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Photoinduced Tandem Three-Component Coupling of Propanedinitrile, 2,5-Dimethylhexa-2,4-diene, and Cyanoarenes

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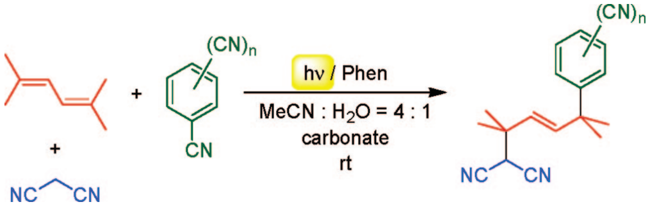
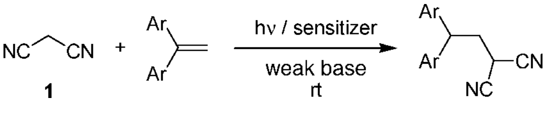


A tandem three-component coupling photoreaction proceeds upon photoirradiation of MeCN/H_2O solutions containing propanedinitrile (**1**, malononitrile), 2,5-dimethylhexa-2,4-diene (**2**), and polycyanoarenes in the presence of phenanthrene and carbonate, leading to selective α-monoalkylation of **1**. The reaction proceeds via photo-NOCAS (Nucleophile−Olefin Combination, Aromatic Substitution) type mechanism: nucleophilic attack of the anion of **1** to photogenerated $\mathbf{2}^{\bullet+}$ is followed by *ipso*-substitution on the radical anion of the polycyanoarene. It advances under mild, safe, and environmentally friendly conditions such as proceeding at ambient temperature without metals and halogens, and in the presence of weak base. The reaction also represents a novel and metal-free cross-coupling reaction that leads to *ipso*-substitution on polycyanoarene via aryl–cyano bond cleavage. In addition, the reaction is a rare example of introducing carbon nucleophile in the photoinduced electron transfer reaction, except that of cyanide ion.

Introduction

The linkage chains to tether two building blocks into intramolecular dyads are important for the development of highly functionalized molecules. One of the most commonly used tools for this purpose is sequential S_N2 reactions of the anion of propanedinitrile (**1**, malononitrile)[1−3] along with those of other active methylene compounds,[4] arising from their reactivity and commercial availability. However, these reactions often resulted in low yield due to overreaction to give symmetrically disubstituted products,[2] and due to oligomerization of the anion intermediates.[1]

To circumvent this difficulty, we have chosen a photochemical method[5] instead of using strong bases, and just reported a novel method for α-monoalkylation of **1**, which proceeds selectively under mild conditions (eq 1).[6]



(1)

In this work, we expanded this strategy to develop a three-component coupling reaction, the so-called photo-NOCAS (Nucleophile−Olefin Combination, Aromatic Substitution) reaction,[7] to obtain tandem α-monoalkylation product of **1** in high yield.

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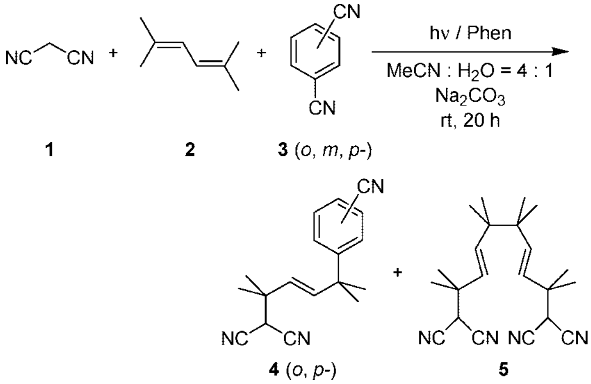
TABLE 1. Coupling Reaction of Dicyanobenzenes[a]

entry	dicyanobenzene	yields[b]/% **4**	yields[b]/% **5**
1	*p*-**3**	87	25
2	*o*-**3**	52	37
3	*m*-**3**	0	47

[a] Conditions: 300-W high-pressure mercury lamp, Pyrex filter, **1** (2.5 mmol), **2** (75 μmol), **3** (25 μmol), Phen (25 μmol), Na_2CO_3 (1.25 mmol), MeCN (4 mL), H_2O (1 mL), under Ar, rt, 20 h. [b] Determined by ^1H NMR based on the amount of **3** (for **4**) and **2** (for **5**) used.

Results and Discussion

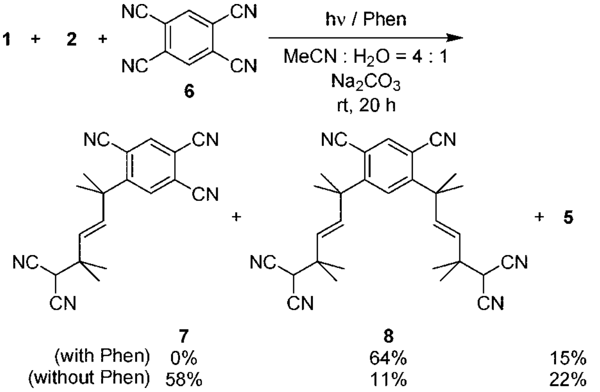
Three-Component Coupling Reaction of Cyanobenzenes. Photoirradiation of an aqueous acetonitrile solution containing malononitrile (**1**), 2,5-dimethylhexa-2,4-diene (**2**), and *p*-dicyanobenzene (*p*-**3**) in the presence of phenanthrene (Phen)[8] and an excess amount of sodium carbonate gives a good yield of three-component coupling product *p*-**4** (87% based on the amount of *p*-**3** used) along with propanedinitrile-incorporated dimer **5** (25% based on the amount of **2** used) (eq 2, and entry 1 of Table 1). The use of *o*-dicyanobenzene (*o*-**3**) also results in the formation of corresponding photoproduct *o*-**4** (52%) together with dimer **5** (37%) (entry 2), while *m*-dicyanobenzene (*m*-**3**) affords a better yield of **5** (47%) as the sole product (entry 3). These reactions also proceed in the absence of Phen, but the yield of **4** decreases (38%) when initiated with *o*-**3**.



(2)

This tandem three-component reaction not only broadens the synthetic usability of the photochemical α-monoalkylation method of **1** that we have reported,[6] but also enables us to accomplish photoinduced cross coupling under mild and safe conditions such as ambient temperature and in the presence of water and weak base, employing a cyano group as a leaving group. While cleavage of the carbon−cyano bond has been highlighted during recent years but is still a challenging task,[7,9,10] this metal-free photoreaction offers a novel methodology of activating aryl−cyano bonds. Besides, this is a rare example of introducing a carbon nucleophile into a photoinduced electron transfer (PET) reaction, except that of a cyanide ion.[6,11]

Not a monosubstituted product **7** but a 1,3-disubstituted one **8** is obtained in 64% yield when 1,2,4,5-tetracyanobenzene (**6**) is employed instead of **3** in the photoreaction (eq 3). This means that **6** undergoes the three-component coupling twice: that is, the first coupling among **1**, **2**, and **6** leads to the primary product **7**, which is rapidly consumed by the second regioselective coupling reaction with **1** and **2** to form **8**. The primary photoproduct **7** can be obtained (58%) along with **8** (11%) and **5** (22%) in the absence of Phen. This result and that of *o*-**3** described above indicate that Phen acts as a reaction accelerator by mediating the electron transfer (acting as a redox photosensitizer or a cosensitizer)[8] to suppress the back electron transfer (BET) deactivation process.



(3)

The structures of all the photoproducts were determined by their spectral data of ^1H and ^{13}C NMR, MS, HRMS, and IR. An X-ray crystallographic analysis was also performed for a single crystal of **7** to confirm its structure (Supporting Information, Figure S1). The disubstituted product **8** was determined as 1,3-disubstituted regioisomer since two resonances appeared in the aromatic region of its ^1H NMR spectrum, while only one identical proton is expected for each of the other possible regioisomers (1,2- and 1,4-product).

