EASY AND EFFICIENT S_NAr REACTIONS ON HALOPYRIDINES IN SOLVENT FREE CONDITIONS

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Abstract - Solid-liquid phase transfer catalysis (PTC) without added solvent efficiently promotes S_NAr reactions on halopyridines with a variety of anionic nucleophiles generated in situ. This methodology gives access to substituted pyridines in very simplified conditions depending on halide nature. Mechanistic investigations are proposed.

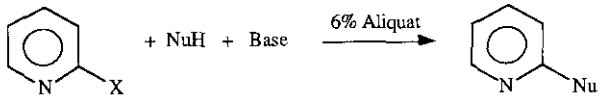
We have recently reported that some S_NAr reactions can be carried out efficiently under solid-liquid phase transfer catalysis (PTC) *in the absence of any organic solvent.*[1] We describe therein an extension to heterocyclic substrates giving access to very active products in therapeutic field (antiarythmic, antiulcer, diuretic and antiinflammatory activities).[2-4]

We thus have studied the behaviour of some typical anionic species : oxyanions with more or less localized charges, and consequently different reactivities [focused charge alkoxide $PhCH_2O^-$, delocalized one PhO^-], as well as carbanions α to aromatic ring. In all these cases, anions are prepared in situ by simple mixing the conjugated acid of involved nucleophiles ($PhCH_2OH$, PhOH or PhCHRCN) in the presence of adequate amount of pulverized solid base and catalytic quantity of Aliquat 336 as transfer agent.

RESULTS AND DISCUSSIONS

Different 2-halopyridines were tested in order to appreciate the leaving group effect (X = F, Cl or Br) on reactivity and yields. With these susbtrats, yields are rather poor and limited when KOH is used as a base ; they are largely improved with KO^tBu showing thus the necessity of a stronger base. The main results are indicated in Table I.

Table I



Relative amounts = 1.5 : 1 : 2

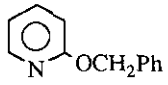
NuH	Base	Time (h)	Temperature (°C)	X	Yield (%)
PhOH	KO^{t}Bu	4	120	F	69[a]
				Cl	10[a]
				Br	50[b]
$PhCH_2OH$	KO^{t}Bu	2	120	F	75[a]
				Cl	85[a]
				Br	93[a]
Ph_2CHCN	KO^{t}Bu	2	120	F	5[b]
				Cl	41[b]
				Br	52[a]
$PhCH_2CN$	KO^{t}Bu	1	85	Cl	47[b]
				Br	52[a]
Ph-CH(Me)-CN	KO^{t}Bu	1	85	Cl	46[a]

(a) Isolated yields.
(b)Glc yield, using an internal standard.

It is obvious to point out that satisfactory yields are reached with PhO^- and $PhCH_2O^-$ (69 and 93% respectively). The halide effect is rather important, the best situations being fluorine with phenolate anion and bromine with benzyl alkoxide. In the case of arylacetonitrile anions, yields are limited to about 50% with chloro- and bromopyridines whereas fluorinated substrate is almost inactive.

COMPARISON WITH LITERATURE DATA

For comparative purposes with the recent different methods from literature, we have collected below the heterogeneous S_NAr reactions giving access to the different products.

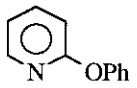
2-Benzyloxypyridine 

The result we obtained in solvent-free conditions (85% within 2 hours at 120°C) can be compared to those described from 2-chloropyridine :

- 84% with KOH or K_2CO_3 in toluene within 4 hours at 120°C in the presence of TDA-1[5] as transfer agent,
- 80% with KOH in toluene within 1 hour at 110°C in the presence of 18-crown-6 under nitrogen and using a Dean-Stark apparatus.[6]

It is obvious to conclude that our method leads to an interesting result (the same as published) in very mild conditions where solvent is avoided. Our method is furthermore characterized by very simplified and easy work up.

This product can be, in an alternate process, synthesized with poorer yields by selective *O*-alkylation of 2-pyridinol with benzyl bromide in the presence of silver carbonate in pentane.[7]

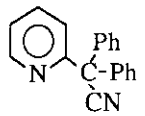
2-Phenoxypyridine 

Classical liquid-liquid PTC conditions are non-operative with 2-chloropyridine : according to Alsaidi,[8] the system aq. NaOH/^{n}Bu$_4$Cl/benzene does not lead to any result even after 24 hours at 95°C.

