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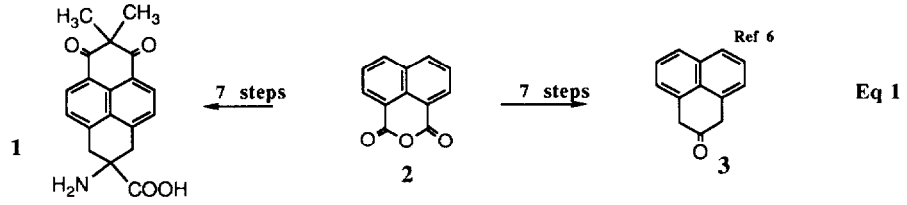
Friedel-Crafts Approach to Electron Deficient Cyclic α– Amino Acids

Sambasivarao Kotha,# Demetrios Anglos, and Atsuo Kuki*@
Department of Chemistry, Baker Laboratory, Cornell University
Ithaca, NY 14853-1301

Key Words: Electron deficient α-amino acid, Friedel-Crafts acylation.

Abstract: An electron deficient 2,2-dimethyl-1-H-phenalene-1,3-dione based cyclic α-amino acid was synthesized in 7 steps using Friedel-Crafts acylation as the key step. A new recipe was found to deprotect the required phthalimide protecting group in highly hindered substrates.

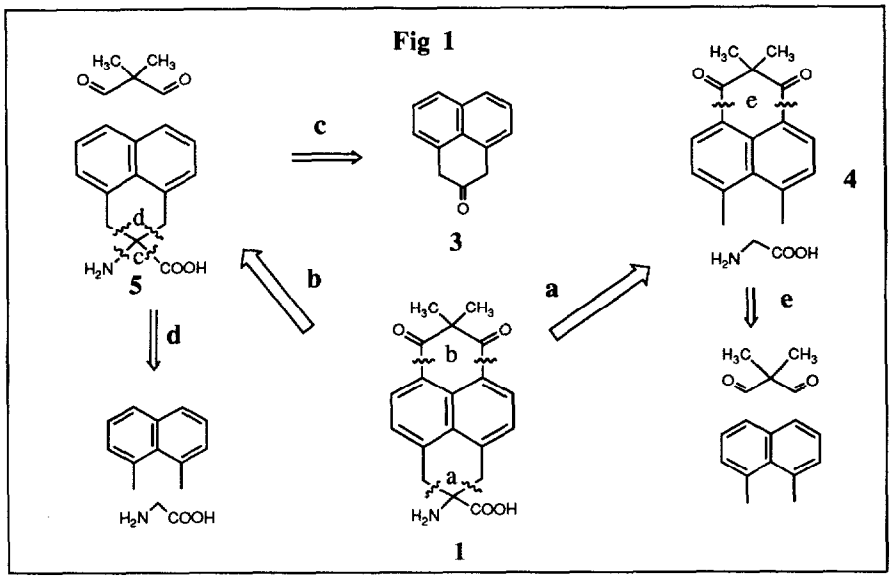
The unusual role of α–aminoisobutyric acid (aib) and other related simple dialkylated amino acids in the design of conformationally restricted peptides has led to a great deal of research activity in this area.[1] Surprisingly, only the very simplest of the cyclic analogues have found application in the peptide arena. This is due to the relative nonavailability of synthetic methods to deliver complex cyclic α-amino acids. In connection with our research on aib rich oligo-peptides capable of light induced electron transfer, we needed



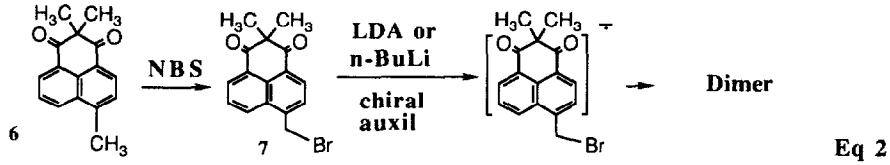
1 2 3 Eq 1

to synthesize the acceptor **1**. Our favorable experience[2] with the photophysical, electrochemical, and spectro-electrochemical properties of 2,2-dimethyl-1H-phenalene-1,3-dione based molecules (e.g. **6**) suggested compound **1** as the chromophore/acceptor amino acid of choice for our electron transfer peptides. This target also has the important characteristic of a highly rigid connection to the peptide backbone. In this communication we describe our successful synthesis of a complex and electron deficient cyclic α-amino acid **1.**

Synthesis of **1**, with two quaternary carbon atoms and four polar functional groups of diverse reactivity, is not a trivial exercise. The first level of retrosynthetic analysis [3] of **1** is greatly simplified by disconnecting two bonds simultaneously, taking advantage of the inherent symmetry element (C_s) present. The crucial question in path **a** was whether or not the unprecedented intramolecular α,α-dialkylation of a glycine enolate equivalent with a highly electron deficient (by design!) substrate **4** could be performed. In particular, good electron acceptors such as **4** may also participate in undesired single electron transfer



processes, which result in dimerization during normal alkylation procedures,[2] as found with **6**, Eq. 2.



