Photoinduced Nitrile Formation from O-(Arylcarbonyl) oxime: Usage as a Photoremovable Protecting Group

Matsubara, Ryosuke ; Idros, Ubaidah Md ; Yabuta, Tatsushi ; Ma, Huiying ; Hayashi, Masahiko ; Eda, Kazuo

(Citation)
Chemphotochem,2(12):1012-1016

(Issue Date)
2018-12

(Resource Type)
journal article

(Version)
Accepted Manuscript

COMMUNICATION

Photoinduced nitrile formation from *O*-(arylcarbonyl)oxime: Usage as a photoremovable protective group

Ryosuke Matsubara,* Ubaidah Md Idros, Tatsushi Yabuta, Huiying Ma, Masahiko Hayashi, Kazuo Eda

Abstract: Employing a photoremovable protective group is a useful technique to achieve precise conditional control over a biological function. This contribution demonstrates the development of a photoremovable protective group for the nitrile moiety. In the process, *O*-(arylcarbonyl)oxime was photochemically converted to the corresponding nitrile in the presence of a carbazole photosensitizer via an electron transfer from the excited carbazole to the arylcarbonyl unit. A variety of alkyl and (hetero)aryl nitriles were generated from the corresponding *O*-(arylcarbonyl)oximes. Moreover, a self-contained variant, in which *O*-(arylcarbonyl)oxime and carbazole units were covalently bonded, exhibited photochemical nitrile formation even in a highly diluted aqueous solution (0.1 mM), thus demonstrating that this molecular motif is potentially applicable in biological systems.

In therapy or biological experiments, targeting, i.e., the quantitative administration of a molecule of interest (e.g., drugs or fluorescent probes) at a specific place and time, is an important technique. In this context, photoremovable protective groups (PPGs) are useful, where light, a non-remaining “reagent”, is used to easily control the release of molecules spatiotemporally by modulating its intensity, wavelength, and irradiation location.[1] Many types of PPGs have been hitherto reported and applied in the masking of various chemicals such as biologically active compounds. Most of these PPGs have been designed to photochemically release alcohols, carboxylic acids, thiols, and amines. However, PPGs for other functional groups remain to be explored.

The nitrile (cyano) group is a functional group frequent in biologically active molecules, dyes, and luminophores (Figure 1).[2] Due to its coordination ability, the nitrile group tends to play a central role in the expression of the molecule’s biological activity.[3] In addition, this valuable functional group also works as an electrophile that interacts directly with thiolates in the active sites of protein targets.[4] Moreover, the photophysical properties of nitrile-containing chromophores are often characterized by the nitrile group, due to its strong electron-withdrawing nature.[5] Therefore, PPGs for the nitrile group could find a wide variety of applications in biochemistry, biomedicine, and chromophoric probes.

The nitrile ligands of certain transition metal complexes are known to dissociate from the respective metal center upon photo-irradiation.[6] To the best of our knowledge, however, there has been hitherto no report on non-metal-mediated PPGs for this functional group. Herein, we report that *O*-(arylcarbonyl)oxime (ACO) moieties could be photochemically converted to nitrile groups by means of photosensitization by carbazole. For the purpose of its use under highly diluted conditions, e.g. biological media, we synthesized an ACO derivative that was covalently bonded by a carbazolyl unit. The nitrile group was released from this ACO molecule via a uni-molecular sensitization pathway, thereby demonstrating its potential applicability as a PPG for nitrile groups. Recent reports show elegant photochemical formations of the nitrile compounds from cyclobutanone oxime derivatives by means of a ring-opening reaction.[7] However, in these studies, the applicable substrates are rather limited.

