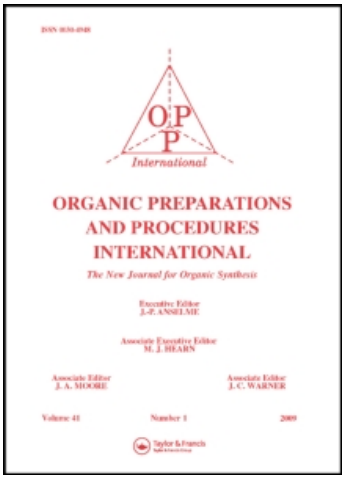

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN EFFICIENT METHOD FOR THE SYNTHESIS OF N-(*p*-AMINOBENZOYL)AMINO ACIDS

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To cite this Article Reddy, A. Panduranga and Reddy, C. Kasi(1990) 'AN EFFICIENT METHOD FOR THE SYNTHESIS OF N-(*p*-AMINOBENZOYL)AMINO ACIDS', Organic Preparations and Procedures International, 22: 1, 117 — 119
To link to this Article: DOI: 10.1080/00304949009356681
URL: http://dx.doi.org/10.1080/00304949009356681

Ethyl ester of 3a (3c):

Anal. Calcd. for $C_{10}H_{10}N_4O_8$: C, 38.22; H, 3.18; N, 17.83

Found: C, 38.55; H, 3.41; N, C, 38.55; H, 3.41; N, 17.60

UV(CH_3CN) λ_{max} (log ε_{max}): 332(4.16); 406(3.87); 248(4.00) nm.

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AN EFFICIENT METHOD FOR THE SYNTHESIS OF N-(p-AMINOBENZOYL)AMINO ACIDS

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p-Aminobenzoyl-L(+)-glutamic acid (2a) is a key intermediate in the preparation of folic acid, a well-known hematopoietic vitamin. A number of methods have been reported for the preparation of N-(p-aminobenzoyl)amino acids from N-(p-nitrobenzoyl)amino acids.[1-5] In particular, these procedures have not been useful for the preparation of p-aminobenzoyl-L(+)-glutamic acid (2a) because of low yields,[1,2] tedious workup procedures and costly reagents such as Pt, Pd, Zn and Ni, etc. In connection with our studies on the synthesis of biologically active amino compounds, we now report a facile process for the manufacture of N-(p-aminobenzoyl)amino acids (2) by the reduction of corresponding N-(p-nitrobenzoyl)amino acids (1) using iron and sodium chloride in water.

1 2

This procedure is superior in terms of yields, use of cheaper reagents, shorter reaction time, and can be achieved in a non-acidic aqueous medium at moderate temperatures. The results are summarized in the Table.

TABLE N-(p-Aminobenzoyl)amino Acids

	Product	Time (hrs)	Yield (%)	mp (°C)	lit. mp. (°C)
2a	N-(p-Aminobenzoyl)-L(+)-glutamic acid	2	91	173	173[1e]
2b	N-(p-Aminobenzoyl)-dl-asparatic acid	3	83	182	182-183[4]
2c	N-(m-Aminobenzoyl)-dl-aspartic acid	2	85	210	210[3]
2d	N-(p-Aminobenzoyl)-dl-alanine	2	90	192-193	192.5-194[5]
2e	N-(p-Aminobenzoyl)-dl-phenylalanine	2	85	195	195-196[5]

EXPERIMENTAL SECTION

General Procedure.- A mixture of iron powder (80-100 mesh, 16.8 g, 0.3 mole), sodium chloride (3 g) and water (50 ml) was stirred at 80-85° for 0.5 hr. An aqueous solution of the sodium salt of the N-(p-nitrobenzoyl)amino acid [from N-(p-nitrobenzoyl)amino acid (0.1 mole) and sodium hydroxide (4 g) in 50 ml water] was then added dropwise maintaining the temperature at 75-85° by heating. After addition, the reaction was maintained at the same temperature for an additional hour and then cooled to 50-55°. A sodium hydroxide solution (8 g/15 ml water) was added and the reaction mixture was stirred for 15 min and filtered. The iron bed was washed with hot water (20 ml x 2). The filtrate and washings were cooled to 5-10° and acidified with conc. HCl to pH 3.0-3.2. The white crystalline slurry was collected and the solid was dried to yield N-(p-aminobenzoyl)amino acid 2 (Table).

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A FACILE SYNTHESIS OF BIOTIN N-HYDROXYSUCCINIMIDE ESTER

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The exceptionally high affinity ($K_d 10^{-15}$M) of avidin, a tetrameric egg white protein of M_r 67,000, for biotin (1) to form the avidin-biotin noncovalent complex has been exploited successfully for the isolation of hormone receptors, affinity chromatography, immunoassay, localization and detection of proteins and enzymes by the blot transfer techniques as evidenced by the growth of avidin-biotin technology.[1] Since only the bicyclic ring of the biotin molecule is important for binding to avidin,[2] the carboxyl group of the valeric acid side-chain has been chemically modified and functionalized to give suitable biotin derivatives for coupling to low- and high-molecular weight molecules.[1] Of the various biotinylating reagents, the active esters of biotin, the p-nitrophenyl ester and the N-hydroxysuccinimide ester, are most commonly used. The synthesis of biotin p-nitrophenyl ester[3] is not straightforward and side-reactions via participation of the ureido nitrogen of the biotin ring in N-acylation and isouronium salt formation have been reported.[3] In view of these difficulties, Hofmann et al.[4] chose the N-hydroxysuccinimide ester of biotin in their work. Since the dicyclohexylcarbodimide (DCC) procedure for the synthesis of N-hydroxysuccinimide esters of N-protected amino acids[5] gave an impure product with biotin,[6,7] a better method employing N,N'-carbonyldiimidazole (CDI) was reported by Jasiewicz et al.[7] The use of DCC reagent leads, besides dicyclohexyl urea as a