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Photochemical Monoalkylation of Propanedinitrile by Electron-Rich Alkenes

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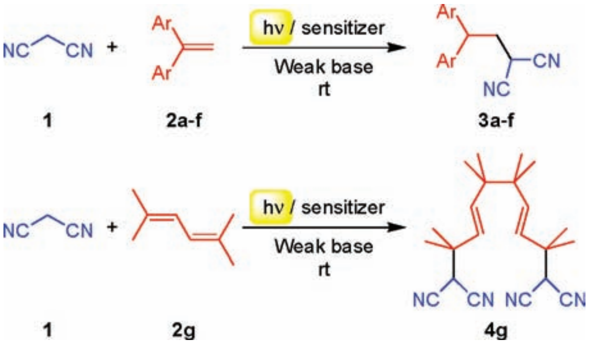
ABSTRACT



The synthesis of monoalkylated propanedinitriles was achieved upon photoirradiation of MeCN/H_2O solutions containing propanedinitrile (1; malononitrile) and electron-rich alkenes in the presence of lithium carbonate and a catalytic amount of 9-cyanophenanthrene or redox-type photosensitizers (electron-mediating photosensitizers), through regioselective anti-Markovnikov photochemical polar addition of 1 into electron-rich alkenes. With 2,5-dimethyl-2,4-hexadiene (2g) as an electron-rich alkene, propanedinitrile-incorporated dimer 4g was obtained.

Propanedinitrile (**1**; malononitrile) is one of the most versatile reagents in organic chemistry as a consequence of the high reactivity of both the methylene and cyano groups.[1] This substance has been employed extensively as a tool to extend alkyl chains and to prepare heterocyclic and biologically active compounds that have medical and industrial utility. In particular, nucleophilic substitution reactions of alkyl halides with the anion of **1**, along with those of malonic esters[2] and other active methylene compounds,[3] have been widely employed as methods to link two building blocks in the construction of intramolecular dyads.[4,5] However, it is often observed that overalkylation occurs in the first alkylation step employing **1** to give undesirable symmetrically disubstituted products.[4] Efforts have been made to overcome this difficulty, including use of highly reactive reagents such as strong bases and tight control of reaction conditions. In addition, indirect approaches have been developed such as Knoevenagel condensation[6] followed by hydrogenation.[7–9]

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(3) (a) Cope, A. C.; Holmes, H. L.; House, H. O. *Org. React.* **1957**, *9*, 107–331. (b) McMurry, J. E.; Musser, J. H. *J. Org. Chem.* **1975**, *40*, 2556–2557. (c) Tiete, L.-F.; Kiedrowski, G. V. *Tetrahedron Lett.* **1981**, *22*, 219–222. (d) Trost, B. M.; Conway, W. P.; Strege, P. F.; Dietsche, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 7165–7167.

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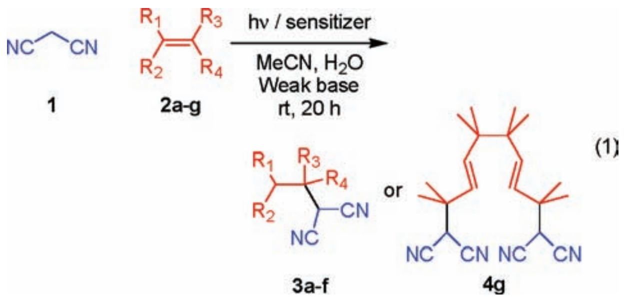
In this paper, we report the first photochemical method for direct alkylation of **1** to produce monoalkylated propanedinitrile derivatives **3** and **4** under mild conditions and in a highly regioselective manner (eq 1).



In exploratory studies, we have found that irradiation of an aqueous acetonitrile solution containing **1**, 1,1-diphenylethene (**2a**), lithium carbonate and a catalytic amount of 9-cyanophenanthrene (9-CP) leads to anti-Markovnikov addition to form the monoalkylated propanedinitrile **3a** in 91% yield (Table 1, entry 1).[10] Importantly, the formation of the dialkylated product was not observed. *p*-Methoxy- and *β*-methylarylalkenes **2b** and **2c**, respectively, as well as styrene and its *p*-*tert*-butyl and α-methyl derivatives (**2d**−**f**) can also be used as alkenes in this photoaddition process to yield the corresponding photoproducts **3b**−**f** (entries 2−6).[11] In contrast, use of diene **2g** as an electron-rich alkene results in formation of dimer **4g** in 52% yield (entry 7).[12] Since the ^{1}H and ^{13}C NMR spectra of **4g** are very simple and no molecular ion peak is observed in the mass spectrum of **4g**, its structure was assigned by analogy with dimethoxy-incorporated dimer[12] and unambiguously by single-crystal X-ray crystallographic analysis (Figure 1).

