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Efficient, practical synthesis of symmetrically α,α-disubstituted α-amino acids

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Abstract—Ni(II)-complex derived from glycine Schiff base with 2-[*N*-(α-picolyl)amino]benzophenone (PABP) was found to be an ideal equivalent of nucleophilic glycine in the reactions with various alkyl halides affording an efficient, generalized and practically useful method for preparing symmetrically α,α-disubstituted α-amino acids.

Symmetrically α,α-disubstituted α-amino acids (*sym*-α,α-AA) represent an extremely important type of sterically constrained tailor-made amino acids.[1] In particular, α,α-dimethylglycine (DMeG) (α-methylalanine, α-amino-*iso*-buturic acid [Aib]), the most available and studied member of the family, has been shown to impart well-defined conformational constraints to a peptide backbone, strongly preferring folded conformations and inducing helical secondary structures of either the 3_{10}– or α-helical type.[2] Similar effects on three-dimensional peptide structures were observed for higher homologues of the family.[3]

However, amino acids other than DMeG are not readily available, and, therefore, their biological properties and applications, as sterically constrained scaffolds, are still awaiting systematic studies. In fact, we were surprised to find out that such a seemingly simple amino acid as α,α-diallylglycine has never been synthesized. Analysis of the literature has revealed that, in spite of tremendous success in the area of stereoselective synthesis of asymmetrically α,α-disubstituted amino acids, there has been no single generalized and practical method for preparing *sym*-α,α-AA developed to date. The only reliable approach to *sym*-α,α-AA reported so far is the Bucherer–Bergs and Strecker reactions of *sym*-dialkyl ketones with cyano-derivatives as a source of an amino function.[4] This explains the high availability of DMeG as a consequence of the abundance of acetone. The most recent publication reporting an alternative approach to *sym*-α,α-AA employs alkylation of ethyl α-nitro acetate as a precursor of glycine. However, this method is limited to activated alkyl halides such as allyl- and benzyl derivatives.[5]

We reasoned that the most direct approach to the synthesis of *sym*-α,α-AA would be the alkylation of a properly protected nucleophilic glycine equivalent. However, this approach has never been utilized to date for the practical synthesis of *sym*-α,α-AA, probably due to the incompatibility of classical glycine equivalents, such as esters or glycine Schiff bases,[6] with the strongly basic reaction conditions required for bis-alkylation to be complete. As some of our current projects required ready access to multi-gram quantities of various *sym*-α,α-AA, we set for ourselves a goal of developing a simple, practical method for preparing these compounds on a relatively large scale. Herein we report our successful preliminary results regarding the development of a simple and generalized method employing inexpensive and readily available reagents, allowing preparation of a variety of *sym*-α,α-AA in excellent chemical yields.

Taking advantage of our extensive experience in chemistry of Ni(II)-complexes of amino acids,[7] we envisioned that the Ni(II)-complex **1** (Scheme 1) derived from a glycine Schiff base with 2-[*N*-(α-picolyl)amino]benzophenone (PABP)[8] **2** would be sufficiently stable under the strongly basic conditions. Indeed, treatment of complex **1** in commercial-grade DMF with allyl bromide (**3a**) (2.5 equiv.) in the presence of KOH (10 equiv.) at ambient temperature resulted in an exothermic reaction, giving rise to the target bis-alkylated product **4a** in high chemical yield

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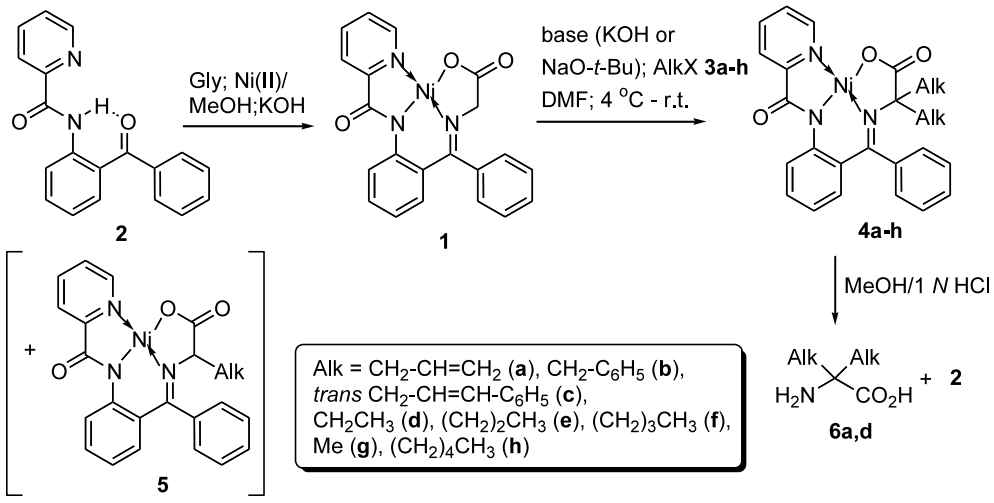

