An expeditious synthesis of thiazolidinones and tetathiazanones

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In the present study, 4-thiazolidinones have been assembled by HBTU mediated three-component reaction of amine, aldehyde and mercapto acid derivatives at room temperature. The final compounds are obtained in excellent yields within 30 minutes.

Keywords: 4-thiazolidinone, metathiazanone, DCC, HBTU, multicomponent reaction

Thiazolidinones have a wide spectrum of biological activity,[1-4] and hence there is interest in their synthesis.[5a-d] Recently, we have published a 1,3-dicyclohexylcarbodiimide (DCC) mediated three-component condensation method for obtaining thaizolidinones in high yields.[6] However, when sterically hindered components or a weakly nucleophilic amine is involved in the reaction the yields were not good. This prompted us to modify our protocol and explore oxybenzotriazole based coupling reagents. Our intention was to ensure that the efficiency of carbodiimide mediated cyclisation was maintained without the ill effects of DCC. We now report the synthesis of thiazolidinones using HBTU.

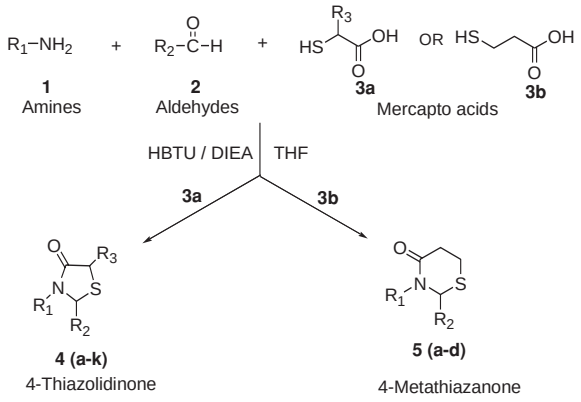
Results and discussion

The physicochemical data of the various 4-thiazolidinones and 4-metathiazanones synthesised by using HBTU as activating agent are presented in Table 1. Compounds **4e** and **4h** were simultaneously synthesised by the DCC and HBTU protocols. The isolated yields of compounds **4e** and **4h** were 45% and 30% by the DCC method in 30 minutes, whereas the isolated yields by HBTU method were 82% and 89% respectively. It is evident that HBTU works equally well or is superior to DCC as a dehydrating agent. The use of carboxylate activating reagent has facilitated cyclisation. The generality of the reaction has been demonstrated by synthesising a variety of 4-thiazolidinones and 4-metathiazanones (Scheme 1) employing different amines, carbonyl compounds (with electron withdrawing and donating substitution) and mercapto-acids (with or without substitution). The reaction proceeds faster as compared to DCC, and the HBTU mediated synthesis described here resulted in higher yields and purity in both 4-thiazolidinones (**4a**–**k**) and 4-metathiazanones (**5a**–**d**). The high yield of 4-metathiazanones is particularly interesting as earlier procedures are reported to give low yields.[5a, 7]

The results of the present study may be summarised as follows: The title compounds namely 4-thiazolidinones and 4-metathiazonones have been prepared in high yields and purity using HBTU and this procedure is free from the drawbacks associated with DCC. Suitable carboxylic activating reagents may be selected from the variety of reagents reported in the literature *viz.* HBTU,[8] BOP[9] and HATU[10] that are commonly used for peptide synthesis.

Experimental

Melting points (m.p.) 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 (2:8) as the solvent system. Iodine was used as the developing reagent. IR spectra were recorded on an FT–IR Perkin-Elmer spectrometer. The ^{1}H NMR spectra were recorded on a DPX-200 Bruker FT–NMR spectrometer. With $(CH_3)_4Si$ (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 the fast atom bombardment (FAB positive) technique. Column chromatography separations were obtained on silica gel (230–400 mesh).



	R1	R2	R3
4a;	Benzyl	4-Methoxyphenyl	H
4b;	Cyclohexyl	4-Methoxyphenyl	H
4c;	Pyridine-2-yl	Phenyl	H
4d;	Pyridine-2-yl	4-Methoxyphenyl	H
4e;	4-Chlorophenyl	4-Chlorophenyl	H
4f;	2-Furfuryl	2-Methoxyphenyl	H
4g;	n-Butyl	1-Naphthyl	H
4h;	pyridine-2-yl	4-Methoxyphenyl	CH3
4I;	4-Chlorophenyl	4-Chlorophenyl	CH3
4j;	2-Furfuryl	2-Methoxyphenyl	CH3
4k;	n-Butyl	1-Naphthyl	CH3
5a;	Benzyl	4-Methoxyphenyl	-
5b;	Benzyl	2-Methoxyphenyl	-
5c;	Pyridine-2-yl	4-Methoxyphenyl	-
5d;	2-Furfuryl	2-Methoxyphenyl	-

