PAPER

Check for updates

Facile one-pot synthesis of novel *N*-benzimidazolyl-α-arylnitrones catalyzed by salts of transition metals†

Mehdi Kalhor, [ID] * Sima Samiei and S. Ahmad Mirshokraei

A novel series of *N*-benzimidazol-2-yl-α-aryl nitrones **3a–j** is synthesized *via* simple one-pot condensation/oxidation of 2-aminobenzimidazole, an aromatic aldehyde and *m*-chloro perbenzoic acid (*m*-CPBA) as an effective oxidant using Mn(NO₃)₂·6H₂O as an efficient catalyst at room temperature. All synthesized *N*-benzimidazolyl nitrones were identified using FTIR, NMR and mass spectroscopy. Also, stability energy theory calculations were performed and ^{1}H NMR computational spectra were generated for the isomeric structures of **3a**; the results show that the stability order is oxaziridine (**4**) followed by the nitrones **3a**$_E$ and **3a**$_Z$. Also, comparing the computational spectroscopy results with the experimental data shows great accordance with nitrone **3a**$_E$. Among the remarkable points of this protocol, stable N-heterocyclic nitrones were prepared for the first time from raw materials under mild oxidative conditions. Therefore, they can easily be applied as high-potential intermediates for synthesizing valuable heterocycles in mild conditions. Due to benefits such as the use of inexpensive and available catalysts, short reaction times, high yields, facile workup to obtain pure product, and facile separation of the side product (*m*-chlorobenzoic acid), this simple protocol complies greatly with the principles of green chemistry.

Introduction

The name "nitrone" is a brevity which was proposed by Pfeiffer in 1916 for a functional group in organic compounds composed of an N-oxide of an imine.[1] The term is a contraction of the terms "nitrogen ketone".[2,3] Nitrones have a 1,3-dipole structure; they are used in 1,3-dipolar cycloadditions[4] (especially for synthesis of oxaziridine, isoxazolines, oxadiazolidines, *etc.*[5]) and formal cycloadditions in the synthesis of many natural products.[6] Increased reactivity of nitrones with metal derivatives has been discovered; therefore, one of the most important applications of nitrones is that some of them can be used as ligands in inorganic chemistry.[7] Nitrones are also applied as spin traps in biological studies[8] as well as therapies in age-related diseases.[9] Many nitrone derivatives have pharmacological activity and form necessary parts of the molecular structures of main drugs.[10–12] Also, they are forecasted to be effective inhibitors of acidic and microbial corrosion.[13] Nitrones are found in many natural alkaloids, such as Huperzine J and K obtained from *Huperzia serrata*,[14] Notoamide U,[15] and Plakinamine isolated from the genus *Corticium*[16] (Fig. 1).

Department of Chemistry, University of Payame Noor, P. O. BOX 19395-4697, Tehran, Iran. E-mail: mekalhor@gmail.com; mekalhor@pnu.ac.ir; Fax: +98 2537179170; Tel: +98 2537179170

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9ra08570j

Resonance structures (**1**–**3**) can be considered for nitrone (Fig. 2). All the azometine N-oxide groups are dipolar, and typical nitrone reactions are dependent on this dipolar state. Due to the importance of nitrones, various methods for their synthesis have been reported. Generally, these are divided into four main methods, including (1) alkylation of oximes with various nitrogen reagents without using oxidant,[2,17] (2) the condensation reaction of a carbonyl compound and a *N*-alkyl or aryl mono-substituted hydroxylamine,[18] (3) oxidation of secondary amines or *N*,*N*-substituted hydroxylamines using oxidizing agents,[19–22] and (4) oxidation of imines by oxidizing reagents such as *m*-CPBA, hydrogen peroxide (H₂O₂), and alkyl hydroperoxides[23,24] (Fig. 2).

Recently, a few methods have been developed for the preparation of nitrones through one-pot condensation/oxidation of primary amines and aldehydes in the presence of methyl trioxorhenium (MTO),[25] Nafion-immobilized MoOCl₄,[26] silica-immobilized oxo-rhenium,[27] or graphite oxide (and oxone as the oxidant) as the catalyst.[28]

There are also reports that isomerization of oxaziridines in the presence of Lewis acids propels the formation of nitrones.[29] Although each of these synthetic strategies has valuable properties, in some cases, these methods present major drawbacks such as low selectivity, procedures that require harsh conditions, tedious workup and purification, inaccessibility of precursors (the hydroxylamines), formation of oxidation by-products, use of hazardous solvents, and
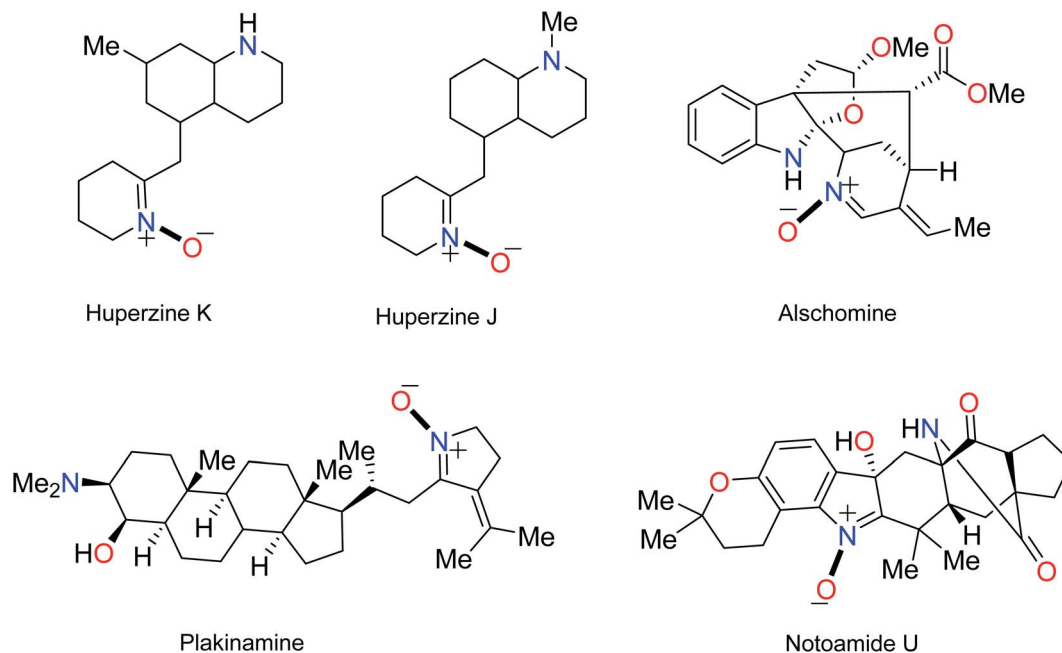
Fig. 1 Natural structures with nitrone frameworks.

expensive catalysts and oxidants. However, the contribution of new, more efficient procedures in this field can still be interesting and beneficial.

