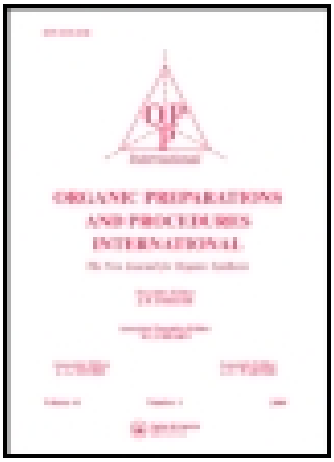

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A MILD AND EFFICIENT METHOD FOR RACEMIZATION OF α-AMINO ESTERS

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A MILD AND EFFICIENT METHOD FOR RACEMIZATION OF α-AMINO ESTERS

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(05/30/03)

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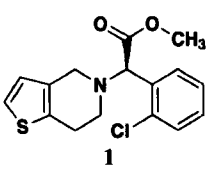
Racemization is an important reaction, whose importance is often overlooked. In industry, a number of enantiomerically pure compounds are produced by diastereomeric salt crystallization, leaving 50% of the undesired isomer. Racemization of this unwanted isomer followed by further kinetic resolution when repeated can lead to the maximum obtainable yield approaching 100%.[1] We became interested in the racemization of clopidogrel (**1**),[2] a tertiary amino ester, which is used to inhibit platelet-aggregation and for its anti-thrombotic effect; the *dextro* rotatory (*S*) form of the compound is marketed as its hydrogen sulfate salt. After separation of the (*S*) enantiomer as a diastereomeric salt, the remaining (*R*) enantiomer has to be recycled. There is no reported method for carrying out this process other than separation of the (*R*) enantiomer as its diastereomeric salt from the (*R*)-enriched mixture.[3]

A survey of methods for the racemization of α-amino esters showed that those having primary amino group have been racemized *via* Schiff base formation when heated in presence of ketones.[4] There are also reports of this reaction having been performed in presence of carboxylic acids[5] or with tertiary amines.[6] However, this methodology is not applicable to tertiary amines such as clopidogrel. If a strong base such as sodium hydride or sodium ethoxide is used, then special care needs to be exercised to prevent hydrolysis and transesterification.[7-8]



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Initial racemization experiments with *R*-**1** using triethylamine were not encouraging; moreover, the work-up was tedious. Stirring it with basic alumina in dichloromethane, even under refluxing conditions failed to racemize *R*-**1** over a 10 hour period; instead, a large amount of impurities was formed (checked by TLC). The use of non-nucleophilic bases such as CsOH, LiOH and KOH in refluxing dichloromethane caused extensive hydrolysis. When *R*-**1** was stirred in dichloromethane with a mixture of solid K_2CO_3[9] and KOH/LiOH under reflux, racemization was complete in 8 hours. The reaction mixture was then worked up by filtering off the solid bases. There was no significant hydrolysis as shown by HPLC, with a ratio of 3:1 K_2CO_3-KOH giving best results. The reaction also proceeded in other common solvents such as toluene, THF and acetone.

Table. Racemization Studies of α-Amino Esters[a]

No.	Substrate	K_2CO_3: KOH (3:1) eq[c]	[α] Observed[d]			% e.e		Yield[b] (%)
			Initial	8 hrs	10 hrs	8 hrs	10 hrs	
1	L-Ala-OMe	1.0	9.3	2.8	0.9	30.1	9.7	98
2	L-Phe-OMe	0.8	45.5	16.7	12.1	36.7	26.6	91
3	L-Tyr-OMe	0.8	91.0	35.0	11.9	38.5	13.0	97
4	L-Trp-OMe	0.8	22.0	12.0	4.4	54.5	20.0	96
5	Z-L-Ala-OMe	1.0	-52.2	-21.4	-9.8	41.0	18.8	94
6	Z-L-Phe-OMe	0.8	-28.3	-12.0	-5.0	42.4	17.7	97
7	Z-L-Tyr-OMe	0.8	-22.0	-7.3	-0.8	33.2	3.6	95
8	Z-L-Trp-OMe	0.8	-11.1	-3.9	-0.2	35.1	1.8	96
9	Bz-L-Ala-OMe	1.0	-19.1	-16.2	-2.3	84.8	12.0	95
10	Bz-L-Phe-OMe	0.8	11.3	3.2	0.9	28.3	8.0	95
11	Bz-L-Tyr-OMe	0.8	-27.5	-6.3	-2.1	22.9	7.6	91
12	Bz-L-Trp-OMe	0.8	-23.3	-2.3	-0.1	9.9	0.4	97
13	Bz-L-Pro-OMe	1.0	-59.8	-52.6	-23.8	87.9	40.0	90
14	Clopidogrel	1.0	-51.5[e]	-1.6	0.0	3.1	0.0	98

