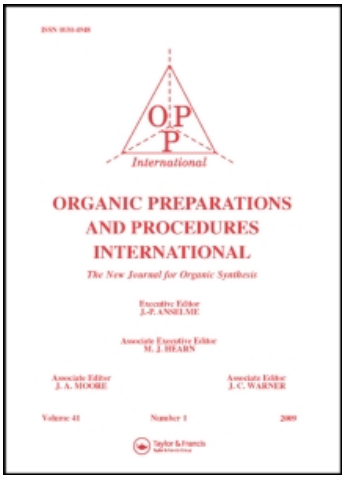

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

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To cite this Article Nyéki, O. , Rill, A. and Klsfaludy, L.(1988) 'RACEMIZATION-FREE PREPARATION OF Boc-Tyr(Et)-OH ACTIVE ESTERS', Organic Preparations and Procedures International, 20: 1, 96 — 99
To link to this Article: DOI: 10.1080/00304948809355874
URL: http://dx.doi.org/10.1080/00304948809355874

RACEMIZATION-FREE PREPARATION OF Boc-Tyr(Et)-OH ACTIVE ESTERS

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Among O-alkyltyrosines, O-ethyltyrosine has proved valuable in the synthesis of oxytocin,[1] of very potent vasopressin antagonists[2] and of oligopeptides with analgesic activity.[3] However, we encountered difficulties in the preparation of the key compound, Boc-Tyr(Et)-OH and could not obtain the physical data reported by Kolodziejczyk and Manning;[4] at the same time, it was surprising how sensitive the optical purity of some tyrosine derivatives was to minor changes in reaction conditions. These facts prompted us to investigate the influence of different factors on racemization.

In our preliminary experiments,[5] Boc-Tyr-OH (1), Boc-Tyr-OMe (2), Boc-Tyr(Et)-OH (3) and Boc-Tyr(Et)-OMe (4) were subjected to conditions generally used for O-alkylation in the absence of an alkylating agent. These experiments showed that the rate of racemization (determined by the optical rotation of the recovered compounds) is highly influenced by the nature and quantity of the base (sodium hydride, sodium methoxide, sodium hydroxide or potassium carbonate), by the temperature (10-95°) and by the solvent (dimethylformamide, benzene, methanol, water or their mixtures). In the case of 2 and 4, the highest rate of racemization (60 to 90% resp.) was observed with the methanol-sodium methoxide system while, under similar conditions, 1 and 3 suffered only minor (a few percent) racemization.

Although under the conditions proposed recently,[6] the extent of racemization was acceptable at room temperature, it was 20% for 1 and 3. It seems that the dimethylformamide-benzene (1:9) mixture is not favorable in this respect, because in the presence of potassium carbonate and 18-crown-6, substantial amounts (up to 12%) of the racemates of 2 and 4 were formed. No detectable racemization occurred with the water-sodium hydroxide system at room temperature, even in the presence of a large excess of the base.[5] In general, it can be stated that the reaction conditions of O-alkylation of Boc-Tyr derivatives in some cases may greatly favor the racemization probably *via* α-proton abstraction. Based on these observations, we prepared Boc-Tyr(Et)-OH from Boc-Tyr-OH using the water-sodium hydroxide and diethyl sulfate system even though this reaction is not complete at room temperature. However, the crude product containing 2-3% unreacted starting material, is suitable for the preparation of optically pure active esters (5-10) in the usual way after one crystallization (Table 1). The active esters were converted to diastereomeric dipeptides which, in turn, were submitted to HPLC analysis to determine the optical purity. Due to brief coupling time, only the pentafluorophenyl (Pfp) esters proved to be suitable for checking the optical purity by this method.

