HETEROCYCLES, Vol. 80, No. 1, 2010, pp. 199 - 206. © The Japan Institute of Heterocyclic Chemistry
Received, 15th July, 2009, Accepted, 18th August, 2009, Published online, 19th August, 2009
DOI: 10.3987/COM-09-S(S)55

SUBSTITUENT EFFECTS ON THE ELECTRON TRANSFER-INITIATED PHOTOCHEMICAL TRANSFORMATION OF 1,2,4-TRIAZOLE-SUBSTITUTED α-DEHYDROARYLALANINAMIDES INTO 2(1*H*)-QUINOLINONE DERIVATIVES

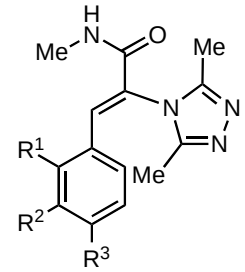
Yuichi Yazawa, Minoru Suzuki, Tetsutaro Igarashi, and Tadamitsu Sakurai*

Department of Material and Life Chemistry, Faculty of Engineering, Kanagawa University, Kanagawa-ku, Yokohama 221-8686, Japan

Abstract – An investigation was undertaken to elucidate substituent effects on the photoreactivity of 1,2,4-triazole-substituted α-dehydroarylalaninamides [(*Z*)-**1**] as well as on the selectivity of 2(1*H*)-quinolinone derivatives (**2**) from a synthetic point of view. It was found that photoinduced electron transfer-initiated cyclization of (*Z*)-**1** bearing a *meta*-substituted phenyl or a 4-substituted naphthalen-1-yl group in methanol proceeds with a moderate to good efficiency affording the corresponding product **2** in a selectivity ranging from 33 to 100%.

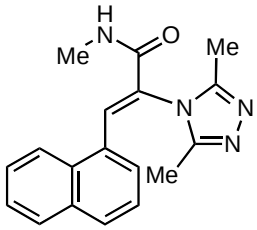
Excited-state chemistry for organic molecules has continued to contribute to the development of convenient methods for synthesizing pharmaceutically useful heterocyclic compounds.[1] Particularly, photoinduced electron transfer (PET) reactions have attracted much recent attention owing to the potential that these reactions are able to construct many types of heteroatom-containing ring systems with high efficiencies.[1a,c,d] In the course of a systematic study on the PET reaction of *N*-acyl-α-dehydroarylalanines, we found that irradiation of (*Z*)-2-(3,5-dimethyl-1,2,4-triazol-4-yl)-3-(1-naphthyl)-2-propenamide and related derivatives [hereafter, referred to as 1,2,4-triazole-substituted α-dehydro(1-naphthyl)alaninamides] in methanol-triethylamine (TEA) afforded benzo[*f*]quinolinones in high selectivities, along with minor amounts of dihydrobenzo[*f*]quinolinones.[2] In addition, anion radicals derived from triazole-substituted α-dehydro(1-naphthyl)alaninamides were shown to have a strong tendency to dissociate into the corresponding triazole anion and α-dehydronaphthylalanyl radicals, which readily cyclize to 2(1*H*)-benzo[*f*]quinolinones in the presence of the TEA cation radical. Although there are several synthetic studies aiming at the construction of a pharmaceutically useful quinolinone ring,[3] convenient photochemical routes to quinolinone and its derivatives are scarcely known.[4] It is, thus, of

significance to develop a novel method for synthesizing 2(1*H*)-quinolinone derivatives through the PET-initiated cyclization of triazole-substituted α-dehydroarylalaninamides. In this communication we synthesized (*Z*)-2-(3,5-dimethyl-1,2,4-triazol-4-yl)-3-aryl-2-propenamides [(*Z*)-**1a**–**i**] and (*Z*)-2-(3-methyl-5-phenyl-1,2,4-triazol-4-yl)-3-aryl-2-propenamides [(*Z*)-**1j**–**n**] to examine substituent effects on the photoreactivity of (*Z*)-**1** as well as on the selectivity of substituted 2(1*H*)-quinolinone as one of the (*Z*)-**1**-derived photoproducts (Chart 1).

