Pergamon

Tetrahedron 58 (2002) 7619–7624

TETRAHEDRON

Carbodiimide mediated synthesis of 4-thiazolidinones by one-pot three-component condensation

Tumul Srivastava, W. Haq and S. B. Katti*

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

Received 22 April 2002; revised 24 June 2002; accepted 18 July 2002

Abstract—In the present study, 4-thiazolidinones have been assembled by DCC mediated three-component reaction of amine, aldehyde and mercaptoacetic acid. The final compounds are obtained in quantitative yields within one hour.

1. Introduction

The structural and therapeutic diversity coupled with commercial viability of small heterocyclic molecules has fascinated organic and medicinal chemists. In recent years, 4-thiazolidinones and oxazolidinones are the most extensively investigated class of compounds. While oxazolidinones are emerging as new class of antibiotics represented by Linezolid,[1] 4-thiazolidinones have many interesting activity profiles namely COX-1 inhibitors,[2] inhibitors of the bacterial enzyme MurB,[3] non-nucleoside inhibitors of HIV-RT[4] and anti-histaminic agents.[5] Consequently, many different protocols have been developed that allow the synthesis of 4-thiazolidinone skeletons. These methods employ a one-pot three-component condensation or a two step synthesis.[6] The reaction is believed to proceed via imine formation in the first step followed by attack of sulfur nucleophile on the imine carbon and finally intramolecular cyclization with the elimination of water. The latter step seems to be critical for obtaining high yields of 4-thiazolidinones. Therefore, variations have been made in the removal of water during the cyclization. Most commonly followed protocols[7] use either azeotropic distillation or molecular sieves. In addition, there are scattered reports of using anhydrous $ZnCl_2$[8] or sodium sulphate[9] as desiccant. In all the above-mentioned methods, the reaction requires prolonged heating at high temperatures (70–80°C) for nearly 17–20 h. Alternatively, reaction is performed in sealed vessels at 70°C using molecular sieves.[7] These protocols tend to be limited by yields ranging from moderate to very good depending on the reactants. Secondly, it is desirable to avoid the use of another solid component like molecular sieves and/or $ZnCl_2$ particularly in solid phase synthesis. In order to circumvent these difficulties we have chosen a radically different approach to generate 4-thiazolodinone scaffolds by simpler methods in quantitative yields. The protocol is ideally suited for the synthesis of a thiazolidinone library.

A variety of desiccants namely, trimethylorthoformate, molecular sieves, sodium sulphate and azeotropic distillation have been reported in the literature for the preparation of thiazolidinones. It is generally believed that the first step in the annulation is addition of sulfur nucleophile to the imine centre followed by attack of the nitrogen on the carboxylic moiety with the expulsion of water giving the cyclized product. The rate-limiting step appears to be the attack of the amine nitrogen at the carbonyl carbon. If this could be enhanced, one could rapidly obtain the thiazolidinones in high yields. Bearing this in mind we surmised that carbodiimides, which are extensively used in peptide synthesis for dehydration leading to peptide bond formation,[10] could be an ideal candidate to activate the carboxyl group of the adduct obtained by the sulfur addition to the imine thereby facilitating cyclization.

