CHEMISTRY LETTERS, pp. 1353-1356, 1979.

SYNTHESIS OF DIHYDRO-1,3-OXAZINES FROM THIOAMIDES

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A new method converting thioamides to the synthetically useful precursor, 2-substituted dihydro-1,3-oxazine, is described, in which the corresponding S-methyl thiouronium salts are refluxed with 4-amino-4-methyl-2-pentanol in ^{t}BuOH or CH_2Cl_2 to give the products in high yields.

Thioamides have been utilized as key intermediates in natural products syntheses such as Vitamin B_{12}[1] and indole alkaloids.[2] Recently we have developed some useful reactions making use of the characteristics of thioamides;[3] the highly stereoselective α-coupling reaction[4] and the Michael addition reaction of wide variety of organometallics to α,β-unsaturated thioamides.[5]

While in these reactions thioamides have been utilized as latent amines,[4,6] enamines,[7] ketene S,N-acetals,[8] amides,[9] etc., almost no report has appeared concerning the conversion of thioamides to the ordinary carbonyl compounds, such as ketones,[10] aldehydes, and esters.[11] We have recently reported the versatile transformation of thioamides to ketene S,S-acetals and 1,3-dithianes,[12] one of the most familiar synthons of ketones and aldehydes. Here we wish to report the very simple method converting thioamides to dihydro-1,3-oxazines, which have been established to serve as useful precursors of aldehydes and ketones by Meyers et al.[13]

The S-methyl thiouronioum salt, isolated by the filtration of a reaction mixture of the thioamide and 2∿3 equiv. of methyl iodide in ether, was allowed to react with 4-amino-4-methyl-2-pentanol[14] in refluxing ^{t}BuOH or CH_2Cl_2 for several hours (Procedure A). The reaction could be also successfully performed without isolation of the thiouronium salt. The salt prepared in situ was subjected directly to the reaction according to the above-mentioned procedure (Procedure B). In both cases, the procedure is very simple and the purification by means of column chromatography or single distillation provided spectroscopically homogeneous dihydro-1,3-oxazines (Scheme 1).[15]

Scheme I

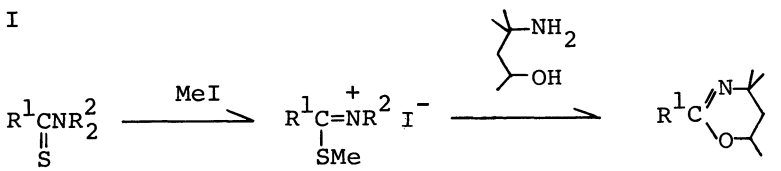
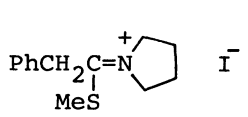
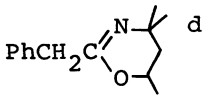
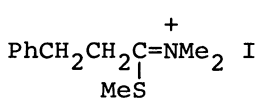
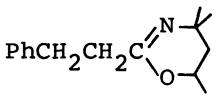
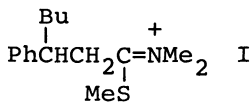
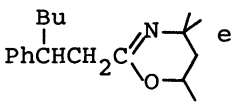
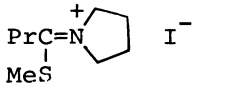
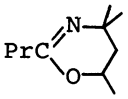
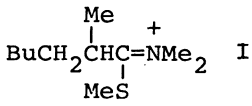
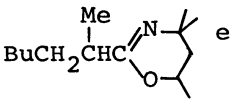
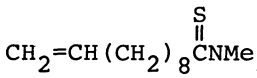
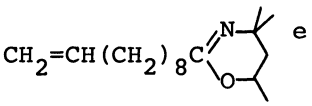
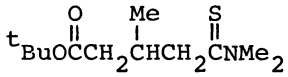
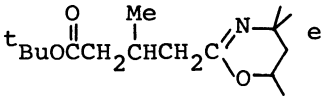


Table I Synthesis of Dihydro-1,3-oxazines from Thioamides

Entry	Reactant	Solvent (Procedure[a])	Product	Bp(°C/Torr)[b] (lit. bp)	Yield[c] (%)
1		^{t}BuOH (A)	 d	120°/0.5 (78-80° /0.25[d])	81
2		^{t}BuOH (A)		120°/0.1	72
3		CH_2Cl_2(A)	 e	120°/0.02	58
4		^{t}BuOH (A)		100°/25	90[f]
5		^{t}BuOH (A)	 e	120°/5	71
6		CH_2Cl_2(B)	 e	140°/0.3	67
7		CH_2Cl_2(B)	 e	120%/0.05	78

a) For the details of the procedure A and B, see text. The reaction mixture was refluxed for 2-4 h in the indicated solvent after addition of 4-amino-4-methyl-2-pentanol.

b) The boiling point is given as the chamber temperature (Kugelrohr distillation).

c) Unless otherwise noted, yields refer to the isolated, spectroscopically (^{1}H NMR, IR, and mass), and chromatographically homogenous materials.

d) Reference 13 (a).

e) Satisfactory analytical results have been obtained for these products.

f) Yield was determined from VPC.

The results with various kinds of thioamides are summarized in Table I, which shows the generality of the reaction for the N,N-dialkylated thioamides including the products of the Michael addition of butyllithium and t-butyl α-lithioacetate to the corresponding α,β-unsaturated thioamides (entries 3, 5, and 7). Noteworthy is the mild reaction condition (weakly basic) in comparison with the previously reported synthesis of 2-substituted dihydro-1,3-oxazines starting from nitriles by the cyclodehydrative process,[14,15] which requires strongly acidic conditions.[17]

Typical reaction procedure is exemplified as synthesis of 2-(2-methyl-3-tert-butoxycarbonylpropyl)-4,6,6-trimethyl-5,6-dihydro-1,3-oxazine (entry 7): N,N,3-trimethyl-4-tert-butoxycarbonylthiobutanoamide (0.927 mmol), obtained by the conjugate addition of tert-butyl α-lithioacetate to N,N-dimethylthiocrotonamide, was treated with 230 mg (1.6 equiv.) of CH_3I in 5 ml of dry CH_2Cl_2 under N_2 at ambient temp. for 1 day. Then 4-amino-4-methyl-2-pentanol (130 mg, 1.2 equiv.) was added and refluxed with stirring for 2.5 h. After allowed to cool, the reaction mixture was treated with H_2O. Extraction with ether and drying over Na_2SO_4, followed by evaporation of the solvents provided yellow oil, which was distilled under reduced pressure to give 204 mg (78% yield) of colorless oil (120°C/0.05 mmHg, Kugel rohr): ^1H NMR (δ, in $CDCl_3$); 0.94 (br.d, J=6 Hz, 3H), 1.16 (br.s, 6H), 1.23 (d, J=6 Hz, 3H), 1.43 (s, 9H), 1.7 (m, 2H), 2.15 (m, 5H), and 4.1 (m, 1H). IR (cm^{-1}, neat film); 1725(s), 1650(s), 1365(s), 1260(m), and 1150(s). Mass (m/e, relative intens.) 287 (M^+, <1.0), 210(18), 182(28), and 141(100).

Acknowledgement: We are grateful for the partial financial support from the Ministry of Education, the Japanese Government (Grant-in Aid for Scientific Research, No. 365306).

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(Received August 27, 1979)