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A MILD AND EFFICIENT SYNTHESIS OF THIOL ESTERS FROM LONG-ALKENYL CHAIN CARBOXYLIC ACIDS AND THEIR ANTIMICROBIAL EVALUATION

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ABSTRACT

A series of thiol esters have been synthesized from long-chain alkenoic acids. The structures of these compounds has been elucidated by elemental and spectral (IR, ^{1}H NMR, ^{13} C NMR, MS) analysis. Furthermore, compounds were screened for *in vitro* antibacterial activity against the representative panel of two Gram-positive and two Gram-negative bacteria. All the synthesized compounds were also tested for their inhibitory action against four strains of fungus. The various compounds show potent inhibitory action against test organisms.

Keywords: Thiol Esters, Antibacterial activity, Antifungal activity

INTRODUCTION

Thiol esters show higher reactivity and selectivity toward nucleophiles than their oxygen analogues[1]. They play important roles in biological systems[2] Among the large number of methods available for the synthesis of thiols those which make use of alkenes and alkyl halides as starting materials have been the most extensively studied[3] Among a variety of methods for the preparation of thiol esters, acylation of thiols with an activated acyl derivatives in presence of an acid or a base catalyst in a suitable organic solvent are also common[4] In the wake of health and economic awareness, it is desirable to device a safe and metal free method with minimum disposable waste. To the best of our knowledge, no generalized study on long-alkenyl chain thiol esters has been made under solvent- and catalyst free conditions. Keeping in mind the principles of green chemistry, a convenient synthesis of thiol esters by the reaction of thiols with long-alkenyl chain carboxylic acid chlorides have been developed and the synthesized compounds were screened for antibacterial and antifungal activity.

EXPERIMENTAL

Undec-10-enoic **(1a)** and (*Z*)-octadec-9-enoic **(1b)** were obtained commercially from Fluka chemicals (Switzerland). (9*Z*, 12*R*)-12-Hydroxyoctadec-9-enoic **(1c)** (ricinoleic) acid was isolated from the natural sources i.e. from *Ricinus communis* seed oil following Gunstone's partition method[7]. Thionyl chloride was obtained from Merck (Mumbai, India) and was further distilled off before use. Benzenethiol **(2a)**, 4-methoxybenzenethiol **(2b)** and 4-nitrobenzenethiol **(2c)** were purchased from Aldrich. Homogeneity of the product was observed on TLC. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-300 instrument. The chemical shifts (δ) were measured relative to internal TMS. Mass spectra were obtained on a Jeol SX-102 (FAB) spectrometer. IR spectra were obtained on Shimadzu 8201 PC FT-IR using KBr pellets.

General procedure for the synthesis of thiol esters from long-alkenyl chain carboxylic acids and thiols:

Thionyl chloride (3 mmoles) and long-alkenyl chain carboxylic acid (2.5 mmoles) was heated at 80 °C for about 2 hrs to form the corresponding acid chloride. The progress of the reaction was monitored by TLC. The excess of thionyl chloride was distilled off and in the next step, thiol (2.5 mmoles) was added to the cooled reaction mixture without any solvent and catalyst under nitrogen for a certain period of time as required for completing the reaction (monitored by TLC). The reaction mixture was diluted with ethyl acetate (15 mL) and a saturated solution of $NaHCO_3$ (10 mL). The organic layer was washed with H_2O (3 x 15 mL), dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, hexane-diethyl ether, 99:1, v/v for **3a**, **3d** and **3g**, 98:2, v/v for **3b** and **3e**, 97:3, v/v for **3c** and **3f**).

Antimicrobial Screening

Antibacterial activity of the synthesized compounds **3a-g** was studied against Gram+ve bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) and Gram-ve bacteria (*Escherichia coli* and *Salmonella typhimurium)* while the antifungal activity was studied against four fungi viz., *Helminthosporum oryzae* (Laboratory isolate), *Aspergillus niger* (Laboratory isolate), *Trichoderma viridae* (Laboratory isolate), and *Candida albicans* (IOA 109). The activity was carried out by the disc diffusion method[8].

