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Regioselective Cycloaddition of *C*-Aryl- and *C*-Carbamoylnitrones to Methyl 2-Benzylidenecyclopropanecarboxylate

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Abstract—*C*-Aryl- and *C*-carbamoylnitrones reacted with methyl 2-benzylidenecyclopropanecarboxylate in highly regioselective fashion to give the corresponding 1,3-dipolar cycloaddition products, substituted methyl 5-oxa-6-azaspiro[2.4]heptane-1-carboxylates as mixtures of two diastereoisomers.

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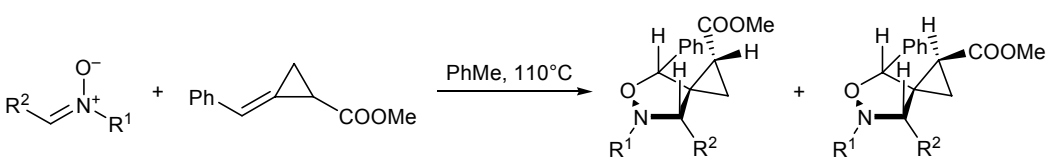
1,3-Dipolar cycloaddition is one of the most powerful tools for the construction of five-membered N,O-heterocyclic systems. An example of such reactions is addition of nitrones at a double carbon–carbon bond, which underlies a widely used method of synthesis of isoxazolidine derivatives [1]. Isoxazolidines attract strong interest due to their potential biological activity and the possibility for converting them into amino alcohols via hydrogenolysis of the N–O bond. Amino alcohols in turn are important as initial compounds for the synthesis of naturally occurring β-lactams and alkaloids. Unlike acyclic unsaturated compounds, sterically strained methylidenecyclopropanes readily react with nitrones according to the [2+3]-cycloaddition pattern with formation of mixtures of isomeric C^4- and C^5-spiro isoxazolidines whose ratio depends on the substituents in both nitrone and methylidenecyclopropane components [2]. We previously found that *C*,*N*-diaryl- and *C*-carbamoyl-*N*-arylnitrones react with methylidenecyclopropanedicarboxylic acid esters to produce only 4-spiro derivatives [3] and that reactions of *C*,*C*-disubstituted nitrones with the same esters lead to azeto- and pyrroloquinolines through intermediate 5-spiro isoxazolidines [4].

The present article reports on the reactions of *N*-aryl(methyl)-*C*-arylnitrones **Ia**–**Id** and *N*-aryl-(methyl)-*C*-carbamoylnitrones **Ie**–**Ih** with methyl 2-benzylidenecyclopropanecarboxylate (**II**). The reactions were carried out in boiling toluene to produce diastereoisomeric 4-spiro oxazolidine derivatives **III** and **IV** with high regioselectivity (Scheme 1).

The structure of cycloadducts **III** and **IV** was determined on the basis of spectral data. Compounds **IIIa**–**IIIh** displayed in the ^{1}H NMR spectra three doublets of doublets at δ 0.59–2.17 ppm (J = 8.7, 5.8; 6.5, 5.8; 8.7, 6.5 Hz) from protons in the cyclopropane ring, two singlets at δ 3.44–4.61 and 5.17–5.35 ppm from CH protons in the oxazolidine ring, and signals from aromatic protons and protons in the ester group. The ^{1}H NMR spectra of **IIIe**–**IIIh** also contained a singlet at δ 8.99–9.13 ppm from the NH proton. The ^{13}C NMR spectra of **IIIa**–**IIIh** contained signals from carbon atoms in the cyclopropane ring at δ_C 14.6–18.7 (CH_2), 24.1–28.5 (CH), and 42.6–47.3 ppm (C_{spiro}),

Scheme 1.



