Tetrahedron Letters,Vol.23,No.2,pp 201-204,1982 0040-4039/82/020201-04$03.00/0
Printed in Great Britain

A NEW CHIRAL RECOGNITION IN AMINOLYSIS OF 3-ACYL-4(R)-METHOXYCARBONYL-1,3-THIAZOLIDINE-2-THIONE WITH RACEMIC AMINES

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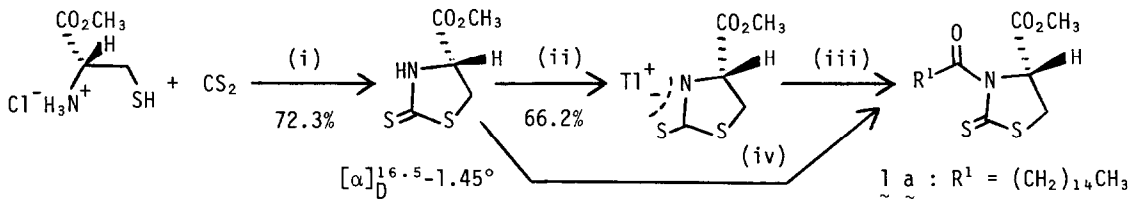
Summary: A chiral recognition was observed in aminolysis of 3-acyl-4(R)-methoxycarbonyl-1,3-thiazolidine-2-thione 1 by racemic amine 2 to give an optically active amide (S-excess) and amine (R-excess).

Our recent interest has been focused on the efficient synthesis of the naturally occurring amide compounds. We reported a new "monitored aminolysis" of 3-acyl-1,3-thiazolidine-2-thione (ATT).[1] This procedure was applied to synthesis of several macrocyclic diamides,[2] macrocyclic spermidine alkaloids,[3] and peptides.[4] The rate of this aminolysis is remarkably affected by steric surroundings of the amines[1]; completion of reaction can easily be judged by disappearance of the original yellow color of ATT. These features of the aminolysis suggested a potential chiral recognition for racemic amines 2 by a chiral ATT derivative.

Thus 3-acyl-4(R)-methoxycarbonyl-1,3-thiazolidine-2-thione [4(R)-AMTT] 1[5] was synthesized from L-cysteine methyl ester hydrochloride and carbon disulfide (Scheme 1).



$[\alpha]_D^{16.5}$ -1.45° (c = 1.31, $CHCl_3$)

1 a : $R^1 = (CH_2)_{14}CH_3$ 78.8%
b : R = Ph 89.6%
c : $R = CH_2Ph$ 79.8%
d : R = 1-adamantyl 29.7%

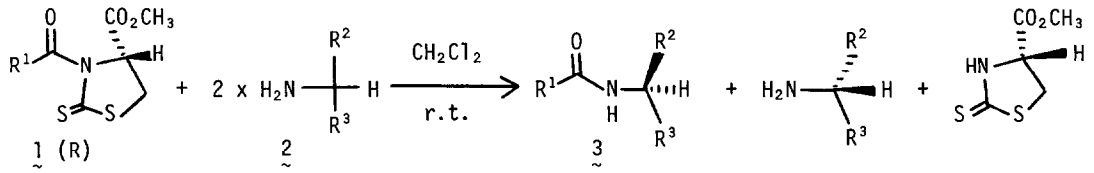
(i) Et_3N/CH_2Cl_2, (ii) TlOAc/EtOH
(iii) R^1COCl/THF, (iv) $R^1COCl/Et_3N/THF$

Scheme 1

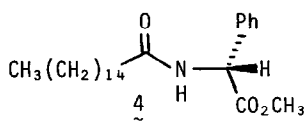
A solution of (±)-phenylglycine methyl ester (330.4 mg, 2 mmol) in CH_2Cl_2 (2 ml) was added to a yellow solution of 4(R)-AMTT 1a (415.5 mg, 1 mmol) in the same solvent (5 ml) with stirring in N_2. After being stirred at room temperature until original yellow color of the medium varnished (12h), the reaction was quenched with 10% HCl and then extracted with CH_2Cl_2. A usual work-up of CH_2Cl_2 extract afforded an optically active amide 3: $R^1=(CH_2)_{14}CH_3$, R^2=Ph, $R^3=CO_2Me$ [chemical yield(cy) = 93.7%, enantiomeric excess percent (ee%) = 64.4 (S excess: $[\alpha]_D^{20}$+50.35° (c = 1.02, $CHCl_3$)) (based on the pure amide 4)]. The aqueous layer on usual treatment gave the

optically active phenylglycine methyl ester hydrochloride [cy = 83.4%, ee% =45.9 (R excess: $[\alpha]_D^{20}$-60.59° (c = 1.03, MeOH)) based on pure (R)-phenylglycine methyl ester hydrochloride: $[\alpha]_D^{20}$-132.13 (c =1.03, MeOH)] (Scheme 2 and entry 1 in Table 1).