Reaction of primary amines and aldehydes with mercapto acid

The appropriate amine (1.0 mmol) and aldehyde (2.0 mmol) were stirred in THF at RT for 5 minutes, followed by addition of mercapto acid (3.0 mmol). After 5 minutes diisopropylethylamine (2.0 mmol) and HBTU (2.0 mmol) was added to the reaction mixture and the reaction mixture was stirred for an additional 15 minutes at room temp. The reaction mixture 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 sulfate and solvent was removed under reduced pressure to afford a crude product that was purified by column chromatography on silica gel using hexane–ethyl acetate as eluent. The structures of final compounds were characterised by TLC, IR, FAB-MS, ^{1}H NMR and ^{13}C NMR.

3-Benzyl-2-(4-methoxy-phenyl)-thiazolidin-4-one (**4a**):[11a] This compound was obtained as a gum in 97% yield, R_f 0.53, ir: (Neat) ν_{max} C=O 1673 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.53 (d, *J*=14.7 Hz, 1H, C$\underline{H}_2$Ph), 3.74 (d, *J*=15.5 Hz, 1H, C$\underline{H}_2$), 3.83 (s, 3H, OC$\underline{H}_3$), 3.89 (d, *J*=15.5 Hz, 1H, C$\underline{H}_2$), 5.16 (d, *J*=14.7 Hz, 1H, C$\underline{H}_2$Ph), 5.36 (s, 1H, C$\underline{H}$), 6.87–7.30 (m, 9H, Ar); FAB-MS *m/z* 300 [M+H]$^+$. Anal. Calcd for $C_{17}H_{17}NO_2S$: C, 68.33; H, 5.72; N, 4.68. Found: C, 68.35; H, 5.94; N, 4.49.

3-Cyclohexyl-2-(4-methoxy-phenyl)-thiazolidin-4-one (**4b**): This compound was obtained as a gum in 96% yield, R_f 0.55, ir: (Neat) ν_{max} C=O 1669 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.98–1.76 (m, 11H, Cyclohexyl), 3.59 (d, *J*=15.4 Hz, 1H, C$\underline{H}_2$), 3.82 (s, 3H, OC$\underline{H}_3$), 3.88 (d, *J*=15.4 Hz, 1H, C$\underline{H}_2$), 5.62 (s, 1H, C$\underline{H}$), 6.85–7.26 (m,

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4H, Ar); FAB-MS: *m/z* 292 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26; N, 4.81. Found: C, 65.98; H, 7.42; N, 4.55.

2-phenyl-3-pyridin-2-yl-thiazolidin-4-one (**4c**):[11b,c] This compound was obtained as a white solid in 89% yield, m.p. 95–100°C; R_f 0.68, ir (KBr): ν_{max} C=O 1690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 3.78 (d, *J*=16.05 Hz, 1H, C$\underline{H}_2$), 4.02 (d, *J*=16.1 Hz, 1H, C$\underline{H}_2$), 6.88 (s, 1H, C$\underline{H}$), 6.97–8.23 (m, 9H, Ar); ^{13}C NMR: (50 MHz, $CDCl_3$) δ 171.78, 151.17, 148.16, 141.57, 138.12, 129.05(2C), 128.49(2C), 126.39, 121.09, 117.62, 63.35, 34.53; FAB-MS: *m/z* 257 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.55; H, 4.72; N, 11.39.

2-(4-Methoxy-phenyl)-3-pyridin-2-yl-thiazolidin-4-one (**4d**):[11d] This compound was obtained as a yellow solid in 88% yield, m.p. 115–118°C; R_f 0.46; ir (KBr): ν_{max} C=O 1692 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.73 (s, 3H, OMe), 3.83 (d, *J*=16.1 Hz, 1H, C$\underline{H}_2$), 4.02 (d, *J*=16.1 Hz, 1H, C$\underline{H}_2$), 5.45 (s, 1H, C$\underline{H}$), 6.75–8.27 (m, 8H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.74, 159.82, 151.17, 148.22, 138.13, 133.19, 128.06(2C), 121.23, 118.3, 114.4(2C), 63.26, 55.62, 34.6; FAB-MS: *m/z* 287 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.73. Found: C, 62.92; H, 5.25; N, 9.79.

