Reaction of 2-Alkoxy-4,5-diphenyl-1,3-oxazin-6-one with Different Alcohols and Elucidation of the Products

Amir Assadieskandar,[a] Mohsen Amini,[a] Matti Haukka,[b] and Abbas Shafiee[c]*

[a]Department of Medicinal Chemistry, Faculty of Pharmacy and Drug Design & Development Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran
[b]Department of Chemistry, Faculty of Science and Forestry, University of Eastern Finland, Joensuu 80101, Finland
[c]Department of Medicinal Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 14176, Iran
*E-mail: ashafiee@ams.ac.ir

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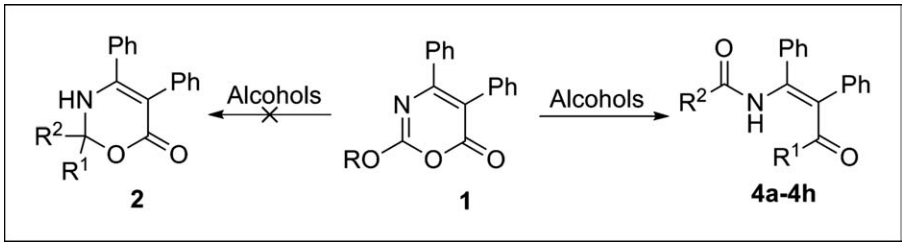

Reaction of 2-methoxy-4,5-diphenyl-1,3-oxazin-6-one **1a** with methanol was studied, and the product of the reaction was determined by spectroscopic data and X-ray analysis. In addition, a series of (*Z*)-alkyl 3-(alkoxycarbonylamino)-2,3-diphenylacrylate **4** was synthesized and characterized.

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INTRODUCTION

Diarylheterocycle scaffold and other central ring pharmacophore templates have been extensively studied as cyclooxygenase (COX) inhibitors. In pursuit of our research on design and synthesis of COX inhibitors [1–3], we focused on the synthesis of diarylheterocycles with central six-membered lactone (2-pyrone, 1,3-oxazin-6-one, and 2,3-dihydro-6*H*-1,3-oxazin-6-one), which is expected to inhibit the COX enzyme. The synthesis of 2-pyrone and 1,3-oxazin-6-one derivatives were reported previously [4–6]. In addition, 2,2-dialkoxy-4,5-disubstituted-2,3-dihydro-6*H*-1,3-oxazin-6-ones were suggested as product by refluxing compound **1** in methanol by Sasaki *et al*. [5]. This structure was assigned by using infrared and NMR data (Scheme 1).

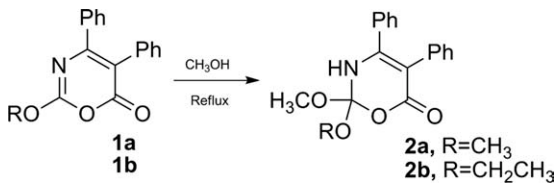
In contrast, our findings have suggested that reaction of 2-alkoxy-4,5-diphenyl-1,3-oxazin-6-one **1** with methanol under reflux condition resulted to carbamate ester **4** involving cleavage of the oxazinone ring as illustrated in Scheme 2. Furthermore, new derivatives of (*Z*)-alkyl 3-(alkoxycarbonylamino)-2,3-diphenylacrylate were prepared *via* reaction of some alcohols (or thioethanol) with **1b**. Based on some previous reports, carbamate ester were expected to have some biological activities such as inhibition of platelet aggregation [7], inhibition of LPS-stimulated production of TNF-α [8], and inhibition of RNA polymerase [9].

