Facile Nucleophilic Substitution Reactions of 1′-Methylthiaminium Salts

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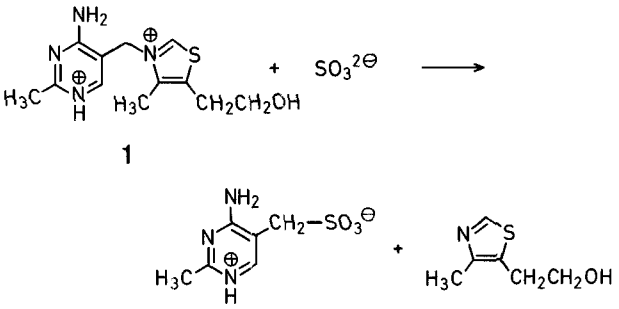
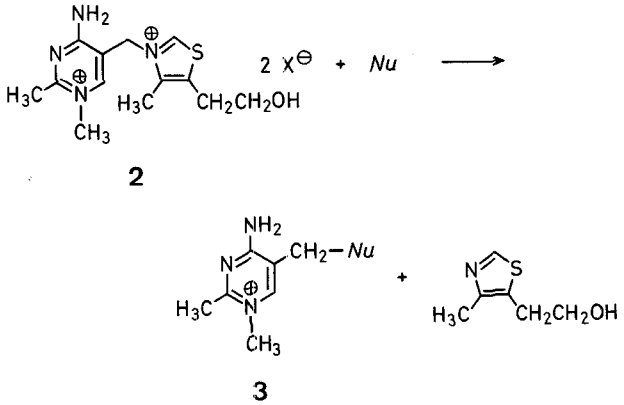
The best known nucleophilic substitution reaction of thiamin (**1**) is the sulfite ion cleavage, accidentally discovered in 1935[1]. In this reaction, the thiazole ring is replaced by the nucleophile (Scheme **A**). We recently provided evidence to show that this process does not proceed by an S_N2 mechanism. Instead, substitution takes place by a multistep sequence. A positively charged pyrimidine ring produced by protonation of N-1′ to give **1** is required for rapid reaction[2].



Scheme **A**

Now we report facile nucleophilic substitution reactions of a thiamin derivative which have broad scope. Again, ready substitution takes place with a thiamin having a positively charged pyrimidine ring, **2**, this time as a consequence of methylation at N-1′. The new reactions conveniently provide access to pyrimidine derivatives **3** having a wide range of groups bonded to the pyrimidine ring (Scheme **B**).



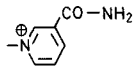
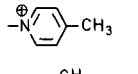
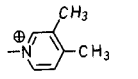
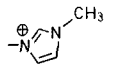
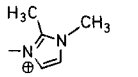
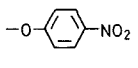
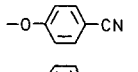
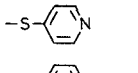
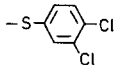
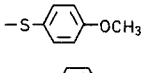
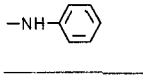
Scheme **B**

Substitution generally takes place rapidly under mild conditions with various kinds of nucleophiles *(Nu)* which include pyridines, imidazoles, phenolate and thiophenolate anions, and aniline.

The yields reported in the Table are not optimized. Higher conversions probably could be achieved with individualized conditions. All the reactions employ methanol as solvent. A preliminary study with pyridine as the nucleophile reveals that substitution is much faster in methanol than in water.