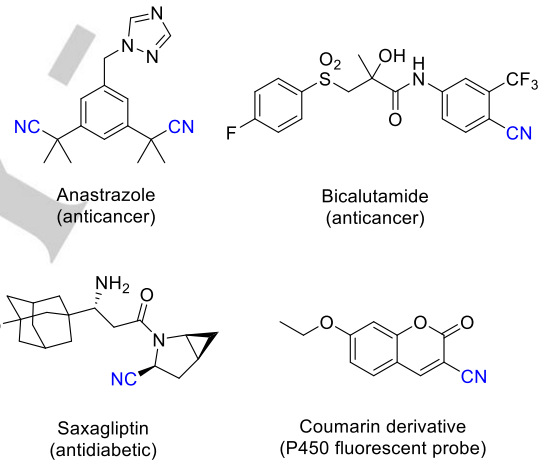
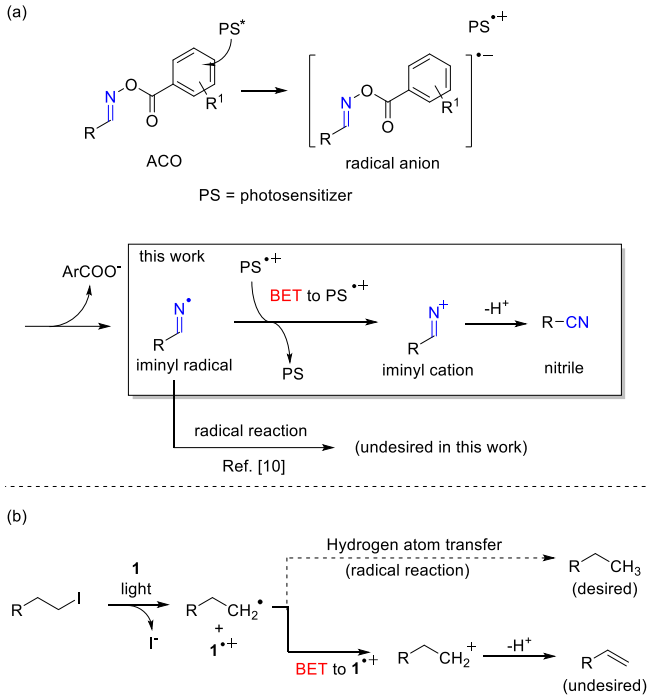


Figure 1. Nitrile-containing functional molecules.

The working hypothesis of this study, i.e., for ACO to release the nitrile group, is delineated in Scheme 1a. Recently, our group has focused on carbazole-catalyzed photochemical electron-transfers[8] that originated from Saito’s seminal works.[9] In our reports, we envisioned that the arylcarbonyl group of ACO accepts an electron from the photo-excited carbazole to generate a radical anion (Scheme 1). Then, a homolytic cleavage of the O–N bond would take place to generate an iminyl radical.[10] The next step is considered to be the branch point of the product distribution. While the iminyl radical acts as a versatile reactive species to effect the various bond-forming reactions as reported by Yu et. al., we surmised that if a back electron transfer (BET) from the iminyl radical to the radical cation of carbazole takes place prior to the radical reaction, an iminyl cation would be formed. The thus-formed iminyl cation would then undergo a deprotonation, leading to the nitrile group. Previously, we have observed a fast BET from the carbon radical to the radical cation of carbazole derivative **1** (Scheme 1b).[11] Considering these previous findings, we expected that, in analogy to the carbon radical, the iminyl radical would undergo a BET with a suitable carbazole-based photosensitizer rapidly enough to compete with the other radical reactions involved with the iminyl radical.

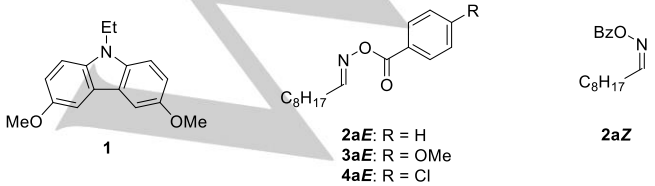
[*] Prof. Dr. R. Matsubara, U. Md Idros, T. Yabuta, H. Ma, Prof. Dr. M. Hayashi, Prof. Dr. K. Eda
Department of Chemistry, Graduate School of Science, Kobe University, 1-1, Rokkodai, Nada, Kobe, 657-8501 (Japan)
Email: matsubara.ryosuke@people.kobe-u.ac.jp

Supporting information for this article is given via a link at the end of the document.



Scheme 1. (a) Working hypothesis of photo-triggered nitrile formation. (b) Inspiring finding in our previous study (ref. [11]).

