Hydrocarbon Activation. Synthesis of β-Cycloalkyl (Di)nitriles through Photosensitized Conjugate Radical Addition

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Photoinduced hydrogen abstraction from aliphatic cyclic hydrocarbons (C_5 to C_7, C_{12}, as well as adamantane) by triplet aromatic ketones in the presence of α,β-unsaturated (di)nitriles offers a straightforward entry to the corresponding alkylated (di)nitriles via the alkyl radicals. Yields are moderate to good depending on the olefins structure (substitution in β slows down the addition to mononitriles, but with α,α-dinitriles electronic activation allows efficient alkylation also of β,β-disubstituted substrates). A tandem alkylation−cyclization process has been obtained with (1-methylpent-4-enylidene)malononitrile.

Introduction

In the last years there has been an increased interest in nitrile-containing natural products.[1] These include various metabolites of both terrestrial and marine origin.[2] A possible entry to such derivatives is the alkylation of α,β-unsaturated nitriles through conjugate addition reactions.[3] In principle, these may be carried out both via anionic and via radical intermediates. However, the application of the former approach for the introduction of simple alkyl groups is severely limited and has been barely used in the 1,4-addition to α,β-unsatured nitriles. Indeed, anionic organometallic derivatives behave as hard nucleophiles and thus 1,2-addition is by far preferred. As an example, Grignard reagents give a mixture of 1,2- and 1,4-adducts[4] except than in a few cases (the alkylation of α-phenylcinnamonitrile[5] and of γ-hydroxy α,β-unsatured nitriles[6]). More recently, organocopper and organosamarium reagents have shown little advantage and in most cases either no reaction occurred,[7,8] or 1,2-addition leading to ketones was obtained.[9−11] Quite recently a single example of a nickel-catalyzed alkylation of acrylonitrile with triorganoindium compounds has been reported to take place in a high yield.[12]

On the contrary, β-(cyclo)alkylnitriles have been easily obtained in high yields from the corresponding unsatured nitriles through radical addition reactions. Radicals were generated in different ways: (a) from the corresponding halides via the Giese method with tin[13] or mercury[14] hydrides, as well as from iron, manganese,[15] or chromium complexes;[16] (b) from cyclohexa-2,5-dienylcarboxilic acid precursors;[17] (c) via a photochemical electron-transfer process from 2,2-dialkyldioxolanes,[18] tetraalkylstannanes,[18,19] and ammonium salts of phenyl trialkylborates.[20] However, most of the radical methods show several limitations due either to the toxicity of the organometallic species involved or to the tedious synthesis of the radical precursors.

Generation of carbon-centered radicals directly from alkanes is an obviously appealing choice and has recently generated a new interest. This is a part of an interest for the direct functionalization of aliphatic alkanes, some examples being direct iodination[21] and nitration[22] of alkanes and intermolecular C−H insertion of carbenoids derived from methyl aryldiazoacetates.[23]

The use of radicals generated from alkanes for the alkylation of electrophilic alkenes has little precedent, although we demonstrated that radicals obtained from cyclic hydrocarbons can be applied to the functionalization of ketene dithioacetal *S*,*S*-dioxides in a high yield.[24a]

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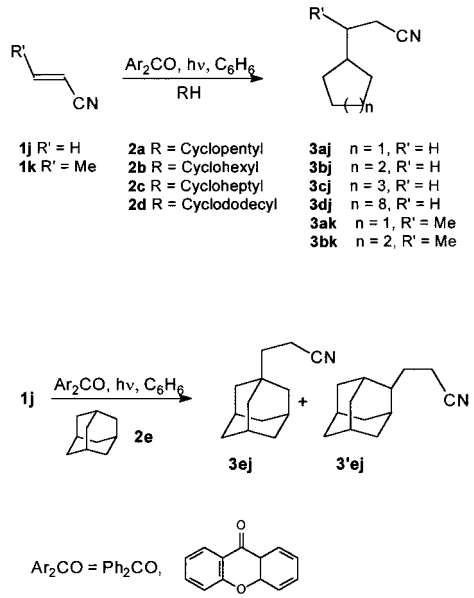
Scheme 1



In the following, we report the smooth synthesis of β-cycloalkylnitriles (via a similar photochemical process) starting from α,β-unsatured nitriles and cyclic hydrocarbons in the presence of aromatic ketones (benzophenone and xanthone) as sensitizers.

Results

In the present work, a variety of aliphatic hydrocarbons were considered as the radical precursors. These were four monocycloalkanes viz. cyclopentane (**2a**) cyclohexane (**2b**), cycloheptane (**2c**), and cyclododecane (**2d**) as well as polycyclic adamantane (**2e**).

Irradiations were carried out using nitriles **1** (5−10 mmol) and an equimolar amount of the sensitizer (benzophenone or xanthone) in the presence of a large excess of the hydrocarbons.

Alkylation of α,β-Unsaturated Mononitriles. Acrylonitrile (**1j**), as well as a β-monoalkyl- (crotonitrile, **1k**), and a β,β-dialkylnitrile (cyclohexylideneacetonitrile, **1l**) were used as radical traps. In the case of **1j**, benzophenone-photosensitized irradiation ($\lambda = 310$ nm) in neat **2a** or **2b** gave a complex mixture containing alkylated nitriles of structure **3aj**, **3bj**, but the reaction was unpractical under these conditions. The same irradiation carried out in a benzene solution of each of the cycloalkanes **2a**−**e** led to a cleaner reaction, and the β-alkylated products **3** were isolated in moderate yields (35−50%; only in the synthesis of **3ej** was the yield less satisfactory). Furthermore, when adamantane was used as the radical precursor, two different regioisomers were detected (**3ej** and **3′ej**), though in a quite different yield (ratio 6/1). The major isomer was isolated and shown to be the 1-adamantane derivative **3ej** (see Scheme 1).