According to the above, this paper reports a facile and clean synthetic method for the preparation of novel nitrones containing the *N*-benzimidazole moiety under mild conditions for
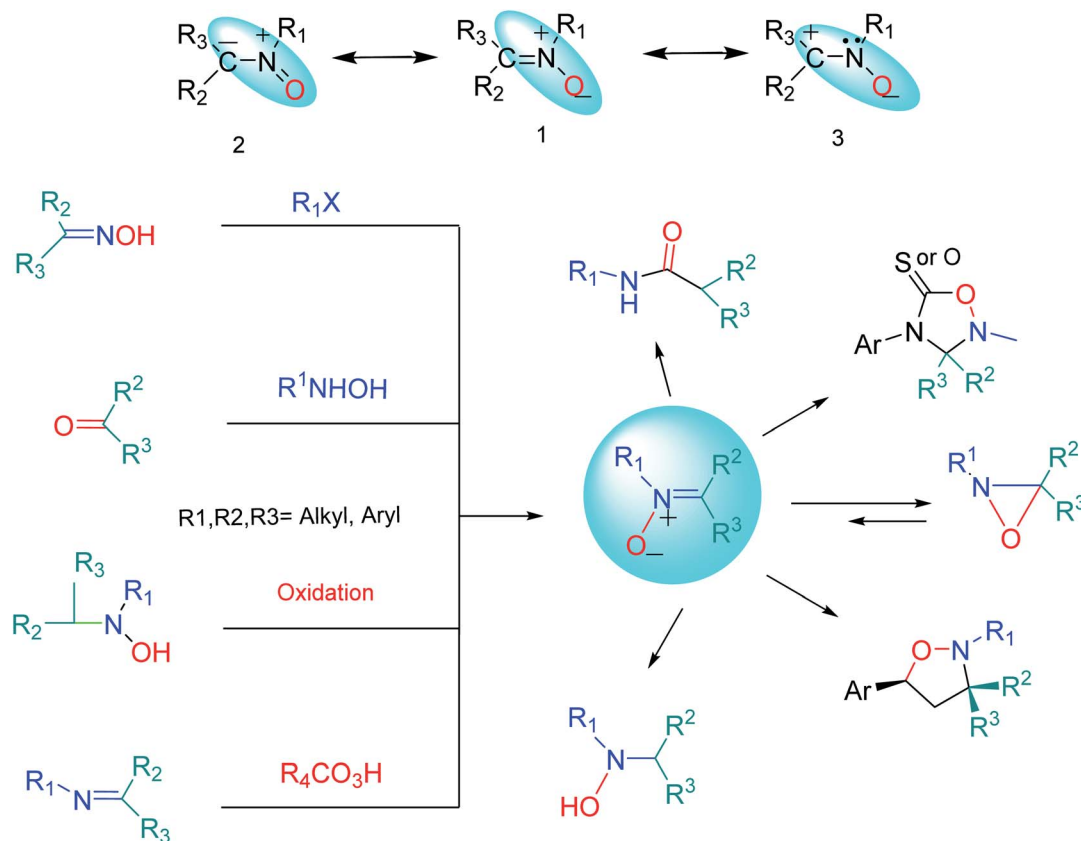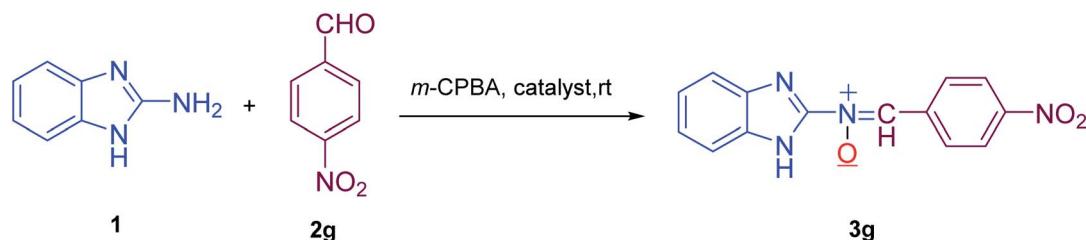

Fig. 2 Four main pathways of synthesis of nitrones and some of their synthetic applications.

Scheme 1 The model reaction for optimizing the reaction conditions.

the first time. These N-heterocyclic nitrones, **3a–j**, are obtained through one-pot reactions of 2-aminobenzimidazole, various aromatic aldehydes and *m*-CPBA as an oxidant reagent by applying $Mn(NO_3)_2 \cdot 6H_2O$ as an effective catalyst at room temperature, with good to excellent yields and simple workup compared to previous reports.

Results and discussion

Firstly, to evaluate and optimize the synthesis conditions of target compounds, the reaction of 2-aminobenzimidazole with 4-nitro benzaldehyde and *m*-CPBA in ethanol in the presence of 10 mol% $Cu(NO_3)_2$ catalyst at room temperature was performed as a model reaction (Scheme 1).

After several tests (Table 1), the best result was obtained when the reaction occurred in the presence of 10 mol% $Mn(NO_3)_2 \cdot 6H_2O$ in ethanol. In this case, the reaction yield and time were 95% and 25 minutes, respectively (Table 1, entry 5).

These results created an incentive to develop an efficient and simple method to produce nitrones **3a–j** *via* the reaction of 2-aminobenzimidazole with various aromatic aldehydes containing electron withdrawing groups or electron donating groups and a per-acid (*m*-CPBA) under the same conditions (Scheme 2).

The results are summarized in Table 2, which shows that the yields of the one-pot condensation/oxidation method used for the production of nitrones from the raw materials are high to excellent. Moreover, the workup is simple, the amount of catalyst used is low and the reaction time is short in comparison to previous methods.

According to our previous knowledge, here, we suggest a probable mechanism for the synthesis of the nitrone in Scheme 3. Initially, an empty orbital of Mn^{2+} cation as a Lewis acid activates the carbonyl group of the aromatic aldehyde for nucleophilic amine (**1**) attack, followed by catalytic oxidation and the loss of a water molecule to form the intermediate **I**.[34]

