Journal of Photochemistry and Photobiology A: Chemistry 321 (2016) 41–47

Contents lists available at ScienceDirect

Journal of Photochemistry and Photobiology A: Chemistry

journal homepage: www.elsevier.com/locate/jphotochem

Influences of alpha-substituent in 4,5-dimethoxy-2-nitrobenzyl-protected esters on both photocleavage rate and subsequent photoreaction of the generated 2-nitrosophenyl ketones: A novel photorearrangement of 2-nitrosophenyl ketones

Noriko Chikaraishi Kasuga[a,b], Yusuke Saito[a], Naomichi Okamura[a], Tatsuya Miyazaki[a], Hikaru Satou[a], Kazuhiro Watanabe[a], Takaaki Ohta[a], Shu-hei Morimoto[a], Kazuo Yamaguchi[a,b,*]

[a] Department of Chemistry, Faculty of Science, Kanagawa University, Tsuchiya, Hiratsuka, Kanagawa 259-1293, Japan
[b] Research Institute for Photofunctionalized Materials, Kanagawa University, Tsuchiya, Hiratsuka, Kanagawa 259-1293, Japan

ARTICLE INFO

Article history:
Received 1 December 2015
Received in revised form 12 January 2016
Accepted 14 January 2016
Available online 15 January 2016

Keywords:
Alpha-substitutent
2-Nitrobenzyl
Esters
2-Nitrosoarene
Branched-acyl-group
Photorearrangment

ABSTRACT

Ultraviolet(UV)-induced photodeprotection of 2-nitrobenzyl esters to release the acid with formation of the corresponding 2-nitrosoketone proceeds rapidly when the α-position in the 2-nitrobenzyl group is substituted by a branched alkyl group. The generated 2-nitrosophenyl ketones undergo multiple photoreactions, including a unique photorearrangement, depending upon the nature of the α-substituent. 2-Nitrosoketone bearing an isopropyl substituent mainly undergoes this rearrangement to afford a bicyclic oxazole via a shift of the isopropyl group to the bridgehead position, resulting in loss of aromaticity of the six-membered ring. 2-Nitrosopheyl ketone bearing a tertiary-butyl substituent gives mainly azoxy and azo compounds via intermolecular reaction of nitrosoketones with loss of isobutene. The photorearrangement does not proceed in the case of the phenyl-substituted compound. These findings will be helpful for the selection and/or design of photolabile protecting groups.

1. Introduction

The 2-nitrobenzyl group (NB) is widely used as a photoremovable protecting group (PPG) for caged compounds, which are inert, but can be deprotected under light irradiation to release (uncage) an active species, such as ATP or biomodulators, in situ [1–7]. Caged compounds are also used in kinetics studies and to examine the concentration dependence of cellular reactions [8–10]. In addition to such biological applications, NBs have been widely employed to protect various functional groups in the fields of organic synthesis and materials science [1,2,11–20].

It is well-known that deprotection of 2-nitrobenzyl derivatives through light-irradiation produces reactive 2-nitrosoarenes, which can undergo nitroso Diels–Alder reactions, *N*-nitroso aldol reactions, and nitroso-ene reactions, and are also intermediates for preparation of functional azo compounds, as described in recent reviews [21–24]. Therefore, to avoid side reactions of 2-nitrosophenyl ketones formed as by-products of photodeprotection reactions, several chemical modifications of the 2-nitrobenzyl group have been investigated [1,7,25].

Our recent research interests have focused on NB-protected silane coupling agents, which are surface-modification agents used to control the hydrophilicity and hydrophobicity of inorganic surfaces, and also to form masking patterns for the production of organic thin film transistors and intelligent materials for biotechnology [26–28]. We have frequently employed PPGs based on 6-nitroveratryl analogs, 4,5-dimethoxy-2-nitrobenzyl derivatives of NB, because they can be deprotected with lower-energy ultraviolet light than unsubstituted NBs [3,7,12].

Structural modifications of NB that have so far been investigated can be divided primarily into two categories: i) modification of the aromatic ring and ii) substitution at the benzylic carbon atom [6]. During the course of our studies of these photolabile materials, we noted that PPG removal proceeded smoothly when the α-position was substituted with a branched alkyl group such as isopropyl (^{i}Pr) or tertiary-butyl (^{t}Bu). In this paper, we report the effect of various α-substituents on the photochemical reactions of

* Corresponding author at: Department of Chemistry, Faculty of Science, Kanagawa University, Tsuchiya, Hiratsuka, Kanagawa 259-1293, Japan. Fax: +81 463 58 9684.
E-mail address: kazu@kanagawa-u.ac.jp (K. Yamaguchi).

http://dx.doi.org/10.1016/j.jphotochem.2016.01.012
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four simple 4-bromobenzoates (**1–4**), in which the carboxylic group is protected by an α-substituted 4,5-dimethoxy-2-nitrobenzyl group, as well as the four 4,5-dimethoxy-2-nitrosoarenes (**5–8**) that are released upon photodeprotection of the corresponding esters, as shown in Fig. 1.