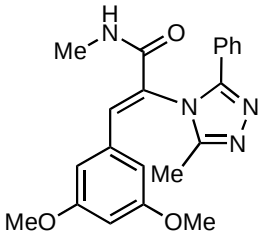


R^1= R^3= H, R^2= OMe (**1a**);
R^1= R^2= H, R^3= OMe (**1b**);
R^1= R^3= OMe, R^2= H (**1c**);
R^1= H, R^2= R^3= OMe (**1d**);
R^1= R^2= R^3= H (**1e**);
R^1= R^3= H, R^2= Cl (**1f**);
R^1= H, R^2= R^3= Cl(**1g**);
R^1= R^3= H, R^2= CN (**1h**)

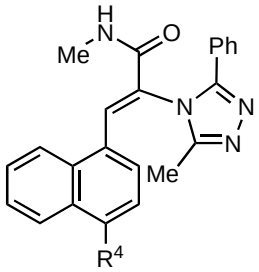
(*Z*)-**1a–h**



(*Z*)-**1i**



(*Z*)-**1j**

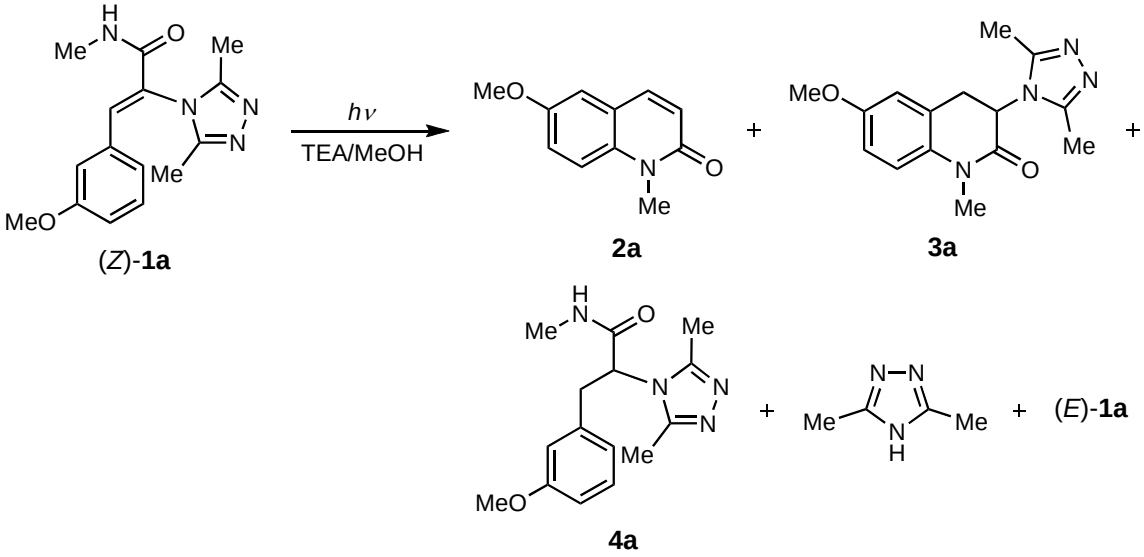


R^4= OMe (**1k**);
R^4= Me (**1l**);
R^4= H (**1m**);
R^4= F (**1n**)

