HETEROCYCLES, Vol. 63, No. 6, 2004, pp. 1273 - 1279
Received, 4th March, 2004, Accepted, 15th April, 2004, Published online, 16th April, 2004

A NOVEL RING-OPENING REACTION OF (*Z*)-2-METHYL-4-ARYLMETHYLENE-5(4*H*)-OXAZOLONE DERIVATIVES WITH ACYLHYDRAZINES

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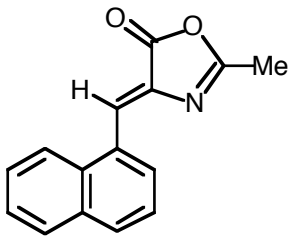
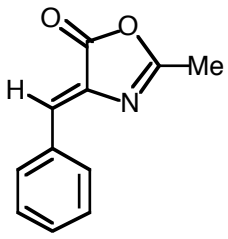
Abstract– The ring-opening mode of the title oxazolones with acylhydrazines was investigated from both synthetic and mechanistic points of view. It was found that the novel ring-opening reaction proceeds to give 1,3,4-triazole-substituted (*Z*)-α-dehydroamino acids in high yields, irrespective of substituents and solvents examined. MM2 and PM5 calculations strongly suggested that the triazole ring is constructed *via* the preferential nucleophilic addition of the hydrazino nitrogen to the C–N double bond in the oxazolone ring.

N-Acyl-α-dehydroarylalanine derivatives have been used as the starting materials in our studies on the photochemistry of α-dehydroamino acids, one of the main constituents of some antibiotics.[1,2] These α-dehydroalanine derivatives were prepared by the nucleophilic ring-opening reactions of substituted 5(4*H*)-oxazolones, which have made a great contribution to advances in the chemistry of α-dehydroamino acids as raw materials.[3] On the other hand, acylhydrazines have frequently been utilized as a convenient building block for the construction of various heterocyclic rings.[4] If we consider that the mechanism of ring-opening reactions of 5(4*H*)-oxazolones with nucleophiles is not well understood, it is of significance to explore the reactions of these oxazolones with acylhydrazines, hoping to shed much light on the mechanism of the ring-opening reactions described above. In order to pave the way for extending our studies regarding the excited-state chemistry of *N*-acyl-α-dehydroamino acids, (*Z*)-4-arylmethylene-5(4*H*)-oxazolone derivatives [(*Z*)-**1a–c**] were synthesized and allowed to react with acetylhydrazine and related hydrazides.[5]

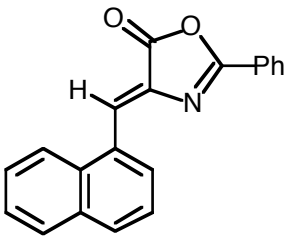
After an acetonitrile solution (15 mL) of (*Z*)-**1a** (2.0 mmol) containing acetylhydrazine (R= Me, 2.4 mmol) was heated under reflux for 0.5 h, the reaction mixture was concentrated to dryness giving the crystalline residue whose ^{1}H NMR spectral analysis showed that the reaction proceeds cleanly but not afford the usual ring-opening product, (*Z*)-2-acetylamino-*N'*-acetyl-3-(1-naphthyl)-2-propenehydrazide (Scheme 1). The successful growth of single crystal made it possible to establish that the novel ring-opening reaction of (*Z*)-**1a** with acetylhydrazine takes place to produce quantitatively (*Z*)-2-(2,5-dimethyl-1,3,4-triazol-1-yl)-3-(1-



(*Z*)-**1a**



(*Z*)-**1b**



(*Z*)-**1c**

$RCONHNH_2$: R= Me, Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, $PhCH_2$, H