RESULTS

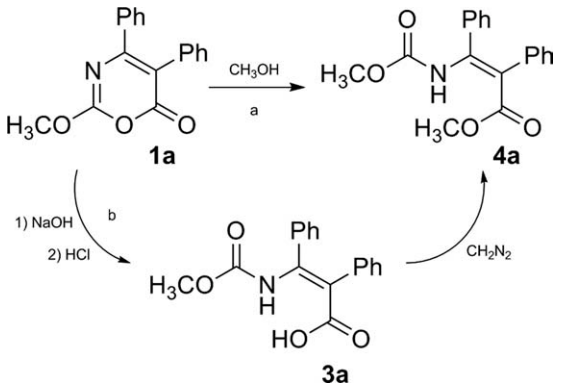
By refluxing compound **1a** in methanol, a product was obtained in good yield. The mass spectra, elemental analysis, and ^{1}H NMR data were similar to that one reported for compound **2a** [5]. In ^{13}C NMR spectra, two deshielded signals were observed at 153.32 and 169.83 ppm that could be assigned to carbon 2 and carbonyl group, respectively. For evaluating the structure of the product, HMBC data were obtained. It was expected that in compound **2a**, correlation between two methoxy groups and carbon 2 was observed. However, a correlation between two methoxy groups at 3.64 and 3.73 ppm was observed with the carbonyl carbons at 153.32 and 169.83, respectively (Fig. 1).

Furthermore, two carbonyl peaks were found at 1751 and 1669 cm^{-1} in infrared spectra. These observations suggested the probability of the cleavage of the ring. For further confirmation of the structure **4a**, carbamate acid **3a** was prepared by route b. A method for cleavage

Scheme 1. Reaction proposed by Sasaki.



Scheme 2. Reaction of compound **1a** with methanol.



of some oxazinone derivatives was reported previously [10]. Hydrolysis of compound **1a** with dilute sodium hydroxide solution at room temperature (r.t.) followed by HCl gave acid **3a** that subsequently was converted to carbamate ester **4a** by diazomethane. Compound **4a**, which was prepared from route b, showed the same spectroscopic data with the one prepared from route a (Scheme 2). However, with considering of closure the ring *via* an internal rearrangement (formation of **2a** from **4a**), it was necessary to establish the structure of compound **4a** with X-ray diffraction analysis. Figure 2 shows the crystal structure of compound **4a** [11].

According to Sasaki *et al*., reaction of compound **1b** with methanol under reflux condition gave only one product, which was assigned as **2b**. Our experiment showed that under similar condition, a mixture of three compounds were obtained in 12.4, 6.8, and 72.1% yields that were assigned as **4a**, **4b**, and **4c**, respectively. Here again, for further confirmation of the structure **4b**, carbamate acid **3b** was prepared by route b. Alkaline hydrolysis of compound **1b** followed by HCl gave compound **3b** that subsequently was converted to carbamate ester **4b** by diazomethane (Scheme 3). In ^{1}H NMR of **4a** and **4d**, two different signals (3.65 and 3.73 ppm) for the two OCH_3 groups and two different signals (4.06 and 4.22 ppm) for the two $O\underline{CH_2}CH_3$ groups were observed, respectively. Furthermore, in compound **4b** that was synthesized by direct methylation of carboxylic group, OCH_3 and $O\underline{CH_2}CH_3$ groups were observed at

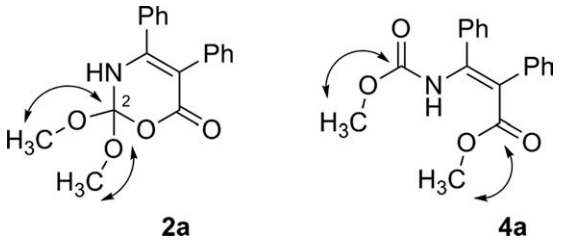


Figure 1. Correlation in HMBC experiment.