Ia–Ih **II** **IIIa–IIIh** **IVa**, **IVb**, **IVe–IVh**

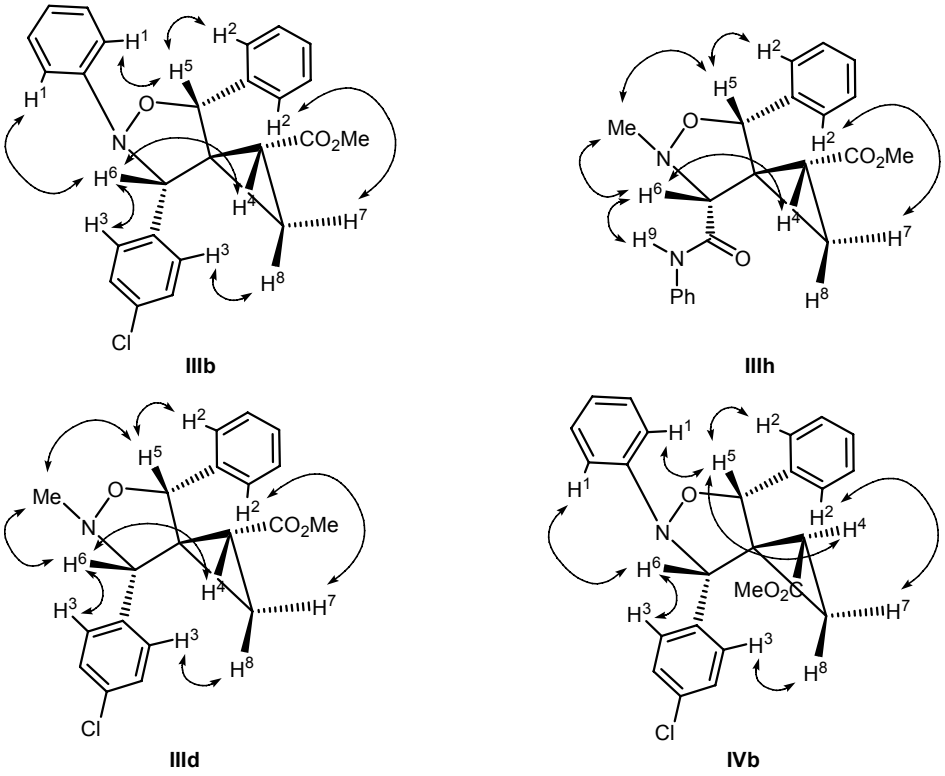
$R^1 = R^2 =$ Ph (**a**); $R^1 =$ Ph, $R^2 = 4\text{-}ClC_6H_4$ (**b**); $R^1 =$ Me, $R^2 =$ Ph (**c**); $R^1 =$ Me, $R^2 = 4\text{-}ClC_6H_4$ (**d**); $R^1 =$ Ph, $R^2 =$ PhNHC(O) (**e**); $R^1 = 4\text{-}MeC_6H_4$, $R^2 =$ PhNHC(O) (**f**); $R^1 = 4\text{-}MeC_6H_4$, $R^2 = 4\text{-}MeOC_6H_4NHC(O)$ (**g**); $R^1 =$ Me, $R^2 =$ PhNHC(O) (**h**).

signals from carbon atoms in the oxazolidine ring at δ_C 75.0–79.4 (NCH) and 80.3–81.7 ppm (OCH), and other signals. In the IR spectra of **IIIa**–**IIId**, absorption bands due to ester carbonyl group were observed in the region 1728–1720 cm^{-1}, and the amide group in **IIIe**–**IIIh** gave rise to absorption bands at 1686–1680 (C=O) and 3363–3344 cm^{-1} (NH). The elemental compositions or high-resolution mass spectra of **IIIa**–**IIIh** were consistent with the assumed structure.

In the ^{1}H NMR spectra of **IVa**, **IVb**, and **IVe**–**IVh** we observed three doublets of doublets from protons in the cyclopropane ring at δ 0.67–2.29 ppm (J = 8.7, 5.8; 6.5, 5.8; 8.7, 6.5 Hz), two singlets from 7-H and 4-H at δ 4.89–5.23 and 5.08–5.25 ppm, and other signals. The NH proton in **IVe**–**IVh** resonated at δ 9.17–9.34 ppm. The ^{13}C NMR spectra of **IVa**, **IVb**, and **IVe**–**IVh** contained signals from carbon atoms in the cyclopropane ring at δ_C 14.8–18.2 (CH_2), 25.2–25.8 (CH), and 42.9–47.4 ppm (C_{spiro}), signals from carbon atoms in the oxazolidine ring at δ_C 67.7–69.7 (C^7) and 85.3–86.1 ppm (C^4), and other signals. Compounds **IVa** and **IVb** showed in the IR spectra ester carbonyl absorption band at 1730–1720 cm^{-1}, and the spectra of **IVe**–**IVh** displayed amide carbonyl absorption at 1688–1680 cm^{-1} and NH absorption at 3363–3340 cm^{-1}. The structure of **IVa**, **IVb**, and **IVe**–**IVh** was also confirmed by their elemental compositions and high-resolution mass spectra.