naphthyl)-2-propenoic acid [(*Z*)-**2a**, 90% isolated yield; hereafter, referred to as 1,3,4-triazole-substituted (*Z*)-α-dehydroamino acid], as shown in Figure 1 and Scheme 1.[6] Interestingly, on treating (*Z*)-**1b** with acetylhydrazine under the same reaction conditions, (*E*)-**2b** was isolated in a 7% yield, along with 1,3,4-triazole-substituted α-dehydroamino acid [(*Z*)-**2b**, 88% yield].[7] A careful inspection of the ^{1}H NMR spectrum of this (*Z*)-**1b**-derived reaction mixture indicated the presence of trace amounts of (*Z*)-**3b** and (*E*)-**3b** (Scheme 2). Since the presence of equimolar amount of acetylhydrazine induced negligible isomerization of (*Z*)-**2a** or (*Z*)-**2b** to the respective (*E*)-isomer even in refluxing acetonitrile, the formation of (*Z*)-**2**, (*E*)-**2**, and **3** suggests that 4-arylmethylene-5(4*H*)-oxazolone derivatives have three sites for the nucleophilic addition of this hydrazide. The first site should be the C–O double bond in the oxazolone

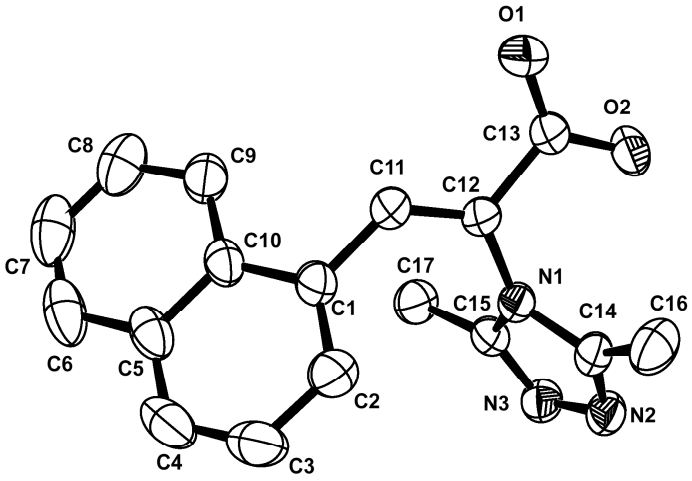
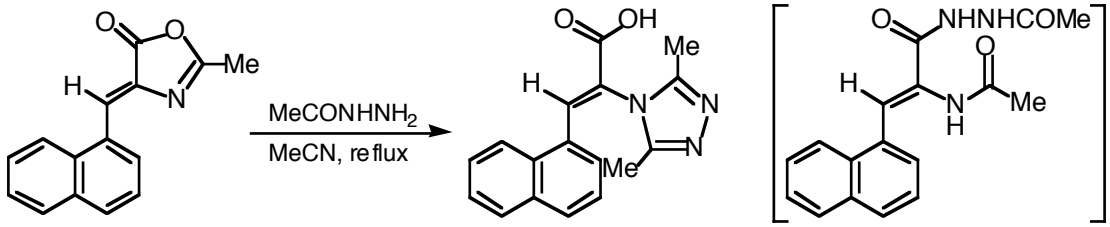
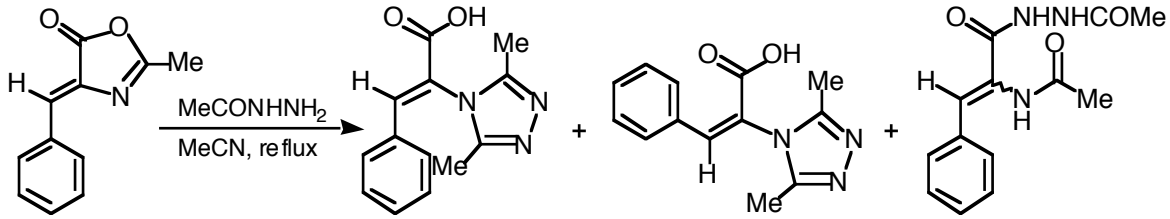


Figure 1. ORTEP drawing of (*Z*)-**2a**.

ring, the second the C–N double bond in this ring, and the third the arylmethylene C–C double bond. In Table 1 are shown product distribution and composition, obtained from the reactions between (*Z*)-**1** and acylhydrazines in refluxing acetonitrile, along with isolated yields of (*Z*)-**2** and (*E*)-**2**. The results obtained demonstrate that in any reaction systems 1,3,4-triazole-substituted (*Z*)-α-dehydroamino acids are formed in high selectivities (>68%) without being greatly affected by the substituents (Ar and R) introduced. In addition, an analysis of substituent effects on the product composition confirms that replacement of the 1-naphthyl group in (*Z*)-**1** by the phenyl group somewhat lowers the composition of (*Z*)-**2** with an increase in composition for (*E*)-**2**. The introduction of the bulky phenyl group instead of the methyl group as the