SPECTRAL DATA

S-phenyl undec-10-ene thioate **(3a):**

IR (KBr): 1660 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.29-7.24 (m, 2H, Ar-*H*), 7.18-7.15 (m, 2H, Ar-*H*), 7.06-7.02 (m, 1H, Ar-*H*), 5.85-5.76 (tdd, 1H, $J_{H-^9CH_2}$ = 6.6 Hz, J_{H-H_Z} =10.2 Hz, J_{H-H_E} = 17.1 Hz, CH_2=C*H*-), 5.03-5.01 (dd, 1H, J_{H_Z-H} = 10.2 Hz, $J_{H_Z-H_E}$ = 3.6 Hz, H_ZC=CH-), 4.90 (dd, 1H, J_{H_E-H} = 17.1 Hz, $J_{H_E-H_Z}$ = 3.6 Hz, H_EC=CH-), 2.65 (t, 2H, *J* = 6.9 Hz, CH_2 α to C=O), 2.07-2.00 (m, 2H, -CH_2-CH=CH_2), 1.88-1.73 (m, 2H, -CH_2 β to C=O), 1.33 (br.s, 10H, chain CH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 134.16 (C-1′), 131.13 (C-2′, C-6′), 129.50 (C-3′, C-5′), 125.76 (C-4′), 194.72 (C-1), 46.80 (C-2), 24.93 (C-3), 29.25 (C-4 - C-8), 34.38 (C-9), 139.21 (C-10), 114.26 (C-11). MS (*m/z* %): 277 (M^+ + 1, 15.7), 276 (M^+, 13.8), 165 (27), 151 (100), 139 (18), 137 (21), 124 (26). Analysis Calcd. for $C_{17}H_{24}OS$: C, 73.87; H, 8.74; S, 11.60%. Found C, 73.95; H, 8.79 %.

S-phenyl (Z)-octadec-9-ene thioate **(3b):**

IR (KBr): 1665 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.26-7.23 (m, 2H, Ar-*H*), 7.18-7.16 (m, 2H, Ar-*H*), 7.08-7.05 (m, 1H, Ar-*H*), 5.34-5.31 (m, 2H, -C*H*=C*H*-), 2.67 (t, 2H, *J* = 7.2 Hz, -CH_2 α to C=O), 2.04-2.02 (m, 4H, -CH_2-CH=CH-CH_2-), 1.86-1.76 (m, 2H, -CH_2 β to C=O), 1.31 (br.s, 20H, chain CH_2), 0.89 (dist.t, 3H, CH_3), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 133.53 (C-1′), 130.06 (C-2′, C-6′),129.89 (C-3′, C-5′), 125.86 (C-4′), 194.43 (C-1), 46.23 (C-2), 25.32 (C-3), 29.53 (C-4 - C-7), 34.56 (C-8 & C-11), 130.54 (C-9 & C-10), 29.19 (C-12 - C-15), 31.20 (C-16), 22.33 (C-17), 14.19 (C-18), MS (*m/z* %): 375 (M^+ + 1, 16), 374 (M^+, 12.8), 275 (28), 261 (24), 237 (21), 165 (17), 151 (100), 137 (23), 222 (25), Analysis Calcd. for $C_{24}H_{38}OS$: C, 76.95; H, 10.22; S, 8.56%. Found C, 77.12; H, 10.31 %.

