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An efficient and stereoselective cycloaddition of *C*-aryl and *C*-amido nitrones to dimethyl 2-benzylidenecyclopropane-1,1-dicarboxylate

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ABSTRACT

1,3-Dipolar cycloadditions of dimethyl 2-benzylidenecyclopropane-1,1-dicarboxylate and a number of *C*-aryl or *C*-amido nitrones proceed with high efficiency and selectivity with the formation of only one isomeric spiro[cyclopropane-1,4-isoxazolidine] cycloadduct.

1. Introduction

1,3-Dipolar cycloaddition is known as one of the most powerful tools to create N,O-five-membered heterocycles. In particular, dipolar cycloaddition of nitrones as 1,3-dipoles to carbon–carbon double bonds of different alkenes allows access to a variety of isoxazolidines. These cycloadducts attracted considerable attention due to their potential biological activities of isoxazolidines.[1,2] Isoxazolidines have also been used as precursors to β-amino alcohols through reductive cleavage of the N–O bond, which are potential precursors for the synthesis of such natural products as β-lactam antibiotics and alkaloids.[3] One of the major limitations of 1,3-dipolar cycloaddition with nitrones is low reactivity of simple alkene dipolarophiles. However, methylenecyclopropanes and bicyclopropylidenes containing activated carbon–carbon double bonds, undergo similar cycloaddition with the formation of the mixture of 4- and 5-spirocyclopropane isoxazolidines.[4–10] Earlier, we found that substitution of the three-membered ring of cyclopropenes and methylenecyclopropanes by an electron-acceptor group can change the reaction activity of these strained compounds in the dipolar cycloadditions with carbonyl ylides and nitrones.[10–12] In particular, substitution of the cyclopropane ring in methylenecyclopropane by two acceptor ester groups RO_2C– at the 1,2-positions changes the regioselectivity of the nitrone cycloaddition so that the 4-spiroisomer can be obtained exclusively.[10] Inspired by such high stereoselectivity, we decided to investigate the reaction of *C*-aryl and *C*-amido nitrones with dimethyl 2-benzylidenecyclopropane-1,1-dicarboxylate, containing two acceptor groups in 1,1-position. Note, the parent 2-benzylidenecyclopropane in the reaction with cyclic nitrone affords a mixture of isomers.[13]

2. Results and discussion

Starting dimethyl 2-benzylidenecyclopropane-1,1-dicarboxylate **1** is easily accessible via dirhodium(II) acetate catalyzed decomposition of esters of diazomalonic acid in the presence of phenylpropadiene in mild conditions with excellent selectivity.[14] In the initial experiments, ester **1** was heated in toluene at 110 °C for 24–80 h in the presence of slight excess (1.1 equiv) of *N*-methyl or *N*-phenyl *C*-aryl nitrones **2a**–**e**. Separation of the crude mixtures on silica gel and subsequent crystallization gave pure samples of isoxazolidines **3a**–**e** as a single isomer in yields of 56–68% (Table 1).

Amidonitrones represent attractive 1,3-dipoles since products of the dipolar cycloaddition of amidonitrones have an additional amido group, which can be further functionalized to give a number of derivatives of aminoacids.[15–18] Unfortunately, there is only one example of the cycloaddition of such nitrones with 2,2-dimethylmethylenecyclopropane proceeding with the formation of 5-spirocyclopropyl isoxazolidine.[19] We found that only 4-isomeric isoxazolidines are formed in the 1,3-dipolar cycloaddition of methylenecyclopropanedicarboxylate **1** with amidonitrones **4a**–**e** as a single isomer (Table 2). Reactions with amidonitrones in this case require significantly shorter reaction times (4 h) compared

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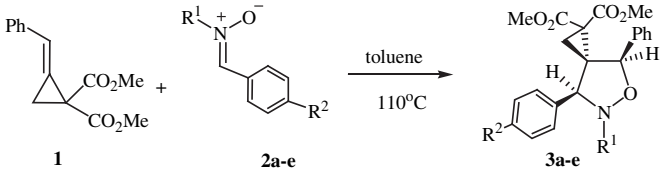
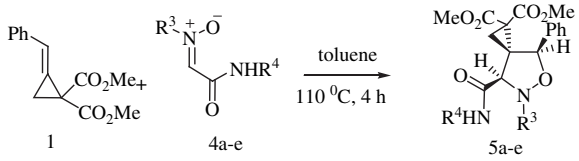
Table 1
Reactions of cyclopropane-1,1-dicarboxylate **1** with nitrones **2a**–**e**