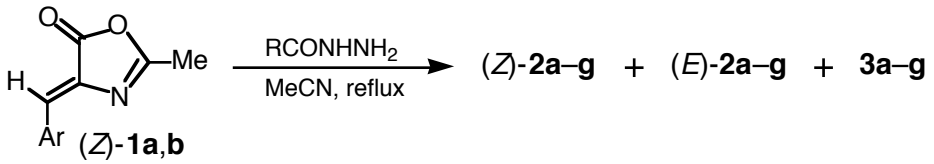


Scheme 1



Scheme 2

Table 1. Product distribution and composition determined from ^{1}H NMR spectral data for a given reaction system



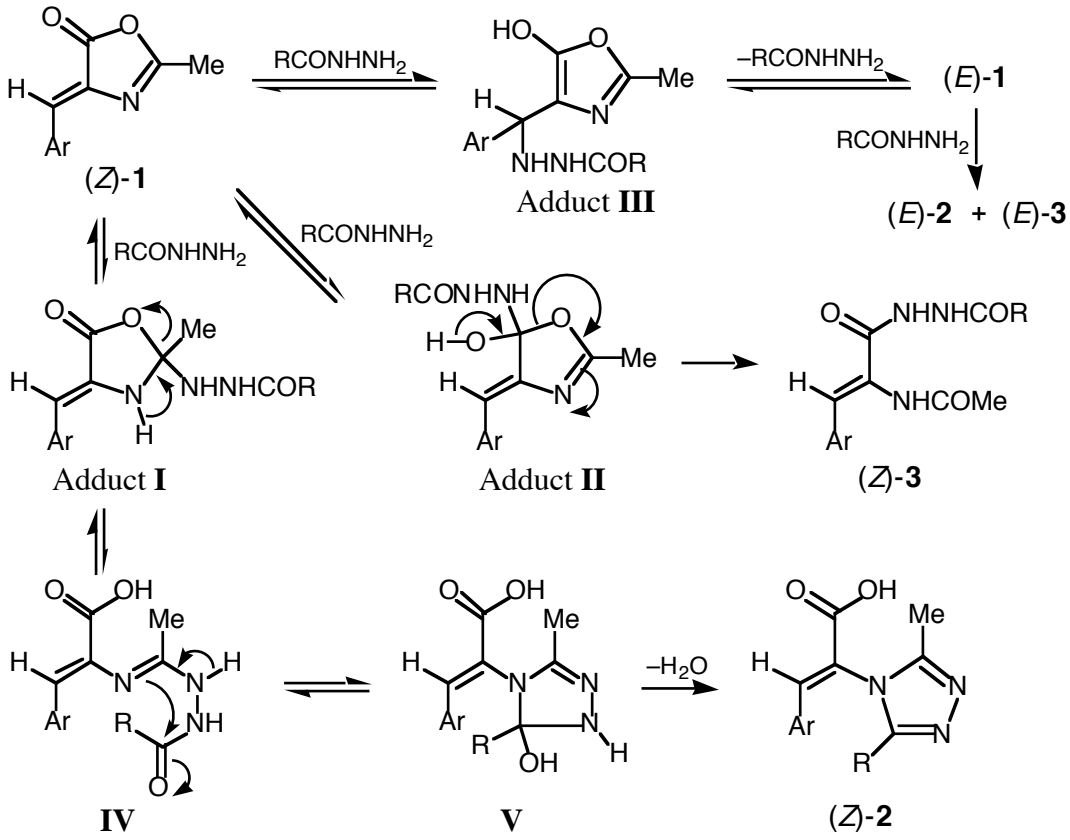
a (Ar = 1-naphthyl, R = Me); **b** (Ar = Ph, R = Me); **c** (Ar = Ph, R = Ph); **d** (Ar = Ph, R = 4-$MeOC_6H_4$); **e** (Ar = Ph, R = 4-$NO_2C_6H_4$); **f** (Ar = Ph, R = $PhCH_2$); **g** (Ar = Ph, R = H)

