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Isonitriles as Source and Fate of Imidoyl Radicals: a Novel Homolytic α-Fragmentation.

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Abstract: Imidoyl radicals **4a-c** react with phenylacetylene to give annulation products and nitrile **12**, arising from β-scission of the intermediate iminyl radical that is involved in the rearrangement of azaspirocyclohexadienyl **8**. In contrast, imidoyls **4d** and **15** do not react with the alkyne and give good yields of the corresponding isonitriles through a novel example of homolytic α-fragmentation.
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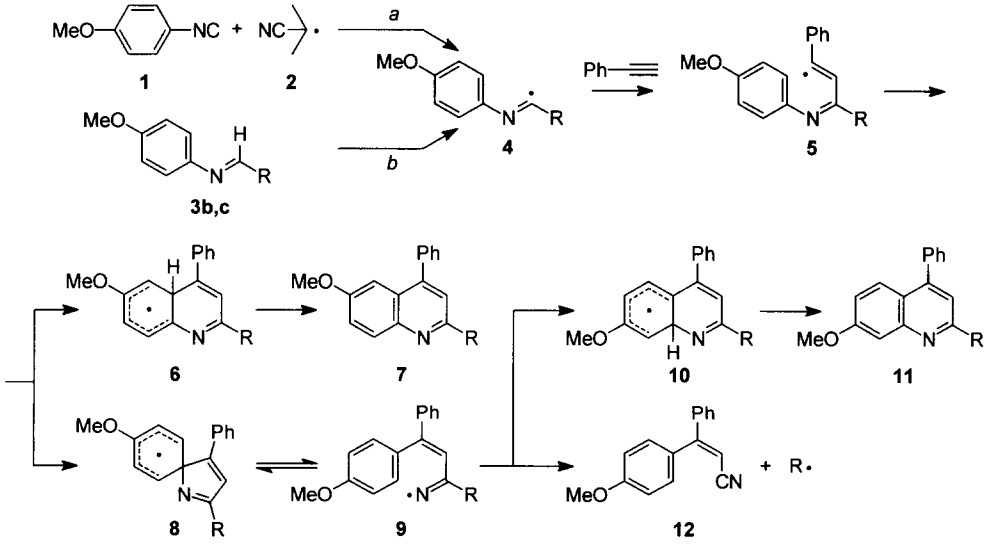
The addition of a wide series of carbon- or heteroatom-centred radicals to isonitriles is a well-known method to generate imidoyl radicals. In the last decades, studies have been reported concerning the spectroscopic properties and the reactivity of imidoyls arising from addition of alkyl, alkoxy, thiyl, silyl, or stannyl radicals to isonitriles.[1] More recently, this process has been extended to the synthetic organic chemistry and a number of heterocycles such as cyclopenta-fused quinolines,[2] camptothecin derivatives,[3] indoles,[4] and pyrrole derivatives[5] have been prepared. Our interest in imidoyl radicals[6] prompted us to investigate further the reactivity and synthetic potential of such intermediates when generated from isonitriles. Recently, we have accomplished the synthesis of cyclopenta-fused quinoxalines[7] through the first trimolecular version of the radical addition, tandem cyclisation strategy.[2,3] In that study, the side-reaction of 2-cyanoprop-2-yl radical **2** with isonitrile **1** (Scheme 1, path *a*) has given new information about the mechanism of the annulation



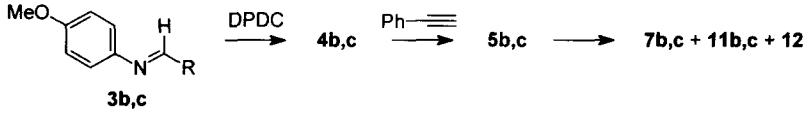
a: R = -C(Me)$_2$CN; **b**: R = *tert*-butyl; **c**: R = -C(Me)$_2$Ph.

Scheme 1

between imidoyl radicals and alkynes. In particular, the formation of minute amounts of nitrile **12**, arising from **9a** by β-fragmentation with loss of the starting radical **2**, shed light in the still-debated[6c,2] mechanism of rearrangement of azaspirocyclohexadienyl **8**.

To get some more insight into the intermediacy of **9** and to prove that the formation of the iminyl is not a minor process, we studied the reactions of a few imidoyl radicals bearing suitable substituents at the α-position and generated by an independent route, *i.e.* hydrogen atom abstraction from the corresponding imines **3** (Scheme 1, path *b*).

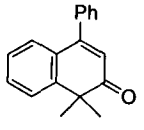
When imine **3b** was allowed to react with phenylacetylene and di-*iso*-propyl peroxydicarbonate (DPDC) in benzene solution at 60 °C,[6] it afforded a mixture of quinolines **7b** and **11b**[8] (65% overall yield, **11b/7b** = 4.4) and only trace amounts of nitrile **12** (Scheme 2): this result is consistent with a very low propensity of iminyl **9b** (R = *tert*-butyl) to fragment with loss of a *tert*-butyl radical.



