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Synthesis of Pyrrole Derivatives Mediated by Dicobalthexacarbonyl

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Abstract: Addition of α- and β-amino acid derivatives to the cobalt stabilized propargylic cation **2** gives dicobalthexacarbonyl complexes with an amino acid derivative at the propargyl position. Oxidation of the resulting complexes with Fe(III) produces propargyl amines **4**. Intramolecular cyclization of **4** with LDA followed by oxidation of the crude product with DDQ affords pyrrole derivatives as the major products.

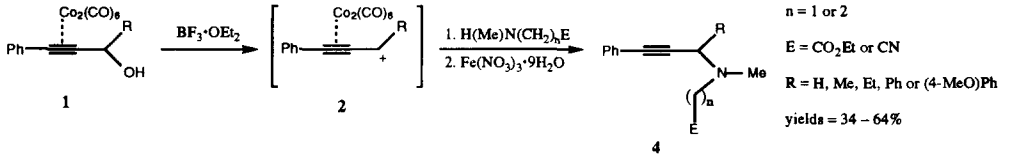
Pyrrole and its derivatives are important heterocycles in organic- and bio-chemistry and have been found in many pyrrole-containing natural products such as heme, chlorophyll, vitamin B_{12} and bile pigments.[2] There are extensive studies on the synthesis and reactivity of pyrrole derivatives.[3] The most widely methods used for synthesis of pyrrole derivatives involve intramolecular cyclization of a heteroatom to a carbon-carbon triple bond in both *exo*[4] and *endo*[5] fashion. However, intramolecular cyclization of carbanions to a carbon-carbon triple bond to give pyrrole derivatives is rare. In this paper we report a convenient method to synthesize pyrrole derivatives mediated by propargyl dicobalthexacarbonyl cation salts.

Cobalt stabilized propargylium complexes have provided a general method for the formation of carbon-carbon bond at the propargyl position.[6] The absence of allenic byproducts is an important feature of these coupling reactions.[7] The reactivity of the propargylium complexes has been studied with a variety of carbon-centered nucleophiles including electron rich aromatics, β-dicarbonyls, ketones and enol derivatives, allylsilanes, metal hydrides, and alkyl-metals such as trialkyl- and alkynyl-aluminum derivatives.[8] Prior to our study, few examples of nitrogen nucleophiles are known to react with propargyl dicobalthexacarbonyl cations to give propargyl amines.[9] To prepare the starting substrates for intramolecular cyclizations, we adopted this well-known strategy developed by Nicholas.[6] Reaction of the commercial available α- and β-amino acid derivatives **3** [$H(Me)N(CH_2)_nE$, n=1 or 2, E=CN or CO_2Et] with propargyl alcohol-cobalt complex **1** generates propargyl amine-cobalt complexes, which are decomplexed by $Fe(NO_3)_3 \cdot 9H_2O$ to produce propargyl amines **4a–4k** (Scheme 1).[10]

Treatment of propargyl amine **4a** with LDA at 25 °C affords pyrrole **5a** (22%) and **7a** (19%), dihydropyrrole **9** (27%) and dihydroazete **6a** (15%). The cyano-stabilized anion may proceed in a 5-*endo-dig* fashion to give anion **8** (path a, Scheme 2). Protonation of anion **8** followed by double bond migration

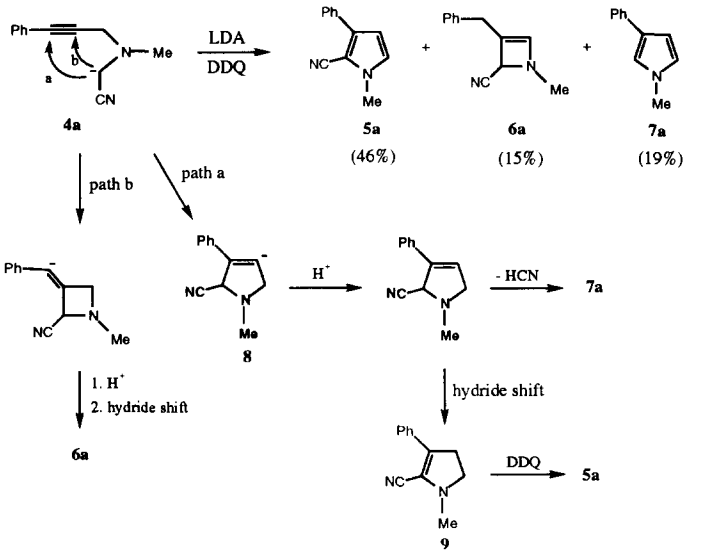
generated **9**. Oxidation of **9** with DDQ (2,3-dichloro-5,6-dicyano-p-benzoquinone, 1.1 equiv) at 25 °C gave pyrrole **5a** in 90% yield.[11] Whereas protonation of anion **8** followed by elimination of HCN would produce

Scheme 1



pyrrole **7a** . It is important to mention that the 4-*exo-dig* cyclization of **4a** to give dihydroazete **6a** is generally considered a disfavored process according to the Baldwin's rules (path b, Scheme 2).[12] Moreover, intramolecular cyclization of propargyl amino ester compound, for example **4b**, gave dihydroazete **6b** (55%) as the major product (entry 2, Table 1). The reason for the formation of the less stable dihydroazete **6b** is not clear. Nevertheless, an additional substituent at the propargyl carbon prevents the formation of dihydroazete, only pyrroles **5c–5f** were isolated (entries 3 and 4, Table 1).

