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One-Pot, Large-Scale Synthesis of Nickel(II) Complexes Derived from 2-[*N*-(α-Picolyl)amino]benzophenone (PABP) and α- or *β*-Amino Acids

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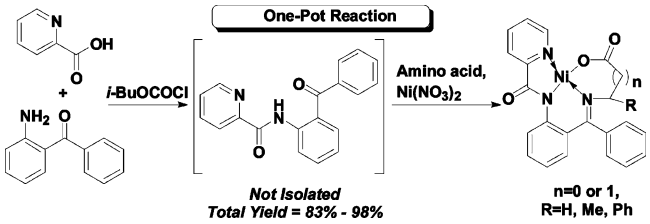

A one-pot, large-scale procedure for preparing the Belokon−Soloshonok nucleophilic glycine equivalent 2-[*N*-(α-picolyl)amino]benzophenone (PABP) derived Ni(II) complex [GlyNi(II)PABP] is described. It has been accomplished by using isobutyl chloroformate to form PABP and then NaH/KOH as mixed bases to afford the corresponding complexes in a one-pot manner (up to an overall yield of 98%). The potential of this method for preparation of *β*-amino acids derivatives, such as *β*-AlaNi(II)PABP and *β*-PheNi(II)PABP, has been demonstrated. The structure of *β*-AlaNi(II)PABP is characterized by single-crystal X-ray diffraction.

Nonproteingenic α- or *β*-amino acids have attracted tremendous attention recently.[1] They are widely utilized for biological, biochemical, pharmaceutical, and asymmetric chemical investigations. Among various methods available to prepare α- or *β*-amino acids in the literature, homologation of α- or *β*-amino acids such as glycine[2] or *β*-alanine[3] equivalents is a direct, facile, tailor-made approach for preparing various nonproteingenic amino acids, in particular, structurally complex and sterically constrained derivatives.[4] The Ni(II) complex of glycine Schiff's base GlyNi(II)PABP (**1a,** Figure 1), which emerged as a new type of efficient and highly reactive achiral nucleophilic glycine equivalent,[5] has several unique features. The Ni(II) complex **1a** is achiral nucleophilic glycine equivalent to offer a stereochemically reliable and efficient homologation via alkyl halide alkylation and Michael addition reaction.[5a,c] Furthermore, the nucleophilic glycine equivalent **1a** features attractive physicochemical characteristics such as high stability in strong bases, high crystallinity, convenient purification, and megatemperature tolerance.[6] The preparation of **1a** and practical synthesis of various α-amino acids with **1a** are well-documented by Belokon's group[5a,6b,7] and Soloshonok's group[5d,6a,d,8] (Scheme 1). However, Belokon's route, which employed excess $SOCl_2$ for the ligand **3** preparation, not only led to incomplete transformation and generally low chemical yields but also led to laborious purification prior to its use for Ni(II) complex formation.[2a,9] Soloshonok's procedure although improved the overall yield (up to 93%),[5d,9] but requires inconvenient inert atmosphere

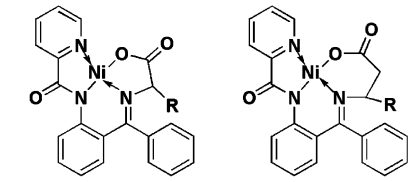

FIGURE 1. Ni(II) complexes derived from PABP and α- or *β*-amino acids.

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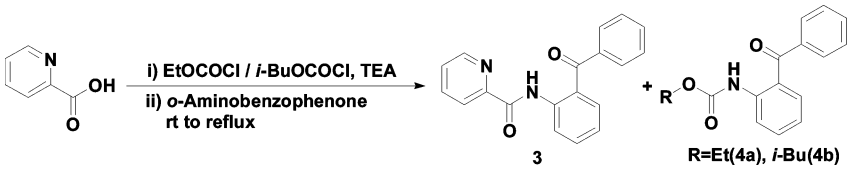
SCHEME 1. Synthesis of Ligand 3 via Ethyl/Isobutyl Chloroformate Coupling



SCHEME 2. One-Pot, Two-Step Synthesis of Ni(II) Complexes

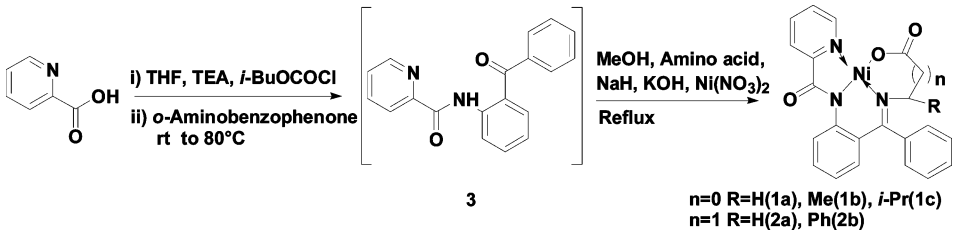
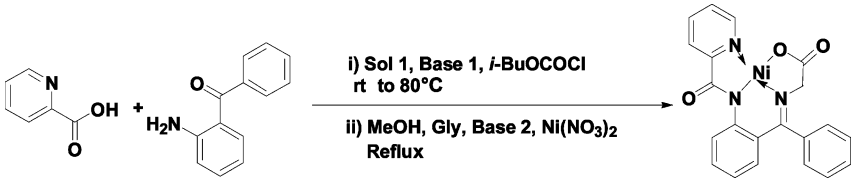