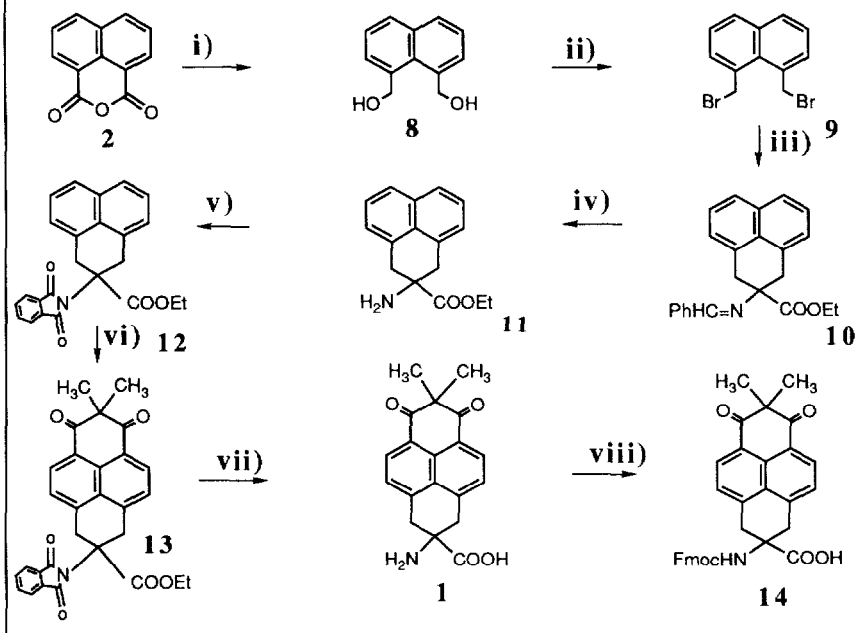
Eq 2

The other logical analysis (path **b**) had two challenges: (1) regiochemical introduction of the electron withdrawing moiety by Friedel-Crafts acylation reaction [4] on the pre-formed amino acid derivative **5**, and (2) introduction and removal of the compatible protecting groups under Friedel-Crafts conditions in a sterically congested environment. The second level of analysis for route **b** would suggest synthesis of the subtarget **5** via (path **c**) the Bucherer-Berg synthesis [5] involving **3**. Unfortunately, the ketone **3** is very labile and air sensitive [6]; its synthesis requires 7 further steps from the readily available 1,8-naphthalic anhydride **2**. The alternative path **d** involves alkylation of the glycine enolate equivalent with a substituted 1,8-naphthalene derivative such as **9**. Recently, we demonstrated[7] a useful variant of the Stork methodology[8] addressing this transformation. Based on these considerations, approach **b d** appeared to be a superior maneuver in the synthesis of **1.**

Dibromide **9** was readily accessible [6] from diol **8** in large quantities, which on treatment with the benzylidene derivative of glycine ethyl ester in the presence of NaHMDS at -78° gave **10** (Scheme 1). Hydrolysis of **10** with 1 N HCl gave the key compound **11** (92% yield from **9**). No difficulty was encountered in protecting the amino functionality of **11** as the phthalimide.[10] Friedel Crafts acylation of **12** with dimethylmalonyl dichloride in dichloroethane gave **13** as the major product along with two minor regio-

isomers which are inseparable by column chromatography. Since it is well documented that Friedel-Crafts reactions with naphthalene derivatives are significantly solvent dependent,[11] we tried several solvents and found that nitrobenzene with 4 eq of $AlCl_3$ gives only the desired isomer **13** in 90% yield.[9] This pleasing absence of unwanted regioisomers is a very important result in view of the practical synthesis of **1**. The traditional hydrazine hydrate conditions[12] for unmasking the amino functionality did not work in the present case. We next investigated the conditions to hydrolyze the ethyl ester. Acidic or basic hydrolysis even under prolonged reaction times gave either the starting materials or decomposed products.[13] Several other variations

Scheme 1



i) LAH, THF ii) PBr_3 iii) $EtOOCCH_2N{=}CHPh$, $NaN(TMS)_2$ -78° iv) 1 N HCl v) phthalic anhydride, Et_3N vi) $ClCOC(CH_3)_2COCl$, $AlCl_3$, $C_6H_5NO_2$ vii) MsOH, HCOOH viii) FmocCl, TMSCl, $(Et)_3N$

for the hydrolysis of the ester functionality[14] and the phthalimide functionality[15] proved unsuccessful. A perusal of the literature revealed that formic acid-methanesulphonic acid[16] is known to cleave the ester functionality by trans-esterification. Although the authors did not discuss the mechanism, it is well established that methanesulphonic acid reactions involve acylium ions as intermediates.[17] Such an acylium intermediate enables hydrolysis or trans-esterification in cases where the standard tetrahedral intermediate is difficult to form due to steric constraints. This alternative recipe hydrolyzed both the ester and the phthalimide group of **13** to deliver the amino acid directly. N-protection of **1** with Fmoc-Cl[18] gave **14** which was used directly in the peptide synthesis.

Our successful synthesis of **1** provides not only an unusual new amino acid, but also a methodology which may serve as an illustrative example for other electron deficient α-amino acids yet to be explored. This strategy, which may be generally applied in cases of sensitive or interfering aromatic functionalities, emphasizes prior C_α-C_β bond assembly of a suitably protected but simple aromatic amino acid followed by further elaboration of the aromatic ring. The new hydrolysis conditions found in this case may also increase the synthetic utility of the phthalimide protecting group in organic synthesis.

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References and Notes:

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

@ Camille and Henry Dreyfus Teacher-Scholar.

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2 Unpublished results from our laboratory. $E_{1/2}$ for the reduction of **6** found to be -1.48 volts vs. SCE in CH_3CN (0.1M TBAP). Derivatives of **1** also have similar values.

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