Tetrahedron 64 (2008) 10521–10530

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Exploiting microwave-assisted neat procedures: synthesis of *N*-aryl and *N*-alkylnitrones and their cycloaddition en route for isoxazolidines

Marta M. Andrade *, Maria Teresa Barros *, Rui C. Pinto

REQUIMTE, CQFB, Departamento de Química, Faculdade de Ciências e Tecnologia, Universidade Nova de Lisboa, 2829-516 Caparica, Portugal

ARTICLE INFO

Article history:
Received 8 April 2008
Received in revised form 16 August 2008
Accepted 29 August 2008
Available online 10 September 2008

Keywords:
Microwave
Neat reactions
Nitrone
1,3-Dipolar cycloaddition
PBN

ABSTRACT

Microwave irradiation allows increasing the speed of several reactions and also offers the possibility of eliminating poisoning organic solvents. In this work we report the microwave-assisted neat synthesis of α-phenyl-*tert*-butylnitrone (PBN) and other alkyl and aryl nitrones and also the rapid synthesis of isoxazolidines resulting from 1,3-dipolar cycloaddition of nitrones to ethyl *trans*-crotonate.

1. Introduction

Microwave (MW) radiation has gained the attention of chemists during the last decades due to its unique advantages, such as shorter reaction times, cleaner reactions, higher yields and better selectivities, being a valuable alternative to accomplish more efficient syntheses.[1–4] MW technology has attained an importance, especially when combined with neat procedures. Avoiding organic solvents during reactions in organic synthesis[5] leads to a clean, efficient and economical technology; safety is largely increased, work-up is considerably simplified, cost is reduced and the reactivities and sometimes selectivities are enhanced.[6] In other words, the absence of solvents coupled with the high yields and short reaction times often associated with MW reactions make these procedures very attractive. Although there are several studies on MW-assisted neat reactions,[7–10] we have noticed that relatively little attention has been given to neat reactions in the absence of a catalyst or a solid support.[11–14]

Nitrones were recognized in the late 60s as spin trapping agents and the most studied one is undoubtedly α-phenyl-*N*-*tert*-butylnitrone (PBN, Fig. 1) (and its derivatives), due to recognized neuroprotective properties.[15–17] Nitrones can be synthesized directly from the corresponding nitro compound and an aldehyde, via in situ reduction with Zn/NH_4Cl followed by acidification[18,19] or in a two-step procedure, in which the hydroxylamine obtained by reduction of the nitro-compound is isolated and later reacts with the aldehyde.[20,21]

Due to the instability of most hydroxylamines, the first procedure is usually preferred. However, as *N*-methylhydroxylamine and *N*-*tert*-butylhydroxylamine are stable as their hydrochloride salts, the second procedure can be applied for these compounds and we have developed a novel methodology for the synthesis of the corresponding nitrones under microwave irradiation in neat conditions.

Among the plethora of dipoles used in 1,3-dipolar cycloaddition (1,3-DC), nitrones are certainly the most popular ones. 1,3-DC reactions play a prominent role in for the production of heteroatom-containing cycloadducts with a maximum atomic economy.[22–25] The application of MW irradiation in 1,3-DC is also very

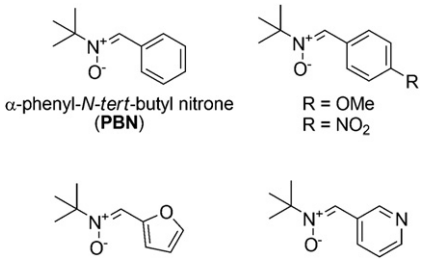


Figure 1. PBN and examples of PBN-like nitrones.

* Corresponding authors. Tel.: +351 212948300; fax: +351 212948550 (M.M.A.); tel.: +351 212948361; fax: +351 212948550 (M.T.B.).
E-mail addresses: marta.andrade@dq.fct.unl.pt (M.M. Andrade), mtbarros@dq.fct.unl.pt (M.T. Barros).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.08.101

useful to overcome the low reactivities of some dienophiles or dipoles.[26–28]

The addition of nitrones to olefinic dipolarophiles leads to isoxazolidines,[29,30] which are versatile intermediates in the synthesis of a multitude of natural compounds, such as alkaloids, amino acids and amino sugars.[22,23] Consequently, numerous methods have been reported for the construction of isoxazolidines by inter- and intramolecular nitrone cycloaddition.[29,31,32] However, many of these procedures require high temperatures and long reaction times, with poor regioselectivity and with the occurrence of other side reactions.

2. Results and discussion

Our approach is based upon 1,3-DC of open chain nitrones with unsaturated esters as dipolarophiles. With the view of analyzing the effect of different substituents on the dipole moieties for these reactions, several nitrones were synthesized and the results obtained are shown in Tables 1 and 2. By varying the type of the substituent at the nitrogen atom (tolyl, phenyl, *tert*-butyl or methyl), we have studied the stereoselectivity of the reaction. In order to study the possibility of electronic effects and, consequently, different regioselectivities, we have also introduced electron withdrawing and electron donating groups at the aromatic moiety.

Table 1
Nitrones obtained from nitrobenzene and nitrotoluene

Entry	Nitro compound	Aldehyde or R^2	Product	Yield (%)
1	**1**	H	**5a**	81
2	**1**	Cl	**5b**	81
3	**1**	NO_2	**5c**	89
4	**1**	OMe	**5d**	58
5	**1**	Furyl	**5e**	84
6	**1**	Pyridyl	**5f**	61
7	**2**	H	**5g**	49
8	**2**	Cl	**5h**	48
9	**2**	NO_2	**5i**	92
10	**2**	OMe	**5j**	58
11	**2**	Furyl	**5k**	85
12	**2**	Pyridyl	**5l**	67

2.1. Neat MW-assisted synthesis of nitrones

A synthesis of *N*-tolyl and *N*-phenyl nitrones was accomplished by applying the direct one-step procedure mentioned before (Scheme 1 and Table 1). However, for *N*-alkylnitrones, a novel microwave-assisted solventless methodology was developed (Scheme 2 and Table 2). *N*-Methyl or *N*-*tert*-butylhydroxylamine (hydrochloride salts) was mixed with sodium acetate, the aldehyde (whether solid or liquid) was added and the homogeneous or heterogeneous mixture submitted to MW irradiation for the times indicated in Table 2. With this procedure, these reactions were very fast, with no need to use a 2 equiv excess of the expensive hydroxylamines[17,33] and/or several days refluxing to obtain good yields.[17] As we have described in previous work[34] it is essential to mention that the melting in this neat reactions between two solid reactants occurs well below the melting point of the starting materials, most probably due to the formation of eutectic mixtures or, as stated by Scott et al.,[35] the reaction actually occurs in a liquid melt. As shown in Table 2, in most cases better yields were obtained when starting from the more bulky *N*-*tert*-butylhydroxylamine, probably due to its high melting point (183–184 °C) when compared to *N*-methylhydroxylamine (84–86 °C), which favours the occurrence of the eutectic mixture. In entry 3, Table 2, the complete melt of both reagents (hydroxylamine and aldehyde) was not observed and only a sticky paste was obtained. Nevertheless, the overall results in terms of costs are improved, due to a lesser waste of costly hydroxylamines.

Table 2
Nitrones synthesized from *N*-methyl and *N*-*tert*-butylhydroxylamine under MW irradiation

Entry	Hydroxylamine	Aldehyde or R^2	Power (W)	Time (min)	T_{final} (°C)	Product	Yield (%)
1	**6**	H	200	2	161	**8a**	90
2	**6**	Cl	80	6	123	**8b**	92
3	**6**	NO_2	100	2	69[a]	**8c**	86
4	**6**	OMe	100	3.5	159	**8d**	72
5	**6**	Furyl	100	2.5	128	**8e**	86
6	**6**	Pyridyl	100	4	130	**8f**	83
7	**7**	H	150	2	137	**8g**	86
8	**7**	Cl	200	2	143	**8h**	85
9	**7**	NO_2	150	5	121	**8i**	92
10	**7**	OMe	100	3	137	**8j**	91
11	**7**	Furyl	100	1.5	115	**8k**	96
12	**7**	Pyridyl	100	4	140	**8l**	97

[a] There is no complete melting in this case and a sticky paste is obtained.

Banerji et al.[33] also reported the synthesis of *C*-aryl-*N*-methylnitrones under MW irradiation; however, their strategy makes use of a chlorinated solvent and also an excess of hydroxylamine. In this sense, the method developed in our group brings an important improvement by eliminating the use of solvents. As far as we know, synthesis of PBN and PBN-like nitrones has not been described under MW-assisted neat technology. Nevertheless, most of the nitrones described here were already synthesized by distinct methodologies and they are spread in the literature over the years. With the purpose of creating an efficient library of nitrones, we have compiled their most relevant data in Section 4.

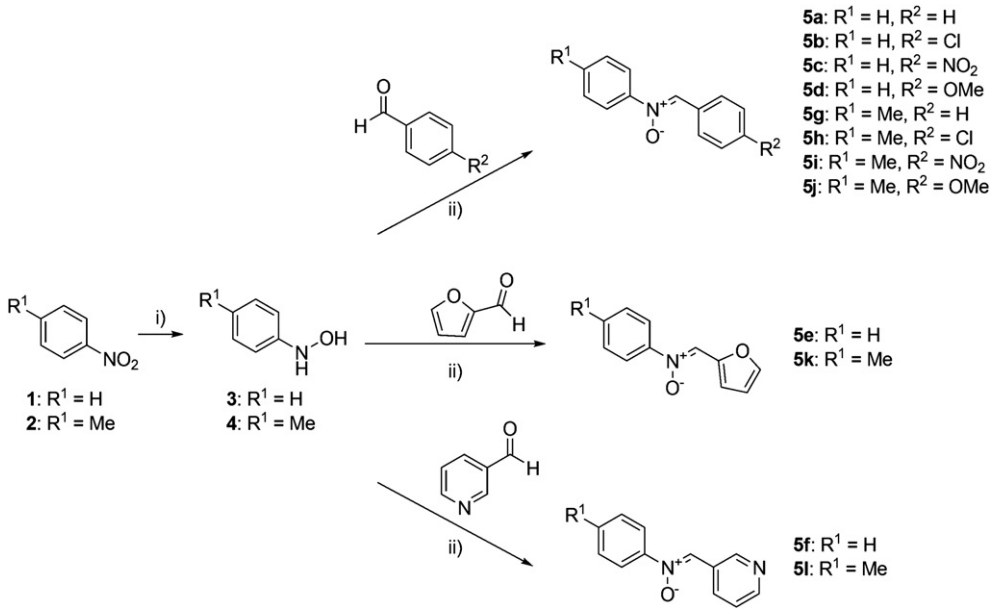
In general, our approach shows clear advantages over the techniques described so far[15–17] and should become a method of choice for this type of syntheses. The emerging area of green chemistry demands the use of alternative energy sources and alternative reaction media, in an attempt to protect human health and environment.

