

NBST (44%). The difference between TPS and NBST seems attributable to 1,2,4-triazole, which can accumulate as NBST reacts and attack the phosphoryl group of 14 and 15 to give phosphorotriazolidines which hydrolyze during workup to water-soluble nucleotidic substances. This view is supported by the fact that treatment of 8a with 1 equiv of 1,2,4-triazole in pyridine at room temperature for 70 h at the same concentration as that of the coupling reaction using NBST gave 12a in 30% yield. On the other hand, when 9b was employed in a similar coupling reaction, the corresponding protected thymidylate (15b) was obtained in 90% yield even in the case of NBST. In fact, an independent experiment in which 8b was mixed with 1 equiv of 1,2,4-triazole in pyridine at room temperature for 70 h resulted in only 2.3% formation of 12b.

Removal of all protecting groups from 15a and 15b<sup>27</sup> was carried out by treatment with 16–20 equiv of silver acetate in aqueous pyridine followed by treatment with zinc powder in the presence of acetylacetone in dimethylformamide–pyridine (2:1, v/v).<sup>28</sup> pTpT was isolated by paper chromatography in more than 99% yields from 15a and 15b. The following one-step removal of two phenylthio groups and 2,2,2-trichloroethyl group should also be noted. When 15a was treated only with zinc–acetylacetone for 30 h, direct conversion to pTpT (65%) was realized. It appears that an active cation,  $\text{ZnCl}^+$ , formed as a result of removal of the 2,2,2-trichloroethyl group, attacked the phenylthio group. This deprotection reaction was accelerated by addition of 4 equiv of benzenethiol (84% of pTpT after 2 h). Mild treatment of 15a and 15b with 4–6 equiv of phosphorous acid in pyridine containing a small amount of water for 1–2 days gave PhSpTp(tc)T and 4-MeOC<sub>6</sub>H<sub>4</sub>SpTp(tc)T. The remaining arylthio groups were easily removed quantitatively by silver acetate (16–20 equiv) for 24 h or iodine (20 equiv) for 1 h in pyridine–water (2:1, v/v). All the dithymidylates obtained through several routes described above were completely degraded by snake venom phosphodiesterase to pT.<sup>27</sup> In a similar manner, (4-MeOC<sub>6</sub>H<sub>4</sub>S)<sub>2</sub>pTp(tc)Tp(tc)T was synthesized in 82% yield. This trinucleotide derivative was also deprotected by the above methods and converted to pTpTpT in 75–97% yields.

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- (18) In each case, only trace amount of S,S-diaryl thymidine 3'-phosphorodithioate (10a or 10b) was formed as a byproduct. Compound 10a or 10b could be distinguished from the corresponding 5'-isomer 9a or 9b on TLC. The major byproduct was 3',5'-bisphosphorylated derivative 16a or 16b. They were also obtained in high yields from thymidine (1 equiv) and 2.4 equiv of 1a or 1b in the presence of 2.4 equiv of TPS.
- (19) A small amount (2%) of S-phenyl thymidine 3'-phosphorothioate (11) was formed. On the contrary, the bis(4-methoxyphenylthio) group was completely stable under the same conditions.
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- (21) Mercuric chloride can be used effectively as well as the silver salts. However, other transition metals such as mercuric acetate, cupric chloride, and cuprous chloride were not effective.
- (22) Treatment of 6–10 with silver acetate gave the products as silver salts. The silver salts could be converted to metal-free pyridinium salts by bubbling hydrogen sulfide into their solution of aqueous pyridine.
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- (24) When 9a was treated with 0.2 N NaOH–dioxane (1:1, v/v), the isomerization of the phosphoryl group from the 3' position to the 5' position occurred partially to give a mixture of PhSpT, cyclic pT, pT, and Tp.
- (25) The reaction proceeded quantitatively because the TLC showed a single spot containing the trityl group.
- (26) It is also noteworthy that 9a was successfully converted to PhSpT quantitatively without isomerization of the phosphoryl group as described in ref 24.
- (27) Before removal of all protecting groups, 15a and 15b were further purified by treatment with monomethoxytrityl chloride in pyridine followed by chromatographical separation on silica gel in order to take off traces of 3'→3' isomers simultaneously formed in the second coupling reactions.<sup>1</sup>
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Mitsuo Sekine, Ken Hamaoki, Tsujiaki Hata\*