2. Experimental

2.1. Materials

The following reagent-grade chemicals were used as received: iodine, HNO_3, veratrol, KBr, dimethyl sulfoxide (DMSO), $CHCl_3$, CH_2Cl_2, MeOH, EtOAc, CH_3CN, tetrahydrofuran, acetone, 1,4-dioxane and acetic anhydride (Wako); 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), 4-dimethylaminopyridine (DMAP) and propionic anhydride, pivalic anhydride (TCI); EtOH (Kanto); $CDCl_3$, DMSO-d_6 and CD_3CN (99.9 D atom %, Isotec).

2.2. Instrumentation/analytical procedures

Photoirradiation was performed with a high-pressure mercury lamp, using an Ushio HB-50106-AA-A/UHC-500-D system. Illumination intensity was measured with a Ushio UIT-201 instrument. HPLC measurements were performed on a Shimadzu LC-20AD system fitted with an Ultron ODS column, with CH_3CN: H_2O = 6:1 as the eluent. CHN elemental analyses were performed with a PerkinElmer PE2400 series II CHNS/O analyzer. ESI MS spectra in positive-ion mode were recorded using a JEOL JMS-T100LC system in the range of *m*/*z* 100–1000. Reserpine was used as an internal reference. ^1H and ^{13}C NMR spectra were recorded on a JEOL ECP300 NMR or a JEOL ECP500 NMR spectrometer with TMS as the internal reference.

A single crystal of **10**, **13** or **14** was mounted on a loop, and intensity data were collected at 120 K on a Rigaku Saturn CCD diffractometer with Mo-Kα radiation for calculation of cell constants. Structures were solved by direct methods and refined by full-matrix least-squares calculation on F^2 using the Yadokari program package [30]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were placed geometrically and treated using the riding model. Crystal data and the results of structural refinement of **10**, **13** and **14** are summarized in Table S1 and have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no. CCDC 988420, 1417307 and 1417308, respectively.

2.3. Synthesis of 1-(4,5-dimethoxy-2-nitrophenyl)-2-methylpropyl 4-bromobenzoate, **2** and the related acetate **2′**

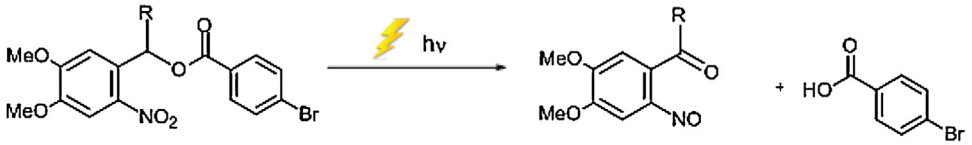
A mixture of 1.33 g of 4-bromobenzoic acid (6.63 mmol), 1.27 g of EDC (6.63 mmol), 1.13 g of 1-(4,5-dimethoxy-2-nitrophenyl)-2-methylpropan-1-ol (4.42 mmol) and 0.65 g of DMAP dissolved in 55 mL of THF was stirred at room temperature for a few hours until the alcohol was completely consumed, as confirmed by TLC. Concentration on a rotary evaporator afforded a residual yellow solid, which was taken up in 80 mL of $CHCl_3$. The organic layer was washed with diluted hydrochloric acid (40 mL of H_2O and 10 mL of 2 M HCl) and saturated $NaHCO_3$ (30 mL × 3), then dried over anhydrous $MgSO_4$, and concentrated. A solution of the residue in 10 mL of ethyl acetate solution was slowly evaporated to give pale-yellow block crystals (1.55 g, 80% yield), which were soluble in $CHCl_3$, CH_2Cl_2, EtOAc and acetone; sparingly soluble in MeOH. Anal. Found: C, 52.07; H, 4.36; N, 3.18. Calcd for $C_{19}H_{20}BrNO_6$ C, 52.07; H, 4.60; N, 3.20%. ^1H NMR (400 MHz, 21.5 °C, $CDCl_3$): δ 1.07 (3H, d, *J* = 6.8 Hz), 1.12 (3H, d, *J* = 6.8 Hz), 2.35 (1H, m), 3.87 (3H, s), 3.94 (3H, s), 6.54 (1H, d, *J* = 5.8 Hz), 6.93 (1H, s), 7.61 (2H, d, *J* = 8.6 Hz), 7.62 (1H, s), 7.93 (2H, d, *J* = 8.6 Hz). ^{13}C NMR (126 MHz, 22.0 °C, $CDCl_3$): δ 17.51, 19.45, 33.47, 56.29, 56.35, 76.33, 107.73, 108.73, 128.45, 128.92, 130.83, 131.00, 131.97, 140.96, 148.05, 153.13, 164.92.

Acetate ester **2′** was similarly prepared, using acetic anhydride instead of 4-bromobenzoic acid and EDC. **2′**. ^1H NMR (400 MHz, 24.2 °C, $CDCl_3$): δ 0.98 (3H, d, *J* = 6.4 Hz), 1.00 (3H, d, *J* = 6.4 Hz), 2.09 (3H, s), 2.18 (1H, m), 3.94 (3H, s), 3.96 (3H, s), 6.33 (1H, d, *J* = 5.6 Hz), 6.90 (1H, s), 7.59 (1H, s). ^{13}C NMR (126 MHz, 22.1 °C, $CDCl_3$): δ 17.42, 19.23, 20.96, 33.29, 56.34, 56.36, 75.22, 107.80, 108.92, 131.09, 141.01, 147.93, 153.06, 170.04. ESI MS 320.1079, calcd for $C_{14}H_{19}NO_4Na$ [M + Na^+] 320.1110.

