Efficient, microwave-assisted intramolecular 1,3-dipolar cycloadditions of oximes and *N*-methylnitrones derived from *o*-alkenylmethoxy-acetophenones

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Abstract: Contrary to literature reports, the *o*-allyloxy- and crotyloxy-acetophenone-oximes (**2a**, **2b**) are transformed to nitrones, which undergo regio- and stereoselective intramolecular 1,3-dipolar cycloadditions, both on microwave heating under solvent free conditions and refluxing in toluene, to afford novel cycloadducts (**5a**, **5b**); the oxazepine-*N*-oxide (**3a**) reported to be formed in 98% yield was obtained only as a minor product (~10%). However, *o*-cinnamyloxy-acetophenone-oxime (**2c**) under similar conditions undergoes intramolecular *N*-alkylation to afford nitrone (**3c**). The reactions carried out under microwave irradiation are cleaner, require shorter reaction times, and have higher yields. Corresponding intramolecular 1,3-dipolar cycloadditions of *N*-methylnitrones (**B**), generated in situ from *o*-alkenylmethoxy-acetophenones (**1a**–**1c**) and *N*-methylhydroxylamine under solvent-free microwave irradiation conditions, are completely regio- and stereoselective, require much shorter reaction times, and afford adducts (**4a**–**4c**) in higher yields, as compared with their thermal counterparts.

Key words: cycloadditions, nitrones, oximes, *o*-alkenylmethoxy-acetophenones, microwave, isoxazolidines.

Résumé : Contrairement à ce qui a déjà été rapporté dans la littérature, les oximes des *o*-allyloxy- et crotyloxy-acétophénones (**2a**, **2b**) se transforment en nitrones qui subissent des cycloadditions 1,3-dipolaires intramoléculaires régio- et stéréosélectives aussi bien par chauffage micro-onde dans des conditions n'impliquant pas de solvant que par reflux dans du toluène pour conduit à la formation de nouveaux cycloadduits (**5a**, **5b**); il avait été rapporté que cette réaction conduisant à la formation du *N*-oxyde de l'oxazépine (**3a**) se formait avec un rendement de 98 %; toutefois au cours de la présente étude, il ne forme qu'un produit mineur obtenu qu'avec environ 10 % de rendement. Toutefois, dans les mêmes conditions, l'oxime de la *o*-cinnamyloxy-acétophénone (**2c**) subit une *N*-alkylation intramoléculaire qui conduit à la formation de la nitrone **3c**. Les réactions effectuées dans des conditions d'irradiation micro-onde sont plus propres, demandent moins de temps et conduisent à de meilleurs rendements. Dans des conditions d'irradiation micro-onde sans solvant, les cycloadditions 1,3-dipolaires intramoléculaires correspondantes des *N*-méthylnitrones (**B**) générées in situ conduisent à des formations complètement régio- et stéréosélectives de *o*-alcénylméthoxy-acétophénones (**1a**–**1c**) et de *N*-méthylhydroxylamine; ces réactions nécessitent des temps de réaction plus courts et conduisent à la formation des produits **4a**–**4c** avec des rendements plus élevés que ceux obtenus dans les réactions thermiques équivalentes.

Mots clés : cycloadditions, nitrones, oximes, *o*-alcénylméthoxy-acétophénones, micro-onde, isoxazolidines.

[Traduit par la Rédaction]

Introduction

Considerable interest is centered on nitrone cycloadditions (1), including the nitrones derived from 1,2-*H* shifts in oximes (2), for generating biologically active molecules or precursors and scaffolds for the same (1–3). However, there are only few examples wherein oxime–nitrone transformation and intramolecular cycloadditions of keto-oximes have been investigated (4). Recently, it has been reported that oximation of *o*-allyloxy-acetophenone and -benzophenone (**1**) affords *E*-oximes (**2**), which are quantitatively converted to dipoles (**3**, Scheme 1) on refluxing in xylene for 14 h (5).

