Novel multicomponent reaction of [60]fullerene: the first example of 1,4-dipolar cycloaddition reaction in fullerene chemistry†

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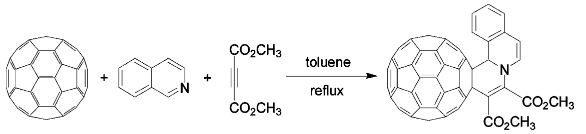
Received 1st September 2006, Accepted 28th September 2006
First published as an Advance Article on the web 9th October 2006
DOI: 10.1039/b612641c

The novel multicomponent reaction of [60]fullerene with dimethyl acetylenedicarboxylate and isoquinoline, quinoline or substituted quinolines was investigated. This type of reaction presents the first example of a 1,4-dipolar cycloaddition reaction in fullerene chemistry.

There has been a steady and progressive interest in chemical modifications of [60]fullerene (C_{60}) since its macroscopic availability in 1990. An impressive number of fullerene derivatives have been synthesized *via* various functionalization methods,[1] and some of them have potential applications in biology and material sciences.[2] Cycloaddition reactions are among the pioneering reactions studied in fullerene chemistry and show considerable promise for functionalization of the fullerene sphere. Generally, there are four major types of cycloaddition reactions concerning fullerenes, that is, the [2 + 1], [2 + 2], [2 + 3] and [2 + 4] cycloaddition reactions.[1] Among these successful functionalization methodologies explored over the years, the reported [2 + 4] cycloaddition reactions are mainly limited to the Diels–Alder reaction of C_{60}.[1] Carbon–carbon and carbon–nitrogen bond-forming reactions mediated by zwitterions generated by the addition of organic nucleophiles such as phosphines, isocyanides, nucleophilic carbenes, pyridines and tertiary amines to activated unsaturated systems such as electron-deficient alkynes, allenes and diethyl azodicarboxylate have been investigated intensively.[3] Nair *et al.* reported that the Huisgen 1,4-dipole derived from isoquinoline and dimethyl acetylenedicarboxylate (DMAD) could readily react with *N*-tosylimines, 1,2- and 1,4-benzoquinones and activated styrenes.[4] In the continuation of our interest in fullerene chemistry,[5] and recognizing the convenience and efficiency of this Nair methodology, we decided to examine the feasibility of this 1,4-dipole and other 1,4-dipoles formed from quinolines and DMAD to the cycloaddition reaction with C_{60} as the dipolarophile. Our investigation attested the validity of this approach, and the result is presented in this paper. Even though the reaction of C_{60} with various 1,3-dipoles such as azomethine ylides, diazo compounds, azides, nitrile oxides, nitrile ylides, nitrile imines, pyrazolinium ylides has been reported,[1] to the best of our knowledge, this is the first example of 1,4-dipolar cycloaddition reaction in fullerene chemistry.

To begin our study, we examined the reaction of C_{60} with isoquinoline (**1a**) and DMAD (**2**) in refluxing toluene for 1.5 h. An exceedingly facile reaction occurred and gave a novel C_{60}-fused isoquinoline derivative **3a** in 62% yield along with 21% of recovered C_{60} (Scheme 1).[6] Another possible product resulted from the different orientation of the isoquinoline appended unit (fusion at the nitrogen atom and C3 atom) was not observed.



1a **2** **3a**

Scheme 1

The identification of compound **3a** was made by its MS, ^{1}H NMR, ^{13}C NMR, IR and UV-vis spectra. The ESI mass spectrum of **3a** showed the ion peak at *m*/*z* 992 (M^+ + 1) as the base peak. The ^{1}H NMR spectrum of **3a** in $CDCl_3$ displayed two singlets at 3.91 ppm and 4.04 ppm for the two OCH_3 groups, and a singlet at 6.31 ppm for the methine proton besides the six aromatic protons. In the ^{13}C NMR spectrum of **3a** in $CDCl_3$, the four peaks at 167.25, 162.61, 53.16 and 52.69 ppm were assigned to the two methoxycarbonyl groups; the peak at 69.42 ppm was due to the methine carbon; the two sp^3-carbons of the C_{60} cage appeared at 79.85 and 66.21 ppm; sixty peaks including six overlapped ones were observed in the range of 155–105 ppm, and were assigned to the fifty-eight sp^2-carbons of the C_{60} skeleton, eight aromatic carbons and two alkenic carbons, consistent with the C_1 symmetry of its molecular structure. The IR spectrum of **3a** exhibited absorptions at 1732 cm^{-1} due to the carbonyl group, and at 1433, 1190, 575 and 527 cm^{-1} for the four characteristic peaks of the C_{60} skeleton. The UV-vis spectrum of **3a** exhibited peaks at 256, 312, 432 and 704 nm, which are diagnostic absorptions for a cycloadduct of C_{60} at the 6:6-junction.

