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Synthesis of thiazolines from fatty acids under solvothermal conditions

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ABSTRACT

A new approach to the synthesis of 2-alkyl thiazolines involving thionation of the amide formed by the heterocyclisation of ethanolamine in the presence of a long chain saturated/unsaturated fatty acid is highlighted under *solvothermal conditions* involving an ecofriendly method without any environmental pollution. The yields are in the range of 75-90%. All the compounds were characterized by IR, ^{1}H and ^{13}C NMR spectral analysis.

KEYWORDS

Fatty acids;
Ethanolamine;
Solvothermal reaction;
Heterocyclisation;
Thionation.

INTRODUCTION

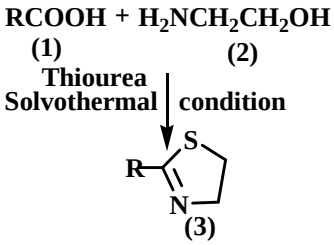
2-thiazolines constitute an important class of heterocycles with varied applications. They showed therapeutic[1] and potent fungicidal and nematocidal properties[2]; they are of utmost importance since they are used for identification of human cells with positive myeloperoxidase[3,4] reactivity. 2-substituted 2-thiazolines exhibited radioprotective activity[5]. A small amount (0.002 to 0.1%) of a 2-thiazoline derivative will effectively reduce (91-8 %) the evolution of hydrogen during pickling of iron or steel[6].

Extensive reviews carrying many synthetic and mechanistic aspects of reactions leading to the synthesis of 2-thiazolines have been submitted[7,8]. Literature surveys leading to the synthesis of 2-thiazoline derivatives indicate the absence of reference available for the direct synthesis of 2-thiazoline from acid and ethanol amine via thionation reaction. Rai et al utilized thiourea as thionating agent for the conversion of 2,5-diaryl-1,3,4-oxadiazole to 2,5-diaryl-1,3,4-thiadiazole[9] and ester to thioester[10] under solvothermal conditions. This success prompted us to utilize thiourea as thionating agent for the synthesis of 2-thiazoline derivatives from ethanolamine and carboxylic acid.

The solvothermal reactions are of interest because they offer the possibility of environmentally benign reaction conditions by reducing the burden of organic solvent disposal. The process involves the heterogeneous chemical reaction occurring in solid-liquid or solid-liquid-gas interfaces under high temperature and pressure conditions.

In an endeavour to explore a new, convenient method for the synthesis of 2-thiazolines, an attempt is made to explore the above principle for the synthesis of 2-thiazolines. The results are promising and is inferred that the solvothermal method is one of the convenient methods for the synthesis of heterocycles in general and 2-thiazolines in particular.

In this paper, how ethanolamine undergoes heterocyclisation conveniently in the presence of carboxylic acid and thiourea, at relatively low temperature and pressure, under solvothermal conditions, is described in length.



(a) R=Pentyl ; (b) R=Lauryl ; (c) R=Myristyl ; (d) R=Stearyl ; (e) R=Oleyl ; (f) Ricinoleyl

SCHEME 1

In a typical synthesis, equimolar quantities of carboxylic acid, ethanolamine and thiourea were taken in a stainless steel SS316 general purpose autoclave provided with a Teflon liner of 30ml capacity. On usual work up, it yielded 75-90 % of the product **(3)**, (SCHEME 1).

EXPERIMENTAL

Melting/boiling points were recorded in open capillaries using Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on FT/IR-460/ 113257 spectrometer (KBr). ^{1}H NMR (300MHz) and ^{13}C NMR (75MHz) spectra were recorded using DMSO-d_6 as the solvent with tetramethylsilane as the internal standard. Chemical shifts are expressed in δ-scale(ppm) coupling constants J are given in Hz. Thin layer chromatography (TLC) was carried out with precoated silica gel plates (Kieselgel 60, F_{254} Merck) using chloroform and acetone in 7:3 ratio as the eluent.