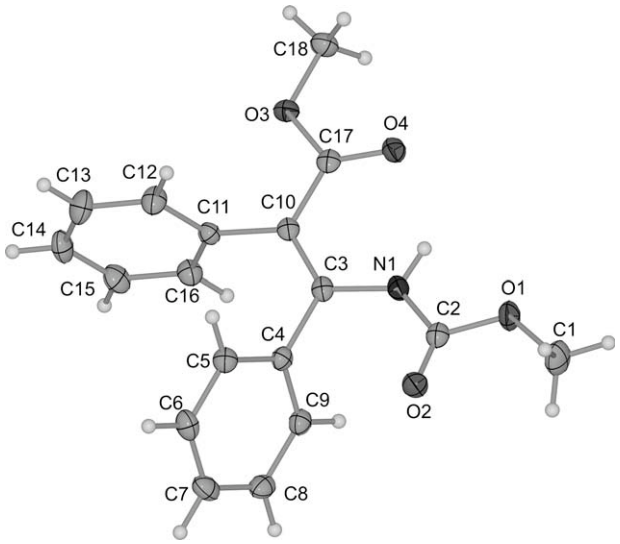


Figure 2. Crystal structure of compound **4a**.

3.73 and 4.06 ppm, respectively. On the other hand, in compound **4c** OCH_3 and $O\underline{CH_2}CH_3$ groups were observed at 3.64 and 4.21 ppm respectively. As a result, for each alkoxy group, two different shield and deshield signals were observed that are related to the carbamate and ester moiety, respectively.

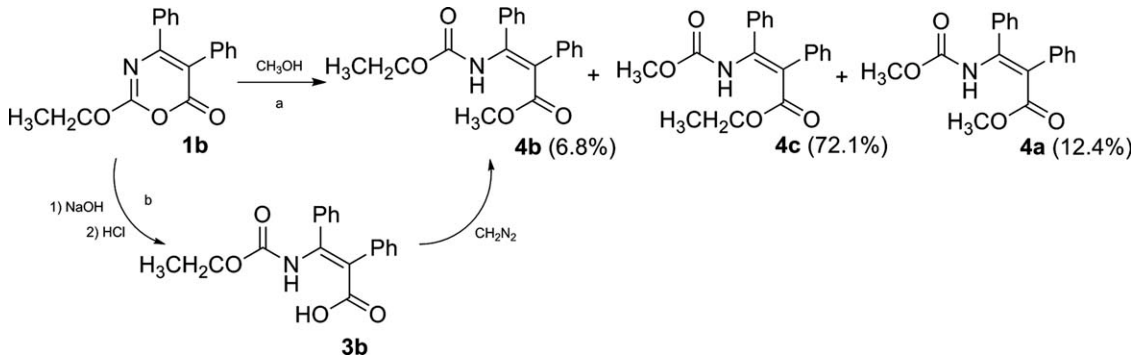
Reaction of compound **1b** with sodium alkoxide for 1 h in related alcohols gave only one product. The structure of all compounds was confirmed by NMR data. Furthermore, similar reaction with sodium ethanethiolate for 1 h in THF gave only one product that was assigned as compound **4h** (Scheme 4, Table 1). In ^{13}C NMR spectra of **4h**, two deshielded signals were observed at 152.90 and 195.36 ppm that could be assigned to carbonyl in carbamate and thioester groups, respectively. For evaluating the structure of compound **4h**, HMBC data were acquired. There was a correlation between two CH_2 groups at 4.06 and 2.87 ppm with the carbons at 152.90 and 195.36, respectively (Scheme 4).

DISCUSSION

Mechanism for ring-opening of 1,3-oxazin-6-one. According to Beccalli and Marchesini report about chemical reactivity of the 2-(dialkylamino)-1,3-oxazin-6-ones [10], a thermal equilibrium between ketene intermediate **a** and **b** in the cleavage of compound **1b** could be postulated (Scheme 5).

It could be assumed that under reflux condition, compound **4c** was formed from nucleophilic attack of methanol to the intermediate **b**. On the other hand, by using sodium alkoxide in related alcohol at r.t., the major products were **4a** and **4d–4g**. Finally, compound **4h** was

Scheme 3. Reaction of compound **1b** with methanol.



prepared from nucleophilic reaction of sodium ethanethiolate with **1b** at r.t.