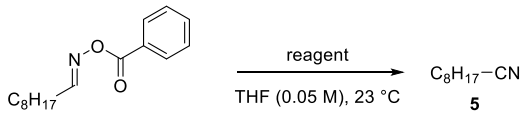
As a substrate for our initial investigations we chose aliphatic aldehyde-derived ACO **2a**, the synthesis of which is worth mentioning. ACO **2a** was synthesized via a reaction of a nonanal-derived aldoxime with benzoyl chloride in the presence of pyridine. Starting from a pure *Z*-configuration of the aldoxime,[12] both stereoisomers **2a*E*** and **2a*Z*** were observed in the crude material. During the aqueous work-up and chromatographic separation, **2a*Z*** was readily converted to nonanenitrile (**5**), while **2a*E*** could be chromatographically isolated as a stable pure form.[13] The susceptibility of ACO with *Z*-configuration (*Z*-ACO) to the nitrile-forming elimination reaction was probably due to the antiperiplanar geometry of the benzoate group to the eliminating imine proton. However, generally, a certain level of stability of a protective group is required for the purpose of practical application. Therefore, the stability of aliphatic ACO with *E*-configuration (*E*-ACO) was further tested by treating **2a*E*** with Et_3N or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF at room temperature (RT). Gratifyingly, after 1 h, no decomposition of **2a*E*** was observed in either case. While the electron-rich ACO **3a*E*** was as stable as **2a*E***, the electron-deficient ACO **4a*E*** readily underwent an elimination reaction to form nitrile **5** during work-up and chromatographic purification processes, probably due to the better leaving ability of the electron-deficient benzoate group.[14] In contrast, in the synthesis of aromatic aldehyde-derived ACOs, *E*-ACOs were selectively obtained in high yields without any detectable formation of *Z*-ACOs or the corresponding nitriles.



Therefore, *E*-ACOs with benzoyl or *p*-methoxybenzoyl groups were the substrates of choice for the following photochemical formation of both aliphatic and aromatic nitriles.

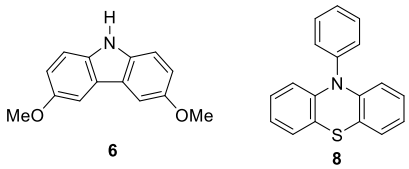
Next, we examined the photochemical reaction of aliphatic aldehyde-derived ACO **2a*E*** (Table 1). Based on the absorption spectra of the substrate and carbazole (Figure 2), UV-LED lamps with an emission maximum of 365 nm were used to selectively excite the photosensitizer (carbazole **1**) without the excitation of substrate **2a*E***. To our delight, the desired photoinduced nitrile formation from ACO successfully took place (entry 1, Table 1). The starting substrate was consumed after a 1-h irradiation, and the desired nonanenitrile (**5**) was obtained in moderate yield. An identical yield was observed also with catalytic amounts (0.1 equiv) of carbazole **1** (entry 2, Table 1), suggesting that **1** works as a catalyst in this reaction. Moreover, no reaction occurred without the use of light (entry 3, Table 1) or photosensitizer **1** (entry 4, Table 1), which suggests that both the photo-irradiation and use of **1** are crucial for the transformation of **2a*E*** to nitrile **5**. Based on the susceptibility of **2a*E*** to elimination reactions, there was a concern that the co-product, benzoic acid (**7**), may assist the nitrile formation as a Brønsted acid catalyst. Therefore, a control reaction was performed to address this concern, in which ACO **2a*E*** was subjected to **7** both with and without photo-irradiation (entries 5 and 6, respectively, Table 1). As a result, no reaction was observed in any of these cases, which essentially ruled out our concern.[15] These results strongly suggest that the nitrile formation from ACO was photoinduced with the catalytic assistance of a photosensitizer, as per our expectation. Additionally, we employed other photosensitizers that generate an excited state with a high electron-donating ability (entries 7 and 8, Table 1). To our delight, the reaction with carbazole **6** gave nitrile **5** in higher yield than that of the reaction with **1**. The reaction with phenothiazine **8**[16] also managed to give **5**, albeit in lower yield. In contrast, triplet sensitizers such as benzophenone,

Table 1. Photoinduced nitrile formation from ACO.



