does not affect so severely to the technique as long as it is not different so significantly. (c) The random noise is also not so sensitive to the technique. (d) Finally, the constant peak shape simulation shows a possibility of simplifying the deconvolution and saving the computing time.

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References


Synthetic Studies on Penems and Carbapenems (III). Transformation of Penicillin G to Derivatives of 6-Bromo-6-phenylacetoxypenicillanic Acid

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Intramolecular rearrangement of N-alkyl-N-nitrosoamides to alkyl esters is well known. Recently Garcia *et al.* nitrosated N-alkylamides at low temperature to transaminate with other amines. Nitrosation reaction is one of the examples in transforming the amino group to a better leaving group in which the nitroso group can delocalize electrons by resonance. Diazotization of an amino group would be another way of achieving reversed reactivity on the a-carbon atom. Although the a-carbon atom of the N-alkyl group retains positive charge, usually the acylamino group itself is a poor leaving group and it is difficult to be substituted with other nucleophiles. However, nitrosation on the nitrogen atom in N-alkylated amides will make the acylamino group a better leaving group since the negative charge at the nitrogen atom in N-nitrosoamides is delocalized to the nitroso group as well as to the acyl group. Consequently, the N-acyl-N-nitrosoamino group should be substituted more easily by other nucleophiles as described with Penicillin G in Scheme 1.

Early in 1970, Schelin and coworkers reported nitrosation of penicillin G and synthesis of new penicillanic acid derivatives having new functional groups at C-6 position of penicillanic acid. We examined N-nitrosopenicillin G further for the possibility of obtaining derivatives of 6,6-dibromopenicillanic acid, which is an important intermediate for stereospecific synthesis of carbapenems and penems. Usually 6,6-dibromopenicillanic acid is obtained by diazotization of 6-aminopenicillanic acid with bromine. In this transformation the carbon atom attached to the diazo group shows dual reactivities to act first as a nucleophile and next as an electrophile. By a similar concept, transformation of penicillin G potassium salt directly to 6,6-dibromopenicillanic acid
would be possible by nitration of the phenylacetamido group in which the hydrogen atom at C-6 carbon atom will become more acidic. A carbanion may be formed easily at C-6 carbon atom of 6-(N-nitrosophenylacetamid)penicillanic acid and it, as a nucleophile, may react with bromine. The reaction may be followed by attack of bromide ion at the back side of the C-6 carbon atom to liberate the N-nitrosophenylacetamid group with yielding 6,6-dibromopenicillanic acid. To test this hypothesis, the potassium salt, benzyl ester, or methyl ester of penicillin G was treated with nitric acid and bromine to yield 6,6-dibromopenicillanic acid.

In a round bottomed flask, 5 ml of methylene chloride was added and cooled in icsalt bath to 5°C with stirring. Then 0.385 ml of bromine (7.5 mmol) was added, followed by addition of 2 ml of 2.5 N sulfuric acid (saturated with sodium chloride) and sodium nitrite (0.345 g, 5.0 mmol) slowly. As the sodium nitrite was added, formation of foam was observed and the upper space of the flask was saturated with dinitrogen tetroxide gas. Then, penicillin G potassium salt (0.939 g, 2.5 mmol) was added slowly for 10 min. After stirring for 30 min, 2 ml of NaHCO3 (5% aq.) was added. Then the reaction mixture became orange color from dark brown. After further stirring for 15 min, the methylene chloride layer was separated. The aqueous layer was further extracted with ethyl acetate and the organic solvent extracts were combined and washed with brine and with water. Then the organic layer was dried over sodium sulfate and evaporated under reduced pressure to give a yellow oily residue (692 mg). The residue showed IR bands at 3400-2630, 1800, 1740, and 1100 cm-1 and 'H NMR peaks (CDCl3-DMSO-d6) at 1.23 (s, 3H), 1.28 (s, 3H), 3.83 (s, 2H), 4.83 (s, 1H), 6.62 (s, 1H), 7.36 (s, 5H) and 7.96 ppm (s, 1H). Methylation of the product with diazomethane gave a product having IR bands at 1805, 1735, and 1200 cm-1, 'H NMR peaks (CDCl3) at 1.48 (s, 3H), 1.56 (s, 3H), 3.84 (s, 2H), 3.90 (s, 3H), 5.35 (s, 1H), 6.30 (s, 1H), and 7.30 ppm (s, 5H), and a molecular ion at m/z 427 (doublet). From these data the compounds obtained were identified as 6-bromo-6-phenylacetoxypenicillanic acid (1a) and its methyl ester (1b), respectively. No observation of characteristic peaks in the region 1600-1700 cm-1 for an anide band in the IR spectrum support our structures. Similar treatment of benzyl ester of penicillin G, which was obtained by stirring penicillin G potassium salt in DMF with benzyl chloride, with bromine and nitric acid gave also the same kind of product (1c) which showed IR bands at 1800, 1750, 1730, 1500, 1455, 1210, and 1100 cm-1, and 'H NMR peaks at 1.24 (s, 3H), 1.33 (s, 3H), 3.69 (s, 2H), 4.40 (s, 1H), 5.15 (s, 2H), 6.39 (s, 1H) and 7.15-7.30 ppm (b. doublet).