2.2. Neat MW-assisted 1,3-dipolar cycloaddition to nitrones

Having synthesized a library of *C*-aryl-*N*-alkyl and *C*,*N*-diarylnitrones, subsequently we have focused our studies on their 1,3-DC to ethyl *trans*-crotonate (Scheme 3). MW irradiation and the absence of solvents were again the main concern. All cycloaddition reactions were performed in a laboratory multimodal microwave apparatus, in the absence of solvents and/or catalysts. For *N*-Me and *N*-aryl nitrones, reactions were complete in 10 min, denoting an enhancement when compared to several hours in refluxing toluene[36] or dichloromethane[17] formerly reported for such reactions (Table 3).

The structures of the isoxazolidines obtained were determined by NOESY experiments (Fig. 2) and also by comparison with similar compounds described in the literature.[36]

A fast analysis of the results shows that, as expected,[36] the same regioisomer is obtained, independent of the substitution pattern at the dipole moiety. *C*,*N*-Diaryl-nitrones (**5a**–**l**) exist mainly as their *Z*-isomers due to the presence of the bulky aromatic groups and in their cycloaddition to ethyl *trans*-crotonate (entries 1–12) we always obtained a marked predominance of the isoxazolidines resulting from *endo*[37] approach of the nitrone (**9** and its enantiomer). In contrast, with *N*-methylnitrones the proportion of isomeric isoxazolidines **9** and **10** is more similar (entries 13–18) due to the possibility of *E*–*Z* interconversion of



Scheme 1. One-pot synthesis of nitrones derived from nitrobenzene (**1**) and nitrotoluene (**2**). (i) Zn, NH_4Cl, H_2O, 2 h; (ii) AcOH, 40 min.

N-Me-nitrones.[24] The presence of an electron withdrawing group (nitro or chloro) in the *para* position of the *C*-aromatic system leads to an increase in selectivity for the *endo* product, with a more well-defined effect for the nitro group (entries 3, 9 and 15). By ^{1}H NMR, traces (<0.5%) of other diastereoisomeric isoxazolidines were detected, but we never identified the presence of regioisomeric products and concluded that the cycloaddition proceeded with full regioselectivity.

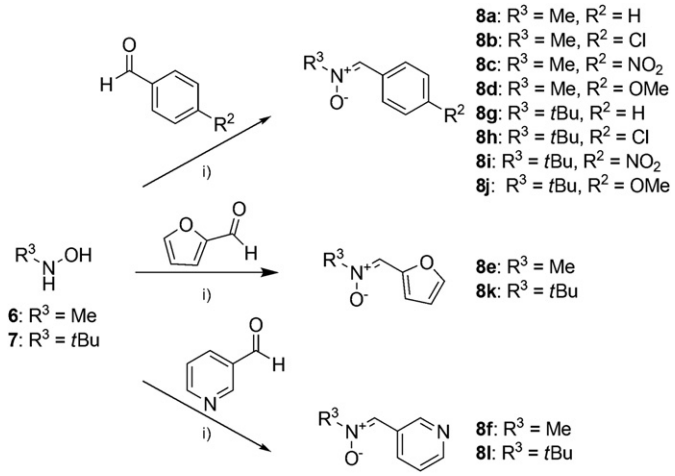
According to Banerji et al.,[36] separation of cycloadducts **9** and **10** can be achieved by column chromatography over deactivated alumina.

To the best of our knowledge, there are no reports in the literature about cycloaddition reactions to olefins with the more bulky *N*-*tert*-butylnitrone. Although all the nitrones studied have a planar geometry, the presence of a *tert*-butyl group makes the faces of the corresponding nitrones more hindered, due to the two methyl groups positioned under and above the plane of the dipole; in consequence, the approach of the dipolarophile is more difficult.

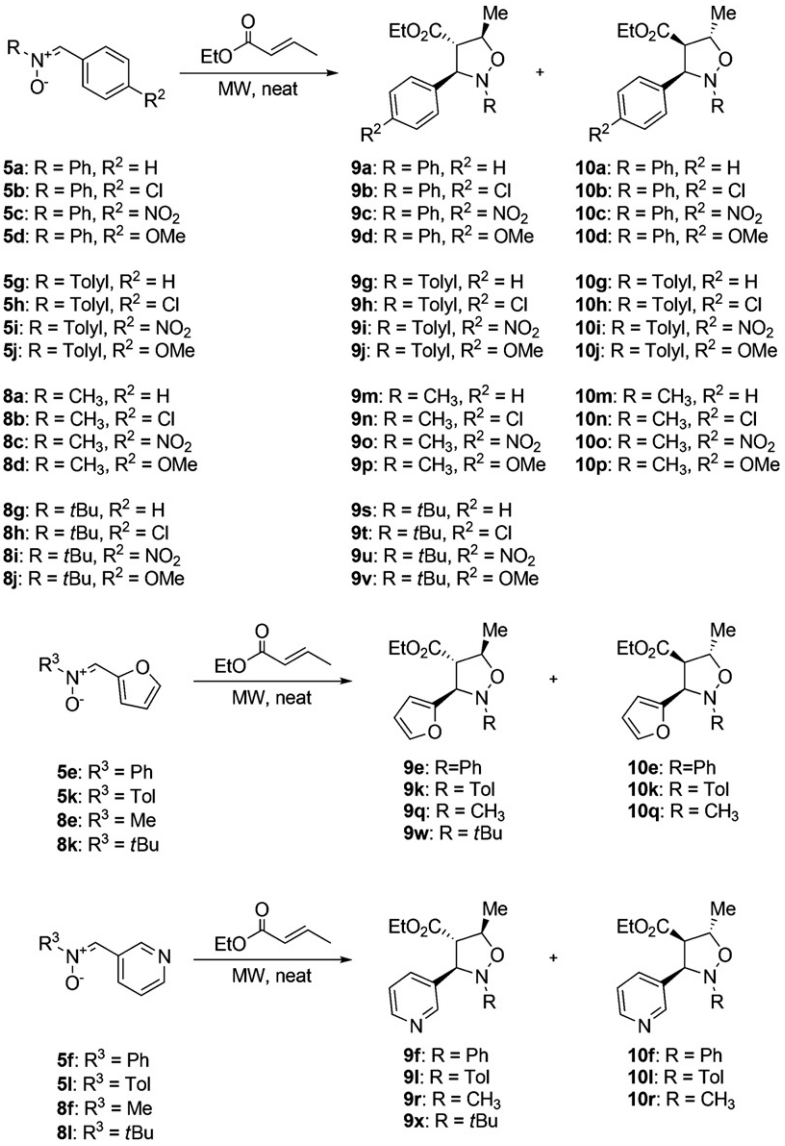
In an attempt to carry out the reaction under 'traditional' conditions (0.1 g/0.56 mmol PBN, 0.2 mL ethyl *trans*-crotonate, 5 mL toluene) we have obtained, after 42 h refluxing, 66% of product and recovered 25% of starting nitrone. Under MW irradiation, these reactions were harder to accomplish than the previous, since they required long irradiation times. We have tested different powers and reaction times in order to maximize the yield of the products and the results obtained are listed in Table 4. Several other adjustments in time/power were tested but only those conducing to interesting results are depicted in the table.

It is interesting to notice that in the cycloaddition to *tert*-butylnitrones only the enantiomeric products showing 3,4-*trans*-4,5-*trans* configuration were obtained, corresponding to *endo* approach, independent of the irradiation time. The *exo* approach is less probable with ^{t}Bu-nitrones due to the steric hindrance between the two methyl groups (one in the dipole and the other in the dipolarophile).

Another result is worthy of note in Table 4. The duration of time for which the power is applied seems to play greater influence in the yield of products than the final temperature. For example, when comparing entries 2 and 9, the final temperatures are similar but the results are completely different: a fast irradiation at 300 W provides better results than a long



Scheme 2. Microwave synthesis of nitrones starting from *N*-methyl- (**6**) or *N*-*tert*-butylhydroxylamine (**7**). (i) NaOAc, 100–200 W, 2–5 min.



Scheme 3. MW-neat synthesis of isoxazolidines (compounds **9** and **10** are racemic and only one enantiomer is depicted).

Table 3
Results obtained by MW-neat 1,3-DC with *N*-aryl and *N*-Me nitrones

Entry	Nitrone	Power (W)	Time (min)	T_{final} (°C)	Products (ratio[a])	Yield (%)[b]
1	**5a**	300	10	142	**9a**+**10a** (89:11)	91
2	**5b**	300	10	156	**9b**+**10b** (91:9)	93
3	**5c**	300	10	157	**9c**+**10c** (94:6)	82
4	**5d**	300	10	146	**9d**+**10d** (84:16)	86
5	**5e**	300	10	134	**9e**+**10e** (78:22)	79
6	**5f**	300	10	145	**9f**+**10f** (87:13)	98
7	**5g**	300	10	151	**9g**+**10g** (87:13)	95
8	**5h**	300	10	150	**9h**+**10h** (91:9)	89
9	**5i**	300	10	146	**9i**+**10i** (94:6)	81
10	**5j**	300	10	144	**9j**+**10j** (83:17)	86
11	**5k**	300	10	136	**9k**+**10k** (76:24)	86
12	**5l**	300	10	145	**9l**+**10l** (90:10)	81
13	**8a**	300	10	132	**9m**+**10m** (56:44)	89
14	**8b**	300	10	137	**9n**+**10n** (60:40)	89
15	**8c**	300	10	151	**9o**+**10o** (76:34)	90
16	**8d**	300	10	139	**9p**+**10p** (55:45)	91
17	**8e**	300	10	142	**9q**+**10q** (60:40)	75
18	**8f**	300	10	134	**9r**+**10r** (66:34)	97

[a] Ratio determined by ^{1}H NMR.
[b] Isolated yields for both isomers.

irradiation at 200 W. In general, the best results were always obtained with an irradiation time of 60 min (entries 6, 7, 11, 15, 18 and 20), corresponding to different final temperatures.

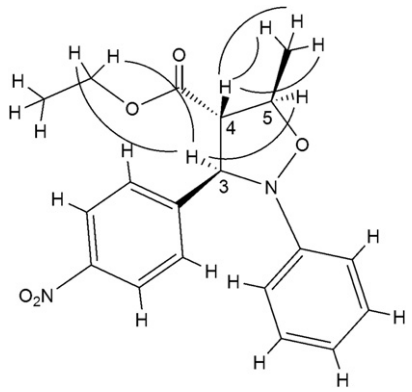


Figure 2. Selective NOESY correlations of **5c**.