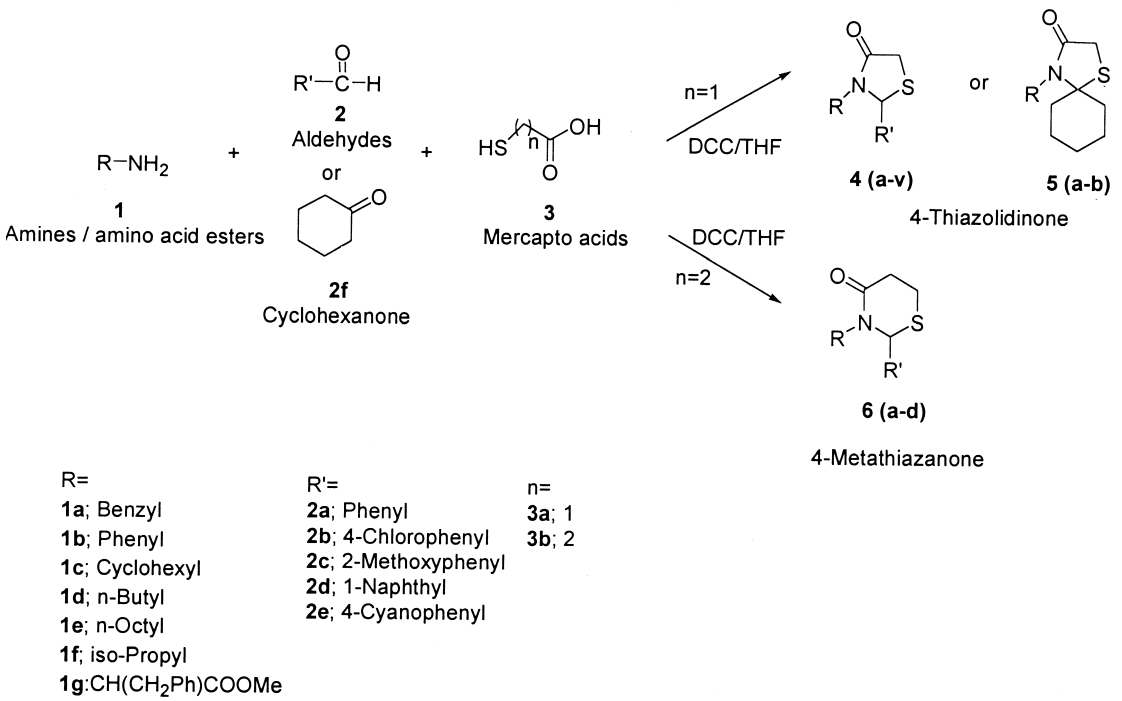
2. Result and discussion

A pilot experiment using benzylamine, benzaldehyde and mercaptoacetic acid proceeded uneventfully and the product was isolated in quantitative yield after work up. To optimize the ratios of reactants, experiments were carried out using different proportions of the reactants. It was observed that the ratios of reactants at 1:2:3 for amine, aldehyde and mercapto acetic acid, respectively gave almost quantitative yields. This is in agreement with the earlier observation by the Holmes et al.[7] In a typical experiment, amine and aldehyde are stirred in THF under ice cooling for 5 min, followed by addition of mercaptoacetic acid and DCC and the reaction mixture is stirred for an additional 55 min. The DCU, which was precipitated, was removed by filtration and

Keywords: thiazolidinones; metathiazanones; carbodiimide.

* Corresponding author. Fax: +91-522-223405;
e-mail: setu_katti@yahoo.com

0040–4020/02/$ - see front matter
PII: S0040-4020(02)00866-9



Scheme 1. Synthesis of 4-thiazolidinone and 4-metathiazanone derivatives.

the usual work-up gave the desired products in almost quantitative yields. We have observed that addition of DCC in ice cold conditions gives better yields as compared with the reaction carried out at ambient temperature.

Encouraged by this result and to gain more insight into the reaction we have synthesized a variety of 4-thiazolidinones with different amines and aldehydes (Scheme 1). It has been observed that sterically hindered and aromatic amines react sluggishly during cyclization, leading to poor yields. In order to avert these shortcomings, sterically hindered amines including amino acids were examined (Table 1). The results obtained were excellent (entries **4f**,**g**,**q**–**v**, **6c**,**d**, Table 1). We next turned our attention to address the scope and limitation of the present protocol. We concentrated on aldehydes having electron donating (**2c**) and electron withdrawing (**2b**, **2e**) substituents. It is evident from the yields reported in Table 1 (entries **4b**,**c**,**e**,**m**,**n**) that the present method obviates the limitations of the earlier methods and is more versatile. Furthermore, the data presented in Table 1 underscores the efficiency of the present method and the yields of the thiazolidinones are independent of the nature of the amine and aldehyde component. As an obvious extension of this protocol, we performed the reaction using a ketone (**2f**) instead of an aldehyde. We obtained the corresponding thiazolidinone in nearly quantitative yield (entries **5a**,**b**, Table 1). This is a significant development considering the fact that there are few reports in the literature for making thiazolidinones using ketones. Generally low yields of thiazolidinones are reported in the literature when amino acids are used as a source of amine,[7] however it may be appropriate to mention here that with present protocol moderate yields were obtained. Bearing in mind the versatility of the protocol and to further enhance the scope of this reaction we concentrated our efforts on adaptation to synthesis of metathiazanones, another biologically active chromophore. Until recently one of the compounds in this series, namely Chlormezanone,[11] was used as skeletal muscle relaxant. The yields are better (entries **6a**–**d**, Table 1) than the reported

Table 1. Isolated yields and FAB-MS data of 4-thiazolidinones and 4-Metathiazanones

Product	1	2	3	% Yield	FABMS $[M+H]^+$	Product	1	2	3	% Yield	FABMS $[M+H]^+$
4a	1a	2a	3a	78	270	**4o**	1e	2d	3a	85	342
4b	1a	2b	3a	86	304	**4p**	1e	2e	3a	82	317
4c	1a	2c	3a	88	300	**4q**	1f	2a	3a	65	222
4d	1a	2d	3a	86	320	**4r**	1f	2b	3a	84	256
4e	1a	2e	3a	95	295	**4s**	1f	2c	3a	59	252
4f	1b	2a	3a	91	256	**4t**	1f	2d	3a	66	272
4g	1b	2b	3a	94	290	**4u**	1g	2a	3a	67	342
4h	1c	2a	3a	60	262	**4v**	1g	2b	3a	65	376
4i	1c	2b	3a	95	296	**5a**	1a	2f	3a	95	262
4j	1c	2c	3a	63	292	**5b**	1e	2f	3a	87	284
4k	1c	2d	3a	54	312	**6a**	1a	2a	3b	92	284
4l	1d	2a	3a	95	236	**6b**	1a	2d	3b	90	334
4m	1d	2b	3a	90	270	**6c**	1g	2a	3b	51	356
4n	1e	2c	3a	94	322	**6d**	1g	2c	3b	52	386

procedures.[7,11] It is apparent from the variety of reactants mentioned in the table that the present method has the potential to generate a battery of thiazolidinones and metathiazanones by solution as well as solid phase combinatorial synthesis.

