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REACTION OF 2-PYRIDYLLITHIUM WITH AZINE N-OXIDES. SIMPLE AND CONVENIENT METHOD FOR THE SYNTHESIS OF 2,2'-BIPYRIDINE 1-OXIDE AND 2,2':6',2'':6''2'''-TETRAPYRIDINE 1'-OXIDE

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In the reaction of 2-pyridyllithium with quinoline 1-oxide and isoquinoline 2-oxide a nucleophilic substitution of hydrogen occurs to form the corresponding pyridin-2-ylquinolines. A dimerization of the substrate occurs with pyridine 1-oxide, 2,2'-bipyridine 1-oxide or quinoxaline N-oxide. A similar dimerization in good yield occurs when treating azine N-oxides with tert-butyllithium and this serves as a simple and convenient method for preparing bi- and tetrapyridines.

Keywords: azine N-oxides, ligands, oligopyridines, dimerization, nucleophilic substitution of hydrogen.

The nucleophilic aromatic substitution of hydrogen (S_N^H) is one of the fastest developing areas in organic synthesis. The synthetic potential of this S_N^H reactions is governed by the basic ability of the C–H bond in π-deficient arenes and hetarenes to undergo fission and change to a C–X bond (where X = C*sp3*, C*sp2*, C*sp*, O, N, S, P etc.) with the action of very different kinds of nucleophiles. Nucleophilic attack on the unsubstituted carbon atom avoids the preliminary introduction into the aromatic ring of so called "good leaving" groups such as Hal, OR, SO_2R, NO_2 etc and this opens novel possibilities for the direct introduction of a substituents thus conferring advantages when compared with classical $S_N^{ipso}Ar$ reactions [1]. There is special interest in formation of the most important C–C bond in organic synthesis by the treatment of π-deficient systems with organolithium compounds. In several examples these processes can serve as an alternative to cross conjugation catalyzed by transition metals (the Suzuki, Sonogashira, and Heck reactions etc) [2, 3] which, as is known, needs the presence of a halogen in the substrate and the use of catalysts.

In this communication we report data regarding the features of the reaction of 2-pyridyllithium with azine oxides and the use of this reaction for synthesizing oligopyridines which are promising ligands potentially able to control the construction of spiral supramolecular systems [4-7].

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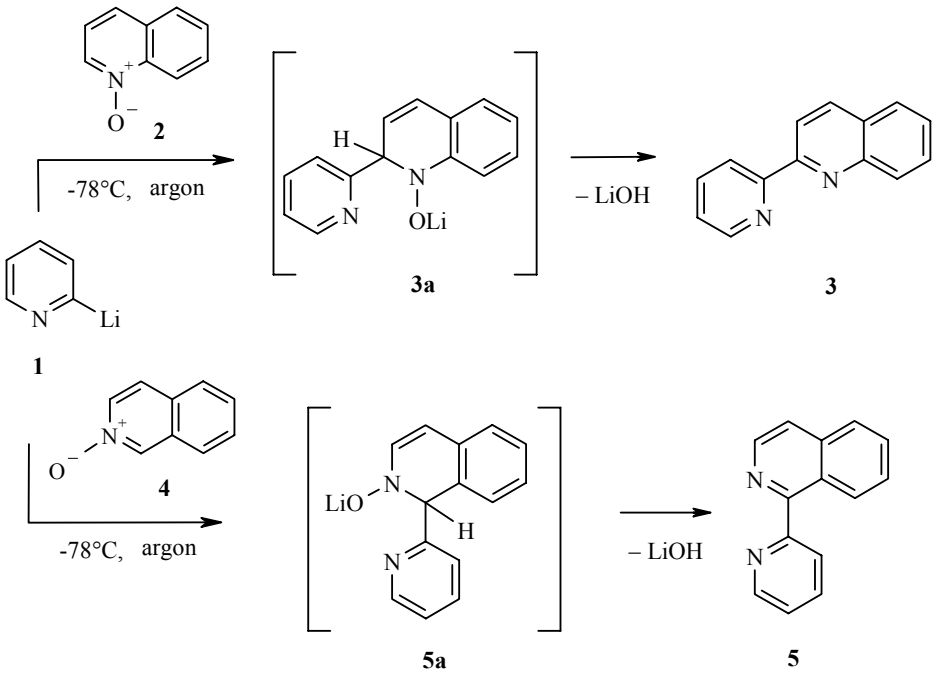
As nucleophiles we selected 2-pyridyllithium **1** which was prepared from 2-bromopyridine and *tert*-butyllithium through exchange of halogen for lithium [8]. The reaction of 2-pyridyllithium with different electrophiles has been reported but there is virtually no data for the reaction with azines, including nucleophilic reactions of hydrogen substitution. It is only known that treatment of 2-pyridyllithium with 3-methylthio-1,2,4-triazine gives an adduct, aromatization of which using the mild oxidant MnO_2 gives the 3-methylthio-5-(pyridin-2-yl)-1,2,4-triazine in 70% yield [9]. A product of nucleophilic substitution of hydrogen was established in the reaction of 2-pyridyllithium with 5-aryl-1,2,4-triazine 4-oxides in the presence of an acylating agent (acyl chloride). Carrying out these reactions demands low temperatures and careful isolation from moisture but, even so, the yields remain low (10-20%) [10].