2,3-Bis-(4-chloro-phenyl)-thiazolidin-4-one (**4e**):[11f] This compound was obtained as a white solid in 82% yield, m.p. 133–136°C; R_f 0.50; ir (KBr): ν_{max} C=O 1678 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.84 (d, *J*=15.9 Hz, 1H, C$\underline{H}_2$), 3.96 (d, *J*=15.9 Hz, 1H, C$\underline{H}_2$), 6.04 (s, 1H, C$\underline{H}$), 7.07–7.29 (m, 8H, Ar); FAB-MS: *m/z* 324 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{11}Cl_2NOS$: C, 55.57; H, 3.42; N, 4.32. Found: C, 55.72; H, 3.43; N, 4.18.

3-Furan-2-ylmethyl-2-(2-methoxy-phenyl)-thiazolidin-4-one (**4f**): This compound was obtained as a gum in 94% yield, R_f 0.43; ir (neat): ν_{max} C=O 1681.5 cm^{-1}, ^1H NMR ($CDCl_3$): δ 3.64 (d, *J*=15.5 Hz, 1H, C$\underline{H}_2$Fu), 3.75 (d, *J*=15.4 Hz, 1H, C$\underline{H}_2$), 3.84 (s, 3H, OC$\underline{H}_3$), 3.88 (d, *J*=15.4 Hz, 1H, C$\underline{H}_2$), 5.0 (d, *J*=15.5 Hz, 1H, C$\underline{H}_2$Fu), 5.88 (s, 1H, C$\underline{H}$), 6.12–7.36 (m, 7H, Ar); FAB-MS: *m/z* 289 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{15}NO_2S$: C, 62.26; H, 5.23; N, 4.34. Found: C, 62.26; H, 5.26; N, 4.49.

3-Butyl-2-naphthalen-1-yl-thiazolidin-4-one (**4g**): This compound was obtained as a gum in 95% yield, R_f 0.67; ir (neat): ν_{max} C=O 1675 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, *J*=7.1 Hz, 3H, C$\underline{H}_3$(CH$_2$)$_3$), 1.25–1.69 (m, 4H, CH$_3$(C$\underline{H}_2$)$_2$CH$_2$), 2.75 (t, *J*=6.4, 2H, CH$_3$(CH$_2$)$_2$ C$\underline{H}_2$), 3.69 (d, *J*=15.8 Hz, 1H, C$\underline{H}_2$), 3.79 (d, *J*=15.8 Hz, 1H, C$\underline{H}_2$), 6.4 (s, 1H, C$\underline{H}$), 7.25–7.94 (m, 7H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.3, 134.65, 130.59 (2C), 129.7 (2C), 127.27, 126.6 (2C), 125.77 (2C), 122.43, 43.79, 33.18, 29.59, 20.43, 14.07; FAB-MS: *m/z* 286 $[M+H]^+$. Anal. Calcd. for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.91. Found: C, 71.56; H, 6.71; N, 4.65.

Reaction of primary amines and aldehydes with thiolactic acid

2-(4-Methoxy-phenyl)-5-methyl-3-pyridin-2-yl-thiazolidin-4-one (**4h**):[11e] This compound was obtained as a gum in 89% yield, R_f 0.53; ir (neat): ν_{max} C=O 1702 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.61 (d, *J*=7.0 Hz, 3H, C$\underline{H}_3$), 3.74 (s, 3H, OC$\underline{H}_3$), 4.20 (q, *J*=7.0 Hz, 1H, C$\underline{H}$CH$_3$), 5.50 (s, 1H, C$\underline{H}$), 6.68–8.27 (m, 8H, Ar); FAB-MS: *m/z* 301 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 64.15; H, 5.37; N, 9.55.

2,3-Bis-(4-chloro-phenyl)-5-methyl-thiazolidin-4-one (**4i**):[11f] This compound was obtained as a gum in 81% yield, R_f 0.61; ir (neat): ν_{max} C=O 1688 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.66 (d, *J*=7.0 Hz, 3H, C$\underline{H}_3$), 4.15 (q, *J*=7.0 Hz, 1H, CH$_3$C$\underline{H}$), 5.96 (s, 1H, C$\underline{H}$), 7.11–7.40 (m, 8H, Ar); FAB-MS: *m/z* 339 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{13}Cl_2NOS$: C, 56.81; H, 3.87; N, 4.14. Found: C, 56.28; H, 4.00; N, 4.41.

3-Furan-2-ylmethyl-2-(2-methoxy-phenyl)-5-methyl-thiazolidin-4-one (**4j**): This compound was obtained as a gum in 93% yield, R_f 0.46; ir (neat): ν_{max} C=O 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (d, *J*=7.2 Hz, 3H, C$\underline{H}_3$), 3.75 (d, *J*=15.4, 1H, C$\underline{H}_2$Fu), 3.80 (s, 3H, OC$\underline{H}_3$), 3.93 (q, *J*=7.0 Hz, 1H, CH$_3$C$\underline{H}$), 4.99 (d, *J*=15.4, 1H, C$\underline{H}_2$Fu), 5.79 (s, 1H, C$\underline{H}$), 6.07–7.31 (m, 7H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 174.86, 157.43, 149.64, 142.88, 130.13, 127.78, 127.18, 126.81, 121.18, 111.51, 110.70, 109.17, 55.96, 41.48, 40.11, 19.16; FAB-MS: *m/z* 304 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 62.96; H, 5.88; N, 4.88.