Entry	Reagent	Irradiation[a]	Time /h	Yield /%[b]
1	**1** (1 equiv)	yes	1	40
2	**1** (0.1 equiv)	yes	4.5	40
3	**1** (1 equiv)	no	1	0
4	none	yes	1	0
5	**1** (1 equiv) + **7** (1 equiv)	no	1	0
6	**7** (1 equiv)	yes	1	0
7	**6** (1 equiv)	yes	1	55
8	**8** (1 equiv)	yes	1	38

[a] Irradiation by two LED lamps (9 W in total, λ_{max} = 365 nm). [b] Determined by ^{1}H NMR analysis using dibenzyl as an internal standard.



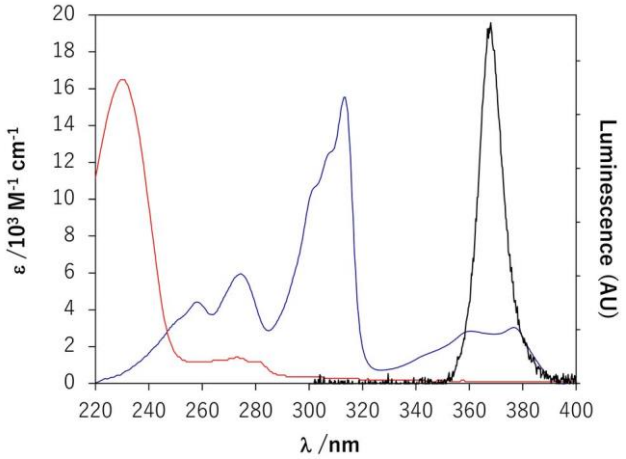
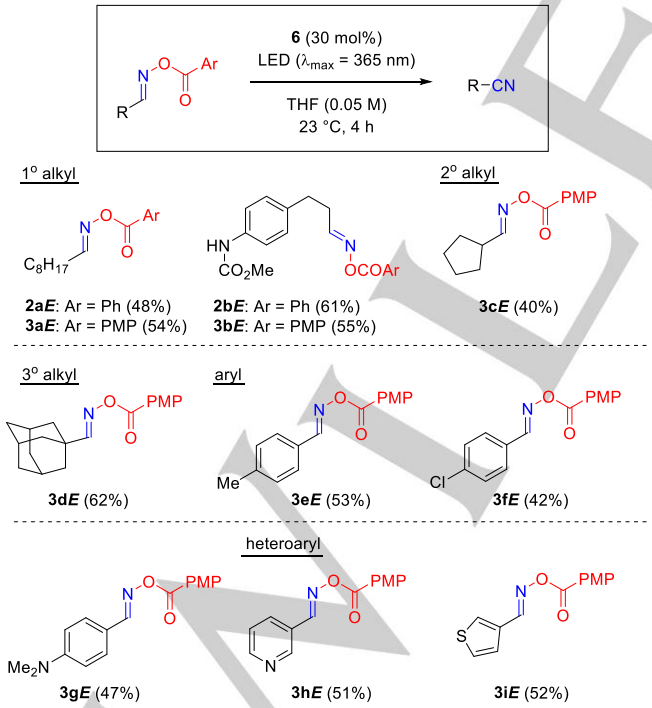


Figure 2. Absorption spectra of **2a*E*** (red) and **1** (blue), and luminescent spectrum of the employed LED lamp (black).

acetophenone, and benzil afforded no products or negligible amounts of products.

Next, we investigated the scope of photoinduced nitrile formation (Table 2). With regard to the substituents on the oxime carbon, 1°, 2°, and 3° alkyl groups were tolerated (**2a*E*–2b*E***, **3a*E*–3d*E*)**. Notably, aromatic aldehyde-derived ACOs were found to be good substrates under conditions identical to those for aliphatic variants. The electronic nature of aromatic rings had little effect on the reactivity (**3e*E*–3g*E***).[13] Moreover, ACO substrates with heteroaryl ring systems also underwent photoinduced nitrile formation (**3h*E*–3i*E***).

