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Synthesis of novel [60]fullerene–flavonoid dyads

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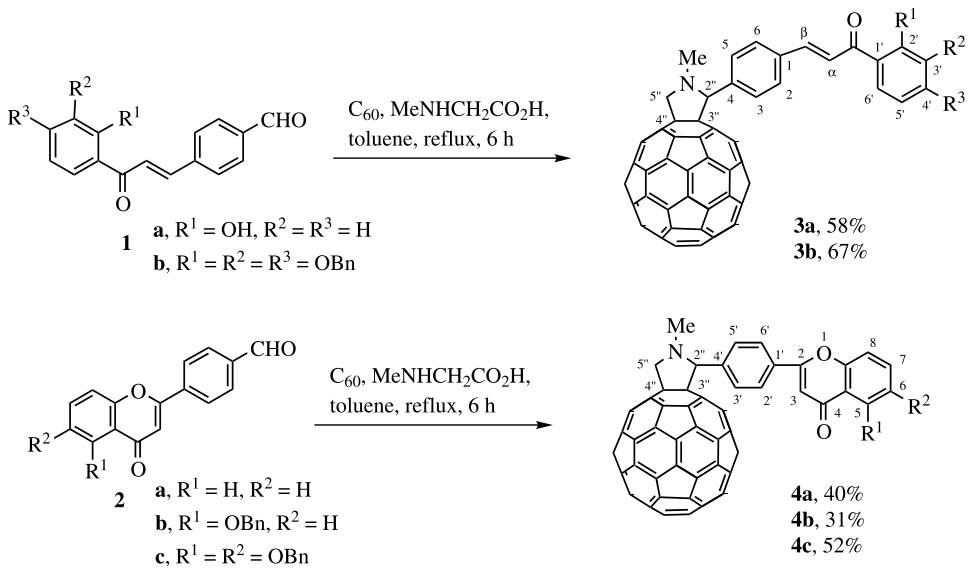
Abstract—[60]Fullerene–chalcone and [60]fullerene–flavone dyads were obtained by 1,3-dipolar cycloaddition reactions of azomethine ylides with C_{60}.

The potential applications of fullerene derivatives makes the study of the chemical, physical and biological properties of these compounds an important subject.[1–5] One of the most promising areas of application of fullerenes is the medicinal chemistry, namely as free radical scavengers[6,7] for the treatment of neurodegenerative diseases, as inhibitors of the HIV-1 protease[8–10] or in the photodynamic therapy of neoplastic tissues.[11–13] Flavonoids are an especially well-studied class of phytochemicals widely distributed in higher plants; many of them, particularly flavones, flavonols and chalcones, are conspicuous components of flowers, fruits and other parts of plants.[14] These compounds contribute to the quality, colour, and taste of many foods (vegetables, fruits) and drinks (tea, wine).[15,16] Many diverse functions have been attributed to them: aside from acting as antioxidants[17] and anticarcinogens,[18,19] they express beneficial effects in inflammatory and immunomodulatory systems.[15,16]

In this communication we present the synthesis of fullerene–chalcone and fullerene–flavone dyads, which may have interesting physical and biological properties. Since the antioxidant activity of flavonoids is highly influenced by the presence of oxygenated groups on the aromatic system,[17] we decided to prepare several com-



Scheme 1.

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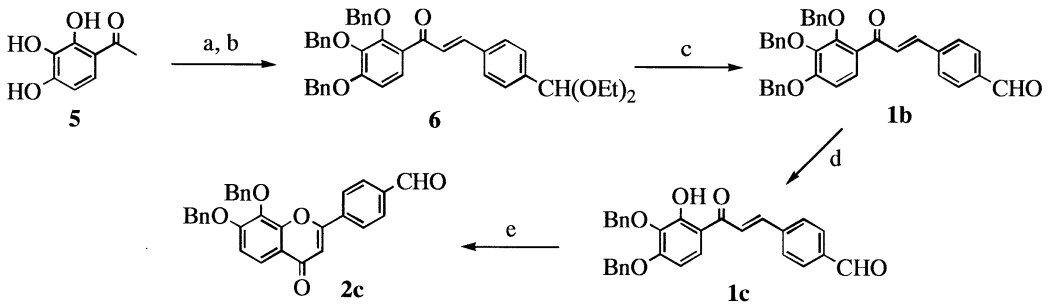

