Synthesis and Transformations of Stereoisomeric Ethyl 2-Isothiocyanato-1-cyclopentanecarboxylates

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Dedicated to the memory of Raymond N. Castle

Ethyl *cis*- and *trans*-2-isothiocyanato-1-cyclopentanecarboxylates **2** and **7** were prepared by the reaction of the corresponding alicyclic ethyl 2-amino-1-carboxylates and thiophosgene. The *cis*-isothiocyanato compound **2** underwent ring closure with amines in one or two steps, resulting in 3-substituted-*cis*-2-thioxocyclopenta[*d*]pyrimidin-4-ones **3a-g**. The *trans* isomer **7** failed to cyclize, but gave carboxamide **8a,b** or thiourea ester derivatives **9a,b**.

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Introduction

Although six-membered saturated 1,3-heterocycles and their benzene ring-fused derivatives have been studied thoroughly, much less attention has been paid to the bicyclic saturated derivatives. The synthesis and conformational study of saturated or partially saturated six-membered 1,3-heterocycles *cis*- or *trans*-fused with 5-, 6-, 7- or 8-membered alicycles has therefore been one of our main research topics [1].

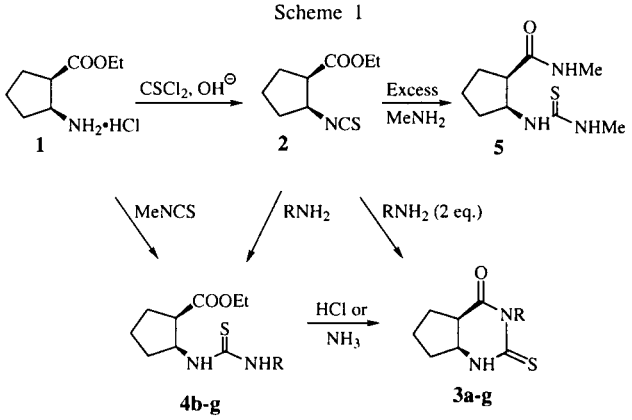
Isocyanato [2] and isothiocyanato compounds [3,4] are widely used for the preparation of ureas, thioureas and heterocyclic derivatives [5], which have a wide range of biological activities. Some of the isothiocyanato compounds have also found applications in the synthesis of agrichemicals and pharmaceuticals [6]. They are particularly valuable building blocks for the synthesis of different heterocycles [2,7-10]. Isothiocyanato compounds have mainly been prepared by the reactions of amines with thiocarbonyl reagents such as carbon disulfide or thiophosgene [11].

Results and Discussion

This paper describes the preparation of ethyl *cis*- and *trans*-2-isothiocyanato-1-cyclopentanecarboxylates **2** and **7**, from the corresponding ethyl 2-amino-1-cyclopentanecarboxylates **1** and **6** with thiophosgene (Schemes 1 and 2).

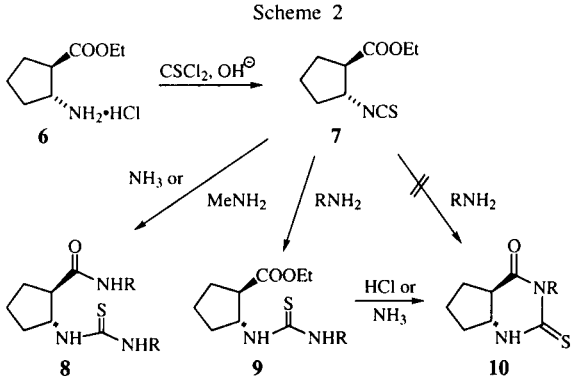
cis-2-Amino-1-cyclopentanecarboxylic acid was prepared from cyclopentene by addition of chlorosulfonyl isocyanate and subsequent ring opening of the resulting azetidinone with hydrochloric acid [12]. The *trans* isomer was obtained by the addition of ammonia to 1-cyclopentene-1-carboxylic acid [13]. The amino acids were transformed to the amino ester hydrochlorides **1** [14] and **6** [15] with thionyl chloride and ethanol. Isothiocyanato compounds **2** and **7** can be prepared through reaction of the ester hydrochlorides **1** or **6** with thiophosgene in the presence of sodium hydrogencarbonate at 40°C and subsequent column chromatography of the crude oily products.