(*Z*)-**1k–n**

Chart 1

The starting (*Z*)-isomers [(*Z*)-**1a**–**n**] were prepared in good yields by the ring-opening reactions of (*Z*)-4-arylmethylene-2-methyl-5(4*H*)-oxazolones with equimolar amounts of the corresponding *N*-substituted hydrazides in acetonitrile, followed by the condensation of the resulting 1,2,4-triazole-substituted 2-propenoic acids with methyl amine in 1,4-dioxane or dimethyl formamide.[5] After a nitrogen-saturated methanol solution of (*Z*)-**1a** (4.0×10^{-3} mol dm^{-3}, 500 mL) containing TEA (0.10 mol dm^{-3}) was irradiated at wavelengths longer than 280 nm from a 400 W high-pressure Hg lamp for 60 min at room temperature (Pyrex glass filter, conversion 95%), the reaction mixture was subjected to preparative thin layer chromatography over silica gel (eluent: EtOAc). Usual workup allowed us to isolate 1-methyl-6-methoxy-2(1*H*)-quinolinone (**2a**; isolated yield, 20%), the regional isomer of which [1-methyl-8-methoxy-2(1*H*)-quinolinone] was not detected.[6] On the other hand, a comparison of the ^{1}H NMR spectrum of this reaction mixture with those of 3,4-dihydro-3-(3,5-dimethyl-1,2,4-triazol-4-yl)-1-methyl-2(1*H*)-benzo[*f*]quinolinone (**3i**) and 3,5-dimethyl-1,2,4-triazole isolated in a previous study showed that the corresponding dihydroquinolinone (**3a**) and triazole derivatives were produced along with (*E*)-**1a** and **4a** (Scheme 1).[2] The arylalaninamide derivative **4a** was isolated by repeated preparative thin layer



Scheme 1

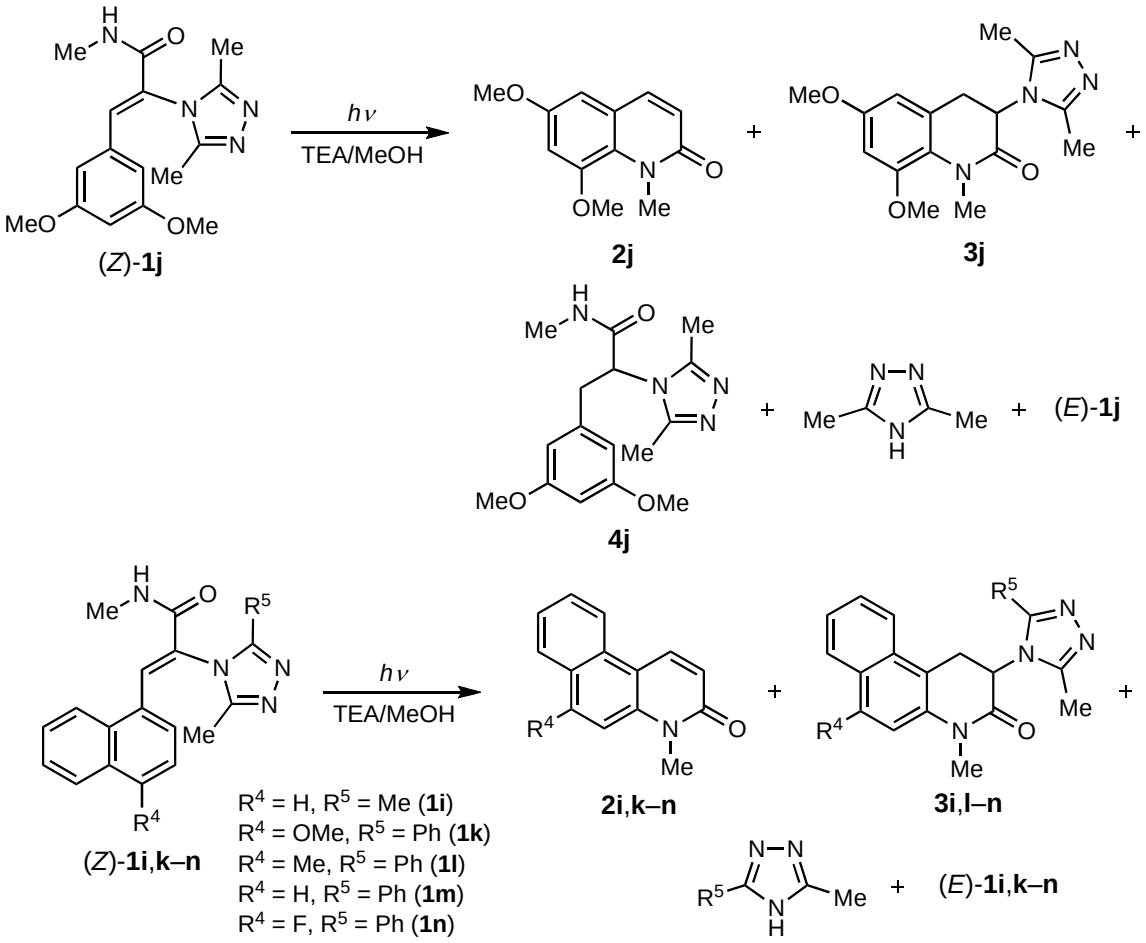
Table 1. Substituent effects on the conversion and composition of each compound obtained by the 30 min irradiation of *(Z)*-**1a–h** in MeOH–TEA at room temperature[a]