1 2a-e 3a-e

Nitrone	R^1	R^2	Time, h	Isolated yield (%)
2a	Ph	H	27	**3a**/68
2b	Ph	Cl	24	**3b**/68
2c	Ph	MeO	27	**3c**/66
2d	Me	H	72	**3d**/56
2e	Me	Cl	80	**3e**/58

Table 2
Reactions of benzylidenecyclopropane-1,1-dicarboxylate **1** with nitrones **4a**–**e**



1 4a-e 5a-e

Nitrone	R^3	R^4	Isolated yield (%)
4a	Ph	Ph	**5a**/85
4b	4-Me–C_6H_4	Ph	**5b**/88
4c	4-$MeOC_6H_4$	Ph	**5c**/80
4d	4-Me–C_6H_4	4-$MeOC_6H_4$	5**d**/89
4e	Me	Ph	5**e**/83

with nitrones **2a**–**e** and give better yields of cycloadducts of up to 89%. Note, the structure of amidonitrones was not unequivocally determined in the previous studies.[15] In this paper, *Z*-configuration of amidonitrones has been established by NOESY ^1H–^1H spectrum of amidonitrone **4b** based on the presence of a cross-signal between the methine proton of the double bond of the nitrone system and the *ortho*-protons of the aromatic ring (Fig. 1).

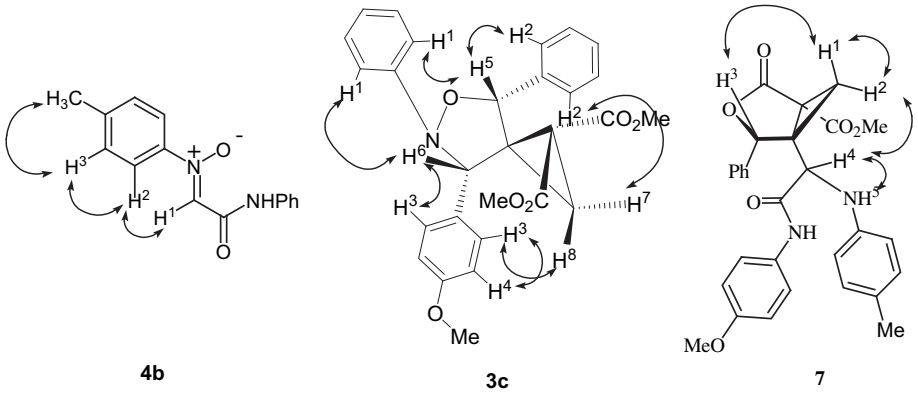
The structure of products **3a**–**e** and **5a**–**e** was established on the basis of their spectral data. Thus, ^1H NMR spectrum of **3a** contains two doublet signals of the cyclopropane ring at 1.22 and 1.50 ppm with the coupling constant of 6.5 Hz, two signals of ester methyl groups at 3.66 and 3.67 ppm. The signals of the methine protons C^3H and C^5H appear as singlets at 5.25 and 5.42 ppm, respectively. This is consistent with their 3,5-disposition in the isoxazolidine ring, otherwise these protons would have nonzero coupling constants. The relative configuration of the products was established on the basis of ^1H–^1H NOESY NMR of the compound **3c** (Fig. 1). In its spectrum cycloadduct **3c** exhibits interactions between the protons H^1 of the *N*-phenyl ring with both methine protons of the isoxazolidine ring H^5 and H^6 indicating their dislocation on the same side of the isoxazolidine ring. In addition, interactions between *o*-protons of the aromatic ring in the position 5 of the isoxazolidine with one proton of the cyclopropane ring, and interactions between *o*-protons of the aromatic ring in the position 3 of the isoxazolidine with the other proton of the cyclopropane ring further confirms the stereochemistry of the product **3c**. On the other hand, in the alternative structure interactions between protons of the cyclopropane ring H^7 and H^8 with protons of isoxazolidine ring H^5 and H^6 should be observed.

Signals of the possible alternative isomeric cycloadducts could not be found in the ^1H NMR spectra of crude reaction mixtures of the dipolar cycloaddition between dimethyl ester **1** and nitrones **2a**–**e** and **4a**–**e**. Such high regio- and stereo-selectivity with the formation of only one isomer suggests the approach of a nitrone dipole from the least hindered side of the cyclopropane ring (Scheme 1, path A). The unfavorable steric interactions between the methoxycarbonyl group of the cyclopropane ring and aryl substituent Ar of nitrones can occur in the alternative transition state (Scheme 1, path B).

