DOI 10.5012/bkcs.2010.31.9.2709

Crystallization Induced Dynamic Resolution of Ethyl Thiazolidine-2-Carboxylate

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Received June 14, 2010, Accepted July 22, 2010

Key Words: Crystallization induced dynamic resolution, Ethyl thiazolidine-2-carboxylate, Tartaric acid

Unnatural amino acids are widely utilized as biological active compounds and synthetic intermediates. Among them, thiazolidine-2-carboxylic acid, which is an unnatural cyclic amino acid, was found in medicinal and organic chemistry area, many of which showed biological activity and used as useful building blocks in organic synthesis.[1-7]

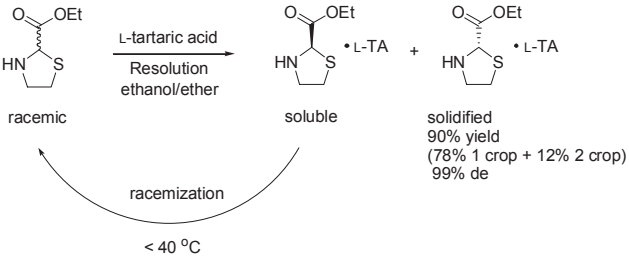
Several approaches for obtaining optically pure thiazolidine-2-carboxylic acid derivatives have been reported. Johnson *et al*.[1] reported the resolution of racemate of thiazolidine-2-carboxylic acid ester in ethanol and ether medium but yield is ranging between 43 - 47%. Shiraiwa *et al*.[8] synthesized optically active thiazolidine carboxylic acid by asymmetric transformation in acetic acid and ethanol medium using (+) or (−) tartaric acid salt and further hydrolysis of salt in triethylamine and methanol gave only ~50% optically active thiazolidine carboxylic acid. This prompted us to develop an efficient crystallization induced dynamic resolution for thiazolidine-2-carboxylic acid derivative. Crystallization induced dynamic resolution (CIDR) is an attractive approach for dynamic resolution, in which one of diastereomers crystallizes preferentially with high selectivity.[9] Among thiazoldine-2-carboxylic acid derivatives, we focused on ethyl thiazolidine-2-carboxylate and herein wish to report the crystallization induced dynamic resolution (CIDR) of racemic ethyl thiazolidine-2-carboxylate.

First, racemic ethyl thiazolidine-2-carboxylate was synthesized by literature method.[10] In order to investigate the possibility of crystallization induced dynamic resolution, the racemization of optically active (*S*)-ethyl thiazolidine-2-carboxylate · L-tartaric acid (TA) salt in ethanol solution was performed and the results are summarized in Table 1. At 20 °C, racemization of 99% de (*S*)-ethyl thiazolidine-2-carboxylate · L-TA salt didn't take place after 24 h (entry 1-2). Whereas at 40 °C, racemization was slowly occurred (entries 3-4). When the reaction was carried out at 80 °C, compound was rapidly racemized. These results suggested that CIDR process of ethyl thiazolidine-2-carboxylate could be possible between 20 - 80 °C.

We investigate the crystallization induced dynamic resolution to obtain optically active ethyl thiazolidine-2-carboxylate through the formation of optically active salt with L-tartaric acid, as a resolving agent as shown in Scheme 1.

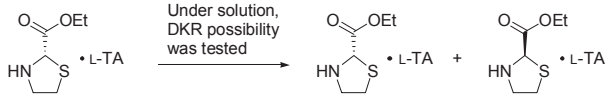
A solution of racemic ethyl thiazolidine-2-carboxylate in ether was mixed with a solution of L-tartaric acid in anhydrous ethanol at room temperature. As the crystals begins to separate, the mixture was repeatedly subjected to heating (< 40 °C) and cooling (~ 20 °C) for 5 days until about 30% of solvent (~ ether) was slowly evaporated. The precipitated crystals was filtered, washed with diethyl ether and dried furnished optically pure ethyl thiazolidine-2-carboxylate · L-TA as 78% yield. The remaining filtrate was heated and cooled for one more time to yield ethyl thiazolidine-2-carboxylate · L-TA as 12% yield (total 90% yield, 99% de).

The absolute configuration of optically pure ethyl thiazolidine-2-carboxylate · L-TA was determined by X-ray crystallo-



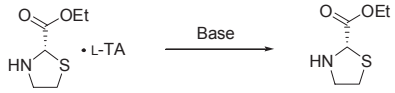
Scheme 1. Crystallization induced dynamic resolution of ethyl thiazolidine-2-carboxylate with L-tartaric acid

Table 1. Racemization of (*S*)-ethyl thiazolidine-2-carboxylate · L-TA in EtOH



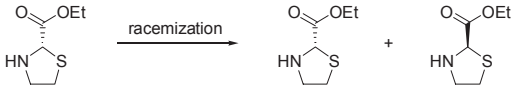
Entry	Reaction temperature	Reaction time	% de
1	20 °C	0 h	99
2	20 °C	24 h	99
3	40 °C	3 h	82
4	40 °C	24 h	48
5	80 °C	0.5 h	0

Table 2. Basification of (*S*)-ethyl thiazolidine-2-carboxylate · L-tartaric acid salt (99% de)



Entry	Base	Reaction time	Temperature	% ee	Yield
1	10% Na_2CO_3	30 min	ice bath	98	90%
2	10% Na_2CO_3	3 h	25 °C	82	92%
3	10% $NaHCO_3$	30 min	ice bath	> 99	94%