TABLE 1. Active Esters of Boc-Tyr(Et)-OH

Active ester[a]	Cryst. Solvent	Yield (%)	mp. °C	$[\alpha]_D^{24}$
5 Boc-L-Tyr(Et)-OPfp	EtOH	68	100-101	-25.8[b]
6 Boc-D-Tyr(Et)-OPfp	EtOH	64	101-102	+26.0
7 Boc-L-Tyr(Et)-OPcp	EtOH	80	133-134	-46.4
8 Boc-D-Tyr(Et)-OPcp	EtOH	84	138-140	+46.8
9 Boc-L-Tyr(Et)-OSu	i-PrOH	78	134-136	-44.0
10 Boc-D-Tyr(Et)-OSu	i-PrOH	88	134-135	+44.4

a) All compounds gave satisfactory microanalysis. b) c 1, DMF

TABLE 2. Spectral Data of 5, 7 and 9

	IR (cm^{-1}, KBr)	^1H-nmr ($CDCl_3/TMS_{int}$)
5	3360, 2990, 2940, 1782, 1695, 1520, 1250, 1120, 770	1.40(t,3H), 1.44(s,9H), 3.16 (d,2H), 4.03(q,2H), 4.75(br.2H), 6.82(d,$2H_{ar}$), 7.2(d,$2H_{ar}$) ppm.
7	3340, 2990, 2940, 1777, 1695, 1535, 1250, 1120, 820	1.43(t,3H), 1.43(s,9H), 3.2 (d,2H), 3.98(q,2H), 4.96(br.2H), 6.8(d,$2H_{ar}$), 7.17(d,$2H_{ar}$) ppm.
9	3360, 2980, 1810, 1780, 1735	1.37(t,3H), 1.42(s,9H), 2.83 (s,2H), 3.15(d,2H), 4.0(q,2H), 4.9(br.2H), 6.83(d,$2H_{ar}$), 7.2(d,$2H_{ar}$) ppm.

EXPERIMENTAL SECTION

Preparation of Boc-Tyr(Et)-OH (3).- To Boc-Tyr-OH (2.81 g, 10 mmol) dissolved in 10 ml of 4N sodium hydroxide, was added diethyl sulfate (2.7 ml, 20 mmol) and the mixture was stirred for 24 hrs at room temperature. The solution was cooled to 0° and acidified with 3N hydrochloric acid. The precipitate was extracted with three 25 ml portions of ethyl acetate and the combined organic extracts were washed with water. After drying (sodium sulfate), the solvent was removed and the residue crystallized from n-hexane to yield 2.9 g (94%) of 3, mp. 74-76°, $[\alpha]_D^{24}$ = +32.5° (c 1, EtOH). This product (containing 3.2% unreacted 1 determined spectrophotometrically) was purified by silica gel column chromatography using benzene-methanol-acetic acid (7:2:1) solvent system to yield 1.5 g (52%) of 3, mp. 80-81°, $[\alpha]_D^{24}$ = +32.6 (c 1, EtOH).

Boc-D-Tyr(Et)-OH, mp. 80-81°, $[\alpha]_D^{24}$ = -31.7° (c 1, EtOH), was prepared analogously in 55% yield.

Preparation of 5-10. General Procedure.- To a solution of Boc-L-(orD)-Tyr(Et)-OH (crude product, 4.0 mmol) and of the hydroxy component (4.4 mmol) in 10 ml of ethyl acetate was added dicyclohexylcarbodiimide (4.4

mmol) at 0°. After stirring for 30 min at 0° and then 3 hrs at room temperature, the precipitated dicyclohexylurea was collected and the filtrate evaporated to dryness. The residue was crystallized from an appropriate solvent (see Tables 1 and 2).

Determination of the Optical Purity of 5 and 6.- To a solution of 0.108 g (0.5 mmol) phenylalanine methyl ester hydrochloride in 3 ml DMF were added 0.07 ml (0.5 mmol) of triethylamine and 0.24 g (0.5 mmol) of Boc-L(D)-Tyr(Et)-OPfp. After stirring at room temperature for 1 hr, the solution was evaporated to dryness and the PfpOH removed by trituration with 9 ml ether-hexane (1:3) mixture. The crude products were submitted to HPLC analysis on silica gel column using 1% methanol containing isooctane as eluent. Both the LL and DL dipeptides gave a single peak with t_R 35.5 min and 42.5 min, resp. The diastereomer contamination was less than 0.1%.

Acknowledgement.- We thank Dr. B. Hegedüs for the IR spectra, A. Csehi for the ^{1}H-NMR spectra and Mrs. H. László for skillful technical assistance.

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