Oxazolone	R	Reaction time (h)	Composition (%)[a]		
			(*Z*)-**2a–g**	(*E*)-**2a–g**	**3a–g**[b]
(*Z*)-**1a**	Me	0.5	>99 (90)[c]	<1	<1
(*Z*)-**1b**	Me	0.5	92 (88)[c]	8 (7)[c]	trace
(*Z*)-**1b**	Ph	1.0	76 (74)[c]	19 (17)[c]	5
(*Z*)-**1b**	4-$MeOC_6H_4$	0.5	68 (57)[c]	23 (20)[c]	9 (–)[c]
(*Z*)-**1b**	4-$NO_2C_6H_4$	1.0	>99 (92)[c]	<1	<1
(*Z*)-**1b**	$PhCH_2$	1.0	83 (75)[c]	17 (15)[c]	trace
(*Z*)-**1b**	H	0.5	>99 (97)[c]	<1	<1

[a] The sum of composition for (*Z*)-**2b**,**f** and (*E*)-**2b**,**f** was regarded as 100% for estimating the relative composition of these two products.
[b] The mixture of (*Z*)-**3** and (*E*)-**3**.
[c] Isolated yield. Attempts to isolate **3d** were unsuccessful owing to its low stability.

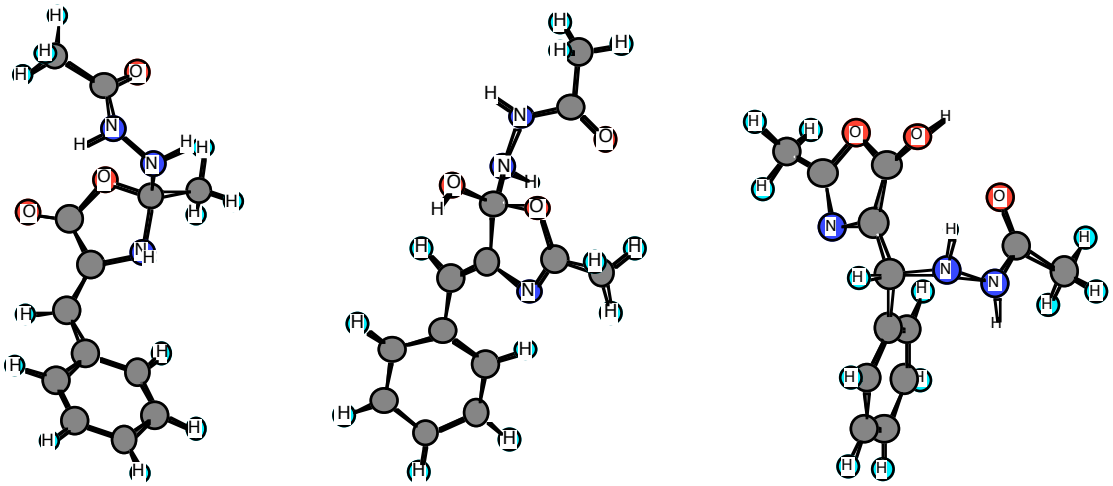
substituent R resulted in a decrease in composition for the corresponding major product [(*Z*)-**2b**], which was

compensated by the increased composition of (*E*)-**2b**. The additional finding is that an increase in the electron-withdrawing ability of aromatic acyl group attached to the hydrazino nitrogen (4-$MeOC_6H_4CO$<PhCO<4-$NO_2C_6H_4CO$) causes an enhancement in the composition for (*Z*)-**2** that accompanies the decreased composition of (*E*)-**2** and **3**. These findings substantiate the existence of the three sites where the nucleophilic addition of acylhydrazine competitively occurs and, hence, led us to propose Scheme 3 in which the adducts **I**, **II**, and **III** were assumed to play pivotal roles as reaction intermediates. As already described, stereoelectronic effects of the substituents Ar and R on the nucleophilic addition of the hydrazino nitrogen to the three sites given above may be a major factor in controlling the relative composition of each product.



