ALKYLATION OF ISOLATED THIAMIN YLIDE

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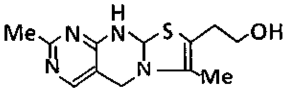
Abstract — Alkylation of isolated thiamin ylide (TY, 3) in EtOH under the neutral conditions afforded thiamin (TH^+Cl^-, 1) and the alkylated yellow form 4, which provides direct chemical evidence for the disproportionation of thiamin ylide into the ion pair of the yellow form (TH^+YF^-, 6) in a protic solvent.

Thiamin (1) shows markedly different behaviors toward bases depending on the nature and mole ratio of the base as well as the solvent. Under the aqueous alkaline conditions, treatment of 1 with two moles of NaOH (with respect to thiamin monochloride, TH^+Cl^-) gives thiamin thiolate (Na salt of anionic moiety of 7, TS^-Na^+), while in the presence of two moles of NaOEt in EtOH, 1 yields the yellow form of thiamin (Na salt of anionic moiety of 6, YF^-Na^+). On the other hand, neutralization of 1 with an equimolar amount of NaOEt takes a different course. Maier and Metzler[1] reported isolation of the tricyclic form 2 (dihydrothiochrome), whose chemical properties remain unexplored.



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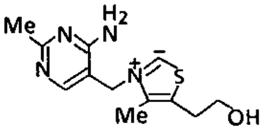
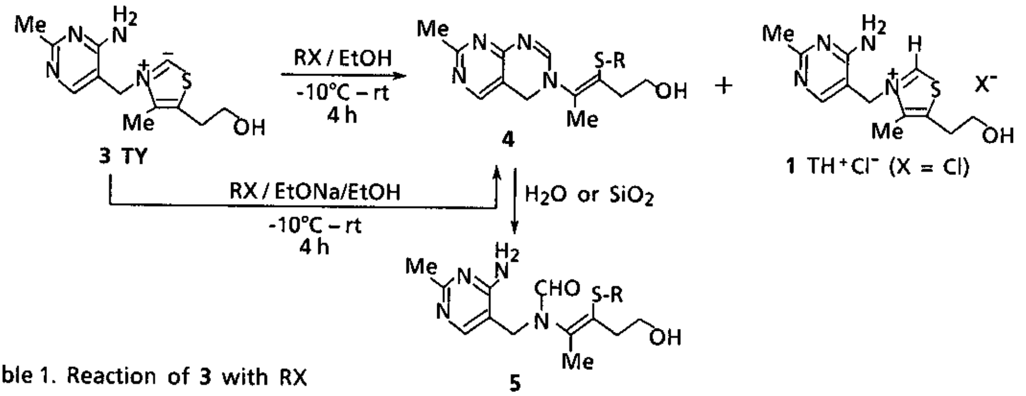


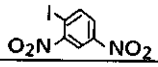
3 TY

We assigned the equimolar NaOEt neutralized product to be thiamin ylide 3, instead of 2. The compound was isolated in high yield as a mixture with NaCl and remained stable under N_2 atmosphere.[2] It exhibited a carbanion character toward a number of electrophiles, such as proton, aldehydes and disulfide, under neutral condition indicating that its reactivity is the same as those of the in-situ generated thiamin ylide.[3] We report here a novel reactivity of the isolated thiamin ylide 3 toward alkylating reagent. Reaction of 3 with RX in EtOH gave thiamin 1 and 2-methyl-6-(1-methyl-2-substituted thio-4-hydroxy-1-butenyl)-5,6-dihydropyrimido[4,5-d]pyrimidine (S-substituted yellow form, 4) in almost quantitative yields. When the same reaction was carried out in the presence of equimolar amount of NaOEt, only 4 was obtained in high yield as shown in Scheme 1 and Table 1.