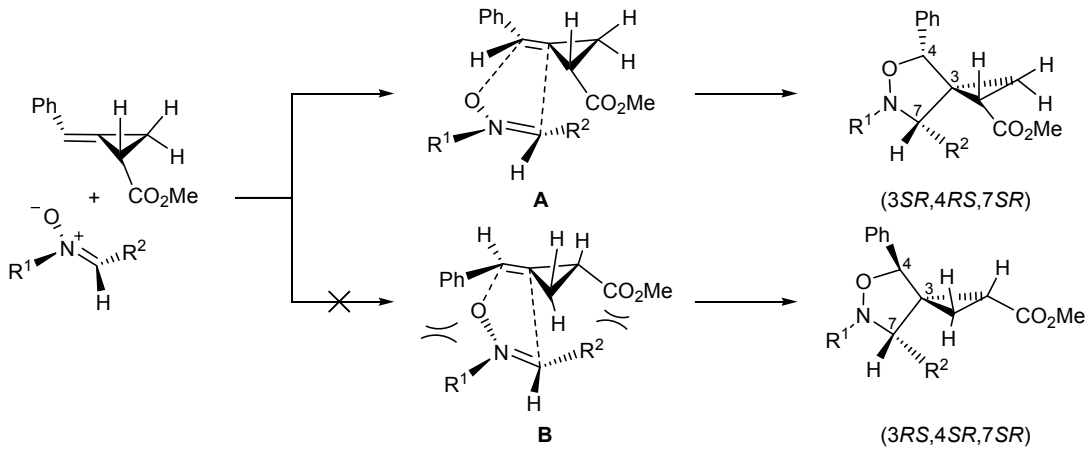
In the ^{1}H NMR spectra of the reaction mixtures only signals corresponding to 4-spiro derivatives were detected. The stereochemical structure of adducts **III** and **IV** was determined on the basis of ^{1}H–^{1}H NOESY data (see figure). Compounds **IIIb**, **IIId**, and **IIIh** showed cross peaks due to interaction between *ortho*-protons (H^1) in the aromatic ring on the nitrogen atom (or protons in the N-methyl group) and H^5 and H^6, indicating that these protons are located at the same side of the isoxazolidine ring. In addition, couplings between protons in the cyclopropane ring (H^4, H^7, H^8), on the one hand, and H^6 and *ortho*-protons in other aromatic rings (H^2 and H^3) were observed. No cross peaks between H^5, H^6 and H^7, H^8, which might be expected for the other diastereoisomer, were detected. Analogous pattern was observed in the ^{1}H–^{1}H NOESY spectrum of **IVb** with the difference that interaction between H^4 and H^5 rather than H^6 was found therein.

The ratio of diastereoisomers **III** and **IV** depended on the substituent in the initial nitrone. *C*,*N*-Diarylnitrones **Ia** and **Ib** gave rise to equimolar mixtures of the corresponding adducts; isomers **IIIc** and **IIId** were formed as the only products from *N*-methylnitrones **Ic** and **Id**; and the ratio of adducts **III** and **IV** in the



Principal correlations in the ^{1}H NOESY spectra of compounds **IIIb**, **IIId**, **IIIh**, and **IVb**.

Scheme 2.



reactions with *C*-carbamoylnitrones **Ie**–**Ih** was 4:1 in all cases.

The addition of nitrone **I** to methylidenecyclopropane **II** may follow two paths. The first of these involves transition state **A** and leads to (3*SR*,4*RS*,7*SR*) stereoisomers **III** and **IV**. The second path should give (3*RS*,4*SR*,7*SR*) stereoisomers through transition state **B**. Presumably, the second path is less favorable since steric repulsion between the phenyl group and R^1 and between the *syn*-oriented ester group and R^2 is possible in transition state **B** (Scheme 2).

The relative reactivities of nitrones were estimated by performing competing reactions. We found that *C*-(phenylcarbamoyl)-*N*-phenylnitrone (**Ie**) is more reactive than *C*,*N*-diphenylnitrone (**Ia**) toward cyclopropane **II** (chloroform, 60°C) by a factor of more than 20 and that *N*-phenyl-*C*-(4-chlorophenyl)nitrone (**Ib**) is more reactive than its *N*-methyl analog **Id** (toluene, 110°C) by a factor 15. These findings indicated that introduction of an electron-withdrawing group to the carbon atom increases the reactivity of nitrone and that replacement of phenyl group on the nitrogen atom in nitrone by alkyl substituent reduces the reactivity.

To conclude, we have demonstrated that *C*-aryl- and *C*-carbamoylnitrone react with methyl 2-benzylidenecyclopropanecarboxylate in regioselective fashion to give substituted methyl 5-oxa-6-azaspiro[2.4]heptane-1-carboxylates as mixtures of two diastereoisomers.

EXPERIMENTAL

The elemental compositions were determined on a Hewlett–Packard 185-B CHN analyzer. The mass spectra were run on a Bruker microTOF instrument (electrospray ionization, positive ion detection). The IR spectra were recorded on a UR-20 spectrometer from 2% solutions in chloroform or KBr pellets. The ^{1}H and ^{13}C NMR spectra were measured from solutions in $CDCl_3$ on a Bruker DPX-300 instrument at 300.13 and 75.47 MHz, respectively. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates.