S-phenyl (9Z, 12R)-12-hydroxyoctadec-9-ene thiooate **(3c):**

IR (KBr): 1655 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.27-7.24 (m, 2H, Ar-*H*), 7.19-7.15 (m, 2H, Ar-*H*), 7.05-7.02 (m, 1H, Ar-*H*), 5.56-5.35 (m, 2H, -C*H*=C*H*-), 3.88-3.84 (m, 1H, -C*H*-OH), 2.65 (t, 2H, *J* = 6.0 Hz, -CH_2 α to C=O) , 2.44-2.40 (m, 1H, -CH-O*H*), 2.06-2.02 (m, 4H, -CH_2-CH=CH-CH_2-), 1.89-1.76 (m, 2H, -CH_2 β to C=O) , 1.29 (br.s, 18H, chain CH_2), 0.88 (dist.t, 3H, CH_3), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 132.60 (C-1′), 130.11 (C-2′, C-6′), 129.79 (C-3′, C-5′), 125.76 (C-4′), 194.15 (C-1), 46.57 (C-2), 25.23 (C-3), 29.39 (C-4 - C-7), 131.96 (C-9 & C-10), 34.48 (C-8 & C-11), 71.51 (C-12), 39.62 (C-

13), 25.31 (C-14), 31.73 (C-15 & C-16), 22.55 (C-17), 14.18 (C-18), MS (*m/z* %): 391 (M^+ + 1, 18.1), 390 (M^+, 11.2), 305 (45), 261 (33), 165 (16), 151 (100), 137 (25), 238 (32), Analysis Calcd. for $C_{24}H_{38}O_2S$: C, 73.80; H, 9.80; S, 8.21%. Found C, 73.95; H, 9.92 %.

S-(4-methoxyphenyl) undec-10-ene thioate **(3d):**
IR (KBr): 1670 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.48-7.47 (m, 2H, Ar-*H*), 7.30-7.27 (m, 2H, Ar-*H*), 5.85-5.76 (tdd, 1H, $J_{H-^9CH_2}$ = 6.4 Hz, J_{H-H_Z} =10.8 Hz, J_{H-H_E} = 17.7 Hz, CH_2=C*H*-), 5.05-5.02(dd, 1H, J_{H_Z-H} = 10.8 Hz, $J_{H_Z-H_E}$ = 3.7 Hz, H_ZC=CH-), 4.90 (dd, 1H, J_{H_E-H} = 17.7 Hz, $J_{H_E-H_Z}$ = 3.7 Hz, H_EC=CH-), 3.65 (s, 3H, -OCH_3), 2.74 (t, 2H, *J* = 7.2 Hz, CH_2 α to C=O), 2.07-2.00 (m, 2H, -CH_2-CH=CH_2), 1.90-1.86 (m, 2H, -CH_2 β to C=O), 1.39 (br.s, 10H, chain CH_2), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 125.76 (C-1′), 129.79 (C-2′- C-6′), 114.26 (C-3′- C-5′), 159.29 (C-4′), 56.78 (C-1′′), 191.58 (C-1), 43.81 (C-2), 24.87 (C-3), 29.43 (C-4 - C-8), 34.38 (C-9), 139.21 (C-10), 114.28 (C-11), MS (*m/z* %): 307 (M^+ + 1, 14), 306 (M^+, 10.4), 195 (30), 181 (100), 167 (24), 139 (22), 124 (28), Analysis Calcd. for $C_{18}H_{26}O_2S$: C, 7.55; H, 8.55; S, 10.46%. Found C, 70.62; H, 8.68 %.