Table 2. Scope of photoinduced nitrile formation from ACOs.[a]



[a] Determined by ^{1}H NMR analysis. PMP = p-methoxyphenyl.

The tolerance of the developed reaction to chemical functionalities and of the chemical functionalities to the reaction conditions were examined using the robustness screening method proposed by Glorius et al.[17] In the process, the reaction of **3e*E*** was chosen as a probe reaction (Figure 3). As a result, we found that most of the tested additives were compatible with the developed reaction conditions. However, thiol additives had considerable detrimental effects on the nitrile formation under these conditions (vide infra).

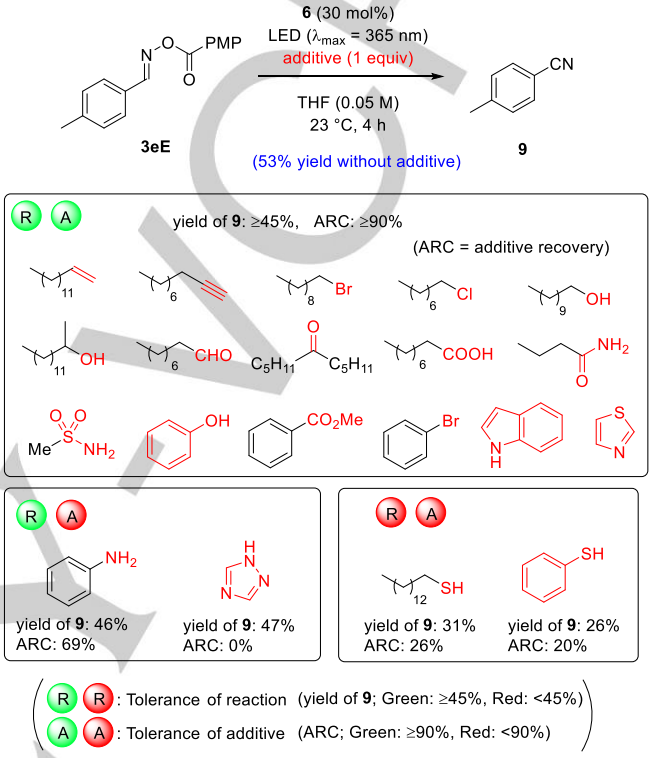
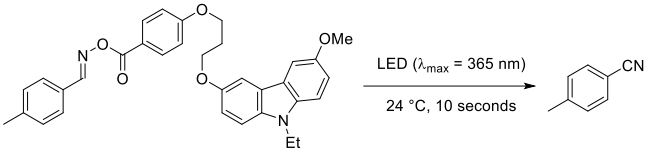


Figure 3. Examination of the functional group compatibility.

With the proof of concept for the photoinduced nitrile formation from ACO in hand, we then turned our attention to the design of the ACO structural motif concerning its application as PPG for the nitrile group. Given the highly diluted conditions and non-uniform compound distribution demanded for their application, e.g., in biological systems, it is required that a self-contained variant with carbazole and ACO units covalently bonded with each other is developed. Therefore, we designed **10**, a polymethylene-linked carbazole–ACO dyad, in which *p*-tolunitrile was arbitrarily chosen as a target nitrile. *N*-Ethyl carbazole was selected as a photosensitizer, instead of an *N*-H variant, in view of the ease of synthesis. Compound **10** can be readily prepared in a modular manner from *p*-tolualdehyde oxime. The photoinduced nitrile formation from "all-in-one" ACO **10** was investigated under diluted conditions (Table 3). Gratifyingly, when a 1.0 mM THF solution of **10** was employed in the reaction, full conversion was obtained after only a 10-s irradiation, and the desired nitrile **9** was afforded in 58% yield (entry 1). This nitrile formation reaction was also monitored at various irradiation times (Figure 4). The yield of the nitrile increased as a function of irradiation time, thereby demonstrating a high level of control over the nitrile formation with compound **10**. The quantum yield of nitrile formation from **10** was determined to be 0.82 using a chemical actinometry method with *o*-nitrobenzaldehyde as a reference (see Supporting Information).