Table 1 Optimizing the reaction conditions for the synthesis of compound **3g**

Entry	Catalyst	Catalyst loading (mol%)	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)
1	$Cu(NO_3)_2 \cdot 6H_2O$	10	EtOH	rt	30	65
2	$Co(NO_3)_2 \cdot 6H_2O$	10	EtOH	rt	30	70
3	$Zn(NO_3)_2 \cdot 6H_2O$	10	EtOH	rt	60	60
4	$Ni(NO_3)_2 \cdot 6H_2O$	10	EtOH	rt	30	87
5	$\mathbf{Mn(NO_3)_2 \cdot 6H_2O}$	**10**	**EtOH**	**rt**	**25**	**95**
6	$Mn(NO_3)_2 \cdot 6H_2O$	5	EtOH	rt	40	70
7	$Mn(NO_3)_2 \cdot 6H_2O$	15	EtOH	rt	25	80
8	$Mn(NO_3)_2 \cdot 6H_2O$	10	CH_3CN	rt	40	65
9	$Mn(NO_3)_2 \cdot 6H_2O$	10	MeOH	rt	35	78
10	$Mn(NO_3)_2 \cdot 6H_2O$	10	CH_2Cl_2	rt	45	70
8	$MnCl_2 \cdot 6H_2O$	10	EtOH	rt	30	85
9	$CoCl_2 \cdot 6H_2O$	10	EtOH	rt	50	75
10	$ZnCl_2 \cdot H_2O$	10	EtOH	rt	80	50
11	$CuCl_2 \cdot H_2O$	10	EtOH	rt	35	72
12	$NiCl_2 \cdot H_2O$	10	EtOH	rt	35	70
13	$Mn(NO_3)_2 \cdot 6H_2O$	10	H_2O	rt	60	0
14	$Mn(NO_3)_2 \cdot 6H_2O$	10	H_2O	90	60	0
15	$Mn(NO_3)_2 \cdot 6H_2O$	10	—	rt	50	20
16	$Mn(NO_3)_2 \cdot 6H_2O$	10	—	80	50	25
17	$Mn(NO_3)_2 \cdot 6H_2O$	5	—	80	50	25
18	CAN^b	10	EtOH	rt	50	0
19	$Ca(IO_3)_2$	10	EtOH	rt	50	0
20	—	—	EtOH	rt	50	0

[a] Isolated yield. [b] Cerium(IV) ammonium nitrate.
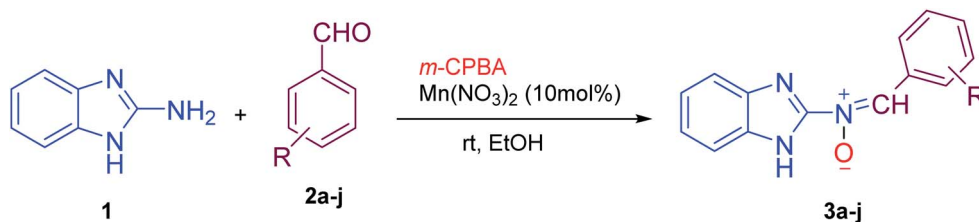
Scheme 2 The synthetic pathway for the preparation of nitrones **3a–j**.

The corresponding Schiff base, under catalytic activation, undergoes nucleophile attack by the third molecule, *m*-CPBA, instantly leading to the formation of intermediate **II**. Immediately, upon the third catalytic activation of the intermediate **II** following intermolecular nucleophile attack, cyclization of *N*-benzimidazolyl oxaziridines can be accomplished.[29] Finally, in the presence of Mn^{2+} cation as a Lewis acid, the corresponding nitrone is formed through rearrangement.[28]

In this project, we also synthesized nitrones **3a–j** in accordance with general method 4 (Fig. 2) in two steps, but with lower yields (42% to 70%), longer reaction times (1.5 to 6 hours) and more complex and tight separation of the pure product (Scheme 4). The reason for the rapid formation and stability of these nitrones (compared to the formation of the oxaziridine ring or amide) may be the presence of intermolecular hydrogen bonds between the hydrogen of the imidazole[30] and the nitrone oxygen[31–33] (Scheme 4). On the other hand, the intense resonance between nitrone, aryl and the benzimidazole ring accelerates this process.

All the synthesized *N*-benzimidazolyl nitrones are new, and their structures were confirmed using FT-IR and NMR spectroscopy and mass spectral data. In the ^{1}H-NMR spectra, the shift of the CH=N (Schiff base) proton signals from 9.38 to 9.78 ppm[34] to 7.82 to 8.80 ppm confirmed the formation of the nitrone structure. In general, in the IR spectrum for a nitrone system, it is expected that there will be five characteristic vibrational frequencies, including C=N, N–O, and C–N stretching and C–H in-plane and out-of-plane bending frequencies.[31] A red shift at the C=NO-vibrational frequency in the *N*-benzimidazolyl nitrones (1535 to 1581 cm^{−1}) relative to the corresponding Schiff bases (1601 to 1621 cm^{−1}) as well as the appearance of a relatively strong band for N–O stretching in nitrones (1012 to 1103 cm^{−1}) confirms the formation of these products. Other signals were revealed in the expected regions which are consistent with their structures. In the mass spectra of compounds **3a–j**, molecular ion peaks (5% to 100%) and all expected fragments consistent with the structures of the annular products were seen.

To show the efficiency of this method, it was compared with reported results in the literature for the direct synthesis of nitrones. The obtained results are listed in Table 3. The results clearly show that this catalytic procedure is superior to other methods in terms of reaction time and yield, economical convenience, *etc.* Therefore, it can be considered as one of the best choices for facile and direct synthesis of N-heterocyclic nitrones under mild conditions.

Theoretical studies

In order to investigate the different probable molecular structures of the nitrones and oxaziridine, a theoretical approach was applied.[31,35] The optimized structures and relative energy comparison of these molecules are shown in Fig. 3. The figure indicates that the relative energies of the isomers are in the order oxaziridine (**4**) > **3a$_E$** > **3a$_Z$**. The stability of **3a$_E$** can be attributed to its full conjugation and aromatic rings.

Also, ^{1}H NMR data for the nitrone and oxaziridine molecules in the gas phase were calculated with the DFT method using the 6-311G (d) basis set. The results and experimental data are presented in Table 4. The table indicates that obtained experimental results for the N–H (11.07 ppm) bond and C–H (8.68 ppm) bond most resemble the **3a$_E$** form of nitrone in the theoretical approach.
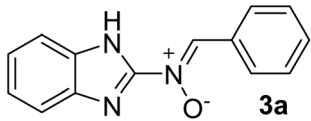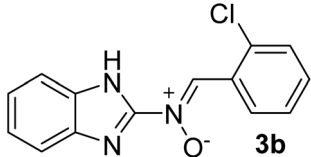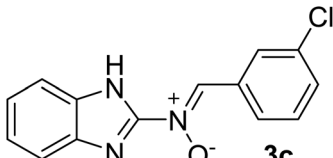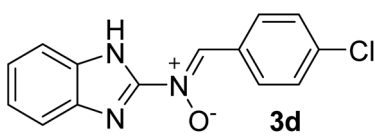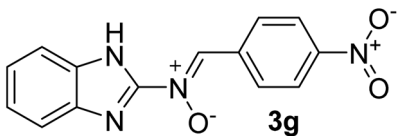
Conclusion
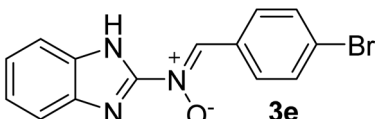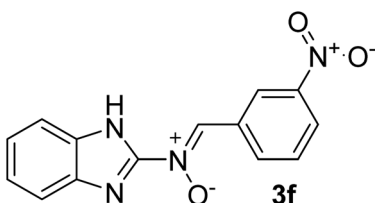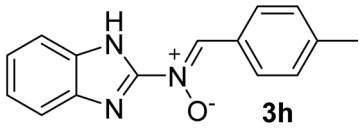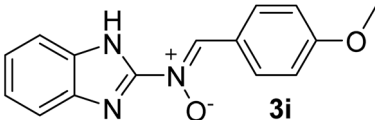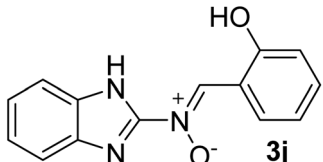
In this project, we succeeded in designing a new procedure for the mild and facile synthesis of novel *N*-benzimidazolyl-α-aryl nitrones for the first time. These compounds were obtained through one-pot reactions of 2-aminobenzimidazole, various aromatic aldehydes and *m*-CPBA as an effective oxidizing reagent in the presence of a catalytic amount of Mn(NO₃)₂·6H₂O at room temperature in good to excellent yields. The method was demonstrated to be simple both in conducting the reaction and in isolating the pure products; thus, it is a useful procedure for the synthesis of the target compounds. Also, theoretical studies showed that the **3a$_E$** form of nitrone is close to the neutral structure of oxaziridine in terms of energy stability and is very similar to the experimental spectral data.

