Novel Highly Functionalized Benzoylaminocarbothioyl Pyrrolidine from Benzoylisothiocyanate and Substitueted Pyrrolidine Derived From α-Aminoasit Ester *via* Imine -Azomethine Ylide-1,3-Dipolar Cycloaddition Cascade

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Abstract: A series of novel highly functionalized benzoylaminocarbothioyl pyrrolidines were prepared by the reaction of benzoylisothiocyanate with substitueted pyrrolidine derived from α -aminoasit ester *via* metal catalsed imine -azomethine ylides-1,3-Dipolar Cycloaddition in excellent yield. An example of chiral version benzoylaminocarbothioyl pyrrolidine were also reported. The chirality oryginated from menthyl acrylate as chiral dipolarophile in the cycloaddition cascade and induced three novell chiral centres.

Introduction:

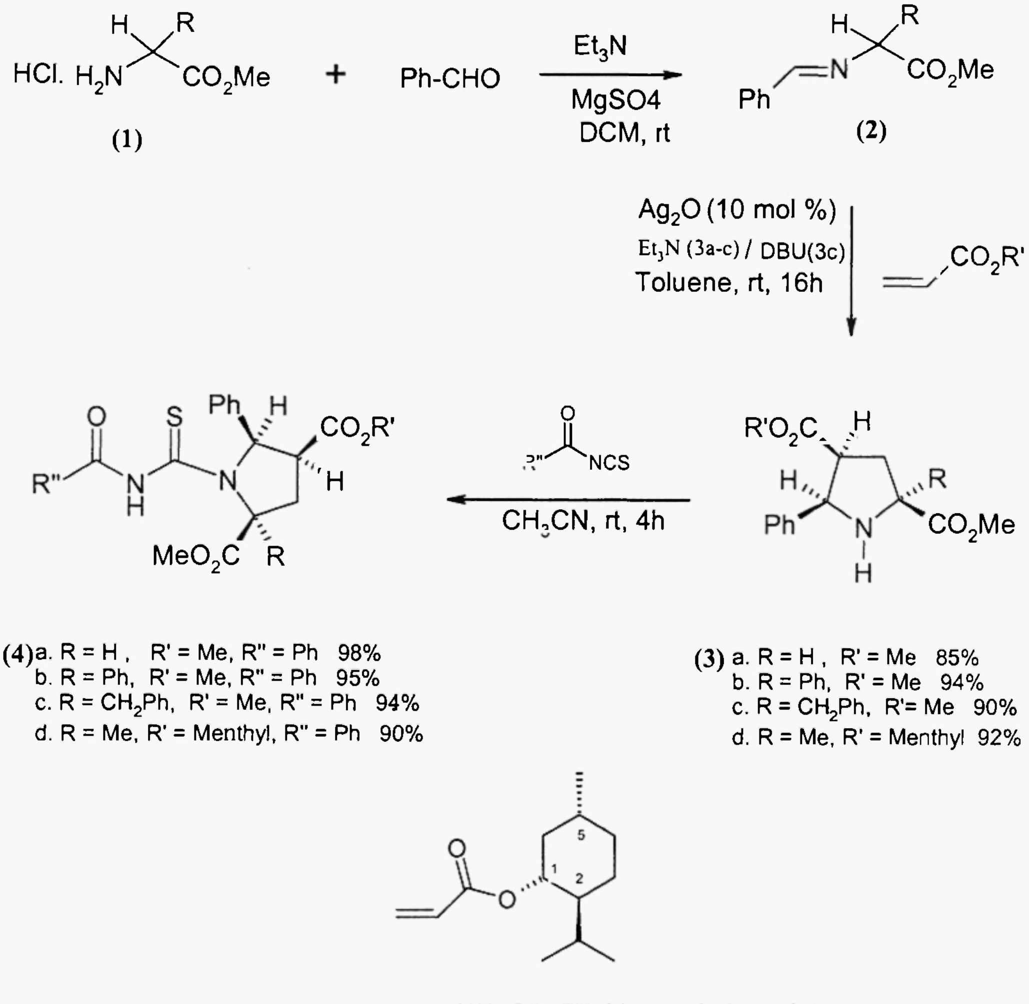
There have been many reports in the literature of thiourea moiety containing N,N'-aryl and alkyl ligands and their metal complexes[1-2]. Some of these compounds show a wide range of pharmaceutical activities such as antifungal[3,4], antitumour[5] antifoulingl[6] properties, and screened for the some other biological actions[3-6]. Among these compounds, N,N'-dialkyl-N'-benzoylthioureas have been found to be useful ligands for the potential determination of traces of the transition metals by means of normal phase chromatography[7]. These reagents have also been shown to selectively extract several of the platinum group metals in the form of stable neutral chelates[8] and their complexation capacity[9,10].

