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Amination of *o*-Alkenylphenols with Alkylamines via Photoinduced Proton Transfer

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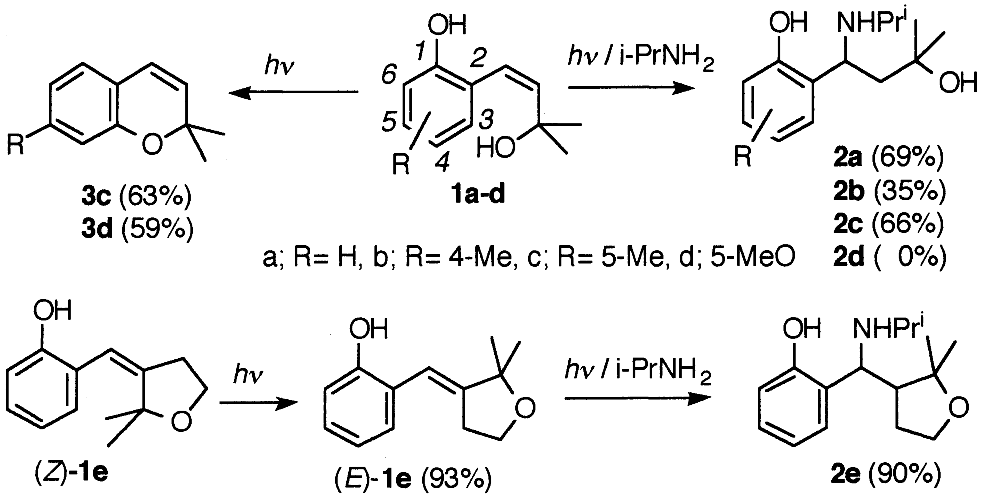
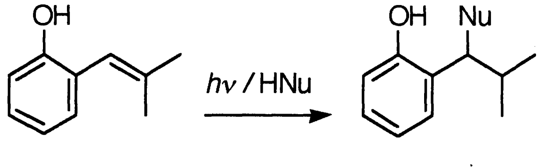
Irradiation of *o*-alkenylphenols with alkylamines resulted in Markovnikov-type amination to give *o*-(1-alkylaminoalkyl)phenols in relatively good yields. The photoamination was initiated by a proton transfer from the ammonium ion to the alkenyl group of *o*-alkenylphenolate anion in the excited state in the ion pair formed between the phenols and the amines. The resulting zwitter ion allowed the nucleophilic addition of the amine at the benzylic cation center.

Markovnikov addition to olefins occurs under acidic condition through the formation of carbocation. However, no addition of such basic reagents as amines to olefins takes place due to lack of protonation of olefins. Photoinduced proton transfer (PPT) as well as photoinduced electron transfer is a useful method to produce cationic intermediates in neutral condition. However, PPT has been scarcely applied to organic synthesis, although the PPT is elementary well-known process from physicochemical aspect.[1] Here, we wish to report the efficient Markovnikov addition of alkylamines to *o*-alkenylphenols by PPT.

Irradiation of a deaerated acetonitrile solution (50 ml) containing (*Z*)-*o*-(3-hydroxy-3-methyl-1-butenyl)phenol derivatives[2] (**1a-c**; 1.5 mmol) and i-$PrNH_2$ (20 mmol) by a high-pressure mercury lamp through a Pyrex filter for 6h resulted in Markovnikov-type amination to give *o*-(1-isopropylamino-3-hydroxy-3-



Scheme 1.



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5a; Nu= $NHPr^i$
5b; Nu= NEt_2
5c; Nu= NH_2
5d; Nu= OH
5e; Nu= $NHCH_2CH_2OH$
5f; Nu= $NHCH_2CH{=}CH_2$
5g; Nu= OMe

Scheme 2.