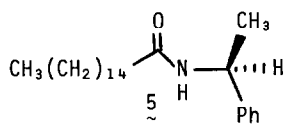
Other examples are summarized in Table 1 (entry 2~9). Calculation of ee% and determination of (S)-configuration for each amide 3 were done on the basis of the specific rotations of the authentic amides (4~12), which were derived from optically inactive ATT and the corresponding optically active pure amine, respectively. Thus, a significant chiral recognition was realized in aminolysis of 4(R)-AMTT with racemic amine; optically active amide was obtained in considerable enantiomeric excess. The use of extremely bulky adamantane-1-carbonyl derivative 1d, however, did not give a good result (see entry 9, Table 1).



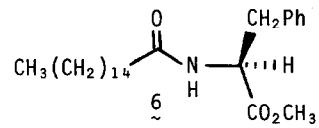
Scheme 2



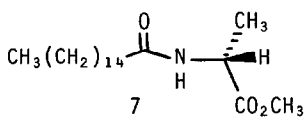
$[\alpha]_D^{26}$-78.23°
(c = 1.20, $CHCl_3$)



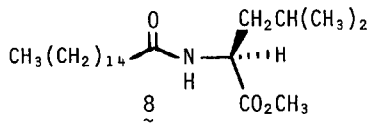
$[\alpha]_D^{26}$-56.08°
(c = 1.03, $CHCl_3$)



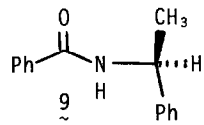
$[\alpha]_D^{22}$+61.42°
(c = 1.13, $CHCl_3$)



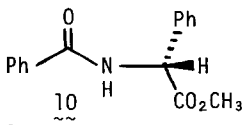
$[\alpha]_D^{22}$-4.23°
(c = 1.40, $CHCl_3$)



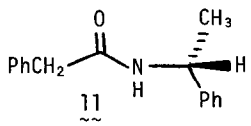
$[\alpha]_D^{19}$+2.95°
(c = 1.12, $CHCl_3$)



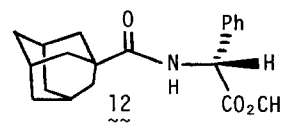
$[\alpha]_D^{26}$-20.07°
(c = 1.02, $CHCl_3$)



$[\alpha]_D^{26}$-15.22°
(c = 1.24, $CHCl_3$)



$[\alpha]_D^{23}$+1.99°
(c = 0.90, $CHCl_3$)



$[\alpha]_D^{17}$-105.89°
(c = 1.10, $CHCl_3$)

It is remarkably interesting that only the (S)-configuration excess amides 3 were afforded in all the cases where we tried. Thus, it is suggested that this new method can be useful for determination of the absolute configuration of amino compounds.[6] Solvent effect was then checked; aprotic solvent was shown to be preferable (see Table 2).

Table 1. Preparation of Optically Active Amide 3 by Aminolysis of 4(R)-AMTT with Racemic Amines[a)]

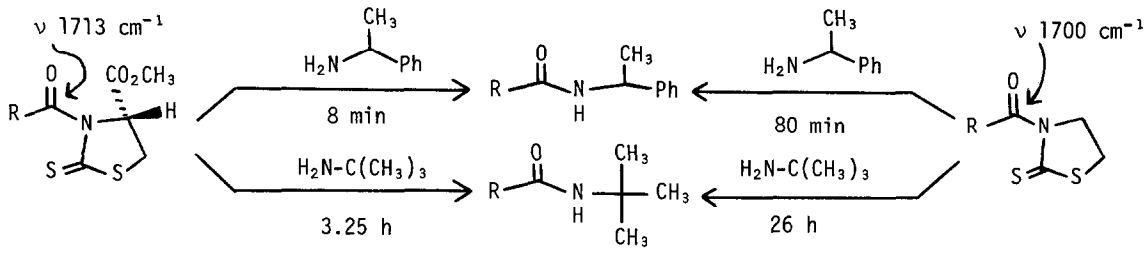
entry	4(R)-AMTT 1	amine 2 R^2	amine 2 R^3	reaction time	amide 3 cy (%)	amide 3 ee (%)
1[b)]	1a	Ph	CO_2CH_3	12 h	93.7	(S) 64.4
2	1a	CH_3	Ph	8 min	99.0	(S) 35.7
3[c)]	1a	CH_2Ph	CO_2CH_3	7 h	93.9	(S) 45.1
4[c)]	1a	CH_3	CO_2CH_3	75 min	93.7	(S) 42.3
5[c)]	1a	$CH_2CH(CH_3)_2$	CO_2CH_3	3.3 h	98.1	(S) 12.4
6	1b	CH_3	Ph	15 min	90.5	(S) 25.1
7[b)]	1b	Ph	CO_2CH_3	12 h	95.0	(S) 12.8
8	1c	CH_3	Ph	2 min	80.8	(S) 44.0
9	1d	Ph	CO_2CH_3	4 min	98.2	(S) 0.2

a) All reactions were carried out in CH_2Cl_2. b) The optically active amines (entry 1: cy = 83.4%, ee = 45.9%; entry 7: cy = 93.8%, ee = 14.6%) were also characterized as their hydrochlorides. c) Because the hydrochloride of amine 2 was used, the reaction was carried out in the presence of Et_3N (2.1 mmol).