Grigg *et al* have reported a range of thermal and metal catalysed imine -azomethine ylides-1,3-Dipolar cycloaddition cascades reactions furnishing azomethine ylides and their cycloadduct pyrrolidine compounds derived from amine and α -aminoasit ester in good to excellent yield[11-14]. This cascade chemistry has provided a series of cephalosporin analogues[15], spirobenzodiazepines related to MK-329[13,14] and a potentially flexible entry into the complex molecular framework of natural products[15-18]

In a recent paper we reported a facile route conformationally constrained R-pro-S-pro peptidomimetics *via* thermal and metal catalysed imine -azomethine ylides-1,3-Dipolar Cycloaddition reaction in good to excellent yield[17]. We have also reported some novell nikkomycin analogous[18] *via* cycloaddition of stabilised and non-stabilised azomethine ylides derived from Uracil Polyyoxin C.

Results and Discussion:

In view of these favourable properties of these ligands, we now report the reaction of benzoylisothiocyanate with substitueted pyrrolidines derived from α -aminoasit ester *via* imine -azomethine ylides-1,3-Dipolar Cycloaddition. The highly functionalized benzoylaminocarbothioyl pyrrolidines were obtained under mild conditions in good to excellent yield.



(4)a. R = H, R' = Me, R" = Ph 98%
b. R = Ph, R' = Me, R" = Ph 95%
c. R = CH_2Ph, R' = Me, R" = Ph 94%
d. R = Me, R' = Menthyl, R" = Ph 90%

(3) a. R = H, R' = Me 85%
b. R = Ph, R' = Me 94%
c. R = CH_2Ph, R'= Me 90%
d. R = Me, R' = Menthyl 92%

(5) (1R, 2S, 5R-(-)-menthyl acrylate

Scheme 1

Thus the substituted pyrrolidines **(3a-c)** were prepared from the corresponding imines **(2a-c)**[12,19] in 85-94% yield as autlined in scheme 1. The reaction of these pyrolidine cycloadducts **(3a-c)** with benzoylisothiocyanate in acetonitrile at ambient temperature for 3-4 h gave benzoylaminocarbothioyl pyrrolidine **(4a-c)** in 90-98% yield (Scheme 1). An example of chiral version of benzoylaminocarbothioyl pyrrolidine derivative was also reported. This was prepared from chiral pyrrolidine **(3d)** oryginated from menthyl acrylate as dipolarophile *via* cycloaddition cascade pocesses.[12,19] The cycloadduct was then treated with benzoylisothiocyanate under similar conditions (MeCN, rt, 4h) to afford chiral benzoylaminocarbothioyl pyrrolidinc **(4d)** in 92% yield as a 3:1 rotomer (scheme 1). The structure and rotomer ratio of **(4a-d)** were determined on the basis of ^{1}Hnmr, ^{13}Cnmr, DEPT and ^{2}D-COSY studies (see experimental). The stereochemistry of substitution on pyrrolidine ring was assigned from n.O.e. data and by the related previous work[14-18] and confirmed as reported before[12-17]. Note that **(4d)** depicts the absolute stereochemistry of cycloadducts derived from 1R, 2S, 5R-(-)-menthyl acrylate **(5)** (see experimental).