We surmised that Huisgen 1,4-dipoles generated from DMAD and quinoline or substituted quinolines might be applied to fullerene functionalizations. To our delight, the reaction of C_{60} with quinoline (**1b**) (or 6-methoxyquinoline (**1c**), 6-methylquinoline (**1d**), 4-methylquinoline (**1e**)) and DMAD in refluxing toluene afforded C_{60}-fused quinoline derivatives **3b**–**3e** (Scheme 2).[6] Compounds **3b–e** were also fully characterized by MS, ^{1}H NMR, ^{13}C NMR, IR and UV-vis spectral data, and exhibited spectral patterns similar to those of adduct **3a**.

The reaction times, yields and recovered C_{60} for the reaction of C_{60} with **1b–e** and DMAD along with those for **1a** are listed in Table 1.

Other reaction conditions were also examined. The dryness of toluene had little effect on the reaction of C_{60} with **1a**–**1e** at 110 °C and gave almost the same result. The reaction in toluene at room

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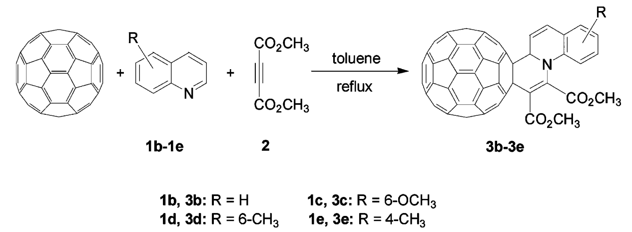
† Electronic supplementary information (ESI) available: Spectral data of products **3a**–**3e**, and spectra of representative **3a** and **3b**. See DOI: 10.1039/b612641c



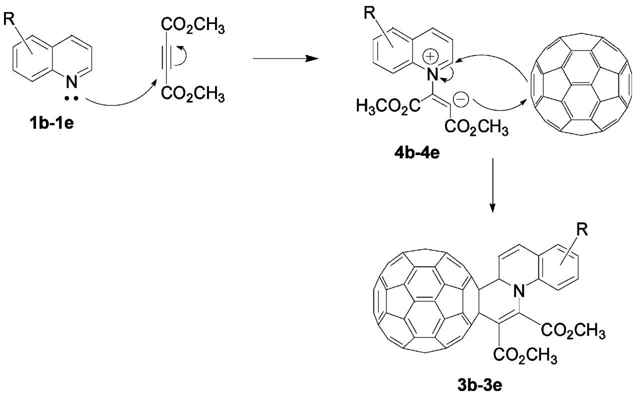
Scheme 2

Table 1 Reaction times, yields and recovered C_{60} for the reactions of C_{60} with DMAD and **1a–e**

Product	Reaction time/h	Yield (%)	Recovered C_{60} (%)
3a	1.5	62	21
3b	5	31	57
3c	5	30	59
3d	5	33	53
3e	3	40	41

temperature could proceed, but it was too sluggish. The reaction in other solvents such as chlorobenzene and 1,2-dichlorobenzene at 110 °C afforded nearly the same product yield as that in refluxing toluene. However, it was more difficult to remove these solvents due to higher boiling points.

The possible mechanism for the reaction of C_{60} with DMAD and quinolines is shown in Scheme 3. Quinolines **1b–1e** react with DMAD to form 1,4-dipolar intermediates **4b–4e**. Cyclizations of 1,4-dipoles **4b–4e** with C_{60} in either stepwise or concerted way give fullerene derivatives **3b–3e**. The reaction pathway for the reaction of C_{60} with DMAD and isoquinoline (**1a**) proceeds by a similar route.[4]



Scheme 3

In summary, the first example of 1,4-dipolar cycloaddition reaction of C_{60} was established through the reaction of C_{60} with DMAD and isoquinoline or quinolines. The current multicomponent reaction provides a simple and straightforward method of integrating the biologically important quinoline and isoquinoline moiety into fullerene derivatives.

We are grateful for the financial support from the National Natural Science Foundation of China (Nos. 20572105, 20321101, and 20125205) and Anhui Provincial Bureau of Personnel Affairs (2001Z019), and Mr Xin Cheng for helpful discussion.

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6 Typical procedure for the preparation of **3a–3e**: A mixture of C_{60} (36.0 mg, 0.05 mmol), DMAD (0.40 mmol) and **1a–1e** (0.40 mmol) was dissolved in toluene (30 mL) and heated at reflux under nitrogen atmosphere. The reaction was monitored by TLC, and stopped at the desired time. The reaction mixture was concentrated to about 5 mL *in vacuo*, and the residue was chromatographed on a silica gel column with carbon disulfide–ethyl acetate as the eluent to afford unreacted C_{60} and fullerene derivatives **3a–3e**.