Two stereoisomers are possible for all the compounds. However, in case when penicillin G potassium salt was reacted, about 10% of the product was composed of another isomer which showed peaks at 3.70 and 4.95 ppm (about 10% in integration ratio) instead of 3.83, and 4.83, respectively. Currently, the configurations of the observed isomers are unknown. When benzyl ester of penicillin G was reacted, the ratio of the isomers decreased to about the ratio, 5:4. The minor isomer of the benzyl ester derivative showed peaks at 1.23 (s, 3H), 1.32 (s, 3H), 3.70 (s, 2H), 4.56 (s, 1H) and 6.30 ppm (s, 1H) instead of the peaks at 1.24 (s, 3H), 1.33 (s, 3H), 3.99, 4.40 and 6.39 ppm respectively. Attempt to isolate these isomers was not succeeded due to poor separation and poor stability. Similar treatment of methyl ester of penicillin G with nitrous acid and bromine gave only decomposed products.

Formation of these products seems to be explained by the mechanism given in Scheme II. Attempt to internucleophilic substitution of the N-nitrosophenylacetamid group attached to C-6 position of penicillanic acid with bromine ion was not succeeded. This seems mainly due to the fact that the compound exists mainly in organic solvent layer instead of aqueous layer and the intramolecular substitution is more favored than the internucleophilic substitution.

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References

A New Method for the Preparation of Isothiocyanates from Amines Using 1,1'- (Thiocarbonyldioxy)dibenzotriazole

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As part of our continuous efforts toward the development of new reactive thiocarbamates as condensing reagents and thiodcarbonyl transfer reagents,4 we wish to report the preparation of 1,1'- (thiocarbonyldioxy)dibenzotriazole, its explosive nature, and its use for the preparation of isothiocyanates from amines.

First, the reaction of 1-hydroxybenzotriazole with an equimolar amount of thiophosgene in the presence of 2 equiv of triethylamine or pyridine in methylene chloride at room temperature was tried but no desired product was obtained. However, as shown in eq. 1, 1,1'- (thiocarbonyldioxy)dibenzotriazole was prepared by treatment of 1-trimethylsilyloxybenzotriazole2 with an equimolar amount of the thiophosgene in methylene chloride at 0°C for 1 h. The reagent was obtained in essentially quantitative yields (90-98%) as a faint yellow crystalline solid.

It is noteworthy that the reagent is violently exploded at 114°C and also we have experienced one violent explosion during the preparation of the reagent.5 Thus, proper safety precautions should be made to prepare the reagent and to carry out the reactions. Furthermore, the explosive nature of the similar type of the reagent, 1,1'- (carbonyl dioxy)dibenzotriazole6, has been independently observed by us and others.6

![Chemical structure of 1,1'- (Thiocarbonyldioxy)dibenzotriazole](image)

Table 1. Preparation of Isothiocyanates from Amines*

<table>
<thead>
<tr>
<th>Amine</th>
<th>Time, min</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH3CH2NH2</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>CH2CH2CH(NH2)CH3</td>
<td>10</td>
<td>89</td>
</tr>
<tr>
<td>(CH3)2CNH</td>
<td>45</td>
<td>84</td>
</tr>
<tr>
<td>CH3=CHCH2NH</td>
<td>5</td>
<td>86</td>
</tr>
<tr>
<td>C-C(=N)NH</td>
<td>10</td>
<td>95</td>
</tr>
<tr>
<td>C6H5CH2NH3</td>
<td>5</td>
<td>93</td>
</tr>
<tr>
<td>C6H4H</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>p-Cl-C6H4NH2</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>p-C6H4=CH2NH3</td>
<td>5</td>
<td>84</td>
</tr>
<tr>
<td>p-NO2-C6H4NH2</td>
<td>30</td>
<td>93</td>
</tr>
</tbody>
</table>

* The reaction was carried out with an equimolar mixture of an amine, triethylamine, and 1,1'- (thiocarbonyldioxy)- dibenzotriazole in methylene chloride at room temperature.5 The isolated yields after Kugelrohr distillation or crystallization. c-C6H4 indicates cyclohexyl group. Physical and spectroscopic data of the products were in accord with reported data.

1-benzotriazolyl benzylthiocarbamate.7 Direct conversion of benzylamine into benzyl isothiocyanate has been achieved by performing the reaction in the presence of 1 equiv of triethylamine in methylene chloride at room temperature or in toluene at 60°C for 3 h without adding triethylamine. The similar behavior has been noted with 1,1'-thiocarbonyldiimidazole.8 However, it is of interest that the reaction of 1,1'- (thiocarbonyldi)-1,2,4-triazole with amines affords 1-(allylthiocarbamoyl)-1,2,4-triazole, which shows no tendency to dissociate isothiocyanates and 1,2,4-triazole in refluxing toluene9 and in the presence of triethylamine in methylene chloride.10

The remaining reactions were carried out in the presence of triethylamine in methylene chloride at room temperature due to the explosive nature of the reagent at an elevated temperature. The preparation of isothiocyanates was performed on a variety of structurally different amines to determine the scope and limitations of the present method and the results are summarized in Table 1. In general, the reaction occurred almost instantly at room temperature for most simple alkyl and aryl amines. Relatively unreactive p-nitroaniline and sterically hindered t-butylamine were smoothly converted into the corresponding isothiocyanates in high yields but required

References: