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A Mild and General Method for the Synthesis of 5-Substituted and 5,5-Disubstituted Fulleroprolines

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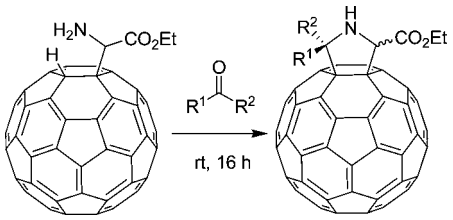
ABSTRACT



The reductive ring-opening of fullerenyldihydropyrrole yields ethyl *N*-benzhydryl fullerenyl[60]glycinate, which is deprotected to give ethyl fullerenylglycinate. The free amine is able to react with a variety of aldehydes and ketones in a Mannich-type process to produce 5-substituted and 5,5-disubstituted fulleroprolines and represents a versatile and general strategy to this class of compounds.

Fullerene[60]-derived molecular and supramolecular structures offer significant potential as novel medicinal chemical agents and nanostructured devices. Fulleroprolines and fulleropyrrolidines have emerged as convenient scaffolds for building such molecular architectures.[1] The fulleroprolines are readily prepared from 1,3-dipolar cycloaddition reactions of fullerene[60] and azomethine ylide. Such intermediates generated *in situ* from the thermal ring-opening of aziridines[1a,2] and *N*-trityloxazolidinone[1a] or from the reactions of *N*-alkyl glycinates (e.g., sarcosine)[1a,b,2] with aldehydes or directly from *N*-iminoglycinates.[3] Although these methods work well, these reactions require high reaction temperatures (typically 110−130 °C, or higher). To date, these latter two methods have been limited to the use of aldehydes or *N*-iminoglycinates derived from aldehydes (usually aromatic or formaldehyde) and have not been extended to the use of ketones. Thus, a milder method allowing reactions with thermally sensitive aldehydes and ketones, and providing access to a more diverse range of compounds, including 5,5-disubstituted fulleroprolines, would be of considerable value.

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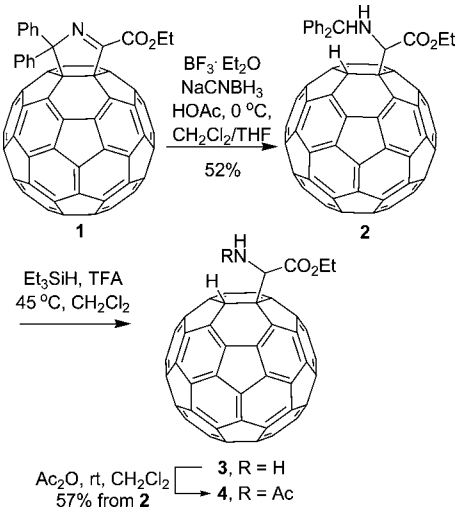
We earlier reported the synthesis of ethyl *N*-benzhydryl fullerenyl[60]glycinate **2**, formed from a novel reductive ring-opening reaction of fullerenyldihydropyrrole **1**.[4] We report here the synthesis of the *N*-deprotected form of this compound, ethyl fullerenyl[60]glycinate **3** which under neutral conditions reacts with both aldehydes and ketones to give 5-substituted and 5,5-disubstituted fulleroprolines in synthetically useful yields and under mild reaction conditions.

Ethyl *N*-benzhydrylfullerenyl[60]glycinate **2** underwent *N*-deprotected upon exposure to Et_3SiH/TFA to give ethyl fullerenyl[60]glycinate **3** (Scheme 1). This compound was

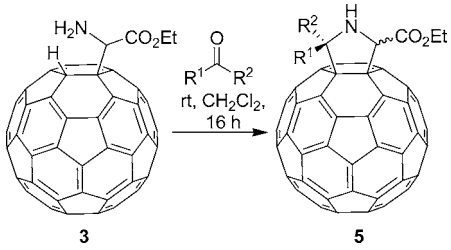
Scheme 1. Reductive Ring-Opening of Fullerenyldihydropyrrole **1**



difficult to fully characterize since it slowly precipitated from solution and was then difficult to redissolve, possibly due to the formation of aggregates. However, satisfactory ^{1}H NMR and ESI MS data were obtained. Ethyl fullerenyl[60]-glycinate **3** could only be isolated in 33% yield after purification by column chromatography but was more readily characterized as its more soluble *N*-acetyl derivative **4**. This was achieved in 57% overall yield from **2** after chromatographic purification (Scheme 1). In subsequent transformations of **3**, it was found that higher overall yields of final products resulted using unpurified **3**, and yields of products are thus based on an overall yield from compound **2**.

