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A Simple Method for the Synthesis of Cyclic α- Amino Acids

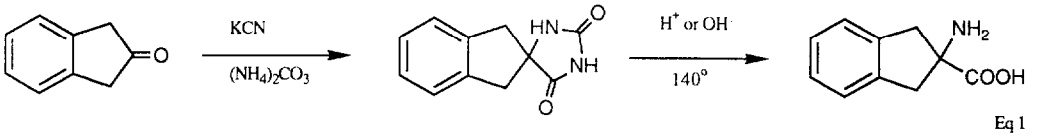
Sambasivarao Kotha# and Atsuo Kuki*[1]

Department of Chemistry, Baker Laboratory, Cornell University
Ithaca, NY 14853-1301

Key Words : Cyclic amino acid synthesis, alkylation of glycine ester

Abstract: The benzylidene derivative of glycine ethyl ester was alkylated with various electrophiles to synthesize cyclic α- amino acids bearing aromatic and aliphatic side chains.

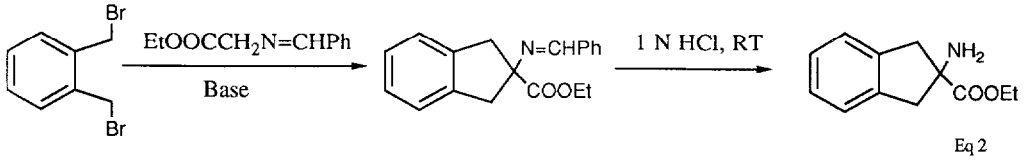
α,α-Dialkylated amino acids and their congeners play an important role in the design and synthesis of conformationally restricted peptides.[2] In connection with another project we needed to synthesize several derivatives of 2-amino-indan-2 carboxylic ester (**1**) as well as derivatives of 2-amino-1,3-dihydrophenalene-2-carboxylic ester (**5**). The conventional method for the preparation of the cyclic amino acid derivative **1** involves a Bucherer-Berg synthesis using an indane-2-one derivative[3a] as the starting material. Although the Bucherer-Berg synthesis continues to provide new amino acids,[4] there are still many limitations to this approach. The synthesis of indane-2-one derivatives requires a multistep sequence.[5] The hydrolysis of the intermediate spiro-hydantoins (Eq 1) further requires drastic reaction conditions (excess barium hydroxide, 140^{0}C or 60% concentrated sulfuric acid 140^{0}C) which often induces side reactions.[6] Consequently it is very difficult to prepare amino acids with sensitive side-chain functionalities by the Bucherer-Berg method:



Eq 1

In this communication we demonstrate that these cyclic amino acids can be prepared easily from the readily available α,α'-dibromo-xylenes (Eq 2). In fact α,α'-dibromo-xylenes are precursors to the indane-2-

ones. For example, the very labile and air sensitive 1,3-dihydro-2-phenalenone, the only possible precursor for the preparation of compound **5** via Bucherer-Berg synthesis, was prepared from 1,8-bis(bromomethyl) napththalene in 5 steps.[11c]



Eq 2

Stork[7] and others[8a] have shown that the benzylidene derivative of glycine ester can be selectively α-alkylated with one or two electrophiles in a stepwise sequence leading to non-cyclic mono and dialkylated amino esters. These alkylated derivatives can be further hydrolyzed to amino esters or amino acids depending on the reaction conditions.[7,8c] However there has been no report on the efficacy of the alternative intramolecular dialkylation of this glycine enolate to generate cyclic amino acids. Towards this end we examined several different substrates and obtained good results giving cyclic α,α-dialkylated benzylidene derivatives of glycine ethyl ester. Various bis(halomethyl) substrates which underwent successful intramolecular dialkylation are shown in Table 1. Since α-functionalized amino acids have potential synthetic applications[9] and also act as enzyme inhibitors [8a,b] this practical and versatile methodology should find interesting applications in synthetic and medicinal chemistry. Our progress in utilizing these cyclic amino acids in peptides of novel design will be reported in due course.