In summary, the straightforward protocol described here has many unique features and should be of general interest for the following reasons. Reaction conditions are extremely simple. The products are obtained in quantitative yields and amenable to scale-up operations. The yields of the thiazolidinones are independent of the nature of the reactants.

3. Experimental

Melting points (mp) were determined on a Complab melting point apparatus and are uncorrected. The C, H, N analyses were carried out on CARLO-ERBA EA1108 elemental analyser. Thin-layer chromatography (tlc) was performed on readymade silica gel plates (Merck) using ethyl acetate–hexane (4:6) as solvent system. Iodine was used as developing reagent. Infrared (IR) spectra were recorded on an FT-IR Perkin–Elmer spectrometer. The ^{1}H spectra were recorded on a DPX-200 Bruker FT-NMR spectrometer. The chemical shifts were reported as parts per million (δ ppm) from $(CH_3)_4Si$ (TMS) as an internal standard. The ^{13}C NMR spectra were recorded on a DPX-200 Bruker FT-NMR (50 MHz) spectrometer. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Column chromatography separations were obtained on silica gel (230–400 mesh).

3.1. Reaction of primary amines (or amino acid esters) and aldehydes with mercaptoacetic acid

The appropriate amine or amino acid ester (1.0 mmol) and aldehyde (2.0 mmol) were stirred in THF under ice cold conditions for 5 min, followed by addition of mercaptoacetic acid (3.0 mmol). After 5 min DCC (1.2 mmol) was added to the reaction mixture at 0°C and the reaction mixture stirred for an additional 50 min at room temp. DCU was removed by filtration and the filtrate was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 5% aq. citric acid, water, 5% aq. sodium hydrogen carbonate and then finally with brine. The organic layer was dried over sodium sulphate and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using hexane–ethyl acetate as eluent.

3.1.1. 3-Benzyl-2-phenyl-1,3-thiazolidin-4-one (4a). This compound was obtained as white solid in 78% yield. mp 152–155°C; Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20 Found: C, 71.80; H, 5.38; N, 4.91; R_f 0.57; IR (KBr) ν_{max} C=O 1672 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.54 (d, J=14.7 Hz, 1H, CH_2Ph), 3.75 (d, J=15.6 Hz, 1H, CH_2), 3.91 (d, J=15.6 Hz, 1H, CH_2), 5.16 (d, J=14.7 Hz, 1H, CH_2Ph), 5.39 (s, 1H, CH), 7.08–7.42 (m, 10H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.61, 139.61, 135.76, 129.59 (2C), 129.51 (2C), 129.16 (2C), 128.81 (2C), 127.57 (2C), 63.17, 46.66, 33.37; FAB-MS m/z 270 [M+H]$^+$.

3.1.2. 3-Benzyl-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (4b). This compound was obtained as gummy matter in 86% yield; Anal. Calcd for $C_{16}H_{14}ClNOS$: C, 63.25; H, 4.64; N, 4.61. Found: C, 63.65; H, 4.87; N, 4.71; R_f 0.57; IR (neat) ν_{max} C=O 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.53 (d, J=14.7 Hz, 1H, CH_2Ph), 3.76 (d, J=15.6 Hz, 1H, CH_2), 3.91 (d, J=15.6 Hz, 1H, CH_2), 5.15 (d, J=14.7 Hz, 1H, CH_2Ph), 5.36 (s, 1H, CH), 7.05–8.04 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.51, 138.14, 135.52, 135.45, 129.72 (2C), 129.22 (2C), 129.01 (2C), 128.76 (2C), 128.41, 62.52, 46.73, 33.33; FAB-MS m/z 304 [M+H]$^+$.

3.1.3. 3-Benzyl-2-(2-methoxyphenyl)-1,3-thiazolidin-4-one (4c). This compound was obtained as gummy matter in 88% yield; Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68. Found: C, 68.48; H, 5.84; N, 4.38; R_f 0.41; IR (neat) ν_{max} C=O 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (d, J=14.8 Hz, 1H, CH_2Ph), 3.75 (d, J=15.7 Hz, 1H, CH_2), 3.79 (s, 3H, OCH_3), 3.83 (d, J=15.7 Hz, 1H, CH_2), 5.15 (d, J=14.8 Hz, 1H, CH_2Ph), 5.75 (s, 1H, CH), 6.88–7.32 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.98, 157.11, 135.65, 129.94, 128.62 (2C), 128.25 (2C), 127.72, 127.38, 126.96, 120.87, 111.20, 57.85, 55.54, 46.54, 32.79; FAB-MS m/z 300 [M+H]$^+$.