TABLE 1. One-Pot, Two-Step Synthesis of 1a



entry[a]	sol **1**	base **1**	base **2**	yield[b] of **1a** (%)
1	CH_2Cl_2	TEA	NaH/KOH	93
2	CH_2Cl_2	NMM	NaH/KOH	94
3	CH_2Cl_2	K_2CO_3	NaH/KOH	83
4	CH_2Cl_2	KOH	NaH/KOH	52
5	MeOH	TEA	NaH/KOH	33
6	THF	TEA	NaH/KOH	98
7	THF	NMM	NaH/KOH	98

[a] All reactions were run in commercial grade solvents without inert atmosphere protection. [b] Isolated yield of pure products based on *o*-aminobenzophenone.

protection, elaborate temperature control for the preparation of ligand **3**, and use of ether for purification, which may cause explosion on industrial manufacture.[9] Furthermore, the byproduct **4a** greatly influenced the yield and product purity in this procedure (Scheme 1).

Dozens of methods were developed to prepare β-amino acid derivatives, such as using nitroolefins, methyl cyanoacetate, or 5,5-diethylbarbituric acid as starting materials.[10] However, most of the methods require expensive starting materials, fussy reaction steps and laborious purification. Fewer studies have been made to improve and discover high reactive tailor-made β-amino acid equivalents.[11] Herein we report a protocol by introducing a general one-pot, two-step procedure to prepare both α-amino acid equivalents **1** and β-amino acid equivalents **2** that can be performed in high yields on multigram scales.

A one-pot, two-step procedure to prepare complex **1a** is described in Scheme 2. In the first step, picolinic acid was coupled to *o*-aminobenzophenone to afford the ligand **3**, and which in the second step was utilized directly in one vessel to condense with glycine and nickel(II) nitrate to form complexes with high transformation efficiency at room temperature without inert atmosphere protection. As we know, amidation of carboxylic acids in general and formation of an amide bond between an aromatic acid and a sterically shielded amino function is rather laborious work, especially when the amino group, as for instance in *o*-aminobenzophenone, is additionally electronically disadvantaged (low basicity). In the first step, to increase the acylation selectivity between the carboxylic acid group and the amino group (Scheme 1) to synthesize ligand **3**, we employed sterically hindered isobutyl chloroformate instead of ethyl chloroformate. Better selectivity was achieved in our experiments. In the second step, we discovered that the mixed bases NaH/KOH are better than single base NaOH, KOH, or NaH, which is due to the complex transformation efficiency being greatly decreased by unpredicted water content in the reaction components such as Ni(II) nitrate hexahydrate

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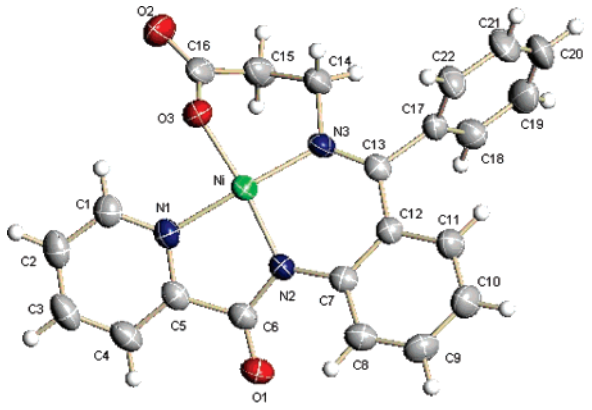

FIGURE 2. X-ray structure of complex **2a**.

and KOH. The use of mixed base takes advantage of NaH as a strong water-removing agent and KOH as a strong coupling catalyst.

On the basis of the above work, we were able to execute the two steps in one vessel, and then optimize the one-pot procedure condition (shown in Table 1). Triethylamine (TEA) and *N*-methylmorpholine (NMM) were isolated as better bases over K_2CO_3 and KOH giving rise to a final product **1a** with a yield of 93% (Table 1, entries 1, 2 vs 3, 4). During the solvent **1** optimization, we found that THF was better than CH_2Cl_2 and MeOH giving rise to a final product **1a** with a yield of 98% (entries 6, 7 vs 1, 5). The one-pot protocol described here involves applications of inexpensive reagents and operationally convenient conditions, therefore allowing the facile preparation of the complexes in bulk quantities (over 60 g).