Scheme 2



Increasing the tether length by one with propargyl amines **4g–4k** led to 33-72% yields of pyrroles **5g–5k** as the major products (entry 5, Table 1).[13] The formation of the 5-membered nitrogen-containing heterocycles proceeds only in the 5-*exo-dig* fashion (Scheme 3), and none of the addition at C-7 (6-*endo-dig*) to give pyridine derivatives was found.

The reactions outlined herein demonstrate that the intramolecular cyclization reaction of propargyl amines can be an effective method for the formation of di- and tri-substituted pyrrole derivatives. The applications of this methodology in the synthesis of other heterocycles are in progress in our laboratory.

A representative experimental procedure is given as follow. To a stirred solution of 0.52 mmol of LDA in

THF (2 mL) was added propargyl amine **4g** (80 mg, 0.4 mmol) at –78 °C under nitrogen. The resulting reaction mixture was allowed to stir at 25 °C for 24 h. The reaction mixture was quenched with saturated aqueous ammonium chloride, followed by standard work-up and flash column chromatography on silica gel

Scheme 3

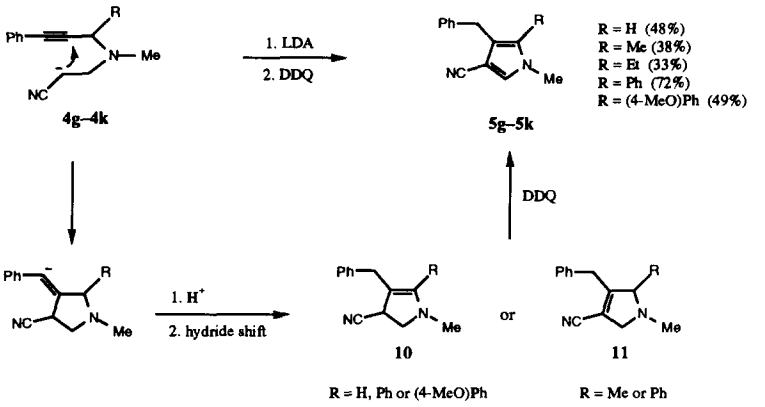
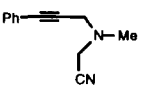
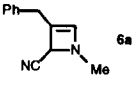
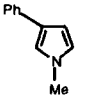
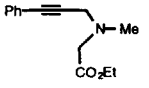
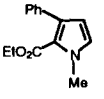
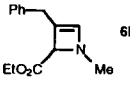
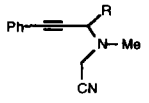
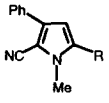
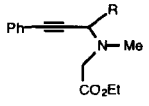
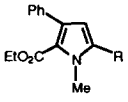
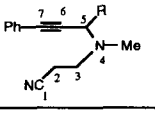
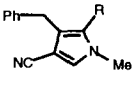


Table 1. Synthesis of pyrrole derivatives from propargyl amines

Entry	propagyl amines	Products (Yield, %)[a]
1	 **4a**	 **5a** (46%)  **6a** (15%)  **7a** (19%)
2	 **4b**	 **5b** (9%)  **6b** (55%)
3	 **4c** R=Me **4d** R=Et	 **5c** R=Me (53%) **5d** R=Et (61%)
4	 **4e** R=Me **4f** R=Et	 **5e** R=Me(40%) **5f** R=Et (64%)
5	 **4g** R= H **4h** R= Me **4i** R= Et **4j** R= Ph **4k** R= (4-MeO)Ph	 **5g** R= H (48%) **5h** R= Me (38%) **5i** R= Et (33%) **5j** R= Ph (72%) **5k** R= (4-MeO)Ph (49%)

[a]All indicated yields were isolated yields. Satisfactory spectral data (IR, ^{1}H and ^{13}CNMR, and HRMS) were obtained for all compounds.

(25% ethyl acetate/hexanes) afforded dihydropyrrole **10** (40 mg, 0.2 mmol) in 50% yield. To a stirred solution of dihydropyrrole **10** (38 mg, 0.19 mmol) and benzene (3 mL) was added DDQ (48 mg, 0.21 mmol) at 25 °C then stirred for 2 h. The reaction mixture was quenched with saturated aqueous sodium bicarbonate followed by standard work-up and flash column chromatography on silica gel (9% ethyl acetate/hexane's) afforded pyrrole **5g** (35 mg, 0.18 mmol) in 95% yield as a colorless oil.

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13. Rigorous proof of the structure of **5j** was accomplished by X-ray diffraction analysis and was consistent with the reaction pathway proposed in Scheme 3.

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