General procedure

A mixture of equimolar quantities of the carboxylic acid **1(a-f)**, ethanolamine and thiourea were taken in the autoclave reaction container (Teflon liner). The lid was placed and was lowered into the autoclaves; the plates were kept over it and the autoclave was closed and tightened. It was kept in the oven at 100^{0}C for about 8 hrs. The products after cooling, treated with water, extracted with ether. The ether extract was repeatedly washed with $NaHCO_3$ solution, to remove the unreacted acids if any, followed by washing with water. The ethereal layer was collected, dried over anhydrous Na_2SO_4 and ether was removed to get 2-thiazoline and was recrystallised from petroleum ether.

2-Pentyl thiazoline

Obtained from Hexanoic acid (1.75ml, 0.015 mmol), ethanol amine (1ml, 0.016mmol) and thiourea (2g, 0.026 mmol) as a colourless crystalline solid in 75% (1.575g) yield. m.p. 65-66^{0}C. IR (KBr) νcm^{-1}: 1645 (C= N). ^{1}H NMR (DMSO-d_6) δ: 1.05 (t, 3H, CH_3), 1.4 (q, 2H, CH2), 3.3 (t, J=6.0Hz, 2H), 4.2 (t, J = 6.7Hz, 2H); ^{13}C NMR (DMSO-d_6) δ: 19.2, 28.8, 29.8, 30.1, 38.9, 41.8, 61.9, 171.7; Anal. calcd. for $C_8H_{15}NS$ (157.28): C, 61.09; H, 9.61; N, 8.91; S, 20.39. Found:C, 60.99; H, 9.52; N, 8.88; S, 20.33%.

2-Lauryl thiazoline

Obtained from lauric acid(2.5g, 0.0125mmol), ethanolamine (1.5ml,0.025mmol) and thiourea(2g, 0.026 mmol) as a colourless crystalline in 80% (2g) yield, m.p. 97-98^{0}C; IR (KBr) νcm^{-1}: 1642 (C= N); ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, CH_3), 1.4 (q, 20 H, CH_2), 3.3 (t, J = 6.0 Hz, 2H), 4.2 (t, J = 6.7Hz, 2H); ^{13}C NMR (DMSO-d_6) δ: 29.4, 35.7, 36.2, 36.8, 38.7, 41.8, 171.4; Anal. calcd. for $C_{14}H_{27}NS$ (241.44): C, 69.65; H, 11.27; N, 5.80; S, 13.28. Found: C, 69.59; H, 11.22; N, 5.72; S, 13.23 %.

2-Myristyl thiazoline

Obtained from myristic acid (3g, 0.013mmol), ethanolamine (1.0ml, 0.016mmol) and thiourea (2g, 0.026mmol) as a colourless crystalline solid in 85 % (2.25g) yield, m.p. 69-70^{0}C; IR (KBr)νcm^{-1}: 1648 (C= N); ^{1}H NMR (DMSO-d_6) δ: 1.05(t, 3H, CH_3), 1.4(q, 20H, CH_2), 3.2 (t, J=6.0Hz, 2H), 4.2 (t, J=6.7Hz, 2H); ^{13}C NMR (DMSO-d_6) δ: 20.1, 25.8, 29.2, 29.7, 35.8, 36.2, 36.7, 38.5, 41.6, 61.8, 171.2; Anal. calcd. for $C_{16}H_{31}NS$ (269.49): C, 71.31; H, 11.59; N, 5.20; S, 11.90. Found: C, 71.27; H, 11.52; N, 5.16; S, 11.83%.