Experimental

All the consumed chemicals were purchased from Merck or Fluka. Melting points were determined using an electro-thermal digital apparatus and are uncorrected. A Galaxy Series FT-IR 5000 spectrometer (using KBr discs) was used to record the IR spectra. ^{1}H and ^{13}C NMR spectra were acquired in DMSO-*d*₆ on a Bruker (300 and 500 MHz) spectrometer. Chemical shifts (*δ*) were presented in ppm using tetramethyl silane (TMS) as an internal standard. The mass spectra were recorded on an Agilent spectrometer, model 5975C VL MSD, with a Triple-Axis Detector at 70 eV. The reactions were monitored by thin layer chromatography (TLC) using silica gel on F₂₅₄ aluminum sheets (Merck).

Table 2   Synthesis of the nitrone derivatives 3a–j[a]

Entry	Compound	Time (min)	Mp (°C)	Yield[b] (%)
1	3a	30	180–182	89
2	3b	30	228	85
3	3c	40	212–214	86
4	3d	25	241–242	91
5	3e	25	260–262	85
6	3f	40	201–204	85
7	3g	25	210–212	95
8	3h	35	187–188	93
9	3i	25	188–190	95
10	3j	35	189–190	91

[a] Reaction conditions: 0.1 mmol 2-aminobenzimidazole (1) with 0.1 mmol of the aromatic aldehyde in the presence of 10 mol% $Mn(NO_3)_2 \cdot 6H_2O$ in ethanol (5 mL), addition of m-CPBA (0.12 mmol) and room temperature. [b] Isolated yield.
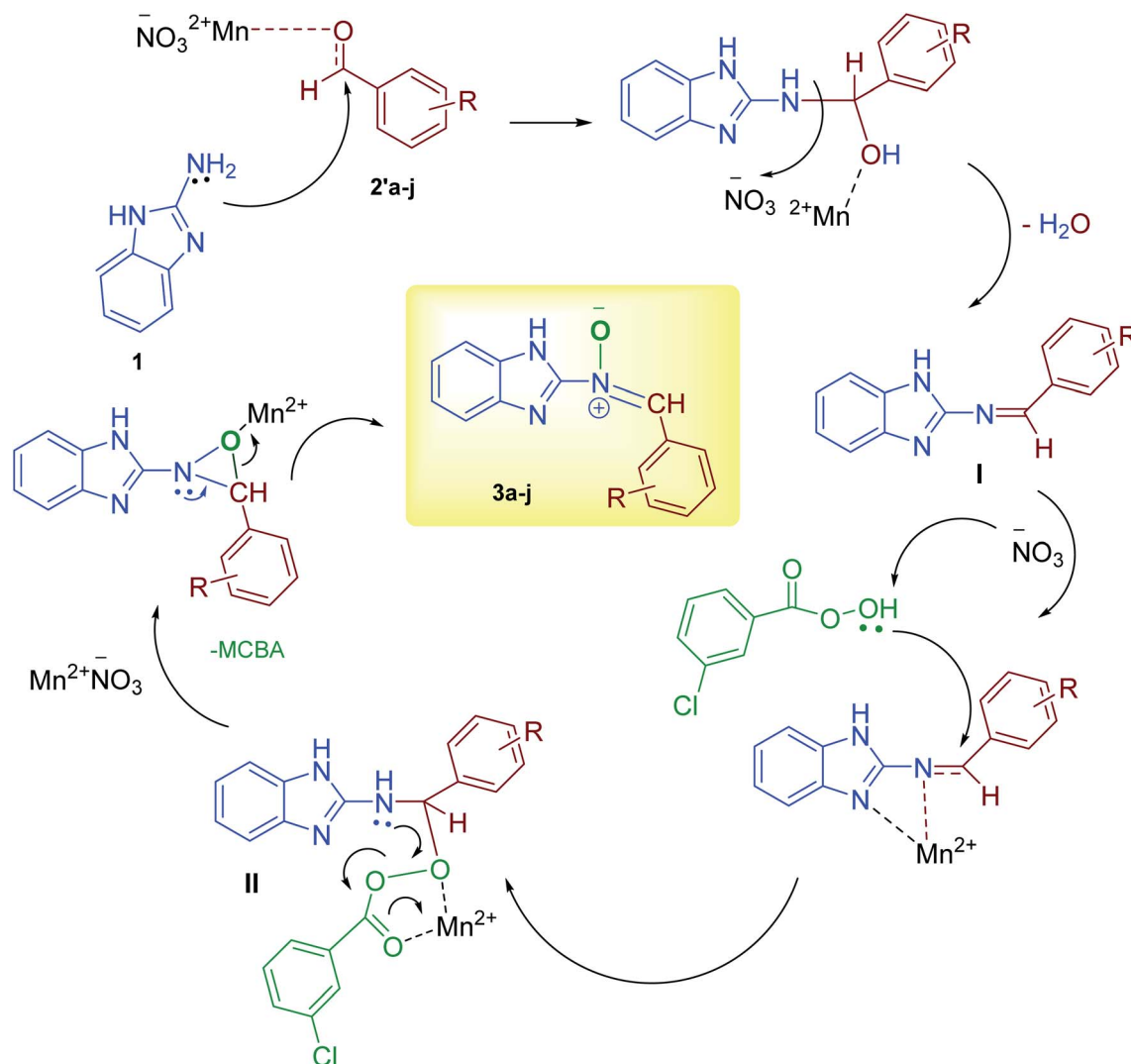
Scheme 3 Proposed mechanism for the synthesis of compounds **3a–j**.