In summary, the versatility of technically simple metal catalysed imine -azomethine ylides-1,3-Dipolar cycloaddition cascades applied to prepare some novel highly functionalized and potential bioactive chiral and achiral benzoylaminocarbothioyl pyrrolidines. The compound were obtained under mild conditions in excellent yield and provides an major increase in molecular complexity . Some more chiral version of these processes and their metal complexes which can be used as chiral catalyst are under investigation. The bioactivities of the final compounds will be done in conjuntion with a pharmaceutical company.

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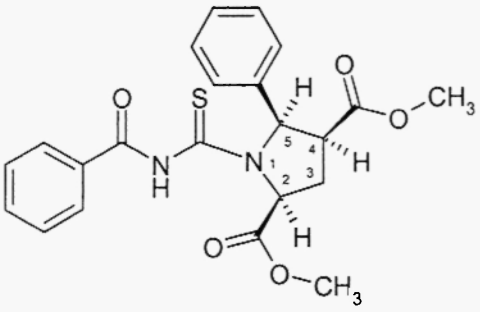
Experimental

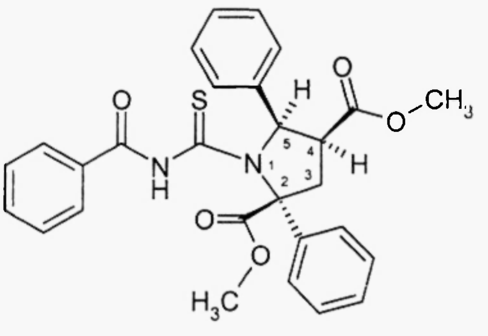
General Technical Data: IR spectra were recorded in the 4000-400 cm^{-1} range on a Shimadzu 435 spectrophotometer, using KBr pellets. Nuclear magnetic resonance spectra and decoupling experiments were determined at 300 MHz. on a Q.E 300 instrument and at 500 MHz on a Bruker AM500 spectrometer as specified. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard. Spectra were determined in deuteriochloroform except where otherwise stated. The following abbreviations are used; s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet, br= broad and brs= broad singlet. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica gel GF$_{254}$ (Merck 7730). Petroleum ether refers the fraction with b.p 40-60 ^{0}C unless otherwise specified. Melting points were determined on a digital electrothermal model 9200 hot stage apparatus and are uncorrected. Microanalyses were obtained using a Carlo - Erba Model 1106 instrument. Mass spectra were recorded at 70 ev on a VG Autospec mass spectrometer. Specific rotations were measured at ambient temperature with an Optical Activity Ltd., AA-1000 polarimeter. All solvents were purified according to procedures given in Purification of Laboratory Chemicals, D.D. Perrin, W.L.F. Armarego, D.R. Perrin, Permagon Press, 1980. The cycloadduct (3d)[19] was prepared from 1R, 2S, 5R-menthyl acrylate. The menthyl acrylate derived from (1R, 2S, 5R)-menthol which was readily synthesised from a reported method[20] by transesterification of ethyl acrylate using a Grignard complex of menthol. Benzoylisothiocyanate was prepared accordig to litterature procedure[2].

General Procedure for the synthesis of Benzoylaminocarbothioyl pyrrolidines. To a sitirred solution of benzoylisothiocyanate (1.22 mmol) in freshly distilled dry degassed acetonitrile (20 ml) was added a solution of pyrrolidine cycloadduct (1.22 mmol) in acetonitrile (10 ml) during 15 min. and stirred at ambient temperature under a nitrogen atmosphere for 3-5 h. The solvent was evaporated under reduced pressure (bath temperature not higher than 30 °C) and the residue was crystallised from an appropriate solvent.

