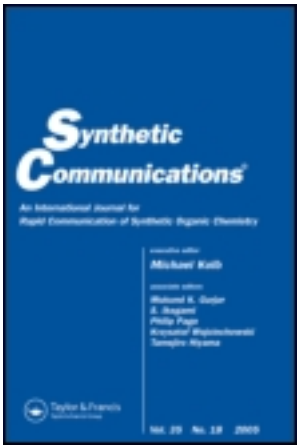

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A Highly Practical Method for Monobenzylation of Amino Acids

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A HIGHLY PRACTICAL METHOD FOR MONOBENZYLATION OF AMINO ACIDS

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Abstract: Amino acids are cleanly monobenzylated at ambient temperature using benzyl chloride in water containing potassium carbonate.

Amino acids are molecules of great importance. As essential building blocks for peptides and proteins, they play an indispensable role in the life processes. Apart from these long recognized functions, the amino acids have also found many other uses in chemistry, biology, and medicine in the last few decades. For instance, the

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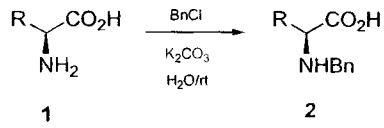

1 2

Scheme 1.

asymmetric carbon centers of the natural amino acids can be used as an inexpensive and readily available chiral pool[1] in modern asymmetric organic synthesis. Both natural and artificial amino acids are also widely employed in the construction of small peptides[2] of special pharmacological activities.

Due to the presence of multifuctionalities, the amino acids normally cannot be directly used in the synthesis; one or two functionalities in the amino acids must be properly masked before they can possibly serve as chiral building blocks for organic synthesis. Monobenzylation of the amino group is one of the most common and useful means among various protecting protocols. Compared with carboxyl protecting groups, the benzyl group enjoys remarkable stability to both acids and bases, while deprotection[3] can still be easily achieved by dissolving metal reduction or catalytic hydrogenation. These advantages presumably account for the relatively wide application of the benzylation.

Many procedures for monobenzylation of amino acids have been documented in the literature. Generally speaking, they fall into two categories; one is based on direct alkylation[4] with benzyl halide, normally either bromide or chloride, the other involves formation[5-7] of a Schiff base with benzaldehyde followed by reduction with hydrides or molecular hydrogen under catalysis of a transition

Table 1. Monobenzylation results.

Cmpd	R	Yield (%)	m.p./decomp. (°C)		$[\alpha]_D^{20}$		Method
			Obs.	Lit.[a]	Obs.[b]	Lit.[a]	
2a	Bn	85.6	247	255	+28.2	+26.9	A
2b	Me	56.3	251	255	+4.3	+3.9	B
2c	Me_2CHCH_2	76.4	242	255	+14.2	+13.0	B
2d	Me_2CH	72.3	255	275	+14.8	+20.2	B
2e	$HOCH_2$	74.8	226	240	+7.2	+5.1	B

a) Taken from ref 5. *b)* Measured under the same conditions as in lit.[5]

metal such as Pd. Both approaches suffer from certain drawbacks, direct alkylation often gives a mixture of mono- and dialkylated products, while condensation/reduction requires additional operations or involves relatively expensive reagents, though it does circumvent undesired complication of dialkylation. Here we report a facile monobenzylation protocol that exploits the solubility difference of the starting amino acids and the monoalkylated products; most amino acids are well-soluble in basic aqueous medium but become less soluble after introducing a benzyl group at the amino functionality. In ideal cases, the monobenzylated species precipitates out from the solution and thus dramatically retards the otherwise more favorable introduction of a second benzyl group, giving much better results than running[4] the reaction at refluxing temperature. Although the yields are somewhat lower than using previous[5-7] methods, the simplicity of the procedure and the inexpensive reagents employed make the present protocol a very attractive one. Some representative results are listed in Table 1.

Experimental

The chemicals were from commercial sources and were used as received without any further purification. The progress of the reaction was monitored by TLC developed with 3:1:1 of ^{n}BuOH/AcOH/H_2O and visualized with ethanolic ninhydrin. The ^{1}H NMR (in d_6-DMSO) and MS of the products were consistent with the expected structures and those data reported in the literature.

Method A. The starting amino acid (1.0 mmol), K_2CO_3 (1.5 mmol) and benzyl chloride (1.5 mmol) were added to water (10 ml) and the resulting mixture was stirred vigorously at ambient temperature. After 1 h, another portion of K_2CO_3 (1.0 mmol) and benzyl chloride (1.0 mmol) were introduced. The stirring was continued at ambient temperature for 24 h before the potassium salt of the monobenzylated amino acid was collected by filtration with suction, washed with diethyl ether, and treated with 6 N HCl. The white precipitate was then collected by filtration with suction, and dried at ambient temperature under reduced pressure to give the monobenzylated amino acid.

Method B. Essentially the same as procedure A, except that the second portions of K_2CO_3 (1.0 mmol) and benzyl chloride (1.0 mmol) were introduced after 13 hour's stirring and in the work-up the potassium salt of the monobenzylated amino acid was extracted into $CHCl_3$ instead of being collected by filtration. The $CHCl_3$ phase was then acidified with 6 N HCl till pH 3~5. The white precipitate was collected by suction filtration and dried at ambient temperature under reduced pressure to give the monobenzylated amino acid.

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