Department of Life Chemistry  
Tokyo Institute of Technology  
4259 Nagatsuta, Yokohama, 227 Japan

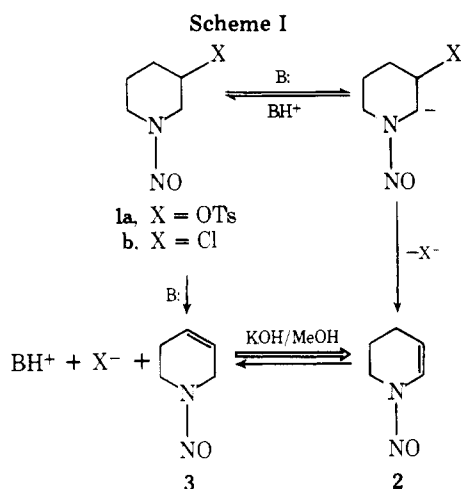
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### Unsaturated Nitrosamines. Formation and Equilibration of Vinylic and Allylic Nitrosamines

**Summary:** Vinylic nitrosamines (*N*-nitrosoenamines), which heretofore have been difficult to prepare, can be formed in good yields by crown ether/potassium hydroxide elimination of the corresponding  $\beta$ -tosyloxy nitrosamines, by base-catalyzed equilibration of the corresponding allylic isomers, or by oxidative elimination of  $\alpha$ -phenylselenenyl nitrosamines.

**Sir:** Little is known about the chemistry and biological effects of  $\alpha,\beta$ -unsaturated nitrosamines, partly due to a lack of generally useful synthetic methods. Only three members of the class have been reported. *N*-Nitrosomethylvinylamine<sup>1</sup> and *N*-nitrosoethylvinylamine<sup>2</sup> have been reported and characterized. The very unstable divinyl nitrosamine has been reported<sup>3</sup> but its characterization is poor. We wish to report three methods of preparation of this interesting class of compounds, which should provide the basis for the study of their chemistry.

The aforementioned nitrosamines were prepared by simple dehydrohalogenation of alkyl( $\beta$ -chloroethyl)nitrosamines using methanolic potassium hydroxide. However, with longer  $\beta$ -chloroalkyl chains, the elimination occurred to give the



