generate neopentyl halides, not readily prepared by S_N2.

2. External nucleophile

- Non-nucleophilic counterion required, e.g. tetrafluoroborate, perchlorate.
- 2,4,6-Triphenyl pyrilium tetrafluoroborate may be heated with sodium acetate or benzoate at 180 ºC to form the readily-hydrolysed ester, thus giving easy access to the alcohol.
- Sodium succinimide and potassium phthalimide, sodium azide and sodium salts of *N*-substituted sulfonamides may also be used to install alternative nitrogen functionality.
- *C*-alkylation of nitronate anions is possible in DMSO to generate *C*-alkylated nitro compounds in ~60% yield, despite the normal tendency for *O*-alkylation. It is postulated that

this reaction proceeds *via* a non-chain radicaloid mechanism involving a charge-transfer complex.

- $NaBH_4$ may be used to reduce to the alkane if heated at 180-200 ºC. This reaction proceeds *via* pyrolysis of the 1,4-dihydropyridine derivative.
- It is also possible to use either morpholine or pyrrolidine to generate a tertiary amine.

Further Developments

This work has been extended to allow modifications of primary amines in natural products, without affecting other functional groups. This requires the preparation of water-soluble pyrilium salts, such as tris(sulfophenyl)pyriliums, Figure 1.[8]

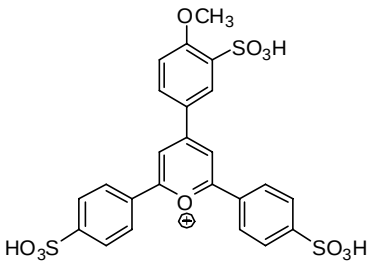


Figure 1: *a water-soluble pyrilium salt*

The terminal amino group in lysine has been replaced in this way by both PhS and $PhCH_2S$ groups in aqueous solution below 75 ºC, and an analogous transformation has been effected on glycyl glycine. This work provides a model for modification of lysine and glycine residues in proteins.

A further recent extension involves transformation of chiral amines.[9] This proceeds with almost complete inversion of configuration and has been used for preparation of the alcohol and azide, the latter being conveniently reduced with H_2/Pd to yield the enantiomeric amine. The overall procedure is operationally easier than the alternative of making the disulfonyl derivative and displacing, and the yields and stereoselectivities are generally higher.

Summary

- Pyrilium reagents have high molecular weight, so method unlikely to be used for simple species where just as easy to make the analogous halide or tosylate and react that.
- However, where the above transformation fails, it is very useful: e.g. *C*-alkylation of nitroalkane anions, preparation of alkyl fluorides.
- Also useful where the amino compound is much more accessible (e.g. from natural sources) than the corresponding halide/alcohol.
- Useful for selective conversion of amino groups, since pyriliums are unreactive with almost all other functional groups found in common natural products. The development of water-soluble pyriliums allows specific transformation of protein NH_2 groups under mild aqueous conditions.

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[1] J. March, *Advanced Organic Chemistry*, 4th Ed; Wiley: New York, **1992**, p353.
[2] *ibid*., 669-671.
[3] Muller; Thi *Helv. Chem. Acta* **1980**, *63*, 2168; Curtis; Knutson; Baumgarten *Tetrahedron Lett*. **1981**, *22*, 199. and references therein.
[4] DeChristopher; Adamek; Lyon; Galante; Boggio; Baumgarten *J. Am. Chem. Soc*. **1969**, *91*, 3284.
[5] Curtis; Schwartz; Hartman; Pick; Kolar; Baumgarten *Tetrahedron Lett*. **1977**, *23*, 1969.
[6] Katritzky *Tetrahedron* **1980**, *36*, 679; Katritzky; Marson *Angew. Chem. Int. Ed. Engl*. **1984**, *23*, 420.
[7] Representative synthesis: Van Allan; Reynolds *J. Org. Chem*. **1968**, *33*, 1102.
[8] Katritzky; Yang *J. Chem. Soc. Perkin Trans. II*, **1984,** 885.
[9] Said; Fiksdahl *Tetrahedron: Asymmetry*, **2001**, *12*, 1947.