Scheme 1.

(Table 1, entry 1). Under the same conditions, reaction of complex **1** with benzyl bromide (**3b**) resulted in complete bis-benzylation of the starting complex **1**, affording product **4b** as an individual product (entry 2).

Our attempts to reduce the amount of the base resulted in incomplete bis-alkylation reactions giving rise to a mixture of the major products **4a**,**b** and *mono*-alkylated derivatives **5a**,**b** (ratios varied from 90/10 to 95/5, respectively). This result is likely due to the poor solubility of potassium hydroxide in DMF. Moreover, formation of some unidentified byproducts lowered the yields of the target products.

Therefore, we decided to use commercially available and inexpensive sodium *tert*-butoxide as a base. To our satisfaction, the reaction of allyl bromide (**3a**) with complex **1** in the presence of only 3 equivalents of base afforded bis-allylated complex **4a** as an individual product with improved chemical yield (entry 3). This reaction was conducted on >10 g scale to produce the free amino acid **6a**. Under the same conditions, reactions of **1** with benzyl (**3b**) and cinnamyl bromide (**3c**) occurred cleanly, giving rise to the target compounds **4b**,**c** in high chemical yields (entries 4, 5).[9]

With the success of the previous reactions, we decided to explore the generality of this method for bis-alkylation of complex **1** using non-activated alkyl halides. Under the same reaction conditions, except for an increase in amounts of the alkylating reagent and base (3.5 equiv. of each), the reaction between complex **1** and ethyl bromide (**3d**) yielded a mixture of compounds **4d** and **5d** in a disappointing ratio of 76/24, respectively (entry 6). However, further increases in the amounts of alkylating reagent/base allowed us to improve the ratio of bis- and *mono*-alkylated products **4d** and **5d** to a satisfactory level of 98/2 (entries 7, 8). Similar results were obtained in the reactions of complex **1** with propyl **3e** and butyl bromides **3f** (entries 9, 10). As gaseous methyl bromide is inconvenient to use as an alkylating reagent, we studied the reactions between complex **1**

Table 1. bis-Alkylations of Ni(II)-complex **1** with alkyl halides **3a**–**h**[a]

Entry	**3a**–**h**	Base	Ratio base/**3a**–**h**	Time	Products **4**, **5**	
					Yield[b] (%)	Ratio **4**/**5**[c]
1	**a**	KOH	10/2.5	30 min	83	>99/1
2	**b**	KOH	10/2.5	1 h	90	>99/1
3	**a**	NaO-*t*-Bu	3.0/3.0	15 min	94	>99/1
4	**b**	NaO-*t*-Bu	3.0/3.0	15 min	89	>99/1
5	**c**	NaO-*t*-Bu	3.0/3.0	15 min	94	>99/1
6	**d**	NaO-*t*-Bu	3.5/3.5	20 min	94	76/24
7	**d**	NaO-*t*-Bu	4.0/4.0	2 h	92	90/10
8	**d**	NaO-*t*-Bu	4.5/4.5	2 h	91	98/2[d]
9	**e**	NaO-*t*-Bu	4.0/4.0	2 h	90	91/9
10	**f**	NaO-*t*-Bu	4.0/4.0	2 h	91	94/6
11	**g**	NaO-*t*-Bu	3.5/3.5	15 min	91	>99/1
12	**h**	NaO-*t*-Bu	3.5/3.5	15 min	93	>99/1

[a] All reactions were run in commercial-grade DMF in the presence of the base indicated at ambient temperature.
[b] Isolated yield of crude product.
[c] Determined by NMR (300 MHz) analysis of the crude reaction mixtures.
[d] The reaction was conducted on >10 g scale.

and methyl iodide (**3g**). We found that only 3.5 equiv. of the alkylating reagent/base is enough for complete, fast, and clean bis-methylation of **1** with **3g** (entry 11). Inspired by these results, we conducted the reaction of complex **1** with pentyl iodide (**3h**), finding a similarly excellent chemical outcome affording the bis-alkylated complex **4h** as an individual product in 93% yield (entry 12).[10] As the prices of alkyl bromides and alkyl iodides are very close, the application of iodides rather than bromides becomes practically useful considering the lower amounts of reagents needed and the enhanced chemical outcome obtained.