Computational methods

Thermodynamic data and investigation of the IR spectra of the nitrone and oxaziridine molecules in the gas phase were calculated with the DFT method using the B3LYP/6-311G (d) basis set.[35,36] The study of the NMR spectra was carried out using the NMR = giao b3lyp/6-311+g(2d,p) level of theory.
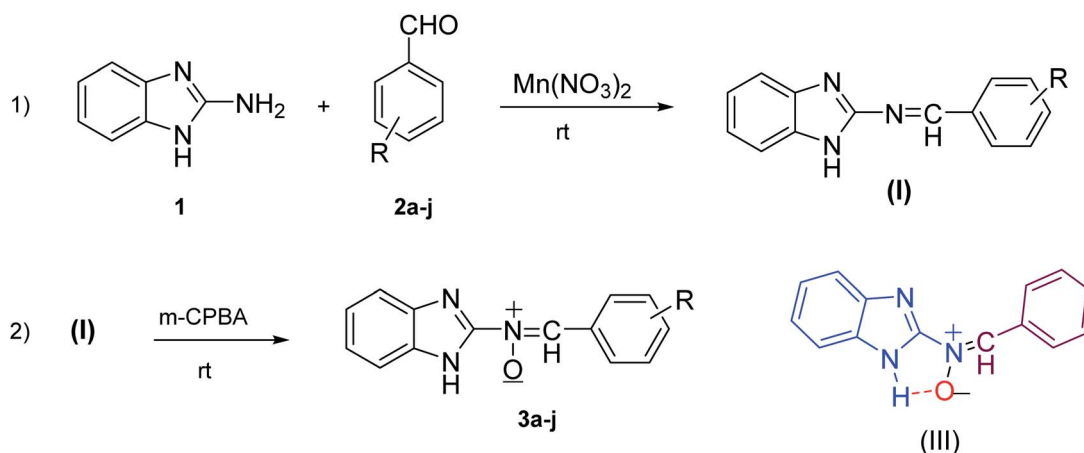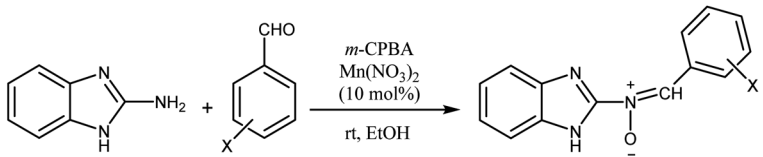

Scheme 4 Synthesis of compounds **3a–j** in two steps without catalyst and intermolecular hydrogen bonding (**III**).

Table 3 Comparison of the catalytic procedure with other methods for the direct synthesis of *N*-aryl or alkyl nitrones

Entry	Reaction conditions	Time (h)	Yield (%)
1	R$_1$ = Ph, Aryl · R = Alkyl · UHP (3 equiv), Re or MO, MTO, MeOH, rt	2.5–9	15–89 (ref. 25)
2	R$_1$ = Ph, Aryl · R = Alkyl · UHP, Re or MO, Nafion-MoCl$_4$, MeOH, rt	3.5–8	50–80 (ref. 26)
3	R$_1$ = Ph, Aryl · R = Alkyl · UHP, Re or MO, SiCl-OReO$_3$, MeOH, rt	3–8	40–75 (ref. 27)
4	ArCHO + RNH$_2$ · R = Ph, Aryl, propyl · GO/OXONE, CH$_3$CN, rt	2–8	50–97 (ref. 28)
5	*m*-CPBA, Mn(NO$_3$)$_2$ (10 mol%), rt, EtOH	**0.4–0.58**	**85–91 (this work)**

Theoretical calculations were performed using the Gaussian 09 package and the Gauss-View molecular visualization program.[37]

General preparation of nitrones 3a–j

To a solution of 2-aminobenzimidazole (1 mmol) and the corresponding aromatic aldehyde (1 mmol) in ethanol (5 mL), Mn(NO$_3$)$_2$·6H$_2$O (10 mol%, 0.027 g) was added. The reaction mixture was stirred magnetically at room temperature. Then, *m*-CPBA (1.2 mmol) was added to the mixture. The reaction progress was monitored by TLC (petroleum ether : ethyl acetate 2 : 1). After completion of the reaction, aqueous NaHCO$_3$ (10%, 15 mL) was added to the mixture, and the resulting precipitate was filtrated to afford pure nitrones **3a–j**. For further purity, these products can be crystallized from a mixture of ether: *n*-hexane (1 : 1). Also, increasing the amount of HCl (10%) in the filtrate causes the *m*-chlorobenzoic acid to precipitate; then, the extraneous acid product is separated by filtration.

Spectroscopic data for nitrones 3a–j

N-(1H-Benzo[d]imidazol-2-yl)-α-phenyl nitrone (3a). Light yellow solid. IR (KBr, ν$_{max}$): 3269 (N–H), 3095 (C–H), 1683, 1608 (C=N), 1535 (–C=N–O), 1419, 1222 (C=C), 1382 (H–C=N), 1263 (C–N), 1029 (N–O), 898, 759 (C–H), 619 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ$_H$ 11.07 (br, 1H, NH, the NH protons disappeared upon D$_2$O addition), 8.68 (s br, 1H, H–C=N$^+$–O$^-$), 7.98 (s br, 2H, H–Ar), 7.49–7.08 (t br, 6H, H–Ar) ppm, ^{13}C NMR (DMSO-d_6, 75 MHz): δ$_C$ 170.1, 153.6, 139.2, 133.2, 132.4, 130.8, 130.2, 129.3, 1^{28}.1, 122.2, 111.5 ppm; MS (*m/z*, %): 237.2 (M$^+$, 5), 156.0 (75), 133.1 (100), 111.1 (58), 85.2 (40), 71.2 (46), 57.2 (62), 43.2 (43).

N-(1H-Benzo[d]imidazol-2-yl)-α-(2-chlorophenyl) nitrone (3b). Gray solid. IR (KBr, ν$_{max}$): 3377 (N–H), 1666, 1631 (C=N), 1579 (–C=N–O), 1519, 1435, 1298, 1273 (C=C), 1456 (H–C=N), 1176 (C–N), 1143, 1020 (N–O), 866 (C–Cl), 744 (C–H) cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ$_H$ 12.27 (br, 1H, NH), 7.68 (d, *J* = 5.91 Hz, 1H, H–C=N$^+$–O$^-$), 7.55–7.45 (m, 6H, H–Ar), 7.12 (s br, 2H, H–Ar) ppm, ^{13}C NMR (DMSO-d_6, 125 MHz): δ$_C$ 167.2, 147.3, 135.8, 135.2, 131.4, 130.2, 129.7, 129.3, 127.0, 121.4, 119.9, 113.8 ppm, MS (*m/z*, %): 271.1 (M$^+$, 46), 236.1 (52), 208.1 (48), 139.1 (100), 111.1 (71), 75.1 (34).

