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Efficient Synthesis of 2-Aminoindane-2-carboxylic Acid via Dialkylation of Nucleophilic Glycine Equivalent

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Abstract: An efficient, easy to scale-up method for preparing 2-aminoindane-2-carboxylic acid via two-step alkylation of a Ni(II)-complex of glycine Schiff base with 2-[*N*-(α-picolyl)amino]benzophenone (PAAP) (**2b**) with *o*-dibromoxylylene (**3**) is reported. The first step, monoalkylation of **2b** with **3**, conducted under phase-transfer conditions, gave the corresponding complex **6** in excellent chemical yield (97.2%). Without any purification the intermediate **6** was cyclized under homogeneous conditions (DMF, NaO-*t*-Bu) to give the product **7** in high chemical yield (93.1%). Decomposition of prepared **7** afforded the target amino acid 2-aminoindane-2-carboxylic acid (**1**) in 97.9% yield, along with recovery of ligand **8**, which was converted back to the starting glycine complex **2b**. Operationally convenient experimental procedures, mild reaction conditions, as well as high chemical and volume yields render the method practical for preparing amino acid **1** and its analogues.

Cyclic α,α-disubstituted α-amino acids represent a unique class of sterically constrained amino acids.[1,2] In this case, a paradigm of the local steric constrain to control the three-dimensional (3-D) structure of peptides and proteins, introduced by Hruby,[3] reaches its almost ultimate level as the steric congestion provided by the α,α-disubstitution is multiplied by the steric inflexibility of a cyclic structure. Synthesis of such highly sterically constrained amino acids proved to be a challenging task; however, research in this area is stimulated by numerous applications of these derivatives ranging from medicinal to materials science. For instance, 2-aminoindane-2-carboxylic acid (Aic, Ind, Ain) (**1**) and its derivatives have been extensively used as a structural scaffold in the design of conformationally constrained peptides for systematic studies of the relationships of the 3-D peptide structure and its biological function.[4] In the field of material science, the unique structural features of **1** and its derivatives were shown to be a very promising structural motif for organic crystals[5] and molecular solids[6] engineering.

Despite the substantial interest and need for cyclic α,α-disubstituted α-amino acids, the synthetic approaches for preparing these compounds are limited and rather impractical. In this paper, we report an efficient, easy to scale-up method for preparing 2-aminoindane-2-carboxylic acid (**1**) via two-step alkylation of nucleophilic glycine equivalent (NiGlyPABP) **2b** with *o*-dibromoxylylene (**3**). Operationally convenient experimental procedures, mild reaction conditions, as well as high chemical and volume yields render the method practical for preparing amino acid **1** and its analogues.

Analysis of the relevant literature revealed that there are two methodologically different approaches for preparing α,α-disubstituted α-amino acids in general and cyclic derivatives in particular (Figure 1). One of them is a well-tried method based on the classical Bucherer−Berg reaction, which involves the use of potassium cyanide to convert a cyclic ketone into the corresponding spirohydantoin.[7] The hydrolysis of prepared hydantoins was shown to be the most problematic step requiring rather harsh, strongly basic or acidic conditions. Another approach, via dialkylation of nucleophilic glycine equivalents, is much less studied,[5a,8] and a potentially more general and straightforward method compared to the Bucherer−Bergs route. However, the dialkylation of glycine equivalents with bifunctional alkylating reagents such as *o*-dibromoxylylene **3** has potential side reactions. The alkylation of a glycine equivalent with dibromide **3** could have two competing pathways, the dialkylation and

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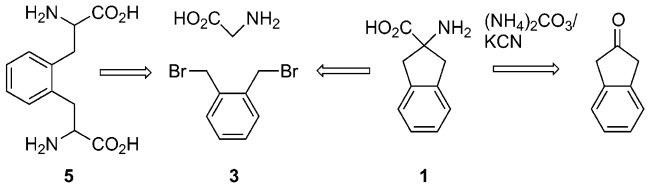


FIGURE 1. Two methodologically different approaches to 2-aminoindane-2-carboxylic acid **1**.