Under solid-liquid PTC conditions, Abele[9] obtained 72% yield within 10 hours at 145°C in *o*-xylene by reacting 2-bromopyridine with potassium phenoxide in presence of dibenzo-18-crown-6.

In our hands, in solid-liquid PTC without solvent, yields are poor (10%) with 2-chloropyridine; they are enhanced up to 69% using 2-fluoropyridine, showing thus the decisive role of halide nature.

The interest of this method is evident when one considers the simplification of the work-up and the low cost of products involved.

2-Pyridinyldiphenylacetonitrile 

According to Alsaidi conditions,[8] we did not observe any product by liquid-liquid PTC. In our hands, the use of $NaNH_2$ either in toluene or liquid ammonia led to about 50% yield. Under solid-liquid PTC without solvent conditions, we remove 52% product in very simple and easy-to-perform process (KO^{t}Bu + Aliquat, 2 hours at 120°C).

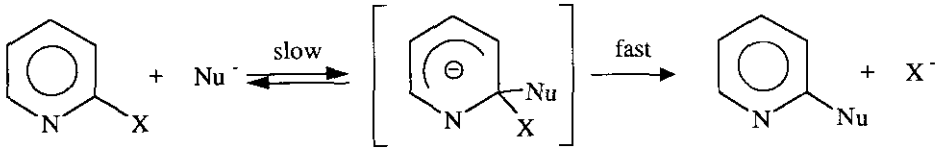
In this case, better yields (about 76%) were obtained by Moon,[10] then Wolfe[11] performing the reaction under near-UV irradiation with $NaNH_2/NH_3$ under nitrogen with special equipments. In consideration of these conditions, our method is highly competitive when one considers its simplicity and efficiency.

HALIDE EFFECT - MECHANISTIC CONSIDERATIONS

The quite surprising effects of halide nature led us, for comprehensive purpose, to try to determine the mechanisms in the different cases.

Three main mechanisms are generally evoked for nucleophilic aromatic substitution:[12,13]

i) Addition-Elimination process[14-16]

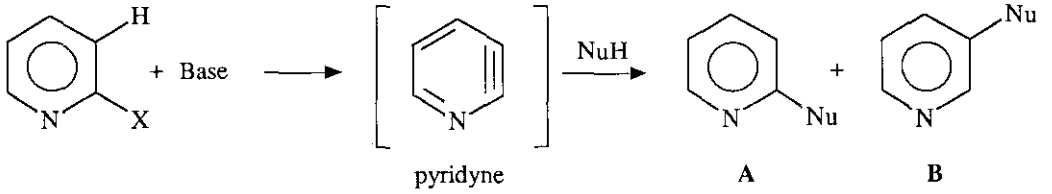


In this mechanism, two possibilities can be considered :

- a charge controlled reaction[17] especially when charge localized anionic species are involved (and HOMO very low in energy) such as RO^-. The halide effect is connected to their ability to develop a stronger charge on carbon atom, i.e. their electronegativity : C-F > C-Cl > C-Br > C-I.
- a frontier orbital controlled reaction when soft nucleophiles (charge delocalized species with high HOMO levels) such as aromatic carbanions α to nitrile.[18] In this situation halide effect is connected to LUMO (σ^*_{C-X}) levels ; the reactivity is enhanced according to the sequence C-I > C-Br > C-Cl > C-F,[19] i.e. the lower LUMO level the more electrophilic system.

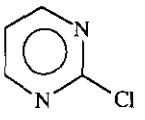
Elsewhere, when neutral nucleophiles are involved (i.e. HNR_2), the same sequence is observed, a fact which is attributed to reversal in relative kinetically determining step, the second becoming the determining one.[20,21]

ii) Elimination-Addition process via aryne intermediate[13,22]



This type of mechanism is favoured when strong bases are involved. As limiting step is HX β-elimination, the reactivity sequence is the following : ArI > ArBr > ArCl > ArF.