Effects of Carbonates. Metal salts are known to play an important role in the reactions containing ionic intermediates, by promoting their charge separation.[12] We have also reported the effect on the various photoinduced electron transfer reactions to drastically improve the efficiency and selectivity.[13] In this course, we checked the salt dependency of the photoreaction of *p*-**3** (entries 1−3, Table 2) and **6** (entries 4−6) by changing the alkali counterions of the carbonate and found that a use of heavier alkali ion leads to a better yield of the coupling products *p*-**4** and **8**. This result is presumably due to the charge separation effect of softer

TABLE 2. Effects of Carbonates[a]

entry	cyanobenzene	carbonate	products (yields[b]/%)	
1	*p*-**3**	Li_2CO_3	*p*-**4** (84)	**5** (23)
2	*p*-**3**	Na_2CO_3	*p*-**4** (87)	**5** (25)
3	*p*-**3**	K_2CO_3	*p*-**4** (96)	**5** (25)
4	**6**	Li_2CO_3	**8** (18)	**5** (36)
5	**6**	Na_2CO_3	**8** (64)	**5** (15)
6	**6**	K_2CO_3	**8** (56)	**5** (25)

[a] Conditions: 300-W high-pressure mercury lamp, Pyrex filter, **1** (2.5 mmol), **2** (75 μmol), *p*-**3** or **6** (25 μmol), Phen (25 μmol), carbonate (1.25 mmol), MeCN (4 mL), H_2O (1 mL), under Ar, rt, 20 h. [b] Determined by ^1H NMR based on the amount of cyanobenzene (for *p*-**4** and **8**) and **2** (for **5**) used.

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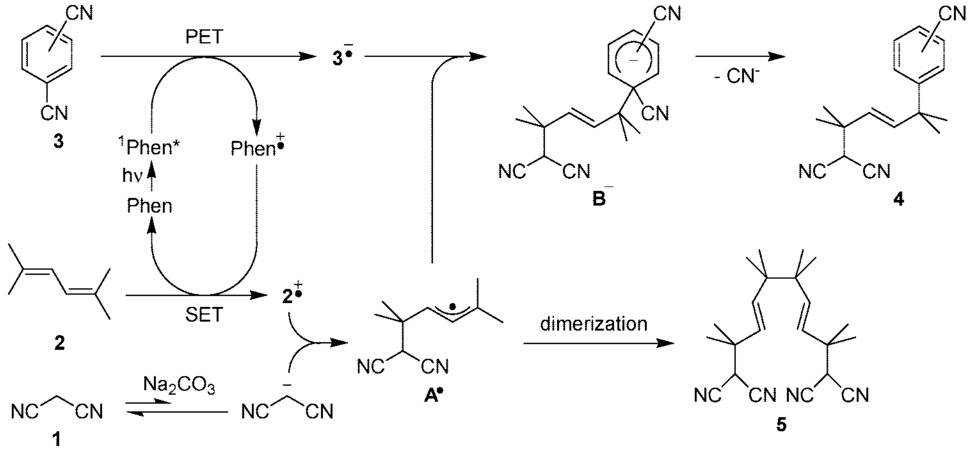
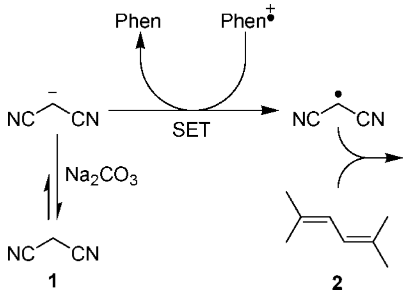
SCHEME 1. A Plausible Mechanism for the Formation of 4 and 5 via Path I



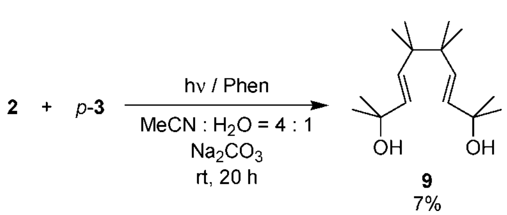
SCHEME 2. A Plausible Mechanism for the Formation of A• via Path II



metal salts (via interaction between the photogenerated radical ion pair and the salts) to suppress BET, which is consistent with the acceleration effect of electron-mediating Phen (vide supra).