It is noteworthy, that in the presence of Lewis acids the same benzylidenecyclopropanedicarboxylate **1** and nitrones **2a**–**e** give the products of [3+3] cycloaddition with ring opening of the three-membered ring.[20] Whereas in our studies, in the absence of any Lewis acids, the reaction proceed, as a normal 1,3-dipolar cycloaddition with retention of the cyclopropane ring.

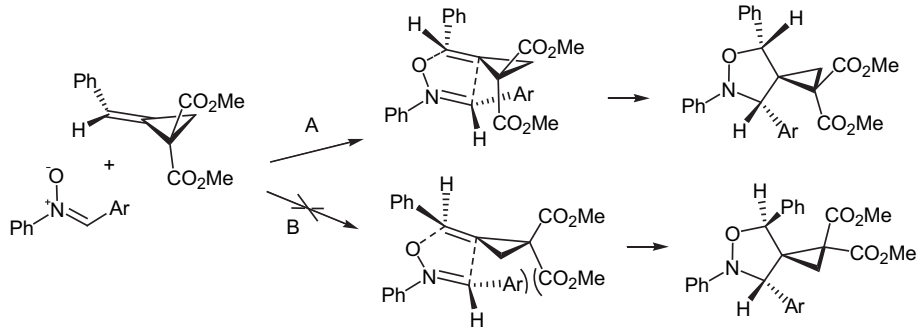
Cleavage of the N–O bond is the most synthetically useful reaction for the modification of the obtained cycloadducts, which can be done by a variety of methods, including hydrogenation over Raney Ni, Pd/C, or $Pd(OH)_2$[21–25], reaction with Zn/H^+[21,22,29], $Mo(CO)_6/H_2O$[26], $Zn/Cu(OAc)_2/AcOH$,[27] and SmI_2.[28] As an illustration, in our studies, the reactions of adducts **3a** and **5d** with activated Zn-dust/AcOH have resulted in smooth N–O bond cleavage with subsequent cyclization to form lactones **6** and **7** in good isolated yields (~60–70%).

The structure of obtained compounds **6** and **7** was established from the spectral data. Thus, ^1H NMR spectra of these compounds contain two doublet signals of protons of the cyclopropane fragment at 1.69–2.19 ppm, the singlet of CH-group in the region 5.68–5.69 ppm, characteristic doublet signals of protons attached to C–NHAr in the region 4.11–4.57 ppm and doublet signals of NH protons at 4.40–5.53 ppm. The IR spectra contain bands of an amino group at 3440 cm^{-1}, lactone group at 1800 cm^{-1}, and carbonyl groups at 1740 cm^{-1}. The relative configuration of the lactone **7** was established on the basis of ^1H–^1H NOESY NMR spectrum of the compound **7** (Fig. 1). In its spectrum lactone **7** exhibits

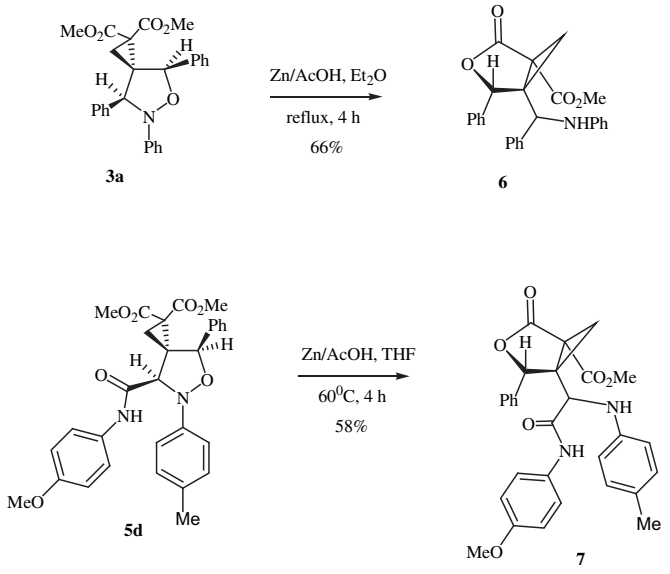


4b 3c 7

Fig. 1. Nitrone **4b**, cycloadduct **3c** and lactone **7** with main NOE interactions in the NOESY spectrum.



Scheme 1. Possible reaction pathways for the reaction of nitrones with benzylidenecyclopropanedicarboxylate **1**.



interactions between the proton of the cyclopropane ring H^1 with methine protons of the lactone ring H^3 indicating their dislocation on the same side of the lactone ring. On the other hand, interactions between protons of the cyclopropane ring H^1 or H^2 with protons of phenyl group should be observed in the alternative structure.

