The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2018**, part iii, 338-353

An eco-compatible access to diversified bisoxazolone and bisimidazole derivatives

Wael Abdelgayed Ahmed Arafa*[a,b] and Ahmed Fawzy Abdel-Magied[c,d]

[a]*Chemistry Department, College of Science, Jouf University, P.O. Box 72341, Sakaka, Aljouf, Kingdom of Saudi Arabia*

[b]*Chemistry Department, Faculty of Science, Fayoum University, P.O. Box 63514, Fayoum City, Egypt*

[c]*Chemistry Department, Royal Institute of Technology, KTH, SE-100 44, Stockholm, Sweden*

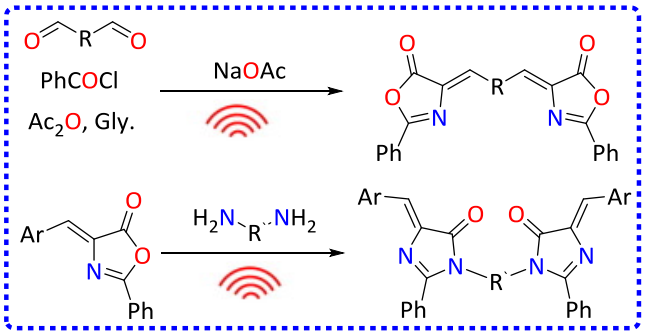
[d]*Nuclear Material Authority, P.O. Box 530, El Maadi, Cairo, Egypt*

Email: waa00@fayoum.edu.eg waarafa@ju.edu.sa

Received 02-21-2018 **Accepted** 04-28-2018 **Published on line** 05-27-2018

Abstract

An efficient, straight-forward and eco-friendly synthetic strategy for the assembly of novel bisoxazolones via a four-component, sequential reaction of dialdehydes, glycine, benzoyl chloride and acetic anhydride, using ultrasound radiation, is described. Additionally, a diverse group of new bisimidazoles has been synthesized in good yields by the sonication of diamines and (*Z*)-4-arylidene-2-phenyloxazol-5(4*H*)-ones. These approaches have resulted in a number of successful routes for the facile synthesis of bis-oxazolone and bis-imidazole frameworks within minutes of irradiation. Excellent outcomes using these environmentally-friendly parameters make these synthetic schemes ideal, sustainable, green-chemistry procedures and provide simple access towards the preparation of bisheterocycles.



Keywords: Bisoxazolones, bis-imidazoles, solvent-free, ultrasound-assisted, multi-component synthesis

DOI: https://doi.org/10.24820/ark.5550190.p010.544 ©**ARKAT USA, Inc**

Introduction

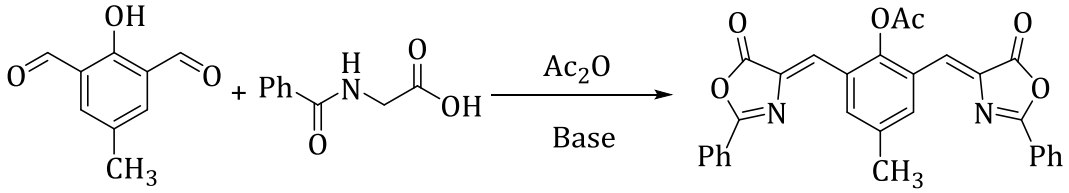
Arylidene azlactones (4-arylidene-2-phenyl-5(4*H*)oxazolones) have attracted much interest with respect to their broad range of chemotherapeutic activities.[1-3] They are convenient, significant intermediates and building blocks for the assembly of a variety of biologically-active compounds comprising peptides[4-7] and amino acids.[8,9] Moreover, these compounds are valuable precursors for the design of photosensitive and biosensors devices for proteins.[10] The best known strategy for the preparation of oxazolones is generally regarded to be the Erlenmeyer reaction, which involves the reaction of *N*-benzoylglycine (hippuric acid) with aldehydes in the presence of a basic catalyst (NaOAc) and dehydrating agent (Ac_2O).[11] After the Erlenmeyer-reaction method, several other catalysts, dehydrating agents and methods have been utilized for condensation of hippuric acid (HA) and several carbonyl compounds.[12-15] Nevertheless, several of these protocols have some disadvantages, including prolonged reaction times, poor yields, use of hazardous chemicals, and often harsh reaction conditions.[16,17] Our group developed a new strategy for the assembly of arylideneoxazolones starting from arylidenemalononitriles using solvent-free conditions.[18] Although several structural analogs have been prepared, a careful literature survey showed that only one synthetic method has been used for the construction of bisoxazolones.[19] Hence, the development of more convenient and eco-friendly strategies for the preparation of oxazolones and bisoxazolones would be advantageous.

Imidazole is one of a number of remarkable N-heterocyclic structures which are present in a variety of synthetic pharmaceuticals and natural products.[20] Regardless of the number of reaction protocols that have been established for the synthesis of imidazole moieties,[20-25] the development of a highly-efficient synthesis for the preparation of a series of novel bis-imidazoles from easily available substances in a one-step reaction, is one of the most intriguing challenges of modern synthetic chemistry. Recently, 'green-chemistry' syntheses, including the employment of ultrasonic- and microwave-irradiation techniques, have received special interest for achieving this goal.[26-29] Ultrasonic irradiation, compared with other conventional techniques, has some inherent merits, e.g., milder reaction conditions, higher yields, shorter reaction times and simpler work-ups. As part of our efforts to prepare bis-heterocyclic systems using environmentally-benign conditions,[30-34] we describe, herein, efficient protocols for the preparation of bis-oxazolones and bis-imidazoles driven by ultrasonic irradiation.

Results and Discussion

As a continuation of our work towards developing novel protocols for the synthesis of oxazolones[18] and bis-heterocycles from dialdehydes,[30,34] we have progressed with respect to the design and preparation of the bis-oxazolones (**2a-f**). In this context, reactive precursors such as dialdehyde derivatives (**1a-f**) can react effectively with hippuric acid (HA) and acetic anhydride (Ac_2O). We commenced our investigation using a model reaction of 2-hydroxy-5-methylisophthalaldehyde (**1a**) with HA and Ac_2O in the presence of sodium acetate (NaOAc). Based on the results of our previous investigations, the reaction of HA with Ac_2O should yield 2-phenyloxazol-5(4*H*)-one, which would subsequently interact with dialdehyde (**1a**) to afford the target bis-oxazolone product (**2a**) (Scheme 1).

 ©**ARKAT USA, Inc**



1a **2a**

Scheme 1. Model reaction of 2-hydroxy-5-methylisophthalaldehyde (**1a**) with hippuric acid (HA) and acetic anhydride (Ac_2O) in presence of sodium acetate (NaOAc).

The three-component reaction could be effected by blending all the substrates under ultrasonic irradiation (40 kHz). The reaction was achieved at room temperature (23 ^{o}C) in a sealed vial for 10 minutes (Table 1, entry 1). Regrettably, the reaction afforded the desired product in poor yield (15%) and the dialdehyde (**1a**) remained mostly unreacted. Slight improvements in yield were observed by increasing both temperature and time (Table 1, entries 2 and 3), however, multiple spots on the TLC plates indicated the presence of other compounds. These unsatisfactory outcomes prompted us to investigate the above-mentioned three-component reaction in a sequential pattern of ultrasound radiation (US), ultrasound radiation plus heating (US/Conv.), and microwave radiation (MW).

We initially carried out the reaction between HA and Ac_2O in the presence of NaOAc with sonication for 3 min at 40 ^{o}C. Interestingly, the formation of 2-phenyloxazol-5(4*H*)-one was completed within 2 min (confirmed by NMR analysis). The dialdehyde (**1a**) was then added and the resulting mixture was sonicated for an additional 3 min at 40 ^{o}C. After cooling, the, hitherto, unreported bisoxazolone derivative (**2a**) was obtained in 83% overall yield (Table 1, entry 4). Reaction analysis (by TLC) indicated the incomplete transformation of the intermediate 2-phenyloxazol-5(4*H*)-one into the final product (**2a**). Therefore, the reaction was repeated at elevated temperatures, *viz.* 50 and 60 ^{o}C, which provided (**2a**) in 90% and 97% yields, respectively (Table 1, entries 5 and 6). It was also observed that a shorter irradiation period (4 min) diminished the yield slightly (Table 1, entry 7) while a longer period (8 min) provided no advantage (Table 1, entry 8). Next, a series of other catalysts, including piperidine (Pip.), zinc oxide (ZnO) and potassium phosphate (K_3PO_4) were screened; of these, NaOAc was found to be the most efficient catalyst for this conversion (see Table 1, entry 8 vs. entries 9-11). In order to compare the effectiveness and applicability of ultrasonic irradiation on the template reaction, a control experiment was performed, utilizing thermal heating (100 ^{o}C) with the NaOAc catalyst (Table 1, entry 12). A good yield was acquired (67%), however, with longer time (2h). These results demonstrated that ultrasonic irradiation can make the current one-pot method occur efficiently and rapidly, while heating decreases the rate and yield of the reaction. Carrying out the model reaction under microwave irradiation produced the desired product (**2a**) in poor yield (Table 1, entry 13, 45%) and generation of a Perkin-condensation product (**4**, Scheme 3).

As shown in Table 1, it was found that the ultrasonic-assisted method is more effective (Table 1, entry 6) than both the conventional heating (Table 1, entry 12) and microwave (Table 1, entry 13) conditions with respect to time and yield. After 2 min of sonication, a yellow color (oxazolone) was observed this, in turn, crystallized out as a yellow mass following addition of dialdehyde (**1a**). This solid was then filtered off to afford the pure bis-oxazolone (**2a**).