Table 1. Photoaddition of Nucleophiles to **4** a)

NuH	Solvent	Yield of **5** / %b)	
i-$PrNH_2$	MeCN	**5a**	71
i-$PrNH_2$	C_6H_6	**5a**	20
Et_2NH	MeCN	**5b**	64
NH_3	MeCN-H_2O	**5c**	35
	(9 : 1)	**5d**	12
$CH_2{=}CHCH_2NH_2$	MeCN	**5e**	88
$HOCH_2CH_2NH_2$	MeCN	**5f**	72
MeOH	MeOH	**5g**	0

a) A deaerated solution (50 ml) containing **4** (1.5 mmol) and NuH (20 mmol) was irradiated for 4-10h. b) Isolated yields based on **4** used.

methylbutyl)phenol derivatives (**2a-c**),3) as shown in Scheme 1. However, no photoaminations of 5-methoxylated derivative (**1d**) and of *O*-acetyl derivatives of **1a-d** with i-$PrNH_2$ occurred at all. Irradiation of **1c-d** in the absence of the amine gave 2,2-dimethylchromene derivatives (**3c-d**).4) Similarly, the photoamina-tion of (*E*)-**1e** with i-$PrNH_2$ occurred efficiently to give the aminated product (**2e**)3) as 1 : 0.1 of diastereomeric mixture, while the photoreaction of (*Z*)-**1e** with i-$PrNH_2$ formed **2e** (9%) and (*E*)-**1e** (72%). In the absence of the amine, the irradiation of (*Z*)-**1e** resulted in one way isomerization to (*E*)-**1e** up to 0/100 of (*Z*)/(*E*) ratio at the photostationary state. The quantum yield for the isomerization from (*Z*)-**1e** to (*E*)-**1e** was determined to be 0.4.

In order to assume the reaction mechanism, similar photoamination was performed for simple *o*-alkenylphenol, *o*-(2-methyl-1-propenyl)phenol (**4**) (Scheme 2). The results are summarized in Table 1. The photoamination of **4** with i-$PrNH_2$ and Et_2NH in MeCN gave the corresponding *o*-(1-alkylamino-2-methylpropyl)phenols (**5a** and **5b**) in relatively good yields, whereas the photoamination with i-$PrNH_2$ in non-polar benzene gave **5a** in poor yield. The photoamination of **4** with NH_3 in MeCN-H_2O (9:1) gave both *o*-(1-amino-2-methyl-propyl)phenol (**5c**) and *o*-(1-hydroxy-2-methylpropyl)phenol (**5d**). The photoaddition of ethanolamine and allylamine to **4** occurred selectively at amino group to give the corresponding aminated compound (**5e** and **5f**) as a consequence of much higher nuclophilicity compared with the vinyl and hydroxyl group, respectively. Moreover, no photoaddition of such weak nucleophiles as MeOH to **4** occurred at all. It should be noted that no photoamination of *O*-methylated and *O*-acetylated derivatives of **4** with the amine occurred to recover the starting materials. Therefore, a phenolic hydroxy group is requisite for these photoaminations.

Figure 1 shows the absorption spectrum of **4** where a peak at λ_{max} = 285 nm was shifted to longer wavelength by the addition of i-$PrNH_2$, showing that an ion-pair (**6**) of an ammonium ion - phenolate anion was formed in ground state between **4** and the amine. It, therefore, is postulated that the photoamination of **4** with i-$PrNH_2$ is initiated by proton transfer from the ammonium ion to the alkenyl group of *o*-alkenylphenolate anion in the excited state to form the *o*-quinodimethane or the zwitter ion (**7**), as shown in Scheme 3. The subsequent nucleophilic addition of the amine occurred at the benzylic cation center of **7** to give the Markovnikov-type product (**5a**). Since no photoamination with i-$PrNH_2$ occurred in the reaction of analogous *p*-(2-methyl-1-