The other related esters **1**, **3**, **3′** and **4** were also similarly prepared. Characterization data are presented in supporting information.

2.4. Isolation of two photolysis products, 2-nitrosoketone (**6**) and its cyclic isomer (**10**), from irradiated solution of isopropyl-substituted 2-nitrobenzyl acetate (**2′**)

Compounds **6** and **10** were isolated using acetate **2′** instead of 4-bromobenzoate **2**, because the generated acetic acid could be easily removed under reduced pressure. A THF solution (100 mL) of



1 R=Me **2** R=^{i}Pr **3** R=^{t}Bu **4** R=Ph

5 R=Me **6** R=^{i}Pr **7** R=^{t}Bu **8** R=Ph

Fig. 1. Photo-cleavage reaction of four 4,5-dimethoxy-2-nitrobenzyl esters.

2′ (3 mM) was prepared in a quartz beaker in air at ambient temperature. Photolysis of the solution was performed using an Ushio UHC-500-D/HB-50106-AA-A system (λ > 300 nm with 50 mW/cm^2 intensity) for 6 h. The reaction progress was monitored by HPLC. Two products, **6** and **10**, were isolated by column chromatography (silica gel, Wako C-300, EtOAc: hexane = 3:1) in 10% and 50% yield, respectively; their structures were established by means of ^{1}H NMR, ^{13}C NMR and ESI MS analyses.

2.4.1. 1-(4,5-Dimethoxy-2-nitrosophenyl)-2-methylpropan-1-one, ***6***

Green viscous liquid. ^{1}H NMR (400 MHz, 24.5 °C, $CDCl_3$) δ: 1.26 (6H, d, J = 6.9 Hz), 3.57 (1H, septet, J = 6.9 Hz), 3.89 (3H, s), 4.06 (3H, s), 6.23 (1H, s), 7.11 (1H, s). ^{13}C NMR (125 MHz, 25.5 °C, $CDCl_3$) δ: 18.56, 43.69, 56.25, 56.84, 91.71, 109.62, 138.57, 150.84, 155.84, 159.40, 209.68. ESI MS 260.0855, calcd for $C_{12}H_{15}NO_4Na$ [M + Na$^+$] 260.0899.

2.4.2. 5,6-Dimethoxy-3a-(1-methylethyl)-2,1-benzisoxazol-3(3aH)-one, ***10***

The isolated powder was dissolved in methanol at 70 °C and brown crystals suitable for single-crystal X-ray analysis were grown by slow evaporation. ^{1}H NMR (400 MHz, 24.1 °C, $CDCl_3$) δ: 0.94 (3H, d, J = 6.9 Hz), 1.12 (3H, d, J = 6 .9 Hz), 1.99 (1H, septet, J = 6.9 Hz), 3.71 (3H, s), 3.84 (3H, s), 5.36 (1H, s), 5.65 (1H, s). ^{13}C NMR (125 MHz, 27.7 °C, $CDCl_3$) δ: 16.21, 17.36, 40.26, 55.16, 55.80, 56.57, 88.26, 97.31, 149.92, 158.41, 168.44, 177.11. Anal. Found: C, 60.51; H, 6.57; N, 5.58. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90.

2.5. Isolation of photolysis products ***7, 12, 13*** *and* ***14*** *from a solution of α-^{t}Bu-substituted 2-nitrobenzyl acetate (****3′****)*

Isolation of products **7**, **12**, **13** and **14** from an irradiated solution of ^{t}Bu-substituted derivative **3′** was difficult because of low yields and instability of the products. Nitroso compound **7** was isolated in 4% yield from an irradiated CH_3CN solution of **3′** (61 mM, λ = 365 nm, intensity 20 mW/cm^2, ambient temperature, 15.5 h). The azoxy and azo compounds **12**, **13** and **14** were obtained from a solution of **3′** in CH_3CN (23 mM, λ = 300 nm, 50 mW/cm^2 intensity, ambient temperature, 5 h) in 10%, 12% and 1% yield, respectively. These products were isolated by column chromatography (silica gel, Wako C-300, EtOAc: hexane = 3:1) followed by recycling preparative HPLC. The structures of **7**, **12**, **13** and **14** were confirmed by ^{1}H, ^{13}C NMR and ESI MS. The molecular structures of **13** and **14** were also established by single-crystal X-ray analysis.

2.5.1. 1-(4,5-Dimethoxy-2-nitrosophenyl)-2,2-dimethylpropan-1-one, ***7***

Green visous liquid. ^{1}H NMR (400 MHz, 22.7 °C, $CDCl_3$) δ: 1.28 (9H, s), 3.91 (3H, s), 4.04 (3H, s), 6.63 (1H, s), 6.80 (1H, s). ^{13}C NMR (125 MHz, 24.3 °C, $CDCl_3$) δ: 27.33, 45.48, 56.21, 56.79, 107.62, 149.52, 155.70, 159.42, 213.46. ESI MS 274.1070, calcd for $C_{13}H_{17}NO_4Na$ [M + Na$^+$] 274.1055.

2.5.2. 2-[2-[2-(2,2-Dimethylpropyl-1-oxo)-4,5-dimethoxyphenyl]-1-oxidodiazenyl]-4,5-dimethoxy-2,2-dimethylpropan-1-one, ***12***

Orange crystals obtained by liquid-liquid diffusion of ethyl acetate solution of **12** and hexane. ^{1}H NMR (400 MHz, 23.7 °C, $CDCl_3$) δ: 1.23 (18H, s), 3.93 (3H,s), 3.94 (3H, s), 3.95 (3H, s), 3.95 (3H, s), 6.60 (1H, s), 6.72 (1H, s), 7.56 (1H, s), 8.64 (1H, s). ^{13}C NMR (125 MHz, 22.9 °C, $CDCl_3$) δ: 27.32, 27.50, 45.20, 45.46, 56.07, 56.17, 56.31, 56.39, 105.17, 106.41, 107.83, 108.38, 129.59, 133.93, 134.49, 138.14, 148.10, 148.71, 149.54, 151.58, 211.23, 212.99. ESI MS 509.2229, calcd for $C_{26}H_{34}N_2O_7Na$ [M + Na$^+$] 509.2264.

2.5.3. 2-[2-[2-(2,2-Dimethylpropyl-1-oxo)-4,5-dimethoxyphenyl]-1-oxidodiazenyl]benzoic acid, ***13***

Yellow crystals obtained by liquid-liquid diffusion of ethyl acetate solution of **13** and hexane. ^{1}H NMR (400 MHz, 25.0 °C, $CDCl_3$) δ: 1.25 (9H, s), 3.97 (3H, s), 3.98 (3H, s), 4.00 (3H, s), 4.02 (3H, s), 6.69 (1H, s), 7.52 (1H, s), 7.89 (1H, s), 8.46 (1H, s). ^{13}C NMR (125 MHz, 25.8 °C, $CDCl_3$) δ: 27.47, 45.47, 56.31, 56.38, 56.48, 56.56, 104.76, 105.05, 108.83, 114.40, 118.70, 130.29, 137.00, 138.00, 149.33, 149.96, 152.00, 152.31, 166.22, 210.59. ESI MS 274.1070, calcd for $C_{13}H_{17}NO_4Na$ [M + Na$^+$] 274.1055.

2.5.4. 2,2′-Azobis[4,5-dimethoxybenzoic acid], ***14***

Brown crystals suitable for single-crystal X-ray analysis were grown by vapor-diffusion of an inner solution of the powder dissolved in hot DMSO with hexane as the external solvent. The crystals were soluble in $CHCl_3$ and DMSO, but insoluble in CH_3CN. Anal. Found: C, 54.14; H, 4.74; N, 6.41. Calcd for **14**·0.5H_2O or $C_{22}H_{27}N_2O_{8.5}$: C, 54.14; H, 4.75; N, 6.41. ^{1}H NMR (400 MHz, 23.3 °C, DMSO-d_6) δ: 3.84 (3H, s), 3.91 (3H, s), 7.23 (1H, s), 7.38 (1H, s). ^{13}C NMR (125 MHz, 25.3 °C, DMSO-d_6) δ: 55.65, 56.08, 99.40, 111.71, 124.61, 145.08, 150.74, 151.35.

3. Results and discussion

The 4,5-dimethoxy-2-nitrobenzyl esters **1**–**4** were prepared quantitatively by EDC-mediated condensation reaction of the corresponding 4,5-dimethoxy-2-nitrobenzyl alcohol and 4-bromobenzoic acid, and purified by crystallization from a mixed solution of ethyl acetate and hexane, or by column chromatography.

Deprotection rates of the 4,5-dimethoxy-2-nitrobenzyl benzoates were determined from HPLC measurements of remaining amounts of each benzoate (**1**–**4**) in 0.1 mM CH_3CN solution irradiated with a high-pressure mercury lamp. The plots of ln (Ct/C_0) (concentration of esters at time t over t = 0 s) versus the irradiation time were linear, as shown in Fig. 2, indicating that the photoreactions of these four model compounds were pseudo first-order within the measurement time.

Photoirradiation of the four benzoates generated 4-bromobenzoic acid and the corresponding 2-nitrosoarenes formed via the *aci*-nitro intermediate [3,31,32]. The area ratio of each ester showed that photocleavage of α-branched alkyl-substituted esters, i.e. ^{i}Pr-substituted (**2**) and ^{t}Bu-substituted esters (**3**), occurred faster than that of the methyl-substituted analog (**1**) (Fig. 2), in

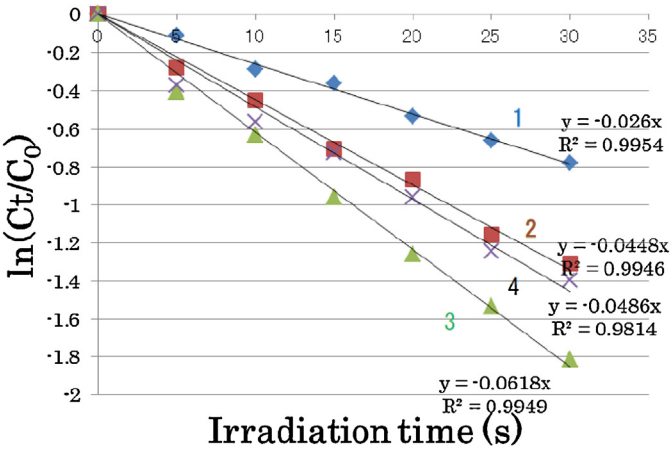


Fig. 2. Plots of ln(Ct/C_0) versus irradiation time of 0.1 mM CH_3CN solutions of **1**–**4**.