 ©ARKAT USA, Inc

Table 1. Optimization of reaction conditions for the preparation of bis-oxazolone derivative (**2a**)

Entry	Catalyst	Conditions	Temperature (^{o}C)	Time (min)	Yield (%)
1	NaOAc	US[a]	23(rt)	10	15
2	NaOAc	US[a]	40	15	23
3	NaOAc	US[a]	40	20	28
4	NaOAc	US[b]	40	6	83
5	NaOAc	US[b]	50	6	90
6	NaOAc	US[b]	60	5	97
7	NaOAc	US[b]	60	4	92
8	NaOAc	US[b]	60	8	97
9	Pip.	US[b]	60	6	84
10	ZnO	US[b]	60	6	73
11	K_3PO_4	US[b]	60	6	80
12	NaOAc	Conv.[b]	100	120	67
13	NaOAc	MW[b]	120	60	45

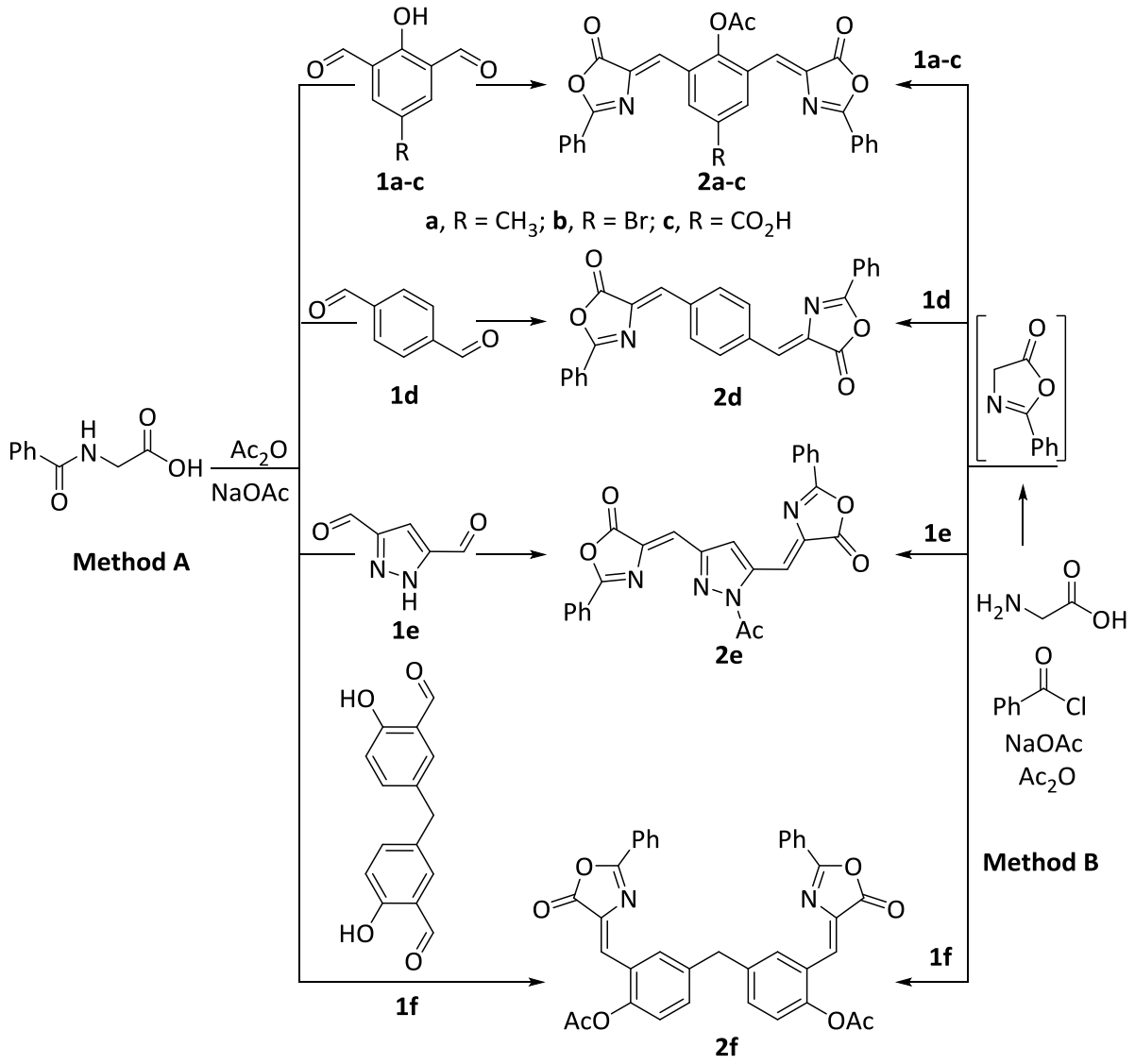
[a] The mixture of **1a** (0.05 mmol), HA (1 mmol) and Ac_2O (1 mL) was sonicated in the presence of NaOAc (1.1 mmol). [b] The mixture of HA (1 mmol), base (1.1 mmol) and Ac_2O (1 mL) was heated using US, US/Conv., Conv. or MW for the indicated times, then 0.05 mmol of **1a** was added and heating was continued for the indicated times. US = ultrasound; Conv. = conventional heating; MW = microwave; Pip. = piperidine

To investigate the generality and scope of this protocol, several dialdehydes bearing an electron-donating group (**1a**) and electron-withdrawing groups (**1b** and **1c**) were reacted with HA and Ac_2O, in the presence of NaOAc, under ultrasonic-assisted conditions (Scheme 2, method A). Interestingly, the respective products (**2a–c**) were acquired in significant yields in both cases. Furthermore, the methodology was successfully extended to other dialdehydes, for instance, terephthalaldehyde (**1d**) in 97% yield (literature-reported yield 78%)[19], heterocyclic dialdehydes such as 1*H*-pyrazole-3,5-dicarbaldehyde (**1e**) (89% yield), and 4-(3-formyl-4-hydroxybenzyl)-2-hydroxybenzaldehyde (**1f**) (94% yield).

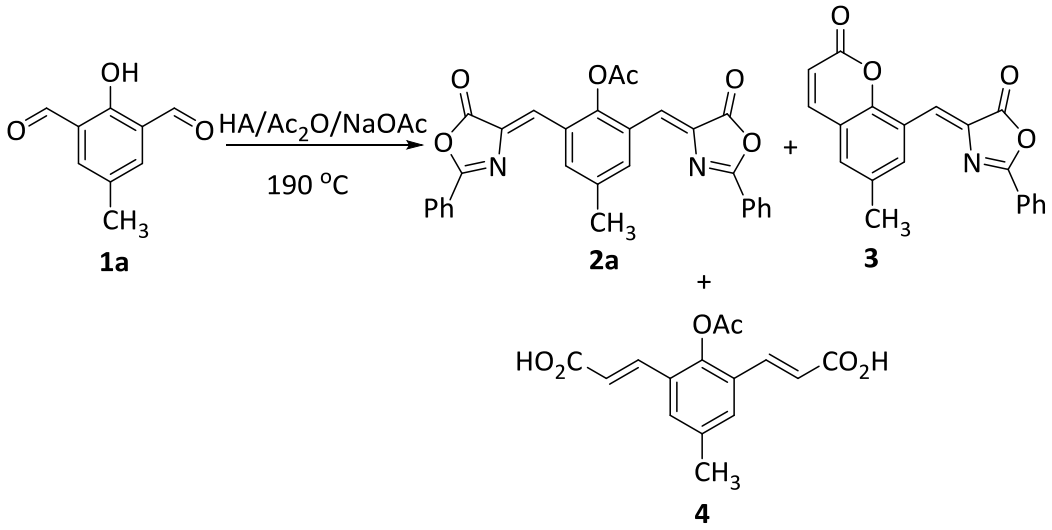
Four-component reactions of dialdehydes (**1a–f**), glycine, benzoyl chloride, and Ac_2O have also been studied, providing direct access to bis-oxazolones (Scheme 2, method B). Benzoyl chloride, glycine, Ac_2O and fused NaOAc were sonicated at 60 ^{o}C for 3 min to furnish 2-phenyloxazol-5(4*H*)-one. Following that, dialdehydes (**1a–f**) were added and sonication was recommenced for another 3 min at the same temperature. The bis-oxazolones (**2a–f**) were obtained in excellent yields and high purity. Notably, this newly developed four-component reaction under sonication gave nearly similar yields compared with method A.

On mixing the model substrates (**1a**), HA, Ac_2O and NaOAc together under increased thermal conditions of 120 ^{o}C, multiple spots were observed in addition to the anticipated product (**2a**) on TLC. Using preparative TLC methodology, the mixture was resolved and three derivatives were isolated and identified as (4*Z*,4′*Z*)-4,4′-((2-hydroxy-5-methyl-1,3-phenylene)bis(methanylylidene))bis(2-phenyloxazol-5(4*H*)-one) (**2a**, 34%), and the unexpected products (*Z*)-4-[(6-methyl-2-oxo-2*H*-chromen-8-yl)methylene]-2-phenyloxazol-5(4*H*)-one (**3**, 60%) and a small amount of the 3,3'-(2-acetoxy-5-methyl-1,3-phenylene)diacrylic acid (**4**, 6%) (Scheme 3). Proposed mechanistic routes to (**2a)**, (**3)** and (**4)** are shown in Scheme 4.