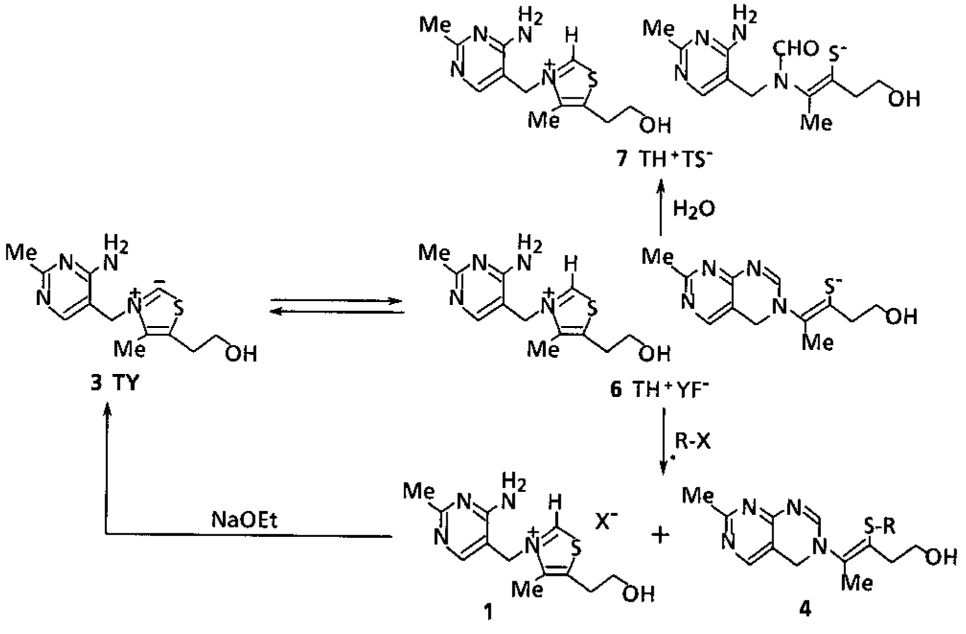
Scheme 1

Table 1. Reaction of 3 with RX

4	RX	Yield (%)
4a	MeI	91
4b	EtI	83
4c		80

The structural proofs were based on their spectroscopic data[4] and chemical behavior of these compounds **4**. Treatment of **4** with H_2O or SiO_2 treatment resulted in the formation of known ring-opened compounds **5**. No C2-substituted thiamin was obtained. No general synthetic route has yet been found to prepare the derivative of the yellow form, thus, alkylation reaction is highly versatile synthetic method for compound **4**.[6]

Discussion: The reaction route is shown in Scheme 2.



Scheme 2

Isolation of 4 indicates that 3 reacted with RX as the thiolate anion. We have reported[3] that the most characteristic feature of 3 is its disproportionation properties, that is, 3 changes into ion pair 6 in a protic solvent even under neutral condition.[11] In neutral water, ion pair 6 is converted further into ion pair 7 (thiamin thiolate, TH^+TS^-) via ring-opening of the pyrimidopyrimidine ring by H_2O.[3] The results of alkylation of 3 indicate that this ion pair 6 is directly trapped by RX to afford 1 and 4, the former being reverted to thiamin ylide in the presence of NaOEt. The disproportionation character of 3 under neutral condition indicates that it has a chemically ambident anionic character (C^- vs. S^-) and its reactivity toward electrophiles depends upon them as well as the solvent. Thus, a number of derivatives of 4 have been reported, but the chemical meaning of the yellow form of thiamin with regard to the coenzyme or non-coenzyme mechanism of thiamin is not fully understood.[12] Many hypotheses have been proposed on the role of the aminopyrimidine ring in the coenzymatic or non-coenzymatic reaction mechanism of thiamin.[15] Our results indicate that it plays an important role in the disproportionation step of thiamin ylide in producing an ion pair of the yellow form 6. Further studies on the reactivity of the isolated 3 are now in progress.