Mechanistic formation of 1,3-oxazin-6-one. Classically, two mechanistic speculations were postulated for the preparation of compound **1a** *via* reaction of *N*-acylpyridinium imines with diphenylcyclopropenone in benzene (Scheme 6) [4,5].

Pathway b passes from ketene intermediate *via* an intramolecular cyclization process. Sasaki *et al*. studied the appearance of ketene intermediate by quenching the reaction. They reported that formation of **4a** (*via* path b) by using methanol instead of benzene was not successful. Their conclusion was based on this fact that they erroneously attributed structure **4a** as **2a**. Therefore, the presence of ketene intermediate could be considered in 1,3-oxazin-6-one formation. Similar study was carried out using *N*-aminopyridinum iodide instead of *N*-acylpyridinium imines in which the presence of ketene intermediate in this reaction was also suggested [12].

EXPERIMENTAL

^{1}H NMR spectra were recorded on a 500 MHz Bruker spectrometer using $CDCl_3$ or DMSO-d_6 as solvent.^{13}C NMR spectra were recorded on a 125 MHz Bruker spectrometer using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane as internal standard. Infrared spectra were acquired on a Nicolet Magna 550-FT spectrometer. IR spectra of solids were recorded in KBr, and the absorption band was given in wave numbers ν in cm^{-1}. Elemental microanalyses were within ±0.4% of the theoretical values for C, H, and N.

General procedure for alkaline hydrolysis of oxazinones. 1,3-Oxazin-6-one **1** (0.4 mmol) was dissolved in dioxane (5 mL), and sodium hydroxide solution (3 mL of 2.7% w/v) was added. The reaction mixture was stirred at r.t. for 12 h. The solution was evaporated under reduced pressure at 40°C. Water (5 mL) was added and, cooling in an ice bath, the solution was acidified with 16% HC1 (1 mL). The precipitate was filtered, dried, and crystallized from methanol.

(Z)-3-(Methoxycarbonylamino)-2,3-diphenylacrylic acid (3a). Yield: 76%; mp 182–185°C; IR (KBr, cm^{-1}): ν 1752, 1646 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.54 (s, 3H, CH_3), 6.9–7.2 (m, 10H, phenyl), 10.86 (bs, 1H, NH), 12.79 (bs, 1H, COOH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.61, 115.14, 126.58, 127.67, 128.32, 129.59, 131.87, 135.66, 136.95, 149.43, 153.24, 170.96. Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.31; H, 5.19; N, 4.61.

(Z)-3-(Ethoxycarbonylamino)-2,3-diphenylacrylic acid (3b). Yield: 72%; mp 155–158°C; IR (KBr, cm^{-1}): ν 1751, 1642 (C=O); ^{1}H NMR (DMSO-d_6): δ 1.11 (t, J = 7 Hz, 3H, CH_3), 3.96 (q, J = 7 Hz, 2H, CH_2), 6.9–7.2 (m, 10H, phenyl), 10.84 (bs, 1H, NH), 12.79 (bs, 1H, COOH); ^{13}C NMR (DMSO-d_6): δ 14.67, 61.29, 114.72, 126.55, 127.64, 128.25, 129.53, 131.91, 135.75, 137.00, 149.79, 152.72, 170.94. Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.32; H, 5.61; N, 4.46.

General procedure for esterification of 3 with diazomethane. A THF solution of acid **3** (0.34 mmol) was esterified with a solution of diazomethane in diethyl ether to give the corresponding ester **4**. Compounds **4a** and **4b** were prepared in 86 and 81% yield, respectively.

Scheme 4. Reaction of compound **1b** with sodium alkoxide and sodium ethanethiolate.