 ©ARKAT USA, Inc



Scheme 2. Proposed synthetic routes to bis-oxazolones (**2a-f**) using methods A and B.

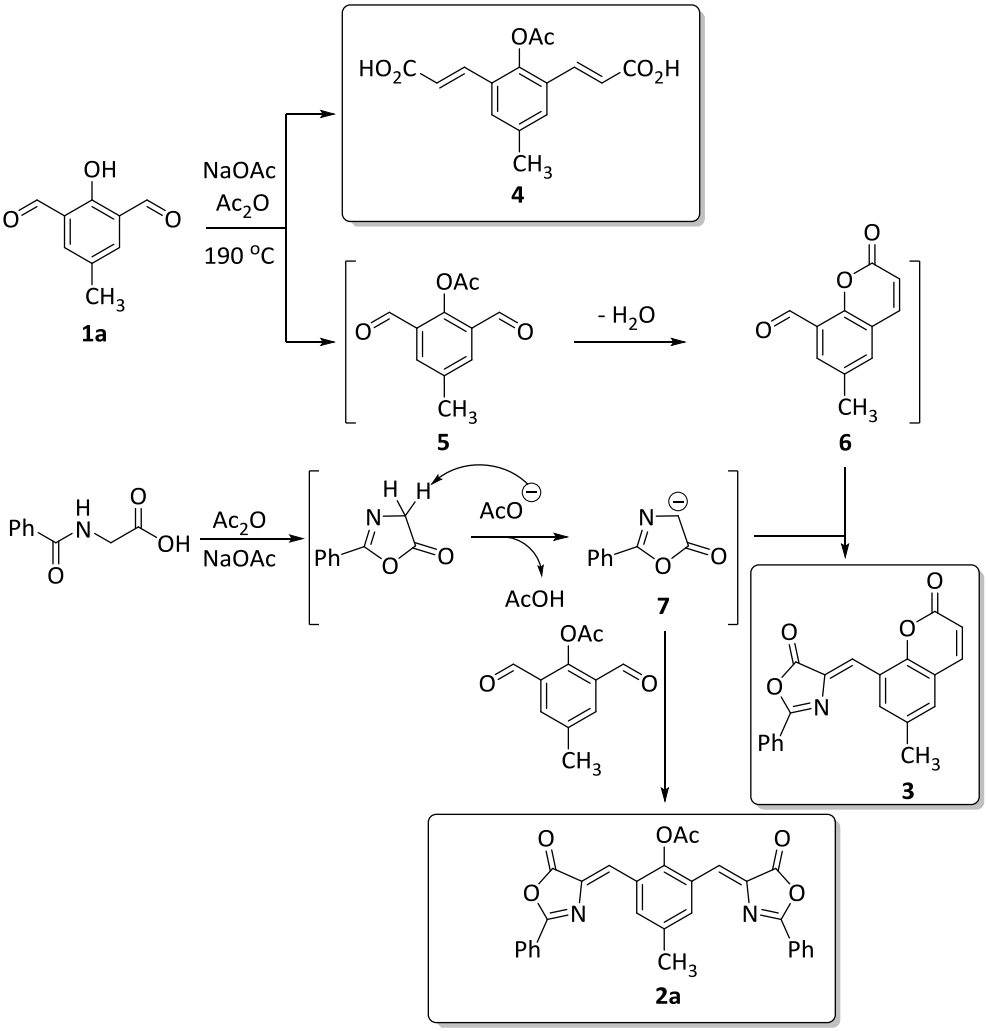


Scheme 3. Formation of (**2a**) and derivatives **(3**) and **(4**) at elevated temperature.

 ©**ARKAT USA, Inc**

The proposed structures of the prepared bisoxazolones (**2a-f**) were confirmed based on the spectral analyses (mass spectra, IR and NMR spectroscopies). The IR spectra of (**2a–f**) exhibited sharp bands around *v* 1790 cm^{-1} assigned to C=O. The constructed heterocyclic system was confirmed by the absence of any bands attributed to amidic NH or carboxylic OH functional groups. Despite the fact that there are two possible geometric isomers for derivatives (**2a–f**), we presumed that the configuration around the C=C double bond would be the thermodynamically more favourable *Z*-isomer, by analogy of the synthetic procedure utilized here with previously reported preparations of *Z*-oxazolones.[35] In the ^{1}H NMR spectra of (**2a–f**), only one set of signals exists in each spectrum, demonstrating that only one of the geometric isomers, the thermodynamically-preferred *Z*-isomer, was formed. Furthermore, the signal patterns denote that the two oxazolone moieties are chemically equivalent, meaning that the oxazolone molecules are symmetric with respect to the central ring.

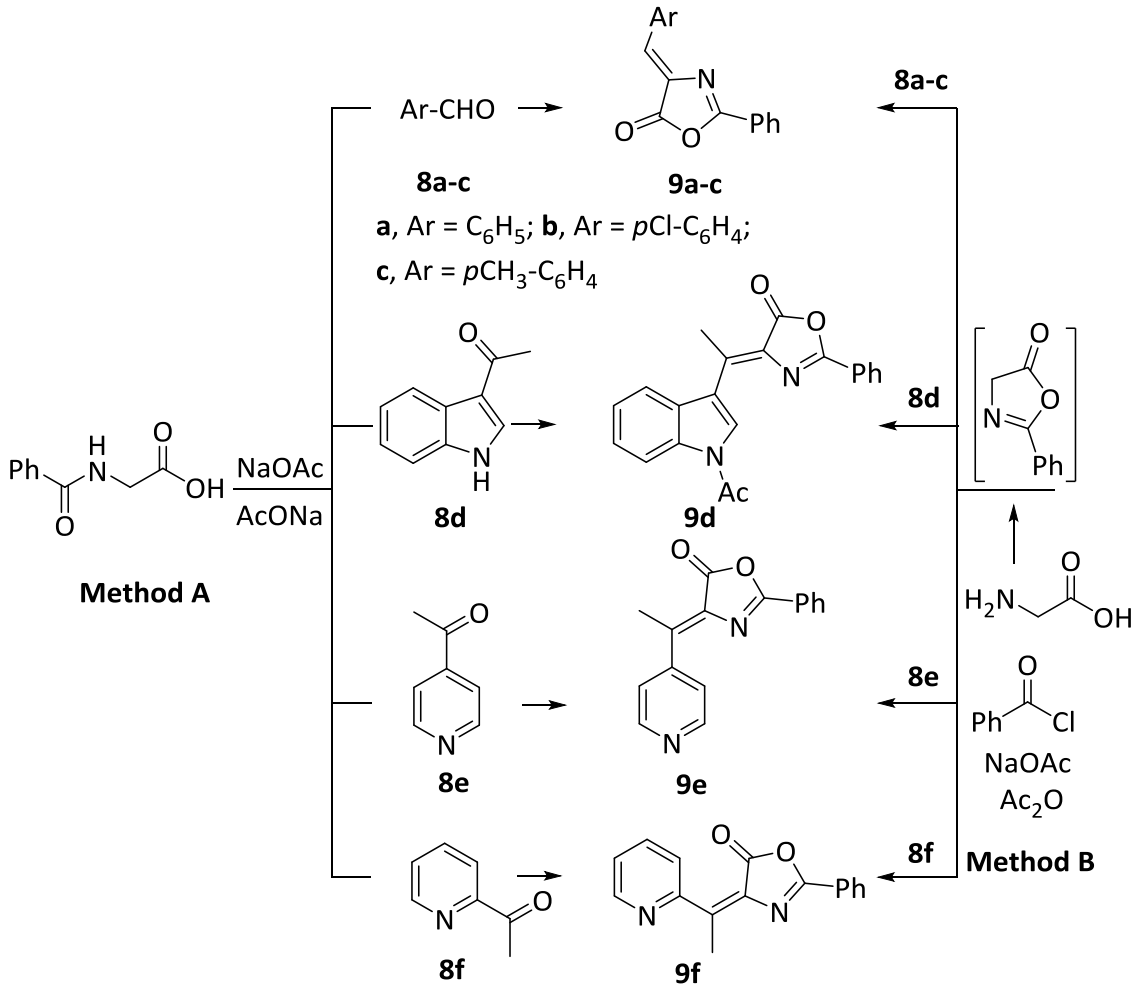
As presented in Scheme 4, a reasonable mechanism of this reaction at 190 ^{o}C would be an intramolecular aldol-type condensation of the initially formed O-acetyl derivative (**5**) to generate the non-isolable coumarin intermediate (**6**). This intermediate could then undergo a condensation reaction with the formed oxazolone anion (**7**), yielding the isolable derivative (**3**). Perkin-condensation compound (**4**) was also formed in this step. The formation of bisoxazolone (**2a**) may be due to the carbanion (**7**) attacking both carbonyl groups of the dialdehyde (**1a**).



Scheme 4. Proposed mechanisms for the syntheses of derivatives (**2a**), (**3**) and (**4**).