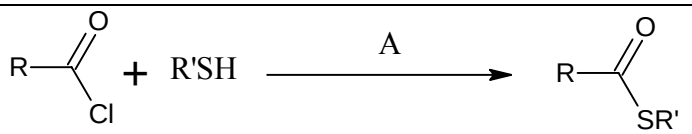
S-(4-methoxyphenyl) (Z)-octadec-9-ene thioate **(3e):**
IR (KBr): 1680 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.49-7.47 (m, 2H, Ar-*H*), 7.31-7.26 (m, 2H, Ar-*H*), 5.34-5.31 (m, 2H, -C*H*=C*H*-), 3.68 (s, 3H, -OCH_3), 2.77 (t, 2H, *J* = 7.2 Hz, -CH_2 α to C=O), 2.04-2.02(m, 4H, -CH_2-CH=CH-CH_2-), 1.86-1.76 (m, 2H, -CH_2 β to C=O), 1.29 (br.s, 20H, chain CH_2), 0.89 (dist.t, 3H, CH_3), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 125.70 (C-1′), 130.21 (C-2′, C-6′), 118.47 (C-3′, C-5′), 159.17 (C-4′), 56.79 (C-1′′), 191.47 (C-1), 44.23 (C-2), 25.67 (C-3), 29.64 (C-4 - C-7), 34.56 (C-8 & C-11), 130.54 (C-9 & C-10), 29.19 (C-12 - C-15), 31.85 (C-16), 22.63 (C-17), 14.12 (C-18), MS (*m/z* %): 405 (M^+ + 1, 18.2), 404 (M^+, 12.7), 305 (40), 291 (38), 237 (17.4), 195 (27), 181 (100), 167 (19), 222 (23), Analysis Calcd. for $C_{25}H_{40}O_2S$: C, 74.21; H, 9.96; S, 7.92%. Found C, 74.35; H, 9.78 %.

S-(4-methoxyphenyl) (9Z, 12R)-12-hydroxyoctadec-9-ene thiooate **(3f):**
IR (KBr): 1685 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 7.42-7.40 (m, 2H, Ar-*H*), 7.34-7.32 (m, 2H, Ar-*H*), 5.52-5.37 (m, 2H, -C*H*=C*H*-), 3.88-3.86 (m, 1H, -C*H*-OH), 3.75 (s, 3H, -OCH_3), 2.78 (t, 2H, *J* = 6.7 Hz, -CH_2 α to C=O) , 2.42-2.41 (m, 1H, -CH-O*H*), 2.04-2.02 (m, 4H, -CH_2-CH=CH-CH_2-), 1.87-1.74 (m, 2H, -CH_2 β to C=O) , 1.27 (br.s, 18H, chain CH_2), 0.88 (dist.t, 3H, CH_3), ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 125.38 (C-1′), 130.04 (C-2′, C-6′), 118.07 (C-3′, C-5′), 158.97 (C-4′), 55.10 (C-1′′), 192.60(C-1), 45.46 (C-2), 25.10 (C-3), 29.72 (C-4 - C-7), 130.21 (C-9 & C-10), 34.48 (C-8 & C-11), 71.98 (C-12), 39.62 (C-13), 25.31 (C-14), 31.73 (C-15 & C-16), 22.55 (C-17), 14.16 (C-18), MS (*m/z* %): 421 (M^+ + 1, 21.2), 420 (M^+, 14.5), 335 (45), 291 (32), 253 (17.2), 195 (25), 181 (100), 167 (20), 238 (32), Analysis Calcd. for $C_{25}H_{40}O_3S$: C, 71.39; H, 9.58; S, 7.62%. Found C, 71.25; H, 9.70 %.

S-(4-nitrophenyl) undec-10-ene thioate **(3g):**
IR (KBr): 1685 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ ppm: 8.10-8.04 (m, 2H, Ar-*H*), 6.64-6.60 (m, 2H, Ar-*H*), 5.85-5.76 (tdd, $J_{H-^9CH_2}$ = 6.6 Hz, J_{H-H_Z} =10.3 Hz, J_{H-H_E} = 17.2 Hz, 1H, CH_2=C*H*-), 5.01-4.91 (dd, J_{H_Z-H} = 10.3 Hz, $J_{H_Z-H_E}$ = 1.2 Hz, 1H, H_ZC=CH-), 4.90 (dd, J_{H_E-H} = 17.2 Hz, $J_{H_E-H_Z}$ = 1.2 Hz, 1H, H_EC=CH-), 2.56 (t, *J* = 8.0 Hz, 2H, CH_2 α to C=O), 2.05-2.01 (m, 2H, -CH_2-CH=CH_2), 1.65-1.59 (m, 2H, -CH_2 β to C=O), 1.36 (br.s, 10H, chain CH_2),
^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm: 138.11 (C-1′), 129.79 (C-2′- C-6′),125.76 (C-3′- C-5′), 149.29 (C-4′), 198.02 (C-1), 43.76 (C-2), 24.87 (C-3), 29.41 (C-4 - C-8), 34.42 (C-9), 139.21 (C-10), 114.26 (C-11), MS (*m/z* %): 322 (M^+ + 1, 18.3), 321 (M^+, 16), 210 (21), 196 (100), 182 (28), 139 (25), 124 (27), Analysis Calcd. for $C_{17}H_{23}NO_3S$: C, 63.53; H, 7.21; N, 4.36; S, 9.97%. Found C, 63.45; H, 7.42; N, 4.23 %.