Table 2. Solvent Effect on The Chiral Recognition to Racemic 1-Phenylethylamine by 4(R)-AMTT 1a

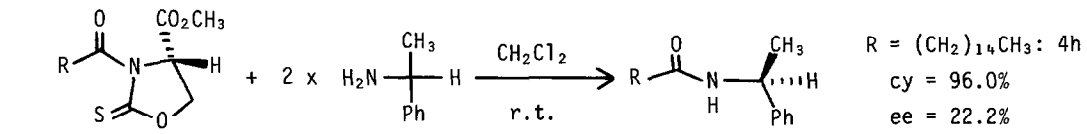
reaction solvent	reaction time	optically active amide 3 cy (%)	ee (%)
CH_2Cl_2	8 min	99	(S) 35.7
THF	10 min	99	(S) 11.9
DMF	25 min	72.6	(R) 1.8
EtOH-THF (5:2)	13 min	94.8	(R) 4.9

Aminolysis rate with 4(R)-AMTT 1 was found to be 8~10 times higher than that with ATT (see Scheme 3). This may be explicable by an activation of the amide carbonyl group which can be attributed to the dipole-dipole (or steric) repulsion to 4-methoxycarbonyl group and also the negative inductive effect of 4-methoxycarbonyl group.



Scheme 3

Finally we investigated the aminolysis of 3-acyl-4(S)-methoxycarbonyl-1,3-oxazolidine-2-thione [4(S)-AMOT] (derived from MOT synthesized from L-serine methyl ester and carbon disulfide) 13[7] and 14[7] in comparison with that of 4(R)-AMTT 1. As the result, 4(R)-AMTT 1 was much superior to 4(S)-AMOT in every point (ee%, reaction time, monitoring, etc.) (see Scheme 4).



"colorless or pale yellow"

13 R = $(CH_2)_{14}CH_3$

14 R = Ph

(racemic)

(S-excess) "colorless"

Scheme 4

There have been several reports on the chiral recognition for racemic amines,[8] but such a nicely monitored procedure as ours has never been encountered.

References and Notes

1) Y. Nagao, K. Seno, K. Kawabata, T. Miyasaka, S. Takao, and E. Fujita, *Tetrahedron Lett.*, 21, 841 (1980).

2) a. Y. Nagao, K. Seno, T. Miyasaka, and E. Fujita, *Chemistry Lett.*, 1980, 159. b. Y. Nagao, T. Miyasaka, K. Seno, and E. Fujita, *Heterocycles*, 15, 1037 (1981).

3) a. Y. Nagao, K. Seno, and E. Fujita, *Tetrahedron Lett.*, 21, 4931 (1980). b. Y. Nagao, S. Takao, T. Miyasaka, and E. Fujita, *J. Chem. Soc., Chem. Commun.*, 1981, 286.

4) Y. Nagao, T. Miyasaka, K. Seno, M. Yagi, and E. Fujita, *Chemistry Lett.*, 1981, 463.

5) 1a: $[\alpha]_D^{22}$-78.17° (c = 1.02, $CHCl_3$), 1b: $[\alpha]_D^{16.5}$+0.43° (c = 1.61, $CHCl_3$), 1c: $[\alpha]_D^{23}$-2.47° (c = 0.73, $CHCl_3$), 1d: $[\alpha]_D^{23}$-0.20° (c = 1.20, $CHCl_3$).

6) Y. Nagao, M. Yagi, T. Ikeda, and E. Fujita, the following paper.

7) 13: $[\alpha]_D^{16.5}$-23.99° (c = 1.11, $CHCl_3$), 14: $[\alpha]_D^{16.5}$-91.23 (c = 1.15, $CHCl_3$).

8) a. A. Horeau and H. B. Kagan, *Tetrahedron*, 20, 2431 (1964) and references cited therein. b. H. Helinger, H. Kleimann, and I. Ugi, *Justus Liebigs Ann. Chem.*, 706, 37 (1967). c. O. Cervinka, E. Kroupova, and O. Belousky, *Collect. Czech. Chem. Commun.*, 33, 3551 (1968). d. O. Cervinka and J. Fusek, *ibid.*, 38, 441 (1973). e. R. Weidmann and A. Horeau, *Bull. Soc. Chim. Fr.*, 1976, 645. f. T. Mukaiyama, M. Onaka, and M. Shiono, *Chemistry Lett.*, 1977, 651.

(Received in Japan 19 September 1981)