 ©**ARKAT USA, Inc**

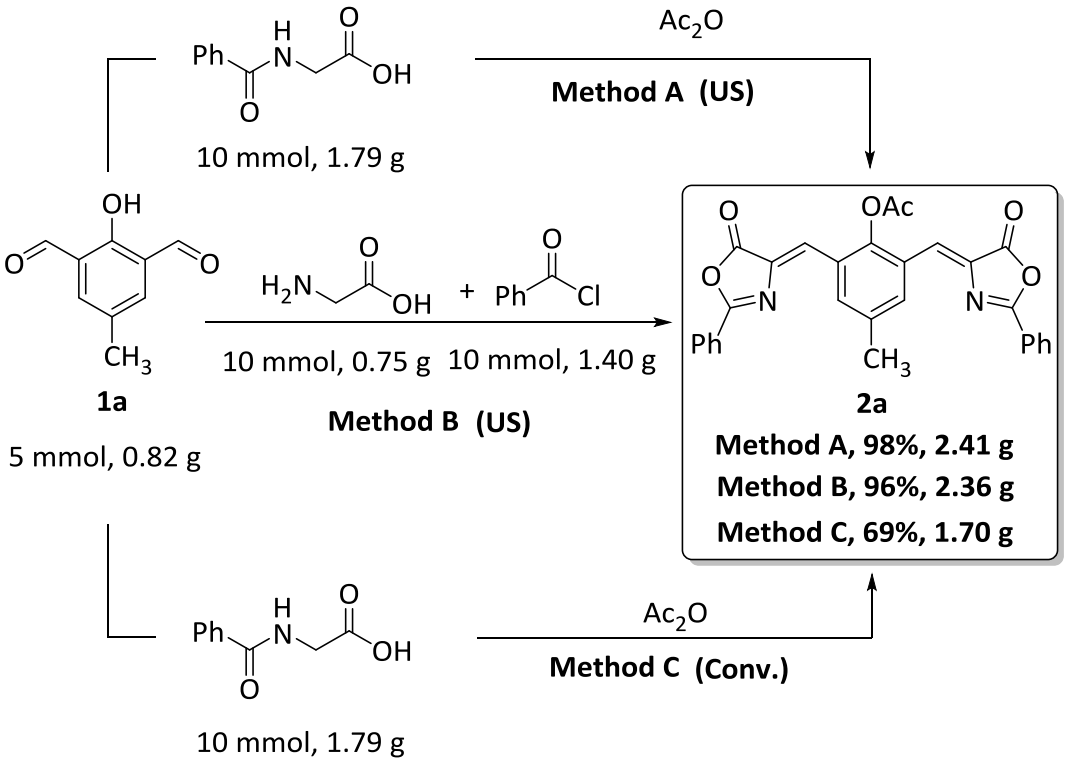
To further expand the scope of the substrates, several aromatic carbonyl compounds (**8a–f**) were also investigated under these sequential protocols (Scheme 5, methods A and B). The reactions afforded the corresponding oxazolones (**9a–f**) in excellent yields.



Scheme 5. Syntheses of oxazolones (**9a-f**) using methods A and B.

From a green-chemistry perspective, it would be valuable to compare our new methods with a conventional solvent/heating method (C) for the construction of bis-oxazolones using several 'green' metrics;[36] for example, Process Mass Intensity (PMI), E-factor, Reaction Mass Efficiency (RME) and Yield Economy (YE), which would then enable us to assess the strength of our chemical procedures. To accomplish this, the reaction should be scalable to gram level. Therefore, we performed gram-scale preparations of derivative (**2a**) utilizing methods A, B and C (Scheme 6). Using Method A, reacting dialdehyde (**1a**) (5 mmol) with HA (10 mmol) under sonication at 60 ^{o}C for 5 min provided 2.41 g of (**2a**) (98% yield) (Table 2, entry 1). Using Method B, reacting dialdehyde (**1a**) (5 mmol) with glycine (10 mmol) and benzoyl chloride (10 mmol) under sonication at 60 ^{o}C for 6 min gave 2.36 g of (**2a**) (96% yield) (Table 2, entry 2). Using Method C, reacting dialdehyde (**1a**) (5 mmol) with HA (10 mmol) in a water bath (100 ^{o}C) for 2h afforded 1.70 g of (**2a**) (69% yield) (Table 2, entry 3).

 ©**ARKAT USA, Inc**



Scheme 6. Scaled-up synthesis of bis-oxazolone (**2a**) using ultrasonic and conventional methods.

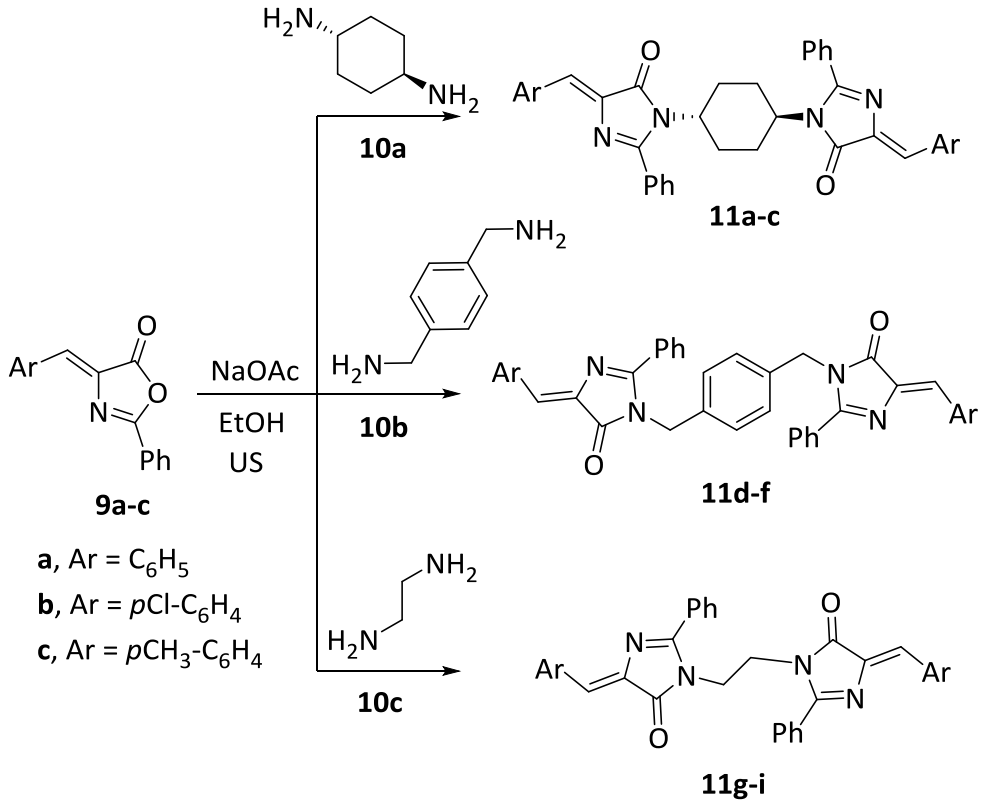
Table 2. Comparison of reaction efficiencies and sustainability metrics of ultrasonic methods (A, B) and conventional method (C) for preparation of bis-oxazolone derivative (**2a**)

Entry	Method	Yield (%)	E-factor	PMI	RME (%)	YE (%)
1	A	98	0.020	1.13	88.86	19.60
2	B	96	0.041	1.30	76.82	16.00
3	C	69	0.309	1.81	55.34	0.575

The higher values of sustainability metrics YE (19 and 16) and RME (88.8 and 76.8), and smaller values of E-factor (0.020 and 0.041) and PMI (1.13 and 1.30), make the investigated ultrasound-assisted protocols A and B ideal sustainable green processes for construction of mono- and bisoxazolones vs. the reported more-conventional process (C) when comparable reaction chemistries are applied.

In the course of our investigations for developing novel protocols to construct bis-heterocycles, we have also established an efficient and simple methodology for the preparation of bisimidazoles. Bis-imidazoles (**11a–i**) were synthesized simply by reacting diamines (**10a–c**) with (*Z*)-4-arylidene-2-phenyloxazol-5(4*H*)-ones (**9a–c**), in the presence of catalytic amounts of NaOAc, using sonication for 10 min at 80 ^{o}C (Scheme 7).

©ARKAT USA, Inc



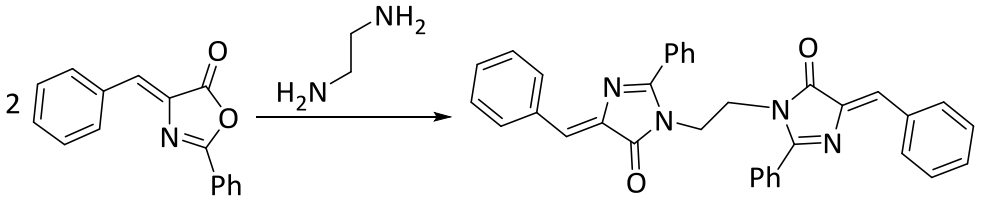
Scheme 7. Synthetic routes to bisimidazoles (**11a–i**).

It is worth mentioning that microwave irradiation also gave the desired bisimidazoles (**11a–i**) in almost the same yields, but following longer reaction times (40 min, 120 ^{o}C). The reaction seems to be tolerant to several substitutions on the oxazolone cores as well as the diamines. A slightly lower yield was obtained, however, in the case of 1,4-phenylenedimethanamine (**10b**) vs. both the 1,4-*trans*-cyclohexane-1,4-diamine (**10a**) and ethylenediamine (**10c**). Oxazolones substituted with methyl- and chloro- functional groups furnished the expected bisimidazoles (**11b**), (**11c**), (**11e**), (**11f**), (**11h**) and (**11i**) in better yields (94–97%). Also, compound (**9a**) afforded the best yield with 1,4-*trans*-cyclohexane-1,4-diamine (**10a**) (95%).

