VICARIOUS NUCLEOPHILIC SUBSTITUTION OF PYRIDINES VIA THEIR DICYANOMETHYLIDE DERIVATIVES

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Vicarious nucleophilic substitution of pyridinium 1-dicyanomethylides with 1-chloromethyl phenyl sulfone gave corresponding 4-substituted derivatives. The dicyanomethylene group was readily eliminated via radical reaction to afford 4-phenylsulfonylmethylpyridines.

KEYWORDS pyridine; pyridinium dicyanomethylide; vicarious nucleophilic substitution; tetracyanoethylene oxide; 1-chloromethyl phenyl sulfone

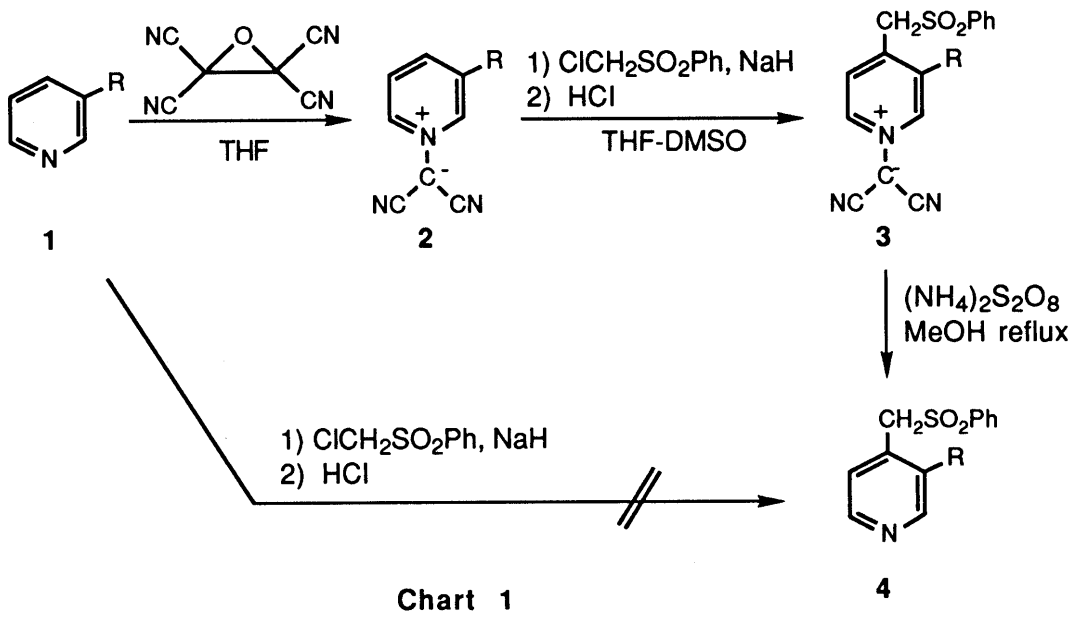
Vicarious nucleophilic substitution (VNS)[1] developed by Makosza *et al.* has been proved to be a general and versatile method for the nucleophilic substitution of nitroarenes. Nitro-substituent of arenes is essential for VNS of benzene, pyridine,[2] pyrroles,[3] thiophenes[4] *etc.*, and only 1,2,4-triazines[5] and pteridines[6] are electron deficient enough to undergo VNS even in the absence of activating substituents.

In the course of our study of heteroaromatic compounds with activating groups,[7] it was revealed that dicyanomethylene group on nitrogen in azaheteroaromatics withdrew π-electrons in the ring to make nucleophilic reaction more feasible.[8] Thus, the method was applied to pyridine derivatives, and it was clarified that pyridinium 1-dicyanomethylides[9] were readily allowed to react under VNS conditions to yield only 4-substituted derivatives, and that the dicyanomethylene group was eliminated by radical reaction to give 4-substituted pyridines. Those results are described in this paper.

3-Substituted pyridines **1** were adopted as substrates in order to test the regioselectivity of the reaction. Pyridinium 1-dicyanomethylides **2** were obtained from the reaction of pyridines **1** with tetracyanoethylene oxide in THF at room temperature. The compounds **2** were allowed to react with 1-chloromethyl phenyl sulfone, which is the most general reagent for VNS reaction, in the presence of sodium hydride followed by the treatment with HCl to afford 4-substituted pyridinium dicyanomethylides **3**.

Although the compounds **3** thus obtained are stable yellow solids, they were readily consumed under the reflux of methanol in the presence of ammonium persulfate to give corresponding 4-substituted pyridines **4** (Chart 1 and Table I).