$\beta,\gamma$ -allylic instead of the  $\alpha,\beta$ -vinyl isomers. For example, 3-chloro-1-nitrosopiperidine reacted under these conditions to give an essentially quantitative yield of 3,4-dehydro-1-nitrosopiperidine. We examined the elimination reactions of a variety of  $\beta$ -substituted nitrosamines. For the purpose of illustration, the discussion here will be in terms of the 3-substituted 1-nitrosopiperidine. The reaction of 3-(tosyloxy)-1-nitrosopiperidine (**1a**) with solid potassium hydroxide in ether catalyzed by 18-crown-6 ether (1 mmol/mol of tosylate) resulted in the formation of 2,3-dehydro-1-nitrosopiperidine (**2**) in essentially quantitative yield in 4 h at room temperature. The product was isolated in near quantitative yield by passage through a short silica column. The reaction of 3-chloro-1-nitrosopiperidine (**1b**) under identical conditions, however, gave the 3,4-dehydro-1-nitrosopiperidine (**3**), also in quantitative yield. Not a trace ( $<1\%$ ) of the other isomer was detected in either of the two reactions. The allylic nitrosamine **3** was converted quantitatively to **2** by heating it at reflux in methanolic potassium hydroxide. Thus, the earlier attempt to prepare the  $\alpha,\beta$  isomers by elimination of the  $\beta$ -chloro nitrosamines failed to give the desired product because the reaction mixtures were not heated at reflux, since the elimination reaction is exothermic. Any allylic nitrosamine can be equilibrated to the vinyl isomer by heating in methanolic potassium hydroxide. This, in fact, is a very convenient way of getting the vinyl isomer, if the allylic one is readily available. The nitrosamine (approximately 1 M) in 1 M methanolic KOH was heated at reflux for about 2 h. The reaction was followed by GLC (8% SE-30 on Chromosorb w/HP column at  $120^\circ\text{C}$ ). The tosylate **1a** was also converted to **2** in methanolic potassium hydroxide. However, if triethylamine in methanol was used as the base, **1a** was converted into a 2:1 mixture of **2** and **3**. Moreover, if the elimination reactions of either **1a** or **1b** were carried out in methanol-*O-d*, the acidic  $\alpha$  protons of both nitrosamines were exchanged rapidly, prior to elimination. The results are summarized in Scheme I. These observations are best accounted for by assuming that the elimination of the tosylate occurs with prior reversible formation of the  $\alpha$ -carbanion. This is the classical  $\text{E}_1\text{cB}$  reaction.<sup>4</sup> The chloride is a much poorer leaving group,<sup>5</sup> and hence, the expulsion of this ion from the carbanion is relatively slow. This allows the formation of **3** by a competing irreversible  $\text{E}_2$  process. Triethylamine is not a strong enough base to promote the  $\text{E}_1\text{cB}$  process efficiently, and as a consequence, the reaction of it with **1a** results in a product mixture containing both **2** and **3**. This mixture is probably a result of the two directions in which the  $\text{E}_2$  reaction can occur, since the amine is not a strong enough base to affect the exchange of the  $\alpha$  protons.

If the allylic unsaturated nitrosamine is difficult to obtain

**Table I. Formation of Representative Vinyl Nitrosamines<sup>a</sup>**

nitrosamine	method <sup>b</sup> (% yield) <sup>c</sup>
	A (94), T (98), S (75)
	A (95)
	S (64)
	S (71)
	(mixture of <i>E</i> and <i>Z</i> ) A (92), T (89)
	A (85)
	A (63)
	T (72)

<sup>a</sup> The nitrosamines were characterized by  $^{13}\text{C}$  NMR and mass spectrometry as well as by elemental analysis. The NMR was particularly useful because of the large downfield shift of the  $\alpha$ -vinyl carbon (128–135 ppm). <sup>b</sup> A = equilibration of the allylic to the vinyl isomer; T = elimination of the tosylate; S = elimination of  $\alpha$ -phenylselenenyl derivative. <sup>c</sup> The quoted yields are the isolated yields.

and if the  $\beta$ -hydroxylated nitrosamine is unavailable, the acidity of the  $\alpha$ -hydrogens of nitrosamines can be used to advantage in the synthesis of vinyl nitrosamines. The formation of the  $\alpha$ -carbanion with lithium diisopropylamide-HMPA (4 equiv)-THF mixture, followed by reaction with phenylselenenyl chloride,<sup>6</sup> results in the formation of  $\alpha$ -phenylselenenyl nitrosamines<sup>7</sup> in 60–75% yields. These reactions were carried out at  $-80^\circ\text{C}$ . The  $\alpha$ -phenylselenenyl derivatives were isolated from the reaction mixture by extracting the reaction mixture with 1 M hydrochloric acid, drying of the organic phase, and removing the solvent under reduced pressure. These selenium derivatives can then be oxidized with *m*-chloroperbenzoic acid to the phenyl selenoxides, which spontaneously eliminate the elements of phenylselenenic acid to generate the  $\alpha,\beta$ -unsaturated nitrosamine in better than 90% yield. The oxidation of the  $\alpha$ -phenylselenenyl nitrosamines was carried out in methylene chloride by dropwise addition of a twofold excess of *m*-chloroperbenzoic acid at such a rate that the temperature of the reaction mixture was maintained at  $30$ – $35^\circ\text{C}$ . Under those conditions phenylselenenic acid eliminated spontaneously. The workup of the reaction mixture