Products **4a**–**h** were isolated simply by first pouring the reaction mixture into ice water containing a calculated amount of acetic acid, followed by filtration of the crystalline compound thus formed. To demonstrate the isolation of the target *sym*-α,α-AA from their Ni(II)-complexes **3**, bis-alkylated complexes **3a** and **3d** were decomposed without any purification under the standard conditions[7,11] to yield free amino acids **6a** and **6d** along with ligand **2**, which was recovered and converted back to the Ni(II)-complex **1**.

In summary, we have demonstrated that the readily available Ni(II)-complex **1** easily undergoes complete bis-alkylation with various alkyl halides, and in particular iodides, affording a generalized and practical access to the corresponding *sym*-α,α-AA. High chemical yields combined with the extreme simplicity of the experimental procedure render this method worth immediate use for multi-gram scale preparation of these amino acids. Full scope of the method is currently under study and will be reported in due course.

Acknowledgements

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9. Reactions of Ni(II)-complex **1** with alkyl halides **3a**–**h**. Into a solution of sodium *tert*-butoxide (3 equiv.) in DMF (10 ml/1g) was added complex **1** (1 equiv.) and alkylating reagent (3 equiv.), allyl bromide **3a**, benzyl bromide **3b**, or cinnamyl bromide **3c**. The reaction was stirred in a rt water bath for 15 min. The reaction mixture was then poured into a solution of ice and 5% acetic acid and the ice was allowed to melt. The resulting solid was filtered off and washed with water and *n*-hexane. Drying the solid resulted in the desired Ni(II)-complexes **4a**–**c** in yields from 89 to 94% and greater than 99% purity. When alkylations were performed with less activated alkyl bromides such as ethyl bromide **3d**, propyl bromide **3e**, butyl bromide **3f**, the procedure was performed as above with 4.0 equiv. of the alkylating reagent and sodium *tert*-butoxide to afford the Ni(II)-complexes **4d**–**f** in yields from 87 to 92% and 90 to 94% purity. This procedure was also used for the alkyl iodides, methyl iodide **3g**, and pentyl iodide **3h** using 3.0 equiv. of the alkylating reagent and base to afford complexes **4g**,**h** in yields from 91 to 93% and greater than 99% purity.
10. As an example of typical spectral characteristics of products **4a**–**h**: Ni(II)-complex of α,α-dipentylglycine Schiff base with 2-[*N*-(α-picolyl)amino]benzophenone (PABP) **4h**: mp 221.8–223.4°C, ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, t,

$J=7.1$ Hz), δ 1.33 (10H, m), δ 1.73 (6H, m), δ 6.70 (2H, m), δ 7.20 (2H, m), δ 7.31 (1H, m), δ 7.48 (4H, m), δ 7.89 (1H, m), δ 7.99 (1H, m), δ 8.39 (1H, m), δ 8.72 (1H, m). ^{13}C NMR ($CDCl_3$) δ 14.67 (s), δ 23.00 (s), δ 24.99 (s), δ 32.20 (s), δ 40.43 (s), δ 83.80 (s), δ 121.51 (s), δ 123.93 (s), δ 123.96 (s), δ 127.03 (s), δ 127.81 (s), δ 127.85 (s), δ 129.14 (s), δ 129.91 (s), δ 132.86 (s), δ 134.70 (s), δ 136.98 (s), δ 140.58 (s), δ 142.50 (s), δ 147.49 (s), δ 153.36 (s), δ 170.18 (s), δ 173.40 (s), δ 182.55 (s). HRMS (ESI) [M+H$^+$] calcd for $C_{32}H_{39}N_3NaNiO_3$ 571.2345, found 571.2650.

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