Entry	Conditions	Yield %
a	BnCl (5 equiv.), K_2CO_3 (4 equiv.), DMF, 150 °C, 3 h.	90
b	NaOH (6 equiv.), terephthalaldehyde mono(diethyl acetal) (1.6 equiv.), MeOH, 60 °C, 2 h.	87
c	HCl (10 %) (3 mL/g), r.t., 3 h.	88
d	$MeCO_2H$/HCl (10:1) (80 mL/g), 40 °C, 1 h.	86
e	I_2 (0.07 equiv.), DMSO, reflux, 20 min.	61

Scheme 2.

pounds differing in the number of oxygenated substituents. Knowing that both moieties can act as radical scavengers, we may expect that these fullerene–flavonoid dyads may behave as 'radical sponges' and, eventually, may be useful as drugs in medicine.

The novel [60]fullerene–flavonoid dyads **3** and **4** were synthesized from formylchalcones **1** and formylflavones **2** via 1,3-dipolar cycloaddition reactions of the corresponding azomethine ylides (generated in situ from the reaction of the formyl group with *N*-methylglycine and then decarboxylation) to [60]fullerene (Scheme 1). All cycloaddition reactions were carried out in refluxing toluene, under nitrogen atmosphere, using an excess of C_{60} (1.4 equiv.) and *N*-methylglycine (5 equiv.). The reaction mixtures were separated by flash chromatography using gradients of toluene:ethyl acetate as eluent. The first fraction was the unchanged C_{60} and the next one was the mono-adduct **3** or **4**. Products with higher polarity, probably bis-adducts, were discharged. The isolated yields are in the range of 31–67%. All adducts **3** and **4** are stable compounds.

The adducts **3** and **4** were characterized by ^{1}H and ^{13}C NMR and MS.[20,21] In the ^{1}H NMR spectra of these compounds the resonance of the *N*-methyl group appears typically at δ 2.82–2.84 ppm and the proton 2″ appears as a singlet at ca. 5.0 ppm. The two non-equivalent protons 5″ appear as two doublets: one centered at ca. 4.3 and the other at ca. 5.0 ppm. The geminal coupling constant for these protons is in the range of 9.4 to 9.5 Hz. The resonances of the protons in the chalcone and flavone moieties in the starting compounds and in the adducts are very similar. It is interesting to note that, in both compounds **3** and **4**, the signals corresponding to the protons of the phenyl group directly attached to the pyrrolidine ring are broadened. This indicates restricted rotation of the phenyl substituent on the pyrrolidine ring, as previously described for similar systems.[22,23] In the ^{13}C NMR spectra of adducts **3** and **4** the signals corresponding to C-5″ and C-2″ appear at ca. 70.0 and 83.0 ppm, respectively, while the signals corresponding to C-4″ and C-3″ (C_{60} sp^3 carbons) appear at ca. 76.5 and 68.8 ppm.

The starting compounds **1a**, **2a** and **2b** were prepared according to the literature procedures.[24] The chalcone **1b** and the flavone **2c** were prepared as indicated in Scheme 2. All products of this sequence were characterized by ^{1}H and ^{13}C NMR and MS.

The study of the photophysical properties and the biological activities of some of these new [60]fullerene–flavonoid derivatives and the synthesis of other fullerene–flavonoid dyads, starting with natural flavonoids, are currently under investigation.