In many of the above irradiations, cycloalkylbenzenes **7**, as well as diphenylcycloalkylmethanols **8**, were detected as byproducts in a small amount by GC-MS; furthermore, some benzopinacol **9** was always formed during the reaction (see Scheme 5, vide infra).

The isolated yields were affected by the different volatility of the starting alkanes **2** and of products **3** as well as by the composition of the raw irradiation mixture before purification. Excess alkanes were easily removed by evaporation in vacuo in the case of **2a**−**c** but not with **2d**,**e**. As an example nitrile **3ej** was formed in 50% yield with 1 M adamantane, but separation of excess alkane was tedious. Using 0.2 M **2e**, the yield was lower, but the separation much faster. Nitriles **3** are separated by means of a careful column chromatography, preceded when appropriate by bulb to bulb distillation. Benzopinacol and unreacted benzophenone caused no problem, but when the mixture contained a significant amount of benzenes **7** or of nonvolatile alkanes, fractionation had to be careful, and isolated yields were significantly lower (by more than 10%) than GC yields as determined in the raw photolyzates. Loss by evaporation was important with low molecular weight products such as **3aj**.

Table 1. Products Yield by Irradiation of Nitriles 1

nitriles	hydrocarbons	products	product yield, %[a]
1j	**2a**	**3aj**	40 (46)
1j	**2a**	**3aj**	16[b]
1j	**2b**	**3bj**	36.5 (48)
1j	**2b**	**3bj**	35[b]
1j	**2c**	**3cj**	50 (54)
1j	**2c**	**3cj**	49.5 (65)[b]
1j	**2d**	**3dj**	50 (53)
1j	**2d**	**3dj**	(5)[b]
1j	**2e**	**3ej**	26.5 (30)
1j	**2e**	**3ej**	(50)[c]
1j	**2e**	**3ej**	*b*, *d*
1k	**2a**	**3ak**	22 (31)
1k	**2b**	**3bk**	39 (44)
1l	**2b**	−	*d*
1m	**2b**	−	*d*
1n	**2b**	**4bn**	66
1n	**2c**	**4cn**	80
1n	**2d**	**4dn**	39.5
1o	**2b**	**5, 6**	11, 28

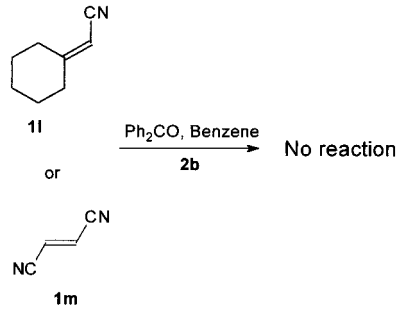
[a] Isolated yield. In parentheses are GC-determined yields. [b] Xanthone as the sensitizer. [c] Concentration of adamantane, 1 M. [d] No alkylation occurred.

Xanthone was a viable alternative to benzophenone as a sensitizer. In this case a successful reaction required that the concentration of alkanes used was larger than in the benzophenone case (see Experimental Section). Under these conditions, the yields of nitriles **3** from low molecular weight cycloalkanes **2a**−**c** are comparable to or larger than (65% in the case of **3cj**) those obtained with Ph_2CO, and the reaction was cleaner since the formation of byproducts **7** and **8** was greatly reduced. Xanthone could not be used with solid hydrocarbons **2d**,**e**, both because these could not be added in a large enough concentration because of the limited solubility and because excess alkane would make troublesome the isolation of products **3** at the end of the reaction. Thus, with this sensitizer, product **3dj** was formed in a poor yield (5%), and no alkylation occurred with **2e** (see Table 1).

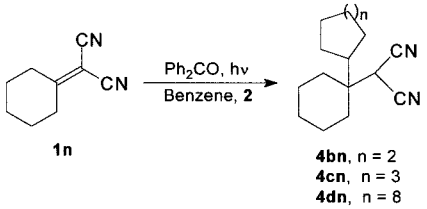
The reaction was similarly carried out with crotonitrile (**1k**), and alkylation was found to occur with all of the above hydrocarbons with only a slightly decreased yield with respect to **1j**. The reaction was carried out in a preparative scale with alkanes **2a**,**b,** and the corresponding nitriles **3a,b** were characterized.

On the other hand, β,β-disubstitution in the case of nitrile **1l** exerted a detrimental effect on alkylation yield. Thus, alkylation of **1l** by **2b** failed even after prolonged irradiation (See Experimental Section and Scheme 2). The final reaction mixture showed a minimal consumption of **1l** (less than 5%) and an enhanced yield of byproducts **7** and **8** with respect to the other two mononitriles.

Scheme 2



Scheme 3



Alkylation of α,β-Unsaturated Dinitriles. To evaluate the scope of the alkylation procedure, the examination was extended to some dinitriles as radical traps. We used both a 1,2-dinitrile (fumaronitrile, **1m**) and 1,1-dinitrile derivative (2-cyclohexylidenemalononitrile, **1n**). To avoid competitive absorbtion of light by the dinitriles with the sensitizer, the irradiation wavelength was in these cases 366 nm. It was found that with a good radical trap such as **1m** neither was the expected alkylated nitrile formed in the presence of **2b**, nor were any of the byproducts above-mentioned detected by GC under the irradiations conditions (Scheme 2).

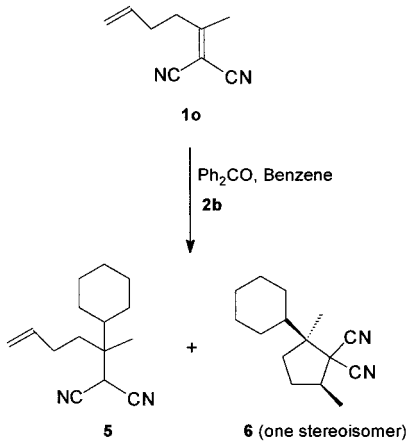
On the contrary, the cyclohexylidene derivative **1n** underwent *β*-alkylation efficiently, despite the steric hindrance, and afforded the highly crowded derivatives **4** (see Scheme 3). Yields ranged from 40% (for the reaction with **2d**) to 80% (for the formation of product **4cn**).