RESULTS AND DISCUSSION

In the continuation of work on the derivatization of fatty acids[5], herein mild and general method for the synthesis of thiol esters from long-alkenyl chain acid chlorides and thiols under solvent- and catalyst-free conditions was developed **(Scheme 1)**.



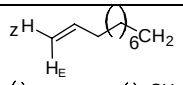
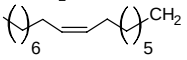
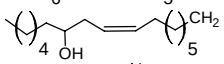
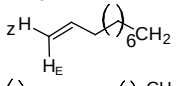
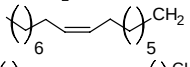
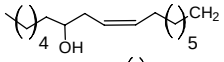
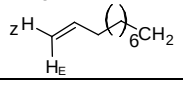
1a-c **2a-c** **3a-g**

A: catalyst- and solvent-free, 55-80 ^{0}C

Scheme-1: Synthesis of thiol esters from long-alkenyl chain carboxylic acids and thiols

Thiol was added to the acid chloride and was stirred at required temperature without solvent and catalyst under nitrogen for an appropriate time as required completing the reaction (as given in **Table 1**).

Table-1: General synthesis of long-alkenyl chain carboxylic acid chlorides with different thiols

Entry	Starting from 1, 2	R	R´	Temp ($^{\circ}$C)	Time (min.)	Product[a]	Product yield (%)[b]
1	1a, 2a		C_6H_5	55	12	3a	94
2	1b, 2a		C_6H_5	60	12	3b	96
3	1c, 2a		C_6H_5	60	12	3c	92
4	1a, 2b		4-$MeOC_6H_4$	65	18	3d	90
5	1b, 2b		4-$MeOC_6H_4$	70	18	3e	90
6	1c, 2c		4-$MeOC_6H_4$	70	19	3f	88
7	1a, 2c		4-$NO_2C_6H_4$	80	21	3g	95

[a]The structure of the obtained esters, was confirmed through the IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analyses.
[b]Isolated yields by column chromatography.

To the prior, acid chloride **1a-c** was synthesized from olefinic and hydroxy olefinic long-chain acids by in situ preparation. Since acid chlorides **1a-c** are not commercially available the present method has greatly solved the problem by facile and efficient in situ preparation [6]. The reaction was spontaneous and after few minutes the corresponding thiol esters were obtained in good to excellent yields (88-96 %).

Initially the reaction of undec-10-enoyl chloride **(1a)** with various thiols was investigated. When the reaction of **1a** with different thiols **2a-d** was carried out, good yields were obtained in almost all cases as shown in **Fig.1**.

The method is applicable for the preparation of a wide variety of thiol esters which support the generality of the procedure. The reactions of benzenethiol **(2a)**, 4-methoxybenzenethiol **(2b)** and 4-nitrobenzenethiol **(2c)** with different acid chlorides gave the corresponding thiol esters in good yields respectively. A product in trace amount was also formed which was not isolated. The results are summarized in **Table 1**.