2-Stearyl thiazoline

Obtained from stearic acid (3g, 0.011mmol), ethanolamine (1.5ml, 0.025mmol) and thiourea (1.5g, 0.02mmol) as a colourless crystalline solid in 90% (2.7g) yield, m.p. 88-89^{0}C; IR (KBr) νcm^{-1}: 1644 (C= N); ^{1}H NMR (DMSO-d_6) δ: 1.05(t, 3H, CH_3), 1.4(q, 20 H, CH_2), 3.2 (t, J = 6.0 Hz, 2H), 4.2 (t, J=6.7Hz, 2H); ^{13}C NMR (DMSO-d_6) δ: 21.2, 27.2, 29.3, 29.8, 36.5, 37.2, 37.6, 39.2, 41.6, 61.5, 171.7; Anal. calcd. for $C_{20}H_{39}NS$ (325.60): C, 73.78; H, 12.07; N, 4.30; S,

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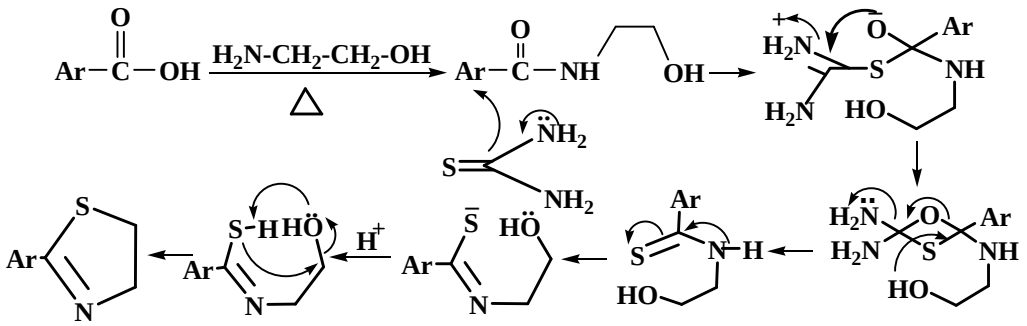

SCHEME 2

9.85. Found: C, 73.73; H, 12.01; N, 4.28; S, 9.81%.

2-Oleyl thiazoline

Obtained from oleic acid (2.0ml, 0.007mmol), ethanolamine (1.0ml, 0.016mmol) and thiourea (1.0g, 0.013 mmol) as a yellowish amorphous solid(pasty mass) in 85 % (1.7g) yield ; IR (KBr) ν cm^{-1} : 1642 (C= N); ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, CH_3), 1.3 (q, 24 H, CH_2), 2 (q, 4H, CH_2) 3.2 (t, J=6.0Hz, 2H), 4.2 (t, J = 6.7Hz, 2H), 5.5 (t, 2H, alkenic H) ; ^{13}C NMR (DMSO-d_6) δ: 35.2, 35.7, 36.2, 37.4, 39.3, 40.9, 60.1, 137.7, 170.2; Anal. calcd. for $C_{20}H_{37}NS$ (323.58): C, 74.24; H, 11.53; N, 4.33; S, 9.91. Found: C, 74.21; H, 11.49; N, 4.28; S, 9.88 %.

2-Ricinoleyl thiazoline

Obtained from ricinoleic acid (2.7ml, 0.009mmol), ethanolamine (1.0ml, 0.016mmol) and thiourea (1.5g, 0.02mmol) as a colourless crystalline solid in 90% (2.7g) yield, m.p. 78 -79^{0}C; IR (KBr) νcm^{-1}: 1644 (C= N); ^{1}H NMR (DMSO-d_6) δ: 1.06 (t, 3H, CH_3), 1.3 (q, 24 H, CH_2), 2 (q, 4H, CH_2) 3.2 (t, J=6.0Hz, 2H), 4.2 (t, J=6.7 Hz, 2H), 5.5(t, 2H, alkenic H) ; ^{13}C NMR (DMSO- d_6) δ: 30.2, 36.7, 37.2, 37.5, 38.6, 39.3, 40.8, 44.1, 47.0, 60.1, 76.9, 137.2, 170.4; Anal. calcd. for $C_{20}H_{37}NOS$ (339.58): C, 70.74; H, 10.98; N, 4.12; O, 4.71; S, 9.44. Found: C, 70.70; H, 10.92; N, 4.08; O, 4.91; S, 9.39 %.