The structures of products (**11a–i**) were fully characterized by NMR, IR, and MS. The IR spectrum of derivative (**11a**) displayed characteristic bands at 1697 and 1635 cm^{-1} which were attributed to oxo-imidazole carbonyl (C=O) and azomethine (C=N) stretching frequencies, respectively. The ^{1}H NMR spectrum of (**11a**) exhibited one down-field singlet at 7.27 ppm which was assigned to the methine-group proton (C=CH); this confirmed the isolation of the thermodynamically more favourable *Z*-isomer preferentially over the *E*-isomer. The protons of the phenyl rings displayed three multiplets in the range of 8.21–7.29 ppm. Additionally, for derivative (**11a**), the protons of the cyclohexane ring were observed as multiplets in the 4.24–1.72 ppm range. Also, the ^{13}C NMR of derivative (**11a**) agreed with the number of carbons. These results were supported further by the mass spectrum which exhibited the molecular-ion peak at *m*/*z* 604.28 (M^{+}, 1.6%), in agreement with the molar mass of the proposed structure. To assess our protocol on the "greenness" scale once again, we performed a gram-scale preparation of bis-imidazole (**11g**) (Table 3) by condensing oxazolone (**9a**) (10 mmol, 2.49 g) with ethylene diamine (5 mmol, 0.3 g) using either ultrasonic irradiation for 10 min at 80 ^{o}C or in refluxing ethanol for 10 min.[37] (Scheme 8). Some green metrics were calculated for these reactions and the results are presented in Table 3. The sonication method achieved good scores in comparison with the

 ©ARKAT USA, Inc

conventional method, thus establishing the sonication methodology to be an ideal green, environmentally-sustainable method.



9a, 10 mmol 5 mmol **11g**, 2.45 g, 94% (US)
2.49 g 0.3 g 1.90 g, 73% (Conv.)

Scheme 8. Scale-up synthesis with yields of bisimidazole (**11g**) by ultrasonic (US) vs. conventional (Conv.) methods.

Table 3. A comparison of reaction efficiencies of different methods for the preparation of derivative (**11g**)

Entry	Method	Time (min)	Yield (%)	E-factor	PMI	RME (%)	YE (%)
1	US[a]	10	94	0.058	1.14	87.81	9.4
2	Conv.[b]	10	73	0.27	1.47	68.10	7.3

[a] Ultrasonic irradiation. [b] Conventional method.[37]

Conclusions

A rapid, scalable and multi-component protocol for the assembly of a novel series of mono- and bis-oxazolone scaffolds through sequential reactions was demonstrated using ultrasonic irradiation. (*Z*)-4-Arylidene-2-phenyloxazol-5(4*H*)-ones underwent ring transformation on sonication with several diamines to afford a new series of bisimidazoles. Key merits of these eco-friendly protocols over conventional methods include excellent functional-group tolerance, high yields, scalability, short reaction times, and easy work-up. These protocols display distinct advantages in terms of green-chemistry/sustainability metrics that can be of potential use for therapeutic-chemistry purposes and parallel synthesis applications.

Experimental Section

General. All chemicals and solvents were received commercially from Merck and Sigma–Aldrich chemical companies. Derivatives (**1a–c**, **1e**) and (**1f)** were prepared following our reported methods.[30,33] All known organic products (**2d**),[35] (**9a–c**),[38,39] and (**11g**)[37] were confirmed by comparison of their physical and spectral data with those of authentic samples. All of the melting points of the prepared compounds were determined on an Electrothermal IA9100 apparatus (UK). IR spectra of the samples were run using KBr disks on a Perkin-Elmer Spectrum One spectrometer. The NMR spectra were measured on a Bruker Avance 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6. Ultrasonication was performed in a SY5200DH-T ultrasound cleaner (40 kHz). Microwave irradiation was carried out using Biotage® Initiator Classic (Biotage AB; Uppsala, Sweden) using sealed vessels.

 ©**ARKAT USA, Inc**

General procedures for the preparation of mono- and bis-oxazolones (2a–f and 9a–f)

Method A. A mixture of hippuric acid (HA) (1.0 mmol), and freshly fused NaOAc (1.1 mmol) was mixed in the presence of Ac_2O (1 mL) and the mixture was sonicated for 3 min at 60 ^oC. Then, 0.5 mmol of dialdehydes (**1a–f**) or 1.0 mmol of carbonyl compounds (**8a–f**) were added and the sonication was resumed for 2 min at the same temperature. Upon completion of the reaction (monitored by TLC), the mixture formed a yellow solid, which was washed with water (2x10 mL), chilled in EtOH (2x10 mL), and recrystallized from EtOH containing a few drops of dioxane to obtain the desired mono- and bisoxazolones (**2a–f** and **9a–f**).

Method B. A mixture of glycine (1.0 mmol), benzoyl chloride (1.0 mmol) and freshly fused NaOAc (2.1 mmol) was mixed in the presence of Ac_2O (1 mL) and the mixture was sonicated for 3 minutes at 60 ^oC. Then 0.5 mmol of dialdehydes (**1a-f**) or 1.0 mmol of carbonyl compounds (**8a–f**) were added and the sonication was resumed for another 3 min. Upon completion of the reaction (monitored by TLC), yellow solids separated out which were washed with water (2x10 mL), chilled in EtOH (2x10 mL), and recrystallized from EtOH containing a few drops of dioxane to obtain the desired mono- and bis-oxazolones (**2a–f** and **9a–f**).

4-Methyl-2,6-bis[(*Z*)-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)methyl]phenol acetate (**2a**). Yellow solid, (477 mg, 97%). mp 211–213 ^oC. IR (solid, KBr, ν_{max}, cm^{-1}): 1793, 1738 (C=O), 1651 (C=N), 1591 (C=C). ^1H NMR (400 MHz, DMSO): δ_H 8.11 (4H, d, *J* 7.5 Hz, 4CH aromatic), 7.84 (2H, s, =C<u>H</u>), 7.47 (2H, s, 2CH aromatic), 7.42–7.34 (6H, m, 6CH aromatic), 2.41 (3H, s, C<u>H</u>$_3$), 2.38 (3H, s, C<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO): δ_C 169.5 (CO), 167.2 (CO), 162.1, 148.1, 135.3, 131.7, 131.0, 129.8, 128.9, 128.8, 126.8, 121.5, 117.9 (C aromatic), 21.0 (<u>C</u>H$_3$), 20.7 (<u>C</u>H$_3$). MS (ESI) *m/z* (%): 492.13 (M^+, 0.8), 105 (100). Anal. calcd. for $C_{29}H_{20}N_2O_6$: C, 70.73; H, 4.09; N, 5.69. Found: C, 70.67; H, 4.14; N, 5.75.

4-Bromo-2,6-bis[(*Z*)-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)methyl]phenol acetate (**2b**). Yellow solid, (545 mg, 98%). mp 242–244 ^oC. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1803, 1737 (C=O), 1652 (C=N), 1598 (C=C). ^1H NMR (400 MHz, DMSO): δ_H 8.10 (4H, d, *J* 7.5 Hz, 4CH aromatic), 7.84 (2H, s, =C<u>H</u>), 7.74 (2H, s, 2CH aromatic), 7.51–7.48 (6H, m, 6CH aromatic), 2.37 (3H, s, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, DMSO): δ_C 169.1 (C=O), 167.5 (C=O), 161.8, 149.7, 132.3, 131.6, 131.1, 128.7, 128.5, 123.8, 118.8, 118.4, (C aromatic), 20.9 (<u>C</u>H$_3$). MS (ESI) *m/z* (%): 556.02 (M^+, 1.3), 105 (100). Anal. calcd. for $C_{28}H_{17}BrN_2O_6$: C, 60.34; H, 3.07; N, 5.03. Found: C, 60.41; H, 2.98; N, 5.11.

4-Acetoxy-3,5-bis[(*Z*)-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)methyl]benzoic acid (**2c**). Yellow solid, (490 mg, 94%). mp 234–235 ^oC. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 3324–3155 (OH), 1799, 1737, 1685 (C=O), 1646 (C=N), 1601 (C=C). ^1H NMR (400 MHz, DMSO): δ_H 11.70 (1H, s, OH), 7.73 (2H, s, 2CH aromatic), 7.97–7.94 (4H, m, 4CH aromatic), 7.79 (2H, s, =C<u>H</u>), 7.53–7.48 (6H, m, 6CH aromatic), 2.39 (3H, s, C<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO): δ_C 169.3 (CO), 167.6 (CO), 167.3 (CO), 162.3, 149.9, 132.5, 131.9, 131.5, 129.3, 128.7, 126.5, 123.7, 118.7 (C aromatic), 21.2 (<u>C</u>H$_3$). MS (ESI) *m/z* (%): 522.10 (M^+, 0.6), 105 (100). Anal. calcd. for $C_{29}H_{18}N_2O_8$: C, 66.67; H, 3.47; N, 5.36. Found: C, 66.62; H, 3.52; N, 5.30.

(4*Z*,4′*Z*)-4,4′-[1,4-Phenylenebis(methanylylidene)]bis(2-phenyloxazol-5(4*H*)-one) (**2d**).[35]Yellow solid, (407 mg, 97%). mp 281–283 ^oC. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1787 (C=O), 1653 (C=N), 1605 (C=C). ^1H NMR (400 MHz, $CDCl_3$): δ_H 8.33 (4H, s, 4CH aromatic), 8.23 (4H, d, *J* 7.2 Hz, 4CH aromatic), 7.65 (2H, t, *J* 7.4 Hz, 2CH aromatic), 7.57 (4H, t, *J* 7.3 Hz, 4CH aromatic), 7.25 (2H, s, =C<u>H</u>). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.4 (CO), 162.2, 133.7, 132.6, 130.1, 129.1, 128.6, 135.8, 134.6, 125.4 (C aromatic). MS (ESI) *m/z* (%): 420.11 (M^+, 12.4%), 67 (100). Anal. calc. for $C_{26}H_{16}N_2O_4$: C, 74.28; H, 3.84; N, 6.66. Found: C, 74.22; H, 3.90; N, 6.59.