N-(1H-Benzo[d]imidazol-2-yl)-α-(3-chlorophenyl) nitrone (3c). Gray solid. IR (KBr, ν$_{max}$): 3307 (N–H), 1624, 1604 (C=N), 1575 (–C=N–O), 1596, 1344 (C=C), 1473 (H–C=N), 1263 (C–N), 1024 (N–O), 918 (C–Cl), 758 (C–H), 740 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ$_H$ 12.22 (br, 1H, NH), 7.68 (d, *J* = 5.49 Hz, 1H, H–C=N$^+$–O$^-$), 7.55–7.48 (t br, 6H, H–Ar), 7.14 (s, 2H, H–Ar) ppm, ^{13}C NMR (DMSO-d_6, 75 MHz): δ$_C$ 167.2, 147.2, 135.6, 135.0, 131.2, 129.9, 129.5, 129.0, 126.9, 124.0, 121.2, 113.6 ppm, MS (*m/z*, %): 271.1 (M$^+$, 21), 243.1 (18), 160.1 (28), 139.1 (100), 111.1 (71), 75.1 (27).

N-(1H-Benzo[d]imidazol-2-yl)-α-(4-chlorophenyl) nitrone (3d). Gray solid. IR (KBr, ν$_{max}$): 3348 (N–H), 1653, 1641 (C=N), 1571

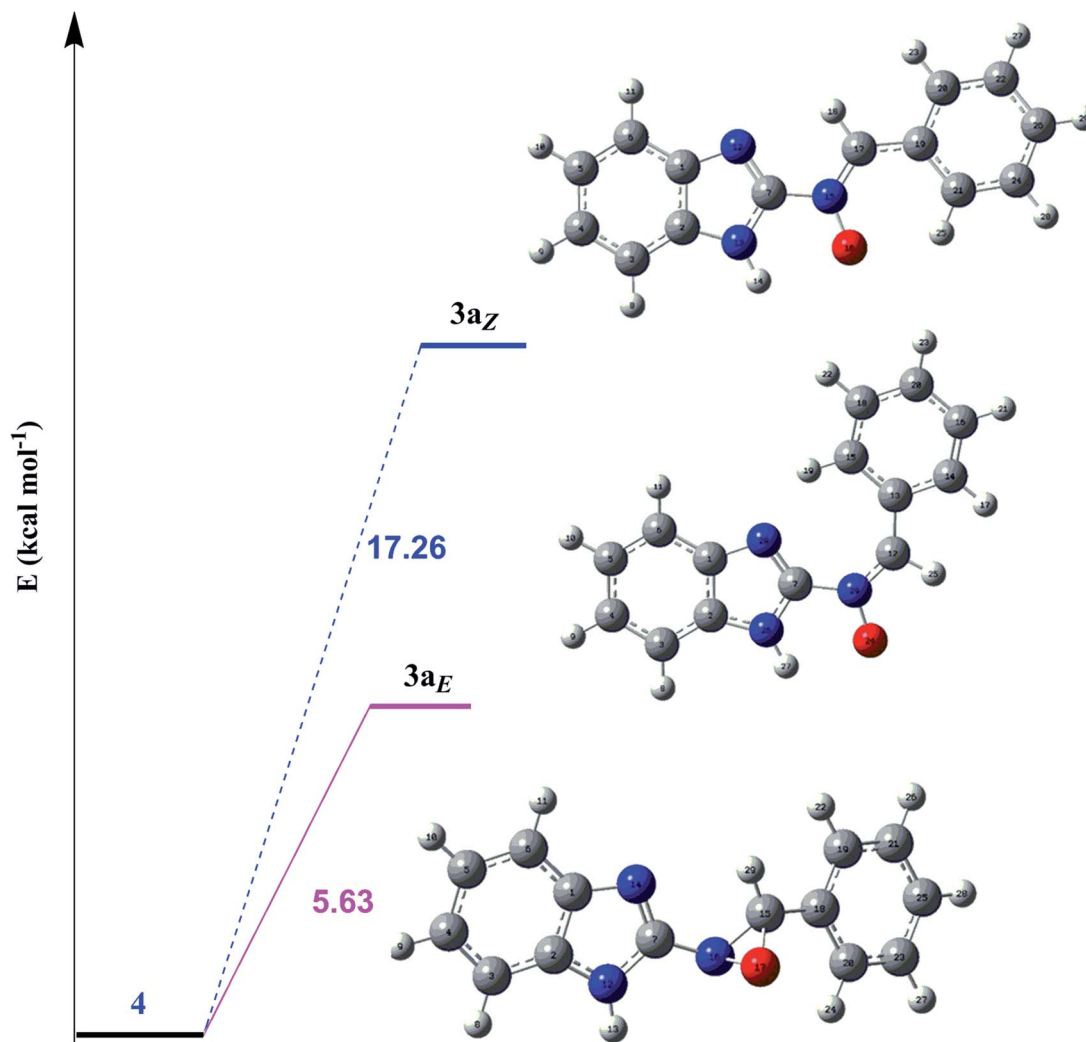Fig. 3 The optimized structures and relative energy comparison of the nitrone (**3a**$_{Z, E}$) and oxaziridine (**4**) molecules.

(–C=N–O), 1591, 1523, 1435 (C=C), 1462 (H–C=N), 1271 (C–N), 1093 (N–O), 844 (C–Cl), 750 (C–H) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ_H 12.33 (br, 1H, NH, the NH protons disappeared upon D$_2$O addition), 8.15 (s br, 1H, H–C=N$^+$–O$^-$), 7.89 (s br, 2H, H–Ar), 7.65–7.53 (t br, 4H, H–Ar), 7.15 (s, 2H, H–Ar) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C 168.8, 150.1, 136.8, 136.4, 134.3, 132.8, 131.0, 130.2, 128.2, 121.8, 119.6, 112.7 ppm, MS (*m/z*, %): 271.1 (M$^+$, 48), 236.2 (51), 208.2 (41), 139.2 (100), 111.2 (45), 75.2 (17).

N-(1H-Benzo[d]imidazol-2-yl)-α-(4-bromophenyl) nitrone (3e). Gray solid. IR (KBr, ν_{max}): 3311 (N–H), 1660, 1624 (C=N), 1550 (–C=N–O), 1571, 1394 (C=C), 1340 (H–C=N), 1273 (C–N), 1012 (N–O), 808 (C–Br), 769 (C–H), 736 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ_H 12.36 (br, 1H, NH), 8.07 (s br, 2H, H–C=N$^+$–O$^-$ and H–Ar), 7.70 (br, 2H, H–Ar), 7.44 (br, 2H, H–Ar), 7.14 (br, 3H, H–Ar) ppm, ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C 169.1, 150.2, 134.8, 132.7, 131.1, 130.4, 129.3, 128.3, 127.7, 125.5, 121.8, 119.0, 112.7 ppm, MS (*m/z*, %): 315.2 (M$^+$, 57), 287.1 (53), 185.1 (100), 155.1 (50), 132 (14), 105.2 (28), 76.2 (28).