3.1.4. 3-Benzyl-2-(1-naphthyl)-1,3-thiazolidin-4-one (4d). This compound was obtained as gummy matter in 86% yield; Anal. Calcd for $C_{20}H_{17}NOS$: C, 75.20; H, 5.36; N, 4.39. Found: C, 74.94; H, 5.41; N, 4.28; R_f 0.20; IR (neat) ν_{max} C=O 1674 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (d, J=15.2 Hz, 1H, CH_2Ph), 3.77 (d, J=15.9 Hz, 1H, CH_2), 3.89 (d, J=15.9 Hz, 1H, CH_2), 5.33 (d, J=15.2 Hz, 1H, CH_2Ph), 6.15 (s, 1H, CH), 7.10–7.94 (m, 12H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.36, 135.78, 134.68, 130.0, 129.65, 129.21 (2C), 128.75 (2C), 128.38, 127.23, 127.02, 126.63, 125.82, 124.39 (2C), 122.44, 63.44, 47.27, 33.18; FAB-MS m/z 320 [M+H]$^+$.

3.1.5. 4-[(3-Benzyl)-4-oxo-1,3-thiazolidin-2-yl] benzonitrile (4e). This compound was obtained as gummy matter in 95% yield; Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N, 9.52. Found: C, 69.28; H, 5.04; N, 9.38; R_f 0.46; IR (neat) ν_{max} C=O 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.57 (d, J=14.8 Hz, 1H, CH_2Ph), 3.77 (d, J=15.7 Hz, 1H, CH_2), 3.92 (d, J=15.7 Hz, 1H, CH_2), 5.15 (d, J=14.8 Hz, 1H, CH_2Ph), 5.40 (s, 1H, CH), 7.06–8.01 (m, 9H, Ar); FAB-MS m/z 295 [M+H]$^+$.

3.1.6. 2,3-Diphenyl-1,3-thiazolidin-4-one (4f). This compound was obtained as gummy matter in 91% yield; Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.87; H, 5.31; N, 5.38; R_f 0.63; IR (neat) ν_{max} C=O 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (d, J=15.7 Hz, 1H, CH_2), 4.0 (d, J=15.7 Hz, 1H, CH_2), 6.09 (s, 1H, CH), 7.14–7.38 (m, 10H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.42, 140.01, 138.01, 129.46 (2C), 129.27 (4C), 127.34 (2C), 126.0 (2C), 66.03, 33.85; FAB-MS m/z 256 [M+H]$^+$.

3.1.7. 2-(4-Chlorophenyl)-3-phenyl-1,3-thiazolidin-4-one (4g). This compound was obtained as white solid in 94%

yield; mp 124–127°C; Anal. Calcd for $C_{15}H_{12}ClNOS$: C, 62.17; H, 4.17; N, 4.83. Found: C, 61.98; H, 4.33; N, 4.90; R_f 0.48; IR (KBr) ν_{max} C=O 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (d, J=15.7 Hz, 1H, CH_2), 3.98 (d, J=15.7 Hz, 1H, CH_2), 6.07 (s, 1H, CH), 7.12–7.34 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.20, 138.47, 137.73, 135.12, 129.59 (2C), 129.50 (2C), 128.81 (2C), 127.61, 126.0 (2C), 65.29, 33.79; FAB-MS m/z 290 $[M+H]^+$.

3.1.8. 3-Cyclohexyl-2-phenyl-1,3-thiazolidin-4-one (4h). This compound was obtained as white solid in 60% yield; mp 118–121°C; Anal. Calcd for $C_{15}H_{19}NOS$: C, 68.93; H, 7.33; N, 5.36. Found: C, 68.88; H, 7.66; N, 5.49; R_f 0.61; IR (KBr) ν_{max} C=O 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94–1.27 (m, 6H, cyclohexyl), 1.50–1.76 (m, 4H, cyclohexyl), 3.59 (d, J=15.5 Hz, 1H, CH_2), 3.80–3.87 (m, 1H, cyclohexyl), 3.91 (d, J=15.5 Hz, 1H, CH_2), 5.64 (s, 1H, CH), 7.21–7.43 (m, 5H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.94, 143.20, 129.27 (2C), 129.07, 126.55 (2C), 62.98, 56.43, 33.46, 31.25, 30.34, 26.29 (2C), 25.62; FAB-MS m/z 262 $[M+H]^+$.