After optimizing the conditions, we next examined the generality of these conditions to other substrates using several α- or *β*-amino acids in this one-pot procedure, such as L-ala, L-val, *β*-ala, and DL-*β*-phe instead of glycine. Fortunately, corresponding complexes **1b**,[2a,5b] **1c**, **2a**, and **2b** were successfully formed in 92%, 84%, 83%, and 98% yield, respectively. The structure of complex **2a** was confirmed by X-ray diffraction analysis. In the structure, we can see that **2a** forms a boat conformation, which deserves higher energy than a chair conformation. This may explain why the *β*-amino acid complex formation demands stronger condensation agents and higher temperature. Complex **2a** and complex **2b** feature megatemperature and strong basic tolerance. Furthermore, the two complexes feature attractive physicochemical characteristics such as excellent solubility in many organic solvents and good crystallinity leading to good operation in the chemical reaction and convenient purification. Our preliminary α-dialkylation and α-monoalkylation by active alkyl halide of **2a** shows exciting results in the preparation of α-substituted *β*-amino acids.[12]

In summary, we have demonstrated a convenient and general one-pot, two-step protocol for the formation of the Ni(II) complexes of Schiff's base derived from PABP and α- or *β*-amino acids. This method does not require the preparation of PABP as a separate step, works well with a variety of α- or *β*-amino acids, and does not need laborious purification. On the other hand, the method can be reproduced successfully on a >60 g scale, which identified its efficiency and practicality. Furthermore, we first synthesized potential *β*-amino acid equivalents **2a** and **2b**. In the end, after the simplest inexpensive one-pot procedure has been discovered, the achiral glycine and *β*-alanine Ni(II) complexes of Shiff's base equivalents will play a more important role in the nonproteingenic amino acid synthesis.

(12) Full experimental details of this work will be reported in a forthcoming publication from our laboratory.

Experimental Section

Large Scale, One-Pot, Two-Step Procedure for the Preparation of the Ni(II) Complex of Glycine Schiff's Base with PABP (1a). To a clear solution of triethylamine (18.96 g, 187.5 mmol) and picolinic acid (25 g, 203.1 mmol) in THF (400 mL) was added isobutyl chloroformate (25.60 g, 187.5 mmol) in one portion at room temperature. After the solution had been stirred for 40 min, *o*-aminobenzophenone (30.81 g, 156.2 mmol) was added in one portion. After 20 min the solution was refluxed at 80 °C overnight. The progress of the reaction was monitored by TLC and upon completion the reaction mixture was stopped and THF was then evaporated carefully under vacuum and MeOH (800 mL) was added as solvent. Gly (58.63 g, 781.0 mmol), $Ni(NO_3)\cdot 6H_2O$ (90.85 g, 312.4 mmol), NaH (55−65% in oil, 37.49 g, 0.9 mol), and KOH (26.24 g, 468.6 mmol) were added successively. The resulting mixture was refluxed for 2 h and then the reaction was terminated and cooled. The solution was neutralized with acetic acid. After 12 h the separated crystalline solid was filtered and washed with 500 mL of ethanol, followed by stirring in methane/water (v/v = 1:2, 2 × 1 L), then filtered to form a red crystal (63.4 g, yield 98%). The complex was sufficiently pure for further use without additional purification.

General One-Pot Two-Step Procedure for the Preparation of 1b, 1c, 2a, and 2b Described as Those for the Ni(II) Complex of *β*-Alanine Schiff's Base with PABP (2a). To a clear solution of triethylamine (0.82 g, 8.1 mmol) and picolinic acid (1 g, 8.1 mmol) in THF (30 mL) was added isobutyl chloroformate (1.11 g, 8.1 mmol) in one portion at room temperature. After the solution had been stirred for 40 min, *o*-aminobenzophenone (1.34 g, 6.8 mmol) was added in one portion. After 20 min the solution was reflux at 80 °C overnight. The progress of the reaction was monitored by TLC and upon completion the reaction mixture was stopped and THF was then evaporated carefully, then MeOH (50 mL) was added as solvent. *β*-Alanine (3.02 g, 33.8 mmol), $Ni(NO_3)\cdot 6H_2O$ (3.94 g, 13.5 mmol), NaH (55−65% in oil, 1.63 g, 40.6 mmol), and KOH (1.14 g, 20.3 mmol) were added successively. The resulting mixture was refluxed for 2 h and then the reaction was terminated and cooled to room temperature. The solution was neutralized with acetic acid and poured into 200 mL of ice−water, then after 12 h, the solid was filtered and washed with 500 mL of water, followed by stirring in hexane, and then filtered to form a red powder (2.41 g, yield 83%).

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for all compounds and X-ray data of compounds **2a.** This material is available free of charge via the Internet at http://pubs.acs.org.

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