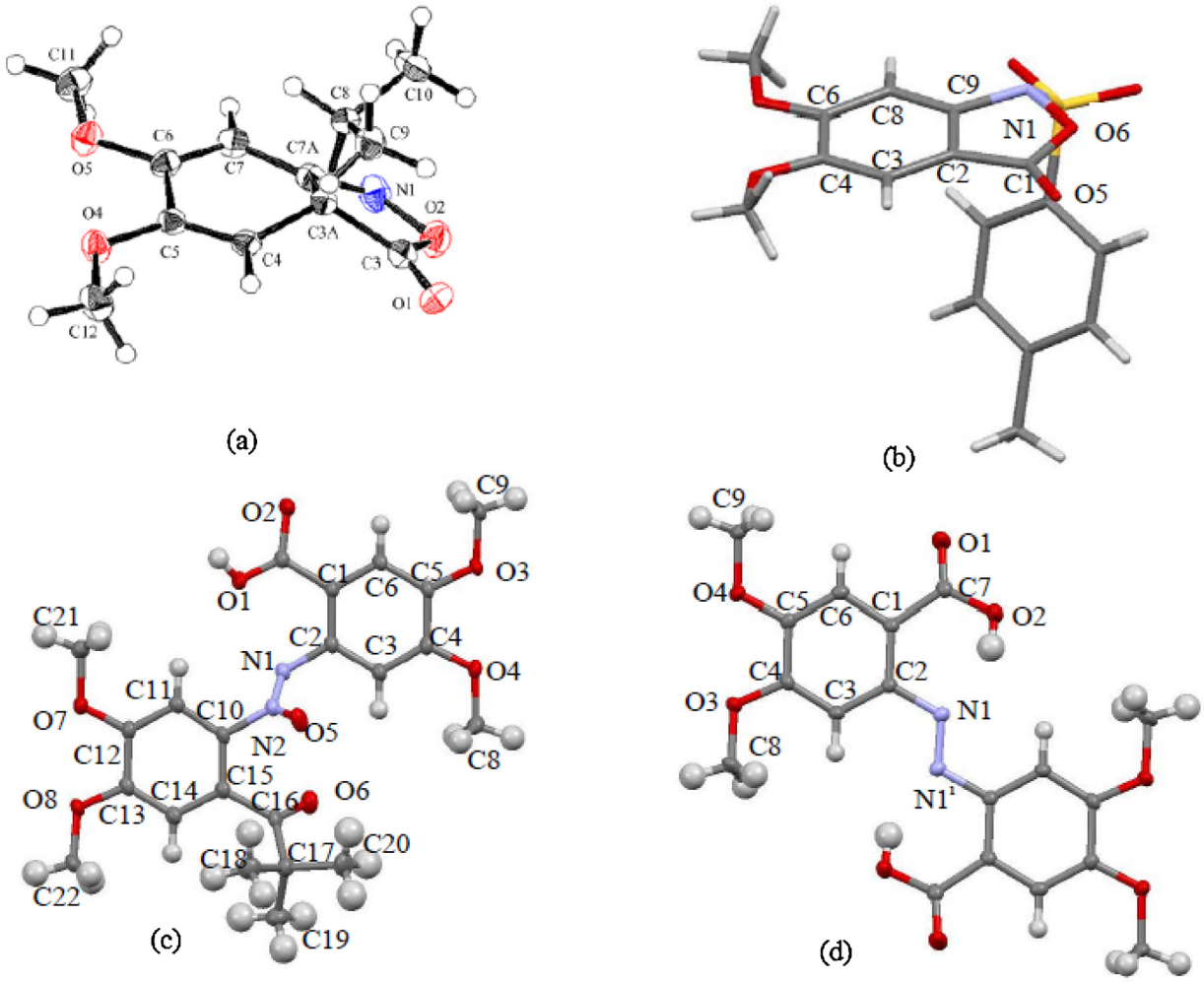


Fig. 3. (a) ORTEP drawing of **10** showing thermal ellipsoids at the 50% probability level. (b) Molecular structure of 5,6-dimethoxy-1-(4-tolylsulfonyl)-benzo[*c*]isoxazol-3(*1H*)-one [33]. (c) Molecular structure of **13**. (d) Molecular structure of **14** in the crystal. (For interpretation of the references to color in the text, the reader is referred to the web version of this article.)

agreement with Metzker's findings on nucleotide protection by ether bonding [29].

To our surprise, however, continued UV irradiation of a solution of **2** produced a large amount of another compound. Using acetate derivative **2′** instead of the benzoate **2** for convenience, we isolated 2-nitrosophenylketone (**6**) and a brown solid (**10**), which was crystallized from methanolic solution. Single-crystal X-ray analysis of **10** revealed the structure depicted in Fig. 3(a).

