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Pyrimidine and Pyrimidone Derivatives of [60]Fullerene

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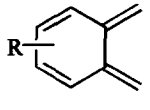
Abstract: Pyrimidine and pyrimidone derivatives of [60]fullerene have been obtained by thermolysis of pyrimidine and pyrimidone fused 3-sulfolenes in the presence of C_{60}. © 1997 Elsevier Science Ltd.

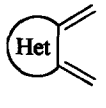
Cycloaddition reactions, specially Diels-Alder and 1,3-dipolar ones, have been the method of choice for the preparation of a wide range of new organic derivatives of C_{60}.[1]

Many studies with C_{60} involving Diels-Alder reactions use *o*-quinodimethanes **1** as dienes. These highly reactive species, which can be generated *in situ* from a large variety of precursors,[2,3] are efficiently trapped with C_{60}, which behaves as an electron defficient dienophile.

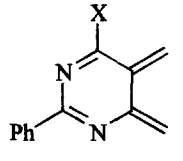
In contrast to the frequent use of *o*-quinodimethanes **1** for the derivatization of C_{60}, their heterocyclic analogues **2** have received scant attention, despite their versatility for the production of heterocyclic derivatives of C_{60}. To the best of our knowledge, the addition of thiophene, benzo[b]thiophene, furan and thiazole *o*-quinodimethane derivatives to C_{60} are the only reported examples in this area.[4] Now, we present our results on the addition of pyrimidine and pyrimidone *o*-quinodimethanes (**3** and **4**) to C_{60}.



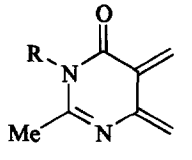
1



2



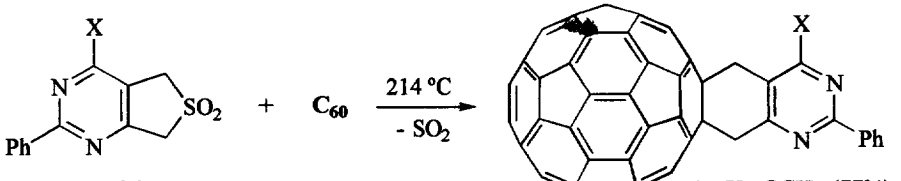
3a, X= OCH_3
3b, X= piperazinyl



4a, R= H
4b, R= CH_3

Recently, we have reported the synthesis of pyrimidine[5] and pyrimidone[6] fused 3-sulfolenes. We found that these compounds, when refluxed in 1,2,4-trichlorobenzene, extrude sulfur dioxide generating the corresponding *o*-quinodimethanes which can be trapped in Diels-Alder reactions with various dienophiles. We decided to extend that work to the synthesis of new fullerene derivatives having pyrimidine and pyrimidone moieties.

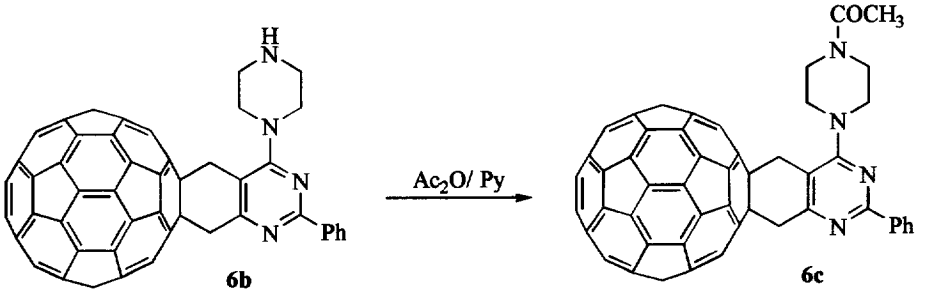
The thermolysis of pyrimidine **5a** in the presence of C_{60} was done in refluxing 1,2,4-trichlorobenzene (3 hours, nitrogen atmosphere).[7] The reaction mixture was purified by column chromatography (silica). The unreacted C_{60} and the trichlorobenzene were eluted with toluene and the adduct **6a** was then eluted with chloroform. After concentration, the adduct was precipitated by the addition of hexane, filtered, dryed and characterized by ^{1}H-, ^{13}C-NMR and MS (LSIMS).[8] As the adduct **6a** is quite soluble in CS_2, its characterization presented no problem. The adduct **6b** was obtained by refluxing a solution of the sulfone **5b**,[9] in refluxing 1,2,4-trichlorobenzene, in the presence of C_{60}. Because of its very low solubility, the adduct **6b** was not purified by column chromatography. It was precipitated from the reaction mixture by the addition of hexane, filtered and the solid was then purified by refluxing it in chloroform.



5a, X= OCH_3
5b, X= piperazinyl

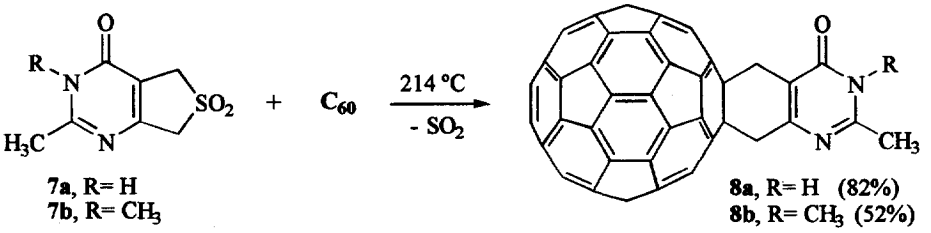
6a, X= OCH_3 (77%)
6b, X= piperazinyl (95%)