Alkylation of a Nitrile Containing an Alkene Moiety. The photosensitized alkylation was extended to a 1,1-dinitrile tethered to an olefin moiety, viz. ((1-methylpent-4-enylidene)malononitrile, **1o**). The photochemical reaction of this dinitrile with cyclohexane led to alkylated derivatives **5** and **6** (in a ca. 1/3 ratio). The structure of the latter compound was recognized by analytical and spectroscopical analysis and shown to result from a cyclization onto the double bond after the cyclohexyl radical attack (see Scheme 4). A single stereoisomer was obtained, and this was shown to have a *cis* orientation of the 2-cyclohexyl with respect to the 5-methyl group on the basis of 2D-NOESY experiments (see Experimental Section).

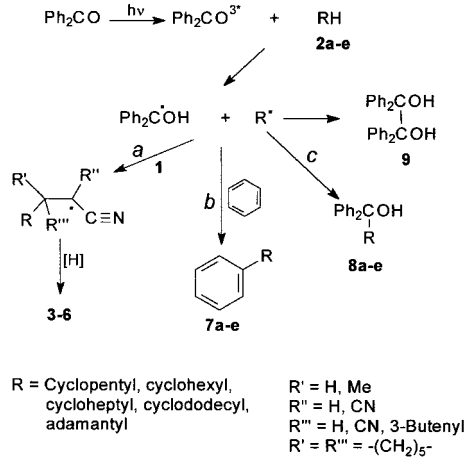
Discussion

Hydrocarbons Activation. Saturated hydrocarbons are the main source of natural feedstock, but selective and efficient reactions at an inactivated C−H bond such as an alkane C−H bond are rarely used in organic synthesis.[25] Activation of alkanes has been mainly obtained either through the action of metal complexes[26] or by inorganic solid acids catalysis.[27] The use of alkanes in synthetic plans aiming to high added-value products usually is limited to oxidation processes.[26] In the present work, alkyl radicals are photochemically generated from

Scheme 4



Scheme 5



alkanes through hydrogen abstraction by triplet benzophenone[28] (see Scheme 5). Hydrogen abstraction by ketones is probably the best known photochemical reaction but is normally applied to substrates possessing activated C−H bonds, e.g., bearing an electron-donating or -withdrawing group in the α position. Hydrogen abstraction from alkanes has been considered only in physicochemical studies.[29] For example Scaiano et al. reported the irradiation of benzophenone in neat cyclohexane.[30] In that case, a complex mixture of products arising from the cyclohexyl radical, such as bicyclohexyl and **8b** was obtained. Recently, we have demonstrated that photogenerated cycloalkyl radicals can be exploited in the nucleophilic addition to electron-poor olefins such as ketene dithioacetal *S*,*S*-dioxides.[24a]

Since our goal was obtaining the chemoselective activation of the C−H bond, the exploration was limited to cyclic hydrocarbons (**2a**−**d**) in order to avoid problems of regioselectivity at this stage. We included, however, adamantane in order to determine whether any dif-

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ferentiation between bridged and bridgehead type C−H bonds was possible.

Choice of the Reaction Conditions. Various conditions were explored for obtaining a successful alkylation of electrophilic alkenes. The desired nitriles **3** were formed upon irradiation in neat hydrocarbons (when liquid, viz. in the case of **2a**−**c**), but they were accompanied by large amounts of byproducts as shown by GC analysis of the raw photolyzate. A solvent, which would not compete with alkanes for hydrogen abstraction while being transparent to the wavelength used for exciting the sensitizers and having good solubility power was benzene. This is known to contribute to the benzophenone triplet decay when used as the solvent,[31] but this seemed to be a minor drawback in the present case. Hence, the reaction was explored in a various cycloalkane−benzene mixtures of nitriles **1** and the sensitizers. The proportion of benzene was adjusted in order to ensure sufficient solubility of the sensitizer (benzophenone and particularly xanthone are poorly soluble in neat cycloalkanes) while not diminishing hydrogen abstraction from the alkane and minimizing competitive trapping of the alkyl radicals to give alkylated benzenes **7**. In practice, the reaction occurred efficiently in a 2 to 1 cycloalkane−benzene mixture for liquid substrates (**2a**−**c**), in a 1 M solution with cyclododecane (**2d**) and in a 0.2 to 1 M solution of adamantane (**2e**). (In the latter case a higher concentration of the hydrocarbon (1 M) incremented the final alkylation yield but made the isolation of **3ej** unpractical.)

The wavelengths employed for the irradiation depended primarily on the nature of the starting nitriles. Irradiations were carried out by means of external phosphor-coated lamps, with center of emission 310 or 366 nm. Both choices were appropriate with benzophenone as the sensitizer, with somewhat better results at 310 nm in the alkylation of mononitriles (**1j**,**k**) and at 366 nm with dinitriles (**1n**,**o**) probably because of the small competitive absorption by these substrates at shorter wavelengths. The latter choice was at any rate advantageous with xanthone as the sensitizer.

Benzophenone was used in an equimolar amount with respect to the olefin. With a lower amount the yields of alkylated nitriles **3** were too low for a synthetic application.[32] Xanthone showed a strongly substrate-dependent efficiency, apparently directly related to the number of abstractable hydrogens in the alkanes (yield with **2c** > **2b** > **2a**, see Table 1) and at any rate required that the alkane were present in at least a 1:1 proportion with benzene; therefore, this sensitizer could not be employed in the reaction with high molecular weight **2d**−**e** where it would have been impossible or unpractical to work at a high enough alkane concentration (see again Table 1). Xanthone is known to have close lying n,π* and π,π* triplets.[33] Phosporescence studies reveal that the former is the lowest triplet in a nonpolar medium such as 3-methylpentane, and the latter in a polar medium.[34] The n,π* state is known to be the only reactive state toward hydrogen abstraction even if exceptions were reported;[35] recently the hydrogen abstraction constant by xanthone triplet excited state in cyclohexane was measured (7.94×10^5 M^{-1} s^{-1}),[36] and the ketyl radical was detected in the same solvent by time-resolved ESR experiment.[35] Thus in an apolar medium, as it is the case here, xanthone is as good a hydrogen abstractor (See Scheme 5) as benzophenone.[37a] The difference is that xanthone is also quenched by benzene at a rate close to that by alkanes (k_q 6.5×10^5 M^{-1} s^{-1}).[37b] This may explain why xanthone is uneffective in a dilute solution of alkane in benzene.