Interestingly, the isopropyl group in **10** is 1,2-shifted onto the 6-membered ring and the nitroso group is incorporated in a 5-membered ring. A similar compound, 5,6-dimethoxy-1-(4-tolylsulfonyl)benzo[*c*]isoxazol-3(*1H*)-one (Fig. 3(b)) [33], has a planar aromatic ring, but in **10**, the ring was distorted. Additionally, the C7–C7A and C3A–C4 bond lengths (1.438(2) and 1.4864(19) Å, respectively) were longer than that of a typical aromatic C—C bond (1.39 Å) as shown in Table 1. Loss of aromaticity in the six-membered ring was supported by the ^{1}H NMR chemical shifts of two signals of **10** in the region between 5 and 6 ppm (marked with orange asterisks in Fig. 4). The signals of the 6-membered ring protons of **10** appeared at 5.39 and 5.74 ppm in $CDCl_3$, i.e., at higher field than the aromatic ring protons of 2-nitrosoarene **6**, which were observed at 6.42 and 7.16 ppm. To our knowledge, this type of rearrangement has not been described before.

In contrast to the photoreaction of ^{i}Pr-substituted esters **2** and **2′**, UV irradiation of ^{t}Bu ester **3** rapidly gave a complex mixture, as can be seen in Fig. 5(b). Although we could not identify all of the products, four compounds were identified. We could not isolate **11**, a cyclic isomer of **7**, but its existence was indicated by the ^{1}H NMR signals between 5 and 6 ppm (Fig. 5(b), marked with green asterisks), at similar chemical shift values to those of **7**. Two azoxy compounds (**12** and **13**) and an azo compound (**14**) were isolated from the mixture by column chromatography and recycling preparative HPLC. Their molecular structures were determined by ESI MS (**12**) or single-crystal X-ray analysis (**13** and **14**), as shown in Fig. 3(c) and (d). Their ^{1}H NMR spectra are shown in Fig. 5(c) and (d). Formation of the intermolecular reaction products, azoxy and azo compounds, proceeded with release of isobutene, as confirmed by GC and ^{1}H NMR (red asterisks). One of the reasons for intermolecular condensation of ^{t}Bu derivative would be explained by elimination of the bulky ^{t}Bu group occurs easily compared to that for the Me and ^{i}Pr derivatives. Unexpected and unclarified behavior of ^{t}Bu compound via ^{i}Pr one has recently reported for Newman–Kwart rearrangement [34]. The yield of **12** was less than that of **13**, judging from the signal areas.

The relative amounts of the photoreaction products are summarized in Table 2.

When methyl-substituted ester **1** was photoirradiated, deprotection proceeded relatively slowly compared to the other three esters. The main product was the 2-nitroso compound, 1-(4,5-dimethoxy-2-nitrosophenyl) ethanone, **5** [35]. The cyclic isomer **9**

Table 1
Selected bond distances (Å), angles (°) and torsion angles (°) of compounds **10**,**13** and **14**.

	10	5,6-Dimethoxy-1-(4-tolylsulfonyl)benzo[*c*]isoxazol-3(*1H*)-one[a]	
C7–C6	1.3554(19)	C9–C8	1.387(3)
C6–C5	1.4871(18)	C8–C6	1.381(3)
C5–C4	1.3578(16)	C6–C4	1.424(3)
C4–C3A	1.5081(18)	C4–C3	1.371(3)
C3A–C7A	1.4862(19)	C3–C2	1.396(4)
C7A–C7	1.438(2)	C2–C9	1.365(3)
C7A–N1	1.2944(18)	C9–N1	1.426(3)
N1–O2	1.4688(17)	N1–O6	1.436(3)
O2–C3	1.3708(18)	O6–C1	1.392(3)
C3–C3A	1.5115(19)	C1–C2	1.451(4)
C3A–C8	1.5935(19)		
C7A–C7–C6	115.83(12)	C9–C8–C6	116.9(2)
C5–C6–C7	121.63(12)	C8–C6–C4	121.4(2)
C4–C5–C6	121.35(12)	C6–C4–C3	120.1(2)
C3A–C4–C5	118.07(12)		
C7–C7A–C3A	120.01(12)		
C5–C6–C7–C7A	−179.81(12)		
C6–C5–C4–C3A	4.93(19)		
C6–C7–C7A–N1	152.61(14)		
C5–C4–C3A–C3	−144.14(13)		
	13		**14**
N1–N2	1.271(2)	N1 ^{i}–N1	1.265(3)
N2–C10	1.462(2)		
N1–C2	1.425(2)	N1–C2	1.410(3)
N2–C10	1.462(2)		
O1–C7	1.228(2)	O1–C7	1.201(3)
O2–C7	1.322(2)	O2–C7	1.324(2)
N2–N1–C2	115.24(15)	N1^{i}–N1–C2	115.5(2)
O5–N2–N1	128.04(16)		
N1–N2–C10	114.61(15)		
C2–N1–N2–O5	3.4(3)	N1 ^{i}–N1–C2–C3	−5.7(3)

Symmetry operation; $i = -x, -y, 2-z$.
[a] Data from Ref. [33].