Scheme 1



R = H: **a**; R = Me: **b**; R = *i*-Pr: **c**; R = Ph: **d**; R = CH_2Ph: **e**; R = CH_2CH_2Ph: **f**; *p*-tolyl: **g**

Scheme 2



R = H: **a** R = Me: **b** R = Ph: **a** R = *p*-tolyl: **b**

It is interesting that the chemical shifts of **6** and **7** happen to be practically the same, probably because of the magnitudes of the electronic and anisotropic effects of the 2-substituent. The difference in the multiplicity of 2-H is caused by the steric difference between NH_2

Table 1

Physical and Analytical Data for Compounds **2-9**

Compound	Yield (%)	Method	Mp (°C)	Formula (Mw)	Calcd C (%)	Found C (%)	Calcd H (%)	Found H (%)	Calcd N (%)	Found N (%)
3a	62	B	200-203 [a] [b]	$C_7H_{10}N_2OS$ (170.24)	49.39	49.02	5.92	6.28	16.46	16.64
3b	60	C	132-135 [c] [d]	$C_8H_{12}N_2OS$ (184.26)	52.15	51.98	6.56	6.61	15.20	15.10
	55	D								
	65	E								
3c	63	E	131-133 [c]	$C_{10}H_{16}N_2OS$ (222.40)	54.90	54.55	7.15	7.25	7.64	7.99
3d	69	E	282-284 [c] [e]	$C_{13}H_{14}N_2OS$ (246.33)	63.39	63.11	5.73	5.67	11.37	11.05
3e	67	E	162-165 [f]	$C_{14}H_{16}N_2OS$ (260.36)	64.59	64.29	6.19	6.43	10.76	10.93
3f	75	E	136-137 [g]	$C_{15}H_{18}N_2OS$ (274.39)	65.66	65.35	6.61	6.84	10.21	10.47
3g	78	E	292-294 [h]	$C_{14}H_{16}N_2OS$ (260.36)	64.59	64.30	6.19	6.28	10.76	10.54
4c	77	F	67-68 [g]	$C_{12}H_{22}N_2O_2S$ (258.39)	55.78	55.92	8.58	8.70	10.84	10.61
4d	69	F	61-64 [g] [i]	$C_{15}H_{20}N_2O_2S$ (292.40)	61.62	61.87	6.89	6.96	9.58	9.39
4e	83	F	80-82 [j]	$C_{16}H_{22}N_2O_2S$ (306.43)	62.72	62.93	7.24	7.60	9.14	9.50
4g	72	F	64-68 [j]	$C_{16}H_{22}N_2O_2S$ (306.43)	62.72	62.78	7.24	7.48	9.14	8.92
5	74	G	100-104 [g]	$C_9H_{17}N_3OS$ (215.32)	50.20	50.33	7.96	8.09	19.52	19.36
8a	60	G	154-157 [c]	$C_7H_{13}N_3OS$ (187.27)	44.90	45.02	7.00	7.29	22.44	22.78
8b	61	G	132-138 [c]	$C_9H_{17}N_3OS$ (215.32)	50.20	50.36	7.96	8.12	19.52	19.22
9a	78	F	78-80 [c] [k]	$C_{15}H_{20}N_2O_2S$ (292.40)	61.62	61.35	6.89	6.99	9.58	9.31
9b	82	F	102-105 [c]	$C_{16}H_{22}N_2O_2S$ (306.43)	62.72	63.05	7.24	7.53	9.14	9.12

[a] From ethyl acetate. [b] Lit. mp [14]: 205-208°C. [c] From diethyl ether/methanol. [d] Lit. mp [16]: 134-137°C. [e] Lit. mp [16]: 285-287°C. [f] From ethyl acetate/diethyl ether. [g] From diethyl ether/diisopropyl ether. [h] From dimethylformamide. [i] Lit. mp [16]: 66-69°C. [j] From diisopropyl ether. [k] Lit. mp [16]: 70-73°C.

and NCS, which could alter the geometry of the cyclopentane ring.