On the other hand, reaction of **1a** (R = CH_3, R^1 = H) with *N*-methylhydroxylamine hydrochloride in the presence of NaOH in aqueous ethanol, under reflux for 36 h, has been reported to furnish cycloadduct **4** (78% yield) derived from intramolecular 1,3-dipolar cycloaddition of an in-situ-generated nitrone (6) (Scheme 1). The same adduct has also been obtained in 49% yield by reaction of *o*-allyloxyphenylacetylene with *N*-methylhydroxylamine in a sealed tube at 110 °C for 46 h (6). Recently, microwave-assisted organic transformations, particularly under solvent free conditions, have emerged as an important component of the modern nonconventional green organic synthetic methodologies,

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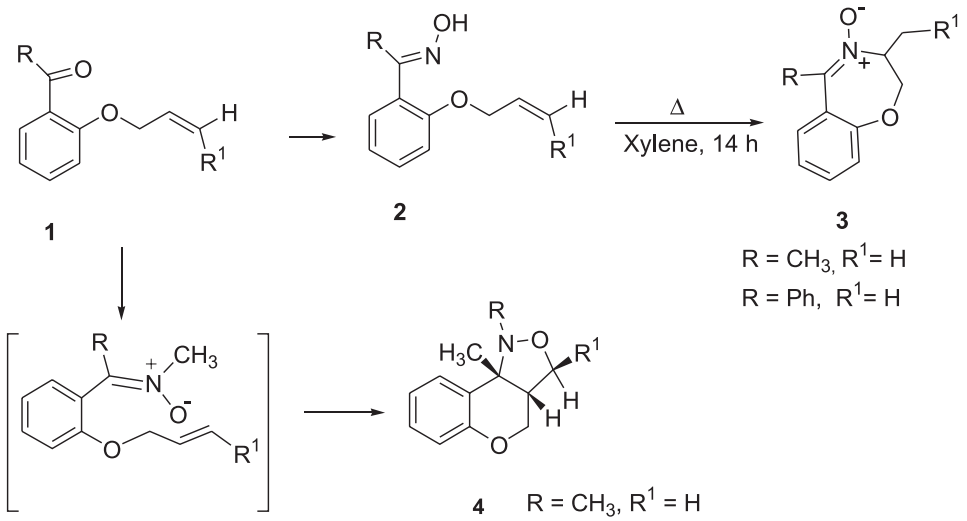
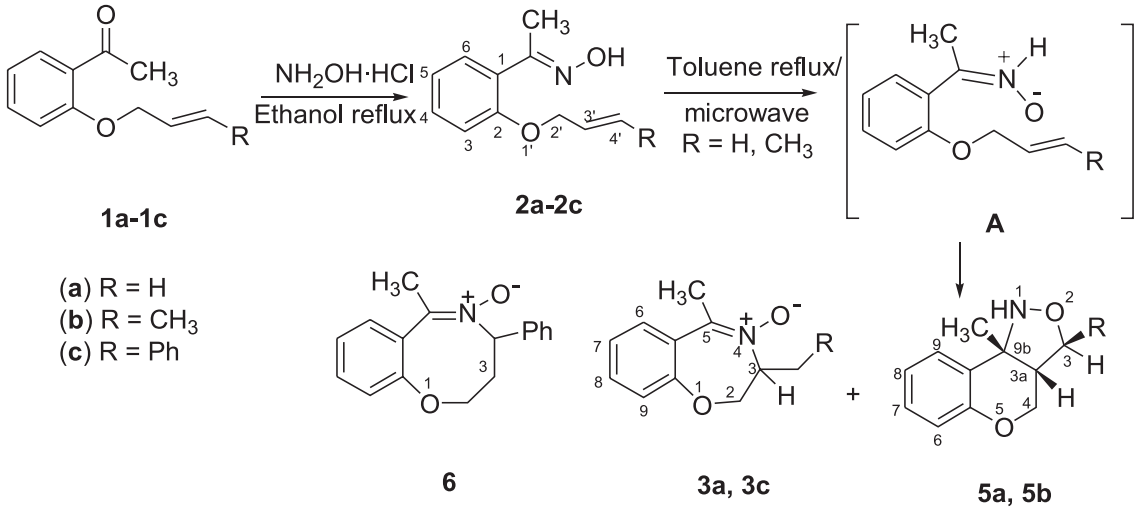
Scheme 1.