Alkylation Reaction. The reaction mechanism is depicted in Scheme 5. Excitation of the sensitizer (benzophenone in Scheme 5) to the triplet state is followed by hydrogen abstraction from the alkanes (**2a**−**e**) yielding a ketyl and an alkyl (R•) radical. The latter is trapped by unsatured nitriles **1** and gives the final adducts **3**−**6** after a further hydrogen abstraction step on the part of the adduct radical, reasonably again from the alkane (path a). The ketyl radicals undergo dimerization to benzopinacol **9**.

Two competitive pathways involving radical R• decrease the efficiency of the formation of β-cycloalkylnitriles **3**. In the first one, benzene present in large excess competes with the electrophilic alkenes as a radical trap (path b). Cycloalkylbenzenes **7a**−**e** are in fact formed in all of the tested reactions, albeit in a small amount (in the reaction of **2b** in the presence of **1o** product **7b** was isolated, see Experimental Section). The other path involves radical coupling yielding diphenylcycloalkylmethanols **8** (path c). Careful chromatographic separation allowed the separation of one of these adducts (**8b**, during the isolation of **3bk**).

The significance of the above competitive paths grows for less reactive unsaturated nitriles **1**, as it is apparent in the case of the β,β-disubstituted **1l**. As expected, the success of the alkylation reaction depends on the combined effects of sterical hindrance and electronic activation in the alkene. With **1j**, alkylation occurs with all of the cycloalkanes tested in moderate yields. Isolated yields are better with liquid and volatile cycloalkanes because of the easier workup. Methyl substitution in β, as in the case of crotonitrile **1k**, decreases the yield (isolated yields, 40% for product **3aj**, 22% with **3ak**) and a further β-alkyl substituent, as with **1l**, limits formation of the adducts to 5%.

A dramatic change occurs with 1,1-dinitriles and these higher electronically activated alkenes are quite efficient traps for cycloalkyl radicals. Photochemical alkylation of **1n** was successful in all of the reactions tested, reaching yields as high as 80% as in the case of **4cn**. This is notable both because highly congested products such as

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(37) (a) Benzophenone has a hydrogen abstraction rate constant of 7.2×10^5 M^{-1} s^{-1} in dilute solutions of cyclohexane in acetonitrile (see ref 29a). (b) A referee suggested that in xanthone-sensitized reactions electron-transfer according to the equation below may be involved and that benzene may stabilize any cationic intermediate. Ar_2CO^* + nitrile $\rightleftarrows$ $Ar_2CO^{+\bullet}$ + nitrile$^{-\bullet}$ That benzene has a more complex role than a simple diluent is likely, although, as mentioned above, the reaction occurs also in neat cyclohexane, albeit less cleanily, but presently we have no support for such a mechanism.

4 are obtained in this way and because this demonstrates that electronic activation overcomes sterical hindrance in this reaction (compare the contrasting results of **1n** and **1l**).[38]

Another interesting issue is the regioselectivity of the formation of compound **3ej** from adamantane. Hydrogen abstraction from **2e** is known to be unselective[39a,b] and both bridged or bridgehead hydrogen atoms are abstracted, though with different selectivity.[39c−e] We previously obtained the 1-adamantyl derivative by photoinduced radicalic alkylation of some vinyl sulfones[24a] and of chiral fumaric acid derivatives[24b] starting from adamantane.

The regioselectivity may result both from different rates of hydrogen abstraction[39] and different efficiencies in the addition of 1- and 2-adamantyl radicals. As far the latter point, different addition yields have been reported in the alkylation of acrylonitrile starting from 1- and 2-adamantyl bromides through the classical chain method.[40]

In the present alkylation of **1j** by **2e** the major regioisomer (the 1-adamantyl derivative **3ej**) was isolated, and the minor one (**3′ej**) was detected by GC/MS (**3ej/3′ej** ratio ca. 6/1), confirming the regioselectivity of the alkylation in these conditions.

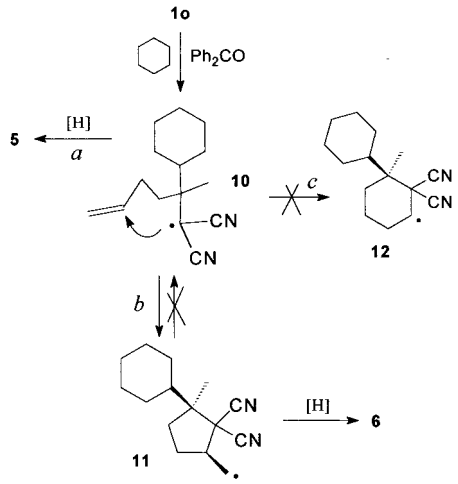
In the case of fumaronitrile **1m**, no functionalization was obtained under our conditions, despite the strong activation toward radical attack[41] of this substrate. The fact that byproducts **7** and **8** are likewise not formed under this condition supports that no hydrogen abstraction occurs. Thus, deactivation of the triplet state sensitizer (S) by **1m** as shown in eq 1 is involved

$$S^{3*} + NC{-}CH{=}CH\text{-}CN \rightarrow S + NC{-}CH{=}CH\text{-}CN^{3*} \quad (1)$$

In fact, the triplet energy of fumaronitrile (263 kJ/mol[42]) is slightly lower than that of both benzophenone (287 kJ/mol[43]) and xanthone (309 kJ/mol[43]), and the additive acts as a quencher.