Table 4
Results obtained by MW-neat 1,3-DC with *N*-^{t}Bu nitrones

Entry	Nitrone	Power (W)	Time (min)	T_{final} (°C)	Product	Yield product/nitrone recovered (%)
1	**8g**	400	30	161	**9s**	40/-
2		300	10	144		26/59
3			20	149		65/16
4			30	149		75/9
5			45	151		40/-
6		250	60	148		78/-
7		200	60	129		77/6
8			75	132		59/5
9			90	132		19/-
10	**8h**	300	30	158	**9t**	63/17
11			60	160		92/-
12	**8i**	300	30	152	**9u**	25/13
13			45	162		37/-
14			60	163		40/-
15		200	60	123		87/-
16	**8j**	300	30	150	**9v**	39/39
17			60	151		78/-
18	**8k**	300	60	148	**9w**	76/-
19		200	60	126		8/56
20	**8l**	300	60	151	**9x**	74/-

3. Conclusion

In summary, we have successfully applied microwave radiation combined with neat methodologies in the synthesis of important nitrones, such as α-phenyl-*N*-*tert*-butylnitrone (PBN), and also for the formation of new isoxazolidines, in short reaction times.

4. Experimental section

4.1. General procedures

All solvents were purified before use. *N*-Methylhydroxylamine hydrochloride and *N*-*tert*-butylhydroxylamine hydrochloride were purchased from Fluka. All reactions were monitored by thin layer chromatography, which was performed on aluminium-backed silica gel Merck 60 F_{254} plates, and compounds were detected by ultraviolet light or by staining with 10% solution of phosphomolybdic acid in ethanol, followed by heating. Flash chromatography was carried out using silica gel from Macherey-Nagel (Kieselgel 60 M). Preparative layer chromatography was performed on glass plates coated with 1 mm of silica gel (Mackerey-Nagel, Kieselgel DGF_{254}). Melting points were determined with a capillary apparatus and are uncorrected. Elemental analyses were performed on Thermo Finnigan-CE Flash EA 1112 CHNS series analyzer. NMR spectra were recorded on a Bruker AMX-400 MHz apparatus in $CDCl_3$, using TMS as internal standard, with chemical shift values (δ) in parts per million. Structural assignment of all new compounds was made by bi-dimensional NMR techniques (COSY-45, HMQC, NOESY, TOCSY). Microwave experiments were conducted in a Milestone Micro-SYNTH apparatus. Internal temperatures were measured with ATC-FO fibre-optic sensor in conjunction with Milestone immersion well.

4.2. Synthesis of nitrones[38]

4.2.1. General method for C-aryl-N-aryl nitrones

Nitrones **5a–l** were synthesized following to the procedure described in the literature,[19] starting from 1 g of the corresponding nitro compound.

*4.2.1.1. C-Phenyl-N-phenyl-nitrone (**5a**).* Yield 1.30 g, 81%, colourless needles, mp 110 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.52 (m, 6H, Ph–*H*), 7.79 (dd, *J*=1.7, *J*=7.7 Hz, 2H, Ph–*H*), 7.93 (s, 1H, C*H*), 8.39–8.42 (m, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.8, 128.7, 129.1, 129.2, 130.0, 130.7, 131.0 (11*C*–Ph), 134.6 (*C*–H), 149.2 (*C*–Ph).

*4.2.1.2. C-p-Chlorophenyl-N-phenyl-nitrone (**5b**).* Yield 1.52 g, 81%, colourless needles, mp 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.52 (m, 6H, Ph–*H*), 7.75–7.78 (m, 2H, Ph–*H*), 7.91 (s, 1H, C*H*), 8.37 (d, *J*=8.4 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.4, 128.7, 129.0, 129.9, 130.0 (10*C*–Ph), 133.2 (*C*–H), 136.1, 148.6 (2*C*–Ph).

*4.2.1.3. C-p-Nitrophenyl-N-phenyl-nitrone (**5c**).* Yield 1.75 g, 89%, yellow needles, mp 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.54 (m, 3H, Ph–*H*), 7.78–7.80 (m, 2H, Ph–*H*), 8.01 (s, 1H, C*H*), 8.32 (d, 2H, *J*=8.8 Hz, Ph–*H*), 8.56 (d, 2H, *J*=8.8 Hz, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.7, 123.9, 129.2, 129.4, 130.7 (9*C*–Ph), 132.3 (*C*–H), 136.2, 148.0, 148.9 (3*C*–Ph).

*4.2.1.4. C-p-Methoxyphenyl-N-phenyl-nitrone (**5d**).* Yield 1.07 g, 58%, colourless needles, mp 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H, CH_3), 7.00 (d, *J*=9.2 Hz, 2H, Ph–*H*), 7.44–7.50 (m, 3H, Ph–*H*), 7.78 (dd, *J*=8.1, 1.5 Hz, 2H, Ph–*H*), 7.86 (s, 1H, C*H*), 8.41 (d, *J*=8.8 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4 (OCH_3), 114.0, 121.7, 123.8, 129.1, 129.6, 131.2 (10*C*–Ph), 134.2 (*C*–H), 148.9, 161.5 (2*C*–Ph).

*4.2.1.5. C-2-Furyl-N-phenyl-nitrone (**5e**).* Yield 1.27 g, 84%, colourless needles, mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.65 (d, *J*=1.5 Hz, 1H, Fur–H), 7.43–7.52 (m, 3H, Ph–*H*), 7.59 (d, *J*=1.0 Hz, 1H, Ph–*H*), 7.75–7.84 (m, 2H, C–*H*, Ph–*H*), 8.02 (d, *J*=3.4 Hz, 1H, Fur-*H*), 8.2 (s, 1H, Fur–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.5, 116.3 (2*C*–Fur), 120.9 (2*C*–Ph), 124.1 (*C*–H), 129.0, 129.8 (3*C*–Ph), 144.5, 147.3 (2*C*–Fur).

*4.2.1.6. C-3-Pyridyl-N-phenyl-nitrone (**5f**).* Yield 0.98 g, 61%, colourless crystals, mp 114–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J*=8.0, 4.9 Hz, 1H, Pyr–*H*), 7.48–7.54 (m, 3H, Ph–*H*), 7.79 (dd, *J*=6.7, 2.7 Hz, 2H, Ph–*H*), 8.01 (s, 1H, C–*H*), 8.65 (d, *J*=3.4 Hz, 1H, Pyr–*H*), 9.12 (s, 1H, Pyr–*H*), 9.22 (d, *J*=8.1 Hz, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 121.6 (2*C*–Ph), 123.7, 127.3 (2*C*–Pyr), 129.3, 130.4 (3*C*–Ph), 131.4 (*C*–H), 134.9 (*C*–Pyr), 148.7 (*C*–Ph), 150.2, 150.8 (2*C*–Pyr).

*4.2.1.7. C-Phenyl-N-tolyl-nitrone (**5g**).* Yield 0.75 g, 49%, colourless needles, mp 125–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 7.26 (d, *J*=8.1 Hz, 2H, Ar–*H*), 7.46 (dd, *J*=5.2, 1.9 Hz, 3H, Ar–*H*), 7.66 (d, *J*=8.4 Hz, 2H, Ar–*H*), 7.90 (s, 1H, C–*H*), 8.39 (dd, *J*=7.1, 2.3 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.9 (*C*H$_3$), 121.3 (2*C*–Tol), 128.4, 128.8 (5*C*–Ph), 129.4 (2*C*–Tol), 130.6 (*C*–Ph), 133.9 (*C*–H), 140.0, 146.6 (2*C*–Tol).

*4.2.1.8. C-p-Chlorophenyl-N-tolyl-nitrone (**5h**).* Yield 0.86 g, 48%, colourless needles, mp 163–164 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 7.26 (d, *J*=8.2 Hz, 2H, Ar–*H*), 7.43 (d, *J*=8.7 Hz, 2H, Ar–*H*), 7.65 (d, *J*=8.4 Hz, 2H, Ar–*H*), 7.88 (s, 1H, C–*H*), 8.35 (d, *J*=8.7 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2 (*C*H$_3$), 121.4 (2*C*–Tol), 128.9, 129.3 (3*C*–Ph), 129.7 (2*C*–Tol), 130.1 (2*C*–Ph), 132.9 (*C*–H), 136.2 (*C*–Ph), 140.4, 146.6 (2*C*–Tol).

*4.2.1.9. C-p-Nitrophenyl-N-tolyl-nitrone (**5i**).* Yield 1.72 g, 92%, yellow crystals, mp 119–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.31 (d, *J*=8.3 Hz, 2H, Ar–*H*), 7.68 (d, *J*=8.5 Hz, 2H, Ar–*H*), 8.05 (s, 1H, C–*H*), 8.31 (d, *J*=9.0 Hz, 2H, Ar–*H*), 8.55 (d, *J*=9.0 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8 (*C*H$_3$), 121.1 (2*C*–Tol),

123.5 (2*C*–Ph), 128.8, 129.5 (2*C*–Ph), 130.1 (2*C*–Tol), 131.4 (*C*–H), 136.0 (*C*–Ph), 140.8, 146.2 (2*C*–Tol), 147.5 (*C*–Ph).

*4.2.1.10. C-p-Methoxyphenyl-N-tolyl-nitrone (**5j**).* Yield 1.02 g, 58%, colourless needles, mp 118–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.98 (d, J=9.0 Hz, 2H, Ar–*H*), 7.25 (d, J=8.2 Hz, 2H, Ar–*H*), 7.66 (d, J=8.4 Hz, 2H, Ar–*H*), 7.83 (s, 1H, C–*H*), 8.39 (d, J=8.9 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1 (*C*H_3), 55.4 (O*C*H_3), 114.0, 121.4, 123.8 (5*C*–Ph), 129.6, 131.2 (4*C*–Tol), 133.9 (*C*–H), 139.8, 146.6 (2*C*–Tol), 161.5 (*C*–Ph).

*4.2.1.11. C-2-Furyl-N-tolyl-nitrone (**5k**).* Yield 1.25 g, 85%, colourless needles, mp 132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (s, 3H, CH_3), 6.64 (d, J=1.6 Hz, 1H, Fur–*H*), 7.27 (d, J=8.1 Hz, 2H, Ph–*H*), 7.58 (s, 1H, C–*H*), 7.69 (d, J=8.4 Hz, 2H, Ph–*H*), 8.00 (d, J=3.4 Hz, 1H, Fur–*H*), 8.14 (s, 1H, Fur–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1 (*C*H_3), 112.6, 116.2 (2*C*–Fur), 120.7 (2*C*–Tol), 123.8 (*C*–H), 129.6 (2*C*–Tol), 140.2, 144.4 (2*C*–Tol), 144.9, 147.5 (2*C*–Fur).

*4.2.1.12. C-3-Pyridyl-N-tolyl-nitrone (**5l**).* Yield 1.04 g, 67%, colourless crystals, mp 131–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 7.29 (d, J=8.2 Hz, 2H, Ph–*H*), 7.45 (dd, J=8.0, 4.9 Hz, 1H, Pyr–*H*), 7.68 (d, J=8.4 Hz, 2H, Ph–*H*), 7.99 (s, 1H, C–*H*), 8.64 (d, J=3.5 Hz, 1H, Pyr–*H*), 9.12 (s, 1H, Pyr–*H*), 9.22 (d, J=8.1 Hz, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0 (*C*H_3), 121.1 (2*C*–Tol), 123.4, 127.2 (2*C*–Pyr), 129.5 (2*C*–Tol), 130.7 (*C*–H), 134.6 (*C*–Pyr), 140.5, 146.2 (2*C*–Tol), 149.9, 150.4 (2*C*–Pyr).