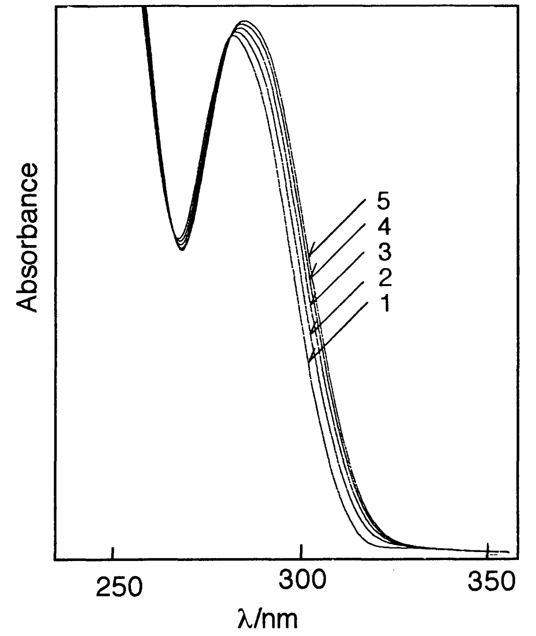
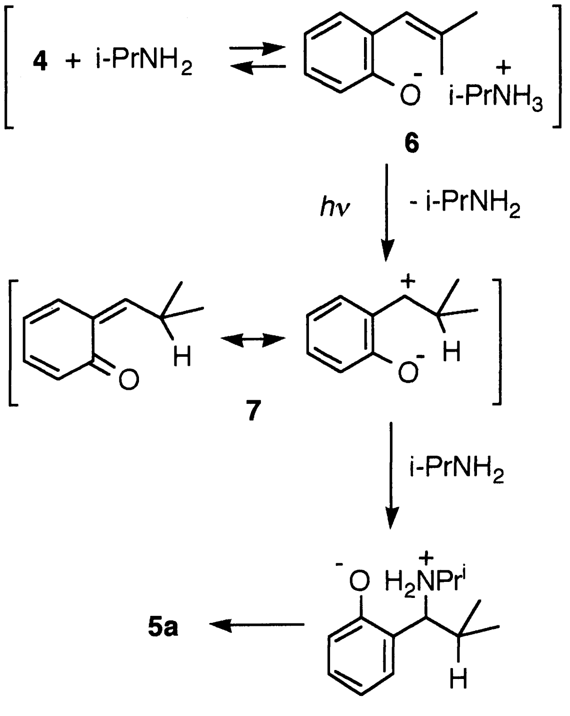


Fig. 1. Absorption spectral change of **4** in MeCN by the addition of various concentration of i-PrNH$_2$: [**4**]= 1x10^{-3} mol dm^{-3}; [i-PrNH$_2$]= (1) 0, (2) 0.1, (3) 0.2, (4) 0.3, and (5) 0.4 mmol dm^{-3}.



Scheme 3.

propenyl)phenol where the ammonium ion might be apart from the vinyl group, the proton transfer may occur within the ion pair. Similar mechanism might operate for the photoamination of **1a-e**. In the case of **1d**, the population of positive charge on the benzylic position may decrease by the resonance with methoxy group on para-position of the benzene ring, thus resulting no occurrence of the nucleophilic addition of the amine.

Consequently, it was found that the amination via PPT occurred efficiently in *o*-alkenylphenols compared with *o*-allylphenols$^{5)}$ and allylnaphthols$^{6)}$ previously reported. The photoamination via PPT has potential application to organic synthesis. Especially, the photoamination of *o*-alkenylphenols will be a useful tool for the synthesis of 2-(aminomethyl)phenol derivatives which have a potentially pharmaceutical interests.$^{7)}$ Further study using the combination of various nucleophiles and amines is in progress.

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2) The (*Z*)-isomers of **1a-d** were selectively prepared by the reaction of commercially available substituted coumarines with MeLi. The preparation of (*Z*)-**1e** was performed by the reaction of 3-(2-hydroxyethyl)coumarin with MeLi; T. Minami, Y. Matsumoto, S. Nakamura, S. Koyanagi, and M. Yamaguchi, *J. Org. Chem.*, **57**, 167 (1992).