The photosensitized alkylation of dinitrile **1o** with cyclohexane gave products **5** and **6**. The process is again initiated by radical attack yielding to the radical adduct **10**. Hydrogen abstraction (path a, leading to product **5**) and a cyclization across the 5-hexenyl moiety (yielding the further radical intermediate **11**, path b) then compete (Scheme 6). The latter path is preferred, and bicyclic **6** (a single diastereoisomer) is the main product after final hydrogen transfer. There are only a few examples of cyclization of highly stabilized 1,1-dicyano-5-hexenyl

Scheme 6



radicals such as **11**,[44] and both 5-exo and 6-endo regioselectivity have been observed in those cases.[45] The former process is reported to be kinetically favored while the latter one predominates at the thermodynamic equilibrium.[45] The structure of product **6** supports that cyclization of **10** occurs under complete kinetic control and that path c (leading to intermediate **12**, Scheme 6) and the reverse of path b are disfavored.[46] The stereochemistry of product **6** indicates that it does not arise via the usually preferred chair-equatorial transition state[47] but rather either from the boat-equatorial or the chair-axial states.

Synthetic Utility. Most of the presently considered nitriles **3** have been previously employed in the synthesis of thiadiazole derivatives known for their antiallergic activity[48] as well as in the synthesis of 9-deazaguanine derivatives used as inhibitors of purine nucleoside phosphorylase.[49] Furthermore, compound **3bj** can be easily transformed in other important building blocks used in the synthesis of molecule of biological interest, e.g., in the corresponding amine,[50] acid,[51] or their homologues.[52]

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In view of the significance of the β-cycloalkylnitriles, the present synthesis directly from cycloalkanes appears to be of interest as a clean and simple method despite the fact that the overall yields are in some cases moderate. Infact, as mentioned in the Introduction, synthesis of such compounds via carbanions is unsatisfactory. On the other hand, except for few cases,[53,54] most of β-cycloalkylnitriles **3** were obtained by alkylation of unsaturated nitriles through radical methods employing organometallic species, such as stannanes,[13a] dimeric metal complexes,[15] mercury derivatives,[14] silanes,[55] nickel boride−borohydride exchange resins,[56] in some cases in a better yield than with the present method. However, elimination of metal residues in the final product is troublesome in these cases in view of the low level allowable in drugs, and this makes a metal-free method for generation of radicals desirable. Devising alternative methods for radical generation it is not easy,[57] and photoinduced hydrogen abstraction may be a useful method.

Conclusion

A mild method of hydrocarbons C−H bonds activation has been explored. Cycloalkyl radicals were generated from the corresponding cycloalkanes via hydrogen atom abstraction by triplet aromatic ketones. The thus-formed radicals alkylate α,β-unsaturated (di)nitriles in moderate to good yields. Substitution in the β position deactivates mononitriles (β,β-dialkyl derivatives do not react) while the strong electronic activation of 1,1-dinitriles allows efficient alkylation also with β,β-disubstituted substrates. As illustrated above, this is a viable method for the metal-free synthesis of nitriles **3** (R′ = H), known as useful intermediates for the synthesis of molecule of pharmacological interest.

Experimental Section

NMR spectra were recorded on a 300 MHz spectrometer. Structural assignments were made on the basis of ^{1}H and ^{13}C NMR; chemical shifts are reported in ppm downfield from TMS. Both unsatured nitriles and hydrocarbons were commercial samples and used as received except nitriles **1o** (see below), **1l**,[58] and **1n**.[59]

The photochemical reactions were performed in quartz tubes by using nitrogen-purged solution and a multilamp reactor fitted with six 15-W phosphor-coated lamps (maximum of emission 310 nm, unless otherwise indicated) for the irradiation except in the synthesis of **3bj** (see below). The reaction course was followed by TLC (cyclohexanes−ethyl acetate) and GC. Workup of the photolytes involved concentration in vacuo and separation by bulb to bulb distillation or column chromatographic using Millipore 60 Å 35−70 μm silica gel.

Synthesis of (1-Methyl-pent-4-enylidene)malononitrile (1o). A mixture of malononitrile (1.43 g, 21.6 mmol), 5-hexen-2-one (2.5 mL, 21.6 mmol), NH_4OAc (166 mg, 2.16 mmol), and acetic acid (250 μL, 4.32 mmol) in benzene (3 mL) was refluxed for 24 h in a flask fitted with a Dean−Stark apparatus. The organic mixture was then washed with water, dried over sodium sulfate, and distilled under vacuum affording 2.56 g (82% yield) of **1o** (bp 70−75 °C, 2 Torr) as a colorless liquid.

1o: ^{1}H ($CDCl_3$) δ 2.3 (s, 3H), 2.4 (m, 2H), 2.7 (t, 2H, J = 7 Hz) 5.05 (m, 1H), 5.15 (m, 1H), 5.7−5.8 (m, 1H). ^{13}C ($CDCl_3$) δ 22.9 (CH_3), 31.8 (CH_2), 37.5 (CH_2), 86.9, 112.1 (CN), 112.2 (CN), 117.8 (CH_2), 135.2 (CH), 181.8. IR, (neat) ν/cm^{-1} 2919, 2229, 1641, 1599, 921. Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N 19.16. Found: C, 73.96; H, 6.86; N 19.12.

Photochemical synthesis of β-Cycloalkylpropio(butyro)nitriles (3). General Procedure. An equimolar solution of the α,β-unsatured nitriles and the sensitizer (5−10 mmol), in the presence of an excess of hydrocarbons (from 2- to 50-fold) was irradiated in benzene as a solvent. Workup of the photolytes involved concentration in vacuo, extraction with pentane, and bulb to bulb distillation or column chromatographic separation to afford the main products, nitriles **3**. In all of the experiments the formation of small amounts of cycloalkylbenzene derivatives **7a**−**e** and diphenylcycloalkylmethanols **8a**−**c** was detected by GC-MS analysis.