4.2.2. General method for C-aryl-N-alkyl nitrones

In an open flask, 0.5 g (1 equiv) of methyl or *tert*-butylhydroxylamine hydrochloride and 1.2 equiv of NaOAc were mixed for a few seconds using a spatula, followed by addition of 1.2 equiv of the aldehyde (solid or liquid); a stirring bar was also placed inside the flask. The flask containing the homogeneous or heterogeneous mixture was positioned in the centre of the microwave cavity, over a Weflon-made support provided by the manufacturer, and irradiated for the time and power indicated in Table 2. Reactions were monitored by TLC. After completion, dichloromethane was added and the solid salt was filtered off. In some cases, the nitrone crystallized directly from dichloromethane, in other cases it was purified by column chromatography, as indicated for each nitrone.

*4.2.2.1. C-Phenyl-N-methyl-nitrone (**8a**).* Eluent: AcOEt. Yield 728.2 mg, 90%, colourless needles, mp 83–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H, N–CH_3), 7.37 (s, 1H, C–*H*), 7.42 (d, J=2.4 Hz, 2H, Ph–*H*), 7.43 (d, J=0.9 Hz, 1H, Ph–*H*), 8.22 (dd, J=3.0, 6.6 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.4 (N–*C*H_3), 128.4, 128.5, 130.4 (6*C*–Ph), 135.2 (*C*–H).

*4.2.2.2. C-p-Chlorophenyl-N-methyl-nitrone (**8b**).* Eluent: AcOEt. Yield 934.2 mg, 92%, colourless needles, mp 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (s, 3H, NCH_3), 7.36 (s, 1H, C–*H*), 8.27 (d, J=8.8 Hz, 2H, Ph–*H*), 8.38 (d, J=8.8 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.4 (N–*C*H_3), 128.7, 128.9, 129.5 (5*C*–Ph), 134.0 (*C*–H), 135.8 (*C*–Ph).

*4.2.2.3. C-p-Nitrophenyl-N-methyl-nitrone (**8c**).* Crystallizes immediately. Yield 927.5 mg, 86%, yellow needles, mp 210–212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (s, 3H, NCH_3), 7.39 (d, J=8.8 Hz, 2H, Ph–*H*), 7.53 (s, 1H, C*H*), 8.18 (d, J=8.8 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.2 (N–*C*H_3), 123.8, 128.7 (4*C*–Ph), 133.1 (*C*–H), 136.0, 147.8 (2*C*–Ph).

*4.2.2.4. C-p-Methoxyphenyl-N-methyl-nitrone (**8d**).* Eluent: AcOEt/MeOH 19:1. Yield 712 mg, 72%, colourless crystals, mp 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 6H, OCH_3, NCH_3), 6.94 (d, J=8.8 Hz, 2H, Ph–*H*), 7.29 (s, 1H, C*H*), 8.21 (d, J=8.8 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.9 (O*C*H_3), 55.3 (N–*C*H_3), 113.8, 123.5, 130.3 (5*C*–Ph), 134.8 (*C*–H), 161.0 (*C*–Ph).

*4.2.2.5. C-2-Furyl-N-methyl-nitrone (**8e**).* Eluent: AcOEt/MeOH 19:1. Yield 644.2 mg, 86%, colourless needles, mp 90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (s, 3H, CH_3), 6.56 (d, J=1.3 Hz, 1H, Fur–*H*), 7.48 (br s, 1H, Fur–*H*), 7.55 (s, 1H, C–*H*), 7.76 (d, J=3.3 Hz, 1H, Fur–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.6 (N–*C*H_3), 112.1, 115.1 (2*C*–Fur), 126.1 (*C*–H), 143.5, 146.5 (2*C*–Fur).

*4.2.2.6. C-3-Pyridyl-N-methyl-nitrone (**8f**).* Eluent: AcOEt/MeOH 19:1. Yield 676.5 mg, 83%, colourless crystals, mp 75–77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H, CH_3), 7.38 (dd, J=7.9, 4.9 Hz, 1H, Pyr–*H*), 7.46 (s, 1H, C–*H*), 8.60 (d, J=3.5 Hz, 1H, Pyr–*H*), 8.97 (s, 1H, Pyr–*H*), 9.01 (d, J=8.09 Hz, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.6 (N–*C*H_3), 123.6, 127.0 (2*C*–Pyr), 132.3 (*C*–H), 134.6, 149.5, 150.5 (3*C*–Pyr).

*4.2.2.7. C-Phenyl-N-tert-butyl-nitrone (**8g**).* Eluent: ether/hexane 2:1. Yield 606.8 mg, 86%, colourless needles, mp 72–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.62 (s, 9H, ^{t}Bu–*H*), 7.35–7.47 (m, 3H, Ph–*H*), 7.55 (s, 1H, C–*H*), 8.29 (dd, J=7.6, 2.1 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 70.8 (*C*(CH$_3$)$_3$), 128.4, 128.8 (4*C*–Ph), 129.9 (*C*–H), 130.1, 131.0 (2*C*–Ph).

*4.2.2.8. C-p-Chlorophenyl-N-tert-butyl-nitrone (**8h**).* Eluent: ether/hexane 1:1. Yield 716.3 mg, 85%, colourless crystals, mp 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 9H, ^{t}Bu–*H*), 7.38 (d, J=8.6 Hz, 2H, Ph–*H*), 7.53 (s, 1H, C–*H*), 8.25 (d, J=8.6 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 71.1 (*C*(CH$_3$)$_3$), 128.6, 128.7, 129.5, 129.9 (6*C*–Ph), 135.4 (*C*–H).

*4.2.2.9. C-p-Nitrophenyl-N-tert-butyl-nitrone (**8i**).* Crystallizes directly from dichloromethane. Yield 813.9 mg, 92%, yellow needles, mp 146–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (s, 9H, ^{t}Bu–*H*), 7.71 (s, 1H, C–*H*), 8.25 (d, J=9.1 Hz, 2H, Ph–*H*), 8.45 (d, J=9.0 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 72.4 (*C*(CH$_3$)$_3$), 123.7 (2*C*–Ph), 127.9 (*C*–H), 128.9, 136.7, 147.6 (4*C*–Ph).

*4.2.2.10. C-p-Methoxyphenyl-N-tert-butyl-nitrone (**8j**).* Eluent: ether/hexane 1:1. Yield 750.9 mg, 91%, colourless needles, mp 94–95 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (s, 9H, ^{t}Bu–*H*), 3.85 (s, 3H, OCH_3), 6.85–7.01 (m, 2H, Ph–*H*), 7.48 (s, 1H, C–*H*), 8.29 (d, J=8.9 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 55.3 (O*C*H_3), 70.1 (*C*(CH$_3$)$_3$), 113.7, 124.0 (3*C*–Ph), 129.6 (*C*–H), 130.8, 160.8 (3*C*–Ph).

*4.2.2.11. C-2-Furyl-N-tert-butyl-nitrone (**8k**).* Eluent: ether/hexane 1:1. Yield 639.0 mg, 96%, colourless needles, mp 68–69 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 9H, ^{t}Bu–*H*), 6.56 (br d, J=1.1 Hz, 1H, Fur–*H*), 7.73 (s, 1H, C–*H*), 7.79 (d, J=3.3 Hz, 1H, Fur–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (C(*C*H_3)$_3$), 69.7 (*C*(CH$_3$)$_3$), 112.2, 114.8 (2*C*–Fur), 121.4 (*C*–H), 143.5, 147.6 (2*C*–Fur).

*4.2.2.12. C-3-Pyridyl-N-tert-butyl-nitrone (**8l**).* This nitrone was washed with ethyl acetate instead of dichloromethane. Eluent: AcOEt. Yield 688.2 mg, 97%, colourless crystals, mp 88–90 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (s, 9H, ^{t}Bu–*H*), 7.36 (dd, J=7.6, 4.9 Hz, 1H, Py–*H*), 7.62 (s, 1H, C–*H*), 8.58 (d, J=3.0 Hz, 1H, Py–*H*), 8.99 (s, 1H, Py–*H*), 9.02–9.26 (m, 1H, Py–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (C(*C*H_3)$_3$), 71.3 (*C*(CH$_3$)$_3$), 123.2 (*C*–Pyr), 126.7 (*C*–H), 127.4 (*C*–Pyr), 134.5 (*C*–Pyr), 149.8 (*C*–Pyr), 149.9 (*C*–Pyr).

4.3. Synthesis of isoxazolidines

4.3.1. General method

A mixture containing 0.1 g of nitrone and 0.2 mL of ethyl *trans*-crotonate was placed in a quartz tube, a weflon magnetic stirrer

was added, the tube was sealed and equipped with fibre-optic temperature probe and placed in the MW cavity. It was then irradiated for the time and power indicated in Tables 3 and 4. Products were purified by preparative layer chromatography with the eluent indicated for each case. Characterization of compounds **9**, **10a**–**d** is according to the literature.[36] Compounds **9**, **10f**[39] and **9**, **10m**[40] are described in the literature with no data. For all minor stereoisomers of **10**, only relevant peaks are depicted in their NMR analysis.

4.3.1.1. 3RS-(3R,4S*,5R*)-2-Phenyl-3-(2-furyl)-4-carbethoxy-5-methyl-isoxazolidine (**9e**) and 3RS-(3R*,4R*,5S*)-2-phenyl-3-(2-furyl)-4-carbethoxy-5-methyl-isoxazolidine (**10e**).* Eluent: ether/hexane 1:2. Yield 127.7 mg, 79%, colourless oil. Ratio **9e**/**10e**=78:22. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.53; N, 4.64. IR (cm^{-1}, NaCl) ν_{max} 3063, 2981, 2935, 2904, 1735, 1598, 1488, 1191, 1031, 756, 695. Compound **9e**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.54 (d, J=5.9 Hz, 3H, CH_3), 3.40 (dd, J=8.4, 6.3 Hz, 1H, H-4), 4.12 (dd, J=14.1, 7.0 Hz, 2H, CH_3CH_2), 4.32–4.46 (m, 1H, H-5), 5.25 (d, J=6.0 Hz, 1H, H-3), 6.27–6.46 (m, 2H, Fur–*H*), 6.94 (br t, J=7.0 Hz, 1H, Ph–*H*), 7.08 (br d, J=8.0 Hz, 2H, Ph–*H*), 7.18–7.33 (m, 2H, Ph–*H*), 7.42 (s, 1H, Fur–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3CH_2), 17.6 (CH_3), 61.1 (C-4), 61.4 (CH_3CH_2), 67.5 (C-3), 77.6 (C-5), 107.1, 110.4 (*C*–Fur), 114.5, 121.9, 128.6, 128.9 (*C*–Ph), 142.7, 151.0 (*C*–Fur), 170.1 (*C*=O). Compound **10e**: Detected in the isomeric mixture by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, J=6.0 Hz, 3H, CH_3), 3.26 (t, J=9.4 Hz, 1H, H-4), 4.83 (dt, J=12.0, 6.1 Hz, 1H, H-5), 4.98 (d, J=9.2 Hz, 1H, H-3).