Table 1. Reaction of **1** with Various Alkenes[a]

$$\mathbf{1} + \mathbf{2a\text{-}g} \xrightarrow{h\nu\ /\ 9\text{-CP}} \mathbf{3a\text{-}f} \text{ or } \mathbf{4g}$$

entry	alkene	R_1	R_2	R_3	R_4	product	yield/[b]%
1	**2a**	Ph	Ph	H	H	**3a**	91
2	**2b**	An	An	H	H	**3b**	46
3	**2c**	Ph	Ph	Me	H	**3c**	52
4	**2d**	Ph	H	H	H	**3d**	40
5	**2e**	*p*-*t*-Bu-C_6H_4	H	H	H	**3e**	33
6	**2f**	Ph	Me	H	H	**3f**	38
7	**2g**	$Me_2C{=}CH$-	H	Me	Me	**4g**	52

[a] Conditions: 300-W high-pressure mercury lamp, Pyrex filter, **1** (2.5 mmol), **2** (75 μmol), 9-CP (25 μmol), Li_2CO_3 (1.25 mmol), MeCN (4 mL), H_2O (1 mL), under Ar, rt, 20 h. [b] Determined by ^{1}H NMR based on the amount of **2** used.

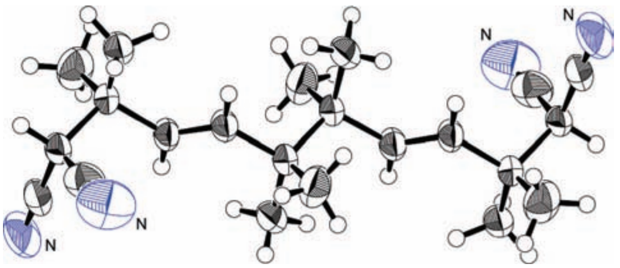


Figure 1. ORTEP diagram of **4g**.

The reaction described above is a novel method for alkylation of **1**. It should find utility as a safe and environmentally friendly synthetic method, since it proceeds under mild conditions (ambient temperture and in the presence of weak base) and, in contrast to the conventional S_N2 alkylation, proceeds halogen-free. Besides, it is also the first example of a process in which a nucleophilic carbon species other than cyanide anion[12b,13] is used in a photoinduced polar addition.[10,14]

Further studies of the scope of this process revealed that a use of heavier alkali ions results in lower yield of **3a** (Table 2, entries 1−5). The photosensitizer can be changed from 9-CP to other electron-accepting sensitizers, e.g., 9,10-dicyanoanthracene (9,10-DCA), with decrease of the yield (entry 6). Also, phenanthrene (Phen) can be used as an electron-donating photosensitizer together with strong electron-accepting co-sensitizers, such as regioisomers of dicyanobenzene (DCB), in a so-called redox photosensitizing system (entries 7−9).[15]

In mechanistic investigations, we observed that deuterium was incorporated into the benzylic position of **3a** with a *d*-content of 90% when deuterium oxide was used instead of water in the mixed solvent system for reaction of **1a** (entry 1, Table 1). This result clearly shows that protonation of the anion intermediate proceeds at its benzylic position. Based on this result, we propose that the reaction is promoted by photoinduced electron transfer (PET) from **2** to the excited singlet state of an electron-accepting photosensitizer (^{1}Sens*)

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Scheme 1. Plausible Mechanism for the Formation of **3** and **4g**