7a: MS (*m*/*z*) 146 (70), 117 (100), 104 (81), 91 (45). **7b:** MS (*m*/*z*) 160 (100), 117 (66), 104 (87), 91 (35), 83 (27). **7c:** MS (*m*/*z*) 174 (9), 117 (46), 104 (100), 91 (44). **7d:** 245 (4, M + 1), 205 (46), 161 (46), 151 (39), 135 (91), 97 (52), 69 (54), 55 (100). **7e:** 212 (81), 155 (100), 135 (27), 91 (23).

8a: MS (*m*/*z*) 235 (40, M − OH), 183 (87), 157 (64), 105 (100), 77 (46). **8b:** MS (*m*/*z*) 249 (100, M − OH), 183 (52), 171 (31), 167 (28), 105 (67), 77 (34). **8c:** MS (*m*/*z*) 263 (18, M − OH), 185 (78), 183 (79), 167 (89), 105 (100), 77 (50), 55 (25).

3-Cyclopentylpropionitrile (3aj). A solution of 9.4 mL of cyclopentane (100 mmol), 330 μL of acrylonitrile (5 mmol), and 910 mg of benzophenone (5 mmol) in 50 mL of benzene was irradiated for 15 h. Chromatography (cyclohexane/ethyl acetate 99:1) gave 240 mg of **3aj** (40% yield) as an oil.

The synthesis (same irradiation time) was also carried out under the following conditions: cyclopentane (149 mmol), acrylonitrile (3 mmol), xanthone (3 mmol) in 30 mL of benzene (irradiation wavelength 366 nm). After purification on column, 60 mg (16% yield) of **3aj** was isolated.

3aj: ^{1}H ($CDCl_3$) δ 0.8−2.0 (m, 11H), 2.30 (t, 2H, J = 7 Hz). ^{13}C ($CDCl_3$) δ 16.3 (CH_2), 24.9 (2 CH_2), 31.3 (CH_2), 32.0 (2 CH_2), 39.0 (CH), 119.9 (CN). IR, (neat) ν/cm^{-1} 2953, 2864, 2241, 1490, 1448. MS (*m*/*z*) 124 (100); 107 (10), 95 (40), 82 (20). Anal. Calcd for $C_8H_{13}N$: C, 77.99; H, 10.64; N, 11.37. Found: C, 78.05; H, 10.60, N, 11.35.

3-Cyclohexylpropionitrile (3bj). A solution of 54 mL of cyclohexane (500 mmol), 660 μL of acrylonitrile (10 mmol), and 1.816 g of benzophenone (10 mmol) in 100 mL of benzene was irradiated for 7 h in an immersion well apparatus fitted with a Pyrex glass filter using a 150 W medium-pressure mercury lamp. Distillation yielded product **3bj** slightly impure of **7b**. After a further purification by column chromatography (cyclohexane/ethyl acetate 99.5:0.5), **3bj** (500 mg, 36.5% yield) was isolated as an oil.

The synthesis (same irradiation time) was also carried out under the following conditions: cyclohexane (103 mmol),

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acrylonitrile (2 mmol), xanthone (2 mmol) in 20 mL of benzene (irradiation wavelength 366 nm). After purification on column, 96 mg (35% yield) of **3bj** was isolated.

3bj: ^{1}H ($CDCl_3$) δ 0.9−1.8 (m, 13H), 2.27 (t, 2H, J = 7.6 Hz). ^{13}C ($CDCl_3$) δ 14.5 (CH_2), 25.8 (2 CH_2), 26.2 (CH_2), 32.4 (2 CH_2), 32.5 (CH_2), 36.4 (CH), 119.9 (CN). IR, (neat) ν/cm^{-1} 2924, 2849, 2243, 1490, 1447. MS (*m*/*z*) 138 (100), 121 (40), 95 (25), 82 (90). Anal. Calcd for $C_9H_{15}N$: C, 78.78; H, 11.02; N, 10.21. Found: C, 78.65; H, 11.09; N, 10.18.

3-Cycloheptylpropionitrile (3cj). A solution of 6 mL of cycloheptane (55.6 mmol), 330 μL of acrylonitrile (5 mmol), and 910 mg of benzophenone (5 mmol) in 50 mL of benzene was irradiated for 15 h. Chromatography (cyclohexane/ethyl acetate 99.5:0.5) gave **3cj** (377 mg, 50% yield) as an oil.

This synthesis (same irradiation time) was also carried out under the following conditions: cycloheptane (248 mmol), acrylonitrile (6 mmol), xanthone (6 mmol) in 30 mL of benzene (irradiation wavelength 366 nm). After purification by means bulb to bulb distillation, 450 mg (49.5% yield) of **3cj** was isolated.

3cj: ^{1}H ($CDCl_3$) δ 1.0−1.8 (m, 15H), 2.35 (t, 2H, J = 7.6 Hz). ^{13}C ($CDCl_3$) δ 15.5 (CH_2), 26.5 (2 CH_2), 28.7 (2 CH_2), 33.5 (CH_2), 34.1 (2 CH_2), 46.3 (CH), 120.4 (CN). IR, (neat) ν/cm^{-1} 2925; 2852; 2242; 1447. MS (*m*/*z*) 152 (70, M+1), 135 (26), 100 (47), 97 (28), 82 (100), 55 (54). Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.35; H, 11.19; N, 9.20.

3-Clododecylpropionitrile (3dj). A solution of 11.6 g of clododecane (69 mmol), 465 μL of acrylonitrile (7 mmol), and 1.27 g of benzophenone (7 mmol) in 70 mL of benzene was irradiated for 15 h. Chromatography (from neat cyclohexane to cyclohexane/ethyl acetate 97:3) gave 460 mg of **3dj** (50% yield) as a colorless solid. A small portion was crystallized from benzene/methanol (mp 193−194 °C).