3.1.9. 2-(4-Chlorophenyl)-3-cyclohexyl-1,3-thiazolidin-4-one (4i). This compound was obtained as crystalline solid in 95% yield; mp 111–113°C; Anal. Calcd for $C_{15}H_{18}ClNOS$: C, 60.90; H, 6.13; N, 4.73. Found: C, 60.74; H, 6.05; N, 4.83; R_f 0.74; IR (KBr) ν_{max} C=O 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96–1.28 (m, 6H, cyclohexyl), 1.51–1.79 (m, 4H, cyclohexyl), 3.59 (d, J=15.5 Hz, 1H, CH_2), 3.63–3.84 (m, 1H, cyclohexyl), 3.88 (d, J=15.5 Hz, 1H, CH_2), 5.61 (s, 1H, CH), 7.22–7.40 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.05, 142.10, 135.01, 129.51 (2C), 127.91 (2C), 62.23, 56.44, 33.34, 31.40, 30.37, 26.24 (2C), 25.58; FAB-MS m/z 296 $[M+H]^+$.

3.1.10. 3-Cyclohexyl-2-(2-methoxyphenyl)-1,3-thiazolidin-4-one (4j). This compound was obtained as gummy matter in 63% yield; Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.58; H, 7.46; N, 4.87; R_f 0.55, IR (neat) ν_{max} C=O 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.32 (m, 6H, cyclohexyl), 1.57–1.79 (m, 4H, cyclohexyl), 3.51 (d, J=15.2 Hz, 1H, CH_2), 3.85–3.95 (m, 1H, cyclohexyl), 3.82 (d, J=15.2 Hz, 1H, CH_2), 3.91 (s, 3H, OCH_3), 5.97 (s, 1H, CH), 6.88–7.28 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.78, 156.94, 131.31, 129.80, 126.73, 121.30, 111.39, 55.85, 33.53, 31.03, 30.56, 30.45, 26.23, 25.78, 25.69, 25.58; FAB-MS m/z 292 $[M+H]^+$.

3.1.11. 3-Cyclohexyl-2-(1-naphthyl)-1,3-thiazolidin-4-one (4k). This compound was obtained as gummy matter in 54% yield; Anal. Calcd for $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50. Found: C, 73.74; H, 6.93; N, 4.48; R_f 0.26; IR (neat) ν_{max} C=O 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90–1.33 (m, 6H, cyclohexyl), 1.54–2.07 (m, 4H, cyclohexyl), 3.60–3.86 (m, 1H, cyclohexyl), 3.82 (d, J=15.4 Hz, 1H, CH_2), 3.96 (d, J=15.4 Hz, 1H, CH_2), 6.42 (s, 1H, CH), 7.25–7.93 (m, 7H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.19, 134.57, 129.70 (2C), 129.21, 128.39, 127.20, 126.52, 125.53 (2C), 122.13, 56.23, 33.54, 31.30, 30.66, 26.18 (2C), 25.55 (2C); FAB-MS m/z 312 $[M+H]^+$.

3.1.12. 3-Butyl-2-phenyl-1,3-thiazolidin-4-one (4l). This compound was obtained as gummy matter in 95% yield; Anal. Calcd for $C_{13}H_{17}NOS$: C, 66.34; H, 7.28; N, 5.95. Found: C, 66.45; H, 7.39; N, 5.87; R_f 0.65; IR (neat) ν_{max} C=O 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J=7.1 Hz, 3H, CH_3C$_3$H$_6$), 1.18–1.46 (m, 4H, CH$_3$(CH_2)$_2$CH$_2$), 2.63–2.68 (m, 2H, C$_3$H$_7$CH_2), 3.67 (d, J=15.5 Hz, 1H, CH_2), 3.76 (d, J=15.5 Hz, 1H, CH_2), 5.63 (s, 1H, CH), 7.26–7.43 (m, 5H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.06, 139.60, 130.42, 129.51, 129.44, 128.74, 127.32, 63.51, 42.62, 32.88, 28.74, 19.86, 13.53; FAB-MS m/z 236 $[M+H]^+$.

3.1.13. 3-Butyl-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (4m). This compound was obtained as gummy matter in 90% yield; Anal. Calcd for $C_{13}H_{16}ClNOS$: C, 57.87; H, 5.98; N, 5.19. Found: C, 57.53; H, 6.06; N, 4.81; R_f 0.23; IR (neat) ν_{max} C=O 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J=7.1 Hz, 3H, CH_3C$_3$H$_6$), 1.19–1.45 (m, 4H, CH$_3$(CH_2)$_2$CH$_2$), 2.62–2.66 (m, 2H, C$_3$H$_7$CH_2), 3.68 (d, J=15.5 Hz, 1H, CH_2), 3.83 (d, J=15.5 Hz, 1H, CH_2), 5.60 (s, 1H, CH), 7.22–7.85 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.36, 138.67, 135.34, 129.69 (2C), 128.72 (2C), 63.26, 43.08, 33.28, 29.20, 20.33, 14.01; FAB-MS m/z 270 $[M+H]^+$.