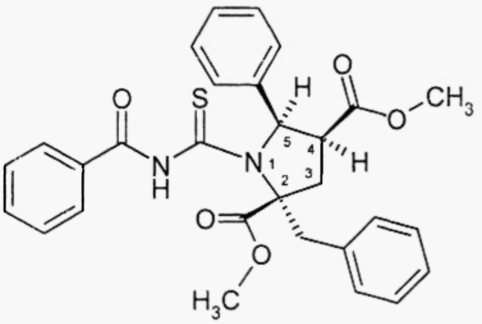
1-Benzoylaminocarbothioyl-5-phenyl-pyrrolidine-2,4-dicarboxylic acid dimethyl ester (4a) After a reaction time of 2h and work up the product as 4:1 mixture of rotomer crystallised from petroleum ether-hexane as a pale yellow amorphous solid in 98% yield. The rotomeric mixture dissapear when heated to 323 K in $CDCl_3$. HRMS (EI) found: 426.4865, $C_{22}H_{20}N_2O_5S$ requires: 426.4864. m/z (%) (ES): 427 (M+1, 100), 264(4) and 143(3). *V max* (KBr): 3300, 2929, 1690 and 1074 cm^{-1}. δ_H(500 MHz) ($CDCl_3$) (323K): 8.17 (brs, 1H, NH), 7.62-7.19(m, 10H, ArH), 5.60 (brd, 1H, J 7.5 Hz, 5-H), 4.90 (brd, 1H, J 8.2 Hz, 2-H), 3.82(s, 3H, OMe), 3.62(m, 1H, 4-H), 3.33(s, 3H, OMe), 2.70(dd, 1H, J 6.1 and 13.2Hz, 3b-H), 2.44(dd, 1H, J 7.2 and 13.6Hz, 3a-H).. δ_C($CDCl_3$) (323K): 178.8(C=S), 170.7 (C=O), 169.14(C=O), 164.09(C=O), 136.4, 133.1, 132.76, 129.1, 128.9, 128.7(2C), 127.8(2C), 127.4, 68.164.5, 62.9, 52.5, 51.4, 48.9, 48.2, 29.8. N.O.e data: Irradiation of 5-H effected enhancement of 3a-H(6) and 4-H(8) and 2-H(4), Irradiation of 4-H effected enhancement of 3a-H(7) and 5-H(9).



1-Benzoylaminocarbothioyl-2,5-diphenyl-pyrrolidine-2,4-dicarboxylic acid dimethyl ester (4b). After a reaction time of 2.5h and work up the product as 3:1 mixture of rotomer crystallised from petroleum ether-hexane as a pale yellow amorphous solid in 95% yield. HRMS (EI), found: 502. 2827, $C_{28}H_{26}N_2O_5S$ requires: 502. 2825; m/z (%) (ES): 503 (M+1, 100) and 143(60). *V max* (KBr): 3306, 2930 and 1696 cm^{-1}. δ_H(500 MHz) ($CDCl_3$): 7.86(brs, 1H, NH), 7.78(m, 2H, Ar-H), 7.70(m, 2H, Ar-H), 7.60(m, 2H, Ar-H), 7.52-7.15(m, 9H, ArH), 5.85(d, 1H, J 8.8 Hz, 5-H, minor rotomer), 5.80.(d, 1H, J 9.0 Hz, 5-H, major rotomer), 3.90(s, 3H, OMe major rotomer), 3.69(s, 3H, OMe minor rotomer), 3.42(m, 1H, 4-H), 3.38(m, 1H, 3b-H), 3.31(s, 3H, OMe minor rotomer), 3.22(s, 3H, OMe major rotomer), 2.55(m, 1H, 3a-H). δ_C($CDCl_3$): 187.0 and 179.7(C=S, rotomer), 174.8 and 172.1(C=O, rotomer), 170.2and 169.4(C=O, rotomer), 168.7 and 164.6(C=O, rotomer).