Scheme 3

In order to elucidate the origin of the preferential formation of (*Z*)-**2**, energy-minimized conformations (MM2) and heats of formation (ΔH_f, PM5) of the adducts **I**, **II**, and **III** (Ar= Ph, R= Me) were calculated and shown in Figure 2.[8] A comparison of the ΔH_f values reveals that the adduct **I** is the most stable intermediate and its formation process is able to provide the least activation energy for the nucleophilic addition of a given acylhydrazine. It is, thus, very likely that no occurrence of cyclization of an intermediate (corresponding to **IV**) in the reactions of (*Z*)-**1** with primary amines or alcohols forces these nucleophiles to choose the alternate addition route affording eventually *N*-acyl-α-dehydroamino acid derivatives *via* an **II**-like intermediate. In addition to substituent effects on the product composition, this thermodynamic consideration substantiates reversibilities of the processes: (*Z*)-**1**→**I**→**IV**→**V**, (*Z*)-**1**→**II**, and (*Z*)-**1**→**III**→(*E*)-**1**. Surprisingly, the reaction of (*Z*)-**1c** (bearing the phenyl group at the 2-position on the oxazolone ring) with acetylhydrazine under the same reaction conditions afforded *N*-benzoyl-α-dehydro(1-naphthyl)alaninehydrazide as a 6:1



Adduct **I** (ΔH_f = –290.1 kJ mol^{-1}) Adduct **II** (ΔH_f = –257.0 kJ mol^{-1}) Adduct **III** (ΔH_f = –226.8 kJ mol^{-1})

Figure 2. Energy-minimized conformations and heats of formation of adducts **I**, **II**, and **III**.

mixture of (*Z*)- and (*E*)-isomers, respectively, without forming the corresponding 1,3,4-triazole-substituted α-dehydroamino acid (^{1}H NMR spectral analysis). This unexpected observation allows us to conclude that the presence of a bulky phenyl group at the 2-position exerts a considerable stereoelectronic effect on the nucleophilic addition of this hydrazine to the C–N double bond to result in an exclusive progress of the other two addition reactions. The mechanism proposed by us also provides a good explanation for the finding that the composition of (*Z*)-**2** is decreased with increasing steric bulkiness of the substituent R (H>Me>CH_2Ph>Ph) and the reverse is applicable to the composition of (*E*)-**2**: Steric hindrance to the cyclization process in **IV** is an additional factor for controlling the product composition.

Table 2. Solvent and temperature effects on the product composition obtained by the reaction of (*Z*)-**1b** and acetylhydrazine

Solvent	Reaction time (h)	Reaction temperature (°C)	Composition (%)		
			(*Z*)-**2b**	(*E*)-**2b**	**3b**
Toluene	2.5	80	84 (78)[a]	16 (13)[a]	trace
CH_2ClCH_2Cl	8.0	22 (rt)	92 (87)[a]	8 (6)[a]	trace
CH_2ClCH_2Cl	0.5	82 (reflux)	81 (76)[a]	19 (16)[a]	trace
MeCN	6.5	22 (rt)	98 (90)[a]	2 (2)[a]	trace
MeCN	0.5	78 (reflux)	92 (88)[a]	8 (7)[a]	trace

[a] Isolated yield.

As shown in Table 2, both solvent polarity and reaction temperature affect the product composition for the (*Z*)-**1b**–acetylhydrazine system to only a small extent. Somewhat different dependence of the overall rate for each reaction pathway on these two factors is considered to be responsible for a slight change in the

observed product composition. Therefore, we are led to conclude that the reaction of (*Z*)-2-methyl-4-arylmethylene-5(4*H*)-oxazolone derivatives with acylhydrazines under mild conditions constitutes a novel method for the construction of a 1,3,4-triazole ring on the amino group side of (*Z*)-α-dehydroamino acids.