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References

1. Hirsh, A. *The Chemistry of the Fullerenes*; Thieme: New York, 1994.
2. Martín, N.; Sánchez, L.; Illescas, B.; Pérez, I. *Chem. Rev.* **1998**, *98*, 2527–2547.
3. Diederich, F.; Gómez-López, M. *Chem. Soc. Rev.* **1999**, *28*, 263–277.
4. Prato, M. *Top. Curr. Chem.* **1999**, *199*, 173–187.
5. Guldi, D. M. *Chem. Commun.* **2000**, 321–327.
6. Dugan, L. L.; Turetsky, D. M.; Du, C.; Lobner, D.; Wheeler, M.; Almli, C. R.; Shen, C. K.-F.; Luh, T.-Y.; Choi, D. W.; Lin, T. S. *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 9434–9439.

7. Bensasson, R. V.; Brettreich, M.; Frederiksen, J.; Göttinger, H.; Hirsch, A.; Land, E. J.; Leach, S.; McGarvey, D. J.; Schönberger, H. *Free Rad. Biol. Med.* **2000**, *29*, 26–33.
8. Friedman, S. H.; DeCamp, D. L.; Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6506–6509.
9. Sijbesma, R.; Srdanov, G.; Wudl, F.; Castoro, J. A.; Wilkins, C.; Friedman, S. H.; DeCamp, D. L.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6510–6512.
10. Marcorin, G. L.; Da Ros, T.; Castellano, S.; Stefancich, G.; Bonin, I.; Miertus, S.; Prato, M. *Org. Lett.* **2000**, *2*, 3955–3958.
11. Da Ros, T.; Prato, M. *Chem. Commun.* **1999**, 663–669.
12. Jensen, W.; Wilson, S. R.; Schuster, D. I. *Bioorg. Med. Chem.* **1996**, *4*, 767–779.
13. Tabata, Y.; Ikada, Y. *Pure Appl. Chem.* **1999**, *71*, 2047–2053.
14. *The Flavonoids—Advances in Research Since 1986*, Haborne, J. B., Ed.; Chapman and Hall: London, 1996.
15. Bors, W.; Heller, W.; Michel, C.; Stettmaier, K. Flavonoids and Polyphenols: Chemistry and Biology, In *Handbook of Antioxidants*; Cadenas, E.; Packer, L., Eds.; Marcel Dekker: New York, 1996; p. 409.
16. *Flavonoids in Health and Diseases*; Rice-Evans, C. A.; Packer, L., Eds.; Marcel Dekker: New York, 1998.
17. Rice-Evans, C. A.; Miller, N. J.; Paganga, G. *Free Rad. Biol. Med.* **1996**, *20*, 933–956.
18. Beudot, C.; De Méo, M. P.; Dauzone, D.; Elias, R.; Laget, M.; Guiraud, M.; Balausard, G.; Dúmenil, G. *Mutat. Res.* **1998**, *417*, 141–153.
19. Akama, T.; Ishida, H.; Shida, Y.; Kimura, U.; Gomi, K.; Saito, H.; Fuse, E.; Kobayashi, S.; Yoda, N.; Kasai, M. *J. Med. Chem.* **1997**, *40*, 1894–1900.