Isothiocyanates **2** or **7** were reacted with different amines and, depending on the reagent, the ratio of the reactants and the configuration of the isothiocyanate, three different products were formed. The *cis* **2** with two equivalents of ammonia or methylamine gave the corresponding *cis*-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]pyrimidin-4-ones **3a** and **3b**, respectively. When an excess of ammonia was used, the product was again **3a**, but with an excess of methylamine, the *cis* **2** gave the thiourea **5**, the ester function was amidated rather than ring closure occurring.

Reactions of substituted amines such as isopropylamine, benzylamine, phenylethylamine, aniline and *p*-toluidine with **2** resulted in the corresponding thioureas **4c-g**. Thiourea **4b** was prepared from **1** with methyl isothiocyanate as described earlier [16]. Thioureas **4** can readily be cyclized using either acid (HCl) or base (*e.g.* NH_3) catalysts.

When the *trans* **7** (Scheme 2) was reacted with amines, the formation of the pyrimidinone **10** was not observed, even under forced conditions. But the reaction with ammonia or methylamine, leads to the thiourea-amide derivatives **8a** and **8b**. With aniline or *p*-toluidine, the *trans* thioureas **9a** and **9b** were formed in good yields. The cyclization of *trans* thioureas **9a** and **9b** failed under both acidic and basic conditions.

It is noteworthy that in the ring closures of the 1,2-disubstituted-1,3-difunctional cyclohexane, cycloheptane and cyclooctane derivatives, no appreciable differences were found in the reactivities of the *cis* and *trans* isomers in the formation of six-membered 1,3-heterocycles fused with carbocycles [1,17]. In contrast, very striking differences were observed in the cyclization reactivities of the *cis*- and *trans*-1,2-disubstituted 1,3-difunctional cyclopentane derivatives, such as 2-hydroxymethyl-1-cyclanols and alicyclic 2-aminomethyl-1-amines, or in the cases of *cis*- and *trans*-2-hydroxy-1-cyclopentanecarboxamides or *cis*- and *trans*-2-amino-1-cyclopen-