3dj: ^{1}H (DMSO) δ 0.9−1.5 (m, 25H); 2.4 (t, 2H, J = 7.5 Hz). ^{13}C (DMSO) δ 12.2 (CH_2); 24.9 (2 CH_2);27.2 (2 CH_2); 27.5 (2 CH_2); 27.6 (CH_2); 28.2 (2 CH_2); 31.8 (2 CH_2); 33.6 (CH_2); 36.7 (CH); 124.7 (CN). IR, (KBr) ν/cm^{-1} 2938; 2868; 2242; 1470; 1446. Anal. Calcd for $C_{15}H_{27}N$: C, 81.38; H, 12.29; N, 6.33. Found: C, 81.44; H, 12.23; N, 6.37.

3-(1-Adamantyl)propionitrile (3ej). A solution of 1.36 g of adamantane (10 mmol), 330 μL of acrylonitrile (5 mmol), and 911 mg of benzophenone (5 mmol) in 50 mL of benzene was irradiated for 20 h. The final product was isolated by means of repeated column chromatography. In the first run, neat cyclohexane was used as eluant in order to eliminate excess adamantane and the second (cyclohexane/ethyl acetate 99:1) allowed to isolate **3ej** (251 mg, 26.6% yield) as a syrup. The 2-adamantyl isomer (**3′ej**, 16% of the corresponding 1-isomer) was only detected by GC-MS technique.

3ej: ^{1}H ($CDCl_3$) δ 1.3−1.95 (m, 17H), 2.30 (t, 2H, J = 7.5 Hz). ^{13}C ($CDCl_3$) δ 10.8 (CH_2); 28.19; 28.2 (3 CH); 36.7 (4 CH_2); 39.2 (CH_2); 41.4 (2 CH_2); 120.7 (CN). IR, (neat) ν/cm^{-1} 2907; 2849; 2247. MS (*m*/*z*) 190 (13), 135 (100), 93 (15), 79 (21). Anal. Calcd for $C_{13}H_{19}N$: C, 82.48; H, 10.12; N, 7.40. Found: C, 82.44; H, 10.10; N, 7.40.

3′ej: MS (*m*/*z*) 189 (62), 146 (40), 135 (74), 107 (45), 93 (62), 91 (63), 79 (100), 67 (68), 41 (59).

3-Cyclopentylbutyronitrile (3ak). A solution of 8.5 mL of cyclopentane (90 mmol), 407 μL of crotonitrile (5 mmol), and 910 mg of benzophenone (5 mmol) in 45 mL of benzene was irradiated for 16 h. The raw photolyzate was purified by column chromatography (cyclohexane/ethyl acetate 99:1). The product was further purified by alumina chromatography (pentane/ ethyl acetate 99:1) yielding 150 mg of **3ak** (22% yield) as an oil.

3ak: ^{1}H ($CDCl_3$) δ 1.1 (d, 3H, J = 7 Hz), 1.15 (m, 2H), 1.5−1.75 (m, 7H), 1.75−1.9 (m, 2H), 2.25 (dd, 1H, J = 7 and 16.5 Hz), 2.4 (dd, 1H, J = 4.5 and 16.5 Hz). ^{13}C ($CDCl_3$) δ 18.8 (CH_3), 24.3 (CH_2), 25.6 (CH_2), 25.7 (CH_2), 30.9 (CH_2), 31.3 (CH_2), 36.4 (CH), 45.8 (CH), 119.5 (CN). IR, (neat) ν/cm^{-1} 2957, 2870, 2238. Anal. Calcd for $C_9H_{15}N$: C, 78.78; H, 11.02; N, 10.21. Found: C, 78.70; H, 10.91; N, 10.23.

3-Cyclohexylbutyronitrile (3bk). A solution of 17.6 mL of cyclohexane (163 mmol), 407 μL of crotonitrile (5 mmol), and 910 mg of benzophenone (5 mmol) in 33 mL of benzene was irradiated for 20 h. The raw photolyzate was purified by column chromatography (cyclohexane/ethyl acetate 99.2:0.8). The product was further purified by alumina chromatography (pentane/ethyl acetate from 99:1 to 60:40) yielding 295 mg of **3bk** (39% yield) as an oil and 45 mg of cyclohexyldiphenylmethanol (**8b**).

3bk: ^{1}H ($CDCl_3$) δ 0.8−1.4 (m, 6H), 1.1 (d, 3H, J = 7 Hz), 1.6−1.85 (m, 6H), 2.2−2.4 (m, 2H, AB part of an ABX system). ^{13}C ($CDCl_3$) δ 16.5 (CH_3), 22.1 (CH_2), 26.2 (CH_2), 26.3 (2 CH_2), 28.9 (CH_2), 30.2 (CH_2), 35.6 (CH), 41.5 (CH), 119.4 (CN). IR, (neat) ν/cm^{-1} 2923, 2852, 2243. Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33; N, 9.26. Found: C, 79.38; H, 11.30; N, 9.24.

8b: ^{1}H ($CDCl_3$) δ 1.0−1.5 (m, 5H), 1.6−1.9 (m, 5H), 2.1 (bs, 1H), 2.5 (m, 1H), 7.2 (m, 2H), 7.3 (m, 4H), 7.6 (m, 4H). ^{13}C ($CDCl_3$) δ 26.9 (CH_2), 27.1 (CH_2), 27.7 (CH_2), 46.1 (CH), 80.8, 126.2 (CH), 126.7 (CH), 128.5 (CH), 146.8. IR, (neat) ν/cm^{-1} 3497, 3055, 2924, 1597. Anal. Calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.60; H, 8.30.

Attempted Alkylation of Alkenes 1l and 1m. A solution of 1.7 mL of cyclohexane (16.3 mmol), nitrile **1l** (or **1m**) (0.3 mmol), and 55 mg of benzophenone (0.3 mmol) in 3.3 mL of benzene was irradiated for 2 days. After this period, GC analysis showed a small consumption of the starting nitriles and no formation of alkylation products.

