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Regioselective 1,3-Dipolar Cycloaddition Reactions of 4-Methylene-2-oxazolidinones with Benzonitrile Oxide

Rebecca Newton[A] *and G. Paul Savage*[A,B]

[A]CSIRO Molecular and Health Technologies, Private Bag 10, Clayton South MDC, VIC 3169, Australia.
[B]Corresponding author. Email: paul.savage@csiro.au

Substituted 4-methylene-2-oxazolidinones were prepared in two steps by cyclizing *O*-propargyl carbamates, which in turn were prepared from propargyl alcohols and phenyl isocyanate. The 4-methylene-2-oxazolidinones underwent a 1,3-dipolar cycloaddition reaction with benzonitrile oxide to give the corresponding spiro heterocycles. Where the substitution pattern on the oxazolidinone engendered facial asymmetry, the cycloadditon reaction proceeded with 5:1 selectivity for the less hindered face of the dipolarophile.

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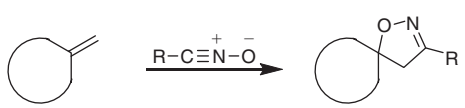
Introduction

The 1,3-dipolar cycloaddition reaction of nitrile oxides with carbon dipolarophiles is a versatile and powerful synthetic method to prepare Δ^2-isoxazolines and isoxazoles, which in turn are useful precursors to β-hydroxy ketones, β-amino alcohols, 1,3-diols, and a range of other 1,3-disubstituted compounds.[1] We have been interested in controlling the stereochemistry and regiochemistry of cycloaddition,[2,3] inhibiting the competing side reaction of nitrile oxide dimerization,[3,4] novel methods of ring-opening isoxazole cycloaddition products,[5–7] and subsequent reactions on the ring-opened products.[8] In particular, we have explored nitrile oxide cycloaddition reactions with exocyclic methylene compounds, which lead to novel spiro heterocyclic compounds (Scheme 1).[9–11]

Despite their ease of formation, and reported biological activity,[12,13] substituted 4-methylene-2-oxazolidinones have received relatively little attention in the literature. In particular, there are no reports in the literature of nitrile oxide cycloaddition reactions with 4-methylene-2-oxazolidinones, and the expected spiro heterocyclic ring system is quite rare. There is one report of nitrone cycloadditions to 4-methylene-2-oxazolidinones,[14] and a single report of a nitrile oxide cycloaddition to a related, if rather obscure, allene oxazolidinone derivative.[15] We now describe the nitrile oxide cycloaddition of 4-methylene-2-oxazolidinones to generate 1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one systems.

Results and Discussion

The most convenient precursors to nitrile oxides are the corresponding hydroximoyl chlorides, which eliminate HCl on treatment with mild bases such as triethylamine and sodium carbonate.[16] Nitrile oxide generation can be carried out in THF, dichloromethane, diethyl ether, or other aprotic solvents. Benzohydroximoyl chloride can be conveniently prepared from commercially available benzaldehyde oxime by treatment with *N*-chlorosuccinimide.[17]



Scheme 1.

Propargyl alcohols react with isocyanates to give *O*-propargyl carbamates, which in turn can undergo base-promoted cyclization. The direct, one-pot reaction to give 4-methylene-2-oxazolidinones has long been established for some specific analogues.[18–20] However, these reported procedures, generally catalyzed by sodium methoxide or pyridine, are extremely exothermic and not well defined. Yields are moderate to poor in most cases. A more recent report describes the addition of a stoichiometric quantity of triethylamine to a solution of the appropriate alcohol and phenylisocyanate in THF at room temperature, to give improved yields of the oxazolidinones.[21] However, although this procedure was satisfactory for propargyl alcohol and monosubstituted derivatives, it is limited in that disubstituted propargyl alcohols give poor yields and products that are difficult to purify. In our hands, the most reliable procedure for preparing disubstituted 4-methylene-2-oxazolidinones was a two-step procedure, isolating the *O*-propargyl carbamate intermediates.

Propargyl alcohols **1a**–**g** were converted to the corresponding phenyl carbamates **2a**–**g** using a modification of literature procedures,[21,22] whereby the alcohol was reacted with phenyl isocyanate at room temperature in THF with an equivalent of triethylamine and a catalytic amount of dimethylaminopyridine (DMAP) (Scheme 2). Yields were very good to quantitative (Table 1), and in most cases the unpurified products could be used for the next step.

A recent publication reports rapid and efficient cyclization of carbamates **2** to the requisite oxazolidinones **3** under mild conditions (10 mol-% LiOH in DMF).[23] Under these conditions, cyclization of **2a** and **2b** was very facile, as reported. Although the report did not include cyclization of any carbamates derived from tertiary alcohols, we found that carbamates **2c**–**g** also underwent cyclization, albeit somewhat more sluggishly.