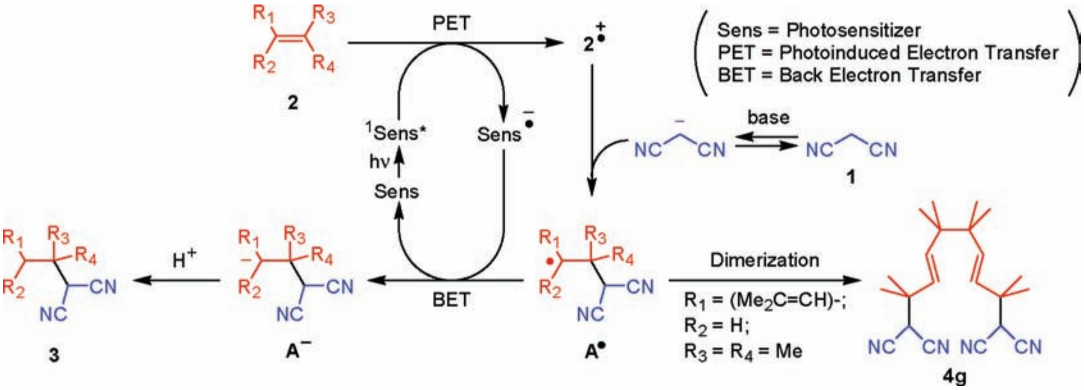

Table 2. Reaction of **1** with **2a** under Various Conditions[a]

$$1 + 2a \xrightarrow{h\nu / \text{sensitizer(s)}} 3a$$

entry	sensitizer(s)	base	yield/[b]%
1	9-CP	Li_2CO_3	91
2	9-CP	Na_2CO_3	66
3	9-CP	K_2CO_3	68
4	9-CP	Rb_2CO_3	23
5	9-CP	Cs_2CO_3	15
6	9,10-DCA	Li_2CO_3	27
7	Phen, *o*-DCB	Li_2CO_3	71
8	Phen, *m*-DCB	Li_2CO_3	60
9	Phen, *p*-DCB	Li_2CO_3	44

[a] Conditions: 300-W high-pressure mercury lamp, Pyrex filter, **1** (2.5 mmol), **2a** (75 μmol), sensitizer(s) (25 μmol each), base (1.25 mmol), MeCN (4 mL), H_2O (1 mL), under Ar, rt, 20 h. [b] Determined by ^{1}H NMR based on the amount of **2a** used.

(Scheme 1). This affords the radical cations of **2a**−**g**, which react with the anion of **1** to form benzylic radical intermediates $\mathbf{A}^\bullet$.[16] In the case of mono-olefins (e.g., **2a**), back electron transfer (BET) from the sensitizer radical anion (e.g., 9-CP$^{\bullet-}$) to $\mathbf{A}^\bullet$ is highly exothermic (e.g., −33.4 kcal/mol by (U)B3LYP/6-31G*) and fast; the resulting anions $\mathbf{A}^-$ are protonated to give the anti-Markovnikov adducts **3a**−**f**. Dimerization of $\mathbf{A}^\bullet$ does not occur owing to steric hindrance and low steady-state concentration of the radical. On the other hand, allylic radical $A^\bullet$ derived from a diene is stable enough to build up a higher steady-state concentration, which enables it to dimerize. The dimerization occurs regioselectively at its terminal position to form **4g**, a result that correlates with the relative stabilities of the three possible dimers. The anion $\mathbf{A}^-$ derived from **2g** dissociates spontaneously ($\Delta G^\ddagger \sim 2$ kcal/mol by HF/3-21G) to form the starting materials (i.e., anion of **1** and **2g**). In the redox-photosensitized process, Phen acts as an electron mediator between alkene and the cosensitizer[16] and the resulting radical ion pair reacts in a similar manner as described above.

In conclusion, a novel, safe and environmentally friendly synthetic method for the direct and mild monoalkylation of propanedinitrile, using photoinduced polar addition with electron-rich alkenes, has been developed. This represents the first example in which a carbon nucleophile, other than cyanide anion, is used in a photoinduced polar addition process.

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Supporting Information Available: Typical experimental procedure, characterization data for **3a**−**f** and **4g**, and crystallographic data for **3a** and **4g**. This material is available free of charge via Internet at http://pubs.acs.org.

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[16] An alternative pathway might involve photoinduced electron transfer from the anion derived from **1** to the excited singlet state of the sensitizer, followed by coupling of the resulting radical with **2** to form $\mathbf{A}^\bullet$.