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A simple approach for the synthesis of new classes of dithiocarbamate-linked peptidomimetics

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ABSTRACT

An efficient protocol for the synthesis of a new series of dithiocarbamate-linked peptidomimetics is described. The in situ generated dithiocarbamic acid intermediate formed by the reaction of an amino acid ester and carbon disulfide in the presence of triethylamine was treated with N-protected amino alkyl iodide to afford title compounds **3a–g** in good to moderate yields. The synthesis of *N*-Fmoc-protected tripeptidomimetics **4a–e** containing two dithiocarbamate linkages is also described. The protocol was further extended to synthesize *N,N′*-orthogonally protected dithiocarbamate-linked dipeptidomimetics **7a–c** as well. The mild reaction conditions and non-toxic reagents are the advantages of the present method.

Natural peptides have been the potent source of lead compounds in drug discovery albeit with limited utility due to their poor pharmacokinetic properties, rapid metabolism and low bioavailability.[1,2] Hence a variety of peptide mimics are being developed to introduce drug-like character along with increased potency, target specificity and longer duration of action. To this end, several classes of peptidomimetics are tailored by replacing the native amide bond with various other tethers and are biologically scrutinized.[3] Our group has been involved in developing efficient methods for the synthesis of peptidomimetics by inserting non-native linkages such as urea,[4] thiourea,[5] retro-amide,[6] carbamate[7] and heterocycles.[8] Recently, we turned our attention towards another useful and biologically important functionality namely dithiocarbamate.[9] Reports in the literature demonstrate that the dithiocarbamate containing molecules show antibacterial, anthelmintic, anti-cancer, fungicidal and growth depressant properties.[10,11] The utility of dithiocarbamate group as linkers in solid phase organic synthesis[12,13] and in certain photochemical applications[14] is also well documented. The dithiocarbamate functionality chelates heavy metals that make them versatile ligands,[15] and are applicable as NO scavengers. Furthermore, the functionalized dithiocarbamates such as benzamide-based thiocarbamates have been developed as HIV-I NCp7 inhibitors.[16]

Earlier approaches for the synthesis of dithiocarbamate esters employed the reaction of an amine with expensive and toxic reagents such as thiophosgene and its derivatives.[17] Synthesis of substituted dithiocarbamates is carried out by a reaction of amine and carbon disulfide (CS_2) on electron-deficient alkene through Michael-type reaction in the presence of a base or solid alkaline Al_2O_3.[18] Ranu et al., recently described a one-pot three-component condensation of an amine, CS_2 and an activated alkene in an ionic liquid.[19] Villa and co-workers, synthesized bis(dithiocarbamate) derivatives of glycerol through a multi-step process and have demonstrated their antifungal activity.[20] A similar chemistry was followed by Rafin and co-workers[21] for the synthesis of dithiocarbamate derivatives of carbohydrate conjugates. A three-component reaction employing Cs_2CO_3, tetrabutylammonium iodide (TBAI) and CS_2 for a reaction between an amine and a substituted halide was reported by Jung and co-workers[22] Strong bases such as anhydrous potassium phosphate have also been used for the reaction of an amine and CS_2 with electrophilic alkenes to obtain corresponding dithiocarbamate compounds.[23] While a one-pot synthesis of dithiocarbamates starting from corresponding alcohols using Mitsunobu reagent was developed by Chaturvedi and Ray,[24] benzotriazole-assisted synthesis of dithiocarbamates by a reaction of *S*-nucleophiles with thiocarbonylbenzotriazoles was developed by Katritzky's group.[25] Saidi and co-workers have described a straightforward catalyst-free one-pot synthesis of dithiocarbamates under solvent-free conditions.[26,27] The same group has also demonstrated a Michael-type reaction between an amine, CS_2 with α,β-unsaturated compounds in water.[28] Dithiocarbamate preparation by a reaction between an epoxide, amine and CS_2 in one-pot fashion is also known.[29]

A thorough literature survey revealed that the dithiocarbamate-linked peptidomimetics are yet to be reported. In correlation with other non-amide tethers such as ureas and carbamates, incorporation of dithiocarbamate into peptide backbone may result in