3. Conclusion

In summary, we have demonstrated that the reaction between dimethyl 2-benzylidenecyclopropanedicarboxylate **1** and a number of *C*-aryl nitrones **2a**–**e** and *C*-amido nitrones **4a**–**e** in the absence of Lewis acid proceeds as a 1,3-dipolar cycloaddition with the formation of 4-spirocyclopropylisoxazolidines as a single isomer with high yields. Transformations of the obtained isoxazolidine cycloadducts are currently being investigated in our laboratory as an approach to various β-amino alcohols and other related products.

4. Experimental section

4.1. General remarks

All reactions were performed in anhydrous solvents under an argon atmosphere. Toluene was distilled from Na metal/benzophenone. Dimethyl 2-benzylidenecyclopropane-1,1-dicarboxylate and nitrones were prepared following known procedures.[14,15,30] Reaction progress was monitored using thin layer chromatography (TLC) on precoated Silufol UV-254 plates. The IR spectra were measured on a UR-20 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker DPX-300 spectrometer.

4.2. General procedure

The mixture of methylenecyclopropanedicarboxylate **1** and the corresponding nitrone **2a**–**e**, **4a**–**e** (1.1 equiv) was heated at reflux in dry toluene (conditions: Table 1 or Table 2). The solvent was removed under reduced pressure, and the products were isolated by chromatography of the residue on silica gel eluting with a petroleum ether/ethyl acetate mixture followed by crystallization from ethanol or petroleum ether.

*4.2.1. Dimethyl 4,6,7-triphenyl-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate **3a**.* Compound **3a** was obtained from 492 mg (2 mmol) of compound **1** and 433 mg (2.2 mmol) of nitrone **2a**. Yield 602 mg (68%), white solid, mp 122–123 °C; [found: C, 72.78; H, 5.61; N, 2.94. $C_{27}H_{25}NO_5$ requires C, 73.12; H, 5.68; N, 3.16%]; R_f (25% EtOAc/hexane) 0.41; ν_{max} ($CHCl_3$) 3070, 2960, 1730, 1605, 1500, 1270, 1130 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.68 (2H, d, *J* 7.3 Hz, Ph), 7.45–7.41 (2H, m, Ph), 7.35–7.31 (8H, m, Ph), 7.13 (2H, d, *J* 8.0 Hz, Ph), 7.02 (1H, t, *J* 7.3 Hz, Ph), 5.42 (1H, s, OCH), 5.25 (1H, s, NCH), 3.77 (3H, s, OMe), 3.63 (3H, s, OMe), 1.50 (1H, d, *J* 6.5 Hz, CH_2), 1.22 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.6 (CO), 167.7 (CO), 150.1 (C), 140.0 (C), 136.7 (C), 130.0 (CH), 129.3 (CH), 129.1 (CH), 128.8 (2CH), 128.7 (CH), 128.0 (CH), 122.7 (CH), 115.5 (CH), 82.3 (CH), 70.8 (CH), 53.3 (CH_3), 52.9 (CH_3), 52.3 (C), 38.4 (C), 23.0 (CH_2).

*4.2.2. Dimethyl 7-(4-chlorophenyl)-4,6-diphenyl-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate **3b**.* Compound **3b** was obtained from 492 mg (2 mmol) of compound **1** and 509 mg (2.2 mmol) of nitrone **2b**. Yield 650 mg (68%), white solid, mp 143–144 °C; [found: C, 67.70; H, 5.07; N, 2.81. $C_{27}H_{24}NClO_5$ requires C, 67.85; H, 5.06; N, 2.93%]; R_f (25% EtOAc/hexane) 0.41; ν_{max} ($CHCl_3$) 3060, 2960, 1730, 1600, 1510, 1495, 1440, 1265, 1115 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.66 (2H, d, *J* 8.7 Hz, Ar), 7.41 (2H, d, *J* 8.7 Hz, Ar), 7.36–7.32 (5H, m, Ar), 7.24–7.21 (2H, m, Ar), 7.11 (2H, d, *J* 8.0 Hz, Ar), 7.03 (1H, t, *J* 7.3 Hz, Ar), 5.40 (1H, s, OCH), 5.27 (1H, s, NCH), 3.78 (3H, s, OMe), 3.61 (3H, s, OMe), 1.45 (1H, d, *J* 6.5 Hz, CH_2), 1.21 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.8 (CO), 167.4 (CO), 149.8 (C), 138.7 (C), 136.2 (C), 133.8 (C), 130.1 (CH), 129.9 (CH), 129.4 (CH), 129.3 (CH), 129.0 (CH), 128.9 (CH), 122.9 (CH), 115.4 (CH), 82.4 (CH), 70.0 (CH), 53.4 (CH_3), 52.9 (CH_3), 52.1 (C), 38.3 (C), 23.0 (CH_2).