20. Selected data for compound **3a**: ^{1}H NMR [300.13 MHz, $CDCl_3/CS_2$) δ (ppm), *J* (Hz)]: 12.74 (s, 1H, 2′-O*H*), 7.92 (d, *J* 15.5, 1H, H-β), 7.90 (m, 3H, H-3′, H-2, H-6), 7.74 (d, *J* 8.4, 2H, H-3, H-5), 7.67 (d, *J* 15.5, 1H, H-α), 7.45 (ddd, *J* 7.8, 7.6 and 1.2, 1H, H-4′), 6.99 (dd, *J* 8.5 and 1.2, 1H, H-6′), 6.92 (ddd, *J* 8.5, 7.6 and 1.1, 1H, H-5′), 5.00 (s, 1H, H-2″), 5.02 (d, *J* 9.3, 1H, H-5″), 4.31 (d, *J* 9.3, 1H, H-5″), 2.86 (s, 3H, N-C*H*$_3$); ^{13}C NMR (75.47 MHz, $CDCl_3/CS_2$) δ: 192.4 (*C*O), 163.5 (C-2′), 152.7, 152.5, 147.1, 146.3, 146.2, 146.0, 145.9, 145.8, 145.7, 145.2, 145.1, 145.0, 144.5 (C-β), 144.4, 144.2, 142.9, 142.5, 142.4, 142.0, 141.9, 141.8, 141.7, 141.6, 141.5, 141.4, 140.1 (C-4), 140.0, 139.4, 136.8, 136.3, 136.2, 135.8, 135.5, 134.7 (C-α), 129.8, 129.4 (C-4′), 128.9, 120.2, 119.8 (C-6′), 119.7, 118.6 (C-5′), 83.0 (C-2″), 76.9 (C-4″), 69.9 (C-5″), 68.8 (C-3″), 39.9 (N-*C*H$_3$). HRMS (FAB) *m*/*z* calculated for $C_{78}H_{18}NO_2$ $(M+H)^+$ 1000.1338, found 1000.1373.
21. Selected data for compound **4a**: ^{1}H NMR [300.13 MHz, $CDCl_3/CS_2$) δ (ppm), *J* (Hz)]: 8.80 (dd, *J* 7.8 and 1.5, 1H, H-5), 8.02 (m, 4H, H-2′, H-3′, H-5′, H-6′), 7.79 (ddd, *J* 8.0, 7.6 and 1.5, 1H, H-7), 7.57 (dd, *J* 8.0 and 0.9, 1H, H-8), 7.45 (ddd, *J* 7.8, 7.6, 0.9, 1H, H-6), 6.83 (s, 1H, H-3), 5.05 (s, 1H, H-2″), 5.04 (d, *J* 9.4, 1H, H-5″), 4.28 (d, *J* 9.4, 1H, H-5″), 2.86 (s, 3H, N-C*H*$_3$); ^{13}C NMR (75.47 MHz, $CDCl_3/CS_2$) δ: 192.2 (C-4), 177.5 (C-2), 155.7 (C-9), 153.5 (C-7), 152.6, 152.3, 147.1, 146.1, 145.8, 145.6, 145.5, 145.4, 145.3, 145.1, 144.6, 144.2, 143.0, 142.9, 142.5, 142.4, 142.1, 142.0, 141.9, 141.8, 141.7, 141.5, 141.4, 140.9 (C-4′), 140.1, 139.8, 139.4, 136.8, 136.2, 135.8, 135.5, 133.5, 131.7 (C-1′), 129.7 (C-3′, C-5′), 126.5 (C-2′, C-6′), 125.7, 125.1 (C-6), 123.8 (C-10), 117.8 (C-8), 107.6 (C-3), 82.9 (C-2″), 76.6 (C-4″), 69.9 (C-5″), 68.8 (C-3″), 39.9 (N-*C*H$_3$). HRMS (FAB) *m*/*z* calculated for $C_{78}H_{16}NO_2$ $(M+H)^+$ 998.1181, found 998.1194.
22. Eckert, J.-F.; Nicoud, J.-F.; Nierengarten, J.-F.; Liu, S.-G.; Echegoyen, L.; Barigelletti, F.; Armaroli, N.; Ouali, L.; Krasnikov, V.; Hadziioannou, G. *J. Am. Chem. Soc.* **2000**, *122*, 7467–7479.
23. De la Cruz, P.; De la Hoz, A.; Font, L. M.; Langa, F.; Pérez-Rodríguez, M. C. *Tetrahedron Lett.* **1998**, *39*, 6053–6056.
24. Patonay, T.; Cavaleiro, J. A. S.; Lévai, A.; Silva, A. M. S. *Heterocycl. Commun.* **1997**, *3*, 223–229.