Initial nitrones **Ia**–**Ih** were synthesized according to the procedures described in [5].

Methyl (*E*)-2-benzylidenecyclopropanecarboxylate (II). A solution of 1.36 g (20 mmol) of methyl diazoacetate in 14 ml of methylene chloride was added over a period of ~4 h to a hot solution of 4.5 g (30 mmol) of phenylallene and 30 mg of $Rh_2(OAc)_4$ in 5 ml of anhydrous methylene chloride. The mixture was heated for 3 h, cooled, and evaporated, and the residue was subjected to column chromatography on silica gel using ethyl acetate–petroleum ether as eluent. Yield 0.87 g (23%), oily substance. IR spectrum ($CHCl_3$), ν, cm^{-1}: 3064, 1724 s, 1600, 1492, 1440, 1363, 1334, 1276. ^{1}H NMR spectrum, δ, ppm: 1.99 d.d.d (1H, CH_2, J = 9.5, 8.0, 2.2 Hz), 2.16 d.d.d (1H, CH, J = 9.5, 4.4, 2.2 Hz), 2.40 d.d.d (1H, CH_2, J = 8.0, 4.4, 2.2 Hz), 3.73 s (3H, CH_3), 6.85 q (1H, =CH, J = 2.2 Hz), 7.28 t (1H, H_{arom}, J = 7.3 Hz), 7.37 t (2H, H_{arom}, J = 7.3 Hz), 7.54 d (2H, H_{arom}, J = 7.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 13.2 (CH_2), 16.3 (CH), 52.4 (CH_3), 120.2 (CH), 123.3 (C), 127.5 (CH), 128.0 (CH), 129.0 (CH), 137.0 (C), 173.1 (C=O). Found: m/z 189.0886 $[M + H]^+$. $C_{12}H_{12}O_2$. Calculated: $[M + H]^+$ 189.0916.

Reaction of nitrones Ia–Ih with methyl 2-benzylidenecyclopropanecarboxylate (II) (*general procedure*). A solution of 1–3 mmol of benzylidene-

cyclopropane **II** and 1.1 equiv of nitrone **Ia**–**Ih** in 10 ml of anhydrous toluene was heated under reflux until the reaction was complete. The solvent was removed under reduced pressure, and stereoisomers **III** and **IV** were separated by column chromatography on silica gel using petroleum ether (bp 40–70°C)–ethyl acetate as eluent. The eluate was evaporated, and the residue was recrystallized from ethanol. We failed to separate diastereoisomers **IIIa** and **IVa**.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)- and (1*SR*,3*SR*,4*RS*,7*SR*)-4,6,7-triphenyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylates (IIIa/IVa). Reaction time 18 h. Yield 470 mg (63%), white powder, R_f 0.58 (EtOAc–hexane, 1:4). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3068, 2952, 1720 s, 1600, 1490, 1452, 1392, 1292, 1168. ^1H NMR spectrum, δ, ppm: 0.68 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 0.74 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 1.01 d.d (1H, CH_2, J = 6.5, 5.8 Hz), 1.09 d.d (1H, CH_2, J = 6.5, 5.8 Hz), 1.71 d.d (1H, CH, J = 8.7, 6.5 Hz), 1.97 d.d (1H, CH, J = 8.7, 6.5 Hz), 3.71 s (3H, CH_3), 3.72 s (3H, CH_3), 4.61 s (1H, CH), 5.23 s (1H, CH), 5.25 s (1H, CH), 5.34 s (1H, CH), 7.01–7.46 m (26H, H_{arom}), 7.70 d (2H, H_{arom}, J = 7.3 Hz), 7.81 d (2H, H_{arom}, J = 7.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.1 (CH_2), 25.4 (CH), 25.8 (CH), 47.2 (C), 47.5 (C), 52.3 (CH_3), 52.4 (CH_3), 69.7 (CH), 76.2 (CH), 80.3 (CH), 85.5 (CH), 114.7 (CH), 117.2 (CH), 122.2 (CH), 123.3 (CH), 127.6 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 135.6 (C), 138.3 (C), 140.9 (C), 141.6 (C), 150.0 (C), 150.8 (C), 172.5 (C=O), 173.4 (C=O). Found, %: C 77.85; H 5.94; N 3.70. $C_{25}H_{23}NO_3$. Calculated, %: C 77.90; H 6.01; N 3.63.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)-7-(4-chlorophenyl)-4,6-diphenyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IIIb). Reaction time 14 h. Yield 410 mg (28%), white powder, mp 55–56°C, R_f 0.32 (EtOAc–hexane, 1:7). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3060, 2956, 1724 s, 1600, 1492, 1444, 1392, 1165. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.78 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 1.06 d.d (1H, CH_2, J = 6.5, 5.8 Hz), 1.98 d.d (1H, CH, J = 8.7, 6.5 Hz), 3.71 s (3H, CH_3), 4.61 s (1H, CH), 5.35 s (1H, CH), 7.05 t (1H, H_{arom}, J = 7.3 Hz), 7.12 d (2H, H_{arom}, J = 7.3 Hz), 7.26–7.32 m (3H, H_{arom}), 7.35–7.43 m (6H, H_{arom}), 7.66 d (2H, H_{arom}, J = 6.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.4 (CH_2), 25.6 (CH), 46.5 (C), 51.9 (CH_3O), 75.2 (CH), 79.9 (CH), 116.7 (CH), 123.1 (CH), 127.8 (CH), 128.1 (CH), 128.2 (CH), 128.8 (CH), 129.1 (CH), 129.4 (CH), 134.0 (C), 136.6 (C), 140.1 (C), 149.4 (C), 171.9 (C=O). Found, %: C 71.49; H 5.17; N 3.66. $C_{25}H_{22}ClNO_3$. Calculated, %: C 71.51; H 5.28; N 3.34.