Scheme 2

Indeed, the reaction of imine **3c** (R = 2-phenylprop-2-yl) under the same conditions gave nitrile **12** in a remarkable 21% yield as well as **7c** and **11c**[8] (41% overall yield, **11c/7c** = 0.9). In this case, the loss of a stable 2-phenylprop-2-yl radical is a much easier process that can drive iminyl **9c**, among other possible routes,[2,7] towards the fragmentation path. As one can see, the **11c/7c** ratio is reversed with respect to the reaction of imine **3b** and all of the other previously reported results;[6] on the other hand, the **(11c + 12)/7c** ratio is consistent with the usual encountered preference for radicals **5** to give 5-membered ipso-cyclisation. This suggests that nitrile **12** should be formed at the expense of quinoline **11**. Although we cannot rule out completely the presence of concomitant rearrangement mechanisms,[2] this result clearly shows that iminyl **9** is involved to a significant extent in the reaction pathway leading from **8** to **11**.

It is worth noting that the reaction of imine **3c** also afforded dicumyl and other products derived from the 2-phenylprop-2-yl radical,[9] and trace amounts of the probable compound **13** as well;[8] **13** could arise from cyclisation of **5c** on the phenyl ring of the cumyl moiety, followed by hydrolysis of the iminic bond. This result is worth of further investigation directed to the synthesis of naphthalenone derivatives.



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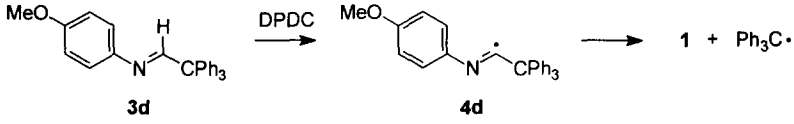
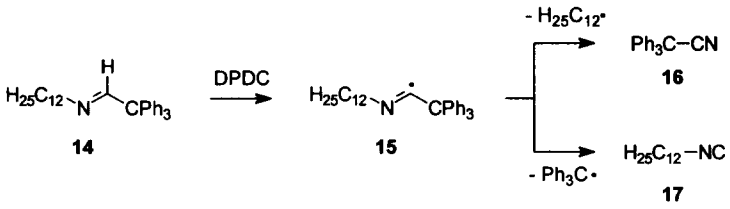
Unexpected results were obtained from imine **3d**[8] (R = triphenylmethyl): in this case the reaction did not afford any product derived from addition of the imidoyl radical to the alkyne, and it gave only isonitrile **1** in 80% yield, together with compounds derived from the triphenylmethyl radical (Scheme 3).[10]



Scheme 3

The formation of the isonitrile can be easily accounted for through an α-fragmentation of imidoyl **4d** with loss of a triphenylmethyl radical: the release of this very stable intermediate appears to be a powerful driving force that prevents radical **4d** to follow any other possible route. The α-scission is the major reaction path even with imine **14** (Scheme 4), and competes successfully with the facile β-fragmentation reported for such *N*-alkyl-substituted imidoyl radicals as **15**:[1] this reaction yielded triphenylacetonitrile **16** and dodecylisonitrile **17** in a 0.6:1 ratio (35% overall yield).[11]



Scheme 4

The reactions of imines **3d** and **14** are a novel example of homolytic α-fragmentation, a rare process that has been encountered, with imidoyl radicals, only in the presence of an α-tinthio-substituent:[12] in that case the imidoyls generated by addition of trialkyltin radicals to isothiocyanates gave isonitriles through loss of trialkyltinsulfanyl radicals. Our reaction is the first example of α-scission involving elimination of a carbon-centred radical. Studies are underway on the synthetic applicability of this process.

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8. New compound: the structure was confirmed by analytical, ^{1}H-NMR, MS, and HRMS data.
9. A GC-MS analysis of the reaction mixture showed small amounts of 2-phenylprop-2-yl *iso*-propyl ether, acetophenone, 2-phenylpropan-2-ol, α-methylstyrene, and 2,2-diphenylpropane, which were identified by comparison with the authentic spectra contained in the instrument database. The same products were also obtained, in the same ratio, by reacting cumene with DPDC under the same conditions.
10. A GC-MS analysis of the reaction mixture showed the presence of triphenylmethyl *iso*-propyl ether, benzophenone, triphenylmethanol, triphenylmethane, and tetraphenylmethane. The same products were

also detected in the reactions of triphenylmethane with DPDC, both in the presence and in the absence of **1**, under the same conditions.

11. This ratio was obtained after 40 min, when some starting material was still present. After 4 h only small amounts of **14** were detected, but the yield of **17** dropped to 5% and a GC-MS analysis of the crude showed major amounts of other products containing the dodecyl moiety. Isonitrile **17** is clearly unstable under the reaction conditions and, probably, the actual **17/16** ratio is much higher than that experimentally obtained.
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