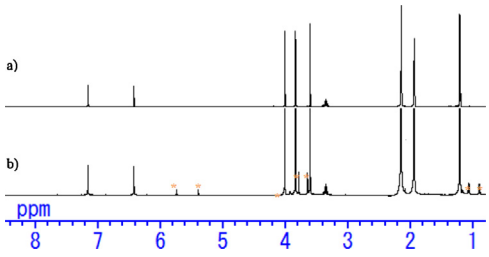


Fig. 4. (a) ^{1}H NMR spectra of **6** in CD_3CN, and (b) after irradiation for 10 min. The orange asterisks show signals of **10**. Two signals near 2 ppm are those of water and acetonitrile and the signal at 3.6 ppm is due to the internal reference, 1,4-dioxane. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

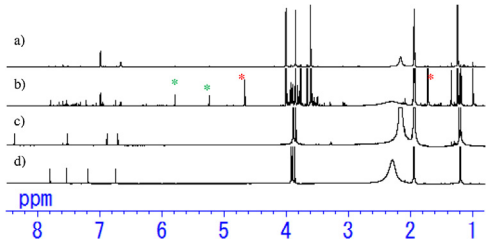


Fig. 5. (a) ^{1}H NMR spectra of **7** in CD_3CN, (b) after irradiation for 10 min, (c) **12** in CD_3CN and (d) **13** in CD_3CN. The signals marked with green asterisks are assigned to **7**. Two signals near 2 ppm are those of water and acetonitrile and the one at 3.6 ppm is due to the internal reference, 1,4-dioxane. The signals at at 1.72 and 4.66 ppm marked with red asterisks are due to isobutene. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

was also formed from **5**, but the yield was very much lower than in the case of isopropyl derivative **2**, and this may be the main reason why this rearrangement has not been reported before. When a solution of ^{i}Pr-substituted ester **2** was irradiated in CD_3CN, signals of **6** and its isomer **10** appeared within 30 min, while signals of the compound formed by intermolecular reaction corresponding to **13** for ^{t}Bu one were observed only after irradiation for 15 h. Irradiation of a solution of ^{t}Bu-substituted derivative **3** afforded a complex mixture, though azo compound **14** was accumulated as a brown solid due to its low solubility in CD_3CN. Other photolysis products of **3** could not be isolated because of their low yield and instability. This would account for the fact that the sum of the yields of **7**, **11**, **12**, **13** and **14** is smaller than the amount of the 4-bromobenzoic acid. Compounds **7** and **11** readily undergo intermolecular condensation, in contrast to the corresponding isopropyl-substituted compounds **6** and **10**.

Photoreaction of the isolated 2-nitrosophenyl ketones, **5**–**8**, was next performed to examine whether their successive reactions were influenced by protons from the deprotected acids (Table 2). The rearrangement product **9** was observed when 1-(4,5-dimethoxy-2-nitrosophenyl) ethan-1-one **5** was irradiated. Intramolecular isomerization of ^{i}Pr-substituted compound **6** also proceeded efficiently. The sum of **6** and **10** was more than 90% and the combined yield of other intermolecular products was less than one percent. Photodegradation of ^{t}Bu-substituted derivative **7** proceeded more rapidly than that of ester **3**. These results indicated that successive photoreaction of the three 2-nitrosophenyl ketones proceeded readily in the absence of protons, even in the case of ^{t}Bu-substituted compound **7**. The phenyl-substituted 2-nitroso compound **8** [36], which can be stored for weeks in a refrigerator at around −18 °C was little changed after 30-min UV irradiation. The photoreaction products of the

Table 2
Ratios (%) of products formed by UV irradiation of 2-nitrobenzyl esters and the isolated 2-nitroarenes.

Starting compound	Ester remaining	4-Bromo-benzoic acid	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
2-nitrobenzyl ester												
1[a]	48	37	31	–	–	–	1	–	–	–	–	–
2[a]	22	66	–	17	–	–	–	28	–	–	–	–
3[a]	5	85	–	–	7	–	–	–	13	2	<1	16
4[a]	22	69	–	–	–	67	–	–	–	–	–	–
2-nitrosophenyl ketone												
5[a]			98	–	–	–	<1	–	–	–	–	–
6[b]			–	45	–	–	–	47	–	–	–	–
7[a]			–	–	<1	–	–	–	8	<1	11	7
8[a]			–	–	–	99	–	–	–	–	–	–

Quantification was done based on the peak area ratio (measured in CD_3CN in quartz NMR tubes) to the internal reference of 1,4-dioxane at 3.6 ppm, except in the case of **7**. Photoirradiation of **3** and **7** gave an insoluble brown precipitate of **14**, which was isolated and weighed.

[a] Irradiation conditions; $\lambda > 300$ nm, 50 mW/cm^2.

[b] Irradiation conditions; $\lambda > 300$ nm, 25 mW/cm^2.