Quantum chemical calculations[23] indicate that, according to this mechanism via this intermediate, substitution may occur exclusively on carbon adjacent to nitrogen and consequently lead to unique **A**. So, in order to determine if this mechanism can be operative, it is obvious to test the behaviour of 2-chloropyrimidine, substrate where such a process is impossible for lack of labile hydrogen α to halide.



iii) Radical Chain Mechanism ($S_{RN}1$)[24-26]

$$ArX + Nu^- \longrightarrow [ArX]^{\bullet -} + Nu^{\bullet}$$
$$[ArX]^{\bullet -} \longrightarrow Ar^{\bullet} + X^-$$
$$Ar^{\bullet} + Nu^- \longrightarrow [ArNu]^{\bullet -}$$
$$[ArNu]^{\bullet -} + ArX \longrightarrow ArNu + [ArX]^{\bullet -}$$

The addition of 2,4-dinitrobenzene as radical scavenger produces large reductions in substitution products when this type mechanism is operative. Halide effect does not seem to be a determining factor in such a situation.

Reaction with benzyl alkoxide (Br = 93% ; Cl = 85% ; F = 75%)
A radical contribution can be excluded as there is no effect of 2,4-dinitrobenzene addition on the reaction yield. Addition-elimination process can be also eliminated as the fluorinated compound is not the most effective.
Arynic mechanism (elimination-addition) seems to be the most propicious as this anion is a strong base (cf pKa = 18 in water for its conjugated acid $PhCH_2OH$).[27] Furthermore, the observed sequence for reactivity is consistent with the foreseeable one for this process. Two new experimental facts are in agreement with such a conclusion :
- the absence of reaction with 2-chloropyrimidine,
- the fact that 3-bromopyridine leads to the same product as with 2-bromopyridine, confirming thus the eventuality of common pyridyne intermediate.

Reaction with phenoxide (F = 69% ; Cl = 10% ; Br = 50%)
As fluorine is the most reactive, one can consider an *addition-elimination* mechanism under *charge control*. Nevertheless, as bromine is also very reactive relative to chlorine, a contribution of the addition-elimination process under *orbital control* can also be considered. These two types of mechanism can coexist in agreement with the specificities of this anion whose charge is rather localized and the HO level is rather high in energy, favouring thus the two types of charge and orbital control.

Reaction with diphenylacetonitrile anion (Br = 52% ; Cl = 41% ; F = 5%)
2,4-dinitrobenzene addition reduces the amount of substitution from 52% to 32%. This result is an indication for a *contribution*, at least partial, *of a radical chain process*.
Elimination-addition (via aryne) process seems to be eliminated since the yield obtained with 2-chloropyrimidine is rather the same as with 2-chloropyridine (53% within 24 h at 120°C).
The reactivity sequence observed is therefore consistent with *an addition elimination mechanism under orbital control*. This conclusion is clearly in agreement that this kind of carbanion is highly conjugated, therefore of consequently delocalized charge and high HO level,[17] and consequently very subjective to react under orbital control.

CONCLUSIONS

From this study, it is obvious to point out that solid-liquid PTC without solvent can be applied successfully to S_NAr reactions of 2-halopyridines.

All reactions were performed with anions generated in situ by reaction of solid KO^tBu with the conjugated acids ($PhCH_2OH$, PhOH, PhCHRCN) under very easy to perform and efficient conditions. They led to large improvements when compared to literature and constitute a new alternative to promote these reactions. This method is characterized by a very simplified work up ; it does not need any solvent during the reaction and also avoids the previous preparation of reagents.

From mechanistic considerations connected to the halide effects, it appears that, according to anionic structure, competitive processes can be involved depending essentially on localization of charge, HOMO level energy and basicity of the species.

EXPERIMENTAL

Standard S_NAr procedure

Three mmol of commercially available NuH were added to 6 mmol of base and 6% mol of the tetraalkylammonium salt (Aliquat 336). The mixture was shaken for 5 min with a mechanical stirrer. The alkylating agent (4.5 mmol) was then added ; the mixture was stirred 5 more min , and left for the indicated time at the appropriate temperature (see Table I). Organic products were removed, after adding 50 ml of dichloromethane, by a simple filtration on Florisil (on which ammonium salts remain absorbed) . They were identified by comparison with authentic samples (gcms, nmr) and analyzed by glc (internal standard).

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Received, 8th July, 1991