3-Butyl-5-methyl-2-naphthalen-1-yl-thiazolidin-4-one (**4k**): This compound was obtained as a gum in 95% yield, R_f 0.61; ir (neat): ν_{max} C=O 1673 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (t, *J*=6.8 Hz, 3H, C$\underline{H}_3$C$_3$H$_6$), 1.25–1.70 (m, 7H, C$\underline{H}_3$ and C$\underline{H}_2$C$\underline{H}_2$), 2.79 (dd, *J*=7.0 Hz, 2H, C$_3$H$_7$C$\underline{H}_2$), 3.95 (q, *J*=7.2, 1H, C$\underline{H}$CH$_3$), 6.30 (s, 1H, C$\underline{H}$), 7.22–7.93 (m, 7H, Ar); FAB-MS: *m/z* 300 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{21}NOS$: C, 72.20; H, 7.07; N, 4.68. Found: C, 72.35; H, 7.15; N, 4.60.

Reaction of primary amines and aldehydes with mercaptopropionic acid

3-Benzyl-2-(4-methoxy-phenyl)-[1,3]thiazinan-4-one (**5a**): This compound was obtained as a white solid in 96% yield, m.p. 124–126°C; R_f 0.33; ir (neat): ν_{max} C=O 1638 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.62–2.98 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$), 3.46 (d, *J*=15.2 Hz, 1H, C$\underline{H}_2$Ph), 3.81 (s, 3H, OC$\underline{H}_3$), 5.65 (d, *J*=15.2 Hz, 1H, C$\underline{H}_2$Ph), 5.71 (s, 1H, C$\underline{H}$), 6.90–7.37 (m, 9H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.1, 156.6, 136.9, 129.7 (2C), 128.2 (2C), 127.8 (2C), 127.1, 126.3, 120.4, 111.7, 55.9, 55.6, 50.0, 35.0, 22.0; FAB-MS: *m/z* 314 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 68.59; H, 6.35; N, 4.27.

3-Benzyl-2-(2-methoxy-phenyl)-[1,3]thiazinan-4-one (**5b**): This compound was obtained as a gum in 98% yield, R_f 0.33**;** ir (neat): ν_{max} C=O 1633 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.62–3.0 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$), 3.46 (d, *J*=15.2 Hz, 1H, C$\underline{H}_2$Ph), 3.80 (s, 3H, OC$\underline{H}_3$), 5.63 (d, *J*=15.2 Hz, 1H, C$\underline{H}_2$Ph), 5.71 (s, 1H, C$\underline{H}$), 6.90–7.36 (m, 9H, Ar), ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.1, 156.6, 136.9, 129.7, 129.0 (2C), 128.2 (2C), 127.8, 127.1, 126.4, 120.4, 111.7, 55.9, 55.7, 50.1, 35.1, 22.0; FAB-MS: *m/z* 314 $[M+H]^+$. Anal. Calcd. for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 68.31; H, 6.38; N, 4.18.

2-(4-Methoxy-phenyl)-3-pyridin-2-yl-[1,3]thiazinan-4-one (**5c**): This compound was obtained as a gum in 87% yield, R_f 0.41; ir (neat): ν_{max} C=O 1712 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.65–3.08 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$), 3.80 (s, 3H, OC$\underline{H}_3$), 5.20 (s, 1H, C$\underline{H}$), 7.80–7.45 (m, 8H, Ar); FAB-MS: *m/z* 301 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.66; H, 5.25; N, 9.12.

3-Furan-2-yl methyl-2-(2-methoxy-phenyl)-[1,3]thiazinan-4-one (**5d**): This compound was obtained as a gum in 82% yield, R_f 0.25; ir (neat): ν_{max} C=O 1635 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.59–2.92 (m, 4H, C$\underline{H}_2$C$\underline{H}_2$), 3.69 (d, *J*=15.4 Hz, 1H, C$\underline{H}_2$Fu), 3.87 (s, 3H, OC$\underline{H}_3$), 5.33 (d, *J*=15.4 Hz, 1H, C$\underline{H}_2$Fu), 5.87 (s, 1H, C$\underline{H}$), 6.18–7.31 (m, 7H, Ar); FAB-MS: *m/z* 304 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.40; H, 5.79; N, 4.74.

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