(4*Z*,4'*Z*)-4,4'-[(1-Acetyl-1*H*-pyrazole-3,5-diyl)bis(methanylylidene)]bis(2-phenyloxazol-5(4H)-one] (**2e**). Yellow solid, (402 mg, 89%). mp 394–397 ^oC. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1787, 1729 (C=O), 1648 (C=N), 1593 (C=C). ^1H NMR (400 MHz, DMSO): δ_H 7.89–7.86 (4H, m, 4CH aromatic), 7.68 (2H, s, =CH), 7.57–7.50 (6H, m, 6CH aromatic), 7.20 (1H, s, pyrazole-C4), 2.78 (3H, s, C<u>H</u>$_3$). MS (ESI) *m/z* (%): 452.11 (M^+, 0.3%), 105 (100). Anal. calc. for $C_{25}H_{16}N_4O_5$: C, 66.37; H, 3.56; N, 12.38. Found: C, 66.42; H, 3.49; N, 12.44.

 ©ARKAT USA, Inc

Methylene bis-{2-[(*Z*)-(5-oxo-2-phenyloxazol-4(5*H*)-ylidene)methyl]-4,1-phenylene} diacetate (**2f**). Yellow solid, (588 mg, 94%). mp > 400 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1803, 1736 (C=O), 1654 (C=N), 1597 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 7.93–7.90 (4H, m, 4CH aromatic), 7.66 (2H, s, =C<u>H</u>), 7.59–7.52 (6H, m, 6CH aromatic), 7.39 (2H, d, *J* 7.4 Hz, 2CH aromatic), 7.32 (2H, s, 2CH aromatic), 7.01 (2H, d, *J* 7.4 Hz, 2CH aromatic), 4.03 (2H, s, C<u>H</u>$_2$), 2.42 (6H, s, C<u>H</u>$_3$). MS (ESI) *m/z* (%): 626.16 (M^+, 0.1%), 105 (100). Anal. calc. for $C_{37}H_{26}N_2O_8$: C, 70.92; H, 4.18; N, 4.47. Found: C, 71.01; H, 4.11; N, 4.39.

(*Z*)-4-Benzylidene-2-phenyloxazol-5(4*H*)-one (**9a**).[38] Yellow solid, (291 mg, 99%). mp 167 °C (lit. mp 166–167). IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1796 (C=O), 1656 (C=N), 1595 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.31 (2H, d, *J* 7.8 Hz, 2CH aromatic), 8.13 (2H, d, *J* 7.5 Hz, 2CH aromatic), 7.61 (1H, t, *J* 7.4, 1CH aromatic), 7.53 (2H, t, *J* 7.7, 2CH aromatic), 7.51–7.42 (3H, m, 3CH aromatic), 7.32 (1H, s, CH=C). MS (ESI) *m/z* (%): 294.08 (M^+, 69%), 105 (100). Anal. calc. for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62. Found: C, 77.17; H, 4.40; N, 5.57.

(*Z*)-4-(4-Chlorobenzylidene)-2-phenyloxazol-5(4*H*)-one (**9b**).[39] Yellow solid, (277mg, 98%). mp 204–206 °C (lit. mp 203–204). IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1790 (C=O), 1662 (C=N), 1599 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H: 8.20 (1H, m, 1CH aromatic), 8.17 (1H, d, *J* 1.5 Hz, 1CH aromatic), 8.15 (1H, d, *J* 1.7 Hz, 1CH aromatic), 8.14 1H, (1H, m, 1CH aromatic), 7.64 (1H, m, 1CH aromatic), 7.54 (2H, t, *J* 7.7 Hz, 2CH aromatic), 7.46 (2H, m, 2CH aromatic), 7.18 (1H, s, C<u>H</u>=C). MS (ESI) *m/z* (%): 283.04 (M^+, 34%), 103 (100). Anal. calc. for $C_{16}H_{10}ClNO_2$: C, 67.74; H, 3.55; N, 4.94. Found: C, 67.71; H, 3.59; N, 4.89.

(*Z*)-4-(4-Methylbenzylidene)-2-phenyloxazol-5(4*H*)-one (**9c**).[39] Yellow solid, (260 mg, 99%). mp 143–145 °C (lit. mp 144–145). IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1788 (C=O), 1641 (C=N), 1603 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.19 (2H, dd, *J* 1.3, 8.2 Hz, 2CH aromatic), 8.10 (2H, d, *J* 8.2 Hz, 2CH aromatic), 7.58 (1H, dd, *J* 4.4, 10.7 Hz, 1CH aromatic), 7.52 (2H, dd, *J* 7.1, 8.2 Hz, 2CH aromatic), 7.30 (2H, d, *J* 8.3 Hz, 2CH aromatic), 7.24 (1H, s, C<u>H</u>=C), 2.41 (3H, s, C<u>H</u>$_3$). MS (ESI) *m/z* (%): 263.09 (M^+, 11%), 91 (100). Anal. calc. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.59; H, 4.96; N, 5.28.

(*Z*)-4-[1-(1-Acetyl-1*H*-indol-3-yl)ethylidene]-2-phenyloxazol-5(4*H*)-one (**9d**). Yellow solid, (333 mg, 97%). mp 312–315 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1795, 1712 (C=O), 1655 (C=N), 1605 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.34 (1H, s, 1CH aromatic), 8.23 (1H, d, *J* 7.6 Hz, 1CH aromatic), 8.20–8.17 (2H, m, 2CH aromatic), 7.55–7.51 (4H, m, 4CH aromatic), 7.24–7.21 (2H, m, 2CH aromatic), 2.49 (3H, s, C<u>H</u>$_3$), 2.43 (3H, s, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 169.7 (CO), 167.3 (CO), 161.4, 149.4, 137.5, 136.6, 134.3, 131.4, 129.0, 128.5, 126.4, 125.3, 122.7, 121.9, 121.3, 117.8, 110.3 (C aromatic), 24.5 (<u>C</u>H$_3$), 20.7 (<u>C</u>H$_3$). MS (ESI) *m/z* (%): 344.11 (M^+, 0.8%), 105 (100). Anal. calc. for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13. Found: C, 73.30; H, 4.61; N, 8.06.

(*Z*)-2-Phenyl-4-[1-(pyridin-4-yl)ethylidene]oxazol-5(4*H*)-one (**9e**). Yellow solid, (258 mg, 98%). mp 215–217 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1788 (C=O), 1650 (C=N), 1611 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.82–8.80 (2H, m, 2CH aromatic), 8.02–7.99 (2H, m, 2CH aromatic), 7.73–7.71 (2H, m, 2CH aromatic), 7.53–7.50 (3H, m, 3CH aromatic), 2.54 (3H, s, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, DMSO): δ_C 167.5 (CO), 161.9, 150.9, 149.2, 142.7, 138.5, 131.1, 128.8, 128.3, 125.9, 121.2 (C aromatic), 21.0 (<u>C</u>H$_3$). MS (ESI) *m/z* (%): 264.08 (M^+, 0.8%), 105 (100). Anal. calc. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.68; H, 4.66; N, 10.54.

(*Z*)-2-Phenyl-4-[1-(pyridin-2-yl)ethylidene]oxazol-5(4*H*)-one (**9f**). Yellow solid, (237 mg, 90%). mp 228–231 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1785 (C=O), 1643 (C=N), 1605 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.69–8.68 (1H, m, 1CH aromatic), 8.04–8.01 (3H, m, 3CH aromatic), 7.84–7.83 (1H, m, 1CH aromatic), 7.54–7.52 (3H, m, 3CH aromatic), 7.48–7.47 (1H, m, 1CH aromatic), 2.52 (3H, s, C<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO): δ_C 167.3 (CO), 161.7, 153.6, 149.7, 148.8, 138.9, 136.4, 131.0, 128.6, 128.1, 127.3, 126.1, 121.5 (C aromatic), 24.2 (<u>C</u>H$_3$). MS (ESI) *m/z* (%): 264.08 (M^+, 2.5), 105 (100). Anal. calc. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.70; H, 4.62; N, 10.57.

 ©ARKAT USA, Inc

Synthesis of derivatives (3) and (4)

A mixture of 2-hydroxy-5-methylisophthalaldehyde (0.5 mmol), HA (1 mmol), Ac_2O (2 mL) and NaOAc (2.1 mmol) was warmed into solution. Heating was then continued on an oil-bath for 1 h. Excess acetic anhydride was decomposed with water, and the residue was triturated with ethanol. The yellow solid product was filtered off and the crude product was subjected to preparative TLC (DCM:MeOH 8:2) to afford derivatives (**2a**) (R_f 0.4), (**3**) (R_f 0.42) and (**4**) (R_f 0.45).