Methyl (1*SR*,3*SR*,4*RS*,7*SR*)-7-(4-chlorophenyl)-4,6-diphenyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IVb). Yield 410 mg (28%), white powder, mp 128–130°C (from EtOH), R_f 0.37 (EtOAc–hexane, 1:7). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3050, 2945, 1730 s, 1610, 1505, 1455, 1402, 1310, 1185, 1105. ^1H NMR spectrum, δ, ppm: 0.67 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 1.03 d.d (1H, CH_2, J = 6.5, 5.8 Hz), 1.71 d.d (1H, CH, J = 8.7, 6.5 Hz), 3.71 s (3H, CH_3), 5.21 s (1H, CH), 5.22 s (1H, CH), 7.02 t (1H, H_{arom}, J = 7.3 Hz), 7.15 d (2H, H_{arom}, J = 8.7 Hz), 7.19–7.22 m (2H, H_{arom}), 7.29 d (2H, H_{arom}, J = 8.0 Hz), 7.33–7.43 m (5H, H_{arom}), 7.75 d (2H, H_{arom}, J = 8.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 17.7 (CH_2), 24.9 (CH), 47.0 (C), 52.0 (CH_3O), 68.6 (CH), 85.0 (CH), 114.3 (CH), 122.0 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 129.4 (CH), 133.0 (C), 134.9 (C), 139.7 (C), 150.0 (C), 173.1 (C=O). Found, %: C 71.50; H 5.28; N 3.52. $C_{25}H_{22}ClNO_3$. Calculated, %: C 71.51; H 5.28; N 3.34.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)-6-methyl-4,7-diphenyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IIIc). Reaction time 69 h. Yield 118 mg (23%), oily liquid, R_f 0.48 (EtOAc–hexane, 1:5). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3052, 2956, 1722 s, 1604, 1492, 1444, 1392, 1168. ^1H NMR spectrum, δ, ppm: 0.61 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 0.85 d.d (1H, CH_2, J = 6.5, 5.8 Hz), 1.77 d.d (1H, CH, J = 8.7, 6.5 Hz), 2.74 s (3H, CH_3), 3.78 s (3H, CH_3), 3.82 s (1H, CH), 5.18 s (1H, CH), 7.28–7.41 m (8H, H_{arom}), 7.81 d (2H, H_{arom}, J = 7.3 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.7 (CH_2), 24.1 (CH), 44.0 (CH_3), 47.3 (C), 52.3 (CH_3), 79.4 (CH), 80.5 (CH), 127.7 (CH), 128.3 (CH), 128.5 (CH), 128.9 (CH), 129.1 (CH), 129.4 (CH), 135.9 (C), 143.0 (C), 173.1 (C=O). Found: m/z 324.1616 $[M+H]^+$. $C_{20}H_{21}NO_3$. Calculated: $[M+H]^+$ 324.1600.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)-7-(4-chlorophenyl)-6-methyl-4-phenyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IIId). Reaction time 70 h. Yield 160 mg (32%), oily liquid, R_f 0.40 (EtOAc–hexane, 1:6). IR spectrum (KBr), ν, cm^{-1}: 3031, 2953, 2871, 1728 s, 1599, 1491, 1444, 1391, 1197, 1168, 1091. ^1H NMR spectrum, δ, ppm: 0.59 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 0.87 d.d (1H, CH_2, J = 6.5, 5.8 Hz), 1.76 d.d (1H, CH, J = 8.7, 6.5 Hz), 2.73 s (3H, CH_3), 3.78 s (3H, CH_3), 3.79 s (1H, CH), 5.17 s (1H, CH), 7.22 d (2H, H_{arom}, J = 8.7 Hz), 7.32–7.43 m (5H, H_{arom}), 7.77 d (2H, H_{arom}, J = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 18.4