ACKNOWLEDGMENTS

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

REFERENCES AND NOTES

1. (a) K. Kubo, M. Koshiba, H. Hoshina, and T. Sakurai, *Heterocycles*, 1998, **48**, 25. (b) H. Hoshina, K. Kubo, A. Morita, and T. Sakurai, *Tetrahedron*, 2000, **56**, 2941. (c) H. Hoshina, H. Tsuru, K. Kubo, T. Igarashi, and T. Sakurai, *Heterocycles*, 2000, **53**, 2261. (d) K. Maekawa, T. Igarashi, K. Kubo, and T. Sakurai, *Tetrahedron*, 2001, **57**, 5515. (e) T. Motohashi, K. Maekawa, K. Kubo, T. Igarashi, and T. Sakurai, *Heterocycles*, 2002, **57**, 269. (f) K. Maekawa, H. Kajiwara, Y. Iseya, T. Igarashi, and T. Sakurai, *Heterocycles*, 2003, **60**, 637. (g) K. Maekawa, K. Kubo, T. Igarashi, and T. Sakurai, *Tetrahedron*, 2004, **60**, 1183. (h) K. Maekawa, T. Sasaki, K. Kubo, T. Igarashi, and T. Sakurai, *Tetrahedron Lett*., 2004, **45**, 3663.
2. K. Noda, Y. Shimohigashi, and N. Izumiya, 'The Peptides-Analysis, Synthesis, Biology,' ed. by E. Gross and J. Meienhofer, Academic Press, New York, 1983, Vol. 5, pp. 285–339.
3. (a) Y. S. Rao and R. Filler, *Synthesis*, 1975, 749. (b) B. Rzeszotarska, J. Karolak-Wojciechowska, M. A. Broda, Z. Galdecki, B. Trzezwinska, and A. E. Koziol, *Int. J. Peptide Protein Res*., 1994, **44**, 313.
4. (a) A. M. Dave, K. N. Bhatt, N. K. Undavia, and P. B. Trivedi, *J. Indian Chem. Soc*., 1988, **65**, 294. (b) A. A. Afify, S. EI-Nagdy, M. A. Sayed, and I. Mohey, *Indian J. Chem., Sect. B*, 1988, **27**, 920. (c) V. Kepe, F. Pozgan, A. Golobic, S. Polanc, and M. Kocevar, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2813. (d) O. H. Hishmat, N. M. Fawzy, D. S. Farrag, and A. S. Abd EI-AII, *Rev. Roum. Chim*., 1999, **44**, 161. (e) C. T. Brain, J. M. Paul, Y. Loong, and P. J. Oakley, *Tetrahedron Lett*., 1999, **40**, 3275. (f) S. Polanc, *Targets in Heterocyclic Systems*, 1999, **3**, 33. (g) F. A. A. EI-Mariah, H. A. Saad, H. A. Allimony, and R. M. Abdel-Rahman, *Indian J. Chem., Sect. B*, 2000, **39**, 36. (h) A. V. Naidu and M. A. Dave, *Asian J. Chem*., 2000, **12**, 679. (i) A. V. Naidu and M. A. Dave, *Asian J. Chem*., 2000, **12**, 914. (j) N. C. Desai, D. Dave, M. D. Shah, and G. D. Vyas, *Indian J. Chem., Sect. B*, 2000, **39**, 277. (k) E. C. Lawson, B. E. Maryanoff, and W. J. Hoekstra, *Tetrahedron Lett*., 2000, **41**, 4533. (l) M. D. Shah, N. C. Desai, K. K. Awasthi, and A. K. Saxena, *Indian J. Chem., Sect. B*, 2001, **40**, 201. (m) F. Pozgan, S. Polanc, and M. Kocebar, *Heterocycles*, 2001, **54**, 1011. (n) S. D. Trivedi, H. T. Kubawat, and H. H. Parekh, *J. Indian Chem. Soc*., 2002, **79**, 282.
5. Selected data for (*Z*)-**1a**: mp 159.0–160.0 °C (hexane-$CHCl_3$); IR (KBr): ν/cm^{-1}= 1760, 1650, 1260; ^1H NMR (600 MHz, $CDCl_3$): δ= 2.43 (3H, s), 7.54 (1H, dd, *J*= 7.3, 7.9 Hz), 7.58 (1H, dd, *J*= 7.3, 8.6 Hz), 7.61 (1H, dd, *J*= 7.3, 8.6 Hz), 7.88 (1H, d, *J*= 7.9 Hz), 7.93 (1H, d, *J*= 8.6 Hz), 8.02 (1H, s), 8.24 (1H, d, *J*= 8.6 Hz), 8.75 (1H, d, *J*= 7.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ= 15.8, 122.8, 125.7,

126.3, 127.1, 127.4, 128.9, 129.1, 131.4, 131.8, 132.3, 133.3, 133.6, 166.8, 167.8. Anal. Calcd for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.90; H, 4.57; N, 6.19.