Scheme 2.



whose effectiveness has also been demonstrated for intramolecular cycloadditions (7). As a part of our ongoing investigations on 1,3-dipolar cycloadditions (8), and with the aim of developing scaffolds for some peptidomimetics, we have investigated the intramolecular 1,3-dipolar cycloaddition of *N*-methylnitrones and nitrones generated from oximes, derived from *o*-allyloxy-, -crotyloxy-, -cinnamyloxy-acetophenones (**1a**–**1c**). The reactions have been carried out under microwave-assisted, solvent-free conditions and the results compared with those of the reactions carried out under conventional (toluene–ethanol reflux) conditions.

Results and discussion

Oximes (**2a**–**2c**) were obtained in high yields (93%–95%) by refluxing corresponding ketones **1a**–**1c** (9) and hydroxylamine hydrochloride in dry ethanol as crystalline solids and characterized spectroscopically. Although oxime **2a** has been reported previously (5) and assigned a geometry –*E*, its melting point has not been reported; the spectroscopic data determined for **2a** is comparable with the data reported in the literature (5). Oximes **2a**–**2c** were adsorbed on silica gel and exposed to microwave heating (500 W, 75 °C) and products **5a**–**5b** and **3a** and **3c** (Scheme 2) were separated by column chromatography over silica gel.

The products were characterized by rigorous spectroscopic (IR, ^{1}H and ^{13}C NMR including COSY, hetero-COSY, and NOESY 2D NMR measurements, and mass spectra) and microanalytical data, and comparison of the data with the data reported for related systems (2, 3, 5). The assigned mode and regiochemistry of the addition in the case of **5a** and **5b** is based on the chemical shift of the C9b-methyl group, which indicated that it is no longer attached to an unsaturated carbon in the product and chemical shift of C3-H(s), which indicated the proximity of C3 to the oxygen; C3-H(s) resonances were easily identified from their multiplicity. The stereochemical disposition between the C9b-methyl group and C3a-H, i.e., the cis arrangement is based on spatial proximity established by the NOESY spectrum. Compound **3a** has been identified from its NMR spectral data (5). The assigned structure of compound **3c** is based, inter alia, on the observation of a 3H singlet (methyl)

Table 1. Reaction conditions, reaction times, and % yields of the products.

Serial No.	Compound	Toluene reflux Temp (°C)	Time (min)	Yield (%)	Microwave irradiation Temp (°C)[a]	Time (min)	Yield (%)
1	**5a**	110	4320	33	75	15	58
2	**5b**	110	4320	35	75	15	61
3	**3c**	110	4320	34	75	15	59

[a]The final temperature was measured at the end of microwave irradiation by introducing a glass thermometer into the reaction mixture.

Scheme 3.

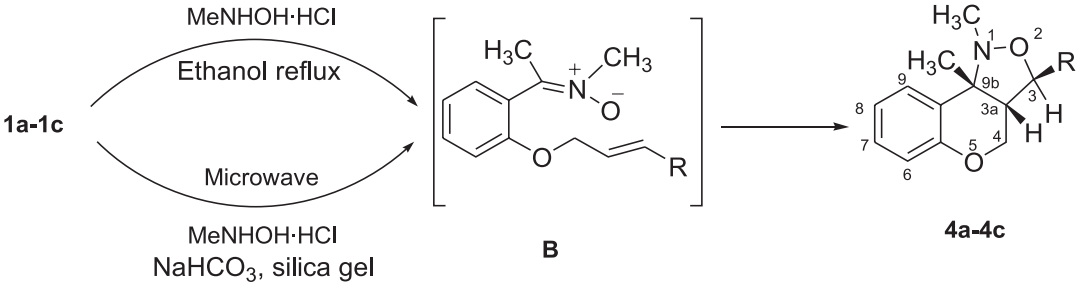


Table 2. Reaction conditions, reaction times, and % yields of the products.