*4.2.3. Dimethyl 7-(4-methoxyphenyl)-4,6-diphenyl-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate **3c**.* Compound **3c** was obtained from 246 mg (1 mmol) of compound **1** and 250 mg (1.1 mmol) of nitrone **2c**. Yield 312 mg (66%), white solid, mp 110–111 °C; [found: C, 70.94; H, 5.76; N, 2.75. $C_{28}H_{27}NO_6$ requires C, 71.02; H, 5.75; N,

2.96%]; R_f (25% EtOAc/hexane) 0.31; ν_{max} ($CHCl_3$) 3050, 2960, 1730, 1610, 1540, 1460, 1280, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (2H, d, *J* 8.7 Hz, Ar), 7.38–7.21 (7H, m, Ar), 7.11 (2H, d, *J* 7.2 Hz, Ar), 7.01 (1H, t, *J* 7.3 Hz, Ar), 6.96 (2H, d, *J* 8.7 Hz, Ar), 5.42 (1H, s, OCH), 5.15 (1H, s, NCH), 3.86 (3H, s, OMe), 3.78 (3H, s, OMe), 3.64 (3H, s, OMe), 1.46 (1H, d, *J* 6.5 Hz, CH_2), 1.23 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.4 (CO), 167.8 (CO), 159.3 (C), 150.0 (C), 137.0 (C), 131.8 (CH), 130.0 (CH), 129.8 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 122.7 (CH), 115.7 (CH), 114.1 (CH), 82.1 (CH), 70.6 (CH), 55.6 (CH_3), 53.4 (CH_3), 52.9 (CH_3), 52.1 (C), 38.3 (C), 23.0 (CH_2).

4.2.4. Dimethyl 6-methyl-4,7-diphenyl-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate ***3d****.* Compound **3d** was obtained from 492 mg (2 mmol) of compound **1** and 297 mg (2.2 mmol) of nitrone **2d**. Yield 427 mg (56%), white solid, mp 125–126 °C; [found: C, 69.31; H, 6.11; N, 3.66. $C_{22}H_{23}NO_5$ requires C, 69.28; H, 6.08; N, 3.67%]; R_f (25% EtOAc/hexane) 0.37; ν_{max} ($CHCl_3$) 3065, 2960, 1740, 1525, 1460, 1270, 1120 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.57 (2H, d, *J* 7.3 Hz, Ar), 7.40–7.30 (8H, m, Ar), 5.32 (1H, s, OCH), 4.13 (1H, s, NCH), 3.80 (3H, s, OMe), 3.72 (3H, s, OMe), 2.80 (3H, s, NMe), 1.34 (1H, d, *J* 6.5 Hz, CH_2), 1.24 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 168.9 (CO), 168.1 (CO), 140.2 (C), 137.5 (C), 129.8 (CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 81.3 (CH), 75.0 (CH), 53.2 (CH_3), 53.0 (CH_3), 51.6 (C), 44.1 (CH_3), 38.1 (C), 23.2 (CH_2).

4.2.5. Dimethyl 7-(4-chlorophenyl)-6-methyl-4-phenyl-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate ***3e****.* Compound **3e** was obtained from 246 mg (1 mmol) of compound **1** and 186 mg (1.1 mmol) of nitrone **1e**. Yield 240 mg (58%), white solid, mp 112–113 °C; [found: C, 63.55; H, 5.41; N, 3.16. $C_{22}H_{22}NClO_5$ requires C, 63.54; H, 5.33; N, 3.37%]; R_f (25% EtOAc/hexane) 0.36; ν_{max} ($CHCl_3$) 3050, 1730, 1540, 1460, 1270, 1110 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.50–7.30 (9H, m, Ar), 5.31 (1H, s, OCH), 4.17 (1H, s, NCH), 3.80 (3H, s, OMe), 3.76 (3H, s, OMe), 2.83 (3H, s, NMe), 1.34 (1H, d, *J* 6.2 Hz, CH_2), 1.23 (1H, d, *J* 6.2 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 168.5 (CO), 168.5 (CO), 139.3 (CH), 136.8 (CH), 134.2 (CH), 130.9 (CH), 129.2 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 81.3 (CH), 73.8 (CH), 53.3 (CH_3), 53.2 (CH_3), 51.4 (C), 44.2 (CH_3), 38.2 (C), 23.0 (CH_2).