4.3.1.2. 3RS-(3R,4S*,5R*)-2-Phenyl-3-(3-pyridyl)-4-carbethoxy-5-methyl-isoxazolidine (**9f**) and 3RS-(3R*,4R*,5S*)-2-phenyl-3-(3-pyridyl)-4-carbethoxy-5-methyl-isoxazolidine (**10f**).* Eluent: ether/hexane 4:1. Yield 154 mg, 98%, colourless oil. Ratio **9f**/**10f**=87:13. Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.44; H, 6.65; N, 9.02. IR (cm^{-1}, NaCl) ν_{max} 3059, 3034, 2981, 2935, 2904, 1730, 1597, 1488, 1194, 1029, 758, 696. Compound **9f**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.52 (d, J=6.0 Hz, 3H, CH_3), 3.13 (dd, J=8.9, 6.8 Hz, 1H, H-4), 4.16 (q, J=7.1 Hz, 2H, CH_3CH_2), 4.45 (qd, J=9.1, 6.0 Hz, 1H, H-5), 5.21 (d, J=6.7 Hz, 1H, H-3), 6.96 (m, 3H, Ph-*H*), 7.16–7.31 (m, 3H, Ph–*H*, Pyr–*H*), 7.91 (br d, J=7.8 Hz, 1H, Pyr–*H*), 8.56 (m, 1H, Pyr–*H*), 8.75 (br s, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3CH_2), 17.5 (CH_3), 61.6 (CH_3CH_2), 65.3 (C-4), 71.3 (C-3), 77.7 (C-5), 114.0, 121.9 (*C*–Ph), 123.8 (*C*–Pyr), 129.1, 130.9, 134.2 (*C*–Ph), 148.3, 149.2, 151.2 (*C*–Pyr), 169.9 (*C*=O). Compound **10f**: Detected in the isomeric mixture by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, J=6.1 Hz, 3H, CH_3), 3.38 (t, J=9.7 Hz, 1H, H-4), 4.80 (qd, J=12.1, 6.0 Hz, 1H, H-5), 4.89 (d, J=10.0 Hz, 1H, H-3).

4.3.1.3. 3RS-(3R,4S*,5R*)-2-Tolyl-3-phenyl-4-carbethoxy-5-methyl-isoxazolidine (**9g**) and 3RS-(3R*,4R*,5S*)-2-tolyl-3-phenyl-4-carbethoxy-5-methyl-isoxazolidine (**10g**).* Eluent: ether/hexane 1:2. Yield 146.9 mg, 95%, colourless oil. Ratio **9g**/**10g**=87:13. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 77.65; H, 7.31; N, 4.34. IR (cm^{-1}, NaCl) ν_{max} 3029, 2980, 2934, 1733, 1612, 1507, 1187, 814. Compound **9g**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.50 (d, J=6.0 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3–Ph), 3.15 (dd, J=8.9, 7.1 Hz, 1H, H-4), 4.14 (q, J=7.1 Hz, 2H, CH_3CH_2), 4.43 (qd, J=9.0, 6.0 Hz, 1H, H-5), 5.10 (d, J=7.0 Hz, 1H, H-3), 6.89 (d, J=8.5 Hz, 2H, Ar–*H*), 7.04 (d, J=8.3 Hz, 2H, Ar–*H*), 7.26–7.33 (m, 1H, Ar–*H*), 7.37 (t, J=7.5 Hz, 2H, Ar–*H*), 7.52 (d, J=7.4 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3CH_2), 17.1 (CH_3), 20.1 (CH_3–Ph), 60.8 (CH_3CH_2), 65.1 (C-4), 73.2 (C-3), 77.0 (C-5), 113.8, 126.0, 127.1, 128.3, 128.9, 130.4, 141.4, 148.9 (*C*–Ar), 169.9 (*C*=O). Compound **10g**: Detected in the isomeric mixture by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, J=6.1 Hz, 3H, CH_3), 3.31 (t, J=9.8 Hz, 1H, H-4), 4.75 (d, J=10.2 Hz, 1H, H-3), 4.81 (qd, J=9.6, 6.1 Hz, 1H, H-5).

4.3.1.4. 3RS-(3R,4S*,5R*)-2-Tolyl-3-(p-chlorophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9h**) and 3RS-(3R*,4R*,5S*)-2-tolyl-3-(p-chlorophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**10h**).* Eluent: ether/hexane 1:2. Yield 130.6 mg, 89%, colourless oil. Ratio **9h**/**10h**=91:9. Anal. Calcd for $C_{20}H_{22}ClNO_3$: C, 66.75; H, 6.16; N, 3.89. Found: C, 66.31; H, 6.27; N, 3.88. IR (cm^{-1}, NaCl) ν_{max} 3027, 2980, 2934, 2872, 1731, 1611, 1507, 1188, 1090, 815. Compound **9h**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.49 (d, J=6.0 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3–Ph), 3.09 (dd, J=8.9, 7.0 Hz, 1H, H-4), 4.15 (q, J=7.1 Hz, 2H, CH_3CH_2), 4.42 (qd, J=9.0, 6.0 Hz, 1H, H-5), 5.07 (d, J=7.0 Hz, 1H, H-3), 6.86 (d, J=8.5 Hz, 2H, Ar–*H*), 7.04 (d, J=8.3 Hz, 2H, Ar–*H*), 7.33 (d, J=8.5 Hz, 2H, Ar–*H*), 7.47 (d, J=8.4 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (CH_3CH_2), 17.0 (CH_3), 19.9 (CH_3–Ph), 60.8 (CH_3CH_2), 64.9 (C-4), 72.4 (C-3), 76.8 (C-5), 113.6, 127.2, 128.3, 128.9, 130.6, 132.7, 139.8, 148.4 (*C*–Ph), 169.6 (*C*=O). Compound **10h**: Detected in the isomeric mixture by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (d, J=6.1 Hz, 3H, CH_3), 3.31 (t, J=9.8 Hz, 1H, H-4), 4.73 (d, J=10.1 Hz, 1H, H-3), 4.77 (m, 1H, H-5).

4.3.1.5. 3RS-(3R,4S*,5R*)-2-Tolyl-3-(p-nitrophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9i**) and 3RS-(3R*,4R*,5S*)-2-tolyl-3-(p-nitrophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**10i**).* Eluent: ether/hexane 1:2. Yield 113.1 mg, 81%, yellow oil. Ratio **9i**/**10i**=94:6. Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 64.83; H, 6.19; N, 7.56. IR (cm^{-1}, NaCl) ν_{max} 2981, 2935, 1732, 1605, 1521, 1347, 1189, 856. Compound **9i**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.51 (d, J=6.0 Hz, 3H, CH_3), 2.28 (s, 3H, CH_3–Ph), 3.09 (dd, J=8.9, 6.7 Hz, 1H, H-4), 4.18 (q, J=7.1 Hz, 2H, CH_3CH_2), 4.45 (qd, J=8.9, 6.0 Hz, 1H, H-5), 5.24 (d, J=6.7 Hz, 1H, H-3), 6.86 (d, J=8.5 Hz, 2H, Ar–*H*), 7.07 (d, J=8.3 Hz, 2H, Ar–*H*), 7.73 (d, J=8.6 Hz, 2H, Ar–*H*), 8.23 (d, J=8.8 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3CH_2O), 17.5 (CH_3), 20.4 (CH_3–Ph), 61.6 (CH_3CH_2O), 65.2 (*C*4), 72.5 (*C*3), 77.5 (*C*5), 114.0, 124.0, 127.2, 129.5, 131.4, 147.4, 148.4, 149.3 (Ph–*C*), 169.8 (CO_2Et). Compound **10i**: Detected in the isomeric mixture by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, J=6.1 Hz, 3H, CH_3), 3.39 (t, J=9.7 Hz, 1H, H-4), 4.77 (qd, J=9.8, 6.0 Hz, 1H, H-5), 4.87 (d, J=10.1 Hz, 1H, H-3).

4.3.1.6. 3RS-(3R,4S*,5R*)-2-Tolyl-3-(p-methoxyphenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9j**) and 3RS-(3R*,4R*,5S*)-2-tolyl-3-(p-methoxyphenyl)-4-carbethoxy-5-methyl-isoxazolidine (**10j**).* Eluent: ether/hexane 1:2. Yield 126 mg, 86%, colourless oil. Ratio **9j**/**10j**=83:17. Anal. Calcd for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 70.75; H, 7.31; N, 3.93. IR (cm^{-1}, NaCl) ν_{max} 2979, 2934, 2837, 1731, 1612, 1513, 1249, 1035, 816. Compound **9j**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.49 (d, J=6.0 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3–Ph), 3.12 (dd, J=8.9, 7.3 Hz, 1H, H-4), 3.81 (s, 3H, OCH_3), 4.14 (q, J=7.1 Hz, 2H, CH_3CH_2), 4.42 (qd, J=9.0, 6.0 Hz, 1H, H-5), 5.02 (d, J=7.2 Hz, 1H, H-3), 6.82–6.93 (m, 4H, Ar–*H*), 7.03 (d, J=8.3 Hz, 2H, Ar–*H*), 7.43 (d, J=8.6 Hz, 2H, Ar–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 (CH_3CH_2), 17.6 (CH_3), 20.5 (CH_3-Ph), 55.2 (OCH_3), 61.1 (CH_3CH_2), 65.6 (C-4), 73.4 (C-3), 77.3 (C-5), 114.1, 114.4, 127.6, 129.3, 130.8, 133.7, 149.3, 158.9 (*C*–Ph), 170.3 (*C*=O). Compound **10j**: Detected in the isomeric mixture by ^1H NMR analysis. ^1H NMR (400 MHz, $CDCl_3$): δ 1.44 (d, J=6.1 Hz, 3H, CH_3), 3.28 (t, J=9.8 Hz, 1H, H-4), 4.71 (d, J=10.2 Hz, 1H, H-3), 4.80 (qd, J=9.5, 6.0 Hz, 1H, H-5).