Serial No.	Compound	Ethanol reflux Temp (°C)	Time (min)	Yield (%)	Microwave irradiation Temp (°C)[a]	Time (min)	Yield (%)
1	**4a**	78 to 79	720	82	75	15	96
2	**4b**	78 to 79	720	84	75	15	97
3	**4c**	78 to 79	720	80	75	15	95

[a]The final temperature was measured at the end of microwave irradiation by introducing a glass thermometer into the reaction mixture.

at δ 2.54 indicating that the methyl group is attached to an unsaturated carbon and the presence of an intense band in its IR spectrum at 1218 cm^{-1}, which is characteristic of the nitrone functionality (10). The alternative structure **6** for this compound was ruled out by ^1H multiplicities and connectivities as well as ^{13}C NMR assignments established by rigorous 2D NMR measurements. For instance, two 1H double doublets at δ 3.50 (^2J = 13.8 Hz and ^3J = 4.9 Hz) and δ 2.87 (^2J = 13.8 Hz and ^3J = 8.2 Hz) have been attributed to benzylic-Hs in **3c**, and such a pattern is not anticipated for C3-Hs in **6**; the hetero-COSY – 2D NMR spectrum revealed the corresponding benzylic-C resonance at δ 32.90.

As the formation of **5a** and **b** was contrary to the reported production (5) of only oxazepine-*N*-oxides (**3**) (5), in the thermal transformations of related oximes, thermal reactions of **2a**–**2c** were reinvestigated by refluxing dry toluene solutions and the products were similarly isolated by column chromatographic separation of the reaction concentrates. The results of thermal and corresponding microwave-assisted transformations are summarized in Table 1 and clearly indicate that similar results are obtained under both sets of conditions as far as the nature of the major products is concerned. However, the reactions carried out under microwave irradiation are attended with higher yields of the cycloadducts (**5a** and **5b**) as well as nitrones (**3c**) with much shortened reaction times.

For reactions of *N*-methylnitrones derived from ketones **1a**–**1c** under microwave heating, the ketones **1a**–**1c** were mixed with *N*-methylhydroxylamine hydrochloride and sodium bicarbonate, adsorbed on silica gel, and exposed to microwave radiation; products were isolated and purified by column chromatography. For corresponding thermal reactions, equimolar solutions of **1a**–**1c** and *N*-methylhydroxylamine hydrochloride in anhydrous ethanol were refluxed and products **4a**–**4c**) were similarly isolated by column chromatography. The results are summarized in Scheme 3 and Table 2.

Compound **4a** could be easily identified from the comparison of its spectroscopic data with the data reported in the literature (6); the assigned structures and stereochemistry in the case of **4b** and **4c** are again based on rigorous spectroscopic analysis, particularly, the NMR spectral data, and comparison of the same with that of the related systems (2, 3*k*, 6).

Thus, contrary to the reported (5) thermal transformation of oxime **2a** and corresponding *o*-allyloxybenzophenone oxime, leading, quantitatively, to bicyclic nitrones such as **3a**, and the recorded observation (5) that the formation of these bicyclic nitrones is related to the preferred *E* geometry of these oximes, the present investigations reveal that intramolecular 1,3-dipolar cycloaddition is the preferred mode of transformation of oximes **2a** and **2b**, both under thermal and

microwave irradiation conditions. Though, the precise reasons for the differential behavior of the oximes under comparable conditions, leading to **3a** and **3c** in the present investigations, are not very clear, in general, the exo-trig processes leading to seven-membered rings are favored (11). Mechanistically, as far as the regiochemistry of addition is concerned, i.e., the preferential formation of annelated products **5a**, **5b**, and **4a**–**4c**) vis-à-vis the bridged products, molecular modeling (MOPAC) studies on both *E* and *Z* forms of the involved nitrones revealed that the obtained regiochemistry as well as stereochemistry of addition are a consequence of the only feasible, less-cumbersome approach for intramolecular cycloadditions of these nitrones.

Conclusions

The present report thus describes regio- and stereoselective microwave-assisted intramolecular 1,3-dipolar cycloadditions of nitrones derived from *o*-allyloxy- and -crotyloxy-acetophenone oximes and *N*-methylnitrones derived from *o*-allyloxy-, -crotyloxy-, and -cinnamyloxy-acetophenones. A comparison with their thermal counterparts reveals that the reactions carried out under microwave irradiation conditions are cleaner, attended with higher yields, along with a drastic reduction in the reaction times. The obtained cycloadducts will be utilized, after opening of the isoxazolidine moiety, for synthesis of some peptidomimetics.