REFERENCES AND NOTES

1. G. D. Maier and D. E. Metzler, *J. Am. Chem. Soc.*, 1957, **79**, 4386, 6583.
2. H. Sugimoto and K. Hirai, *Tetrahedron Lett.*, 1985, **26**, 883.
3. H. Sugimoto and K. Hirai, *Heterocycles*, 1987, **26**, 13.
4. Physicochemical data of 4. (4a) oil, ^{1}H n.m.r. ($CDCl_3$): δ 2.03 (s, 3 H, Pm-Me), 2.20 (s, 3 H, SMe), 2.57 (s, 3 H, =-Me), 4.68 (s, 2 H, Pm-CH_2), 7.30 (s, 1 H, Pm-C7H), 8.07 (s, 1 H, Pm-C4H), ^{13}C n.m.r. ($CDCl_3$): 15.1 (Me), 17.0 (Me), 25.6 (Pm-Me), 33.6 (CH_2CH_2OH), 43.8 (Pm-CH_2), 60.0 (CH_2OH), 110.0 (Pm-C4a), 132.7 (=), 134.7 (=), 153.5, 157.3, 160.8, 168.3; u.v. max (EtOH) 245 (s), 335; mass (m/z) 278 (M^+) (5%), 263 (14), 249 (18), 147 (100), 136 (82), 122 (60). Horman[5] reported that the fragment with m/z = 147 was the base peak for yellow form (4, R = Na). (4b) oil, ^{1}H n.m.r. ($CDCl_3$): δ 1.16 (t, 3 H, J = 6 Hz, Me of SEt), 2.04 (s, 3 H, Pm-Me), 2.57 (s, 3 H, =-Me), 2.66 (m, 4 H, CH_2CH_2OH and Et), 3.83 (t, 2 H, J = 6 Hz, CH_2CH_2OH), 4.36 (bs, 1 H, OH), 4.67 (s, 1 H, Pm-CH_2), 7.21 (s, 1 H, Pm-C7H), 8.05 (s, 1 H, Pm-C4H). (4c) mp 116-119°C, hygroscopic. ^{1}H n.m.r. ($CDCl_3$): δ 2.32 (s, 3 H, Pm-Me), 2.54 (s, 3 H, =-Me), 4.70 (s, 2 H, Pm-Me), 7.40 (s, 1 H, Pm-C7H), 8.05 (s, 1 H, Pm-C4H), 7.6-9.0 (m, 3 H, Ar); i.r. (nujol cm^{-1}) 1597, 1530; u.v. (EtOH) λ_{max} (log ε) 227 (4.28), 270 (s, 3.97), 334 (4.20). Satisfactory ^{1}H n.m.r. data were obtained with 5a-c and agreed with the reported data.
5. I. Horman, *Helv. Chim. Acta*, 1984, **67**, 1478.
6. Several reactions were reported where the derivative of the yellow form of thiamin was formed by the reaction of in-situ generated thiamin ylide with an electrophile. Zima and Williams[7] isolated Na salt

of the yellow form (4, R = Na). Kasahara[8] reported the formation of neocyanothiamine (4, R = CN). The dimeric form of the free yellow form has been reported.[9] Risinger and Hsieh[10] obtained yellow crystals of the phenacyl derivative (4, R = phenacyl).

7. O. Zima and R. R. Williams, *Ber.*, 1940, **73**, 941.
8. S. Kasahara, *Chem. Pharm. Bull.*, 1960, **8**, 340.
9. G. E. Risinger, P. N. Parker and H. H. Hsieh, *Experientia*, 1965, 434.
10. G. E. Risinger and H. H. Hsieh, *Chem. & Ind.*, 1966, 1600.
11. Maier and Metzler[1] observed the existence of disproportionation properties with their isolated neutralized product of thiamin which was assigned to be dihydrothiochrome (**2** to **7**).
12. For alkali-induced transformation of thiamin into thiamin thiolate, Hopmann et al.[13] and Hormann[5] proposed a yellow form as one of its intermediates, however, for its acid-induced reverse reaction, Tee et al.[14] ruled out the yellow form as an intermediate. We have proposed a new mechanism including the crucial contribution of the ion pair of yellow form **6**.[3]
13. R. F. W. Hopmann, *Anal. N.Y. Acad. Sci.*, 1982, **378**, 32.
14. O. S. Tee, G. D. Spiropoulos, R. S. McDonald, V. D. Geldart and D. Moor, *J. Org. Chem.*, 1986, **51**, 2150.
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