3.1.14. 2-(2-Methoxyphenyl)-3-octyl-1,3-thiazolidin-4-one (4n). This compound was obtained as gummy matter in 94% yield; Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 67.29; H, 8.71; N, 4.37; R_f 0.56; IR (neat) ν_{max} C=O 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, J=6.8 Hz, 3H, CH_3C$_7$H$_{14}$), 1.23–1.47 (m, 12H, CH$_3$(CH_2)$_6$CH$_2$), 2.62–2.67 (m, 2H, C$_7$H$_{15}$CH_2), 3.60 (d, J=15.3 Hz, 1H, CH_2), 3.75 (d, J=15.3 Hz, 1H, CH_2), 3.87 (s, 3H, OCH_3), 5.99 (s, 1H, CH), 6.89–7.30 (m, 4H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.18, 157.30, 130.14, 128.36, 126.89, 121.28, 111.44, 58.19, 55.98, 43.55, 33.08, 32.12, 29.54, 29.47, 27.30, 27.14, 22.97, 14.41; FAB-MS m/z 322 $[M+H]^+$.

3.1.15. 2-Naphthyl-3-octyl-1,3-thiazolidin-4-one (4o). This compound was obtained as gummy matter in 85% yield; Anal. Calcd for $C_{21}H_{27}NOS$: C, 73.86; H, 7.97; N, 4.10. Found: C, 74.01; H, 8.07; N, 3.95; R_f 0.63; IR (neat) ν_{max} C=O 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (t, J=6.8 Hz, 3H, CH_3C$_7$H$_{14}$), 1.11–1.70 (m, 12H, CH$_3$(CH_2)$_6$CH$_2$), 2.65–2.74 (m, 2H, C$_7$H$_{15}$CH_2), 3.75 (d, J=15.2 Hz, 1H, CH_2), 3.87 (d, J=15.2 Hz, 1H, CH_2), 6.40 (s, 1H, CH), 7.26–7.94 (m, 7H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.22, 134.66, 130.63, 130.36, 129.69, 127.25, 126.58, 125.75, 123.25, 122.81, 122.46, 44.05, 33.20, 32.81, 32.09, 29.51, 29.45, 27.48, 27.17, 22.96, 14.41; FAB-MS m/z 342 $[M+H]^+$.

3.1.16. 4-(3-Octyl-4-oxo-1,3-thiazolidin-2-yl) benzonitrile (4p). This compound was obtained as gummy matter in 82% yield; Anal. Calcd for $C_{18}H_{24}N_2OS$: C, 68.32; H, 7.64; N, 8.85. Found: C, 68.44; H, 7.82; N, 8.76; R_f 0.61; IR (neat) ν_{max} C=O 1679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J=6.7 Hz, 3H, CH_3C$_7$H$_{14}$), 1.22–1.68 (m, 12H, CH$_3$(CH_2)$_6$CH$_2$), 2.57–2.64 (m, 2H, C$_7$H$_{15}$CH_2), 3.65 (d, J=15.3 Hz, 1H, CH_2), 3.80 (d, J=15.3 Hz, 1H, CH_2), 5.64, (s, 1H, CH), 7.40 (d, J=8.2 Hz, 2H, Ar), 7.70 (d, J=8.2 Hz, 2H, Ar); FAB-MS m/z 317 $[M+H]^+$.

3.1.17. 3-(Isopropyl)-2-phenyl1,3-thiazolidin-4-one (4q). This compound was obtained as white solid in 65% yield;

mp 99–102°C; Anal. Calcd for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 64.94; H, 6.93; N, 6.49; R_f 0.63; IR (KBr) ν_{max} C=O 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (d, J=6.9 Hz, 3H, CH_3CHCH_3), 1.26 (d, J=6.9 Hz, 3H, CH_3CHCH_3), 3.61 (d, J=15.4 Hz, 1H, CH_2), 3.89 (d, J=15.4 Hz, 1H, CH_2), 4.02–4.16 (m, 1H, CH_3CHCH_3), 5.63 (s, 1H, CH), 7.24–7.44 (m, 5H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.67, 140.59, 127.15 (2C), 127.07, 124.72 (2C), 60.93, 46.10, 31.45, 18.59, 17.78; FAB-MS m/z 222 $[M+H]^+$.

3.1.18. 2-(4-Chlorophenyl)-3-isopropyl-1,3-thiazolidin-4-one (4r). This compound was obtained as gummy matter in 84% yield; Anal. Calcd for $C_{12}H_{14}ClNOS$: C, 56.35; H, 5.52; N, 5.48. Found: C, 56.57; H, 5.60; N, 5.61; R_f 0.63, IR (neat) ν_{max} C=O 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (d, J=6.9 Hz, 3H, CH_3CHCH_3), 1.25 (d, J=6.9 Hz, 3H, CH_3CHCH_3), 3.61 (d, J=15.5 Hz, 1H, CH_2), 3.87 (d, J=15.5 Hz, 1H, CH_2), 4.02–4.16 (m, 1H, CH_3CHCH_3), 5.61 (s, 1H, CH), 7.24–7.43 (m, 4H, Ar); FAB-MS m/z 256 $[M+H]^+$.