The reaction of a further diluted solution (0.1 mM) under otherwise identical conditions gave a similar yield of **9** (entry 2). The significant enhancement of the reaction rate observed in the reactions with **10**, compared to those of ACO with a separated photosensitizer (e.g. Table 2), can be attributed not only to the dilution effect, which is typically observed in photoreactions, but also to the intramolecularity or proximity effect of the electron transfer. Based on this assumption, we surmised that the detrimental effect of thiol additives, which was confirmed in the aforementioned compatibility study (Figure 3), could be avoided by using an "all-in-one" system. To our delight, the nitrile formation from **10** in an aqueous media containing L-cysteine (5 mM) proceeded without any loss of product yield (entry 3), indicating that the herein developed system is potentially applicable to biological systems.[18] Lastly, no nitrile was formed from **10** without any photo-irradiation in THF or aqueous media (entries 4 and 5).

Table 3. Photoinduced nitrile formation from carbazole–ACO dyad **10.**



10 **9**

Entry	Conditions	Yield of **9** /%
1	1.0 mM in THF	58
2	0.1 mM in THF	59
3	0.1 mM in THF–H_2O (1:1) with L-cysteine (5 mM)	59
4[a]	1.0 mM in THF	0
5[a,b]	1.0 mM in THF–H_2O (1:1)	0

[a] No light. [b] For 72 h.

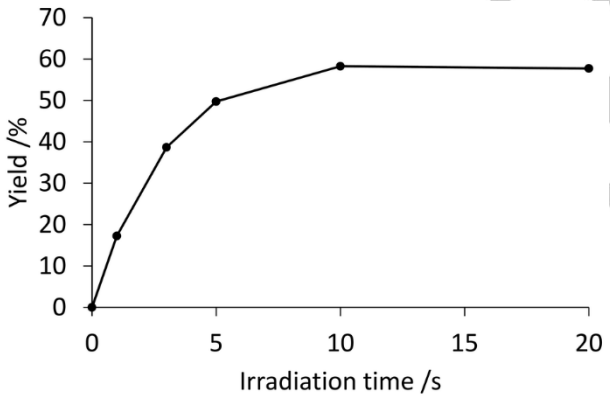
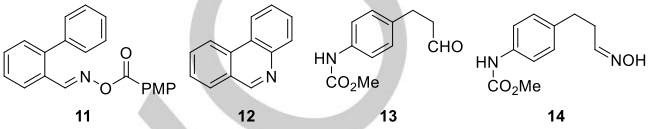


Figure 4. Nitrile formation from **10** as a function of the irradiation time (Table 1, entry 1). Conditions: 24 °C, 1.0 mM in THF, LED (λ_{max} = 365 nm). Yields determined by HPLC analysis using toluene as an internal standard.

To gain insight into the reaction mechanism, we conducted an intramolecular trapping of the transient active species. The photo-irradiation of a THF solution of ACO **11** (0.05 M) in the presence of **6** (30 mol%) at room temperature afforded cyclized product **12** (21% yield), thereby suggesting that the corresponding iminyl radical or iminyl cation derived from **11** was once formed. This result is in good agreement with the suggested reaction mechanism shown in Scheme 1a, and can rule out the possibility that the nitrile product was formed via a simple E2 elimination of the carboxylic acid from ACO, driven by an unexpected photochemical generation of a strong base.[19] Moreover, the main non-negligible byproducts were identified in the photoinduced nitrile formation from **3b*E*** (reaction shown in Table 2). Along with the desired nitrile (55% yield), aldehyde **13** and oxime **14** were obtained in 15% and 23% yield, respectively. The same reaction conditions, but without photo-irradiation, gave neither **13** nor **14**, thus revealing that the generation of aldehyde **13** and oxime **14** was not due to the simple hydrolysis of **3b*E*** by adventitious water contaminants.[20]



11 **12** **13** **14**

In conclusion, we demonstrated that ACO operates as a photoremovable protective group for nitrile groups[21] with the photocatalytic intermediacy of the carbazole molecule. In particular, a single electron transfer occurs from the excited carbazole to ACO to afford the iminyl radical, which then gives up an electron to the radical cation of carbazole, eventually leading to the nitrile formation. Both alkyl and (hetero)aryl nitriles were found to be suitable for this chemistry, with various functional groups being compatible. Moreover, an ACO that was covalently bonded to a carbazole substructure had the capability of self-contained photoinduced nitrile formation even under highly diluted conditions and in organic and aqueous media. This result demonstrated that the strategy presented herein is potentially viable in biological systems. Our ongoing research focuses on modifying the developed ACO with minute tuning of the substituents, in order to make it applicable to living systems.