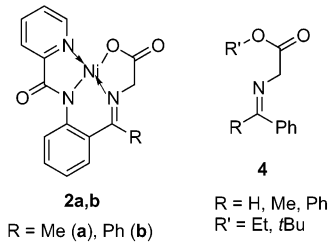
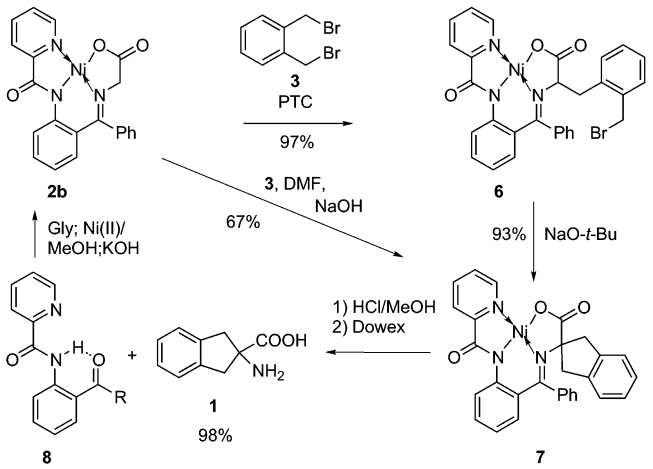


FIGURE 2. Equivalents of nucleophilic glycine of types **2** and **4**.

bis-mono-alkylation leading to the target cyclic product **1** and the bis-amino acids of type **5**, respectively (Figure 1). Considering these two outcomes, one may expect that the bis-mono-alkylation might occur with a substantially faster reaction rate since the alternative dialkylation is a sterically unfavorable process and involves the formation of the less CH acidic enolate. This assumption concurs with our recent data on the dialkylation of nucleophilic glycine equivalents[9] and is strongly supported by results reported by Lygo et al.[10] The latter demonstrated that alkylation of glycine equivalent **4** (Figure 2) with **3**, conducted under phase-transfer conditions (PTC), is a very efficient, high-yielding, and reliable method for preparing bis-amino acids **5**. The problem of the bis-mono-alkylation could be suppressed by using a low concentration of starting reagents that might make the intramolecular cyclization more competitive with the intermolecular alkylation. Thus, Mash et al.[5a] synthesized derivatives of amino acid **1** by the reaction between glycine equivalent **4** and the corresponding dibromoxylylene, conducted at −78 °C and with use of 36 mL of dried THF per 1 mmol of **4** as well as a 25 mol % excess of **4**, over the alkylating reagent. The consequent hydrolysis of the intermediate dialkylated Schiff base afforded the target amino acid in only 33% chemical yield.

In a recent series of publications, we showed that the readily available[11] and inexpensive Ni(II)-complexes **2a**,**b** (Figure 2), derived from the glycine Schiff base with 2-[*N*-(α-picolyl)amino]acetophenone (PAAP)[12] and 2-[*N*-(α-picolyl)amino]benzophenone (PABP),[13] respectively, can

SCHEME 1



be successfully used as alternative nucleophilic glycine equivalents to the expensive and hydrolytically unstable Schiff bases **4**.[14] In particular, we demonstrated an efficient application of complexes **2a**,**b** as glycine equivalents for the asymmetric synthesis of β-substituted pyroglutamic acids, via Michael additions[12,15] and for preparation of α,α-disubstituted α-amino acids by the dialkylation of **2b** with alkyl halides[9] under operationally convenient conditions. The synthetic success in the application of complex **2b** for the dialkylation prompted us to study its reactions with dibromoxylylene **3** to develop a more practical approach for preparing amino acid **1**. Since dibromide **3** is an analogue of benzyl bromide, initially the reaction between complex **2b** and **3** was conducted under the conditions we used for the dialkylation of **2b** with activated alkyl halides. The reaction was carried out at ambient temperature in commercial-grade DMF (8.3 mL per 1 mmol of **2b**) and NaOH occurred with relatively high rate affording the target cyclic derivative **7** along with a substantial amount of high molecular weight (HMW) byproducts. The latter formed presumably due to the bis-mono-alkylation and further cross-dialkylation reactions (Scheme 1; Table 1, entry 1). Application of 3 equiv of NaO-*t*-Bu as a base resulted in a decreased amount of the HMW byproducts. However the formation of cyclic complex **7** was incomplete because the mono-alkylated derivative **6** and target **7** were isolated in approximately a 1:1 ratio (entry 2). An increased amount of base led to the complete cyclization of **6** to **7**, but unfortunately, an increased amount of the HMW byproducts. Next, a series of reactions were conducted with less concentrated solutions of the starting **2b** in DMF that allowed us to suppress but not eliminate the formation of the undesired HMW byproducts. Applications of other solvents and bases as well as low temperatures led to some improvements but not to complete elimination of the HMW byproducts. The results obtained were successful (as great as 70% yield of **7**) but suggested that the direct dialkylation of glycine equiva-