(*Z*)-4-((6-Methyl-2-oxo-2*H*-chromen-8-yl)methylene)-2-phenyloxazol-5(4*H*)-one (**3**). Yellow solid, (198 mg, 60%). mp 201–203 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1788, 1736 (C=O), 1636 (C=N), 1612 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 7.99–7.98 (2H, m, 2CH aromatic), 7.92 (1H, d, *J* 9.6 Hz, 1CH aromatic), 7.80 (1H, s, C<u>H</u>=C), 7.46–7.44 (3H, m, 3CH aromatic), 7.26–7.25 (2H, m, 2CH aromatic), 6.42 (1H, d, *J* 9.6 Hz, 1CH aromatic), 2.40 (3H, s, C<u>H</u>$_3$). MS (ESI) *m/z* (%): 331.07 (M^+, 1.5%), 103 (100). Anal. calc. for $C_{20}H_{13}NO_4$: C, 72.50; H, 3.96; N, 4.23. Found: C, 72.53; H, 3.99; N, 4.19.

3,3'-(2-Acetoxy-5-methyl-1,3-phenylene)diacrylic acid (**4**)**.** Yellow solid, (17 mg, 6%). mp 187–189 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 3411-2877 (OH), 1715, 1689 (C=O), 1605 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 12.76 (2H, br, O<u>H</u>), 8.12 (2H, d, *J* 14.9 Hz, C<u>H</u>=CH-CO), 7.32 (2H, s, 2CH aromatic), 6.25 (2H, d, *J* 9.4 Hz, CH=C<u>H</u>-CO), 2.39 (3H, s, C<u>H</u>$_3$), 2.36 (3H, s, C<u>H</u>$_3$). ^{13}C NMR (100 MHz, DMSO): δ_C 171.2 (CO), 169.5 (CO), 143.2, 142.7, 133.0, 128.4, 124.3, 117.0 (C aromatic), 21.1 (<u>C</u>H$_3$), 20.4 (<u>C</u>H$_3$). MS (ESI) *m/z* (%):290.05 (M^+, 0.1%), 202 (100). Anal. calc. for $C_{15}H_{14}O_6$: C, 62.07; H, 4.86. Found: C, 62.11; H, 4.82.

General protocol for the synthesis of bis-imidazoles (11a–i)

A mixture of (*Z*)-4-arylidene-2-phenyloxazol-5(4*H*)-ones (**9a–c**, 1 mmol) and diamines (**10a–c**, 0.5 mmol) in ethanol (10 mL) containing a catalytic quantity of NaOAc was sonicated for 10 min at 80 °C (monitored by TLC). The formed crude products were filtered, dried and recrystallized from dioxane containing a few drops of DMF.

(*Z*)-3,3'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis-[5-((*Z*)-benzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (**11a**)**.** Yellow solid, (547 mg, 95%). mp 219–221 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1705 (C=O), 1622 (C=N), 1597 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.27–8.21 (4H, m, 4CH aromatic), 7.56–7.47 (6H, m, 6CH aromatic), 7.43–7.29 (10H, m, 10CH aromatic), 7.11 (2H, s, C<u>H</u>=C), 4.22 (2H, b, cyclohexyl), 1.77–1.75 (4H, m, cyclohexyl), 1.44–1.40 (4H, m, cyclohexyl). ^{13}C NMR (100 MHz, DMSO): δ_C 170.9 (CO), 152.7, 138.7, 132.0, 130.5, 128.9, 128.8, 127.2, 126.7, 117.7, 116.9 (C aromatic), 57.8 (C aliphatic), 30.8 (C aliphatic). MS (ESI) *m/z* (%): 576.25 (M^+, 0.5%), 90 (100). Anal. calc. for $C_{38}H_{32}N_4O_2$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.19; H, 5.51; N, 9.65.

(*Z*)-3,3'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis[5-((*Z*)-4-chlorobenzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (**11b**)**.** Yellow solid, (624 mg, 97%). mp 312–315 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1701 (C=O), 1641 (C=N), 1604 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.21-8.12 (8H, m, 8CH aromatic), 7.66 (2H, m, 2CH aromatic), 7.57 (4H, m, 4CH aromatic), 7.43 (4H, m, 4CH aromatic), 7.21 (2H, s, C<u>H</u>=C), 4.20 (2H, b, cyclohexyl), 1.76–1.73 (4H, m, cyclohexyl), 1.44–1.42 (4H, m, cyclohexyl). MS (ESI) *m/z* (%): 644.17 (M^+, 0.9%), 103 (100). Anal. calc. for $C_{38}H_{30}Cl_2N_4O_2$: C, 70.70; H, 4.68; N, 8.68. Found: C, 70.75; H, 4.61; N, 8.60.

(*Z*)-3,3'-((1*R*,4*R*)-Cyclohexane-1,4-diyl)bis[5-((*Z*)-4-methylbenzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (**11c**)**.** Yellow solid, (570 mg, 96%). mp 279–282 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1697 (C=O), 1635 (C=N), 1586 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.21-8.17 (8H, m, 8CH aromatic), 7.60-7.57 (6H, m, 6CH aromatic), 7.33-7.29 (4H, m, 4CH aromatic), 7.27 (2H, s, C<u>H</u>=C), 4.24 (2H, b, cyclohexyl), 2.42 (6H, s, C<u>H</u>$_3$), 1.78–1.72 (4H, m, cyclohexyl), 1.46–1.42 (4H, m, cyclohexyl). MS (ESI) *m/z* (%): 604.28 (M^+, 1.6%), 103 (100). Anal. calc. for $C_{40}H_{36}N_4O_2$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.49; H, 5.97; N, 9.21.

 ©**ARKAT USA, Inc**

(*Z*)-3,3'-[1,4-Phenylenebis(methylene)]bis[5-((*Z*)-benzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (11d). Yellow solid, (550 mg, 92%). mp 284–286 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1712 (C=O), 1641 (C=N), 1601 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.25-8.23 (4H, m, 4CH aromatic), 7.55-7.48 (6H, m, 6CH aromatic), 7.48-7.25 (10H, m, 10CH aromatic), 7.23 (4H, s, 4CH aromatic), 7.06 (2H, s, C<u>H</u>=C), 4.69 (4H, s, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, DMSO): δ_C 170.9 (CO), 152.8, 138.9, 136.5, 132.1, 131.2, 129.0, 128.8, 128.1, 127.2, 117.5 (C aromatic), 53.0 (C aliphatic). MS (ESI) *m/z* (%): 598.23 (M^+, 0.33%), 90 (100). Anal. calc. for $C_{40}H_{30}N_4O_2$: C, 80.25; H, 5.05; N, 9.36. Found: C, 80.21; H, 5.10; N, 9.29.

(*Z*)-3,3'-[1,4-Phenylenebis(methylene)]bis[5-((*Z*)-4-chlorobenzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (11e). Yellow solid, (626 mg, 94%), mp 379–382 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1701 (C=O), 1639 (C=N), 1612 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.23-8.17 (8H, m, 8CH aromatic), 7.67-7.61 (6H, m, 6CH aromatic), 7.46-7.43 (4H, m, 4CH aromatic), 7.23 (2H, s, C<u>H</u>=C), 7.22 (4H, s, 4CH aromatic), 4.65 (4H, s, C<u>H</u>$_2$). MS (ESI) *m/z* (%): 666.16 (M^+, 1.61%), 103 (100). Anal. calc. for $C_{40}H_{28}Cl_2N_4O_2$: C, 71.97; H, 4.23; N, 8.39. Found: C, 72.01; H, 4.21; N, 8.35.

(*Z*)-3,3'-[1,4-Phenylenebis(methylene)]bis[5-((*Z*)-4-methylbenzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (11f). Yellow solid, (588 mg, 94%). mp 368–370 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1708 (C=O), 1648 (C=N), 1597 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.24-8.19 (8H, m, 8CH aromatic), 7.55-7.53 (2H, m, 2CH aromatic), 7.48-7.39 (8H, m, 8CH aromatic), 7.24 (4H, s, 4CH aromatic), 7.14 (1H, s, C<u>H</u>=C), 4.66 (4H, s, C<u>H</u>$_2$), 2.42 (3H, s, C<u>H</u>$_3$). MS (ESI) *m/z* (%): 626.27 (M^+, 10.6%), 91 (100). Anal. calc. for $C_{42}H_{34}N_4O_2$: C, 80.49; H, 5.47; N, 8.94. Found: C, 80.53; H, 5.44; N, 8.89.

(*Z*)-3,3'-(Ethane-1,2-diyl)bis[5-((*Z*)-benzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (11g).[37] Yellow solid, (490 mg, 94%). mp 145–147 °C (lit mp 140–142 °C). IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1701 (C=O), 1637 (C=N), 1612 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.28–8.23 (4H, m, 4CH aromatic), 7.56–7.43 (6H, m, 6CH aromatic) 7.44–7.27 (10H, m, 10CH aromatic), 7.12 (2H, s, C<u>H</u>=C), 4.36 (4H, s, C<u>H</u>$_2$). ^{13}C NMR (100 MHz, DMSO): δ_C 170.9 (CO), 152.8, 139.0, 132.3, 130.7, 129.1, 128.8, 127.3, 127.0, 117.6 (C aromatic), 51.3 (C alphatic). MS (ESI) *m/z* (%): 522.20 (M^+, 2.5%), 103 (100). Anal. calc. for $C_{34}H_{26}N_4O_2$: C, 78.14; H, 5.01; N, 10.72. Found: C, 78.19; H, 4.96; N, 10.68.

(*Z*)-3,3'-(Ethane-1,2-diyl)bis-[5-((*Z*)-4-chlorobenzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (11h). Yellow solid, (560 mg, 95%). mp 312–314 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1713 (C=O), 1641 (C=N), 1609 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.21-8.15 (8H, m, 8CH aromatic), 7.68-7.60 (6H, m, 6CH aromatic), 7.44-7.40 (4H, m, 4CH aromatic), 7.22-7.18 (2H, m, 2CH aromatic), 4.33 (4H, s, C<u>H</u>$_2$). MS (ESI) *m/z* (%): 590.12 (M^+, 2.5%), 103 (100). Anal. calc. for $C_{34}H_{24}Cl_2N_4O_2$: C, 69.04; H, 4.09; N, 9.47. Found: C, 69.09; H, 4.05; N, 9.42.