Experimental

Instrumentation and general procedures

Bruker AC-200FT (200 MHz) and JEOL AL-300FT (300 MHz) spectrometers were used to record ^{1}H and ^{13}C NMR spectra. IR spectra were recorded on a Shimadzu DR-2001 FT-IR spectrophotometer in $CHCl_3$ solution or as KBr pellets. Mass spectra, EI and ESI methods were recorded on Shimadzu GC–MS QP-2000A and Bruker Daltonics Esquire 300 mass spectrometers, respectively. Elemental analyses were carried out on a PerkinElmer 240C elemental analyzer and are reported in % atomic abundance. All melting points are uncorrected and were measured in open glass capillaries. Thin layer chromatography (TLC) was carried out on silica gel G-coated (Loba Chemie, containing 13% $CaSO_4$ as a binder) (1 mm thick layer) glass plates.

General procedure for preparation of oximes

Solutions of ketones **1a**–**1c** (200 mg, (9)) and hydroxylamine hydrochloride (1.0 molar equiv.) in dry ethanol were refluxed for 15–18 h. After the completion of the reaction (TLC, $CHCl_3$ solvent), the solvent was removed under reduced pressure. The residue was taken up in chloroform (20 mL) and washed successively with aqueous bicarbonate and water. After drying over anhydr. Na_2SO_4, the solutions were concentrated to one-fifth of their volume and triturated with hexane when colorless solids separated out.

o-*Allyloxyacetophenone oxime (2a)*

Yield: 95%; colorless solid, mp 48–50 °C (hexane:chloroform, 2:1). IR (KBr, cm^{-1}): 3260, 1610, 1595, 1480, 1440, 1380, 1355, 1280. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.75 (br, 1H, -OH), 7.34–7.28 (m, 2H, arom.-Hs), 6.99–6.88 (m, 2H, arom.-Hs), 6.03 (ddt, 1H, *J* = 5.0, 10.5, and 17.3 Hz, C3′-H), 5.39 (dd, 1H, *J* = 1.3 and 17.3 Hz, C4′-H), 5.27 (dd, 1H, *J* = 1.1 and 10.5 Hz, C4′-H), 4.57 (d, 2H, *J* = 5.0 Hz, C2′-Hs), 2.26 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 158.20 (quat.), 156.42 (quat.), 133.01 (CH), 130.08 (CH), 129.48 (CH), 127.19 (C1), 120.82 (CH), 117.41 (=*C*H$_2$), 112.39 (CH), 69.09 (O*C*H$_2$), 15.38 (*C*H$_3$). MS (EI) *m*/*z*: 192 (M$^+$ + 1), 191 (M$^+$).

o-*Crotyloxyacetophenone oxime (2b)*

Yield: 93%; colorless solid, mp 43–45 °C (hexane:chloroform, 2:1). IR (KBr, cm^{-1}): 3280, 1605, 1490, 1440, 1368, 1275. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 8.63 (br, 1H, -OH), 7.33–7.26 (m, 2H, arom.-Hs), 6.97–6.87 (m, 2H, arom.-Hs), 5.81–5.63 (m, 2H, C3′-H and C4′-H), 4.49 (d, 2H, *J* = 5.5 Hz, C2′-Hs), 2.25 (s, 3H, CH_3), 1.76 (dd, 3H, *J* = 1.0 and 5.9 Hz, C4′-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 157.12 (quat.), 156.60 (quat.), 130.03 (CH), 129.93 (CH), 128.30 (CH), 127.20 (C1), 125.91 (CH), 120.60 (CH), 112.47 (CH), 69.03 (OCH_2), 17.80 (CH_3), 15.34 (CH_3). MS (ESI) *m*/*z*: 228 (M + Na)$^+$.

o-*Cinnamyloxyacetophenone oxime (2c)*

Yield: 95%; colorless solid, mp 106–108 °C (hexane:chloroform, 2:1). IR (KBr, cm^{-1}): 3285, 1605, 1495, 1430, 1368, 1225. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 9.10 (br, 1H, -OH), 7.45–7.28 (m, 7H, arom-Hs), 6.99 (td, 2H, arom.-Hs, *J* = 1.0 and 8.8 Hz), 6.74 (d, 1H, *J* = 15.9 Hz, C4′-H), 6.41 (dt, 1H, *J* = 5.6 and 15.9 Hz, C3′-H), 4.76 (dd, 2H, *J* = 1.1 and 5.6 Hz, C2′-Hs), 2.31 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 156.96 (quat.), 156.46 (quat.), 136.38 (quat.), 132.79 (CH), 130.12 (CH), 129.52 (CH), 128.57 (CH), 127.86 (CH), 127.27 (C1), 126.55 (CH), 124.27 (CH), 120.89 (CH), 112.58 (CH), 69.05 (OCH_2), 15.43 (CH_3). MS (ESI) *m*/*z*: 290 (M + Na)$^+$.