4.3.1.7. 3RS-(3R,4S*,5R*)-2-Tolyl-3-(2-furyl)-4-carbethoxy-5-methyl-isoxazolidine (**9k**) and 3RS-(3R*,4R*,5S*)-2-tolyl-3-(2-furyl)-4-carbethoxy-5-methyl-isoxazolidine (**10k**).* Eluent: ether/hexane 1:2. Yield 134.1 mg, 86%, colourless oil. Ratio **9k**/**10k**=76:24. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.43; H 6.75; N 4.42. IR (cm^{-1}, NaCl) ν_{max} 2981, 2934, 1735, 1612, 1507, 1191, 817, 740. Compound **9k**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, J=7.1 Hz, 3H, CH_3CH_2), 1.54 (d, J=6.0 Hz, 3H, CH_3), 2.27 (s, 3H, CH_3–Ph), 3.39

(dd, *J*=8.5, 6.3 Hz, 1H, H-4), 4.12 (q, *J*=7.1 Hz, 2H, CH_3CH_2), 4.40 (qd, *J*=12.0, 6.0 Hz, 1H, H-5), 5.21 (d, *J*=6.2 Hz, 1H, H-3), 6.35 (td, *J*=4.7, 3.4 Hz 2H, Fur–*H*), 6.98 (d, *J*=8.4 Hz, 2H, Ph–*H*), 7.07 (d, *J*=8.4 Hz, 2H, Ph–*H*), 7.41 (s, 1H, Fur–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3CH_2), 17.7 (CH_3), 20.6 (CH_3–Ph), 60.9 (C-4), 61.4 (CH_3CH_2), 67.6 (C-3), 77.4 (C-5), 107.1 (*C*–Fur), 110.4, 114.8, 116.3, 129.4 (*C*–Ph), 142.6, 148.6 (*C*–Fur), 170.2 (*C*=O). Compound **10k**: Detected in the isomeric mixture by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.48 (d, *J*=6.1 Hz, 3H, CH_3), 3.25 (t, *J*=9.3 Hz, 1H, H-4), 4.81 (qd, *J*=11.9, 6.0 Hz, 1H, H-5), 4.92 (d, *J*=9.3 Hz, 1H, H-3).

4.3.1.8. 3RS-(3R,4S*,5R*)-2-Tolyl-3-(3-pyridyl)-4-carbethoxy-5-methyl-isoxazolidine (**9l**) and 3RS-(3R*,4R*,5S*)-2-tolyl-3-(3-pyridyl)-4-carbethoxy-5-methyl-isoxazolidine (**10l**).* Eluent: ether/hexane 4:1. Yield 167.5 mg, 81%, colourless oil. Ratio **9l**/**10l**=90:10. Anal. Calcd for $C_{19}H_{22}N_2O_3$: C, 69.92; H, 6.79; N, 8.58. Found: C, 69.71; H, 6.77; N, 8.57. IR (cm^{-1}, NaCl) ν_{max} 3029, 2980, 2934, 1731, 1612, 1508, 1193, 1026, 814, 715. Compound **9l**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.51 (d, *J*=6.0 Hz, 3H, CH_3), 2.27 (s, 3H, CH_3–Ph), 3.12 (dd, *J*=8.8, 6.8 Hz, 1H, H-4), 4.16 (q, *J*=7.1 Hz, 2H, CH_3CH_2), 4.46 (qd, *J*=8.8, 6.0 Hz, 1H, H-5), 5.17 (d, *J*=6.7 Hz, 1H, H-3), 6.88 (d, *J*=8.4 Hz, 2H, Ph–*H*), 7.06 (d, *J*=8.2 Hz, 2H, Ph–*H*), 7.32 (dd, *J*=7.7, 4.9 Hz, 1H, Pyr–*H*), 7.92 (d, *J*=7.9 Hz, 1H, Pyr–*H*), 8.56 (d, *J*=3.7 Hz, 1H, Pyr–*H*), 8.74 (s, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (CH_3CH_2), 17.1 (CH_3), 20.0 (CH_3–Ph), 61.0 (CH_3CH_2), 64.7 (C-4), 70.8 (C-3), 77.0 (C-5), 113.8 (*C*–Ph), 123.2 (*C*–Pyr), 129.0, 130.9 (*C*–Ph), 133.8, 137.1, 147.6, 148.2, 148.4 (*C*–Pyr), 169.4 (*C*=O). Compound **10l**: Detected in the isomeric mixture by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, *J*=6.1 Hz, 3H, CH_3), 3.37 (t, *J*=9.7 Hz, 1H, H-4), 4.73–4.81 (m, 1H, H-5), 4.82 (d, *J*=10.1 Hz, 1H, H-3).

4.3.1.9. 3RS-(3R,4S*,5R*)-2-Methyl-3-phenyl-4-carbethoxy-5-methyl-isoxazolidine (**9m**) and 3RS-(3R*,4R*,5S*)-2-methyl-3-phenyl-4-carbethoxy-5-methyl-isoxazolidine (**10m**).* Eluent: ether/hexane 1:2. Yield 163.4 mg, 89%, colourless oil. Ratio **9m**/**10m**=56:44. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.71; H, 7.73; N, 5.57. IR (cm^{-1}, NaCl) ν_{max} 3063, 3032, 2980, 2932, 2872, 1734, 1455, 1377, 1279, 1184, 1044, 756, 701. Compound **9m**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.47 (d, *J*=6.2 Hz, 3H, CH_3), 2.62 (s, 3H, N–CH_3), 3.05 (dd, *J*=8.4, 6.5 Hz, 1H, H-4), 3.95 (d, *J*=5.8 Hz, 1H, H-3), 4.13 (q, *J*=7.1 Hz, 2H, CH_3CH_2), 4.49 (p, *J*=6.2 Hz, 1H, H-5), 7.29 (m, 5H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3CH_2), 21.0 (CH_3), 43.3 (CH_3–N), 61.0 (CH_3CH_2), 64.6 (C-4), 76.1 (C-5), 76.3 (C-3), 128.0, 128.2, 128.7, 138.5 (6*C*–Ph), 171.4 (*C*=O). Compound **10m**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.74 (t, *J*=7.0 Hz, 3H, CH_3CH_2), 1.35 (d, *J*=6.1 Hz, 3H, CH_3), 2.64 (s, 3H, N–CH_3), 3.16 (dd, *J*=10.3, 7.9 Hz, 1H, H-4), 3.49–3.75 (m, 2H, CH_3CH_2), 3.86 (d, *J*=10.3 Hz, 1H, H-3), 4.69 (qd, *J*=12.3, 6.2 Hz, 1H, H-5), 7.29 (m, 5H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5 (CH_3CH_2), 18.4 (CH_3), 43.4 (CH_3–N), 60.4 (CH_3CH_2), 61.1 (C-4), 75.5 (C-5), 76.1 (C-3), 127.6, 128.1, 128.4, 136.4 (6*C*–Ph), 170.4 (*C*=O).

4.3.1.10. 3RS-(3R,4S*,5R*)-2-Methyl-3-(p-chlorophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9n**) and 3RS-(3R*,4R*,5S*)-2-methyl-3-(p-chlorophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**10n**).* Eluent: ether/hexane 1:2. Yield 148.8 mg, 89%, colourless oil. Ratio **9n**/**10n**=60:40. Anal. Calcd for $C_{14}H_{18}ClNO_3$: C, 59.26; H, 6.34; N, 4.94. Found: C, 59.29; H, 6.37; N, 5.01. IR (cm^{-1}, NaCl) ν_{max} 2980, 2932, 2873, 1733, 1492, 1376, 1184, 1091, 1044, 819. Compound **9n**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.47 (d, *J*=6.1 Hz, 3H, CH_3), 2.63 (s, 3H, N–CH_3), 2.99 (dd, *J*=8.1, 6.6 Hz, 1H, H-4), 3.96 (d, *J*=6.6 Hz, 1H, H-3), 4.16 (q, *J*=7.1 Hz, 2H, CH_3CH_2), 4.50 (p, *J*=6.1 Hz, 1H, H-5), 7.27–7.37 (m, 4H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3CH_2), 20.9 (CH_3), 43.4 (CH_3–N), 61.2 (CH_3CH_2), 64.5 (C-4), 75.4 (C-3), 76.1 (C-5), 128.4, 128.9, 133.5, 136.8 (6*C*–Ph), 170.9 (*C*=O). Compound **10n**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.36 (d, *J*=6.1 Hz, 3H, CH_3), 2.60 (s, 3H, N–CH_3), 3.18 (t, *J*=8.5 Hz, 1H, H-4), 3.55–3.79 (m, 2H, CH_3CH_2), 3.85 (d, *J*=10.3 Hz, 1H, H-3), 4.67 (qd, *J*=12.3, 6.1 Hz, 1H, H-5), 7.27–7.37 (m, 4H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6 (CH_3CH_2), 18.4 (CH_3), 43.3 (CH_3–N), 60.6 (CH_3CH_2), 60.9 (C-4), 75.2 (C-3), 75.6 (C-5), 128.9, 129.8, 133.9, 135.1 (6*C*–Ph), 170.1 (*C*=O).

4.3.1.11. 3RS-(3R,4S*,5R*)-2-Methyl-3-(p-nitrophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9o**) and 3RS-(3R*,4R*,5S*)-2-methyl-3-(p-nitrophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**10o**).* Eluent: ether/hexane 1:2. Yield 147.2 mg, 90%, yellow oil. Ratio **9o**/**10o**=76:34. Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 56.99; H, 6.17; N, 9.49. IR (cm^{-1}, NaCl) ν_{max} 2981, 2934, 2874, 1732, 1524, 1349, 1187, 856. Compound **9o**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.27 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.48 (d, *J*=6.1 Hz, 3H, CH_3), 2.70 (s, 3H, N–CH_3), 2.99 (dd, 1H, *J*=7.6, 6.8 Hz, 1H, H-4), 4.20 (m, 3H, H-3, CH_3CH_2), 4.53–4.61 (m, 1H, H-5), 7.62 (d, *J*=8.7 Hz, 2H, Ph–*H*), 8.21 (d, *J*=8.9 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3CH_2), 20.5 (CH_3), 43.8 (CH_3–N), 61.5 (CH_3CH_2), 64.7 (C-4), 74.8 (C-3), 76.1 (C-5), 123.9, 128.3, 147.1, 147.6 (6*C*–Ph), 170.9 (*C*=O). Compound **10o**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, *J*=7.2 Hz, 3H, CH_3CH_2), 1.39 (d, *J*=6.1 Hz, 3H, CH_3), 2.64 (s, 3H, N–CH_3), 3.27 (dd, *J*=10.4, 8.2 Hz, 1H, H-4), 3.55–3.78 (m, 2H, CH_3CH_2), 4.01 (d, *J*=10.5 Hz, 1H, H-3), 4.67 (m, 1H, H-5), 7.57 (d, *J*=8.7 Hz, 2H, Ph–*H*), 8.18 (d, *J*=9.0 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3CH_2), 18.3 (CH_3), 43.5 (CH_3–N), 60.8 (CH_3CH_2), 60.9 (C-4), 74.8 (C-3), 75.9 (C-5), 123.3, 129.5, 144.3, 147.7 (6*C*–Ph), 169.7 (*C*=O).

