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Solvent-free Phase Transfer Catalysis under Microwaves in Fullerene Chemistry. A convenient preparation of N-alkylpyrrolidino[60]fullerenes.

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Abstract: *A facile synthesis of a series of N-alkylpyrrolidino[60]fullerenes by phase transfer catalysis without solvent under microwave irradiation is described.*

The potential utility of fullerene derivatives as a source for new materials or biologically active compounds has generated significant research focused on methods to link fragments to the fullerene core.[1] Nevertheless, only a few examples of side-chain reactions have been presented and these reactions proceed fairly slowly or fail.[2]

Preparation of pyrrolidino[60]fullerenes by addition of azomethine ylides to C_{60} is one of the most powerful methods for derivatising fullerenes.[3] N-Methylpyrrolidino[60]fullerenes have been extensively prepared[4] and their properties studied[5] but the examples with alkyl substituents other than methyl on the nitrogen atom are scarce due to the need to prepare the required N-substituted aminoacid.

The Prato[6] and Wilson[7] groups have described the preparation of N-unsubstituted pyrrolidino[60]fullerenes which can provide an entry into further functionalizated derivatives at the nitrogen atom. In spite of the great interest in the chemistry of these compounds, alkylation of NH-pyrrolidino[60]fullerenes has not been described probably because of the low reactivity of these compounds. Pyrrolidino[60]fullerenes are less basic than the correspondent pyrrolidine and react 500 times slower.[8]

Solvent-free PTC has been successfully applied to a wide range of organic reactions including alkylation of heterocyclic compounds.[9] Its utility, when combined with microwave irradiation, has been shown in anionic reactions that proceed slowly, in low yield or which requires harsh conditions.[10]

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In this paper, we describe the synthesis of a series of N-alkylpyrrolidino[60]fullerenes **2** by the combination of PTC without solvent and microwave irradiation techniques. To the best of our knowledge, this is the first example of the application of PTC without solvent for the preparation of fullerene derivatives.

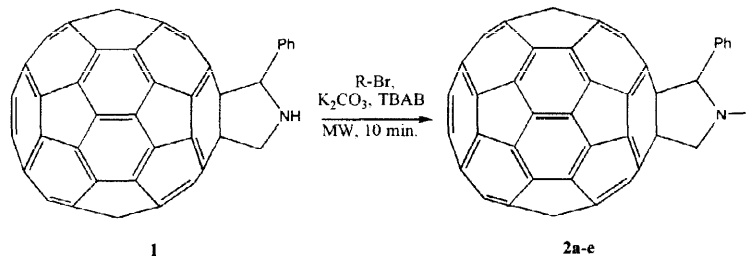
As starting materials we have chosen 2-phenylpyrrolidino[60]fullerene **1**[7,11] and the alkyl or benzyl bromides reported in Table 1.

Table 1. Preparation of **2a-e** by PTC without Solvent under Microwave Irradiation

Compound	R	Yield (%)[a]	1 (recovered)
2a	C_6H_5-CH_2-	70	15
2b	4-NO_2-C_6H_4-CH_2-	35	35
2c	4-MeO_2C-C_6H_4-CH_2-	27	37
2d	n-C_8H_{17}-	31	44
2e	H_2C=CH-CH_2-	39	32

[a] Isolated product. Yields are not optimised. Power : 780 W (Commercial oven)

Reactions were performed in a commercial microwave oven using a closed Teflon vessel. Typically, a mixture of **1** (40 mg, 0.047 mmol), the alkyl or benzyl bromide (10 eq.), potassium carbonate (22 mg, 0.019 mg) and TBAB (30 mg, 0.094 mmol) was irradiated at 780 W for 10 min. In all cases the final temperature was 80°C, but working at a smaller scale, absorption of the radiation is not efficient enough to heat the reaction mixture.[12]



1 2a-e

Scheme 1

The introduction of long aliphatic chains into fullerene derivatives has been used for the preparation of LB-films.[13] However, their introduction needs stronger conditions and the reaction proceeds slowly giving very low yields; [14] nevertheless, using PTC, no solvent, and microwave irradiation, octyl bromide shows the same extent of reaction as those alkyl halides which are more reactive under other conditions.[15] Such observation is consistent with a remark of Lewis[16] stating that *"slower reacting systems tend to show a greater effect under microwave irradiation than reacting systems"*.

In order to evaluate the synergy between dry media and microwave irradiation[17] in this reaction, several experiments were tried: If the preparation of **2e** is carried out in refluxing toluene as solvent, the yield is only 16% after 24 hours (17% of C_{60} is obtained and 9 % of **1** is recovered); moreover, if the reaction is done in dry media but under classical heating at a higher temperature (100 °C) instead of microwave irradiation, no reaction is detected by TLC after 10 min and after 3 h (18 times more than under microwaves) the yield is 31%, but only 18 % of **1** is recovered and 7 % of C_{60} and other non-identified products of decomposition are obtained.