(CH_2), 24.1 (CH), 43.9 (CH_3), 47.1 (C), 52.3 (CH_3O), 78.6 (CH), 80.4 (CH), 127.7 (CH), 128.2 (CH), 128.4 (CH), 129.3 (CH), 130.6 (CH), 134.6 (C), 134.7 (C), 142.7 (C), 172.8 (C=O). Found: *m*/*z* 358.1225 $[M+H]^+$. $C_{20}H_{20}ClNO_3$. Calculated: $[M+H]^+$ 358.1210.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)-4,6-diphenyl-7-phenylcarbamoyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IIIe). Reaction time 70 min. Yield 275 mg (64%), white powder, mp 149–150°C (from EtOH), R_f 0.36 (EtOAc–hexane, 1:3). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3356, 3064, 2956, 1724 s, 1684 s, 1600, 1528, 1490, 1444, 1392, 1324, 1172. ^1H NMR spectrum, δ, ppm: 1.09 d.d (1H, CH_2, *J* = 6.5, 5.8 Hz), 2.04 d.d (1H, CH_2, *J* = 8.7, 6.5 Hz), 2.20 d.d (1H, CH, *J* = 8.7, 5.8 Hz), 3.57 s (3H, CH_3), 4.23 s (1H, CH), 5.25 s (1H, CH), 7.11–7.23 m (4H, H_{arom}), 7.34–7.49 m (9H, H_{arom}), 7.59 d (2H, H_{arom}, *J* = 8.0 Hz), 9.06 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.7 (CH_2), 28.0 (CH), 43.0 (C), 52.2 (CH_3), 75.1 (CH), 81.7 (CH), 115.5 (CH), 120.5 (CH), 124.0 (CH), 125.2 (CH), 128.9 (CH), 129.0 (CH), 129.5 (CH), 129.8 (CH), 137.4 (C), 137.8 (C), 149.0 (C), 167.6 (C=O), 172.0 (C=O). Found, %: C 72.79; H 5.50; N 6.45. $C_{26}H_{24}N_2O_4$. Calculated, %: C 72.88; H 5.65; N 6.54.

Methyl (1*SR*,3*SR*,4*RS*,7*SR*)-4,6-diphenyl-7-phenylcarbamoyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IVe). Yield 70 mg (16%), waxy material, R_f 0.44 (EtOAc–hexane, 1:3). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3356, 3036, 2956, 1722 s, 1688 s, 1600, 1528, 1490, 1444, 1394, 1174. ^1H NMR spectrum, δ, ppm: 0.95 d.d (1H, CH_2, *J* = 8.7, 5.8 Hz), 1.60 d.d (1H, CH_2, *J* = 8.7, 6.5 Hz), 2.26 d.d (1H, CH, *J* = 6.5, 5.8 Hz), 3.59 s (3H, CH_3), 4.94 s (1H, CH), 5.11 s (1H, CH), 7.12–7.45 m (13H, H_{arom}), 7.68 d (2H, H_{arom}, *J* = 8.0 Hz), 9.25 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 15.6 (CH_2), 25.2 (CH), 43.6 (C), 52.4 (CH_3), 67.9 (CH), 86.1 (CH), 115.2 (CH), 120.4 (CH), 123.8 (CH), 124.9 (CH), 128.6 (CH), 128.9 (CH), 129.3 (CH), 129.5 (CH), 129.7 (CH), 135.9 (C), 137.9 (C), 148.9 (C), 168.1 (C=O), 172.9 (C=O). Found: *m*/*z* 451.1641 $[M + Na]^+$. $C_{26}H_{24}N_2O_4$. Calculated: $[M + Na]^+$ 451.1634.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)-6-(4-methylphenyl)-4-phenyl-7-phenylcarbamoyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IIIf). Reaction time 70 min. Yield 290 mg (66%), white powder (from EtOH), R_f 0.36 (EtOAc–hexane, 1:4). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3348, 3048, 2956, 1726 s, 1686 s, 1600, 1528, 1506, 1444, 1392, 1176. ^1H NMR spectrum, δ, ppm: 1.08 d.d (1H, CH_2, *J* = 6.5, 5.8 Hz), 2.05 d.d (1H, CH_2, *J* = 8.7, 6.5 Hz), 2.19 d.d (1H, CH, *J* = 8.7, 5.8 Hz), 2.37 s (3H, CH_3), 3.58 s (3H, CH_3), 4.20 s (1H, CH), 5.23 s (1H, CH), 7.12 d (2H, H_{arom}, *J* = 8.7 Hz), 7.18–7.49 m (10H, H_{arom}), 7.59 d (2H, H_{arom}, *J* = 8.0 Hz), 9.08 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.8 (CH_2), 21.1 (CH_3), 28.0 (CH), 43.1 (C), 52.1 (CH_3), 75.1 (CH), 81.7 (CH), 115.8 (CH), 120.5 (CH), 125.2 (CH), 128.9 (CH), 129.0 (CH), 129.5 (CH), 130.3 (CH), 133.6 (C), 137.5 (C), 137.9 (C), 146.6 (C), 167.7 (C=O), 172.0 (C=O). Found, %: C 73.39; H 5.84; N 6.25. $C_{27}H_{26}N_2O_4$. Calculated, %: C 73.28; H 5.92; N 6.33.

