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Amino Acids as Precursors for N-unsubstituted Fulleropyrrolidine Derivatives.

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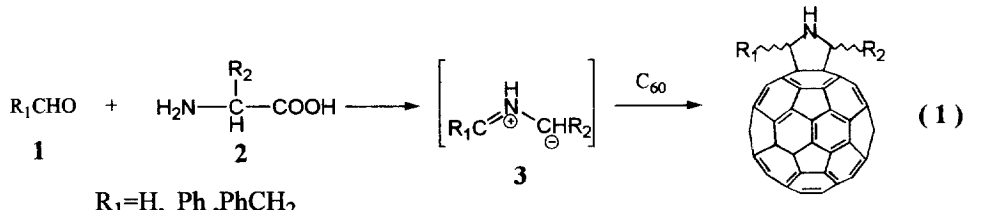
Abstract: The formation of azomethine ylides **3** directly from aminoacids and aldehydes and their addition to C_{60} is reported. The method provides a new route to N-unsubstituted fulleropyrrolidines **4a-4g**.

Functionalization of fullerenes continues to be a current focus of research leading to the useful application of fullerene derivatives in biological and materials science.[1] One of the most important methods for C_{60} functionalization involves formation of N-alkyl-fulleropyrrolidines by 1,3-dipolar cycloaddition of azomethine ylides to C_{60}. This reaction was first reported by Prato[2] and later by some other groups,[3,4] and has served as an excellent and high yield process for fullerene functionalization.[5]

Since N-unsubstituted fulleropyrrolidines provide an entry into further functionalized derivatives by reaction at the nitrogen atom, a pathway to such compounds would be very useful. Prato reported methods for preparing unsubstituted fulleropyrrolidines employing N-trityl protected glycine as a precusor.[2,5b] Another method, involving the reaction of C_{60} with an α-aminoester imine was reported by another group.[4] We report here the reaction of C_{60} with azomethine ylides generated directly from aldehydes and amino acids through a decarboxylation route,[6] by which N-unsubstituted fulleropyrrolidines were readily obtained in one step (equation 1).



1 **2** **3** **4** **(1)**

R_1=H, Ph ,$PhCH_2$
R_2=H, CH_3, Ph, $PhCH_2$

Azomethine ylides **3a-g** were prepared *in situ* from aldehydes and amino acids as shown in the Table. In a typical procedure, 2 equivalents of amino acid **2**, 5 equivalents of aldehyde **1**, were mixed in toluene with an equivalent of C_{60} and heated at reflux for several hours. The rates of reactions depended upon the

reactivities of the ylides, and the reactions could be monitored by TLC. Fulleropyrrolidine products were purified by flash chromatography on silica gel.

Table. Yields and spectroscopic data[7,8] for 1,3-dipolar cycloaddition product **4** (equation 1).

Entry	Compd	R_1	R_2	Yield[a]	^{1}H-NMR (2:1 CS_2/$CDCl_3$, 200 MHz)
1	**4a**	H	CH_3	20%	4.95 (d, J=12.0Hz, 1H), 4.80 (q, J=6.6Hz, 1H), 4.74 (d , J=12.0Hz, 1H), 2.10 (d, J=6.6Hz, 3H)
2	**4b**	Ph	H	35%	7.83-7.79 (m, 2H), 7.46-7.36 (m, 3H), 5.82 (s, 1H), 5.12 (d, J=10.7Hz, 1H), 4.90 (d, J=10.7Hz, 1H)
3	**4b**	H	Ph	26%	Same as above
4	**4c**	H	$PhCH_2$	24%	7.50-7.21 (m, 5H), 4.93 (d, J=11.1Hz, 1H), 4.90 (dd, J_1=3.1Hz, J_2=10.8Hz, 1H), 4.65 (d, J=11.1Hz, 1H), 4.00 (dd, J_1=3.1Hz, J_2=14.1Hz, 1H), 3.39 (dd, J_1=14.1Hz, J_2=11.1Hz, 1H)
5	**4d**	Ph	CH_3	26% *trans* 23% *cis*	*trans*: 7.83-7.79 (m, 2H), 7.45-7.33 (m, 3H), 5.86 (s, 1H), 5.01 (q, J=6.4Hz, 1H), 2.18 (d, J=6.4Hz, 3H) *cis*: 7.79-7.76 (m, 2H), 7.45-7.32 (m, 3H), 6.14 (s, 1H), 5.39 (q, J=7.0Hz, 1H), 2.25 (d, J=7.0Hz, 3H)
6	**4e**	Ph	$PhCH_2$	15% *trans* 20% *cis*	*trans:* 7.86-7.81 (m, 2H), 7.62-7.57 (m, 2H), 7.49-7.32 (m, 6H), 5.71 (s, 1H), 5.04 (dd, J_1=2.7 Hz, J_2=11.1Hz, 1H), 4.05 (dd, J_1=2.6Hz, J_2=13.2Hz, 1H), 3.53 (dd, J_1=11.1Hz, J_2=13.2Hz, 1H), 2.90 (bs, 1H) *cis:* 7.84-7.79 (m, 2H), 7.56-7.20 (m, 2H), 6.20 (s, 1H), 5.41 (dd, J_1=4.0Hz, J_2=11.5Hz, 1H), 4.05 (dd, J_1=11.5Hz, J_2=13.6Hz, 1H), 3.72 (dd, J_1=4.0Hz, J_2=13.6Hz, 1H), 2.93 (bs, 1H)
7	**4f**	Ph	Ph	38%	8.06-8.02 (m, 4H), 7.51-7.35 (m, 6H), 6.04 (s, 2H)
8	**4g**	$PhCH_2$	$PhCH_2$	17%[b] *trans/cis* (62/38)	*trans:* 7.66-7.10 (m, 10H), 4.80 (dd, J_1=3.1Hz, J_2=10.5Hz, 2H), 3.93 (dd, J_1=3.1Hz, J_2=13.5Hz, 2H), 3.38 (dd, J_1=10.5Hz, J_2=13.5Hz, 2H) *cis*: 7.66-7.10 (m, 10H), 5.17 (dd, J_1=3.6Hz, J_2=10.8Hz, 2H), 3.74 (dd, J_1=3.6Hz, J_2=13.4Hz, 2H), 3.54 (dd, J_1=11.1Hz, J_2=13.5Hz, 2H)