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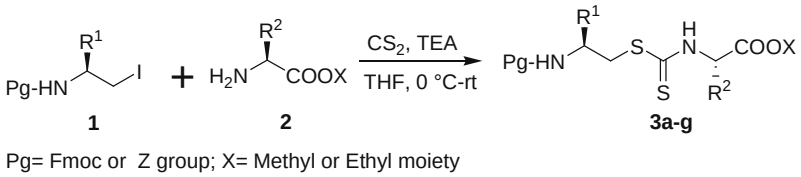
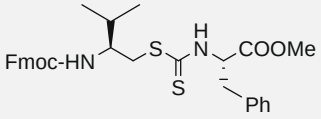
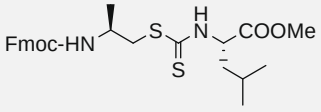
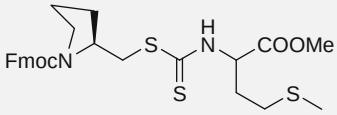
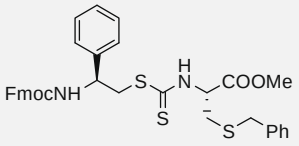
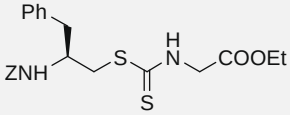
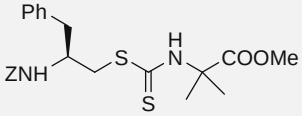
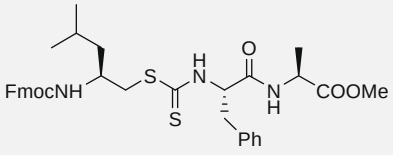


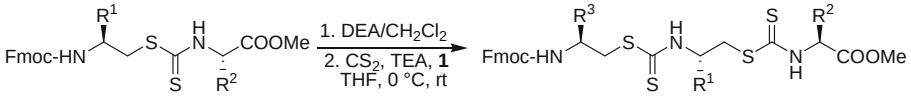
Scheme 1. Synthesis of dithiocarbamates **3a–g**.

interesting class of molecules. Similar to the strategy described earlier by Salvatore et al.,[22] we, in the present Letter report a simple synthesis of dithiocarbamate-linked peptidomimetics by a reaction of CS_2 with suitably chosen amino acid derived amine and halide components in the presence of triethylamine (TEA).

The reaction between carbon disulfide and an *N*-nucleophile involves addition of CS_2 to NH bonds. It results in dithiocarbamate salt that can be transformed into various intermediates and products such as isothiocyanates. Recently, we reported the preparation of N-protected amino alkyl isothiocyanates employing CS_2 and TEA.[5] During this study, it was envisaged that the intermediate dithiocarbamic acid salts react with electron-deficient carbon centres such as alkyl halides to afford respective class of dithiocarbamate compounds. This chemistry was explored to prepare new classes of peptidomimetics and the results are discussed here. Our first target was a dipeptidomimetic of the type **3**. This was accomplished by a reaction of an amino acid ester, CS_2, TEA and N-protected amino alkyl iodide. The iodo intermediates used in the present studies were prepared by following a reported protocol.[30] Briefly, an N-protected amino acid was reduced into corresponding aminol and the hydroxy group was subjected to Mitsunobu reaction using PPh_3, imidazole and iodine to afford corresponding N-protected amino alkyl iodide **1**. In a typical reaction, the preparation of compounds **3** involved first treatment of a