N-(1H-Benzo[d]imidazol-2-yl)-α-(3-nitrophenyl) nitrone (3f). Red solid. IR (KBr, ν_{max}): 3317 (N–H), 1705, 1618 (C=N), 1581
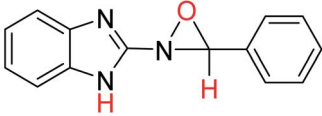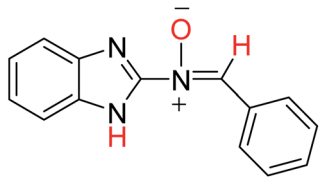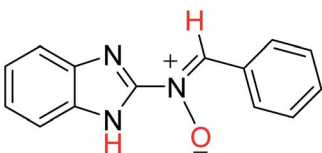
(–C=N–O), 1531, 1348 (–NO$_2$), 1597, 1469, 1419 (C=C), 1400 (H–C=N), 1263 (C–N), 1080 (N–O), 923, 752 (C–H), 731, 715 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (the NH proton exchanges with deuterium in D$_2$O, which is present in DMSO-d_6), 8.96 (s, 1H, H–C=N$^+$–O$^-$), 8.57–8.50 (m, 1H, H–Ar), 8.36 (d, J = 6.66 Hz, 1H, H–Ar), 7.91–7.74 (m, 2H, H–Ar), 7.34 (d, J = 7.50 Hz, 2H, H–Ar), 7.15 (br, 2H, H–Ar) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 170.1, 137.6, 135.3, 135.0, 131.9, 131.4, 130.1, 128.9, 125.7, 124.4, 123.4, 122.4, 112.5 ppm, MS (*m/z*, %): 282.1 (M$^+$, 50), 160.1 (50), 132.1 (100), 105.1 (50), 76.1 (37).

N-(1H-Benzo[d]imidazol-2-yl)-α-(4-nitrophenyl) nitrone (3g). Red solid. IR (KBr, ν_{max}): 3346 (N–H), 1670, 1651 (C=N), 1575 (–C=N–O), 1521, 1352 (–NO$_2$), 1597, 1309 (C=C), 1462 (H–C=N), 1278 (C–N), 1103 (N–O), 850, 740 (C–H), 715 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ_H 12.56 (br, 1H, NH), 8.34 (d, J = 6.99 Hz, 3H, H–C=N$^+$–O$^-$ and H–Ar), 8.13 (d, J = 8.07 Hz, 2H, H–Ar), 7.44–7.18 (d br, 4H, H–Ar) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 170.6, 152.4, 151.0, 149.4, 143.3, 140.4, 131.0, 130.1, 124.6, 123.7, 122.8, 112.5 ppm; MS (*m/z*, %): 282 (M$^+$, 100), 254 (57), 235 (12), 219 (12), 160 (99), 121 (104), 104 (77).

Table 4 The ^{1}H NMR data (calculated and experimental) and total energies for the isomeric compounds **3a**

No.	Compound	E^a (E, kcal mol^{-1})	C–H^b (ppm) (experimental)	N–H^b (ppm) (experimental)
4		−779.68669653 (−489253.40207)	6.62 —	8.60 —
3a$_E$		−779.69570020 (−489259.05187)	8.52 (8.68)	10.62 (11.07)
3a$_Z$		−779.71431871 (−489270.73499)	9.55 (8.68)	10.13 (11.07)

^{a} Total energies in hartree. ^{b} ^{1}H NMR data in the gas phase.

N-(1*H*-Benzo[*d*]imidazol-2-yl)-α-(*p*-tolyl) nitrone (3h). Gray solid. IR (KBr, ν_{max}): 3396 (N–H), 2924 (C–H), 1658, 1633 (C=N), 1573 (–C=N–O), 1527, 1456, 1313, 1257 (C=C), 1431 (H–C=N), 1168 (C–N), 1020 (N–O), 842, 767, 750 (C–H), 611 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ_H (the NH proton exchanges with deuterium in D$_2$O, which is present in DMSO-d_6), 8.08 (d, J = 7.50 Hz, 2H, H–C=N$^+$–O$^-$ and H–Ar), 7.08–7.42 (m, 7H, H–Ar), 2.36 (s, 3H, CH$_3$) ppm; ^{13}C NMR (DMSO-d_6, 75 MHz): δ_C 168.8, 151.1, 142.0, 135.7, 133.0, 129.2, 128.8, 121.3, 113.7 ppm, MS (m/z, %): 251.2 (M$^+$, 96), 223.2 (56), 119.1 (100), 91.1 (87), 65.1 (25).

N-(1*H*-Benzo[*d*]imidazol-2-yl)-α-(4-methoxyphenyl) nitrone (3i). Gray solid. IR (KBr, ν_{max}): 3327 (N–H), 1660, 1624 (C=N), 1556 (–C=N–O), 1602, 1573, 1458, 1519 (C=C), 1346 (H–C=N), 1286 (C–O), 1273 (C–N), 1020 (N–O), 910, 767 (C–H), 731 cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ_H 12.18 (br, 1H, NH), 8.12 (d, J = 6.55 Hz, 1H, H–C=N$^+$–O$^-$), 7.87 (t, J = 8.55 Hz, 1H, H–Ar), 7.66 (d, J = 7.75 Hz, 1H, H–Ar), 7.53–7.44 (q br, 2H, H–Ar), 7.12–6.90 (m, 4H, H–Ar), 3.83 (s, 3H, OMe) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C 166.9, 162.3, 148.5, 134.7, 131.6, 130.2, 125.8, 121.1, 114.4, 113.5, 55.3 ppm; MS (m/z, %): 267.1 (M$^+$, 13), 263.1 (14), 220.1 (72), 133.1 (54), 105.1 (27), 77.1 (25), 44 (100).

N-(1*H*-Benzo[*d*]imidazol-2-yl)-α-(2-hydroxyphenyl) nitrone (3j). Gray solid. IR (KBr, ν_{max}): 3369 (N–H), 1683, 1635 (C=N), 1560 (–C=N–O) 1580, 1381 (C=C), 1458 (H–C=N), 1290 (C–O), 1273 (C–N), 1047 (N–O), 744 (C–H) cm^{-1}; ^{1}H NMR (DMSO-d_6, 500 MHz): δ_H 11.95 (br, 1H, NH), 11.04 (br, 1H, OH), 8.11 (s, 1H, H–C=N$^+$–O$^-$), 7.85 (s, 1H, H–Ar), 7.37–7.28 (d br, 2H, H–Ar), 6.97 (t br, 2H, H–Ar), 6.87–6.78 (m, 5H, H–Ar) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ_C 169.5, 154.0, 138.6, 133.68, 133.63, 133.2, 131.0, 130.3, 129.3, 128.1, 121.7, 111.6 ppm; EIMS (m/z, %): 253.1 (M$^+$, 22), 225.1 (13), 160.0 (17), 121.1 (100), 93.1 (54), 65.1 (82).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

References

1 A. Padwa and W. H. Pearson, in *Synthetic application of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products*, John Wiley and Sons, Hoboken/NJ, vol. 59, 2003, ISBN: 978-0-471-28061-3.