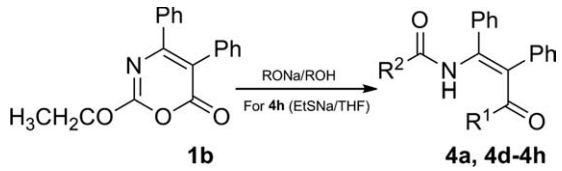


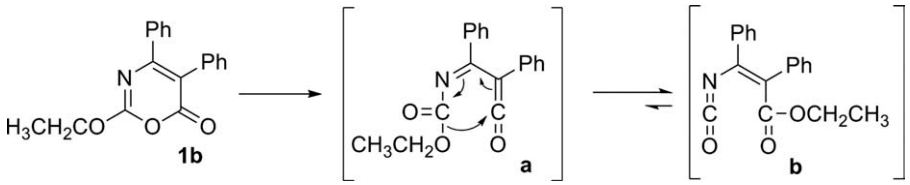
Table 1

Synthesis of compounds **4a** and **4d–h**.

Products	R^1	R^2	Yield[a] (%)	mp (°C)
4a	OMe	OMe	76	166–169
4d	OEt	OEt	68	84–86
4e	O*n*Pr	O*n*Pr	52	50–52
4f	O*i*Pr	O*i*Pr	56	98–100
4g	O*n*Bu	O*n*Bu	42	46–48
4h	SEt	OEt	72[b]	110–112

[a] All products were purified by preparative thin layer chromatography on silica gel using ethyl acetate-petroleum ether (1:10) as mobile phase and crystallized from methanol.
[b] Compound **4h** was crystallized from diethyl ether-*n*-hexane.

Scheme 5. Rearrangement for the ethoxy group in 1,3-oxazin-6-one ring.



Reaction of compound 1b with methanol. A solution of the oxazin-6-one **1b** (0.4 mmol) in methanol (30 mL) was heated under reflux for 24 h. The mixture was then concentrated under reduced pressure, and the residue was purified by preparative thin layer chromatography on silica gel using ethyl acetate–petroleum ether (1:10) as mobile phase. The product was crystallized from methanol.

(Z)-Methyl 3-(methoxycarbonylamino)-2,3-diphenylacrylate (4a). Yield: 12.4%; mp 166–169°C; IR (KBr, cm^{-1}): ν 1751, 1669 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.65 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 6.9–7.3 (m, 10H, phenyl), 11.12 (bs, 1H, NH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.09, 52.59, 111.26, 126.46, 127.35, 128.17, 128.85, 131.90, 134.65, 135.33, 152.79, 153.32, 169.83. Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.31; H, 5.32; N, 4.61.

(Z)-Methyl 3-(ethoxycarbonylamino)-2,3-diphenylacrylate (4b). Yield: 6.8%; mp 135–138°C; IR (KBr, cm^{-1}): ν 1752, 1663 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7 Hz, 3H, CH_3), 3.73 (s, 3H, CH_3), 4.06 (q, J = 7 Hz, 2H, CH_2), 6.9–7.3 (m, 10H, phenyl), 11.05 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.27, 52.05, 61.56, 111.00, 126.41, 127.32, 128.10, 128.83, 131.93, 134.79, 135.40, 152.83, 152.96, 169.85. Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.32; H, 5.96; N, 4.48.

(Z)-Ethyl 3-(methoxycarbonylamino)-2,3-diphenylacrylate (4c). Yield: 72.1%; mp 136–139°C; IR (KBr, cm^{-1}): ν 1751, 1664 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.21 (t, J = 7 Hz, 3H, CH_3), 3.64 (s, 3H, CH_3), 4.21 (q, J = 7 Hz, 2H, CH_2), 6.9–7.3 (m, 10H, phenyl), 11.11 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.14, 52.55, 60.88, 111.79, 126.28, 127.33, 128.11, 128.88, 131.92, 134.77, 135.42, 152.34, 153.37, 169.37. Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.28; H, 5.78; N, 4.46.

General procedure for the reaction of 1b with sodium alkoxide. Sodium (20 mg) was added in related alcohol (50 mL) and mixed. Compound **1b** was added, and the reaction was allowed to stir for 1 h at r.t. The mixture was then concentrated under reduced pressure, and the residue was purified by preparative thin layer chromatography on silica gel using ethyl acetate–petroleum ether (1:10) as mobile phase. The product was crystallized from methanol.