General procedure for the transformations of oximes under microwave irradiation

Oximes **2a**–**2c** (200 mg) were dissolved in chloroform (10 mL) and to the solution was added silica gel (G, 3.0 g) and the solvent was removed under vacuum. The obtained powder was exposed to microwave irradiation (500 W) for 15 min (five cycles, 3 min each); the exposure time optimization is based on TLC ($CHCl_3$ solvent) monitoring. The adsorbed material was then extracted with ethyl acetate (25 mL) and dried over anhydr. Na_2SO_4. The solvent was then distilled off under reduced pressure. The products were isolated by column chromatographic separation over silica gel (60–120 mesh, 30 g). The column was packed in hexane and hexane – ethyl acetate gradients were used for elution.

(3aS,9bR)-9b-Methyl-1,3a,4,9b-tetrahydro-3H-chromeno[4,3-c]isoxazole (5a)

Elution of the column initially with hexane – ethyl acetate (9:1) afforded **1a** (14 mg, 7%) and unreacted oxime **2a** (30 mg, 15%) with hexane – ethyl acetate (7:1). Further elution with hexane – ethyl acetate (3:1) afforded cycloadduct **5a** (116 mg, 58%) as a yellow oil. R_f 0.37 ($CHCl_3$). IR ($CHCl_3$, cm^{-1}): 3260, 1585, 1510, 1482, 1430, 1290. ^{1}H

NMR ($CDCl_3$, 200 MHz) δ: 7.48 (dd, 1H, J = 1.7 and 7.7 Hz, arom.-H), 7.21 (ddd, 1H, arom.-H, J = 8.8, 7.3, and 1.7 Hz), 7.24–6.89 (m, 2H, arom.-Hs), 4.34 (unresolved dd, 1H, $^2J \cong {}^3J \sim 8.3$ Hz, C3-H), 4.21 (dd, 1H, ^2J = 11.6 and J = 4.6 Hz, C4-H), 3.78 (dd, 1H, ^2J = 11.6 and J = 8.1 Hz, C4-H), 3.73 (dd, 1H, ^2J = 8.1 and 5.1 Hz, C3-H), 2.78–2.69 (m, 1H, C3a-H), 1.56 (s, 3H, C9b-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.69 (C5a), 128.92 (CH), 128.69 (CH), 124.67 (C9a), 121.89 (CH), 117.15 (CH), 72.50 (C3), 65.41 (C9b), 61.13 (C4), 47.66 (C3a), 26.29 (CH_3). MS (EI) m/z: 192 (M^+ + 1), 191 (M^+). Anal. calcd. for $C_{11}H_{13}NO_2$: C 69.09, H 6.85, N 7.32; found: C 68.97, H 6.99, N 7.20. Further elution with hexane – ethyl acetate (1:1) afforded **3a** as a reddish oil (20 mg, 10%) (5). R_f 0.16 ($CHCl_3$).

*(3S,3aS,9bR)-9b-Dimethyl-1,3a,4,9b-tetrahydro-3*H*-chromeno[4,3-*c*]isoxazole (5b)*