3.1.19. 3-Isopropyl-2-(2-methoxyphenyl)-1,3-thiazolidin-4-one (4s). This compound was obtained as gummy matter in 59% yield; Anal. Calcd for $C_{13}H_{17}NO_2S$: C, 62.12; H, 6.82; N, 5.57. Found: C, 62.06; H, 6.85; N, 5.52; R_f 0.55; IR (neat) ν_{max} C=O 1668 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (d, J=6.9 Hz, 3H, CH_3CHCH_3), 1.26 (d, J=6.9 Hz, 3H, CH_3CHCH_3), 3.52 (d, J=15.2 Hz, 1H, CH_2), 3.84 (d, J=15.2 Hz, 1H, CH_2), 3.88 (s, 3H, OCH_3), 4.17–4.24 (m, 1H, CH_3CHCH_3), 5.97 (s, 1H, CH), 6.87–7.29 (m, 4H, Ar); FAB-MS m/z 252 $[M+H]^+$.

3.1.20. 3-Isopropyl-2-(1-naphthyl)-1,3-thiazolidin-4-one (4t). This compound was obtained as gummy matter in 66% yield; Anal. Calcd for $C_{16}H_{17}NOS$: C, 70.81; H, 6.31; N, 5.16. Found: C, 70.95; H, 6.37; N, 4.92; R_f 0.68; IR (neat) ν_{max} C=O 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (d, J=7.2 Hz, 3H, CH_3CHCH_3), 1.32 (d, J=7.2 Hz, 3H, CH_3CHCH_3), 3.63 (d, J=15.3 Hz, 1H, CH_2), 3.88 (d, J=15.3 Hz, 1H, CH_2), 4.13–4.24 (m, 1H, CH_3CHCH_3), 6.41 (s, 1H, CH), 7.25–7.93 (m, 7H, Ar); FAB-MS m/z 272 $[M+H]^+$.

3.1.21. Methyl-2-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)-3-phenylpropanoate (4u). This compound was obtained as gummy matter in 67% yield; Anal. Calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.53; H, 5.50; N, 4.14; R_f 0.54; IR (neat) ν_{max} C=O 1683 and C=O 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25–3.36 (m, 2H, CH_2), 3.58–3.75 (m, 2H, CH_2Ph), 3.73 (s, 3H, $COOCH_3$), 4.42 (bs, 1H, α-H, Phe), 5.63 (s, 1H, CH), 7.09–7.40 (m, 10H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.85, 169.19, 137.85, 137.18, 129.89, 129.64, 129.33, 129.15, 129.08, 128.91, 128.81, 128.70, 127.61, 127.07, 65.37, 59.14, 52.88, 34.63, 32.91; FAB-MS m/z 342 $[M+H]^+$.

3.1.22. Methyl-2-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-3-phenylpropanoate (4v). This compound was obtained as gummy matter in 65% yield; Anal. Calcd for $C_{19}H_{18}ClNO_3S$: C, 60.71; H, 4.83; N, 3.73. Found: C, 60.49; H, 4.96; N, 3.44; R_f 0.56; IR (neat) ν_{max} C=O 1685 and C=O 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.26–3.36 (m, 2H, CH_2), 3.64–3.70 (m, 2H, CH_2Ph), 3.74 (s, 3H, $COOCH_3$), 4.36 (bs, 1H, α-H, Phe), 5.58 (s, 1H, CH), 6.87–7.38 (m, 9H, Ar); FAB-MS m/z 376 $[M+H]^+$.

3.2. Reaction of primary amines and cyclohexanone with mercaptoacetic acid

The appropriate amine (1.0 mmol) and cyclohexanone (2.0 mmol) were stirred in THF under ice cold conditions for 5 min, followed by addition of mercaptoacetic acid (3.0 mmol). After 5 min DCC (1.2 mmol) was added to the reaction mixture at 0°C and the reaction mixture is stirred for an additional 50 min at room temperature. DCU was removed by filtration and the filtrate was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 5% aq. citric acid, water, 5% aq. sodium hydrogen carbonate and then finally with brine. The organic layer was dried over sodium sulphate and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using hexane–ethyl acetate as eluent.

3.2.1. 4-Benzyl-1-oxa-4-azaspiro[4.5]decan-3-one (5a). This compound was obtained as gummy matter in 95% yield; Anal. Calcd for $C_{15}H_{19}NOS$: C, 68.93; H, 7.33; N, 5.36. Found: C, 68.63; H, 7.64; N, 5.42; R_f 0.66; IR (neat) ν_{max} C=O 1673 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53–1.72 (m, 10H, cyclohexyl), 3.61 (s, 2H, CH_2), 4.57 (s, 2H, CH_2Ph), 7.22–7.27 (m, 5H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.15, 138.47, 128.91 (2C), 127.60, 127.52 (2C), 74.75, 45.62, 38.77 (2C), 31.75, 24.95, 23.88 (2C); FAB-MS m/z 262 $[M+H]^+$.