3) Satisfactory elemental analysis and spectral data were obtained for **2a-e**. **2a**; mp 93.0-94.0 °C; ^{1}H NMR δ= 1.06 (3H, d, *J*= 6.4 Hz), 1.14 (3H, d, *J*= 6.4 Hz), 1.27 (3H, s), 1.30 (1H, brs), 1.37 (3H, s), 1.60 (1H, dd, *J*= 14.8, 2.1 Hz), 2.18 (1H, dd, *J*= 14.8, 11.2 Hz), 2.77 (1H, sept, *J*= 6.4 Hz), 4.18 (1H, dd,

J= 11.2, 2.1 Hz), 5.65 (2H, brs), 6.71-6.78 (2H, m), 6.90 (1H, d, *J*= 7.5 Hz), 7.10 (1H, t, *J*= 7.5 Hz); ^{13}C NMR δ= 21.17, 23.66, 27.20, 32.91, 46.59, 47.78, 58.71, 71.75, 116.90, 118.84, 127.13, 127.61, 128.07, 158.25; Found: C, 70.83; H, 9.81; N, 5.77%. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90%. **2b**; ^{1}H NMR δ=1.08 (3H, d, *J*= 6.4 Hz), 1.16 (3H, d, *J*= 6.4 Hz), 1.20 (1H, brs), 1.27 (3H, s), 1.36 (3H, s), 1.62 (1H, d, *J*= 14.8 Hz), 2.16-2.30 (1H, m), 2.22 (3H, s), 2.80 (1H, sept, *J*= 6.3 Hz), 4.21 (1H, d, *J*= 10.7 Hz), 6.52 (2H, brs), 6.72 (1H, d, *J*= 7.5 Hz), 6.77 (1H, s), 6.90 (1H, d, *J*= 7.5 Hz); ^{13}C NMR δ= 20.47, 20.81, 23.38, 27.14, 32.63, 46.71, 47.37, 58.30, 71.45, 116.65, 126.15, 127.99, 128.33, 128.73, 155.30; Exact mass Found: *m/z* 251.1908. Calcd for $C_{15}H_{25}NO_2$: M, 251.1884. **2c**; ^{1}H NMR δ= 1.06 (3H, d, *J*= 6.3 Hz), 1.14 (3H, d, *J*= 6.3 Hz), 1.20 (1H, brs), 1.28 (3H, s), 1.37 (3H, s), 1.58 (1H, d, *J*= 14.8 Hz), 2.14-2.24 (1H, m), 2.24 (3H, s), 2.77 (1H, sept, *J*= 6.3 Hz), 4.18 (1H, d, *J*= 11.0 Hz), 6.57 (1H, d, 7.5 Hz), 6.62 (1H, s), 6.70 (2H, brs), 6.81 (1H, d, *J*= 7.5 Hz); ^{13}C NMR δ= 21.14, 25.68, 27.13, 32.74, 46.44, 47.88, 58.26, 71.47, 117.47, 119.73, 124.21, 127.49, 135.91,157.79; Exact mass Found: *m/z* 251.1852. Calcd for $C_{15}H_{25}NO_2$: M, 251.1884. **2e**; major isomer, ^{1}H NMR δ= 0.85 (3H, s), 1.06 (3H, d, *J*= 6.4 Hz), 1.11 (3H, d, *J*= 6.4 Hz), 1.24 (3H, s), 2.01-2.22 (2H, m), 2.59 (1H, q, *J*= 8.0 Hz), 2.76 (1H, sept, *J*= 6.3 Hz), 3.76-3.94 (3H, m), 6.70 (2H, brs), 6.73-6.82 (2H, m), 6.94 (1H, d, *J*= 7.5 Hz), 7.14 (1H, t, *J*= 8.4 Hz); ^{13}C NMR δ= 21.39, 22.14, 23.62, 27.05, 28.82, 46.45, 52.11, 62.27, 64.01, 81.58, 117.12, 118.79, 124.66, 128.58, 129.92, 158.23; Exact mass Found: *m/z* 263.1906. Calcd for $C_{16}H_{25}NO_2$: M, 263.1884.

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