Table 2

^{1}H-NMR Parameters of Compounds **2-9**

Compounds	^{1}H NMR data
2	4.35 m, 1 H (1); 4.30-4.16 m, 2 H (CH_2CH_3); 2.92 m, 1 H (2); 2.16 m, 1 H; 2.07-1.90 m, 4 H; 1.75 m, 1 H; 1.32 t, 3 H, J= 7.1 (CH_2CH_3)
3a	8.38 brs, 1 H (NH); 7.13 brs, 1 H (NH); 4.08 m, 1 H (7a); 2.88 m, 1 H (4a); 2.23 m, 1 H; 2.11-1.99 m, 2 H; 1.95-1.72 m, 3 H
3b	7.83 brs, 1 H (NH); 4.00 m, 1 H (7a); 3.56 s, 3 H (NCH_3); 2.95 m, 1 H (4a); 2.22 m, 1 H; 2.07-1.86 m, 4 H; 1.75 m, 1 H
3c	7.16 brs, 1 H (NH); 5.70 sep, 1 H, J= 6.8 ($CH(CH_3)_2$); 3.95 m, 1 H (7a); 2.85 m, 1 H (4a); 2.20 m, 1 H; 2.02-1.71 m, 5 H; 1.47 d, 3 H, J= 6.8 ($CH(CH_3)_2$); 1.42 d, 3 H, J= 6.8 ($CH(CH_3)_2$.)
3d	9.82 brs, 1 H (NH); 7.39-7.38 m, 2 H (Ar); 7.33-7.31 m, 1 H (Ar); 7.20-7.05 m, 2 H (Ar); 4.05 m, 1 H (7a); 3.05 m, 1 H (4a); 2.11 m, 1 H; 1.98 m, 2 H; 1.85 m, 1 H; 1.72 m, 2 H
3e	7.39 d, 2 H, J= 7.3 (Ar); 7.35 brs, 1 H (NH); 7.32-7.21 m, 3 H (Ar); 5.55 d, 1 H, J= 14.6 ($PhCH_2$); 5.49 d, 1 H, J= 14.6 ($PhCH_2$); 3.97 m, 1 H (7a); 2.94 m, 1 H (4a); 2.18 m, 1 H; 2.08-1.70 m, 5 H
3f	7.53 brs, 1 H (NH); 7.34-7.27 m, 4 H (Ar); 7.24-7.21 m, 1 H (Ar); 4.53-4.39 m, 2 H ($ArCH_2$); 3.95 m, 1 H (7a); 3.05-2.85 m, 3 H (NCH_2, 4a); 2.18 m, 1 H; 2.01-1.70 m, 5 H
3g	7.26-7.24 m, 2 H (Ar); 7.13 brs, 1 H (NH); 7.04-7.03 m, 2 H (Ar); 4.16-4.15 m, 1 H (7a); 3.06 m, 1 H (4a); 2.39 s, 3 H ($ArCH_3$); 2.32 m, 1 H; 2.18 m, 1 H; 2.09-1.80 m, 4 H
4b	6.64 brs, 1 H (NH); 6.01 brs, 1H (NH); 4.87 m, 1H (2); 4.10-4.17 m, 2H (CH_2CH_3); 3.10-3.05 dd, 1H, J= 7.64, 14.4 (1); 2.92, d, 3H, J= 4.8 (NCH_3); 2.16-2.13 m, 1H; 2.00-1.9 m, 2H; 1.82-1.61 m, 3H; 1.38-1.25 t, 3H, J= 7.64, 14.4 (CH_2CH_3)
4c	6.59 d, 1 H, J= 4.3 (NH); 5.83 d, 1 H, J= 5.8 (NH); 4.88 m, 1 H (2); 4.20-4.08 m, 2 H (CH_2CH_3); 3.9 m, 1 H; 3.08 m, 1 H (1); 2.19-1.93 m, 3 H; 1.86-1.61 m, 3 H; 1.27 t, 3 H, J= 7.1 (CH_2CH_3); 1.23 d, 3 H, J= 6.7 ($CH(CH_3)_2$); 1.21 d, 3 H, J= 6.7 ($CH(CH_3)_2$)
4d	8.01 brs, 1 H (NH); 7.44-7.39 m, 2 H (Ar); 7.30-7.27 m, 1 H (Ar); 7.20-7.17 m, 2 H (Ar); 6.93 d, 1 H, J= 7.8 (NH); 5.01 m, 1 H (1); 4.03 q, 2 H, J= 7.1 (CH_2CH_3); 3.10 m, 1 H (2); 2.13 m, 1 H; 2.04-1.85 m, 2 H; 1.80-1.59 m, 3 H; 1.17 t, 3 H, J= 7.1 (CH_2CH_3)