RESULTS AND DISCUSSION

The limitations in the conventional methods of synthesis of thiazolines have been the use of toxic reagents that are difficult to handle and also harmful to the environment. Hence, it is desirable to develop a rapid, easily manipulative and above all environment friendly solvent free protocol. In view of the above observations we thought of synthesizing thiazolines using thiourea as thionating agent under solvothermal conditions. The synthetic sequence is outlined in (SCHEME 1).

Long chain fatty acids, viz: hexanoic acid, lauric acid, myristic acid, stearic acid, oleic acid and ricinoleic acid react with ethanolamine in presence of thiourea as a thionating agent under solvothermal conditions to give 2-alkyl thiazolines **3(a-f)** via heterocyclization. The qualitative element tests (Lassaigne's Test) were performed to find the presence of N, S in all cases and also elemental analysis (for C, H, N and S) was performed for all the compounds wherein the experimental and calculated values were in concurrence. IR spectra of the thiazolines prepared in this study showed only one strong band in the 1500-1700cm^{-1} region, lying between 1640-1648cm^{-1}. ^{1}H NMR showed peaks in the expected region. The resonances for ^{13}C NMR spectra were satisfactory.

The probable mechanism for the formation of thiazoline involves the intermolecular condensation reaction between the carboxylic acid and ethanolamine to give the substituted amide. The thiourea now undergoes electromeric effect to generate S^-(nucleophile) which attacks the carbonyl carbon to give the intermediate which followed by loss of a molecule of water undergoes cyclisation to give 2-substituted 2- thiazoline (SCHEME 2).

As is evident from the mechanism, it involves the nucleophilic attack on the carbonyl carbon, of the S^-. More the localization of positive charge on carbon, more pronounced the reaction would be i.e. the electron-inducing group (R) decreases the rate of the reaction. Since we have used the long chain fatty acids the effect can be only due to inductive effect which is very negli-

TABLE 1: Showing the fatty acids 1(a-f) and the respective alkyl groups

1	Carboxylic acid	Alkyl Groups
a	Hexanoicacid	R= $CH_3(CH_2)_4$
b	Lauric acid	R= $CH_3(CH_2)_{10}$
c	Myristic acid	R= $CH_3(CH_2)_{12}$
d	Stearic acid	R= $CH_3(CH_2)_{16}$
e	Oleic acid	R= $CH_3(CH_2)_7CH=CH(CH_2)_7$
f	Ricinoleic acid	R= $CH_3(CH_2)_5CHOH.CH_2.CH=CH.(CH_2)_7$

TABLE 2: Showing the 2-alkyl thiazolines 3(a-f), their melting points, % yield, M.F., IR and NMR spectra

3	M.P.^{0}C	% yield	M.F.	IR (KBr) SPECTRA (C= N)ν cm^{-1}	^{1}H NMR (DMSO-D_6)δ
a	65-66	75	$C_8H_{15}NS$	1645	1.05(T), 1.4(Q), 3.3(T), 4.2(T).
b	97-98	80	$C_{14}H_{27}NS$	1642	1.06(T), 1.4(Q), 3.3(T), 4.2(T).
c	69-70	85	$C_{16}H_{31}NS$	1648	1.05(T), 1.4(Q), 3.2(T), 4.2(T).
d	88-89	90	$C_{20}H_{39}NS$	1644	1.05(T), 1.4(Q), 3.3(T), 4.2(T).
e	-	85	$C_{20}H_{37}NS$	1642	1.06(T), 1.3(Q), 2(Q), 3.2(T), 4.2(T), 5.5(T).
f	78-79	90	$C_{20}H_{37}NOS$	1644	1.06(T), 1.3(Q), 2(Q), 3.2(T), 4.2(T).

gible. Hence all acids gave very good yield. The least is in the case of hexanoic acid.

CONCLUSION

It can be a promising method of synthesis of versatile 2-alkyl thiazolines since the starting compounds are inexpensive, readily available, non toxic, employs uncomplicated and economic reaction conditions and above all the yields are excellent. The liquid crystal study and antimicrobial activity of these compounds is under progress in our laboratory.

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