Cycloaddition of nitrile oxides to [60]fullerene

Tatiana Da Ros,[a] Maurizio Prato,*†[a] Fabiola Novello,[b] Michele Maggini,[b] Marco De Amici[c] and Carlo De Micheli[c]

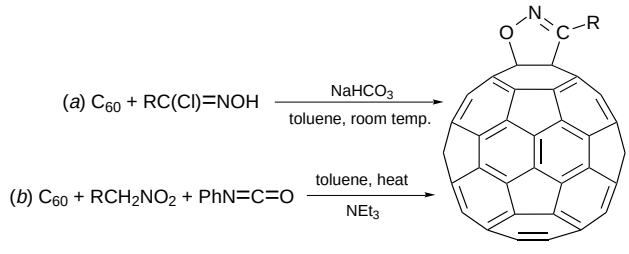
[a] *Dipartimento di Scienze Farmaceutiche, Università di Trieste, Piazzale Europa 1, 34127 Trieste, Italy*
[b] *Centro Meccanismi di Reazioni Organiche del CNR, Dipartimento di Chimica Organica, Università di Padova, Via Marzolo 1, 35131 Padova, Italy*
[c] *Istituto Chimico-Farmaceutico, Università di Milano, Viale Abruzzi 42, 20131 Milano, Italy*

The addition of nitrile oxides to [60]fullerene is examined and it is found that the reaction products regenerate [60]fullerene under relatively mild conditions; the result is potentially useful for better control of fullerene functionalization.

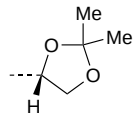
The use of fullerenes as frameworks for molecular assemblies is becoming increasingly popular.[1,2] The regiochemistry of multiple additions has been the subject of thorough investigations[3,4] and methodologies for the octahedral[4,5] or tetrahedral[6] functionalization of [60]fullerene have been successfully developed. However, complete control over the addition chemistry of fullerenes has yet to be reached, especially as new discoveries continue to emerge.[7,8] In connection with this, the reversibility of some reactions has been shown to be useful to reach challenging new targets.[6,9] Here we report that the products of the cycloaddition of nitrile oxides to [60]fullerene can regenerate quantitatively [60]fullerene under specific conditions and that this fact may be used to better control fullerene chemistry.

According to previous reports,[10,11] nitrile oxides, generated under different conditions, add readily to [60]fullerene giving rise to fullerene-fused isoxazolines (Scheme 1).‡

The most common way to generate nitrile oxides is the dehydrochlorination of hydroximoyl chlorides, which, in turn, can be prepared from the corresponding aldehydes (path *a*, Scheme 1, compounds **1a**–**e**, **h**, **i**). Alternatively, nitrile oxides can be efficiently prepared by dehydration of primary nitroalkanes (path *b*, Scheme 1, compounds **1f**, **g**). We have prepared, *via* path *a*, an optically active fullerene derivative, starting from the corresponding homochiral hydroximoyl chloride, readily available from d-mannitol[12] (**1i**, Scheme 1).



1

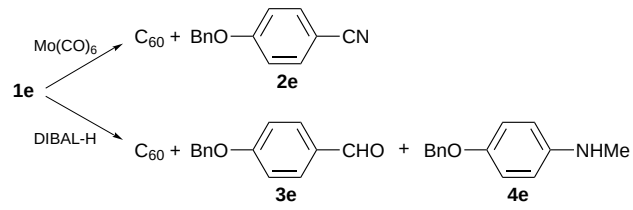
a R = $CH_2OCH_2CH_2OCH_2CH_2OMe$
b R = 9-anthryl
c R = COPh
d R = CO_2Et
e R = C_6H_4-4-OBn
f R = $CH_2CO_2Bu^t$
g R = $CH_2CH_2CO_2Me$
h R = $CH_2CH_2CH_2CH_2N(Boc)CH_2CO_2Bu^t$
i R = 

Scheme 1

Fullerene-fused isoxazolines (isoxazolinylfullerenes) are relatively stable and revert back to [60]fullerene only at very high temperatures (280–400 °C).[10] Compounds **1** are also stable to acids. Addition of 10 equiv. of trifluoroacetic acid to a solution of **1d** in chlorobenzene under reflux gave only traces of [60]fullerene after 10 d. Addition of *N*-phenylmaleimide as a retrocycloaddition trapping agent did not result in the formation of the corresponding adduct, even in chlorobenzene under reflux.