The treatment of 2-pyridyllithium with 3,5-dichloro-4-tolylpyrimidine gave the S_N^H product 3,5-dichloro-2-(pyridin-2-yl)- 4-tolylpyrimidine [11].

We have shown that reaction of 2-pyridyllithium **1** with quinoline 1-oxide (**2**) at -78ºC gives 2-(pyridin-2-yl)quinoline (**3**). With the literature data for the nucleophilic substitution of hydrogen in azine N-oxides [12] in mind it can be proposed that the intermediate compound is the adduct **3a** which aromatizes with elimination of lithium hydroxide and leads to compound **3** (Scheme 1). In a similar way 2-pyridyllithium **1** and the isoquinoline 2-oxide **4** react to form the 1-(pyridin-2-yl)isoquinoline **5**.

Scheme 1

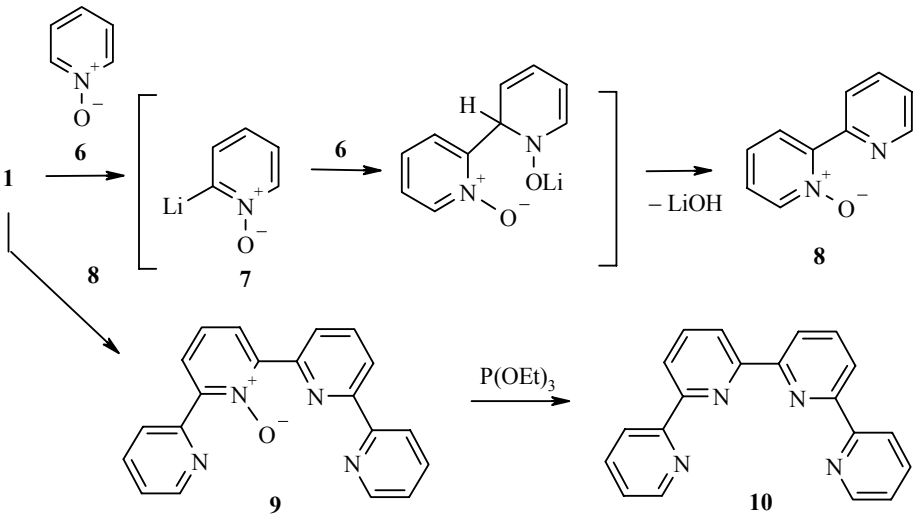


The structures of compounds **3** and **5** were in agreement with elemental analytical data and spectroscopic parameters.

Treatment of 2-pyridyllithium **1** with pyridine 1-oxide **6** under the same conditions unexpectedly gave 2,2'-bipyridine 1-oxide **8** and not the 2,2'-bipyridine which would have been expected by analogy with quinoline N-oxides (Scheme 2). An oxidative route for aromatization of the intermediate adduct is not realized as judged by the end product. Oxidation by atmospheric oxygen would have given 2,2'-bipyridine 1,1'-dioxide but this was not seen in the reaction product. Observing such behavior for the adduct should infer its instability and also the ability to aromatize, even under the conditions of the Schlenk procedure.