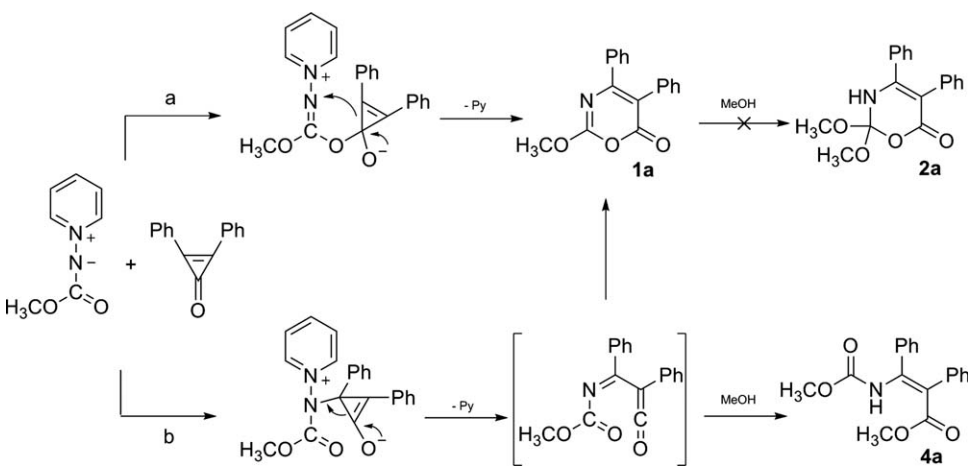
(Z)-Ethyl 3-(ethoxycarbonylamino)-2,3-diphenylacrylate (4d). Yield: 68%; mp 84–86°C; IR (KBr, cm^{-1}): ν 1756, 1663 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.21 (m, 6H, CH_3), 4.06 (q, J = 7 Hz, 2H, CH_2), 4.21 (q, J = 7 Hz, 2H, CH_2), 6.9–7.3 (m, 10H, phenyl), 11.05 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 14.15, 14.27, 60.82, 61.51, 111.53, 126.24, 127.28, 128.03, 128.89, 131.96, 134.95, 135.52, 152.51, 152.88, 169.38. Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.82; H, 6.11; N, 4.34.

(Z)-Propyl 2,3-diphenyl-3-(propoxycarbonylamino)acrylate (4e). Yield: 52%; mp 50–52°C; IR (KBr, cm^{-1}): ν 1752, 1658 (C=O); ^{1}H NMR ($CDCl_3$): δ 0.84 (t, J = 7 Hz, 3H, CH_3), 0.92 (t, J = 7 Hz, 3H, CH_3), 1.5–1.7 (m, 4H, CH_2), 3.98 (t, J = 7 Hz, 2H, CH_2), 4.12 (t, J = 7 Hz, 2H, CH_2), 6.9–7.2 (m, 10H, phenyl), 11.1 (bs, 1H, NH). Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.78; H, 6.56; N, 3.94.

(Z)-Isopropyl 3-(isopropoxycarbonylamino)-2,3-diphenylacrylate (4f). Yield: 56%; mp 98–100°C; IR (KBr, cm^{-1}): ν 1753, 1650 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.18 (d, J = 7 Hz, 6H, CH_3), 1.2 (d, J = 7 Hz, 6H, CH_3), 4.81 (septet, J = 7 Hz, 1H, CH), 5.10 (septet, J = 7 Hz, 1H, CH), 6.9–7.2 (m, 10H, phenyl), 11.0 (bs, 1H, NH). Anal. Calcd. for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.19; H, 6.53; N, 3.68.

(Z)-Butyl 3-(butoxycarbonylamino)-2,3-diphenylacrylate (4g). Yield: 42%; mp 46–48°C; IR (KBr, cm^{-1}): ν 1754, 1662

Scheme 6. Mechanistic formation of 1,3-oxazin-6-one ring.