In a typical experimental procedure (1 mmole) benzylidene derivative of glycine ethyl ester was suspended in dry tetrahydrofuran (10 ml) and cooled to -78^{0}C under nitrogen. Then 2.2 equivalents of base (NaHMDS or LiHMDS) were added via syringe and the stirring continued for 45 min at -78^{0}C. The dibromide or dichloride (1mmole) in dry THF (10ml) was added and the reaction mixture was slowly brought to room temperature. After 2 h the reaction mixture was poured into water (50 ml) and extracted with ethyl acetate (3x30 ml). The organic layers were combined and washed with brine and dried ($MgSO_4$). Removal of the solvent gave a crude oily product which was subjected to hydrolysis using 1N hydrochloric acid-ethyl ether (1:1) and the products were isolated in a similar manner to that reported by Stork[7] to give the desired amino esters as exclusive products. Amino esters **3** and **5** were synthesized on the 100 mmol scale without any complications, and carried forward to further elaboration on the aromatic rings with no additional purification. Thus the present method can provide multi-gram scale syntheses which enables the further use of the cyclic amino esters as aromatic precursors to more complex amino acids. **Precaution**: The electrophiles used in this study are lachrymators and irritants and must be handled with proper care. Some are potent mutagens. Long storage of benzylidene derivative of glycine ethyl ester gave erroneous results. The freshly prepared ethyl ester can be used within a week without any problem if stored at a temperature below 4^{0}C.

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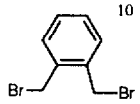
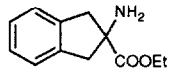
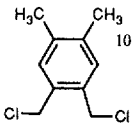
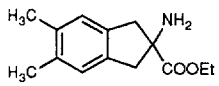
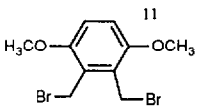
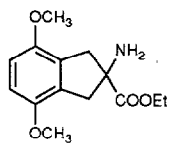
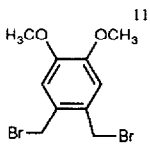
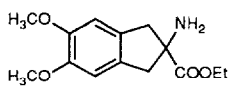
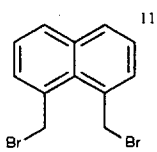
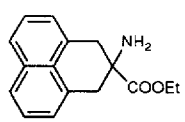
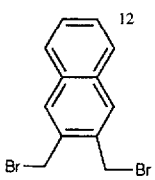
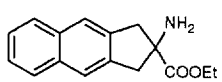
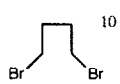
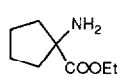
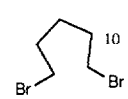
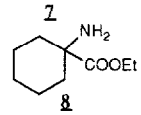
TABLE 1

Electrophile	Base	Product	Steps[13]	%Yield[14]
	NaHMDS	 **1**	2	**53**
	NaHMDS	 **2**	2	**46**
	NaHMDS	 **3**	4	**60**
	NaHMDS	 **4**	5	**40**
	NaHMDS	 **5**	4	**92**
	LiHMDS	 **6**	3	**30**
	LiHMDS	 **7**	2	**38**
	LiHMDS	 **8**	2	**30**

References and Notes:

Also published as Kotha Sambasiva Rao and Kotha Sambasivarao in the past.

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10 These starting materials are available from Aldrich chemical company.

11 These compounds were made according to literature procedures.
(a) 2,3-Bis(bromomethyl)-1,4-dimethoxybenzene was prepared from 2,3-Dimethylhydroquinone via the methylation and bromination sequence; see Eck, G.; Julia, M.; Pfeiffer, B.; Rolando, C., Tetrahedron Lett., **1985,** 26, 4725-26. (b) 2,3-Bis(bromomethyl)-5,6-dimethoxybenzene was prepared from veratrole; see Bruce, J. M.; Sutcliffe, F. K., J. Chem. Soc., **1956,** 3820-3823, and 3824-29; McHale, D.; Mamalis, P.; Marcinkiewicz, S.; Green, J., J.Chem. Soc., **1959,** 3358-3362. (c) 1,8-Bis(bromomethyl) naphthalene was prepared from 1,8-Naphthalic anhydride; see Mitchell, D.; Eilert, J. H.; Bauld, N. L., Tetrahedron Lett., **1979,** 2865-2866.; Jorgensen, F. S.; Thomsen, T., Act. Chem. Scan., B, **1984,** 38, 113-116.

12 2,3-dimethylnaphthalene was purchased from Lancaster Synthesis and brominated with NBS.

13 Steps refer to the total number of steps from commercially available starting materials to product.

14 Yields refer to the combined yield of the alkylation and hydrolysis steps only.

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