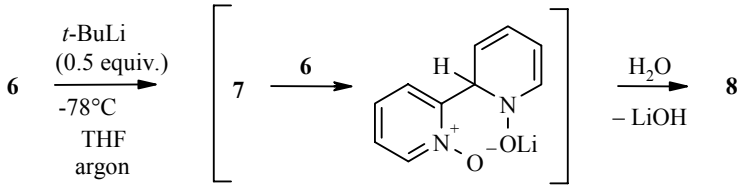
In a similar way treatment of compound **1** with 2,2'-bipyridine 1-oxide **8** gives only the single product 2,2':6',2":6",2"'-tetrapyridine 1'-oxide **9**, the expected terpyridine not being observed, even in trace amounts.

Scheme 2



The formation of compounds **8** and **9** can be rationalized if it is proposed that the process includes translithiation of 2-pyridyllithium (**1**) to form 2-lithiopyridine 1-oxide (**7**) which takes part as a nucleophile reacting with free pyridine-1-oxide **6** (Scheme 2). The following facts support this: it is known that dimerization of pyrimidine [13], pyridine, quinoline, and isoquinoline [14] occurs upon attempted lithiation by non-nucleophilic superbase reagents, although in low yield. Dimerization of 2-pyridyllithium is also observed when treated with phosphorus trichloride [15]. Confirmation of the scheme proposed followed from the formation of 2,2'-bipyridine 1-oxide **8** in good yield as the result of treating compound **6** with 0.5 equivalents of *tert*-butyllithium (Scheme 3). The yield of compound **8** was 67%. The reaction occurs very rapidly, even when carrying out the lithiation at about -100ºC. We were unable to "trap" the lithiated pyridine 1-oxide **7** using various electrophiles (trimethylchlorosilane, benzaldehyde), only the dimerization product **8** being separated.

Scheme 3



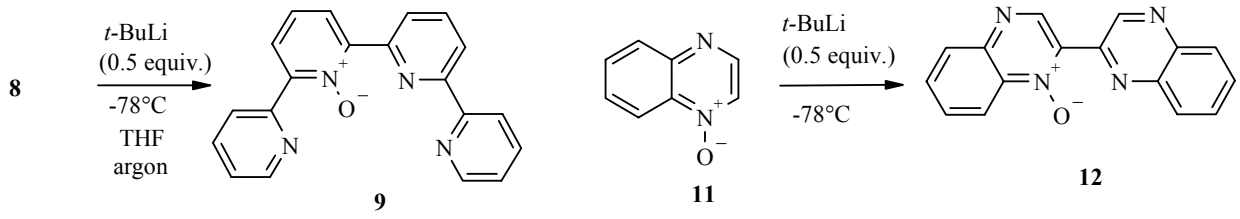
Under these conditions the action of 0.5 equivalents of *tert*-butyllithium on compound **8** or quinoxaline 1-oxide (**11**) gave 2,2':6',2":6",2"'-tetrapyridine-1'-oxide (**9**) and 2,2'-bisquinoxaline-1-oxide (**12**) respectively (Scheme 4).

The mass spectrum of compound **9** showed the presence of a molecular ion peak. In the ^{1}H NMR spectrum the multiplet at 7.5 ppm can be assigned to the resonances of the protons at positions 4 and 4"'. The tetrapyridine 1'-oxide **9** was quantitatively reduced to 2,2':6',2":6",2"'-tetrapyridine **10** upon treatment with $P(OEt)_3$ (Scheme 2).

The given reaction can serve as a simple and convenient method for the synthesis of bi- and tetrapyridines allowing one to obtain these compounds in good yield without the use of expensive catalysts.

A particular interest in this original method is in the synthesis of the 2,2':6',2":6",2"'-tetrapyridine **10**. The main advantage of its metal complexes is that they contain a planar ligand in a tetradentate coordinated

Scheme 4



state and this feature is specially important for ions with an octahedral or square planar geometry. In the case of tetrahedral geometry, usually d^{10} configured copper(I) and silver(I), there are formed binuclear, dispiral complexes where the tetrapyridine plays the role of bridging ligand spirally turning about the metal thanks to rotation about C–C bonds between the pyridines [4-6]. Compound **10** was obtained by us in this way in 73% yield and this exceeds the results obtained by an aza Diels-Alder reaction between bicyclo[2.2.1]hepta-2,5-diene and 1,2,4-triazine [16] (overall yield 67%, the synthesis demanding prolonged holding at the stage of preparation of the 3,5-disubstituted 1,2,4-triazine), by a cross conjugation Stille reaction [17] (yield 46%), and also the results of a cross conjugation reaction of 6-chloro-2,2'-bipyridine in the presence of the nickel catalyst $Ni(PPh_3)_2Cl_2$ and excess zinc (yield 40-63%) [18].