Contrary to compound **6a**, adduct **6b** is virtually insoluble in any solvent and for that reason we could not even obtain its ^{1}H-NMR. However, its mass spectrum (LSIMS) confirms the expected molecular weight (M+H= 988). To circumvent this solubility problem, adduct **6b** was transformed into its N-acetyl derivative **6c** by reaction with acetic anhydride. This compound, which is very soluble in chloroform, was characterized by ^{1}H-, ^{13}C-NMR and MS (LSIMS) confirming the proposed structure of **6b**.[10]



6b **6c**

Thermolysis of pyrimidones **7a** and **7b** in the presence of C_{60}, under similar conditions to those used for the preparation of adducts **6a** and **6b**, yielded the corresponding adducts **8a** and **8b** in moderate to good yields.[12]



7a, R= H
7b, R= CH_3

8a, R= H (82%)
8b, R= CH_3 (52%)

Adduct **8a** was characterized only by its MS (LSIMS, M+H= 857) and IR spectra because of its very low solubility. However, adduct **8b** was fully characterized by NMR, MS and IR.[13] All the spectra are consistent with the proposed structure.

Recent studies on the biochemical and medicinal properties of some fullerene derivatives revealed important biological activities, both *in vitro* and *in vivo*.[14] The inhibition of HIV-protease and the site-specific cleavage of DNA are two of the most important applications of these compounds. The possibility of interaction of the pyrimidine and pyrimidone moieties of compounds **6** and **8** (or other analogues) with the pyrimidine and/or purine bases of DNA and RNA makes these adducts potential bioactive compounds. The synthesis of water soluble adducts of this type is in progress in our laboratories.

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7. Typical procedure: C_{60} (72 mg; 0.1 mmol) and pyrimidine **5a** (28 mg; 0.1 mmol) were heated in refluxing 1,2,4-trichlorobenzene (5ml), under nitrogen atmosphere, for 3 hours. After cooling to room temperature, the mixture was applied to the top of a column of silica; the trichlorobenzene and the unreacted C_{60} were eluted with toluene and the adduct was then eluted with chloroform.
8. All adducts (**6a, 6b, 8a, 8b**) have melting points higher than 320 °C. Adduct **6a**: **^{1}H-NMR** (300 MHz, CS_2/DMSO-d_6), δ= 4.23 (s, 3H, OCH_3), 4.66 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 7.38-7.44 (m, 3H, ArH), 8.53-8.53 (m, 2H, ArH); **^{13}C-NMR** (75 MHz, CS_2/DMSO), δ= 36.1, 45.8, 53.4, 64.6, 64.7, 114.2, 128.0, 128.1, 190.3, 135.1, 135.2, 137.0, 139.7, 141.17, 141.21, 141.6, 141.7, 142.1, 142.6, 144.16, 144.19, 144.8, 144.9, 145.0, 145.1, 145.3, 145.7, 146.0, 147.1, 155.8, 162.2, 165.3, 166.5; **MS** (LSIMS; NBA) [M + H] = 933, [C_{60}] = 720
9. Sulfone **5b** was obtained by the procedure described in ref. 5. **M.p.**= 225-226 °C; **^{1}H-NMR** (300 MHz, $CDCl_3$), δ= 3.0 (t, 4H), 3.67 (t, 4H), 4.36 (s, 2H), 4.38 (s, 2H), 7.45-7.48 (m, 3H), 8.32-8.35 (m, 2H); **^{13}C-NMR** (75 MHz, $CDCl_3$), δ= 46.0, 47.6, 56.6, 57.0, 106.2, 128.1, 128.4, 130.9, 137.2, 160.0, 160.3, 163.5; **MS** (EI^+) m/z (rel.int.) 330 (M+, 4%), 262 (60), 224 (13), 211 (27), 210 (30), 198 (36), 181 (18), 104 (100), 85 (19), 77 (35), 69 (29)
10. The ^{13}C-NMR spectrum of compound **6c** shows nine signals corresponding to nine sp^3 carbons. This means that the four carbon atoms of the piperazinyl group are not magnetically equivalent. This effect (not observed in sulfone **5b** lacking the acetyl group)[9] is probably due to the restricted rotation of the acetyl group about the C-N bond (a phenomenon common to N,N'-disubstituted amides) (ref. 11).
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12. In the reaction of C_{60} with **7b** the adduct **8b** was accompaigned by a minor fraction corresponding to 2:1 adducts (two pyrimidone *o*-quinodimethanes added to one fullerene molecule), as indicated by its mass spectrum.
13. Adduct **8b**: **^{1}H-NMR** (300 MHz, CS_2/$CDCl_3$), d= 2.72 (s, 3H), 3.72 (s, 3H), 4.47 (s, 2H), 4.51 (s, 2H); **^{13}C-NMR** (75 MHz, CS_2/$CDCl_3$), δ= 23.4, 31.3, 36.8, 45.9, 64.88, 64.91, 119.0, 135.1, 135.4, 139.9, 140.0, 141.40, 141.44, 141.8, 141.9, 142.3, 142.9, 144.3, 144.5, 144.8, 145.1, 145.2, 145.3, 145.5, 146.0, 146.2, 146.3, 147.3, 147.4, 155.6, 155.8, 158.4, 160.0, 160.7; **MS** (LSIMS; NBA) [M + H] = 871, [C_{60}] = 720; **IR** ν_{max} (KBr) 2360, 2341, 1666, 1540, 1428, 669, 526
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