Table 1
List of dithiocarbamate tethered peptidomimetics **3**

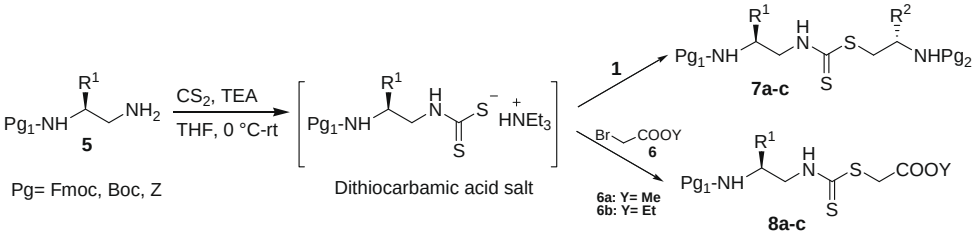
Compd No.	Dithiocarbamate	$[\alpha_D^{25}]$ *c* 1, $CHCl_3$	Yield (%)	HRMS obsd/calcd
3a		−44.6	72	585.1831 (585.1858)
3b		−52.7	74	523.1698 (523.1701)
3c		−38.1	65	567.1429 (567.1422)
3d		−110.1	68	665.1583 (665.1578)
3e		−19.8	70	469.1222 (469.1232)
3f		+17.5	69	483.1394 (483.1388)
3g		+9.0	62	670.2380 (670.2385)



3 **4a-e**

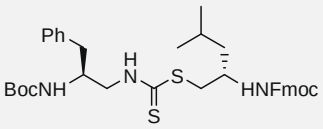
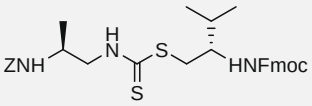
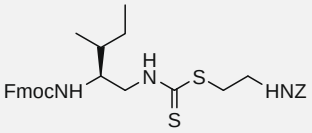
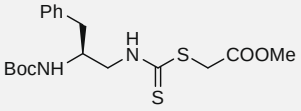
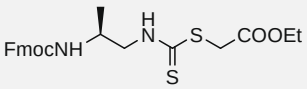
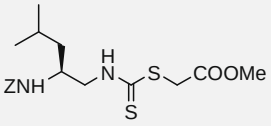
Comp. No.	R^1	R^2	R^3	$[\ ]^{25}_D$ c 1, $CHCl_3$	Yield (%)
4a	$CH(CH_3)_2$	$CH_2C_6H_5$	CH_3	-78.7	58
4b	CH_3	$CH_2CH(CH_3)_2$	$CH_2C_6H_5$	-32.0	61
4c	H	$(CH_2)_2SCH_3$	$CH(CH_3)_2$	+11.8	55
4d	$-(CH_2)_3-$	$(CH_2)_2SCH_3$	$CH_2CH(CH_3)_2$	-85.2	60
4e	CH_3	$CH_2CH(CH_3)_2$	$CH(CH_3)CH_2CH_3$	-74.6	53

Scheme 2. Synthesis of dithiocarbamate-linked tripeptidomimetics through N-terminal elongation.



Scheme 3.

Table 2
Dithiocarbamate-linked dipeptidomimetics **7**, **8**

Compd No.	Dithiocarbamates	$[\alpha^{25}_D]$ *c* 1, $CHCl_3$	Yield (%)	HRMS obsd (calcd)
7a		−46.8	72	670.2757 (670.2749)
7b		−19.3	68	614.2119 (614.2123)
7c		−12.7	65	614.2133 (614.2123)
8a		+29.7	62	421.1230 (421.1232)
8b		+33.5	67	481.1220 (481.1232)
8c		−8.2	70	421.1229 (421.1232)

chilled solution of HCl·H–Phe–OMe in dry THF with TEA and CS_2. This was followed by the addition of a solution of *N*-Fmoc-Val-Ψ[CH_2–I]. The reaction was complete in about an hour as adjudged by TLC. A simple work-up followed by column chromatography yielded pure N-protected dithiocarbamate-linked dipeptidomimetic **3a** in 72% yield (Scheme 1).[31] The generality of this reaction was demonstrated with a series of *N*-Fmoc/Z-amino alkyl iodides and amino acid esters to afford the corresponding dipeptidomimetics **3b–g** in good to moderate yields (Table 1). The products were found to be analytically pure and the protocol was racemization free as evident by HPLC and NMR analyses.[32]