EXPERIMENTAL

^{1}H NMR spectra (in DMSO-d_6 with addition of CCl_4) were recorded on a Bruker WM-250 instrument (250 MHz) with internal standard TMS. Mass spectra were obtained on a Varian MAT-311A instrument ionized by an electron stream, ionization energy 70 eV, direct introduction of the sample, and ionization chamber temperature 100-300ºC. Elemental analysis was carried out on a Perkin-Elmer 2400-II CHN analyzer. Melting points were not corrected. Monitoring of the reaction course and the purity of the compounds prepared was performed by TLC on Silufol UV-254 plates with ethyl acetate eluent and revealed using UV light. Pyridine-1-oxide [19] and quinoxaline-1-oxide [20] were synthesized according to the literature methods.

2-(Pyridin-2-yl)quinoline (3) and 1-(pyridin-2-yl)isoquinoline (5) (General Method). A solution of 2-bromopyridine (487 mg, 3.08 mmol) in absolute ether (10 ml) was placed in a 50 ml round-bottomed Schlenk flask. The flask was evacuated, filled with argon, cooled to -78ºC, and a solution of *tert*-butyllithium (1.5 M) in hexane (2.15 ml, 3.24 mmol) was introduced by syringe through a membrane. The reaction product was held for 10-15 min, the solution became dark in color, and a solution of the corresponding azine N-oxide (3.08 mmol) in absolute ether (10 ml) was added by syringe. The product was held for 30 min and left to warm up to room temperature (1-2 h) when a crystalline product was formed. Treatment with a saturated solution of NH_4Cl (taken in excess) gave a two-phase, transparent system. This was extracted with ether, the extract was evaporated *in vacuo*, and the resinous residue was dissolved in dry acetonitrile and mixed with a solution of weighted amount $ZnCl_2$ (equal to the weight of the resin) in dry acetonitrile, and then left to stand for 1 day. The precipitate formed was filtered off and dissolved in concentrated aqueous ammonia solution (50 ml). The product was extracted with methylene chloride, evaporated *in vacuo*, and crystallized from the corresponding solvent.

Compound 3. Yield 489 mg (77%); mp 89ºC (hexane); mp 95ºC [21]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.45 (1H, m, Py); 7.60 (1H, m, Py); 7.76 (1H, m, Py); 7.95 (2H, m); 8.10 (1H, d, ^3J = 9); 8.37 (1H, d, ^3J = 9); 8.55-8.75 (3H, m). Mass spectrum, *m/z* (I_{rel}, %): 206 $[M]^+$ (100). Found, %: C 81.29; H 4.64; N 13.56. $C_{14}H_{10}N_2$. Calculated, %: C 81.53; H 4.89; N 13.58.

1-(Pyridin-2-yl)isoquinoline (5). Yield 406 mg (64%); mp 65-70ºC (chloroform); 72ºC [21]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.47 (1H, m, Py); 7.60 (1H, m, Py); 7.73 (1H, m, Py); 7.81 (1H, d, ^3J = 6, H-4); 7.90-8.10 (3H, m); 8.57 (1H, d, ^3J = 6, H-3); 8.70-8.80 (2H, m). Mass spectrum, *m/z* (I_{rel}, %): 206 $[M]^+$ (100). Found, %: C 81.25; H 4.72; N 13.24. $C_{14}H_{10}N_2$. Calculated, %: C 81.53; H 4.89; N 13.58.