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TABLE 1. Alkylation of Glycine Equivalent 2b with Dibromide 3 and Cyclization of Complex 6 To Form 7[a]

	conditions					
entry	solvent	base (equiv)	reactant	*T* (h)	ratio[b] **6**/**7**	yield,[c] %
1	DMF	NaOH (10)	**2b**	0.5	>1/99	67
2	DMF	NaO-*t*-Bu (3)	**2b**	0.75	48/52	41
3	CH_2Cl_2/H_2O[d]	NaOH[e]	**2b**	1.0	>99/1	87
4	CH_2Cl_2/H_2O[d]	NaOH[f]	**2b**	1.0	>99/1	91
5	CH_2Cl_2/H_2O[d]	NaOH[g]	**2b**	2.0	>99/1	97
6	DMF	NaO-*t*-Bu (3)	**6**	0.17	31/69	67
7	DMF	NaO-*t*-Bu (3.5)	**6**	0.08	>1/99	93

[a] All reactions were conducted at ambient temperature under the indicated conditions using a 1:1.1 ratio of **2b** and **3**. [b] Determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] Isolated yield of pure **6** or **7**. [d] The reaction was conducted under the PTC. [e] 50% aqueous NaOH and 15 mol % of tetrapropylammonium bromide. [f] 30% aqueous NaOH and 15 mol % of tetrapropylammonium bromide. [g] 30% aqueous NaOH and 15 mol % of tetrapropylammonium iodide.

lent **2b** with dibromide **3** is generally plagued by the formation of undesired HMW byproducts. Therefore, the usage of low concentrations of the starting compounds may be the only procedure to increase the chemical yields of product **7**. Alternatively, application of low concentrations of the starting compounds, as in the literature procedures,[5a,8] automatically leads to lower volume yields than we desire. Therefore, we envisioned a two-step approach including a selective preparation of the mono-alkylated product **6** and its further cyclization into the target **7**. For the first step, application of mild PTC was found to give the desired result. Thus, the reaction between complex **2b** and dibromide **3** conducted under the PTC with dichloromethane/saturated aqueous NaOH and tetrapropylammonium bromide as the catalyst afforded the mono-alkylated **6** in 87% yield along with less than 10% of the HMW byproducts (entry 3). Application of the less concentrated base was found to give a better yield of **6** and a smaller amount of the HMW byproducts (entry 4). The best results were obtained by using tetrapropylammonium iodide as a catalyst, allowing isolation of product **6** in 97% yield (entry 5). The product **6** was isolated in a crystalline state by evaporation of the organic phase and without purification was used directly for the cyclization step. The first attempts to convert **6** to **7** in DMF solution with NaOH as a base gave rather satisfactory results. However, the application of NaO-*t*-Bu allowed the acceleration of the cyclization rate and achieved the complete, fast, and clean transformation of **6** to **7** in 93% yield (entry 7).

Decomposition of the complex **7** and isolation of amino acid **1** was conducted under the standard conditions by heating a suspension of **7** in methanol/3 N HCl. The ligand PABP **8** was recovered in 73.4% yield and converted back to the starting glycine complex **2b** according to the previously described procedure.[11] The amino acid **1** was isolated in 97.9% yield with use of Dowex cation-exchange resin and was shown to be of greater than 95% purity.

In summary, we have demonstrated that the readily available Ni(II)-complex **2b** serves as an efficient nucleophilic equivalent of glycine for preparation of cyclic α,α-disubstituted α-amino acid **1** via a two-step procedure. High chemical and volume yields as well as the simplicity of the experimental procedures render this method useful immediately for synthesis of amino acid **1** and its derivatives.

Experimental Section

General. Unless otherwise noted, all reagents and solvents were obtained from commercial suppliers and used without further purification. All the reactions were carried out under atmosphere without any special caution to exclude air. Unless indicated, ^{1}H and ^{13}C NMR spectra were taken in $CDCl_3$ solutions at 299.95, 282.24, and 75.42 MHz, respectively, on an instrument in the University of Oklahoma NMR Spectroscopy Laboratory. Chemical shifts refer to TMS as the internal standards. Unless otherwise noted, the R_f values (TLC) were obtained with chloroform/acetone mixture in a volume ratio of 7/1.

Yields refer to isolated yields of products of greater than 95% purity as estimated by ^{1}H and ^{13}C NMR spectrometry. All new compounds were characterized by ^{1}H NMR, ^{13}C NMR, and high-resolution mass spectrometry (HRMS/ESI).

Monoalkylation of Ni(II)-Complex 1 with *o*-Xylylene Dibromide (3) under PTC. Synthesis of Complex 6. To a solution of 5.08 g (12.2 mmol) of complex **2b**, 3.55 g (13.1 mmol) of *o*-xylylene dibromide (**3**), and 0.573 g (1.83 mmol) of tetrapropylammonium iodide in 50 mL of CH_2Cl_2 (4 mL/1 mmol of complex **2b**) was added 30 mL of 30% aq NaOH (2.5 mL/1 mmol of complex **2b**). The reaction was vigorously stirred at room temperature for 2 h, and upon completion (monitored by TLC) 100 mL of water was added and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). Combined organic fractions were dried over $MgSO_4$ and evaporated to afford 7.10 g (97.2% yield) of complex **6**.