(C=O); ^{1}H NMR ($CDCl_3$): δ 0.88 (t, J = 6.7 Hz, 3H, CH_3), 0.92 (t, J = 6.7 Hz, 3H, CH_3), 1.27 (sextet, J = 6.7 Hz, 2H, CH_2), 1.35 (sextet, J = 6.7 Hz, 2H, CH_2), 1.5–1.6 (m, 4H, CH_2), 4.02 (t, J = 6.7 Hz, 2H, CH_2), 4.17 (t, J = 6.7 Hz, 2H, CH_2), 6.9–7.2 (m, 10H, phenyl), 11.09 (bs, 1H, NH). Anal. Calcd. for $C_{24}H_{29}NO_4$: C, 72.89; H, 7.39; N, 3.54. Found: C, 72.65; H, 7.51; N, 3.75.

(Z)-S-Ethyl 3-(ethoxycarbonylamino)-2,3-diphenylprop-2-enethioate (4h). Thioethanol (0.7 mmol) was dissolved in THF (50 mL) and 20 mg of sodium was added. After completing the reaction, compound **1b** (0.68 mmol) was added and stirred for 1 h at r.t. The mixture was then concentrated under reduced pressure, and the residue was crystallized from diethyl ether-*n*-hexane in 72% yield; mp 110–112°C; IR (KBr, cm^{-1}): ν 1755, 1610 (C=O); ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J = 7 Hz, 3H, CH_3), 1.25 (t, J = 7 Hz, 3H, CH_3), 2.87 (q, J = 7 Hz, 2H, CH_2), 4.06 (q, J = 7 Hz, 2H, CH_2), 6.9–7.3 (m, 10H, phenyl), 11.53 (bs, 1H, NH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.31, 14.39, 22.74, 61.69, 118.37, 127.34, 127.56, 127.68, 128.11, 128.51, 133.34, 134.53, 134.61, 149.22, 152.89, 195.35. Anal. Calcd. for $C_{20}H_{21}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.34; H, 5.79; N, 3.76.

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REFERENCES AND NOTES

[1] Navidpour, L.; Shadnia, H.; Shafaroodi, H.; Amini, M.; Dehpour, A. R.; Shafiee, A. Bioorg Med Chem 2007, 15, 1976.

[2] Navidpour, L.; Shafaroodi, H.; Abdi, K.; Amini, M.; Ghahremani, M. H.; Dehpour, A. R.; Shafiee, A. Bioorg Med Chem 2006, 14, 2507.

[3] Rao, P. N. P.; Amini, M.; Li, H.; Habeeb, A. G.; Knaus, E. E. J Med Chem 2003, 30, 4872.

[4] Eicher, T.; Hansen, A. Tetrahedron Lett 1967, 1169.

[5] Sasaki, T.; Kanematsu, K.; Kakehi, A. J Org Chem 1971, 36, 2451.

[6] Potts, K. T.; Baum, J. S. Chem Rev 1974, 74, 189.

[7] Monge, A.; Palop, J. A.; Parrado, P.; Perez-Ilzarbe, C.; Fernandez-Alvarez, E. J Heterocycl Chem 1987, 24, 437.

[8] Fujita, M.; Seki, T.; Ikeda, N. Bioorg Med Chem Lett 2002, 12, 1897.

[9] Arhin, F.; Belanger, O.; Ciblat, S.; Dehbi, M.; Delorme, D.; Dietrich, E.; Dixit, D.; Lafontaine, Y.; Lehoux, D.; Liu, J.; McKay, G. A.; Moeck, G.; Reddy, R.; Rose, Y.; Srikumar, R.; Tanaka, K. S.; Williams, D. M.; Gros, P.; Pelletier, J.; Parr, T. R., Jr.; Far, A. R. A. Bioorg Med Chem 2006, 14, 5812.

[10] Beccalli, E. M.; Marchesini, A. J Org Chem 1987, 52, 3426.

[11] CCDC 776452 contains the supplementary crystallographic data of compound **4a**. These can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[12] Kascheres, A.; Marchini, D., Jr. J Org Chem 1975, 40, 2985.