3.2.2. 4-Octyl-1-oxa-4-azaspiro[4.5]decan-3-one (5b). This compound was obtained as gummy matter in 87% yield; Anal. Calcd for $C_{16}H_{29}NOS$: C, 67.79; H, 10.31; N, 4.94. Found: C, 67.73; H, 10.55; N, 5.03; R_f 0.66; IR (neat) ν_{max} C=O 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (t, J=6.6 Hz, 3H, $CH_3C_7H_{14}$), 0.99–1.21 (m, 12H, $CH_3(CH_2)_6CH_2$), 1.50–1.73 (m, 10H, cyclohexyl), 3.08–3.16 (m, 2H, $C_7H_{15}CH_2$), 3.41 (s, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.35, 74.32, 42.92, 38.85, 32.15, 31.78, 29.95, 29.63, 27.64, 26.31, 25.90, 24.96, 23.83, 22.97, 21.80, 14.40; FAB-MS m/z 284 $[M+H]^+$.

3.3. Reaction of primary amines (or amino acid esters) and aldehydes with mercaptopropionic acid

The appropriate amine or amino acid ester (1.0 mmol) and aldehyde (2.0 mmol) were stirred in THF under ice cold conditions for 5 min, followed by addition of mercaptopropionic acid (3.0 mmol). After 5 min DCC (1.2 mmol) was added to the reaction mixture at 0°C and the reaction mixture is stirred for an additional 50 min at room temp. DCU was removed by filtration and the filtrate was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 5% aq. citric acid, water, 5% aq. sodium hydrogen carbonate and then finally with brine. The organic layer was dried over sodium sulphate and solvent was removed under reduced pressure to get a crude product that was purified by column chromatography on silica gel using hexane–ethyl acetate as eluent.

3.3.1. 3-Benzyl-2-phenyl-1,3-thiazinan-4-one (6a). This compound was obtained as gummy matter in 92% yield; Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 71.92; H, 6.25; N, 5.07; R_f 0.50; IR (neat) ν_{max} C=O 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78–2.99 (m, 4H, CH_2CH_2), 3.54 (d, J=15.2 Hz, 1H, CH_2Ph), 5.40 (s, 1H, CH), 5.76 (d, J=15.2 Hz, 1H, CH_2Ph), 7.20–7.43 (m, 10H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.83, 139.49, 136.70, 129.12 (2C), 128.55 (2C), 128.32 (2C), 127.97 (2C), 126.91 (2C), 61.24, 49.94, 34.96, 22.14; FAB-MS m/z 284 $[M+H]^+$.

3.3.2. 3-Benzyl-2-(1-naphthyl)-1,3-thiazinan-4-one (6b). This compound was obtained as gummy matter in 90% yield; Anal. Calcd for $C_{21}H_{19}NOS$: C, 75.64; H, 5.74; N, 4.20. Found: C, 75.48; H, 5.84; N, 4.31; R_f 0.47; IR (neat) ν_{max} C=O 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.82–3.05 (m, 4H, CH_2CH_2), 3.48 (d, J=15.2 Hz, 1H, CH_2Ph), 5.80 (d, J=15.2 Hz, 1H, CH_2Ph), 6.12 (s, 1H, CH), 7.18–7.93 (m, 12H, Ar); FAB-MS m/z 334 $[M+H]^+$.

3.3.3. Methyl-2-(4-oxo-2-phenyl-1,3-thiazinan-3-yl)-3-phenylpropanoate (6c). This compound was obtained as gummy matter in 51% yield; Anal. Calcd for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.48; H, 5.84; N, 4.18; R_f 0.34; IR (neat) ν_{max} C=O 1641 and C=O 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71–2.91 (m, 4H, CH_2CH_2), 3.12–3.39 (m, 2H, CH_2Ph), 3.30 (s, 3H, $COOCH_3$), 4.71 (t, J=6.7 Hz, 1H, α-H, Phe), 5.79 (s, 1H, CH), 7.01–7.37 (m, 10H, Ar); FABMS m/z 356 $[M+H]^+$.

3.3.4. Methyl-2-[2-(2-methoxyphenyl)-4-oxo-1,3-thiazinan-3-yl]-3-phenylpropanoate (6d). This compound was obtained as gummy matter in 52% yield; Anal. Calcd for $C_{21}H_{23}NO_4S$: C, 65.43; H, 6.01; N, 3.63. Found: C, 65.37; H, 6.15; N, 3.83; R_f 0.28; IR (neat) ν_{max} C=O 1641.0 and C=O 1741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67–2.87 (m, 4H, CH_2CH_2), 3.05–3.38 (m, 2H, CH_2Ph), 3.23 (s, 3H, $COOCH_3$), 3.90 (s, 3H, OCH_3), 4.95 (t, J=6.7 Hz, 1H, α-H, PheOMe), 6.12 (s, 1H, CH), 6.87–7.28 (m, 9H, Ar); FAB-MS m/z 386 $[M+H]^+$.

Acknowledgments

The authors thank the RSIC staff for providing the spectral data. One of us, T. S. thanks the Department of Biotechnology, New Delhi for financial assistance in the form of fellowship. CDRI Communication No. 6261.

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