Treatment of a freshly prepared solution of crude **3** with 2−10 molar equiv of the aldehydes or ketones shown in Table 1 at rt for 16 h gave the fulleroprolines **5a**−**j** in yields ranging from 37 to 64% from **2** (Table 1), with the exception of acetophenone which gave the fulleroproline **5k** in 14%. Both aromatic and aliphatic aldehydes gave their respective

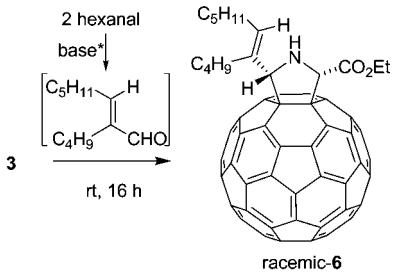
Table 1. Reaction of Ethyl Fullerenyl[60]glycinate with Aldehydes and Ketones Giving 5-Substituted Fulleroprolines



entry	R^1, R^2	product (yield from **2**, %)	cis:trans
1	H, *i*-Pr	**5a** (49)	3:1
2	H, *t*-Bu	**5b** (47)	3:1
3	H, *c*-C_6H_{11}	**5c** (48)	2:1
4	H, Ph	**5d** (58)	2.5:1
5	H, ferrocenyl	**5e** (37)	5:1
6	Me, Me	**5f** (64)	-
7	Et, Et	**5g** (61)	-
8	-$(CH_2)_4$-	**5h** (54)	-
9	-$(CH_2)_5$-	**5i** (51)	-
10	-$(CH_2)_6$-	**5j** (54)	-
11	Me, Ph	**5k** (14)	2.5:1

5-substituted fulleroproline derivatives **5a**−**d** as mixtures of cis and trans isomers (Table 1, entries 1−4). The cis isomer was favored in each case as determined from ROESY NMR experiments (cross-peaks were observed between H-2 and H-5 of the proline ring in the cis isomers). In the case of benzaldehyde, the cis:trans ratio was similar to that reported from the reaction of fullerene[60] with methyl *N*-benzylideneglycinate at 110 °C for 24 h,[3] whereas reaction with ferrocene carboxaldehyde proceeded smoothly. The straight chain aldehyde hexanal gave a mixture of products upon its reaction with **3** (Scheme 2). Only the major adduct **6** could

Scheme 2. Reaction of Hexanal with Ethyl Fullerenylglycinate **3**



* base is the amine from **3**

be isolated pure and was the product from the reaction of **3** with an aldol-dehydration product of the parent aldehyde. ROESY and 1D NOE NMR experiments indicated that **6** had the 2,5-cis stereochemistry (cross-peaks were observed between H-2 and H-5 of the proline ring).

Both acyclic and cyclic ketones reacted with **3** to give the corresponding 5,5-disubstituted fulleroproline derivatives

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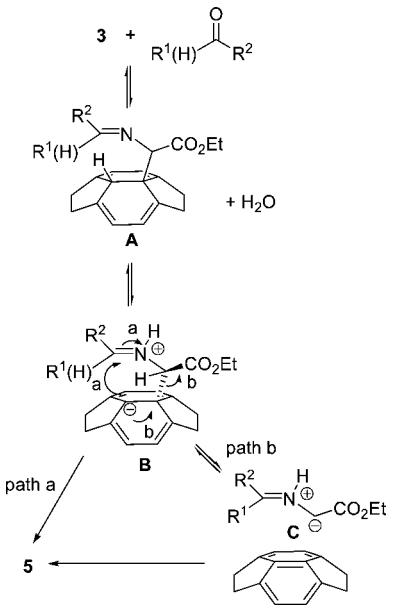
Scheme 3. Possible Reaction Mechanisms for the Formation of Fulleroprolines from Ethyl Fullerenylglycinates



5f−**k** in consistent yields (14−64%, Table 1, entries 6−11). These ketone adducts are all novel compounds except the acetone adduct **5f**, which was reported in less than 5% yield from the thermolysis of fullerene[60] with ethyl glycinate.[5] It was speculated that this compound arises from the 1,3-dipolar cycloaddition of the ylide derived from the imine formed between ethyl glycinate and a trace impurity of acetone. However the yields of this adduct did not increase when acetone was purposely added to the reaction and a mixture of least five products resulted.[5] The reaction of acetophenone with **3** required gentle heating (42 °C) and gave the expected fulleroproline **5k** albeit in 14% in a 5:2 cis:trans ratio.

The formation of fulleroprolines **5** and **6** is consistent with formation of the imine derivative **A** of **3**, followed by the zwitterion intermediate **B**, due to the relatively high acidity of the fullerenyl proton (the pK_a of $C_{60}H_2$ has been determined to be 4.9)[6] (Scheme 3). Intramolecular cyclization of the fullerenyl carbanion onto the highly electrophilic iminium ion carbon of **B** (path a), in a typical Mannich-type reaction mechanism, would give the fulleroproline derivatives **5** or **6**. The cis selectivity of these reactions can be explained by the reactive conformation **B** in which 1,2-allylic strain is minimized. An alternative 1,3-dipolar cyclization pathway is also possible (path b), and although related 1,3-dipolar cycloadditions are known,[1−3] they require high reaction temperatures (e.g., above 110 °C), likely to be required to generate the 1,3-dipole (e.g., **C**, Scheme 3). If the former mechanism (path a) is operating, then this work would represent the first example of the Mannich reaction applied to a dihydrofullerene.

Thus, a mild method has been developed for the synthesis of fulleroprolines. This method allows for the first time general access to 5,5-disubstituted fulleroprolines and provides access to a more diverse range of these important compounds.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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