2 L. Smith, *Chem. Rev.*, 1938, **23**, 193–285.

3 J. M. Hamer and A. Macaluso, *Chem. Rev.*, 1964, **64**, 473–495.

4 T. Zhu, J. Xiang, Z. Liu, Q. Dang and X. Bai, *Synlett*, 2015, **26**, 238–242.

5 (*a*) J. Yang, *Synlett*, 2012, **23**, 2293–2297; (*b*) S.-I. Murahashi and Y. Imada, *Chem. Rev.*, 2019, **119**, 4684–4716.

6 A. Goti, V. Fedi, L. Nannelli, F. D. Sarlo and A. Brandi, *Synlett*, 1997, **5**, 577–579.

7 (*a*) G. Masson, S. Py and Y. Vallée, *Angew. Chem.*, 2002, **41**, 1772–1775; (*b*) I. S. Young and M. A. A. Kerr, *Angew. Chem.*, 2003, **26**, 3023–3026; (*c*) F. Cardona and A. Goti, *Angew. Chem.*, 2005, **44**, 7832–7835.

8 (*a*) H. Zhang, J. Joseph, J. Vasquez-Vivar, H. Karoui, C. Nsanzumuhire, P. Martásek, P. Tordo and B. Kalyanaraman, *FEBS Lett.*, 2000, **473**, 58–62; (*b*) G. Durand, A. Polidori, J. P. Salles and B. Pucci, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 859–862; (*c*) S. Morandat,

G. Durand, A. Polidori, L. Desigaux, M. Bortolato, B. Roux and B. Pucci, *Langmuir*, 2003, **19**, 9699–9705.

9 R. A. Floyd, *Aging Cell*, 2006, **5**, 51–57.

10 R. A. Floyd, R. D. Kopke, C. H. Choi, S. B. Foster, S. Doblas and R. A. Towner, *Free Radical Biol. Med.*, 2008, **45**, 1361–1374.

11 D. P. Xu, K. Zhang, Z. J. Zhang, Y. W. Sun, B. J. Guo, Y. Q. Wang, P. M. Hoi, Y. F. Han and S. M. Lee, *Neurochem. Int.*, 2014, **78**, 76–85.

12 R. A. Floyd, H. C. C. F. Neto, G. A. Zimmerman, K. Hensley and R. A. Towner, *Free Radical Biol. Med.*, 2013, **62**, 145–156.

13 S. Chen, K. Zhao and G. Chen, *J. Chem.*, 2015, **2015**, 1–6.

14 W. Gao, Y. Li, S. Jiang and D. Zhu, *Planta Med.*, 2000, **66**, 664–667.

15 (*a*) I. Kagiyama, H. Kato, T. Nehira, J. C. Frisvad, D. H. Sherman, R. M. Williams and S. Tsukamoto, *Angew. Chem.*, 2016, **55**, 1128–1132; (*b*) C. Y. Choo, Y. Hirasawa, C. Karimata, K. Koyama, M. Sekiguchi, J. Kobayashid and H. Morita, *Bioorg. Med. Chem.*, 2007, **15**, 1703–1707.

16 H. S. Lee, Y. Seo, J. R. Rho, J. Shin and V. J. Paul, *J. Nat. Prod.*, 2001, **64**, 1474–1476.

17 P. A. S. Smith and J. E. Robertson, *J. Am. Chem. Soc.*, 1962, **84**, 1197–1204.

18 S. R. Sandler and W. Karo, *Organic Functional Group Preparations*, E-Book, 1989, vol. 3, pp. 351–376, ISBN: 9780080925585.

19 J. W. W. Zajac, T. R. Walters and M. G. Darcy, *J. Org. Chem.*, 1988, **53**, 5856–5860.

20 H. Mitsui, S. Zenki, T. Shiota and S. I. Murahashi, *J. Chem. Soc., Chem. Commun.*, 1984, **13**, 874–875.

21 S. Murahashi, H. Mitsui, T. Shiota and T. Tsuda, *J. Org. Chem.*, 1990, **55**, 1736–1744.

22 S. I. Murahashi, T. Shiota and Y. Imada, *Org. Synth.*, 1991, **70**, 265.

23 S. Yamazaki, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 877–883.

24 (*a*) C. Gella, E. Ferrer, R. Alibes, E. F. Busqu, P. De March, M. Figueredo and J. Font, *J. Org. Chem.*, 2009, **74**, 6365–6367; (*b*) R. Saladino, V. Neri, F. Cardona and A. Goti, *Adv. Synth. Catal.*, 2004, **346**, 639–647; (*c*) G. Soldaini, F. Cardona and A. Goti, *Org. Lett.*, 2007, **9**, 473–676.

25 F. Cardona, M. Bonanni, G. Soldaini and A. Goti, *ChemSusChem*, 2008, **1**, 327–332.

26 B. Singh, S. L. Jain, P. K. Khatri and B. Sain, *Green Chem.*, 2009, **11**, 1941–1944.

27 B. Singh, S. L. Jain, B. S. Rana, P. K. Khatri, A. K. Sinha and B. Sain, *ChemCatChem*, 2010, **2**, 1260–1264.

28 M. Mirza-Aghayan, M. Molaee Tavana and R. Boukherroub, *Tetrahedron Lett.*, 2014, **55**, 5471–5474.

29 K. S. Williamson, D. J. Michaelis and T. P. Yoon, *Chem. Rev.*, 2014, **114**, 8016–8036.

30 C. Nájera and M. Yus, *Tetrahedron Lett.*, 2015, **56**, 2623–2633.

31 H. Shindo and B. Umezawa, *Chem. Pharm. Bull.*, 1962, **10**, 492–503.

32 K. Tanekazu, Y. Masumi and M. Yutaka, *Bull. Chem. Soc. Jpn.*, 1960, **33**, 109–114.

33 E. G. Petkova, K. Domasevitch, M. V. Gorichkob, V. Y. Zuba and R. D. Lampekaa, *Z. Naturforsch., B: Chem. Sci.*, 2014, **56**, 1264–1270.

34 A. Mobinikhaledi, N. Forughifar and M. Kalhor, *Turk. J. Chem.*, 2010, **34**, 367–373.

35 C. Lee, W. Yang and R. G. Parr, *Phys. Rev.*, 1988, **37**, 785–789.

36 M. M. Francl, W. J. Pietro, W. J. Hehre, J. S. Binkley, M. S. Gordon, D. J. DeFrees and J. A. Pople, *J. Chem. Phys.*, 1982, **77**, 3654–3665.

37 A. Frisch, *Gaussian 09 Reference*, Gaussian, Inc., Wallingford, CT, 2009.