In the typical experiment, **1a** (1 mmol) was treated with 2 mmol of tetracyanoethylene oxide in tetrahydrofuran (THF, 20 ml) at 0°C for 3 h, and succeeding alumina chromatography gave pyridinium dicyanomethylide **2a**. To the THF solution (3 ml) of chloromethyl phenyl sulfone (1 mmol) and sodium hydride (60%, 1.6 mmol), which was preincubated for 30 min at room temperature, dimethyl sulfoxide (DMSO) solution (3 ml) of **2a** (0.5 mmol) was added at 0°C and the mixture was allowed to stand at 0°C for 1 h. Then 10 ml of 5% aqueous HCl was added and the reaction mixture was extracted with ethyl acetate. The organic layer was evaporated off to leave the residue, which was chromatographed on alumina to afford **3a**.



1 2 3 4

Chart 1

Table I. Isolated Yields of the Compounds **2**, **3**, and **4**

Entry	R	Yield of 2	Yield of 3	Yield of 4
a	H	90% [9]	76%	Quant.
b	Me	88%	81%	Quant.
c	Et	87%	92%	95%
d	Bu	Quant.	83%	86%
e	OMe	94%	86%	98%
f	OEt	89%	87%	97%

When **3a** (0.5 mmol) was suspended in methanol (20 ml) and the solvent was refluxed in the presence of ammonium persulfate (1 mmol) for 1h, the compound **4a** was obtained as a sole product. Intermediates **2** and **3** were obtained in high yields, and they readily solidified as yellow solids which have high melting points (over 200°C). In contrast, direct VNS of **1** to **4** did not proceed, and thus the reaction sequence is suggested to be of synthetic use. Moreover, the above reaction afforded only γ-substituted products, while general VNS has *o,p*-directivity.[1)]

The reaction mechanism was supposed to be shown as Chart 2. The carbanion formed by the treatment of chloromethyl phenyl sulfone with sodium hydride attacked exclusively at *para*-position of **2** because of the steric hindrance derived from the planar nature[10)] of dicyanomethylene group to pyridine ring. The adduct **5** was subject to dehydrochlorination by the excess carbanion and succeeding protonation afforded **3**. Ammonium persulfate is known to produce hydroxymethyl radical when it is decomposed in methanol.[11)] Hydroxymethyl radical might attack dicyanomethylene carbon to form the radical **7**, which abstracted hydrogen from the solvent followed by 1,4-elimination to give **4**.

Nucleophilic substitution of pyridines *via* their quaternary salts has been extensively studied,[12)] but few examples[13)] were reported that underwent γ-substitution exclusively. Thus our method might afford a new synthetic method for γ-substituted pyridines through an electron-deficient *N*-ylide derivative, which is an entirely new approach.

In conclusion, the first VNS reaction of pyridines was performed using their dicyanomethylide derivatives. The reaction was entirely regioselective to the γ-position under the steric control of the dicyanomethylene group, which was easily removed by radical reaction. The introduction of other substituents using this method is under investigation.

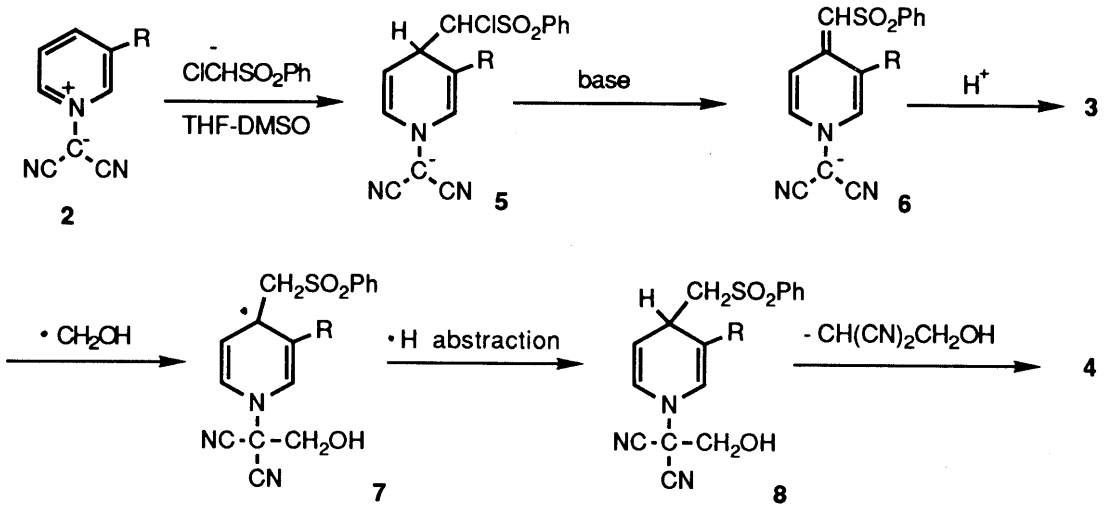


Chart 2

ACKNOWLEDGMENT This work was supported in part by the Hoansha Foundation and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan.

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(Received November 6, 1992)