4e	7.37-7.29 m, 5 H (Ar); 6.63 d, 1 H, J= 8.1 (NH); 6.33 brs, 1 H (NH); 4.85 m, 1 H (1); 4.52 brs, 2 H ($PhCH_2$); 4.13-4.00 m, 2 H (CH_2CH_3); 3.03 m, 1 H (2); 2.10-1.85 m, 3 H; 1.74-1.57 m, 3 H; 1.24 t, 3 H, J= 7.2 (CH_2CH_3)
4f	7.34-7.29 m, 2 H (Ar); 7.26-7.21 m, 3 H (Ar); 6.61 brs, 1 H (NH); 5.98 brs, 1 H (NH); 4.80 m, 1 H (2); 4.17-4.05 m, 2 H (CH_2CH_3); 3.67-3.53 m, 2 H; 3.04 m, 1H (1); 2.89 m, 2 H; 2.13-1.92 m, 3 H; 1.84-1.59 m, 3 H; 1.25 t, 3 H, J= 7.1 (CH_2CH_3)
4g	8.17 brs, 1 H (NH); 7.23-7.20 d, 2 H, J= 8.3 (Ar); 7.09-7.07 d, 2 H, J= 8.3 (Ar); 6.82 d, 1 H, J= 9.1 (NH); 5.01 m, 1 H (1); 4.03 q, 2 H, J= 7.1 (CH_2CH_3); 3.10 m, 1 H (2); 2.35 s, 3 H (Ar-Me); 2.10 m, 1 H; 2.02-1.85 m, 2 H; 1.79-1.58 m, 3 H; 1.18 t, 3 H, J= 7.1 (CH_2CH_3)
5	7.62-7.23 brs, 1 H (NH); 7.14-7.03 brs, 1 H (NH); 6.52-6.36 brs, 1 H (NH); 4.87 m, 1 H (1); 3.18 m, 1 H (2); 3.02 d, 3 H, J= 3.5 (NCH_3); 2.70 d, 3 H, J= 4.8 (NCH_3); 2.10-1.89 m, 3 H; 1.83 m, 1 H; 1.66-1.50 m, 2 H
6	4.30 dt, 1 H, J= 6.5, 6.5 (1); 4.18 q, 2 H, J= 7.3 (CH_2CH_3); 2.93 m, 1 H (2); 2.19-2.07 m, 2H; 1.92-1.70 m, 4 H; 1.25 t, 3 H, J= 7.3 (CH_2CH_3)
7	4.30 dd, 1 H, J= 12.6, 6.3 (1); 4.18 q, 2 H, J= 7.0 (CH_2CH_3); 2.93 m, 1 H (2); 2.19-2.07 m, 2 H; 1.93-1.73 m, 4 H; 1.29 t, 3 H, J= 7.0 (CH_2CH_3)
8a	7.53 d, 1H, J= 7.4 (NH); 7.20-6.70 m, 4H (NH_2, NH_2); 3.20 m, 1H (2); 2.54 m, 1H (1); 1.98 m, 1H; 1.88 m, 1H; 1.65-1.55 m, 3H; 1.45 m, 1H
8b	7.7 brs, 1 H (NH); 6.4 brs, 1 H (NH); 4.4 brs, 1 H (NH); 3.07 d, 3 H, J= 4.3 (NCH_3); 2.82 d, 3 H, J= 4.8 (NCH_3); 2.62 m, 1 H (1); 2.18-1.98 m, 2 H; 1.85-1.70 m, 3 H; 1.60 m, 1 H
9a	7.4 m, 2 H (Ar); 7.35-7.22 m, 3 H (Ar); 6.2 brs, 1 H (NH); 4.8 brs, 1 H (NH); 4.19 q, 2 H, J = 7.1 (CH_2CH_3); 2.66 m, 1 H (2); 2.31 m, 1 H (1); 2.06-1.87 m, 2 H; 1.79-1.66 m, 2 H; 1.55-1.44 m, 2 H; 1.28 t, 3 H, J= 7.1 (CH_2CH_3)
9b	7.25-7.10 m, 4 H (Ar); 6.0 brs, 1 H (NH); 4.8 brs, 1 H (NH); 4.19 q, 2 H, J= 7.1 (CH_2CH_3); 2.63 m, 1 H (1); 2.36 s, 3 H ($ArCH_3$); 2.32 m, 1 H (2); 2.04-1.88 m, 2 H; 1.80-1.64 m, 2 H; 1.46 m, 1 H; 1.28 t, 3 H, J= 7.1 (CH_2CH_3)