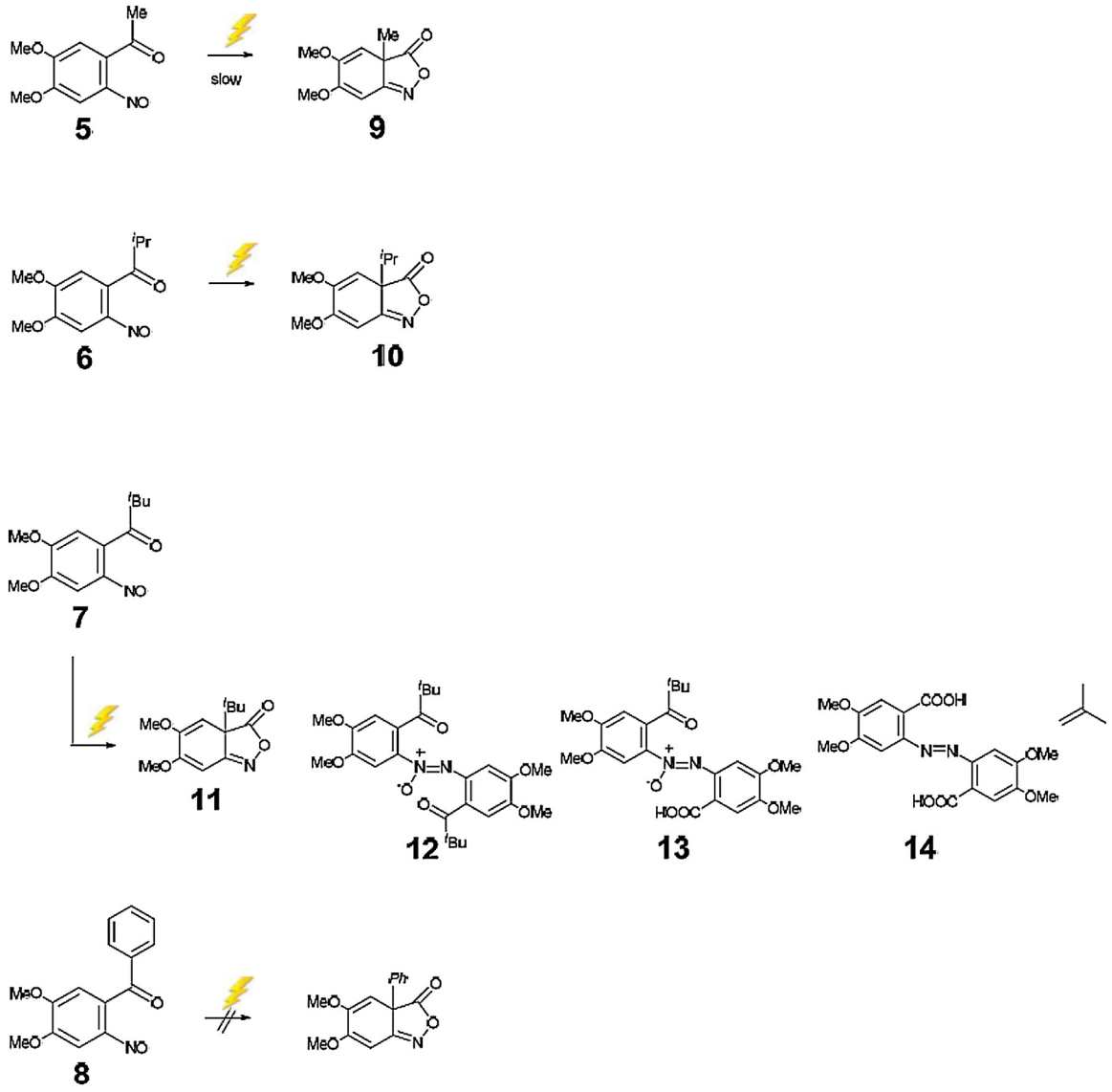


Fig. 6. Photoreaction products **9**–**14** obtained from 2-nitrosophenyl ketones **5**–**7**.

2-nitrosophenyl ketones (**5**–**8**) identified in this work are summarized in Fig. 6. These results show that the stability of 2-nitrosophenyl ketones and their isomers is significantly influenced by the nature of the α-acyl substituent. A bulky branched aliphatic group, especially ^{t}Bu, decreases the stability of the 2-nitrosoarene. From the point of view of usage as a protecting group, an isopropyl-substituted 2-nitrobenzyl group may be very effective, because deprotection proceeds faster and the 2-nitrosophenylketone

formed mainly undergoes intramolecular rearrangement or remains intact, so that unwanted intermolecular reactions are minimized.

4. Conclusions

We found that the substituent group at the α-position of 2-nitrobenzyl esters has a significant influence not only on the uncaging rate, but also on the stability of the 2-nitrosophenylketone formed. The nature of the acyl group also has a substantial influence on the photoreaction products of 2-nitrosophenyl ketones. Isopropyl-substituted 2-nitrosoarene **6** rearranges to a unique bicyclic oxazole, accompanied by 1,2-shift of the alkyl group onto the bridgehead, which breaks delocalization of the aromatic ring. The ^{t}Bu-substituted derivative **7** affords a more complex mixture of products, including intermolecularly formed azoxy and azo compounds, with release of isobutene gas. Photorearrangement of methyl-substituted nitrosoketone **5** to the cyclic isomer **9** also occurs, but is very much slower than that of **6**. The phenyl-substituted derivative **8** was stable under UV irradiation. These findings will be helpful for the selection and/or design of photolabile protecting groups for various purposes. Further mechanistic studies on the photoreaction of 2-nitrosophenyl ketones are in progress.

Acknowledgements

We acknowledge financial support (grant for specified joint research) from Kanagawa University, Japan. We thank Professor Tadashi Sugawara of Kanagawa University for use of the recycling preparative HPLC instrument. We also thank Professor Nobuhiro Kihara for helpful discussions.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jphotochem.2016.01.012.

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