The NMR spectra of compounds **2**[18] in $CDCl_3$ solution show typical signals of the 2-arylpyrrolidino[60]fullerene system, a singlet for H-2 and a AB system for CH_2-5 with a J_{AB} = 9.4-9.6 Hz. NOE experiments indicate that the more deshielded proton has a *cis* relationship with the phenyl group. Similarly the N-CH_2 group appears as two signals with a geminal coupling of 13.4-14.1 Hz. At 273 K the ^{1}H-NMR shows a broad signal for the *ortho*-H phenyl indicating that rotation of the phenyl ring is hindered by the proximity of the fullerene system and the substituent in N-1. At 333 K rotation of the phenyl group is accelerated showing a broad doublet for both *ortho*-H while at 223 K the process is frozen and two doublets for the *ortho*-H are shown. This effect is not observed in unsubstituted pyrrolidino[60]fullerenes.

Variable temperature NMR spectra permits the determination of the coalescence temperature and the activation free energy of the rotation of the 2-phenyl group (table 2).

Table 2. Activation Free Energies for rotation of the 2-phenyl group.

Compound	Coalescence temperature[a]	$\Delta G^{\ddagger}$ (kcal mol^{-1})[b]
2[a]	277	12.92
2c	273	12.76
2c	251[c]	12.39
2d	273	12.95
2e	263	12.34

[a] determined from *ortho*-H; [b] according to ref. 19; [c] determined from *meta*-H

We think that this methodology can be extended to other reactions of fullerene derivatives, particularly those which fail under classical conditions.

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18. Representative experimental data for compounds **2a-e: 2a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (bs, 2H), 7.69 (d, 2H, J= 6.8 Hz) 7.16-7.52 (m, 6H), 5.21 (s, 1H), 4.86 (d, 1H, J= 9.7 Hz), 4.59 (d, 1H, J= 13.4 Hz), 4.16 (d, 1H, J= 9.7 Hz), 3.67 (d, 1H, J= 13.4 Hz). Electrospray-MS: m/z 930 $(MH)^+$. **2b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, 2H, J= 8.4 Hz), 7.92 (d, 2H, J= 8.4 Hz), 7.88 (bs, 2H), 7.37-7.50 (m, 3H), 5.28 (s, 1H), 4.82 (d, 1H, J= 9.3 Hz), 4.65 (d, 1H, J= 14.3 Hz), 4.18 (d, 1H, J= 9.3 Hz), 3.78 (d, 1H, J= 14.3 Hz), Electrospray-MS: m/z 975 $(MH)^+$. **2c:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 2H, J= 8.3 Hz), 7.93 (bs, 2H), 7.78 (d, 2H, J= 8.3 Hz), 7.34-7.49 (m, 3H), 5.23 (s, 1H), 4.81 (d, 1H, J= 9.5 Hz), 4.62 (d, 1H, J= 13.8 Hz), 4.15 (d, 1H, J= 9.5 Hz),. 3.96 (s, 3H), 3.72 (d, 1H, J= 13.8 Hz), Electrospray-MS: m/z 988 $(MH)^+$. **2d:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (bs, 2H), 7.42 (d, J= 6.6, 7.8 Hz, 2H), 7.33 (t, J= 7.8 Hz, 1H), 5.10 (d, J= 9.3, 1H), 5.06 (s, 1H), 4.12 (d, J= 9.3, 1H), 3.22 (m, 1H), 2.78 (m, 1H), 1.67 1.7-1.3 (m, 12H); 0.92 (t, J= 7 Hz, 3H) Electrospray-MS: m/z 952 $(MH)^+$. **2e:** ^{1}H NMR (300 MHz, $CDCl_3$) δ. 7.82 (bs, 2H), 7.43 (t, J= 6.6, 8 Hz, 2H), 7.34 (tt, J= 6.7, 1.2 Hz, 1H); 6.29 (dddd, J= 17.1, 10.2, 7.7, 4.7 Hz, 1H), 5.56 (dq, J= 17.1, 1 Hz, 1H), 5.38 (dt, J= 10.2, 1 Hz, 1H), 5.14 (s, 1H); 5.06 (d, J = 9.6 Hz, 1H); 4.19 (d, J = 9.6 Hz, 1H); 4.0 (ddt, J = 13.4, 4.7, 1 Hz, 1H); 3.2 (dd, J = 13.4, 7.7 Hz, 1H). Electrospray-MS: m/z 880 $(MH)^+$. (Electrospray MS were carried out using a Micromass Ltd. Platform II single quadrapole mass spectrometer. For continuous infusion experiments, a syringe pump (Harvard Apparatus, Inc.) and a glass syringe were used to deliver analyte solutions to the ESI interface. Analyte solutions were pumped at a rate of 15-30 µl/min through a short length of µm i.d. Sample were prepared immediately before injection. 0.1 mg of analyte are dissolved in 1 ml of $HCCl_3$ 100 µl of this solution are added to 100 µl of the reacting solution (100 ml $CHCl_3$, 3 mg. DDQ, 0.2 ml. TFA) and 100 µl of CH_3OH have also to be added to improve the spray. This is sonicated for 30 sec. before injection. ES-MS parameters : Capillary voltage : 3,5 Kv. Sample cone voltage : 30, 70, 100, 130. Source Temp.: 100°C)
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