Acknowledgements

Financial supports from JSPS KAKENHI Grant Number JP16K18844, Shorai Foundation for Science and Technology, and Research Foundation for Opto-Science and Technology are greatly appreciated. This work was also supported by the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, and by Special Coordination Funds for Promoting Science and Technology, Creation of Innovation Centers for Advanced Interdisciplinary Research Areas (Innovative Bioproduction Kobe), MEXT, Japan.

Keywords: nitriles • photochemistry • photosensitizers • protective groups • radicals

[1] a) A. P. Pelliccioli, J. Wirz, *Photochem. Photobiol. Sci.* **2002**, *1*, 441-458; b) H. Yu, J. Li, D. Wu, Z. Qiu, Y. Zhang, *Chem. Soc. Rev.* **2010**, *39*, 464-473; c) C. Brieke, F. Rohrbach, A. Gottschalk, G. Mayer, A. Heckel, *Angew. Chem. Int. Ed.* **2012**, *51*, 8446-8476; d) P. Klán, T. Šolomek, C. G. Bochet, A. Blanc, R. Givens, M. Rubina, V. Popik, A. Kostikov, J. Wirz, *Chem. Rev.* **2013**, *113*, 119-191.

[2] F. F. Fleming, L. Yao, P. C. Ravikumar, L. Funk, B. C. Shook, *J. Med. Chem.* **2010**, *53*, 7902-7917.

[3] a) M. Recanatini, A. Bisi, A. Cavalli, F. Belluti, S. Gobbi, A. Rampa, P. Valenti, M. Palzer, A. Palusczak, R. W. Hartmann, *J. Med. Chem.* **2001**,

44, 672-680; b) A. Wissner, D. M. Berger, D. H. Boschelli, M. B. Floyd, Jr., L. M. Greenberger, B. C. Gruber, B. D. Johnson, N. Mamuya, R. Nilakantan, M. F. Reich, R. Shen, H.-R. Tsou, E. Upeslacis, Y. F. Wang, B. Wu, F. Ye, N. Zhang, *J. Med. Chem.* **2000**, *43*, 3244-3256.

[4] P. D. Greenspan, K. L. Clark, R. A. Tommasi, S. D. Cowen, L. W. McQuire, D. L. Farley, J. H. van Duzer, R. L. Goldberg, H. Zhou, Z. Du, J. J. Fitt, D. E. Coppa, Z. Fang, W. Macchia, L. Zhu, M. P. Capparelli, R. Goldstein, A. M. Wigg, J. R. Doughty, R. S. Bohacek, A. K. Knap, *J. Med. Chem.* **2001**, *44*, 4524-4534.

[5] a) A. Mordzinski, A. L. Sobolewski, D. H. Levy, *J. Phys. Chem. A* **1997**, *101*, 8221-8226; b) D. Yu, F. Huang, S. Ding, G. Feng, *Anal. Chem.* **2014**, *86*, 8835-8841.

[6] a) J. del Mármol, O. Filevich, R. Etchenique, *Anal. Chem.* **2010**, *82*, 6259-6264; b) Y.-J. Tu, S. Mazumder, J. F. Endicott, C. Turro, J. J. Kodanko, H. B. Schlegel, *Inorg. Chem.* **2015**, *54*, 8003-8011; c) A. Li, C. Turro, J. J. Kodanko, *Chem. Commun.* **2018**, *54*, 1280-1290.

[7] L. Yang, P. Gao, X.-H. Duan, Y.-R. Gu, L.-N. Guo, *Org. Lett.* **2018**, *20*, 1034-1037.