2,2'-Bipyridine 1-oxide (8). A. A solution of 2-bromopyridine (0.79 g, 5 mmol) in absolute THF (5 ml) was placed in a 50 ml round-bottomed Schlenk flask. The flask was evacuated, filled with argon, cooled to -78ºC, and a solution of *tert*-butyllithium (1.5 M) in hexane (3.5 ml, 5.25 mmol) was introduced by syringe through a membrane. The reaction product was held for 10-15 min at this temperature, the solution became dark in color, and a solution of the pyridine N-oxide (0.475 g, 5 mmol) in absolute THF (20 ml) was added by syringe. The product was held for 30 min and left to warm up to room temperature (1-2 h). It was then evaporated *in vacuo* and the residue was treated with distilled water, extracted with ethyl acetate, and dried over anhydrous sodium sulphate. The extract was evaporated *in vacuo*. The residue was crystallized from *n*-butanol. Yield 267 mg (62%); mp 60ºC; mp 58.5-59.5ºC [23].

B. A solution of pyridine N-oxide (1.58 g, 10 mmol) in absolute THF (50 ml) was placed in a 100 ml round-bottomed Schlenk flask. The flask was evacuated, filled with argon, cooled to -78ºC, and a solution of *tert*-butyllithium (1.5 M) in hexane (3.7 ml, 5.5 mmol) was introduced by syringe through a membrane. The reaction product was held for 30 min at his temperature and left to warm up to room temperature (1-2 h). It was then evaporated *in vacuo* and the residue was treated with distilled water. The suspension obtained was filtered and the precipitate on the filter was washed with distilled water, dried in air and crystallized from *n*-butanol. Yield 576 mg (67%); mp 60ºC.

2,2':6',2'':6'',2'''-Tetrapyridine 1'-oxide (9) and 2,2'-bisquinoxalinyl 1-oxide (12) (General Method). A solution of the corresponding azine mono N-oxide (10 mmol) in absolute THF (50 ml) was placed in a 100 ml round-bottomed Schlenk flask. The flask was evacuated, filled with argon, cooled to -78ºC, and a solution of *tert*-butyllithium (1.5 M) in hexane (3.7 ml, 5.5 mmol) was introduced by syringe through a membrane. The reaction product was held for 30 min at this temperature and left to warm up to room temperature (1-2 h). It was then evaporated *in vacuo* and the residue was treated with distilled water. The suspension obtained was filtered and the residue was washed with distilled water, dried *in vacuo*, and crystallized from *n*-butanol.

Compound 9. Yield 1.20 g (74%); mp 204ºC. ^{1}H NMR spectrum, δ, ppm: 7.5 (2H, m); 7.6 (1H, m); 7.9-8.0 (2H, m); 8.0-8.1 (2H, m); 8.3 (1H, m); 8.5 (2H, m), 8.6 (2H, m), 8.7 (2H, m). Mass spectrum, *m/z* (I_{rel}, %): 326 $[M]^+$ (100). Found, %: C 73.56; H 4.16; N 17.36. $C_{20}H_{14}N_4O$. Calculated, %: C 73.61; H 4.32; N 17.17.

Compound 12. Yield 0.89 g (59%); mp 235-237ºC. ^{1}H NMR spectrum, δ, ppm: 7.90-8.10 (4H, m); 8.20-8.35 (3H, m); 8.64 (1H, m); 9.50 (1H, s); 10.00 (1H, s). Mass spectrum, *m/z* (I_{rel}, %): 274 $[M]^+$ (100). Found, %: C 69.84; H 3.65; N 19.86. $C_{16}H_{10}N_4O$. Calculated, %: C 70.06; H 3.67; N 20.43.

2,2':6',2'':6'',2'''-Tetrapyridine (10). Compound **9** (978 mg, 3 mmol) and triethylphosphite (1.5 ml, 9 mmol) were placed in a 10 ml round-bottomed flask fitted with a reflux condenser. The mixture was refluxed with the condenser until TLC showed no starting tetrapyridine-N-oxide remained. The mixture was evaporated *in vacuo*. The residue was recrystallized from ethanol. Yield 911 mg (98%); mp 210-212ºC. ^{1}H NMR spectrum, δ, ppm: 8.8-8.6 (6H, m); 8.5 (2H, m); 8.1 (2H, m); 7.9 (2H, m); 7.4 (2H, m). Mass spectrum, *m/z* (I_{rel}, %): 310 $[M]^+$ (100). Found, %: C 76.63; H 4.55; N 17.82. $C_{20}H_{14}N_4$. Calculated, %: C 77.40, H 4.55; N 18.05.

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