Methyl (1*SR*,3*SR*,4*RS*,7*SR*)-6-(4-methylphenyl)-4-phenyl-7-phenylcarbamoyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IVf). Yield 73 mg (17%), waxy material, R_f 0.44 (EtOAc–hexane, 1:4). ^1H NMR spectrum, δ, ppm: 0.93 d.d (1H, CH_2, *J* = 8.7, 5.8 Hz), 1.58 d.d (1H, CH_2, *J* = 8.7, 6.5 Hz), 2.26 d.d (1H, CH, *J* = 6.5, 5.8 Hz), 2.37 s (3H, CH_3), 3.61 s (3H, CH_3), 4.90 s (1H, CH), 5.08 s (1H, CH), 7.08–7.48 m (12H, H_{arom}), 7.68 d (2H, H_{arom}, *J* = 8.0 Hz), 9.27 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 15.6 (CH_2), 21.1 (CH_3), 25.2 (CH), 43.7 (C), 52.4 (CH_3), 67.8 (CH), 86.0 (CH), 115.4 (CH), 120.4 (CH), 124.8 (CH), 128.6 (CH), 128.8 (CH), 129.3 (CH), 129.5 (CH), 130.2 (CH), 133.4 (C), 136.0 (C), 138.0 (C), 148.9 (C), 168.2 (C=O), 172.9 (C=O). Found: *m*/*z* 465.1806 $[M + Na]^+$. $C_{27}H_{26}N_2O_4$. Calculated: $[M + Na]^+$ 465.1790.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)-7-(4-methoxyphenylcarbamoyl)-6-(4-methylphenyl)-4-phenyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IIIg). Reaction time 70 min. Yield 305 mg (68%), white powder (from EtOH), R_f 0.35 (EtOAc–hexane, 1:4). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3363, 2956, 1724 s, 1680 s, 1596, 1512, 1442, 1414, 1392, 1248, 1172. ^1H NMR spectrum, δ, ppm: 1.07 d.d (1H, CH_2, *J* = 6.5, 5.8 Hz), 2.03 d.d (1H, CH_2, *J* = 8.7, 6.5 Hz), 2.20 d.d (1H, CH, *J* = 8.7, 5.8 Hz), 2.37 s (3H, CH_3), 3.58 s (3H, CH_3), 3.83 s (3H, CH_3), 4.19 s (1H, CH), 5.23 s (1H, CH), 6.92 d (2H, H_{arom}, *J* = 8.7 Hz), 7.11 d (2H, H_{arom}, *J* = 8.7 Hz), 7.18 t (2H, H_{arom}, *J* = 8.7 Hz), 7.31–7.38 m (3H, H_{arom}), 7.46 d (2H, *J* = 8.7 Hz), 7.49 d (2H, *J* = 8.7 Hz), 8.99 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.7 (CH_2), 21.1 (CH_3), 28.0 (CH), 43.1 (C), 52.1 (CH_3), 55.9 (CH_3), 75.0 (CH), 81.6 (CH), 114.6 (CH), 115.7 (CH), 122.2 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 130.3 (CH), 130.6 (C), 133.6 (C), 137.9 (C), 146.6 (C), 157.1 (C), 167.4 (C=O), 172.1 (C=O). Found, %: C 71.09; H 5.96; N 5.90. $C_{28}H_{28}N_2O_5$. Calculated, %: C 71.17; H 5.97; N 5.93.