a. Isolated yields.

b The isomers of compound **4g** could not be cleanly separated by flash chromatography. (R_f value = 0.23 (*trans*) and 0.19 (*cis*) on SiO_2, eluent: 1:1 toluene/hexane).

Those reactions using paraformaldehyde gave relatively low yields compared to reactions with other aldehydes. Possibly paraformaldehyde reacts with N-unsubstituted fulleropyrrolidines[6] to produce cross-linked dimers which precipitate from the reaction mixture. Dimeric fullerene derivatives are barely soluble in most organic solvents and characterization of such compounds has proven difficult.[9]

Compounds **4d-4g** are 1,3-disubstituted fulleropyrrolidines which may exist as either *cis* or *trans* isomers. That compounds **4d, 4e** and **4g** exist as *cis/trans* mixtures is shown by ^{1}H-NMR (table) and HPLC.[10] ^{1}H-NMR of the *cis*-and *trans*- isomers showed distinctive chemical shifts for the pyrrolidine

methine protons. The signals for the *cis*-isomers always appear further downfield than the corresponding signals for the *trans*-isomers. (Assignments are based on the stereochemistry expected from steric effects on the known azomethine ylide reaction mechanism, *vida infra.*) The *cis*-isomer of **4d** shows a methine singlet at 6.14 ppm and a methine quartet at 5.39 ppm, while the corresponding methines from *trans*-**4d** appear as singlet at 5.86 ppm and a quartet at 5.01 ppm. Similarly, the pyrrolidine methine signals for *cis*-**4e** appears as a singlet at 6.20 ppm and a doublet of doublets at 5.41 ppm. The spectrum of *trans*-**4e** shows a singlet at 5.71 ppm, and a doublet of doublets at 5.04 ppm.

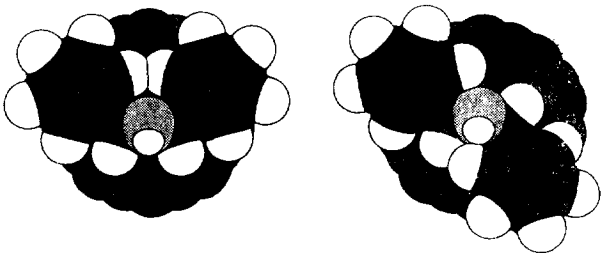


Figure 1. Computer models of *cis*-**4g** (a *meso* compound) and *trans*-**4g** (a C_2 symmetric *d,l*-compound.)

We have previously studied the resolution of chiral C_{60} derivatives[11] and thus had an interest in compounds **4f** and **4g**. The *cis*-isomers of **4f** or **4g** are *meso* compounds, but the *trans*-isomers are chiral C_2 symmetric racemic compounds (Figure 1). Unfortunately, the reaction leading to compound **4f** gave a single isomer as shown by HPLC[10] and ^{1}H-NMR. This compound was assigned the *cis*-configuration based on its ^{1}H-NMR spectrum which shows a (downfield) singlet at 6.04 ppm for the pyrrolidine -CH- protons. On the other hand, compound **4g** was formed as a 38/62 *cis/trans*-mixture by ^{1}H-NMR and HPLC. The structure assignments were again based on ^{1}H-NMR, where the more downfield methine signal (5.17 ppm vs. 4.80 ppm) was assigned to the *cis*-isomer.

The observed differences in chemical yields for *cis/trans*- isomers could be due to relative stabilities and reactivities of *syn*- vs. *anti*-ylides.[12] Based on literature precedent, the *trans*- isomer must be formed from the *anti*-ylide and the *cis*-isomer from the *syn*-ylide. The *syn*- and *anti*-ylides will probably equlibrate before they are trapped by dipolarophiles and it has been suggested that bulky R groups favor formation of the *syn*-ylides for steric reasons.[12] Our results are consistent with a steric argument since the proportion of *cis*-compound increases in the series Me->$PhCH_2$>Ph.

In conclusion, we report a convenient synthesis of N-unsubstituted fulleropyrrolidines using readily available amino acids as starting materials. Chiral, C_2 symmetric *trans*-1,3-disubstituted fulleropyrrolidines are suitable for resolution and might be of interest in asymmetric catalysis.

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