(1-Cyclohexylcyclohexyl)malononitrile (4bn). A solution of 16.6 mL of cyclohexane (90 mmol), 440 mg of **1n** (3 mmol), and 550 mg of benzophenone (3 mmol) in 30 mL of benzene was irradiated for 19 h. Extraction with pentane and chromatography (cyclohexane/ethyl acetate 98:2) gave 455 mg of **4bn** (66% yield) as a syrup.

4bn: ^{1}H ($CDCl_3$) δ 1.0−2.0 (m, 21H), 4.0 (s, 1H). ^{13}C ($CDCl_3$) δ 21.2 (CH_2), 25.0 (CH_2), 26.2 (CH_2), 27.0 (CH_2), 27.3 (CH_2), 28.8 (CH), 30.5 (CH_2), 43.1, 43.3 (CH), 112.6 (CN). IR, (neat) ν/cm^{-1} 2930, 2247, 1453. MS (*m*/*z*) 230 (1), 121 (28), 83 (100), 55 (45). Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.12; H, 9.68; N, 12.12.

(1-Cycloheptylcyclohexyl)malononitrile (4cn). A solution of 3.6 mL of cycloheptane (33.4 mmol), 440 mg of **1n** (3 mmol), and 550 mg of benzophenone (3 mmol) in 30 mL of benzene was irradiated for 40 h. Extraction with pentane and chromatography (cyclohexane/ethyl acetate 99:1) gave 590 mg of **4cn** (80% yield) as a syrup.

4cn: ^{1}H ($CDCl_3$) δ 1.25−2.0 (m, 23H), 4.0 (s, 1H). ^{13}C ($CDCl_3$) δ 21.2 (CH_2), 25.0 (CH_2), 27.5 (CH_2), 27.6 (CH_2), 28.2 (CH_2), 28.8 (CH), 30.5 (CH_2), 43.3 (CH), 44.1, 112.6 (CN). IR, (neat) ν/cm^{-1} 2926, 2247, 1459. Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.62; H, 9.88; N, 11.49.

(1-Clododecyl-cyclohexyl)malononitrile (4dn). A solution of 2.45 g of clododecane (14.5 mmol), 215 mg of **1n** (1.5 mmol), and 275 mg of benzophenone (1.5 mmol) in 15 mL of benzene was irradiated for 36 h. Chromatography (cyclohexane/ethyl acetate 99:1) gave 182 mg of **4dn** (39.5% yield) as a syrup.

4dn: ^{1}H ($CDCl_3$) δ 1.1−1.9 (m, 33H), 4.1 (s, 1H). ^{13}C ($CDCl_3$) δ 21.9 (CH_2), 23.9 (CH_2), 24.2 (CH_2), 24.8 (CH_2), 25.4 (CH_2), 25.9 (CH_2), 26.9 (CH_2), 29.3 (CH), 31.3 (CH_2), 41.1 (CH), 45.0, 113.1 (CN). IR, (neat) ν/cm^{-1} 2933, 2246, 1445. Anal. Calcd for $C_{21}H_{34}N_2$: C, 80.20; H, 10.90; N, 8.91. Found: C, 80.30; H, 10.83; N, 8.79.

Photochemical Alkylation of 1o with Cyclohexane. A solution of 16 mL of cyclohexane (148 mmol), 435 μL of **1o** (3 mmol), and 550 mg of benzophenone (3 mmol) in 30 mL of benzene was irradiated for 15 h at 360 nm. Purification by column chromatography (cyclohexane/ethyl acetate 99:1) yielded 44 mg of **7b**, 76 mg of (1-cyclohexyl-1-methyl-pent-4-enyl)-malononitrile **5** (11% yield) and an impure fraction which was further purified on column to give pure (2*S*,5*S*)-2-cyclohexyl-2,5-dimethyl-cyclopentane-1,1-dicarbonitrile **6** (192 mg, 28% yield). The stereochemistry of diastereoisomer **6** was proven with NOE experiments; thus, the irradiation of 2-methyl hydrogens at 1.2 ppm caused an enhancement of the H-5 signal (3%) in the corresponding 1D-NOE difference spectrum. This correlation was further confirmed by 2D-NOESY experiment.

7b: ^{1}H ($CDCl_3$) δ 0.8−1.9 (m, 11H), 7.3 (m, 5H).[60]

5: ^{1}H ($CDCl_3$) δ 1.0−1.45 (m, 8H), 1.5−1.85 (m, 8H), 2.1−2.3 (m, 2H), 3.75 (s, 1H), 5.1 (m, 2H), 5.8 (m, 1H). ^{13}C ($CDCl_3$) δ 21.8 (CH_3), 26.5 (CH_2), 27.1 (CH_2), 27.3 (CH_2), 27.8 (CH_2), 27.9 (CH_2), 28.4 (CH_2), 31.9 (CH), 35.9 (CH_2), 43.6, 44.1 (CH), 112.8 (CN), 116.0 (CH_2), 137.6 (CH). IR, (neat) ν/cm^{-1} 3078, 2927, 2248, 1641, 1450, 916. MS (*m*/*z*) 230 (1, M), 147 (30), 109 (41), 83 (97), 55 (100). Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.18; H, 9.66; N, 12.10.

6: ^{1}H ($CDCl_3$) δ 1.05−1.4 (m, 4H), 1.2 (s, 3H), 1.4 (d, 3H, J = 7 Hz), 1.5−2.15 (m, 11H), 2.8 (m,1H). ^{13}C ($CDCl_3$) δ 16.4 (CH_3), 18.7 (CH_3), 26.6 (CH_2), 26.7 (CH_2), 27.0 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 29.4 (CH_2), 37.4 (CH_2), 44.5 (CH), 48.2 (CH), 51.2, 55.4, 113.7, 116.5. IR, (neat) ν/cm^{-1} 2934, 2854, 2243. MS (*m*/*z*) 231 (19, M + 1), 217 (36), 121 (72), 109 (57), 83 (82), 67 (49), 55 (100). Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.22; H, 9.60; N, 12.11.

(60) According with the literature data: Olah, G. A.; Surya Prakash, G. K. *Synthesis* **1978**, 397.

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