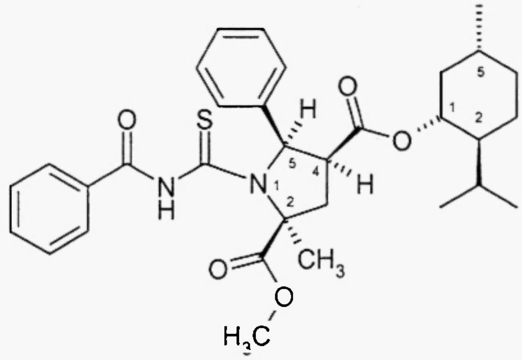


1-Benzoylaminocarbothioyl-2-benzyl-5-phenyl-pyrrolidine-2,4-dicarboxylic acid dimethyl ester (4c). After a reaction time of 4h and work up the product as 2:1 mixture of rotomer crystallised from petroleum ether-hexane as a pale yellow amorphous solid in 94% yield.. HRMS (EI), found: 516.6093. $C_{29}H_{28}N_2O_5S$ requires: 516.6090. m/z (%) (ES): 517 (M+1, 100), 319(5) and 143(6). *V max* (KBr): 3290, 2890 and 1702 cm^{-1}. δ_H(500 MHz) ($CDCl_3$): 8.15 (d, 1H, Ar-H), 7.93(brs, 1H, NH), 7.51-7.01(m, 14H, ArH), 5.25.(d, 1H, J 9.95 Hz, 5-H, minor rotomer), 5.17d, 1H, J 10.0 Hz, 5-H, major rotomer), 4.63(d, 1H, J12.4 Hz, 4-H major rotomer), 4.23(d, 1H, J12.6 Hz, 4-H minor rotomer), 3.93(s, 3H, OMe major rotomer), 3.79(s, 3H, OMe minor rotomer), 3.45 and 2.95 (2xd, 2x1H, J 13.3 Hz, $\underline{CH_2}$Ph minor rotomer), 3.33 and 2.85 (2xd, 2x1H, J 13.5 Hz, $\underline{CH_2}$Ph major rotomer), 3.11(s, 3H, OMe minor rotomer), 3.05(s, 3H, OMe major rotomer), 2.52-2.15(m, 2H, 3b-H and 3a-H), δ_C($CDCl_3$): 186.5 and 177.9(C=S, rotomer), 173.4 and 172.0(C=O, rotomer), 169.7and 169.2(C=O, rotomer), 163.9 and 163.4(C=O, rotomer). N.O.e data: Irradiation of 4-H effected enhancement of 3a-H(5) and 5-H(6).



(2S,4S,5R)-1-Benzoylaminocarbothioyl-2-methyl-5-phenyl-pyrrolidine-2,4-dicarboxylic acid 4-((1R,2S,5R)-2-isopropyl-5-methyl-cyclohexyl) ester 2-methyl ester (4d). After a reaction time of 4h and work up the product as 3:1 mixture of rotomer crystallised from petroleum ether-hexane as a pale yellow amorphous solid in 90% yield. $[\alpha]_D^{20}$ - 22.3 (0.5 g / 100 ml, EtOH). HRMS (EI), found: 565. 7442, $C_{32}H_{41}N_2O_5S$ requires: 565. 7444. m/z (%) (ES): 565 (M+1, 100) and 402(13). *V max* (KBr): 3306, 2929 and

1074 cm^{-1}. δ_H(500 MHz) ($CDCl_3$): 8.10 (m, 1H, Ar-H), 7.95(brs, 1H, NH), 7.65-7.25(m, 9H, ArH), 5.82.(d, 1H, J 9.4 Hz, 5-H, minor rotomer), 5.60.(d, 1H, J 9.5 Hz, 5-H, major rotomer), 5.60(m, 1H, OCH menthyl), 3.87(s, 3H, OMe major rotomer), 3.80(m, 1H, 4-H), 3.74(s, 3H, OMe minor rotomer), 3.05(m, 1H, 3b-H), 2.22(m, 1H, 3a-H), 1.94(s, 3H, Me, major rotomer), 1.90(s, 3H, Me, minor rotomer), 1.50(m, 3H, menthly-H), 1.18(m, 2H, menthyl-H), 0.95(m, 1H, menthyl-H), 0.90-0.75(m, 3H, menthyl-H), 0.82 and 0.73(2xd, 2x3H, J 6.4Hz, $CH\underline{Me_2}$, 0.56(d, 3H, J 7.0 Hz, Me). δ_C($CDCl_3$): 185.3 and 177.7(C=S, rotomer), 173.4 and 172.3(C=O, rotomer), 171.1and 168.4(C=O, rotomer), 167.2 and 164.4(C=O, rotomer). N.O.e data: Irradiation of 2-Me effected enhancement of 3a-H(8) and 4-H(4) and 5-H(2), Irradiation of 4-H effected enhancement of 3a-H(5) and nd 5-H(6).



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