0039-7881/80/0332-0218 $ 03.00

Table. Pyrimidine Derivatives **3** (Thiamin Analogs) prepared

Nu in **3**	Nucleophile employed	Yield [%][a] of **3**	Reaction time [h]	m.p. [°C] of **3**	Molecular formula[b]
	substituted pyridine	56	72	175–176.5 (dec.)	$C_{13}H_{17}Cl_2N_5O_9$ (458.2)
	substituted pyridine	80	2.2	276–280 (dec.)	$C_{13}H_{18}Cl_2N_4O_8$ (429.2)
	substituted pyridine	76	3.8	170–171	$C_{13}H_{18}Cl_2N_4O_8$ (429.2)
	substituted pyridine	64	24	219–220.5 (dec.)	$C_{14}H_{20}Cl_2N_4O_8$ (443.2)
	substituted imidazole	94	3.5	211–212 (dec.)	$C_{11}H_{17}Cl_2N_5O_8$ (418.2)
	substituted imidazole	94	3.5	262–266 (dec.)	$C_{12}H_{19}Cl_2N_5O_8$ (432.2)
	substituted phenol/NaOH	54	3.5	218–219 (dec.)	$C_{13}H_{15}ClN_4O_7$ (376.8)
	substituted phenol/NaOH	68	4	251.5–253 (dec.)	$C_{14}H_{15}ClN_4O_5$ (354.7)
	4-mercaptopyridine/ NaOH	71	3	187.5–188.5	$C_{12}H_{15}ClN_4O_4S$ (346.8)
	substituted thiophenol/NaOH	69	1	169–172 (dec.)	$C_{13}H_{14}Cl_3N_3O_4S$ (414.7)
	substituted thiophenol/NaOH	64	1	176–178.5	$C_{14}H_{18}ClN_3O_5S$ (375.8)
	aniline	57[c]	26	161–163	$C_{13}H_{17}ClN_4O_4$ (328.8)

[a] Yield of recrystallized product (perchlorate sults).
[b] The microanalyses were in satisfactory agreement with the calculated values (C ± 0.19, H ± 0.06, N ± 0.09).
[c] 10% of starting material **2** was recovered as well.

Substitution may well be reversible. The reaction of **2** with 3-aminocarbonylpyridine is especially interesting in this regard. After the first attempt at substitution, a mixture consisting of both starting material and product was formed. However, when the liberated thiazole was removed and the mixture was treated with the nucleophile again, the conversion to product was essentially complete.

Attempts to bring about conversion with weak nucleophiles such as 2,4-dinitrophenolate ion, 4-methylpyridine *N*-oxide or 2,6-dimethylpyridine were unsuccessful. Steric hindrance probably accounts for the lack of reaction in the latter case. However, the reaction is successful with the less encumbered 2-methylpyridine.

The new pyrimidine derivatives **3** also undergo sulfite ion cleavage in aqueous solution. This makes it possible to study the sulfite ion substitution reaction with thiamin derivatives and analogs having a graded series of leaving groups. The results of our kinetic studies showing the effects of these leaving groups on reactivity will appear shortly.

Nucleophilic Substitution of 1′-Methylthiaminium Salts 2; General Procedure:

To 1′-methylthiaminium diperchlorate[3] (**2**; 5.0 g, 10.4 mmol) suspended in dry methanol (50 ml) is added an excess of nucleophile. Generally 2 or 3 equivalents are employed, except in the cases of 3-aminocarbonylpyridine and aniline when 5 and 7 equivalents, respectively, were used. Anionic nucleophiles are generated by the addition of sodium hydroxide. The mixture is heated for the time indicated in the Table, for work-up, see below. All products are recrystallized from 0.1 molar perchloric acid. Melting points are uncorrected. Satisfactory microanalyses were obtained for all products after drying under reduced pressure.

When the nucleophile was an imidazole, a sodium phenolate, 2-methylpyridine, or the sodium salt of 4-thiopyridone, a suspension is formed. The product is removed from the cold mixture by filtration and recrystallized. With the other nucleophiles a clear solution results on heating. Solvent is removed under reduced pressure. Addition of absolute ethanol leads to the formation of a solid which is removed and recrystallised. After heating the 3-aminocarbonylpyridine mixture for 48 h, the solvent is removed and the resultant oil is extracted with a mixture of absolute ethanol (200 ml) and methanol (50 ml). The oil is then dissolved in methanol (50 ml) along with 5 equivalents of nucleophile and heated for an additional 24 h to produce a solution which is treated in the usual way.

Our work was kindly supported by grant AM-17442 from the National Institutes of Arthritis, Metabolism and Digestive Diseases. Mr. D. Daly kindly carried out the reaction with 3,4-dichlorothiophenol.

Received: October 24, 1979

[1] R. R. Williams, *J. Am. Chem. Soc.* **57**, 229 (1935).
[2] J. A. Zoltewicz, G. M. Kauffman, *J. Am. Chem. Soc.* **99**, 3134 (1977).
[3] J. A. Zoltewicz, T. D. Baugh, *Synthesis* **1980**, 217.