(*Z*)-**1**	Conversion (%)	Composition (%)					Selectivity of
		(*Z*)-**1**	(*E*)-**1**	**2**	**3**	**4**	**2** (%)[b]
1a	24	68	8	8	14	2	33
1b	6	77	17	6	0	0	100
1c	0	36	64	0	0	0	0
1d	32	34	34	20	12	0	63
1e	0	77	23	0	0	0	0
1f	17	71	11	2	15	0	12
1g	48	27	25	8	40	0	17
1h	0	59	41	0	0	0	0

[a][(*Z*)-**1a–h**]= 4.0×10^{-3} mol dm^{-3}; [TEA]= 0.10 mol dm^{-3}.
[b]Selectivity of **2** was estimated by dividing the composition for **2** by the sum of composition for **2**, **3**, and **4**.

chromatography and the ^{1}H NMR spectral data substantiated the structure of this reduction product.[7] The result that the photocyclization reaction of (*Z*)-**1a** proceeds without forming any byproducts enabled us to monitor this reaction by means of ^{1}H NMR spectroscopy (Scheme 1). However, prolonged irradiation (>60 min) resulted in a side reaction to a definitely detectable extent depending on the structure of (*Z*)-**1a**–**h** and, hence, the ^{1}H NMR composition of each compound was determined and compared after 30 min irradiation to analyze substituent effects on the photoreactivity of **1** and the selectivity of **2** (Table 1).

The data collected in Table 1 demonstrate that substituents introduced into the benzene ring of (*Z*)-**1e** exert great electronic and steric effects (which are beyond our expectations) on both the photoreactivity and the product composition. Replacement of hydrogens at the *para*- and *meta*-positions on the ring by methoxy or chloro groups increases the conversion of **1** but replacement at the latter position lowers the composition ratio of **2** to **3**. In addition. the presence of a bulky methoxy group at the *ortho*-position (**1c**) or an electron-withdrawing cyano group at the *meta*-position (**1h**) resulted in a considerable decrease in photoreactivity. The finding that irradiation of (*Z*)-**1i** under the same conditions enables the complete conversion into the corresponding photoproducts **2i** (isolated yield, 72%; selectivity, 76%) and **3i** (R^4= H, R^5= Me in Scheme 2) confirms that the phenyl moiety in **1e** has a much lower ability to accept an electron from TEA in its excited state, as compared to the naphthyl in **1i**. As mentioned above, either a methoxy or a chloro substituent introduced at the *meta*-position on the benzene ring of (*Z*)-**1e** has a tendency to enhance the electron-accepting ability of this ring to exhibit the so-called "*meta* effect" although the selectivity of the quinolinone derivative **2** is decreased by this effect.[8]



Scheme 2

In a previous study we found (through analysis of the effects of substituents attached to the triazole ring on the product composition) that the phenyl substituent increases the composition ratio of **2** to **3** by a factor of about 2 with keeping the conversion of **1** nearly constant.[2] Additionally, taking into account