A Plausible Mechanism. We propose that the reaction is promoted by single electron transfer (SET) from the excited singlet state of Phen (^{1}Phen*) to **3**, followed by a secondary SET from **2** to Phen$^{\bullet+}$ (Scheme 1).[8] SET from Phen or **2** to ^{1}**3*** (or ^{1}**6*** in the case of eq 3) can also take place. These processes afford **2**$^{\bullet+}$, which is trapped by the anion of **1** to form an allylic radical intermediate **A**$^\bullet$ (path I). An alternative pathway might involve SET from the anion of **1** to Phen$^{\bullet+}$, followed by coupling of the resulting radical with **2** to form **A**$^\bullet$ (path II, Scheme 2). Radical coupling between **A**$^\bullet$ and **3**$^{\bullet-}$ takes place to give **B**$^-$. Stabilization of the anion charge of **B**$^-$ by a cyano group on the ortho- or para-position of the former benzene ring is crucial for the success of the radical coupling (entry 3, Table 1). Elimination of cyanide ion from the *ipso*-position of **B**$^-$ regenerates the aromaticity of the benzene ring to afford three-component coupling product **4**.[7] If **A**$^\bullet$ diffuses out of the solvent cage, it dimerizes regioselectively at its terminal position to produce **5**, a result that correlates with the relative stabilities of the three possible dimers. The third competitive pathway for the consumption of **A**$^\bullet$ is the BET from **3**$^{\bullet-}$, but the resulting anion **A**$^-$ dissociates spontaneously ($\Delta G^\ddagger \approx 2$ kcal/mol by HF/3-21G) to form the starting materials (i.e., the anions of **1** and **2**).

To elucidate whether path I or II is dominant, the concentration of the anion of **1** was estimated as follows: An ICP-AES (Inductively Coupled Plasma−Atomic Emission Spectrometry) analysis was performed to determine the solubility of sodium carbonate as 1.8×10^{-5} M. From this value and known pK_a values for the carbonate and **1**,[14] the concentration of the anion of **1** was calculated to be around 2×10^{-5} M. Since this value is about 800 times smaller than that of **2** (15 mM) and efficient exergonic SET is predicted for both paths,[15] we concluded that path I is the major path, although these are in competition. In fact, the PET reaction occurs even in the absence of **1**, producing dihydroxy-incorporated dimer **9** (eq 4); that is, **2**$^{\bullet+}$ formed by an electron transfer is captured by water (or formally hydroxide ion) as a weak nucleophile, and the resulting radical undergoes dimerization to give **9**.



(4)

The low concentration of the anion of **1** described above is the feature of our photoreaction system. Nucleophilic species usually have lower oxidation potential than that of alkenes. Therefore, their coexistence at similar concentration in the reaction mixture results in exclusive one-electron oxidation of nucleophiles, not alkenes, and the resulting radicals tend to dimerize or give complex product mixtures. One of the solutions for this problem presented from electroorganic chemists is the separation of active sites, or concentration effects,[16] which uses, for example, adsorption of alkenes on anodes, diffusion of the alkene radical cations over a boundary of two liquid phases, or solid-supported nucleophiles to localize the existence of nucleophilic species. Our reaction system employs in situ genera-

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(15) $\Delta G_{SET} = -0.29$ (path I) and -0.92 eV (path II), according to the redox potentials of the reactants; Cf.: Rehm, D.; Weller, A. *Isr. J. Chem* **1970**, *8*, 259–271.

