# BEHAVIOR OF THE ACTIVE ALDEHYDE GENERATED FROM THIAMINE AND ITS DERIVATIVES

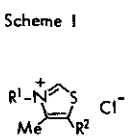
Kentaro Hirai and Hirohiko Sugimoto

Shionogi Research Laboratories, Shionogi & Co., Ltd.,

Fukushima-ku, Osaka 553, JAPAN

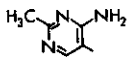
Methylsulfinylmethylthiamine (MSIT, 1b) was prepared as a sulfur derivative of thiamine (1a) and its chemical reactivity was investigated.[1] As an extension of this work, we studied the reactivity of the active aldehyde produced by the reaction of 1 or its related compounds with base ($NEt_3$) in EtOH or MeCN in the presence of aldehyde (2-furaldehyde, 2) and Michael acceptor (acrylonitrile, 3). The results are shown in Scheme I.

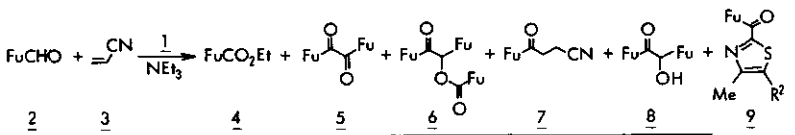
Scheme I



1

| | $R^1$ | $R^2$ |
|---|---|---|
| 1a | $PmCH_2$ | ~OH |
| 1b | $PmCH_2$ | ~SOMe |
| 1c | Me | ~SOMe |
| 1d | Me | ~OH |
| 1e | $PmCH_2$ | Ph |
| 1f | Me | Ph |

Pm = 



2 3 4 5 6 7 8 9

| Run | Solv. | 1 | Cond.[a] | Yield (%)[b] 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | EtOH | 1a | rt, 2 h | | 3 | | | 23 | 10 |
| 2 | EtOH | 1b | rt, 2 h | | 5 | | | 21 | |
| 3 | MeCN | 1b | rt, 24 h[c] | | | | | | |
| 4 | MeCN | 1c | rt, 4 h | | | 28 | 14 | | |
| 5 | MeCN | 1d | rt, 4 h | | | 17 | 28 | | |
| 6 | EtOH | 1c | rt, 2 h | 13 | 2 | 2 | 30 | 13 | |
| 7 | EtOH | 1d | rt, 2 h | 3 | | | 46 | 6 | |
| 8 | EtOH | 1e | rt, 2 h | | | | 5 | 10 | 8 |
| 9 | EtOH | 1f | rt, 2 h | 10 | | | 48 | | |

[a] Molar ratio of the reactants 2 : 3 : 1 = 5 : 6 : 1. [b] Based on 2. [c] Slow reaction.

Reaction in EtOH was faster than in MeCN. Ester 6 was obtained only in MeCN with thiazolium salts 1c,d. Substituent $R^1$ of 1 had an marked effect on the reactivity of the active aldehyde. Thiamine derivatives (1a,b) underwent only acyloin condensation yielding 5 and 8 with almost no isolation of ester 4 in EtOH. Acylthiazole was produced in about 50% yield based on 1, which was formed via base induced fragmentation of the active aldehyde. On the other hand, with thiazolium salts bearing N-Me group, reaction in EtOH gave predominantly Michael-Stetter product (7) and acyloin product (8) was a minor product, while in MeCN, 1c,d,f catalyzed the both reactions giving a mixture of 7 and 6 (instead of 8). Furthermore, the reaction using 1c,d,f was always accompanied by the formation of ester 4 or 6, which indicated the alcoholysis of the active aldehyde.

(1) K.Hirai, T.Ishiba, H.Sugimoto, T.Takahashi, and K.Inazu, Chem. Pharm. Bull., 26, 3675 (1978).