Table 3. Racemization of (*S*)-ethyl-2-thiazolidine carboxylate



Condition	Time (h)	(*S*)-Ethyl-2-thiazolidine carboxylate solvent free (solid)	(*S*)-Ethyl-2-thiazolidine carboxylate in ethanol	(*S*)-Ethyl-2-thiazolidine carboxylate in CH_2Cl_2
20 °C	0	99% ee	99% ee	99% ee
20 °C	24	99% ee	99% ee	99% ee
25 °C	24		99% ee	91% ee
30 °C	24		98% ee	
40 °C	24		93% ee	

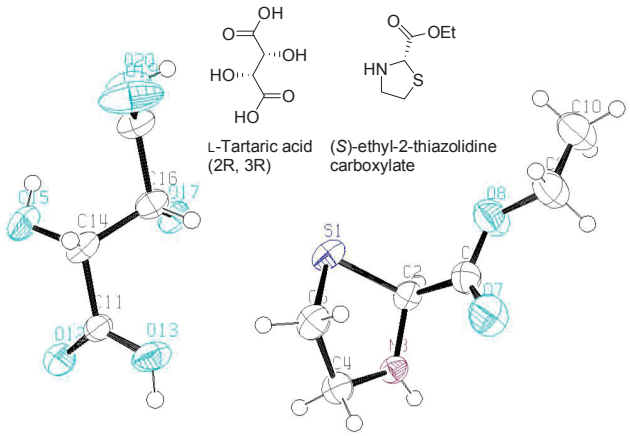


Figure 1. X-ray structure of (*S*)-ethyl thiazolidine-2-carboxylate · L-tartaric acid salt (2R, 3R).

graphy. (*S*)-Ethyl thiazolidine-2-carboxylate was crystallized with L-tartaric acid salt (2R, 3R) as shown in Figure 1.

In order to obtain free form of (*S*)-ethyl thiazolidine-2-carboxylate, basification condition was optimized with weak bases as shown in Table 2. It was found that by stirring with 10% $NaHCO_3$ in ice bath results excellent yield and % ee of the (*S*)-ethyl thiazolidine-2-carboxylate.

Finally, we investigated the optical purity of (*S*)-ethyl thiazolidine-2-carboxylate under solvent free or in different solvent and at various temperatures as shown in Table 3. We used (*S*)-ethyl thiazolidine-2-carboxylate with 99% ee. Solvent free (solid, crystalline form) and solution of (*S*)-ethyl thiazolidine-2-carboxylate were stable below 20 °C.

(*R*)-Ethyl thiazolidine-2-carboxylate was also obtained with the same procedure by using (*D*)-tartaric acid as a resolving agent.

In conclusion, crystallization induced dynamic resolution of racemic ethyl thiazolidine-2-carboxylate was described herein. Using CIDR, (*S*)-ethyl thiazolidine-2-carboxylate and L-tartaric acid salt (2R, 3R) was obtained in good yields (90%) and % de (99% de). Also, absolute configuration of (*S*)-ethyl thiazolidine-2-carboxylate was determined by X-ray crystallography.

Experimental

(*S*)-Ethyl thiazolidine-2-carboxylate · L-tartaric acid (TA) salt. To a stirred solution of L-tartaric acid (18.91 g, 0.126 mol) dissolved in anhydrous ethanol (103 mL) was added racemic ethyl thiazolidine-2-carboxylate (20.316 g, 0.126 mol) dissolved in diethyl ether (35 mL) at room temperature. As the crystals begins to separate, the mixture was repeatedly subjected to heating and cooling for 5 days until about 30% of the reaction solvent was slowly evaporated. The precipitated crystals was filtered, washed with diethyl ether and dried furnished pure L-tartaric acid salt of (*S*)-ethyl thiazolidine-2-carboxylate as white solid (31.38 g, 78%). The remaining filtrate was heated and cooled for one more time to yield ethyl thiazolidine-2-carboxylate · L-TA as white solid (4.83 g, 12%) (total 90% yield, 99% de); mp 115 - 117 °C.

(*S*)-Ethyl thiazolidine-2-carboxylate. (*S*)-Ethyl thiazolidine-2-carboxylate · L-TA salt (16.55 g, 50 mmol) was added in 10% sodium bicarbonate solution (~ 500 mL) and the mixture was stirred at 10 °C or less, for 30 min. The reaction mixture was extracted with diethyl ether (3 × 100 mL) and washed with distilled water. The combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to furnish (*S*)-ethyl thiazolidine-2-carboxylate (7.32 g, 94%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (brs, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.72-3.63 (m, 1H), 3.13-2.98 (m, 2H), 2.90-2.81 (m, 1H), 2.33 (br, 1H), 1.32 (t, J = 7.1 Hz, 3H).

HPLC: Daicel OD column 4.6*250 mm, EtOH/*n*-Hexane (1/9) with 0.1% diethylamine, 1.0 mL/min, 254 nm UV detector; (*S*)-Ethyl thiazolidine-2-carboxylate, 6.5 min), (*R*-form, 7.4 min); mp 27 - 29 °C.

Acknowledgments. This research was supported by the Center for Biological Modulators of the 21st Century Frontier R&D Program, Ministry of Education, Science and Technology, Korea.

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