Chromatographic processes led to the isolation of products **3a-g** which was characterized by spectroscopic means. In the IR spectra, all the long-chain thiol esters exhibited an additional band at 1655-1685 cm^{-1} corresponding to the ester carbonyl. In the ^{1}H NMR spectra of compounds **3a-g** aromatic proton values were obtained. In ^{13}C NMR spectra all the synthesized compounds showed the peak at δ 191.47-195.76 corresponding to carbonyl carbon. The characteristic signal at δ 43.56 - 46.80 was obtained for C-2 in all the synthesized compounds. The characteristic signal of C-1′ was appeared at δ 132.60-134.16 in compounds **3a-c**, at δ 121.38-125.76 in compounds **3d-f** and at δ 138.11 in compound **3g**. All the synthesized thiol esters showed the correct molecular ion peak (M^{+}) in the mass spectra.

All the compounds **3a-g** were screened for antibacterial and antifungal activity. Screening results are summarized in **Table 2** and **Table 3**. The minimum inhibitory concentrations (MIC) of all the tested compounds were 0.1 mg/ml. The newly generated compounds have exerted significant inhibitory activity against the growth of the test bacterial strains. The data pertaining to **Table 2** reveals that **3a-g** have significant influence on antibacterial profile of Gram+ve bacteria (*Bacillus subtilis* and *Staphylococcus aureus*). The synthesized compounds also showed good inhibitory results against the Gram-ve bacteria (*Escherichia coli* and *Salmonella typhimurium).*

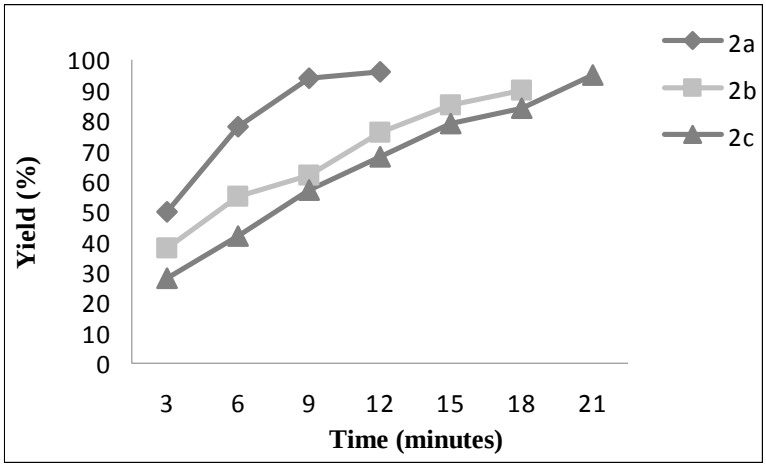


Fig.-1: Reaction of undec-10-enoyl chloride with thiols under solvent- and catalyst-free conditions as a function of time: (2a) benzenethiol, (2b) 4-methoxybenzenethiol and (2c) 4-nitrobenzenethiol.

Table-2: Antibacterial activity of compounds 3a-g

Compound	Diameter of zone of inhibition (mm) at 0.1mg/ml			
	Gram negative		*Gram positive*	
	E. coli	*S. typhimurium*	*B. subtilis*	*S. aureus*
3a	14	21	35	28
3b	14	23	34	29
3c	15	23	34	29
3d	14	23	34	31
3e	13	22	35	31
3f	13	22	35	30
3g	15	25	36	32
Chloramphenicol	20	28	40	36
Control DMSO	---	---	---	---

In another set of experiments, the above mentioned compounds were also examined for antifungal activity **(Table 3)**. Nystatin was used as standard drug for the comparison of antifungal results. Against all fungal strains (*Helminthosporum oryzae*, *Aspergillus niger*, *Trichoderma viridae*, *and Candida albicans)*, compounds **3a-g** showed good inhibitory results.

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Table-3: Antifungal activity of compounds 3a-g

Compound	Diameter of zone of inhibition (mm) at 0.1mg/ml			
	C.albicans	*H.oryzae*	*A.niger*	*T. viridae*
3a	24	13	15	16
3b	23	12	14	17
3c	23	12	14	16
3d	24	15	16	15
3e	23	14	15	15
3f	23	15	15	16
3g	26	16	16	16
Nystatin	30	20	20	20
Control DMSO	---	---	---	---

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