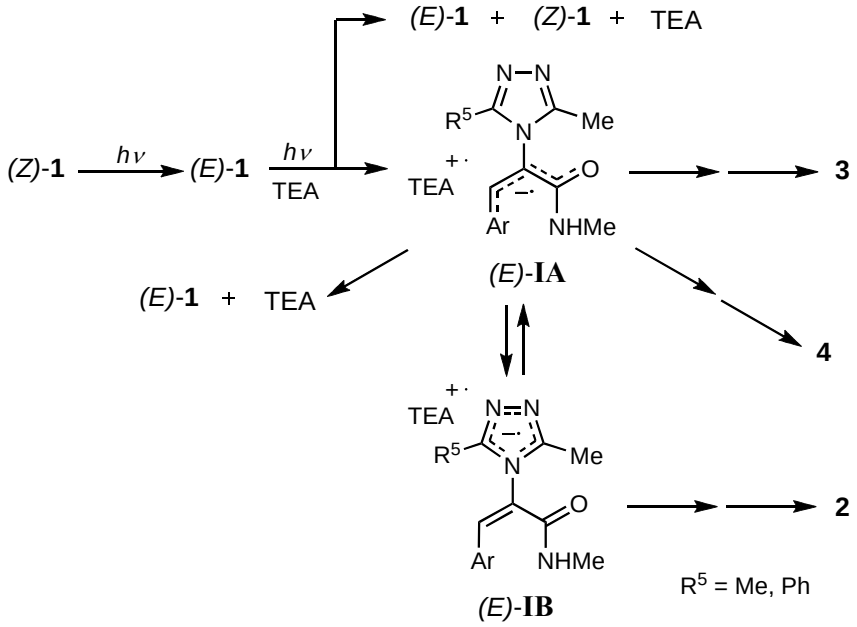
the fact that methoxy and benzo groups increase both the photoreactivity of **1** and the selectivity of **2**, we synthesized (*Z*)-**1j**–**n** to explore the *meta* effect as well as the effect of substituent (attached to the naphthalene ring) on the reactivity and selectivity. In Table 2 are summarized the conversion of **1** and the product composition, obtained under the same irradiation conditions as those for (*Z*)-**1a**–**i**. Replacement of one of the two methyl groups attached to the triazole ring by the phenyl increased the selectivity of **2** from 74% (**2i**) to 84% (**2m**), being consistent with our previous results (76%→86%).[2] Interestingly, substitution of two methoxy groups for the *meta*-hydrogens (**1j**) enhanced not only the photoreactivity (conversion) of **1a** (24%→79%) but also the selectivity of **2a** (33%→71%). However, the presence of the fluoro-substituted naphthalene ring in **1n** (R^4= F, R^5= Ph in Scheme 2) fairly reduced both the selectivity of the benzoquinolinone derivative **2m** (84% for **2m** and 40% for **2n**) and the photoreactivity of **1m** (R^4= H, R^5= Ph). Furthermore, the introduction of an electron-donating methyl group (**1l**) exerted only a very minor effect on these two parameters but replacement of this methyl group by a methoxy (**1k**) substantially reduced the conversion of **1m** (100% for **1m** and 13% for **1k**) with the selective formation of **2k**. As seen from these considerations, the selectivity of the benzoquinolinone derivative **2** has a clear tendency to increase with an increase in the electron-donating ability of the substituent R^4 in (*Z*)-**1k**–**n**, whereas this substituent has a complicated influence on the excited-state reactivity of the triazole-substituted 1-naphthylalaninamide derivative **1**.

Table 2. Substituent effects on the conversion and composition of each compound obtained by the 30 min irradiation of *(Z)*-**1j–n** in MeOH–TEA at room temperature[a]

(*Z*)-**1**	Conversion (%)	Composition (%)					Selectivity of **2** (%)[b]
		(*Z*)-**1**	(*E*)-**1**	**2**	**3**	**4**	
1j	79	16	5	56	20	3	71
1k	13	33	54	13	0	0	100
1l	100	0	0	90	10	0	90
1m	100	0	0	84	16	0	84
1n	48	21	31	19	29	0	40

[a][(*Z*)-**1j–n**]= 4.0×10^{-3} mol dm^{-3}; [TEA]= 0.10 mol dm^{-3}.
[b]Selectivity of **2** was estimated by dividing the composition for **2** by the sum of composition for **2**, **3**, and **4**.