4.2.6. Dimethyl 4,6-diphenyl-7-(N-phenylcarbamoyl)-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate ***5a****.* Compound **5a** was obtained from 246 mg (1 mmol) of compound **1** and 264 mg (1.1 mmol) of nitrone **4a**. Yield 410 mg (85%), white solid, mp 121–122 °C; [found: C, 69.21; H, 5.43; N, 5.72. $C_{28}H_{26}N_2O_6$ requires C, 69.12; H, 5.39; N, 5.76%]; R_f (25% EtOAc/hexane) 0.30; ν_{max} ($CHCl_3$) 3350, 3050, 1730, 1695, 1600, 1540, 1450, 1300, 1120, 965 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.23 (1H, s, N*H*Ar), 7.66 (2H, d, *J* 7.3 Hz, Ar), 7.45–7.12 (13H, m, Ar), 5.22 (1H, s, CH), 5.20 (1H, s, CH), 3.72 (3H, s, OMe), 3.61 (3H, s, OMe), 2.64 (1H, d, *J* 6.5 Hz, CH_2), 1.37 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.3 (CO), 167.8 (CO), 167.5 (CO), 148.4 (C), 137.7 (C), 136.2 (C), 129.6 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 125.0 (CH), 124.0 (CH), 120.4 (CH), 115.6 (CH), 82.8 (CH), 68.3 (CH), 53.3 (CH_3), 53.0 (CH_3), 48.5 (C), 37.0 (C), 20.7 (CH_2).

4.2.7. Dimethyl 6-(4-methylphenyl)-4-phenyl-7-(N-phenylcarbamoyl)-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate ***5b****.* Compound **5b** was obtained from 246 mg (1 mmol) of compound **1** and 280 mg (1.1 mmol) of nitrone **4b**. Yield 440 mg (88%), white solid, mp 131–132 °C; [found: C, 69.55; H, 5.64; N, 5.62. $C_{29}H_{28}N_2O_6$ requires C, 69.59; H, 5.64; N, 5.60%]; R_f (25% EtOAc/hexane) 0.31; ν_{max} ($CHCl_3$) 3350, 3030, 2960, 1750, 1725, 1685, 1600, 1540, 1505, 1440, 1360, 1300, 1260, 1170, 1115 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.26 (1H, s, N*H*Ar), 7.66 (2H, d, *J* 8.0 Hz, Ar), 7.42–7.16 (10H, m, Ar), 7.11 (2H, d, *J* 8.0 Hz, Ar), 5.20 (1H, s, CH), 5.16 (1H, s, CH), 3.74 (3H, s, OMe), 3.61 (3H, s, OMe), 2.65 (1H, d, *J* 6.5 Hz, CH_2), 2.38 (3H, s, C_6H_4*Me*), 1.35 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.2 (CO), 167.9 (CO), 167.6 (CO), 145.9 (C), 137.7 (C), 136.2 (C), 133.5 (C), 130.1 (CH), 129.5 (CH), 129.3 (CH), 129.1 (CH), 125.0 (CH), 120.4 (CH), 115.8 (CH), 82.8 (CH), 68.3 (CH), 53.3 (CH_3), 53.0 (CH_3), 48.5 (C), 37.0 (C), 21.1 (CH_3), 20.8 (CH_2).

4.2.8. Dimethyl 6-(4-methoxyphenyl)-4-phenyl-7-(N-phenylcarbamoyl)-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate ***5c****.* Compound **5c** was obtained from 246 mg (1 mmol) of compound **1** and 297 mg (1.1 mmol) of nitrone **4c**. Yield 410 mg (80%), white solid, mp 162–164 °C; [found: C, 67.45; H, 5.45; N, 5.46. $C_{29}H_{28}N_2O_7$ requires C, 67.43; H, 5.46; N, 5.42%]; R_f (25% EtOAc/hexane) 0.19; ν_{max} ($CHCl_3$) 3350, 3030, 2960, 1750, 1725, 1685, 1600, 1535, 1505, 1440, 1300, 1260, 1180, 1115, 1040 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.26 (1H, s, N*H*Ar), 7.64 (2H, d, *J* 8.0 Hz, Ar), 7.39–7.13 (10H, m, Ar), 6.92 (2H, d, *J* 8.7 Hz, Ar), 5.15 (1H, s, CH), 5.13 (1H, s, CH), 3.83 (3H, s, C_6H_4O*Me*), 3.73 (3H, s, OMe), 3.61 (3H, s, OMe), 2.62 (1H, d, *J* 6.5 Hz, CH_2), 1.33 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.2 (CO), 167.8 (CO), 167.6 (CO), 156.7 (C), 141.6 (C), 137.7 (C), 136.2 (C), 129.5 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 125.0 (CH), 120.4 (CH), 117.7 (CH), 114.8 (CH), 82.7 (CH), 68.2 (CH), 55.9 (CH_3), 53.3 (CH_3), 53.0 (CH_3), 48.5 (C), 37.0 (C), 20.8 (CH_2).