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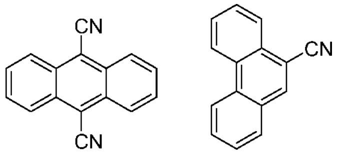
CHART 1

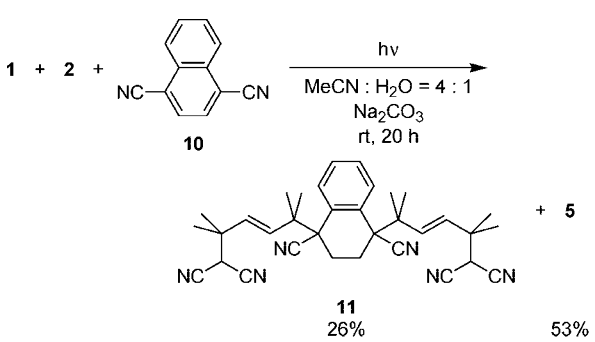


12 13

tion of nucleophilic anion species by use of weak base, which can also be classified as an example of the active-site separation.

Three-Component Coupling Reaction of Polycyclic Cyanoarenes. We have developed the coupling reaction using some π-expanded polycyclic cyanoarenes.

1,4-Dicyanonaphthalene (**10**) does not undergo substitution reaction but partially loses its aromaticity under a photoirradiation to afford tetralin derivative **11** in 26% yield (eq 5). Only dual adduct **11** is obtained in the reaction. In this case, in contrast to the observation for the reaction of **6**, monoadduct is never obtained even in the absence of phenanthrene. This can be attributed to the highly reactive nature of α-cyanostyrene moiety of the monoadduct.[17] We assume that this reaction proceeds in a similar mechanism to that of **3**, except that the protonation instead of cyanide elimination occurs on the anion intermediate that corresponds to $\mathbf{B}^-$, due to the lower rearomatization energy of the 1,2-dihydronaphthalene ring.



(5)

On the other hand, neither substitution nor addition is observed for the photoreaction of 9,10-dicyanoanthracene (**12**) and 9-cyanophenanthrene (**13**), as in the case of *m*-**3** (Chart 11). The former is probably due to the steric hindrance among peri-hydrogens, while the latter might be due to insufficient stability of the corresponding anion intermediate.

Conclusions

A novel tandem three-component coupling reaction between **1**, **2**, and polycyanoarenes leading to selective and high-yielding α-monoalkylation of **1** is developed. The reaction proceeds via photo-NOCAS-type mechanism under mild, safe, and environmentally friendly conditions such as ambient temperature, absence of metals and halogens, and using a weak base. We believe that the photoreaction will serve to broaden the synthetic usefulness of the photochemical α-monoalkylation method of **1**, which we have just reported.[6]

The reaction also represents a new type of cross-coupling reaction that leads to aryl−cyano bond cleavage in the absence of metals. In addition, the reaction is a rare example of introducing carbon nucleophile in the PET reaction, except that of cyanide ion.

Experimental Section

Typical Experimental Procedure (entry 1 in Table 1). To a Pyrex-made glass tube (1 cm ϕ) was added an acetonitrile (4 mL)−water (1 mL) solution containing **1** (165 mg, 2.5 mmol), **2** (10.7 μL, 75 μmol), *p*-**3** (3.2 mg, 25 μmol), phenanthrene (4.5 mg, 25 μmol), and sodium carbonate (132 mg, 1.25 mmol). Argon gas was bubbled through the solution for 5 min to reduce the amount of molecular oxygen dissolved, and then the tube was sealed with a rubber septum. After 20 h of irradiation by a 300-W high-pressure mercury lamp, the reaction mixture was neutralized by the addition of dilute hydrochloric acid and extracted with toluene−diethyl ether twice. The organic extracts were combined and concentrated in vacuo giving a residue (87% and 25% yield of *p*-**4** (based on the amount of *p*-**3** used) and **5** (based on the amount of **2** used), respectively, determined by ^{1}H NMR by using dibromomethane as an internal standard), which was chromatographed on silica gel (ethyl acetate after toluene) to give a crude product mixture. Further purification by HPLC (GPC column, chloroform) gave pure *p*-**4** (colorless oil) and **5** (colorless oil).