a) Solvent used was dichloromethane at 40°C. b) Crude yields; the products were characterized by comparing their HPLC retention times with the starting compounds. c) Equivalent with respect to substrate mole percent. d) The values reported for entries **1-4** are as HCl salt. Values taken for, **1** (c 2 in MeOH); **2** (c 2 in EtOH); **3** (c 3 in pyridine); **4** (c 3 in MeOH); **13** (neat) and for **5-12** and **14** (c 1 in MeOH). e) Value observed at l 589.

Further, when the reaction was performed in presence of phase-transfer catalysts (PTCs) such as PEG-400, the time was reduced to 4 hours and the yield of the racemized product after several water washings was 95%.[10] This result can be explained by the solid-liquid PTC

activation of the solid bases with the help of the 'omega phase' water that facilitates a proton abstraction from an organic acid of moderate strength.[11]

We wanted to extend our methodology to racemize a variety of α-amino esters. In order to determine that basic mixture would abstract α-protons that are less acidic than the benzylic proton of **1**, both aromatic and non-aromatic amino esters and some of their N-protected derivatives were used and all the amino esters were racemized without significant hydrolysis. The results are summarized in the Table. The reactions were monitored by polarimetry.[12] Further, the N-protected amino esters were analysed by HPLC to check for hydrolysis. Even in these cases, racemization time was reduced significantly when PEG-400 was used.

In conclusion, we report here a very simple and practical method for the racemization of clopidogrel that can be performed on a large scale, and the extension of this methodology to a variety of α-amino esters.

EXPERIMENTAL SECTION

All the chemicals were obtained from Sigma-Aldrich in highest purity. Clopidogrel was obtained from Ind-Swift Laboratories Ltd. The esterification of amino acids was carried out with diazomethane, using standard methods. The optical rotations were determined on Polarimeter Autopol(R) IV. The enantiomeric excess was checked using HPLC Shimadzu–10A *VP*. Infrared spectra were obtained on Nicolet Impact 410 spectrometer. The mass spectra were obtained on GCMS Shimadzu QP-5000 and LCMS Finnigan- MAT.

(±) Methyl 2-(2-chlorophenyl)-2-(4,5,6,7-tetrahydrothieno [3,2-c] pyridin-5-yl) acetate (Racemic Clopidogrel).- A mixture of 95.0 g (0.295 mole) of *levo* enriched clopidogrel (Ind-Swift), K_2CO_3 (30.52g, 0.22 mole) and KOH (4.14 g, 0.07 mole) was refluxed for 6 hrs with vigorous stirring in dichloromethane. The reaction mixture was filtered to remove the solid bases. The filtrate was washed with 150 mL of saturated sodium bicarbonate; finally the filtrate was washed with 300 mL of brine. The solvent was evaporated to afford racemic clopidogrel as colourless oil (90.0 g; 95% yield) of 99.5% purity as determined by HPLC: (BDS, C-18, 5μm) methanol and buffer (0.005M 1-octanesulfonic acid sodium salt monohydrate) in the ratio of 65:35, pH 2.5, R_t = 18.4 min. [α] = 0, c = 1 in methanol The oil when treated with dry hydrogen chloride in ether, afforded clopidogrel hydrochloride as white crystalline solid, mp. 116-117°C, *lit*[3] mp. 117°C.

General Procedure for Racemization of Naturally Occurring α-Amino Esters.- L-α-amino esters (free or N-protected) (1.0 mmole), K_2CO_3 (0.75 mmole) and KOH (0.25 mmole) was refluxed for 10 hrs with vigorous stirring in dichloromethane. The reaction mixture was filtered to remove the solid bases. The filtrate was washed with saturated sodium bicarbonate and dried over sodium sulfate. Evaporation of solvent *in vacuo* gave racemic α-amino ester in high yield. The enantiomeric excess was checked on HPLC (Chiralcel OD-H) hexane/2-propanol = 95/5 (v/v).

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