In the subsequent study, the chain elongation of dipeptidomimetics **3** on N-terminal was undertaken to synthesize tripeptidomimetics containing two dithiocarbamate linkages in the backbone. Starting with **3a**, the amine was deprotected using 50% diethylamine (DEA) in CH_2Cl_2 and the resulting amino-free dipeptidomimetic was reacted with CS_2, TEA and *N*-Fmoc-Ala-ψ[CH_2–I] **1** to afford *N*-Fmoc-tripeptidomimetic **4a** possessing two dithiocarbamate groups (Scheme 2). Employing this protocol, four more dithiocarbamate-linked tripeptidomimetics **4b–e** were prepared and isolated successfully that were adequately characterized.[33]

Finally, the protocol was further explored to describe two other types of dithiocarbamate-linked peptidomimetics starting from N-protected amino acid derived vicinal diamines **5**. The required N-protected amino alkyl amines **5** were synthesized using known protocol. *N*-Fmoc amino alkyl amines[34] were prepared by reducing the corresponding alkyl azides under catalytic hydrogenation, while *N*-Boc and *N*-Z-amino alkyl amines were synthesized by $LiAlH_4$-mediated reduction of their nitriles.[5] Then a reaction of **5** with CS_2 in the presence of TEA gave the corresponding dithiocarbamic acid intermediate which without isolation, was treated with either N-protected amino alkyl iodide **1** or bromo acetic acid ester **6** to afford dithiocarbamate-linked orthogonally protected dipeptidomimetics **7a–c** and simple dipeptidomimetics **8a–c**, respectively (Scheme 3, Table 2). All the compounds were isolated after a simple work-up as gummy solids and fully characterized using mass and NMR spectroscopic techniques.

In conclusion, we report a simple and mild protocol for the synthesis of a new class of dithiocarbamate-linked peptidomimetics using CS_2, TEA and corresponding amines and appropriate halides. The reaction is fast, high yielding and is devoid of the use of toxic reagents. The protocol is racemization free and all the synthesized compounds were isolated and well characterized.

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31. *Typical procedure for the synthesis of dithiocarbamate-linked dipeptidomimetic* **3a**: To a chilled solution of HCl·H–Phe–OMe (3 mmol) and TEA (8 mmol) in dry THF (15 mL) was added CS_2 (6 mmol). After 10 min, a solution of *N*-Fmoc-Val-ψ[CH_2–I] (4 mmol) in THF was added slowly and the reaction mixture was allowed to warm to rt gradually and stirred for two hours. After completion of the reaction (TLC), it was evaporated under vacuum and the crude was partitioned between ethyl acetate (15 mL) and water. The organic layer was washed with citric acid solution (10%, 10 mL), water and brine. After drying over sodium sulfate, the organic phase was concentrated and the crude was purified through column chromatography using EtOAc in hexane (10–15%) as eluent.
32. *Note:* To confirm the optical purity of the synthesized dithiocarbamates, a model study was carried out as follows: Two epimeric dithiocarbamate compounds were prepared by coupling *N*-Fmoc-Phe-ψ[CH_2–I] with (*R*)- and (*S*)-1-phenylethylamines separately. The ^{1}H NMR spectra of methyl group of these two compounds contained distinct doublets at δ values 1.35, 1.37 and 1.38, 1.40 ppm, respectively, indicating the absence of racemization during the course of the reaction. Also, the HPLC profiles of the samples of these two epimers had peak at R_t values 16.4 and 17.1, respectively, while the equimolar mixture of these epimers prepared by reacting racemic phenylethylamine with Fmoc-Phe-ψ[CH_2–I] had two distinct peaks at R_t values 16.5 and 17.1 min. This confirmed that the samples of the epimers were optically pure.
33. *Spectral data for selected compounds*: Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 6H, *J* = 6.3 Hz), 1.30 (d, 3H, *J* = 5.8 Hz), 1.72–1.74 (m, 3H), 2.04 (m, 2H), 3.73 (s, 3H), 3.77 (m, 1H), 3.80 (m, 1H), 4.20 (t, 1H, *J* = 4.8 Hz), 4.39 (d, 2H, *J* = 6.7 Hz), 5.15 (br, 1H), 5.16 (br, 1H), 7.29–7.76 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.2, 19.9, 20.3, 23.4, 28.1, 40.1, 43.3, 47.5, 50.7, 52.5, 65.2, 126.6, 127.2, 127.9, 128.1, 141.2, 143.7, 154.6, 173.0, 195.3 ppm; IR: 1741, 1696, 1119 cm^{-1}.
Compound **3c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.71 (m, 2H), 1.92 (m, 2H), 2.03 (s, 3H), 2.55 (m, 4H), 2.83 (d, 2H, *J* = 5.5 Hz), 3.72 (t, 2H, *J* = 7.1 Hz), 3.76 (s, 3H), 4.13 (t, 1H, *J* = 4.8 Hz), 4.23 (d, 2H, *J* = 6.2 Hz), 4.42 (m, 2H), 5.29 (br, 1H), 7.31–7.77 (m, 8H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.3, 21.4, 26.4, 29.2, 30.7, 33.7, 46.3, 47.5, 49.8, 50.9, 55.6, 65.4, 127.2, 127.7, 128.4, 128.7, 140.0, 141.3, 155.7, 172.4, 194.2 ppm; IR: 1747, 1712, 1125 cm^{-1}.