Elution of the column initially with hexane – ethyl acetate (9:1) afforded **1b** (20 mg, 10%) and unreacted oxime **2b** (30 mg, 15%) with hexane – ethyl acetate (7:1). Further elution with hexane – ethyl acetate (3:1) afforded cycloadduct **5b** (122 mg, 61%) as a yellow oil. R_f 0.37 ($CHCl_3$). IR ($CHCl_3$, cm^{-1}): 3270, 1615, 1585, 1490, 1450, 1380, 1298, 1235, 1125. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.43 (dd, 1H, J = 1.2 and 7.9 Hz, arom.-H), 7.22–7.16 (m, 1H, arom.-H), 7.00–6.83 (m, 2H, arom.-Hs), 4.17 (dd, 1H, ^2J = 11.7 and J = 4.3 Hz, C4-H), 3.95 (dd, 1H, J = 4.2 and 6.0 Hz, C3-H), 3.88 (dd, 1H, J = 6.1 and 11.7 Hz, C4-H), 2.19–2.14 (m, 1H, C3a-H), 1.60 (s, 3H, C9b-CH_3), 1.45 (d, 3H, J = 6.0 Hz, C3-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.37 (C5a), 128.86 (CH), 128.13 (CH), 125.86 (C9a), 122.08 (CH), 117.29 (CH), 81.37 (C3), 65.52 (C9b), 61.96 (C4), 56.12 (C3a), 27.98 (C9b-*C*H_3), 18.84 (C3-*C*H_3). MS (ESI) m/z: 228 (M + Na)$^+$. Anal. calcd. for $C_{12}H_{15}NO_2$: C 70.22, H 7.37, N 6.82; found: C 70.15, H 7.49, N 6.73.

3-Benzyl-5-methyl-2,3-dihydro-benzo[f][1,4]oxazepine-4-oxide (3c)

Elution of the column initially with hexane – ethyl acetate (9:1) afforded **1c** (20 mg, 10%) and unreacted oxime **2c** (40 mg, 20%) with hexane – ethyl acetate (7:1). Further elution with hexane – ethyl acetate (1:1) afforded cycloadduct **3c** (118 mg, 59%) as a yellow oil. R_f 0.16 ($CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1600, 1573, 1490, 1447, 1288, 1218. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.41–6.91 (m, 9H, arom-Hs), 4.65–4.55 (m, 2H, C2-Hs), 4.49–4.41 (m, 1H, C3-H), 3.50 (dd, 1H, ^2J = 13.8 and ^3J = 4.9 Hz, benzylic-H), 2.87 (dd, 1H, ^2J = 13.8 and ^3J = 8.2 Hz, benzylic-H), 2.54 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.48 (C9a), 142.97 (quat.), 136.93 (CH), 130.75 (CH), 129.26 (CH), 128.74 (CH), 126.94 (C5a), 124.12 (CH), 123.11 (CH), 121.39 (CH), 75.64 (C3), 71.85 (C2), 32.90 (benzylic-*C*), 18.89 (CH_3). MS (ESI) m/z: 290 (M + Na)$^+$. Anal. calcd. for $C_{17}H_{17}NO_2$: C 76.48, H 7.29, N 6.94; found: C 76.38, H 6.41, N 5.24.

General procedure for thermal transformations of oximes

Oximes **2a**–**2c** (200 mg) were refluxed in dry toluene (50 mL) for 72 h. After the completion of the reaction (TLC, $CHCl_3$ solvent), the solvent was removed under reduced pressure and the products were isolated by similar column chromatographic separations of the concentrate. From the reaction of **2a** were obtained **1a** (84 mg, 42%), **2a** (30 mg, 15%), and **5a** (66 mg, 33%), eluted with hexane – ethyl acetate 9:1, 7:1, and 3:1, respectively.

From the reaction of **2b** were obtained **1b** (80 mg, 40%), **2b** (32 mg, 16%), and **5b** (70 mg, 35%), eluted, respectively, with hexane – ethyl acetate 9:1, 7:1, and 3:1.

From the reaction of **3c** were isolated **1c** (86 mg, 43%), **2c** (28 mg, 14%) and **3c** (68 mg, 34%), eluted with hexane – ethyl acetate 9:1, 7:1, and 1:1, respectively.

General procedure for the reactions of ketones 1a–1c with *N*-methylhydroxylamine hydrochloride under microwave irradiation

Ketones **1a**–**1c** (200 mg) were mixed with *N*-methylhydroxylamine hydrochloride (equimolar) and sodium bicarbonate (1.0 g), and adsorbed on silica gel (G, 3.0 g) as described earlier. The reaction mixture was exposed to microwave radiation (500 W) for 15 min (five cycles, 3 min each); exposure time optimization is based on TLC ($CHCl_3$ solvent) monitoring. The adsorbed material was then extracted with ethyl acetate (25 mL), and dried over anhydr. Na_2SO_4. The solvent was then distilled off under reduced pressure. The products were isolated by column chromatographic separation over silica gel (60–120 mesh, 30 g). The column was packed in hexane and hexane – ethyl acetate gradients were used for elution.