4.2.9. Dimethyl 6-(4-methylphenyl)-4-phenyl-7-(N-(4-methoxyphenyl)carbamoyl)-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate ***5d****.* Compound **5d** was obtained from 246 mg (1 mmol) of compound **1** and 312 mg (1.1 mmol) of nitrone **4d**. Yield 470 mg (89%), white solid, mp 147 °C; [found: C, 67.87; H, 5.67; N, 5.28. $C_{30}H_{30}N_2O_7$ requires C, 67.91; H, 5.70; N, 5.28%]; R_f (33% EtOAc/hexane) 0.45; ν_{max} ($CHCl_3$) 3383, 1730, 1683, 1594, 1510, 1245, 1112 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.14 (1H, s, N*H*Ar), 7.56 (2H, d, *J* 8.7 Hz, Ar), 7.34–7.25 (5H, m, Ar), 7.19 (2H, d, *J* 8.7 Hz, Ar), 7.10 (2H, d, *J* 8.7 Hz, Ar), 6.92 (2H, d, *J* 8.7 Hz, Ar), 5.20 (1H, s, CH), 5.13 (1H, s, CH), 3.83 (3H, s, C_6H_4O*Me*), 3.73 (3H, s, OMe), 3.61 (3H, s, OMe), 2.66 (1H, d, *J* 6.5 Hz, CH_2), 2.37 (3H, s, C_6H_4*Me*), 1.34 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.2 (CO), 167.9 (CO), 167.3 (CO), 157.0 (C), 146.0 (C), 136.4 (C), 133.5 (C), 130.9 (CH), 130.1 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 122.1 (CH), 115.8 (CH), 114.6 (CH), 82.8 (CH), 68.2 (CH), 55.9 (CH_3), 53.3 (CH_3), 52.9 (CH_3), 48.6 (C), 37.1 (C), 21.1 (CH_3), 20.8 (CH_2).

4.2.10. Dimethyl 6-methyl-4-phenyl-7-(N-phenylcarbamoyl)-5-oxa-6-azaspiro[2.4]heptane-1,1-dicarboxylate ***5e****.* Compound **5e** was obtained from 246 mg (1 mmol) of compound **1** and 196 mg (1.1 mmol) of nitrone **4e**. Yield 350 mg (83%), white solid, mp 127–128 °C; [found: C, 65.10; H, 5.68; N, 6.49. $C_{23}H_{24}N_2O_6$ requires C, 65.08; H, 5.70; N, 6.60%]; R_f (25% EtOAc/hexane) 0.19; ν_{max} ($CHCl_3$) 3325, 1717, 1675, 1588, 1513, 1430, 1244 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.34 (1H, s, C(O)N*H*Ar), 7.63 (2H, d, *J* 8.0 Hz, Ar), 7.40–7.35 (2H, m, Ar), 7.30–7.27 (3H, m, Ar), 7.20–7.14 (3H, m, Ar), 5.18 (1H, s, CH), 4.18 (1H, s, CH), 3.84 (3H, s, OMe), 3.83 (3H, s, OMe), 3.03 (3H, s, NMe), 2.69 (1H, d, *J* 6.5 Hz, CH_2), 1.34 (1H, d, *J* 6.5 Hz, CH_2); δ_C (75 MHz, $CDCl_3$) 169.0 (CO), 168.3 (CO), 167.7 (CO), 137.8 (C), 136.9 (C), 129.4 (CH), 129.2 (CH), 129.0 (CH), 124.9 (CH), 120.3 (CH), 82.1 (CH), 69.9 (CH), 53.4 (CH_3), 53.3 (CH_3), 47.7 (C), 43.8 (C), 37.9 (C), 20.1 (CH_2).