Compound **3f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 6H), 2.36 (d, 2H, J = 7.1 Hz), 3.61 (s, 3H), 3.71 (d, 2H, J = 6.6 Hz), 3.82 (m, 1H), 5.11 (s, 2H), 5.62 (br, 2H), 7.11- 7.62 (m, 10H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3, 39.6, 43.1, 51.3, 52.2, 60.1, 66.2, 127.1, 127.4, 127.6, 128.3, 128.8, 129.1, 140.1, 140.7, 154.3, 172.4, 192.3 ppm IR: 1738, 1693, 1179 cm^{-1}.

Compound **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, 3H, J = 6.2 Hz), 1.28 (d, 3H, J = 5.8 Hz), 2.48 (d, 2H, J = 5.7 Hz), 2.51–2.67 (m, 4H), 3.58 (s, 3H), 3.71–3.92 (m, 3H), 4.17–4.32 (m, 3H), 5.92 (br, 1H), 6.11 (br, 2H), 7.25–7.79 (m, 13H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 17.4, 31.2, 32.5, 35.4, 40.7, 45.6, 48.6, 49.8, 52.1, 68.8, 126.6, 127.3, 127.5, 128.0, 128.3, 128.6, 129.1, 139.6, 140.7, 142.3, 160.2, 173.4, 192.5, 193.2 ppm; ESI-MS calcd for $C_{33}H_{37}N_3NaO_4S_4$: 690.15, found: 690.20 [M+Na]; IR: 1752, 1708, 1085, 1101 cm^{-1}.

Compound **7a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (d, 6H, J = 5.2 Hz), 1.25 (s, 9H), 1.77 (m, 3H), 2.48–2.53 (m, 4H), 2.61 (d, 2H, J = 4.9 Hz), 3.48 (m, 1H), 3.51 (m, 1H), 4.06 (t, 1H, J = 4.2 Hz), 4.31 (d, 2H, J = 7.7 Hz), 6.47 (br, 2H), 7.11–7.82 (m, 13H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 23.1, 27.3, 38.7, 39.8, 41.5, 46.7, 47.7, 48.9, 51.3, 65.2, 81.2, 127.3, 127.5, 127.6, 128.2, 128.4, 128.9, 129.1, 141.6, 142.2, 143.4, 155.7, 156.3, 194.2 ppm; IR: 1712, 1696, 1059 cm^{-1}.

Compound **8c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.01 (d, 6H, J = 5.8 Hz), 1.62 (m, 2H), 1.77 (m, 1H), 2.61 (m, 2H), 3.41 (m, 1H), 3.42 (s, 3H), 3.65 (s, 2H), 5.07 (s, 2H), 6.37 (br, 2H), 6.92–7.34 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.6, 22.8, 37.2, 41.7, 43.4, 51.2, 53.1, 63.4, 127.3, 127.7, 128.6, 140.8, 154.6, 166.8, 191.5 ppm; IR: 1734, 1689, 1147 cm^{-1}.

34. Boeijen, A.; van Ameijde, J.; Liskamp, R. M. J. *J. Org. Chem.* **2001**, *66*, 8454–8462.