(*Z*)-3,3'-(Ethane-1,2-diyl)bis(5-[(*Z*)-4-methylbenzylidene)-2-phenyl-3,5-dihydro-4*H*-imidazol-4-one] (11i). Yellow solid, (533 mg, 97%). mp 199–202 °C. IR (solid, KBr, $\nu_{max,}$ cm^{-1}): 1698 (C=O), 1628 (C=N), 1610 (C=C). ^{1}H NMR (400 MHz, DMSO): δ_H 8.15-8.08 (8H, m, 8CH aromatic), 8.17-8.15 (4H, m, 4CH aromatic), 7.59-7.66 (6H, m, 6CH aromatic), 7.35-7.29 (4H, m, 4CH aromatic), 7.21 (2H, s, C<u>H</u>=C), 4.37 (4H, s, C<u>H</u>$_2$), 2.40 (6H, s, C<u>H</u>$_3$). MS (ESI) *m/z* (%): 550.23 (M^+, 5.3%), 91 (100). Anal. calc. for $C_{36}H_{30}N_4O_2$: C, 78.52; H, 5.49; N, 10.17. Found: C, 78.56; H, 5.51; N, 10.11.

References

1. Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. *Tetrahedron Lett.* **2004**, *45*, 425–427. https://doi.org/10.1016/j.tetlet.2003.10.125.
2. Sierra, F. M. P.; Pierre, A.; Burbridge, M.; Guilbaud, N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1463–1466.

 ©**ARKAT USA, Inc**

https://doi:org/10.1016/S0960-894X(02)00197-X.

3. Takenaka, K.; Tsuji, T. *J. Heterocyclic Chem.* **1996**, *33*, 1367–1370. https://doi:org/10.1002/jhet.5570330459
4. Mohammed, K. K.; Mughal, M. R.; Hassan, K. M. T. *Bioorg. Med. Chem.* **2006**, *14*, 6027–6033. https://doi:org/10.1016/j.bmc.2006.05.014.
5. Weber, M.; Frey, W.; Peters, R. *Adv. Synth. Catal.* **2012**, *354*, 1443–1449. https://doi:10.1002/adsc.201200085.
6. Esguevillas, M. G.; Adrio, J.; Carretero, J. C. *Chem. Commun.* **2013**, *49*, 4649–4652. https://doi:10.1039/C3CC41663A
7. Tian, L.; Xu, G. Q.; Li, Y. H.; Liang, Y. M.; Xu, P. F. *Chem. Commun.* **2014**, *50*, 2428–2430. https://doi:10.1039/C3CC49504C
8. Wang, T.; Yu, Z.; Hoon, D. L.; Phee, C. Y.; Lan, Y.; Lu, Y. *J. Am. Chem. Soc.* **2015**, *138*, 265–271. https://doi:10.1021/jacs.5b10524
9. Cavalier, F.; Verducci, J. *Tetrahedron Lett.* **1995**, *36*, 4425–4428. https://doi.org/10.1016/0040-4039(95)00762-2
10. Avenoza, A.; Busto, J. H.; Cativiela, C.; Peregrina, J. M. *Tetrahedron Lett.* **2002**, *43*, 4167–4170. https://doi:org/10.1016/S0040-4039(02)00744-X
11. Erlenmeyer, E. *Ann.* **1892**, *271*, 137.
12. Hermanson, G.T.; Mattson, G. R.; Krohn, R. I. *J. Chromatogr. A* **1995**, *691*, 113–122.
13. Bautista, F. M.; Campelo, J. M.; Garcıa, A.; Luna, D.; Marinas, J. M.; Romero, A. A. *J. Chem. Soc., Perkin Trans.* **2002**, *2*, 227–234. https://doi:10.1039/B109413K
14. Banafshe, S.; Ghaleh, T.; Valiollah, M.; Iraj, M. B.; Majid, M.; Shahram, T.; Mahbubeh, R.; Ahmad, R. K. *J. Inorg. Organomet. Polym.* **2013**, *23*, 758–765. https://doi:org/10.1007/s10904-012-9810-9
15. Conway, P. A.; Devine, K.; Paradisi, F. *Tetrahedron*. **2009**, *65*, 2935–2938. https://doi:org/10.1016/j.tet.2009.02.011
16. Yu, C.; Zhou, B.; Su, W.; Xu, Z. *Synth. Commun.* **2006**, *36*, 3447–3453. https://doi:org/10.1080/00397910600941521
17. Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432-1440. https://doi:10.1039/b511113g
18. Ramadan, M. A.; Hadeer, M. B.; Gammal, H. T.; Wael, A. A. A. *J. Heterocyclic Chem.* **2012**, *49*, 1071-1076. https://doi:10.1002/jhet.938
19. Roiban, G. D.; Soler, T.; Grosu, I.; Cativiela, C.; Urriolabeitia, E. P. *Inorg. Chim. Acta* **2011**, *368*, 247-251. https://doi:org/10.1016/j.ica.2010.12.054
20. Esmail, V.; Somayeh, S. A.; Akram, H.; Ladan, E.; Ahmadreza, B. *RSC Adv.* **2017**, *7*, 7079-7091. https://doi:10.1039/C6RA25816F
21. Masoud, N. E.; Morteza, M.; Tooba, A. *Chem. Pap.* **2015**, *69*, 1491–1499. https://doi:org/10.1515/chempap-2015-0156
22. Rani, N.; Sharma, A.; Singh, R. *Mini-Rev. Org. Chem.* **2015**, *12*, 34-65. https://doi:10.2174/1570193X11666141028235010.
23. Mossaraf, H.; Kiran, P.; Ashis, K. N. *Tetrahedron Lett.* **2017**, *58*, 3772-3776. https://doi:org/10.1016/j.tetlet.2017.08.047

 ©**ARKAT USA, Inc**

24. Serykh, V. Y.; Kaliev, A. R.; Ushakov, I. A.; Borodina, T. N.; Smirnov, V.I.; Rozentsveig, I. B.; *Arkivoc* **2018**, *iii*, 62-75. https://doi.org/10.24820/ark.5550190.p010.357
25. Leila, Z. F.; Mohammad, N.; Roghayeh, M. *J. Mol. Liq.* **2016**, *222*, 77-81. https://doi:org/10.1016/j.molliq.2016.07.009
26. Hu, Y.; Shen, Y.; Wu, X.; Tu, X.; Wang, G. X. *Eur. J. Med. Chem.* **2018**, *143*, 958-969. https://doi:org/10.1016/j.ejmech.2017.11.100
27. Kokel, A.; Schafer, C.; Torok, B. *Green Chem.* **2017**, *19*, 3729-3751. https://doi:10.1039/C7GC01393K
28. Banerjee, B. *Ultrason. Sonochem.* **2017**,*35*, 1-14. https://doi:org/10.1016/j.ultsonch.2016.09.023
29. Karoui, H.; Ritchie, C. *New J. Chem.* **2018**, *42*, 25-28. https://doi:10.1039/C7NJ02820B.
30. Arafa, W. A. A.; Abdel-Magied, A. F. *Arkivoc*, **2017**, (*v*), 327-340. https://doi:org/10.24820/ark.5550190.p010.197
31. Arafa, W. A. A.; Mohamed, A. M.; Abdel-Magied, A. F. *Heterocycles* **2017**, *94*, 1439-1455. https://doi:10.3987/COM-17-13726
32. Arafa, W. A. A.; Fareed, M. F.; Rabeh, S. A.; Shaker, R. M. *Phosphorus Sulfur Silicon Relat. Elem.* **2016**, *191*, 1129-1136. https://doi:org/10.1080/10426507.2016.1146276
33. Arafa, W. A. A.; Shaker, R. M.; Rabeh, S. A. *Heterocycles* **2016**, *92*, 1224-1243. https://doi:10.3987/COM-16-13479.
34. Arafa, W. A. A.; Kärkäs, M. D.; Lee, B. L.; Åkermark, T.; Liao, R. Z.; Berends, H. M.; Messinger, J.; Siegbahn, P. E. M.; Åkermark , B. *Phys. Chem. Chem. Phys.* **2014**, *16*, 11950-11964. https://doi.org/10.1039/c3cp54800g
35. Roiban, G. D.; Serrano, E.; Soler, T.; Contel, M.; Grosu, I.; Cativiela, C.; Urriolabeitia, E. P. *Organometallics* **2010**, *29*, 1428-1435. https://doi:10.1021/om901068f.
36. González, C. J.; Constable, D. J. C.; Ponder, C. S. *Chem. Soc. Rev.* **2012**. *41*, 1485–1498. https://doi:10.1039/C1CS15215G
37. Manoj, D. P. *Asian J. Chem.* **2001**, *13*, 226-230.
38. Canan, K.; Ezgi, U.; Elçin, D. Ö.; Benay, C. E. *Turk. J. Pharm. Sci.* **2017**, *14*, 174-178. https://doi:10.4274/tjps.70299
39. Satya, P.; Puja, N.; Rajive, G.; Andre, L. *Tetrahedron Lett.* **2004**, *45*, 425–427. https://doi:org/10.1016/j.tetlet.2003.10.125.

 ©**ARKAT USA, Inc**