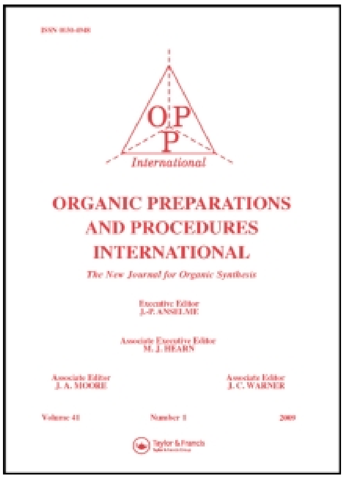

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O-*p*-METHOXYBENZYL-L-TYROSINE

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O-p-METHOXYBENZYL-L-TYROSINE

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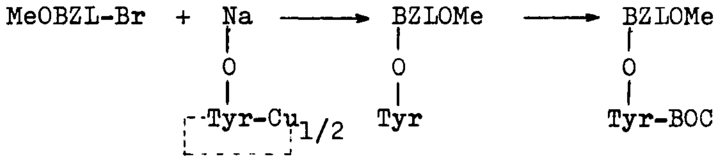
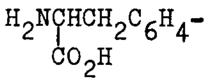
In peptide synthesis, tyrosine is used with or without a blocked phenolic function. In the former case, the *t*-butyl ether derivative which is frequently used, is only accessible *via* a multi-step reaction.[1] Since the *p*-methoxybenzyl group[2] is removed under conditions similar to those used for the *t*-butyl residue, it seemed possible that the O-*p*-methoxybenzyl-L-tyrosine could be used instead of the O-*t*-butyl derivative. We now report a facile, one-step synthesis of O-*p*-methoxybenzyl-L-tyrosine Tyr(BZLOMe, II) by the reaction of the Cu-complex of tyrosine[3] with *p*-methoxybenzylbromide (MeOBZL-Br, I).[4]



I II III

BOC = *t*-BuOCO-; Tyr =



$H_2N\underset{CO_2H}{CH}CH_2C_6H_4-$

Since the synthesis of *p*-methoxybenzylbromide from *p*-methoxybenzyl alcohol and hydrogen bromide according to known methods is sometimes difficult and not reproducible, We also describe a novel method for its preparation. The Tyr-(BZLOMe) obtained is a versatile compound which can be used for syntheses of various N-derivatives as well as C-derivatives; for example reaction with *t*-butylazidoformate gives N-*t*-butyloxycarbonyl-O-*p*-methoxybenzyl-L-tyrosine (III), which can be used for peptide synthesis with tyrosine as the N-terminal amino acid.

EXPERIMENTAL

p-Methoxybenzylbromide (I). - Nitrogen gas was bubbled through a solution of *p*-methoxybenzyl alcohol (26.7 g) in 30 ml benzene, placed in a three-necked round bottom flask (100 ml) fitted with an efficient stirrer. After 10 min., with continued stirring and bubbling of N_2, the flask was placed in a bath cooled -18° and immediately hydrogen bromide, purified by passing through naphthalene and tetralin, was bubbled in. After the solution solidified, stirring was stopped, the cooling bath and the stirrer were removed. The flask was warmed gradually to room temperature and the bottom aqueous layer was siphoned off. To the remaining benzene solution, anhydrous $MgSO_4$ previously deaerated with nitrogen, was added. After drying, the magnesium sulphate was filtered *in vacuo* under nitrogen and benzene removed on a rotary evaporator with the bath temperature not exceeding 50°. The residual liquid (I) is distilled (bath temperature 150-160°) under reduced pressure (2 mm) using a cold finger, to afford 22-23 g (92-94.5%) of colorless liquid, bp. 108-109°/2 mm. During all operations, the solution of I must be colorless or at most slightly yellow.[5]

Anal. Calcd. for C_8H_9BrO: Br, 39.75; Found: Br, 40.05.

O-p-methoxybenzyl-L-tyrosine (II). - To a solution of 1.81 g (10 mmoles) L-tyrosine in 10 ml 2 N NaOH, 1.5 ml of a saturated aqueous solution of $CuSO_4$ (5 mmoles) was added, followed by 10 ml 1 N HCl. The precipitated copper complex of L-tyrosine was filtered, washed with water, dried to constant weight and dissolved in 56 ml ethanol containing 1.36 g (20 mmoles) sodium ethoxide. A stream of dry nitrogen was bubbled through the resulting solution for 10 min., then 2.9 ml (20 mmoles) of I added. After 2 hrs. at room temperature, the precipitated copper complex (II) was filtered, washed with water and methanol and then ground in a mortar with 40 ml 1 N HCl. The precipitate was collected, washed on the Buchner funnel successively with 2 N NH_4OH (until a Cl^- test is negative), methanol, then acetone-ethyl ether (1:1). After recrystallization from 80% acetic acid, 1.42-1.50 g (47-50%) of (II), mp. 223° (dec.), was obtained. Tlc:[6] R_f A 0.43; R_fB 0.66; $[\alpha]^{24}_{578}$ +4.8° (c 1.25, acetic acid).

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.75; H, 6.35; N, 4.64;
Found: C, 67.52; H, 6.60; N, 4.75.

N-t-butyloxycarbonyl-O-p-methoxybenzyl-L-tyrosine (III). - The method of Schnabel[7] (variant c) was adapted for the preparation of III, which after crystallization from ethyl acetate-petroleum ether was obtained in 92% yield, mp. 110°; tlc[6] R_f A 0.92; R_f B 0.75; $[\alpha]^{26}_{578}$ +34.5° (c 2, ethyl acetate).

Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.77; N, 3.48;
Found: C, 65.34; H, 7.01; N, 3.86.

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5. If a nitrogen atmosphere is not maintained, decomposition takes place and the solution becomes red or brown. If this happens, the preparation must be repeated from the beginning. *p*-Methoxybenzylbromide must be stored in a dark bottle under nitrogen.
6. Thin layer chromatograms were run on commercially prepared sheets DC-Alufolien Kieselgel Merck using following systems: A - *n*-butanol-acetic acid-water (4:1:5), B - *n*-butanol-pyridine-water (2:1:2).
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