4.2.10.1. Reductive cleavage of isoxazolidines with Zn. To a solution of isoxazolidine (0.5 mmol) in Et_2O or THF (20 mL/mmol) kept in an ice bath were added glacial acetic acid (2.93 mL/mmol) and activated Zn dust (20 equiv). The suspension was allowed to reach reflux in Et_2O (or at 60 °C in THF) and was stirred vigorously for 4 h. The solids were filtered off and the filtrate was neutralized with 2 M NaOH under cooling. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were concentrated in a vacuum and the residue was purified by column chromatography on silica gel eluting with a petroleum ether/ethyl acetate mixture.

4.2.11. Methyl 2-oxo-4-phenyl-5-[phenyl(phenylamino)methyl]-3-oxabicyclo[3.1.0]hexane-1-carboxylate ***6****.* Yield 135 mg (66%), white solid, mp 78–79 °C; [found: C, 75.49; H, 5.84; N, 3.42. $C_{26}H_{23}NO_4$ requires C, 75.53; H, 5.61; N, 3.39%]; R_f (33% EtOAc/hexane) 0.45; ν_{max} ($CHCl_3$) 3440, 3060, 2970, 1795, 1740, 1615, 1520, 1460, 1330, 1100 cm^{-1}; δ_H (300 MHz, acetone-d_6) 7.45–7.35 (5H, m, Ar), 7.28–7.18 (5H, m, Ar), 6.89 (2H, t, *J* 8.0, Ar), 6.49 (1H, t, *J* 7.3, Ar), 6.21 (2H, d, *J* 8.0 Hz, Ar), 5.69 (1H, s, OC*H*Ph), 5.53 (1H, d, *J* 9.5 Hz, N*H*CHPh), 4.57 (1H, d, *J* 9.5 Hz, NHC*H*Ph), 3.36 (3H, s, OMe), 2.19 (1H, d, *J* 5.8 Hz, CH_2), 1.69 (1H, d, *J* 5.8 Hz, CH_2); δ_C (75 MHz, acetone-d_6) 172.2 (CO), 164.5 (CO), 147.0 (C), 137.7 (C), 137.2 (C), 129.7 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.9 (CH), 117.7 (CH), 113.6 (CH), 84.2 (CH), 55.9 (CH), 52.7 (CH_3), 46.0 (C), 36.0 (C), 19.2 (CH_2).

4.2.12. Methyl 5-[(4-methoxyphenylcarbamoyl)-(4-tolylamino) methyl]-2-oxo-4-phenyl-3-oxabicyclo[3.1.0]hexane-1-carboxylate ***7****.* Yield 145 mg (58%), white solid, mp 159–161 °C; [found: C, 69.60; H, 5.66; N, 5.66. $C_{29}H_{28}N_2O_6$ requires C, 69.59; H, 5.64; N, 5.60%]; R_f (33% EtOAc/hexane) 0.29; ν_{max} ($CHCl_3$) 3415, 3360, 3050, 2960, 1800, 1740, 1695, 1615, 1530, 1460, 1315, 1270, 1100 cm^{-1}; δ_H (300 MHz, acetone-d_6) 9.07 (1H, s, C(O)N*H*Ar), 7.45–7.42 (7H, m, Ar), 6.87–6.82 (4H, m, Ar), 6.31 (2H, d, *J* 8.0 Hz, Ar), 5.68 (1H, s, OC*H*Ph), 4.40 (1H, d, *J* 9.5 Hz, N*H*CHC=O), 4.11 (1H, d, *J* 9.5 Hz, NHC*H*C=O), 3.75 (3H, s, C_6H_4O*Me*), 3.44 (3H, s, OMe), 2.42 (1H, d, *J* 5.8 Hz, CH_2), 2.13 (3H, s, C_6H_4*Me*), 1.76 (1H, d, *J* 5.8 Hz, CH_2); δ_C (75 MHz, acetone-d_6) 171.4 (CO), 167.7 (CO), 165.5 (CO), 156.8 (C), 144.5 (C), 137.0 (C), 131.7 (C), 129.9 (CH), 129.7 (CH), 129.2 (CH), 128.0 (CH), 121.9 (CH), 114.4 (CH), 114.0 (CH), 83.1 (CH), 58.5 (CH_3), 55.1 (CH), 52.8 (CH_3), 44.5 (C), 35.2 (C), 22.8 (CH_2), 19.9 (CH_3).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.02.013. These data include MOL files and InChiKeys of the most important compounds described in this article.

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