Selected data for (*Z*)-**1b**: mp 152.0–152.5 °C (hexane-$CHCl_3$); IR (KBr): ν/cm^{-1}= 1779, 1659, 1266; ^{1}H NMR (600 MHz, $CDCl_3$): δ= 2.38 (3H, s), 7.13 (1H, s), 7.39–7.44 (3H, m), 8.04–8.09 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ= 15.6, 128.8 (2C), 131.1, 131.4, 132.1 (2C), 132.5, 133.1, 166.1, 167.8. Anal. Calcd for $C_{11}H_9NO_2$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.74; H, 4.92; N, 7.33.

6. Selected data for (*Z*)-**2a**: mp 239.5–240.0 °C (EtOH); IR (KBr): ν/cm^{-1}= 3048, 1709, 1639, 1553; ^{1}H NMR (600 MHz, DMSO-d_6): δ= 1.99 (6H, s), 6.79 (1H, d, *J*= 7.6 Hz), 7.38 (1H, dd, *J*= 7.6, 8.3 Hz), 7.62 (1H, dd, *J*= 7.6, 7.6 Hz), 7.67 (1H, dd, *J*= 7.6, 8.3 Hz), 7.98 (1H, d, *J*= 7.6 Hz), 7.99 (1H, d, *J*= 8.3 Hz), 8.12 (1H, d, *J*= 8.3 Hz), 8.70 (1H, s); ^{13}C NMR (150 MHz, DMSO-d_6): δ= 10.3 (2C), 123.4, 125.1, 125.5, 126.1, 126.8, 127.7, 128.2, 128.9, 130.8, 130.9, 133.1, 138.0, 150.5 (2C), 164.2. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.48; H, 4.84; N, 14.18.

   Crystal data for (*Z*)-**2a**: $C_{17}H_{15}N_3O_2$, f_w= 293.32; colorless prism, 0.40×0.30×0.30 mm, monoclinic, space group $P2_1/n$; a= 10.34(1), b= 9.97(2), c= 14.19(2) Å, β= 96.23(8)°, V= 1455(3) Å^3; Z= 4; D_{calcd}= 1.339 g cm^{-3}; R= 0.056, $wR(F^2)$= 0.176.

7. Selected data for (*Z*)-**2b**: mp 218.0–219.0 °C (EtOH); IR (KBr): ν/cm^{-1}= 3431, 1708, 1691, 1546; ^{1}H NMR (600 MHz, DMSO-d_6): δ= 2.06 (6H, s), 6.95 (2H, d, *J*= 7.4 Hz), 7.39 (2H, dd, *J*= 7.4, 7.4 Hz), 7.45 (1H, dd, *J*= 7.4, 7.4 Hz), 8.09 (1H, s); ^{13}C NMR (150 MHz, DMSO-d_6): δ= 10.1 (2C), 122.2, 129.3 (2C), 129.7 (2C), 131.3, 131.4, 139.9, 150.0 (2C), 164.4. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.81; H, 5.07; N, 17.09.

   Selected data for (*E*)-**2b**: mp 160.0–161.0 °C (EtOH); IR (KBr) : ν/cm^{-1}= 3309, 1726, 1689, 1579; ^{1}H NMR (600 MHz, DMSO-d_6): δ= 2.05 (3H, s), 2.20 (3H, s), 7.09 (1H, s), 7.44–7.48 (3H, m), 8.23 (2H, d, *J*= 6.9 Hz), 10.75 (1H, s); ^{13}C NMR (150 MHz, DMSO-d_6): δ= 14.0, 20.2, 126.6, 128.7 (2C), 130.4, 132.1 (2C), 133.6, 136.1, 163.2, 167.0, 168.9. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 63.88; H, 5.14; N, 17.07.

   Physical properties and spectroscopic data for (*Z*)-**2c**–**g** and (*E*)-**2c**,**d**,**f** will be given elsewhere.

8. MM2 and PM5 calculations were accomplished by using CAChe 5.0 for Windows available from Fujitsu Ltd (2002).