2-[*trans*-4-(4-Cyanophenyl)-1,1,4-trimethylpent-2-enyl]propanedinitrile (*p*-4): colorless oil; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.39 (s, 6H), 1.44 (s, 6H), 3.56 (s, 1H), 5.50 (d, $J = 15.9$ Hz, 1H), 5.87 (d, $J = 15.9$ Hz, 1H), 7.42 (AA′XX′, $J = 8.7$ Hz, 2H), 7.60 (AA′XX′, $J = 8.7$ Hz, 2H) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz) δ 25.6 (2C), 28.9 (2C), 36.1, 40.6, 41.6, 110.3, 111.9 (2C), 119.1, 127.2 (2C), 129.6, 132.3 (2C), 141.4, 153.3 ppm; MS (EI+) *m/z* 277 (4, M$^+$), 212 (18, M$^+$ − CH(CN)$_2$), 182 (14), 170 (100, M$^+$ − CMe$_2$CH(CN)$_2$), 156 (18); HRMS (EI+) calcd for $C_{18}H_{19}N_3$ 277.1579, found 277.1572; IR (NaCl) 840, 2228 (−CN), 2252 (w, −CN), 2972 cm^{-1}.

***trans,trans*-2,11-Dicyano-3,3,6,6,7,7,10,10-octamethyldodeca-4,8-dienedinitrile (5):**[6] colorless blocks, mp 111−112 °C; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.00 (s, 12H), 1.36 (s, 12H), 3.61 (s, 2H), 5.36 (d, $J = 15.8$ Hz, 2H), 5.80 (d, $J = 15.8$ Hz, 2H) ppm; ^{13}C NMR (CDCl$_3$, 75 MHz) δ 23.4 (4C), 25.9 (4C), 35.9 (2C), 40.8 (2C), 41.5 (2C), 112.3 (4C), 129.8 (2C), 140.1 (2C) ppm; MS (EI+) *m/z* 175 (39, M$^+$/2), 110 (100, M$^+$/2 − CH(CN)$_2$), 109 (35, M$^+$/2 − CH$_2$(CN)$_2$), 95 (30, M$^+$/2 − MeCH(CN)$_2$); HRMS (CI+) calcd for [$C_{22}H_{30}N_4$ + H] 351.2549, found 351.2555; IR (NaCl) 800, 1019, 1093, 1261, 2238 (w, CN), 2252 (w, CN), 2968 cm^{-1}. Anal. Calcd for $C_{22}H_{30}N_4$: C, 75.39; H, 8.63; N, 15.98. Found: C, 75.15; H, 8.47; N, 15.86.

Determination of the Solubility of Sodium Carbonate in Acetonitrile. Twenty milliliters of saturated solution of sodium carbonate in acetonitrile at 18 °C was evaporated in vacuo, and to the residue was added deionized water to give 20 mL of the aqueous solution. An ICP-AES analysis was performed on the sample solution, using 5×10^{-5} and 5×10^{-6} M aqueous solutions of sodium carbonate as external standards (correlation coefficient: 0.9999) to determine the concentration of sodium ion as 3.6×10^{-5} M, hence the solubility was elucidated as 1.8×10^{-5} M ($K_{sp} = 2.3 \times 10^{-14}$ M^3).

Acknowledgment. We thank Dr. Masahiro Yasuda and Mr. Seiji Nakashima at Osaka Prefecture University for helping us to perform ICP-AES analysis, and Dr. Akihiro Nomoto at Osaka Prefecture University for X-ray crystallographic analysis. This work was partially supported by Grant-in-Aids for Scientific Research on Priority Areas (420) (No. 16033252) and (444) (No. 19020060), Scientific Research (C) (No. 20550049), and JSPS Fellows (No. 20-4975) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

Supporting Information Available: Spectral data and ^{1}H and ^{13}C NMR spectra of the photoproducts (*p*-**4**, *o*-**4**, **5**, **7**−**9**, **11**, and **14**), and crystallographic data for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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