4.3.1.12. 3RS-(3R,4S*,5R*)-2-Methyl-3-(p-methoxyphenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9p**) and 3RS-(3R*,4R*,5S*)-2-methyl-3-(p-methoxyphenyl)-4-carbethoxy-5-methyl-isoxazolidine (**10p**).* Eluent: ether/hexane 1:2. Yield 153.2 mg, 91%, colourless oil. Ratio **9p**/**10p**=55:45. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.71; H, 7.57; N, 4.97. IR (cm^{-1}, NaCl) ν_{max} 2978, 2934, 2839, 1732, 1612, 1514, 1377, 1250, 1182, 1036, 834. Compound **9p**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.21 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.48 (d, *J*=6.2 Hz, 3H, CH_3), 2.60 (s, 3H, CH_3–N), 3.04 (dd, *J*=8.6, 6.5 Hz, 1H, H-4), 3.80 (s, 3H, OCH_3), 3.78–3.93 (m, H-3), 4.14 (q, *J*=7.1 Hz, 2H, CH_3CH_2), 4.48 (p, *J*=6.1 Hz, 1H, H-5), 6.88 (d, *J*=8.7 Hz, 2H, Ph–*H*), 7.31 (d, *J*=8.7 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3CH_2), 21.1 (CH_3), 43.3 (CH_3–N), 55.2 (OCH_3), 61.0 (CH_3CH_2), 64.4 (C-4), 75.5 (C-3), 76.0 (C-5), 114.1, 129.6, 132.0, 159.4 (6*C*–Ph), 171.4 (*C*=O). Compound **10p**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, *J*=7.2 Hz, 3H, CH_3CH_2), 1.36 (d, *J*=6.1 Hz, 3H, CH_3), 2.60 (s, 3H, CH_3–N), 3.14 (dd, *J*=10.1, 8.1 Hz, 1H, H-4), 3.57–3.76 (m, 2H, CH_3CH_2), 3.78 (s, 3H, OCH_3), 3.78–3.93 (m, H-3), 4.68 (qd, *J*=12.3, 6.1 Hz, 1H, H-5), 6.84 (d, *J*=8.7 Hz, 2H, Ph–*H*), 7.26 (d, *J*=8.7 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3CH_2), 18.4 (CH_3), 43.3 (CH_3–N), 55.2 (OCH_3), 60.4 (CH_3CH_2), 61.0 (C-4), 75.5 (C-3, C-5), 113.6, 128.8, 130.0, 159.4 (6*C*–Ph), 170.5 (*C*=O).

4.3.1.13. 3RS-(3R,4S*,5R*)-2-Methyl-3-(2-furyl)-4-carbethoxy-5-methyl-isoxazolidine (**9q**) and 3RS-(3R*,4R*,5S*)-2-methyl-3-(2-furyl)-4-carbethoxy-5-methyl-isoxazolidine (**10q**).* Eluent: ether/hexane 1:2. Yield 142.4 mg, 75%, colourless oil. Ratio **9q**/**10q**=60:40. Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.24; H, 7.22; N, 5.92. IR (cm^{-1}, NaCl) ν_{max} 2979, 2933, 2874, 1736, 1376, 1187, 1044, 742. Compound **9q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.01 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.36 (d, *J*=6.1 Hz, 3H, CH_3), 2.65 (s, 3H, CH_3–N), 3.16 (br s, 1H, H-4), 3.84–3.97 (m, 2H, CH_3CH_2), 4.02 (br s, 1H, H-3), 4.59–4.76 (m, 1H, H-5), 6.32 (dd, *J*=8.8, 2.5 Hz, 2H, Fur–*H*), 7.36 (s, 1H, Fur–*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7 (CH_3CH_2), 18.3 (CH_3), 43.5 (CH_3–N), 58.8 (C-4), 60.6 (CH_3CH_2), 69.1 (C-3), 75.3 (C-5), 110.2, 110.3, 142.3, 149.7 (4*C*–Fur), 169.9 (*C*=O). Compound **10q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, *J*=7.1 Hz, 3H, CH_3CH_2), 1.49 (d, *J*=6.0 Hz,

3H, C*H*$_3$), 2.65 (s, 3H, C*H*$_3$–N), 3.33 (br s, 1H, H-4), 4.14 (d, *J*=10.3 Hz, 1H, H-3), 4.18 (dd, *J*=14.2, 7.1 Hz, 2H, CH$_3$C*H*$_2$), 4.48 (br s, 1H, H-5), 6.32 (dd, *J*=8.8, 2.5 Hz, 2H, Fur–*H*), 7.41 (s, 1H, Fur–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.0 (*C*H$_3$CH$_2$), 18.3 (*C*H$_3$), 43.6 (*C*H$_3$–N), 60.0 (C-4), 61.1 (CH$_3$*C*H$_2$), 69.1 (C-3), 76.1 (C-5), 108.4, 108.7, 142.7, 149.7 (4*C*–Fur), 171.2 (*C*=O).

4.3.1.14. 3RS-(3R,4S*,5R*)-2-Methyl-3-(3-pyridyl)-4-carbethoxy-5-methyl-isoxazolidine (**9r**) and 3RS-(3R*,4R*,5S*)-2-methyl-3-(3-pyridyl)-4-carbethoxy-5-methyl-isoxazolidine (**10r**).* Eluent: ether/hexane 4:1. Yield 178.5 mg, 97%, colourless oil. Ratio **9r**/**10r**=66:34. Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.26; H, 7.44; N, 11.12. IR (cm^{-1}, NaCl) ν_{max} 2980, 2933, 2874, 1731, 1577, 1429, 1188, 1038, 715. Compound **9r**: ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.24 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.49 (d, *J*=6.1 Hz, 3H, C*H*$_3$), 2.66 (s, 3H, C*H*$_3$–N), 2.98–3.08 (m, 1H, H-4), 4.04 (d, *J*=7.2 Hz, 1H, H-3), 4.17 (q, *J*=7.1 Hz, 2H, CH$_3$C*H*$_2$), 4.48–4.61 (m, 1H, H-5), 7.30 (dd, *J*=7.8, 4.9 Hz, 1H, Pyr–*H*), 7.78 (d, *J*=7.8 Hz, 1H, Pyr–*H*), 8.55 (d, *J*=2.5 Hz, 1H, Pyr–*H*), 8.62 (s, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.5 (*C*H$_3$CH$_2$), 20.1 (*C*H$_3$), 42.9 (*C*H$_3$–N), 60.7 (CH$_3$*C*H$_2$), 63.8 (C-4), 72.9 (C-3), 75.3 (C-5), 123.0, 134.3, 135.2, 148.8, 149.4 (5*C*–Pyr), 170.3 (*C*=O). Compound **10r**: ^{1}H NMR (400 MHz, CDCl$_3$): δ 0.79 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.38 (d, *J*=6.1 Hz, 3H, C*H*$_3$), 2.63 (s, 3H, C*H*$_3$–N), 3.24 (dd, *J*=10.1, 8.4 Hz, 1H, H-4), 3.57–3.78 (m, 2H, CH$_3$C*H*$_2$), 3.93 (d, *J*=10.4 Hz, 1H, H-3), 4.68 (qd, *J*=12.5, 6.1 Hz, 1H, H-5), 7.26 (dd, *J*=9.0, 6.1 Hz, 1H, Pyr–*H*), 7.74 (d, *J*=7.9 Hz, 1H, Pyr–*H*), 8.53 (d, *J*=5.0 Hz, 1H, Pyr–*H*), 8.62 (s, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.0 (*C*H$_3$CH$_2$), 17.6 (*C*H$_3$), 42.7 (*C*H$_3$–N), 60.0 (CH$_3$*C*H$_2$), 60.2 (C-4), 72.6 (C-3), 75.1 (C-5), 122.6, 131.8, 134.0, 148.7, 148.9 (5*C*–Pyr), 169.3 (*C*=O).

4.3.1.15. 3RS-(3R,4S*,5R*)-2-tert-Butyl-3-phenyl-4-carbethoxy-5-methyl-isoxazolidine (**9s**).* Eluent: ether/hexane 1:2. Yield 133.3 mg, 77%, colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.08 (s, 9H, ^{t}Bu-*H*), 1.19 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.35 (d, *J*=5.9 Hz, 3H, C*H*$_3$), 2.96 (t, *J*=9.5 Hz, 1H, H-4), 4.06–4.19 (m, 2H, CH$_3$C*H*$_2$), 4.34 (qd, *J*=9.5, 5.9 Hz, 1H, H-5), 4.67 (d, *J*=9.5 Hz, 1H, H-3), 7.21 (t, *J*=7.3 Hz, 1H, Ph–*H*), 7.28 (t, *J*=7.3 Hz, 2H, Ph–*H*), 7.46 (d, *J*=7.2 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.2 (*C*H$_3$CH$_2$), 18.1 (*C*H$_3$), 26.2 (3C, (*C*H$_3$)$_3$C–N), 60.5 ((CH$_3$)$_3$*C*–N), 61.0 (CH$_3$CH$_2$O), 66.1 (C-4), 67.0 (C-3), 77.6 (C-5), 127.0, 127.2, 128.4, 142.5 (*C*–Ph), 170.3 (*C*=O). IR (cm^{-1}, NaCl) ν_{max} 3064, 3030, 2977, 2935, 2907, 2874, 1731, 1601, 1454, 1364, 1215, 1183, 1030, 752, 702. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.00; H, 8.78; N, 4.74.

4.3.1.16. 3RS-(3R,4S*,5R*)-2-tert-Butyl-3-(p-chlorophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9t**).* Eluent: ether/hexane 1:2. Yield 141.1 mg, 92%, colourless crystals, mp 51–53 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.06 (s, 9H, ^{t}Bu–*H*), 1.21 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.34 (d, *J*=5.9 Hz, 3H, C*H*$_3$), 2.90 (t, *J*=9.5 Hz, 1H, H-4), 4.09–4.19 (m, 2H, CH$_3$C*H*$_2$), 4.32 (qd, *J*=11.8, 5.9 Hz, 1H, H-5), 4.65 (d, *J*=9.5 Hz, 1H, H-3), 7.26 (d, *J*=8.4 Hz, 2H, Ph–*H*), 7.41 (d, *J*=8.3 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.8 (*C*H$_3$CH$_2$), 17.6 (*C*H$_3$), 25.7 (3C, (*C*H$_3$)$_3$C–N), 60.2 ((CH$_3$)$_3$*C*–N), 60.7 (CH$_3$*C*H$_2$), 65.5 (C-4), 65.8 (C-3), 77.2 (C-5), 127.9, 128.2, 132.5, 140.7 (*C*–Ph), 169.6 (*C*=O). IR (cm^{-1}, NaCl) ν_{max} 2977, 2936, 2907, 2873, 1732, 1490, 1363, 1184, 1090, 832. Anal. Calcd for $C_{17}H_{24}ClNO_3$: C, 62.67; H, 7.42; N, 4.30. Found: C, 62.76; H, 7.70; N, 4.29.