We previously proposed (through a detailed analysis of solvent and substituent effects on the composition ratio of **2i** to **3i**) that the relative stability of the (*E*)-**1i**-derived anion radical intermediates (*E*)-**IA** and (*E*)-**IB** (which are in equilibrium with each other) determines the magnitude of this ratio (Scheme 3).[2] Since electron-donating substituents such as methoxy and methyl is considered to shift the equilibrium to the



Scheme 3

(*E*)-**IB** side by destabilizing the former intermediate, the finding that these substituents tend to enhance the selectivity of **2** provides additional evidence in support of our proposal. Taking into account that the photocyclization eventually yielding **2** and **3** is initiated by ET from TEA to the excited-state (*E*)-**1**, we propose that the photoreactivity of this (*E*)-isomer may be determined by the relative rate for ET to the (*E*)-isomer as well as by the relative rate for back ET from (*E*)-**IA** and (*E*)-**IB** to the TEA cation radical. It is thus likely that substituents introduced into the benzene or naphthalene ring of **1** exert their electronic and steric effects on these ET and back ET processes in a complicated manner. Negligible formation of the cyano-substituted products **2h** and **3h** may be due to either the exclusive deactivation of the excited-state (*E*)-**1h** or the exclusive back ET in (*E*)-**IA**. On the other hand, it seems strange that **1a** and **1j** underwent PET-initiated reduction to give **4a** and **4j** as minor products (Schemes 1 and 3). The *meta* effect of electron-donating methoxy groups in these two α-dehydroarylalanines might be responsible for the increased reactivity of the anion radical intermediate (*E*)-**IA** toward hydrogen abstraction from methanol.

As described above, the PET-initiated cyclization reactions of (*Z*)-**1** bearing a methoxy group attached at the *meta*- or the *para*-position on the benzene ring (as well as an electron-donating or an electron-attracting group introduced into the naphthalene ring) were found to proceed with moderate to good efficiencies affording the corresponding quinolinone derivatives **2** in 33–100% selectivities. Taking the relatively high photostability of these derivatives into account, we may conclude that the photocyclization reactions provide a novel synthetic method for the construction of several substituted 2(1*H*)-quinolinone rings although the introduction of an electron-attracting group into the benzene or the naphthalene ring renders this method less attractive.

ACKNOWLEDGMENTS

This research was partially supported by a "Scientific Frontier Research Project" from the Ministry of Education, Sports, Culture, Science and Technology, Japan.

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5. Selected data for (*Z*)-**1a**: IR (KBr) ν/cm^{-1}= 3232, 1666; ^{1}H NMR (600 MHz, DMSO-d_6) δ= 2.03 (6H, s), 2.70 (3H, d, *J*= 4.6 Hz), 3.60 (3H, s), 6.18 (1H, s), 6.44 (1H, d, *J*= 8.0 Hz), 6.95 (1H, d, *J*= 7.4 Hz), 7.25 (1H, dd, *J*= 7.4, 8.0 Hz), 7.78 (1H, s), 8.24 (1H, q, *J*= 4.6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ= 10.8 (2C), 27.1, 55.5, 114.0, 117.2, 122.4, 125.9, 130.9, 133.5, 135.6, 150.6, 160.0, 163.3.
6. Selected data for **2a**: IR (KBr) ν/cm^{-1}= 1678; ^{1}H NMR (600 MHz, DMSO-d_6) δ= 3.56 (3H, s), 3.78 (3H, s), 6.58 (1H, d, *J*= 9.7 Hz), 7.20 (1H, dd, *J*= 2.8, 9.7 Hz), 7.23 (1H, d, *J*= 2.8 Hz), 7.40 (1H, d, *J*= 9.2 Hz), 7.79 (1H, d, *J*= 9.2 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ= 29.0, 55.5, 110.5, 115.9, 119.0, 120.8, 121.6, 134.2, 138.6, 154.1, 154.8, 160.6.
7. Selected data for **4a**: ^{1}H NMR (600 MHz, DMSO-d_6) δ= 2.05 (6H, s), 2.63 (3H, d, *J*= 4.6 Hz), 2.99 (1H, dd, *J*= 11.6, 14.3 Hz), 3.38 (1H, dd, *J*= 4.6, 14.3 Hz), 3.63 (3H, s), 4.95 (1H, dd, *J*= 4.6, 11.6 Hz), 6.56 (1H, s), 6.57 (1H, d, *J*= 7.4 Hz), 6.73 (1H, d, *J*= 8.0 Hz), 7.10 (1H, dd, *J*= 7.4, 8.0 Hz), 8.06 (1H,

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