Methyl (1*SR*,3*SR*,4*RS*,7*SR*)-7-(4-methoxyphenylcarbamoyl)-6-(4-methylphenyl)-4-phenyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IVg). Yield 75 mg (17%), waxy material, R_f 0.44 (EtOAc–hexane, 1:4). ^{1}H NMR spectrum, δ, ppm: 0.92 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 1.57 d.d (1H, CH_2, J = 8.7, 6.5 Hz), 2.27 d.d (1H, CH, J = 6.5, 5.8 Hz), 2.37 s (3H, CH_3), 3.60 s (3H, CH_3), 3.83 s (3H, CH_3), 4.89 s (1H, CH), 5.08 s (1H, CH), 6.92 d (2H, H_{arom}, J = 8.7 Hz), 7.09 d (2H, H_{arom}, J = 8.7 Hz), 7.16–7.23 m (4H, H_{arom}), 7.30–7.38 m (3H, H_{arom}), 7.59 d (2H, H_{arom}, J = 9.5 Hz), 9.17 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.8 (CH_2), 21.1 (CH_3), 25.2 (CH), 43.6 (C), 52.3 (CH_3), 55.9 (CH_3), 67.7 (CH), 86.1 (CH), 114.6 (CH), 115.4 (CH), 122.0 (CH), 128.6 (CH), 129.3 (CH), 129.6 (CH), 130.2 (CH), 133.3 (C), 136.1 (C), 136.7 (C), 145.9 (C), 156.9 (C), 166.6 (C=O), 167.8 (C=O). Found: m/z $[M + Na]^+$ 495.1909. $C_{28}H_{28}N_2O_5$. Calculated: $[M + Na]^+$ 495.1896.

Methyl (1*RS*,3*SR*,4*RS*,7*SR*)-6-methyl-4-phenyl-7-phenylcarbamoyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IIIh). Reaction time 9 h. Yield 295 mg (48%), white powder, mp 121–122°C (from EtOH), R_f 0.35 (EtOAc–hexane, 1:2). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3344, 3064, 2956, 1724 s, 1684 s, 1602, 1532, 1444, 1392, 1324, 1170. ^{1}H NMR spectrum, δ, ppm: 1.03 d.d (1H, CH_2, J = 6.5, 5.8 Hz), 2.17 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 2.27 d.d (1H, CH, J = 8.7, 6.5 Hz), 3.02 s (3H, CH_3), 3.44 s (1H, CH), 3.79 s (3H, CH_3), 5.19 s (1H, CH), 7.17 t (1H, H_{arom}, J = 7.3 Hz), 7.28–7.39 m (7H, H_{arom}), 7.59 d (2H, H_{arom}, J = 8.0 Hz), 9.13 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.2 (CH_2), 28.1 (CH), 42.2 (C), 43.9 (CH_3), 52.0 (CH_3), 75.5 (CH), 80.6 (CH), 120.0 (CH), 124.6 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 129.1 (CH), 137.2 (C), 138.1 (C), 167.2 (C=O), 171.8 (C=O). Found, %: C 68.68; H 5.98; N 7.59. $C_{21}H_{22}N_2O_4$. Calculated, %: C 68.84; H 6.05; N 7.65.

Methyl (1*SR*,3*SR*,4*RS*,7*SR*)-6-methyl-4-phenyl-7-phenylcarbamoyl-5-oxa-6-azaspiro[2.4]heptane-1-carboxylate (IVh). Yield 75 mg (12%), oily substance, R_f 0.32 (EtOAc–hexane, 1:2). IR spectrum ($CHCl_3$), ν, cm^{-1}: 3340, 3068, 2956, 1724 s, 1688 s, 1602, 1526, 1444, 1394, 1324, 1170. ^{1}H NMR spectrum, δ, ppm: 0.86 d.d (1H, CH_2, J = 8.7, 5.8 Hz), 1.93 d.d (1H, CH_2, J = 8.7, 6.5 Hz), 2.29 d.d (1H, CH, J = 6.5, 5.8 Hz), 2.99 s (3H, CH_3), 3.79 s (3H, CH_3), 3.93 s (1H, CH), 5.17 s (1H, CH), 7.15–7.19 (3H, H_{arom}), 7.27–7.30 m (3H, H_{arom}), 7.37 t (2H, H_{arom}, J = 8.0 Hz), 7.66 d (2H, H_{arom}, J = 8.7 Hz), 9.34 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 14.7 (CH_2), 25.4 (CH), 42.5 (C), 43.3 (CH_3), 52.1 (CH_3), 68.8 (CH), 84.9 (CH), 119.8 (CH), 124.2 (CH), 128.1 (CH), 128.8 (CH), 128.9 (CH), 129.0 (CH), 136.1 (C), 137.6 (C), 167.7 (C=O), 172.3 (C=O). Found: m/z 367.1673 $[M + H]^+$. $C_{21}H_{22}N_2O_4$. Calculated: $[M + H]^+$ 367.1658.

The relative reactivities of nitrones toward 2-benzylidenecyclopropane were estimated by the yields of the final products. The reaction was carried out using 1 equiv of 2-benzylidenecyclopropane and 4 equiv of each nitrone. The ratio of adducts **III** and **IV** was determined from the ^{1}H NMR spectra of the reaction mixtures.

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