4.3.1.17. 3RS-(3R,4S*,5R*)-2-tert-Butyl-3-(p-nitrophenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9u**).* Eluent: ether/hexane 1:2. Yield 132 mg, 87%, yellow crystals, mp 60–62 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.06 (s, 9H, ^{t}Bu–*H*), 1.22 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.35 (d, *J*=5.8 Hz, 3H, C*H*$_3$), 2.90 (t, *J*=9.4 Hz, 1H, H-4), 4.06–4.24 (m, 2H, CH$_3$CH$_2$), 4.35 (qd, *J*=11.7, 5.8 Hz, 1H, H-5), 4.78 (d, *J*=9.4 Hz, 1H, H-3), 7.66 (d, *J*=8.7 Hz, 2H, Ph–*H*), 8.16 (d, *J*=8.7 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.6 (*C*H$_3$CH$_2$), 17.4 (*C*H$_3$), 25.5 (3C, (*C*H$_3$)$_3$C–N), 60.1 ((CH$_3$)$_3$*C*–N), 60.8 (CH$_3$*C*H$_2$), 65.1 (C-4), 65.4 (C-3), 77.3 (C-5), 123.2, 127.2, 146.7, 149.9 (*C*–Ph), 169.1 (*C*=O). IR (cm^{-1}, NaCl) ν_{max} 2977, 2937, 2908, 2874, 1732, 1599, 1523, 1348, 1186, 855, 836. Anal. Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.53; H, 7.23; N, 8.36.

4.3.1.18. 3RS-(3R,4S*,5R*)-2-tert-Butyl-3-(p-methoxyphenyl)-4-carbethoxy-5-methyl-isoxazolidine (**9v**).* Eluent: ether/hexane 1:2. Yield 121 mg, 78%, colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.07 (s, 9H, ^{t}Bu–*H*), 1.20 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.34 (d, *J*=5.9 Hz, 3H, C*H*$_3$), 2.93 (t, *J*=9.5 Hz, 1H, H-4), 3.78 (s, 3H, OC*H*$_3$), 4.07–4.18 (m, 2H, CH$_3$C*H*$_2$), 4.32 (qd, *J*=11.8, 5.9 Hz, 1H, H-5), 4.62 (d, *J*=9.6 Hz, 1H, H-3), 6.82 (d, *J*=8.7 Hz, 2H, Ph–*H*), 7.37 (d, *J*=8.6 Hz, 2H, Ph–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 13.8 (*C*H$_3$CH$_2$), 17.6 (*C*H$_3$), 25.8 (3C, (*C*H$_3$)$_3$C–N), 54.8 (O*C*H$_3$), 60.1 ((CH$_3$)$_3$*C*–N), 60.5 (CH$_3$CH$_2$O–), 65.6 (C-4), 66.2 (C-3), 76.9 (C-5), 113.3, 127.6, 134.0, 158.4 (*C*–Ph), 169.9 (*C*=O). IR (cm^{-1}, NaCl) ν_{max} 2979, 2934, 1732, 1612, 1511, 1248, 1182, 1034, 815. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.15; H, 8.51; N, 4.37.

4.3.1.19. 3RS-(3R,4S*,5R*)-2-tert-Butyl-3-(2-furyl)-4-carbethoxy-5-methyl-isoxazolidine (**9w**).* Eluent: ether/hexane 1:2. Yield 128 mg, 76%, colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.11 (s, 9H, ^{t}Bu–*H*), 1.24 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.37 (d, *J*=5.9 Hz, 3H, C*H*$_3$), 3.22 (t, *J*=9.0 Hz, 1H, H-4), 4.17 (m, 2H, CH$_3$C*H*$_2$), 4.32 (ddd, *J*=11.8, 9.0, 5.9 Hz, 1H, H-5), 4.74 (d, *J*=8.9 Hz, 1H, H-3), 6.27 (m, 2H, Fur–*H*), 7.35 (br s, 1H, Fur–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.2 (*C*H$_3$CH$_2$), 18.4 (*C*H$_3$), 26.0 (3C, (*C*H$_3$)$_3$C–N), 60.2 ((CH$_3$)$_3$*C*–N), 60.7 (C-3), 61.1 (CH$_3$*C*H$_2$), 62.1 (C-4), 77.5 (C-5), 107.0, 110.2, 141.9, 153.9 (*C*–Fur), 170.3 (*C*=O). IR (cm^{-1}, NaCl) ν_{max} 2978, 2934, 2874, 1735, 1364, 1184, 1030, 736. Anal. Calcd for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.13; H, 8.23; N, 5.03.

4.3.1.20. 3RS-(3R,4S*,5R*)-2-tert-Butyl-3-(3-pyridyl)-4-carbethoxy-5-methyl-isoxazolidine (**9x**).* Eluent: ether/hexane 4:1. Yield 121 mg, 74%, colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 1.08 (s, 9H, ^{t}Bu–*H*), 1.22 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$), 1.37 (d, *J*=5.89 Hz, 3H, C*H*$_3$), 2.94 (t, *J*=9.5 Hz, 1H, H-4), 4.03–4.24 (m, 2H, CH$_3$C*H*$_2$), 4.36 (qd, *J*=11.7, 5.8 Hz, 1H, H-5), 4.70 (d, *J*=9.5 Hz, 1H, H-3), 7.25 (br dd, *J*=7.7, 4.8 Hz, 1H, Pyr–*H*), 7.88 (d, *J*=7.8 Hz, 1H, Pyr–*H*), 8.46–8.52 (m, 1H, Pyr–*H*), 8.62 (br s, 1H, Pyr–*H*). ^{13}C NMR (100 MHz, CDCl$_3$): δ 14.2 (*C*H$_3$CH$_2$), 18.0 (*C*H$_3$), 26.2 (3C, (*C*H$_3$)$_3$C–N), 60.7 ((CH$_3$)$_3$*C*–N), 61.3 (CH$_3$*C*H$_2$), 64.6 (C-3), 65.8 (C-4), 77.7 (C-5), 123.5, 134.7, 138.3, 148.8, 148.9 (*C*–Pyr), 169.8 (*C*=O). IR (cm^{-1}, NaCl) ν_{max} 2977, 2936, 2910, 2874, 1731, 1589, 1479, 1191, 1026, 767, 716. Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.65; H, 8.45; N, 9.47.

References and notes

1. Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
2. Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563–2591.
3. Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284.
4. Stadler, A.; Pichler, S.; Horeis, G.; Kappe, C. O. *Tetrahedron* **2002**, *58*, 3177–3183.
5. Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975–2978.
6. Kidwai, M. *Pure Appl. Chem.* **2001**, *73*, 147–151.
7. Hren, J.; Kranjc, K.; Polanc, S.; Kocevar, M. *Synthesis* **2008**, 452–458.
8. An, L. T.; Ding, F. Q.; Zou, J. P.; Lu, X. H. *Synth. Commun.* **2008**, *38*, 1259–1267.
9. Varma, R. S. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2006**, *45*, 2305–2312.
10. Kidwai, M.; Mothsra, P. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2006**, *45*, 2330–2336.
11. Kidwai, M.; Rastogi, S. *Heteroat. Chem.* **2005**, *16*, 138–141.
12. Ješelnik, M.; Varma, R. S.; Polanc, S.; Kocevar, M. *Chem. Commun.* **2001**, 1716–1717.
13. Saravanan, S.; Srinivasan, P. C. *Synth. Commun.* **2001**, *31*, 823–826.
14. Kranjc, K.; Kocevar, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2001–2007.

15. Balogh, G. T.; Vukics, K.; Könczöl, A.; Kis-Varga, A.; Gere, A.; Fischer, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3012–3015.
16. Dhainaut, A.; Tizot, A.; Raimbaud, E.; Lockhart, B.; Lestage, P.; Goldstein, S. *J. Med. Chem.* **2000**, *43*, 2165–2175.
17. Kim, S.; Vilela, G. V. M. D.; Bouajila, J.; Dias, A. G.; Cyrino, F. Z. G. A.; Bouskela, E.; Costa, P. R. R.; Nepveu, F. *Bioorg. Med. Chem.* **2007**, *15*, 3572–3578.
18. Gautheron-Chapoulaud, V.; Pandya, S. U.; Cividino, P.; Masson, G.; Py, S.; Vallée, Y. *Synlett* **2001**, 1281–1283.
19. West, P.R.; Davis, G.C. U.S. Patent 4,709,107, 1987.
20. Dicken, C. M.; DeShong, P. *J. Org. Chem.* **1982**, *47*, 2047–2051.
21. Hassan, A.; Wazeer, M. I. M.; Perzanowski, H. P.; Ali, S. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 411–418.
22. Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
23. Martin, J. N.; Jones, R. C. F. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley-Interscience: New Jersey, NJ, 2003; pp 1–81.
24. Rück-Braun, K.; Freysoldt, T. H. E.; Wierschem, F. *Chem. Soc. Rev.* **2005**, *34*, 507–516.
25. Charmier, M. A. J.; Kukushkin, V. Y.; Pombeiro, A. J. L. *Dalton Trans.* **2003**, 2540–2543.
26. Baruah, B.; Prajapati, D.; Baruah, A.; Sandhu, J. S. *Synth. Commun.* **1997**, *27*, 2563–2567.
27. Kusurkar, R. S.; Kannadkar, U. D. *Synth. Commun.* **2001**, *31*, 2235–2239.
28. Loupy, A.; Petit, A.; Bonnet-Delpon, D. *J. Fluorine Chem.* **1995**, *75*, 215–216.
29. Frederickson, M. *Tetrahedron* **1997**, *53*, 403–425.
30. Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485–504.
31. Diev, V. V.; Stetsenko, O. N.; Tung, T. Q.; Kopf, J.; Kostikov, R. R.; Molchanov, A. P. *J. Org. Chem.* **2008**, *73*, 2396–2399.
32. Rios, R.; Ibrahem, I.; Vesely, J.; Zhao, G. L.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 5701–5705.
33. Banerji, A.; Biswas, P. K.; Sengupta, P.; Dasgupta, S.; Gupta, M. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2004**, *43*, 880–881.
34. Andrade, M. M.; Barros, M. T.; Rodrigues, P. *Eur. J. Org. Chem.* **2007**, 3655–3668.
35. Rothenberg, G.; Downie, A. P.; Raston, C. L.; Scott, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8701–8708.
36. Banerji, A.; Dasgupta, S.; Sengupta, P.; Prangé, T.; Neuman, A. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **2004**, *43*, 1925–1933.
37. *endo*/*exo* assignments are made relatively to the ethoxycarbonyl substituent.
38. Most of these nitrones are already described in the literature, spread in several publications. With the purpose of creating a library of nitrones, we decided to compile here their most relevant spectroscopic data and melting points.
39. Singh, G.; Ishar, M. P. S.; Girdhar, N. K.; Singh, L. *J. Heterocycl. Chem.* **2005**, *42*, 1047–1054.
40. Huisgen, R.; Hauck, H.; Grashey, R.; Seidl, H. *Chem. Ber.* **1968**, *101*, 2568–2584.