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A CONVENIENT SYNTHESIS OF 2-PHENYL-Δ^2-THIAZOLINES.

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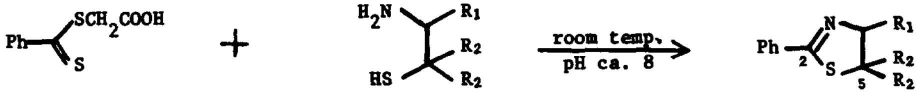
Although there have been many reports published concerning the synthesis of 2-substituted thiazolines,[1,2] most of them required stronger reaction conditions, such as at high temp., in strongly basic or acidic media. On the contrary, effective synthesis of an unstable thiazoline such as Firefly Luciferin (3a) was carried out by condensation of 2-cyano-6-hydroxybenzothiazole (1a) and cysteine (2a) under extremely mild conditions, i.e., at room temp. at pH ca. 8.[2]

1a: Ar=2-(6-Hydroxybenzothiazolyl)	2a: R=COOH	3a: Firefly Luciferin
1b: Ar=Ph	2b: R=H	3b: 49%

We found that although 2-phenyl-Δ^2-thiazoline (3b) could be prepared from benzonitrile (1b) and cysteamine (2b) according to the method as above (required refluxing in EtOH), attempted condensation of 1b and other aminothiols, i.e., cysteine (2c), its methyl ester (2d) and penicillamine (2e) under the similar condition did not give the corresponding thiazolines (3c–3e). Hence, we wish to report on a convenient synthesis of 2-phenyl-Δ^2-thiazolines (3b–3e) which were obtained in excellent yields under milder conditions.



4	2b: $R_1=R_2=H$	3b:	87%
	2c(2a): R_1=COOH; R_2=H	3c:	79%
	2d: R_1=COOMe; R_2=H	3d:	84%
	2e: R_1=COOH; R_2=Me	3e:	88%

General procedure is as follows: Thiobenzoylthioacetic acid (4)[3] (1.0 mmol) and aminothiol (2b–2e)(1.1 mmol) were dissolved in MeOH (15 ml), adjusting its pH to ca. 8 with aqueous 1N NaOH. The mixture was stirred at room temp. under slightly reduced pressure to remove generated H_2S untill a red color of 4 disappeared. The pH of the mixture was checked occasionally and kept ca. 8 by intermittent additions of the aqueous alkali. After the mixture was acidified with aqueous 1N HCl and then concentrated under reduced pressure bellow 40°, followed by extracting with ether, chloroform or ethyl acetate. Evaporation of the extracts and/or crystallization gave liq. (3b) or crystalline compounds (3c, 3d and 3e) in good yields.[4-7]

IR and NMR spectra of 3b, 3c and 3d were identical with those of the corresponding authentic samples, respectively.[4-6] IR spectrum of 3e was very similar to that of 3c, MS showed molecular peak at m/e 235 (M^+), and NMR spectral data supported the structure 3e [(δ ppm; DMSO-d_6) 1.44 and 1.72(s; 2 Me), 4.81(s; methine), 7.50 and 7.78(m; mono-substd. benzene)].[7]

Reagents of type 4, $RCS_2CH_2CO_2H$, were intensively investigated by Jensen and his co-workers till 1961.[8] Thus, alkyl, aralkyl and aryl carboxymethyl dithioate were easily obtained from the corresponding RX, $RCCl_3$ or RCHO. So this method may be expected as a convenient method for syntheses of various 2-substituted thiazolines. Further investigations are in progress.

REFERENCES AND FOOTNOTES

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2) E.H.White, F.McCapra & G.F.Field, J.Am.Chem.Soc., 85, 337 (1963), and references cited therein.

3) 4: F.Kurzer & A.Lawson, Org.Syn., Coll. V, 1046 (1973); F.Kurzer, Chem. Ind., 1333 (1961).

4)3b:(a) From 4 + 2b (room temp. for 5 hrs.). Colorless liq., bp 129-130.5°/10 mm[lit.[1b] bp 110° /5 mm]. NMR($CDCl_3$) 3.35(2H,t,J=8 Hz), 4.42(2H,t, 8), 7.45(3H,m), 7.89(2H,m). (b) From 1b + 2b: by analogous method described in the lit.[2] (refluxed in EtOH for 5 hrs.). bp 128-132.5°/10mm.

5)3c:(a) From 4 + 2c(2a)(room temp. for 23 hrs). Colorless crystalline powder, mp 116-117.5° (recrystallized from benzene)[lit.[1c] mp 122°]. IR(KBr) 1735 cm^{-1}. NMR(DMSO-d_6) 3.65(2H,d,d, 4, 8), 5.27(1H,t, 8), 7.50(3H,m), 7.77(2H,m). (b) From 3b (95%),[1c] mp 113-116°.

6)3d: From 4 + 2d (room temp. for 3.5 hrs.). Colorless fine needles, mp 112-114° [as HCl salt; lit.[1c] mp 113-4°]. IR(KBr) 1745, 1225 cm^{-1}. NMR($CDCl_3$) 3.65(2H,d,d, 4, 10), 3.84(3H,s), 5.26 (1H,t, 10), 7.40(3H,m), 7.52(2H,m). (b) From thiobenzoylserine methyl ester (47%)[1c], mp 113-4°.

7)3e: From 4 + 2e (room temp. for 22 hrs). Colorless plates, mp 120-121.5° (recrystallized from ether). IR(KBr) 1735 cm^{-1}.

8) K.A.Jensen & C.Pedersen, Acta Chem. Scand., 15, 1087 (1961), and references cited therein.