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 \(\pi\)-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.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield of 2</th>
<th>Yield of 3</th>
<th>Yield of 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>90% 9)</td>
<td>76%</td>
<td>Quant.</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>88%</td>
<td>81%</td>
<td>Quant.</td>
</tr>
<tr>
<td>c</td>
<td>Et</td>
<td>87%</td>
<td>92%</td>
<td>95%</td>
</tr>
<tr>
<td>d</td>
<td>Bu</td>
<td>Quant.</td>
<td>83%</td>
<td>86%</td>
</tr>
<tr>
<td>e</td>
<td>OMe</td>
<td>94%</td>
<td>86%</td>
<td>98%</td>
</tr>
<tr>
<td>f</td>
<td>OEt</td>
<td>89%</td>
<td>87%</td>
<td>97%</td>
</tr>
</tbody>
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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 nature10) 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 examples13) 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.

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REFERENCES AND NOTES
   b) idem, ibid., 1990, 7193;
10. All azinium dicyanomethylides (pyridinium, pyridazinium, triazinium, etc.) have characteristic yellow colors, which suggest the intense resonance of dicyanomethylene group and azaaromatic rings.
    b) idem, ibid., 1982, 3935;

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