[8] R. Matsubara, Y.-S. Shin, T. Shimada, M. Hayashi, *Asian J. Org. Chem.* **2014**, *3*, 1054-1057.

[9] I. Saito, H. Ikehira, R. Kasatani, M. Watanabe, T. Matsuura, *J. Am. Chem. Soc.* **1986**, *108*, 3115-3117.

[10] a) H. Jiang, X. An, K. Tong, T. Zheng, Y. Zhang, S. Yu, *Angew. Chem. Int. Ed.* **2015**, *54*, 4055-4059; b) X.-D. An, S. Yu, *Org. Lett.* **2015**, *17*, 2692-2695.

[11] R. Matsubara, T. Shimada, Y. Kobori, T. Yabuta, T. Osakai, M. Hayashi, *Chem. Asian J.* **2016**, *11*, 2006-2010.

[12] a) G. J. Karabatsos, R. A. Taller, F. M. Vane, *J. Am. Chem. Soc.* **1963**, *85*, 2326-2327; b) G. J. Karabatsos, R. A. Taller, *Tetrahedron* **1968**, *24*, 3347-3360.

[13] The *E*-configuration of **2a*E*** and **3e*E*** was determined by X-ray diffraction analysis. The configurations of the other substrates were speculated in analogy. CCDC 1843044 and 1843045 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[14] X.-D. An, S. Yu, *Org. Lett.* **2015**, *17*, 5064-5067.

[15] The acidity of some Brønsted acids increased upon photo-irradiation. M. Shirai, M. Tsunooka, *Prog. Polym. Sci.* **1996**, *21*, 1-45.

[16] E. H. Discekici, N. J. Treat, S. O. Poelma, K. M. Mattson, Z. M. Hudson, Y. Luo, C. J. Hawker, J. R. de Alaniz, *Chem. Commun.* **2015**, *51*, 11705-11708.

[17] K. D. Collins, F. Glorius, *Nature Chem.* **2013**, *5*, 597-601.

[18] Biothiols exist in living cells at millimolar concentrations. M. Cao, H. Chen, D. Chen, Z. Xu, S. H. Liu, X. Chen, J. Yin, *Chem. Commun.* **2016**, *52*, 721-724.

[19] When *N*-H carbazole **6** is used the alternative mechanism for nitrile formation can be proposed; the formed radical cation of **6** undergoes the deprotonation of the acidic proton on the carbazole nitrogen to afford the nitrogen radical species, which abstracts the hydrogen atom from the iminyl radical to grant the corresponding nitrile. We acknowledge the anonymous reviewer for this fruitful suggestion.

[20] Although the detailed mechanism for the generation of byproducts is still unknown, the formation of aldehyde **13** can be explained by taking into account the hydrogen abstraction by the generated iminyl radical. The formation of oxime **14** may occur through the O–COAr bond cleavage, following the initial single electron transfer.

[21] The photoinduced nitrile formation from oxime esters, which bear chromophores on the carbon atom of the C=N double bond, was reported as a side reaction of the iminyl radical generation: a) R. Alonso, P. J. Campos, B. García, M. A. Rodríguez, *Org. Lett.* **2006**, *8*, 3521-3523; b) R. T. McBurney, A. M. Z. Slawin, L. A. Smart, Y. Yu, J. C. Walton, *Chem. Commun.* **2011**, *47*, 7974-7976. Note that in these reported cases the efficiency of nitrile releasing is determined by the substrate structure. Therefore, the application as a photoremovable protective group could not be achieved.

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION

In this work, a photoremovable protective group for nitrile moieties was developed. The reaction mechanism was based on the single electron transfer from the photosensitizer (carbazole) to *O*-(arylcarbonyl)oxime. A wide range of nitriles could be applied, with a variety of functional groups being well tolerated. This methodology was also successful in a highly diluted aqueous solution, thus demonstrating the potential applicability to biological systems.

Ryosuke Matsubara, Ubaidah Md Idros, Tatsushi Yabuta, Huiying Ma, Masahiko Hayashi, Kazuo Eda*

Page No. – Page No.

Photoinduced nitrile formation from *O*-(arylcarbonyl)oxime: Usage as a photoremovable protective group