tanecarboxylic acids [1]. The *cis* isomers react readily, while their *trans* counterparts do not undergo ring closure in most cases [1].

The difference observed in the present study may serve as supporting evidence for the difference in the ring closure reactivities of *cis* and *trans*-1,2-disubstituted-1,3-difunctional cyclopentane derivatives [1].

EXPERIMENTAL

The ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solution in 5 mm tubes at room temperature at 400.13 MHz on a Bruker AVANCE DRX 400 spectrometer, using the ^{2}H signal of the solvent as the lock and TMS as internal standard. Melting points were determined with a Kofler apparatus and the values are not corrected. The physical and analytical data on the compounds prepared are listed in Table 1. The ethyl *cis*- and *trans*-2-amino-1-cyclopentanecarboxylates **1** and **6** and the thiourea **4b** were prepared according to literature methods [12-16].

Preparation of Isothiocyanato Compounds **2** and **7** (Method A).

To a stirred mixture of chloroform (150 ml), water (80 ml), thiophosgene (5.75 g, 0.05 mol) and sodium hydrogencarbonate (12.6 g, 0.15 mol), a solution of ethyl *cis*- or *trans*-2-amino-1-cyclopentanecarboxylate hydrochloride **1** or **6** (0.05 mol) in water (80 ml) was added dropwise during a period of 40 minutes (Caution: thiophosgene is volatile and highly toxic - use hood.) After stirring for 3 hours at 40°C, the chloroform layer was separated and dried over magnesium sulfate. It was diluted with *n*-hexane (400 ml), and purified by passing through a silica gel

passing through a silica gel column. The ^{1}H-NMR spectra indicated that the oily isothiocyanato compounds **2** and **7** obtained had a purity > 96% (Table 2).

cis-2-Thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]-pyrimidin-4-one **3a** (Method B).

To a methanolic solution of isothiocyanate **2** (398 mg, 2 mmol in 10 ml), two equivalents of ammonia (25%, 0.3 ml) in methanol was added and the mixture was left to stand at ambient temperature overnight. After evaporation to dryness, the solid residue **3a** was recrystallized.

cis-3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta[*d*]-pyrimidin-4-one (**3b**) (Method C).

To a methanolic (absolute) solution of isothiocyanate **2** (398 mg, 2 mmol in 10 ml), two equivalents of methylamine (40%, 0.35 ml) in methanol was added and the mixture was left to stand at ambient temperature overnight. After evaporation to dryness, the solid residue **3b** was recrystallized.

cis-3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta-[*d*]pyrimidin-4-one **3b** (Method D).

The thiourea derivative **4b** (253 mg, 1.1 mmol) was dissolved in absolute methanol (15 ml), and ammonia (25%, 0.2 ml) in methanol was added dropwise. The mixture was left to stand at ambient temperature overnight. The solvent was evaporated, diethyl ether (5 ml) was added to the oily residue and the precipitate was collected by filtration to give **3b**.

cis-3-Methyl-2-thioxo-1,2,3,4a,5,6,7,7a-octahydrocyclopenta-[*d*]pyrimidin-4-one **3b** (Method E).

The thiourea derivative **4b** (2 mmol) was dissolved in hydrochloric acid (10%, 15 ml) and the solution was refluxed for 12 hours. After keeping for overnight, the crystalline product obtained was separated by filtration and recrystallized. Compounds **3c-g** were prepared as above.

N-Isopropyl-*N'*-(2-ethoxycarbonylcyclopentyl)thiourea **4c** (Method F).

Isothiocyanato compound **2** (398 mg, 2 mmol) was dissolved in methanol (15 ml), and the equivalent amount isopropylamine in methanol (10 ml) was added. The mixture was left to stand overnight at ambient temperature. After evaporation to dryness, the solid residue was recrystallized. Compounds **4d-g** and **9a,b** were prepared as above. The oily product **4f** was purified by column chromatography (toluene:methanol = 19:1)

N-Methyl-*N'*-(2-methylaminocarbonylcyclopentyl)thiourea **5** (Method G).

Isothiocyanate **2** (398 mg, 2 mmol) was dissolved in absolute methanol (15 ml), and an excess of methylamine (40%, 10 ml) in methanol was added dropwise. The mixture was left to stand overnight at ambient temperature. After evaporation to dryness, the solid residue was recrystallized. Compounds **8a,b** were prepared as above.

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