Conventional isoxazolines are versatile synthons in many transformations, as they are reduced under a variety of conditions to a range of functional groups (*e.g.* amino alcohols, amino carbonyls, nitrile alcohols, *etc.*).[13] On the contrary, isoxazolinylfullerenes appear to be resistant to further functionalization.[10] This could be due to two reasons. First of all, functionalities spatially close to the fullerene sphere have been found to be less reactive than usual.[14] Furthermore, if the N–O bond opens up, a hydroxy functionality directly attached to [60]fullerene would be generated. A single hydroxy group on a fullerene is presumed to be unstable, and is expected to eliminate.[7] Thus, it is not surprising that, when isoxazolines **1a**–**i** were treated with $Mo(CO)_6$ under conditions that usually favour N–O bond cleavage (anhydrous chlorobenzene under reflux for 24 h),[15] [60]fullerene was recovered quantitatively. The addition of protic solvents (either water or methanol, 0.025 m) accelerates the reaction.[15] Under these conditions, the reaction completed in 2 h. The reaction of **1e** with $Mo(CO)_6$ was investigated as a representative example (Scheme 2). Nitrile **2e** (identified by comparison to an authentic sample) was recovered quantitatively along with [60]fullerene. This result can be tentatively explained by initial N–O bond cleavage followed by expulsion of the fragments from [60]fullerene. More extended work will be necessary to clarify the detailed mechanism.

A similar result was obtained with the treatment of **1** with DIBAL-H (diisobutyl aluminium hydride, 10 equiv.) at room temperature in toluene. In this case, the reaction of **1e**, besides the quantitative production of [60]fullerene, yielded aldehyde **3e** and amine **4e** (identified by comparison with authentic samples) in 31 and 64% isolated yields respectively. Whereas aldehyde **3e** was probably formed by DIBAL-H reduction of

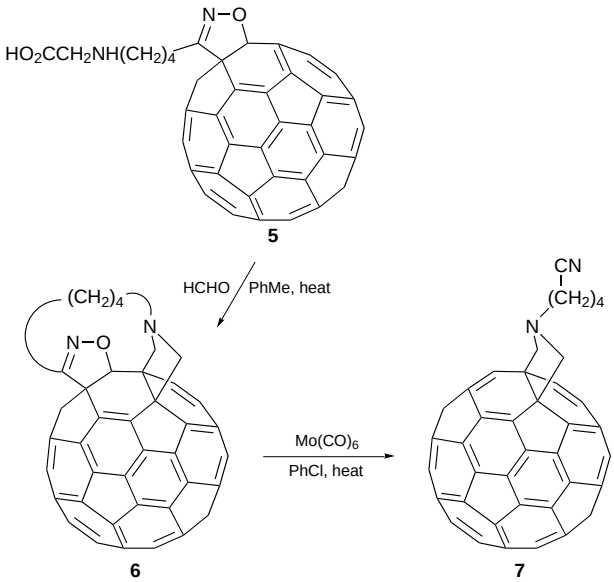


Scheme 2

nitrile **2e**, amine **4e** could have been formed from the rearrangement of nitrile oxide to the corresponding isocyanate[16] which was then reduced to **4e**. In any case, all attempts to trap the transient nitrile oxide under reductive conditions failed.

In light of the results reported here, several applications of the addition of nitrile oxides to fullerenes can be envisioned. The solubility of [60]fullerene, which is a real problem in a number of instances, can be improved by the temporary addition of a solubilizing appendage (see, for example, **1a**, Scheme 1). The examples reported here may be considered an attractive alternative to known methodologies.[17] In fact, the trioxanonane chain in **1a** can be easily attached *via* the corresponding nitrile oxide cycloaddition and then easily removed, in one single step, under two very different conditions, either of which are compatible with the reactivity of [60]fullerene and also with that of most functional groups. Furthermore, the use of a chiral chain (**1i**) can be used to chemically resolve racemic mixtures of chiral fullerenes or fullerene derivatives.[18]

As an example of the potential of the described methodology, isoxazoline **1h** was treted with trifluoroacetic acid to afford the corresponding glycine derivative **5** (as a trifluoroacetate salt) in quantitative yield (Scheme 3). When **5** was heated to reflux in toluene in the presence of 10 equiv. formaldehyde,[19] a single product was isolated by chromatography in 67% yield. Structure **6** is tentatively assigned to this product, based on analytical and spectroscopic data, with the help of AM1 optimization.§ Once treated with $Mo(CO)_6$, **6** led to **7** as the only isolated product. The structure of **7** was confirmed by the reaction of *N*-(4-cyanobutyl)glycine and formaldehyde with [60]fullerene.[19] Scheme 3 shows a specific site-directed functionalization of [60]fullerene using a temporary anchor point.



Scheme 3

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Footnotes

† E-mail: prato@univ.trieste.it

‡ All new compounds exhibited satisfactory analytical and spectroscopic data.

§ Compound **6** is highly favoured over other possible positional isomers (MACSPARTAN program running on a Power Macintosh 9500).

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