Ni(II)-complex of 2-amino-3-(2-bromomethyl-phenyl)-propanoic acid Schiff base with PABP (6): R_f 0.47, mp 239.2−242.0 °C; ^{1}H NMR δ 3.33 (2H, ABX, J = 14.4, 6.0, 4.2 Hz), 4.37 (1H, dd, J = 6.0, 4.2 Hz), 4.42 (2H, AB, J = 10.5 Hz), 6.85−6.82 (2H, m), 6.88 (1H, d, J = 4.2 Hz), 6.90 (1H, d, J = 4.2 Hz), 7.13 (1H, m), 7.20 (2H, t, J = 1.2 Hz), 7.30−7.40 (4H, m), 7.56−7.60 (3H, m), 7.71 (1H, d, J = 5.1 Hz), 7.83 (1H, m), 7.94 (1H, td, J = 7.5, 1.2 Hz), 8.80 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 32.56, 37.19, 73.18, 121.83, 123.85, 124.03, 126.84, 127.15, 127.68, 128.00, 128.96, 129.60, 129.65, 130.41, 130.77, 133.12, 133.55, 133.89, 134.83, 135.04, 138.12, 140.33, 143.36, 146.74, 153.27, 159.82, 169.51, 171.90, 178.11. HRMS [M + H$^+$] calcd for $C_{29}H_{22}BrN_3NiO_3$ 598.0205, found 598.0273.

Cyclization of Ni(II)-Complex 6 to 7. To a solution of 1.44 g (15.0 mmol) of sodium *tert*-butoxide and 26 mL of DMF (18 mL/1 g of *tert*-butoxide) was added 2.57 g (4.30 mmol) of complex **6**. After the solution was stirred at room temperature for 5 min, the reaction mixture was poured into 600 mL of ice water. The resulting crystals were filtered and washed with water and hexane, affording 2.07 g (93.1% yield) of complex **7**.

Ni(II)-complex of 2-amino-indan-2-carboxylic acid Schiff base with PABP (7): R_f 0.41, mp 308.2−308.3 °C; ^{1}H NMR δ 3.67 (4H, AB, J = 17.9 Hz), 6.58 (1H, m), 6.65−6.70 (3H, m), 6.88−7.00 (7H, m), 7.30 (1H, m), 7.47 (1H, m), 7.93 (1H, m), 8.02 (1H, m), 8.45 (1H, d, J = 5.1 Hz), 8.71 (1H, d, J = 8.7 Hz); ^{13}C NMR δ 50.71, 121.06, 123.32, 123.53, 125.85, 126.35, 126.61, 128.47, 128.64, 128.73, 132.47, 133.68, 134.55, 139.72, 140.19,

141.87, 146.90, 148.20, 152.91, 169.61, 174.26, 184.53. HRMS [M + H^+] calcd for $C_{29}H_{21}N_3NiO_3$ 518.0943, found 518.1301.

Decomposition of Ni(II)-Complex 7. Recovery of PABP 8 and Amino Acid 1. To a solution of 22 mL (14.5 mL/1 g of complex 4) of MeOH and 11 mL (7.25 mL/1 g of complex **7**) of 3 N HCl at 70 °C was added 1.508 g (2.912 mmol) of complex **7**. The solution was stirred for 30 min. Upon the complete loss of red color the solution was evaporated. The acid **1** and $NiCl_2$ were dissolved in 50 mL of DI water and the HCl salt of ligand **8**, 0.724 g (73.4%), was collected on a filter. The aqueous phase was evaporated and the residue was loaded on an ion-exchange column with use of Dowex 50 × 2−100 resin. The column was first washed with deionized water until neutral pH followed by 8% aq ammonium hydroxide (500 mL) to elute acid (**1**). Evaporation of the solution afforded 0.506 g (2.85 mmol, 97.9% yield) of acid (**1**). The $NiCl_2$ was eluted with concentrated HCl after the column was returned to neutral pH with deionized water.

2-Amino-indan-2-carboxylic acid (1):[4a] mp 261.1 °C dec; ^{1}H NMR δ 3.09 (2H, d, J = 17.4 Hz), 3.49 (2H, d, J = 17.4 Hz), 7.109−7.183 (4H, m). HRMS [M + H^+] calcd for $C_{10}H_{11}NO_2$ 178.0797, found 178.0918.

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