*(3S,3aS,9bR)-1,3,9b-Trimethyl-1,3a,4,9b-tetrahydro-3*H*-chromeno[4,3-*c*]isoxazole (4b)*

Elution with hexane – ethyl acetate (3:1) afforded cycloadduct **4b** (223 mg, 97%) as a colorless oil. R_f 0.35 ($CHCl_3$). IR ($CHCl_3$, cm^{-1}): 1610, 1575, 1490, 1430, 1290, 1245, 1235. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.35 (d, 1H, J = 7.5 Hz, arom.-H), 7.16 (unresolved dd, 1H, $J \sim 7.5$ Hz, arom.-H), 6.96 (unresolved dd, 1H, $J \sim 7.5$ Hz, arom.-H), 6.82 (d, 1H, J = 8.1 Hz, arom.-H), 4.27–4.09 (m, 3H, C3-H and C4-Hs), 2.89 (s, 3H, *N*-CH_3), 2.27–2.19 (m, 1H, C3a-H), 1.51 (s, 3H, C9b-CH_3), 1.42 (d, 3H, J = 6.3 Hz, C3-CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 154.59 (C5a), 128.29 (CH), 128.09 (CH), 126.1 (quat.), 121.16 (CH), 117.03 (CH), 74.89 (C3), 65.0 (C4), 63.64 (C9b), 39.29 (*N*-CH_3), 54.04 (C3a), 20.33 (C3-CH_3 and C9b-CH_3, hetero-COSY). MS (EI) m/z: 220 (M^+ + 1, 6), 219 (M^+, 40). Anal. calcd. for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39; found: C 71.34, H 7.70, N 6.21.

*(3R,3aS,9bR)-1,9b-Dimethyl-3-phenyl-1,3a,4,9b-tetrahydro-3*H*-chromeno[4,3-*c*]isoxazole (4c)*

Elution with hexane – ethyl acetate (3:1) afforded cycloadduct **4b** (211 mg, 95%) as a colorless solid, mp 43–45 °C (hexane:chloroform, 2:1). R_f 0.35 ($CHCl_3$). IR (KBr, cm^{-1}): 1610, 1575, 1495, 1430, 1290, 1245, 1235. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.48–7.16 (m, 7H, arom.-Hs), 7.03–6.90 (m, 2H, arom.-Hs), 5.05 (d, 1H, J = 7.5 Hz, C3-H), 4.26–4.18 (m, 2H, C4-Hs), 2.78 (s, 3H, *N*-CH_3), 2.67–2.60 (m, 1H, C3a-H), 1.59 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 54.77 (C5a), 140.92 (quat.), 128.56 (CH), 128.14 (CH), 127.71 (CH), 126.29 (quat.), 125.98 (CH), 121.39 (CH), 117.20 (CH), 80.58 (C3), 64.76 (C9b), 64.07

(C4), 56.15 (C3a), 39.98 (N-CH_3), 23.43 (CH_3). MS (ESI) *m/z*: 304 $(M + Na)^+$. Anal. calcd. for $C_{18}H_{19}NO_2$: C 76.84, H 6.81, N 4.98; found: C 76.69, H 6.97, N 4.82.

General procedure for the reactions of ketones 1a–1c with *N*-methylhydroxylamine hydrochloride under thermal conditions

Solutions of ketones **1a**–**1c** (200 mg) and *N*-methylhydroxylamine hydrochloride (equimolar) in anhydrous ethanol (50 mL) were refluxed in the presence of sodium bicarbonate (1.0 g, excess) for 12 h. After the completion of the reaction (TLC, $CHCl_3$ solvent), the solvent was removed under reduced pressure. The residue was taken up in chloroform (20 mL) and washed with water. After drying over anhydr. Na_2SO_4, the products were isolated by similar column chromatographic separations of the concentrate over a silica gel column employing hexane – ethyl acetate (3:1) as the eluent. The cycloadducts **4a**–**4c** were obtained in 191 mg (82%), 193 mg (84%), and 178 mg (80%) yields, respectively.

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