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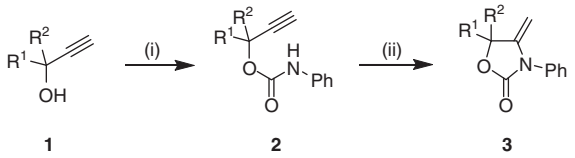
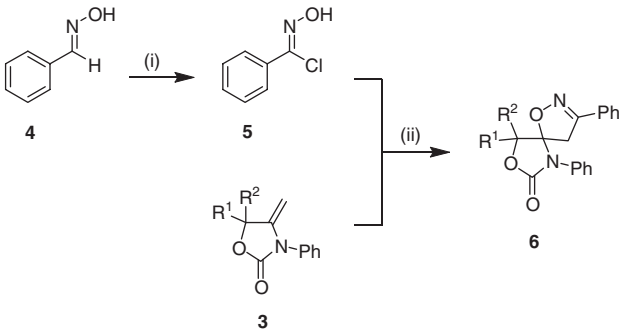


(i) PhNCO, Et_3N, DMAP (0.12 eq), THF, room temp., 90 h;
(ii) $LiOH \cdot H_2O$ (0.1 eq), DMF, room temp., 1–90 h

Scheme 2.

Table 1. Yields of carbamates 2 and oxazolidinone 3 formation

Entry	R^1	R^2	Yield of carbamate **2**	Yield of oxazolidinone **3**
a	H	H	100%	90%
b	H	Et	84%	94%
c	Me	Me	88%	100%
d	—$(CH_2)_4$—		89%	100%
e	—$(CH_2)_5$—		100%	80%
f	Me	Et	100%	92%
g	Me	Ph	74%	100%



(i) NCS, DMF;
(ii) triethylamine, dichloromethane, 0°C room temp. over 16 h, aqueous workup

Scheme 3.

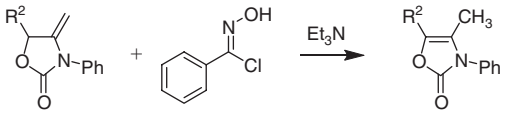
Whereas unhindered carbamates **2a** and **2b** cyclized within 1 h at room temperature, the more hindered derivatives **2c**–**g** took up to 90 h to cyclize. After modifying the reported procedure to incorporate an aqueous workup, oxazolidinones **2a**–**g** were prepared in excellent yields (Scheme 2).

Benzaldehyde oxime **4** was converted to benzohydroximoyl chloride **5** with *N*-chlorosuccinimide in DMF, according to the literature procedure.[17] Benzonitrile oxide, generated in situ by treating benzohydroximoyl chloride with triethylamine in either THF or dichloromethane, reacted with oxazolidinones **3a**–**g** to give the corresponding spiro cycloadducts (Scheme 3). The yields were similar with either solvent; however, dichloromethane led to an easier workup (Table 2). In each case, the cycloaddition was regiospecific, in that the oxygen of the nitrile oxide became attached to the disubstituted end of the double bond.[1] This was established by observing the ^1H NMR chemical shifts for the methylene protons of the newly formed isoxazoline rings. In each case, the characteristic AB system of these diastereotopic protons fell in the range of 3.0–3.5 ppm, which is indicative of protons on C4 of the isoxazoline ring rather than C5 (4.5–5.0 ppm),[11] hence establishing the regiochemistry of cycloaddition as shown (Scheme 3).

Table 2. Yields of cycloaddition reactions

Entry	R^1	R^2	Yield of spiro cycloadduct **6**
a	H	H	86%
b	H	Et	75%[A]
c	Me	Me	64%
d		—$(CH_2)_4$—	63%
e		—$(CH_2)_5$—	50%
f	Me	Et	58%[B]
g	Me	Ph	53%[C]

[A] Mixture of *anti* and *syn* addition products, 4.4:1.
[B] Mixture of *anti* and *syn* addition products, 5:1.
[C] Mixture of *anti* and *syn* addition products, 5:1.



Scheme 4.

In the case of cycloaddition reactions with oxazolidinones **3a** and **3b**, where $R^1 = H$, the order of reagent addition was critical. Typically, with nitrile oxide cycloaddition reactions, base is added to a preformed mixture of hydroximoyl chloride and the cycloaddition substrate.[1] However, when triethylamine was added to a solution of benzohydroximoyl chloride and oxazolidinones **3a** or **3b**, acid-catalyzed isomerization of the exocyclic double bond to give the *endo*-isomers **7a**, **b** was observed (Scheme 4). The resulting tri- or tetra-substituted double bonds were resistant to cycloaddition through steric hindrance. Adding benzohydroximoyl chloride slowly to a solution of oxazolidinone containing a slight excess of triethylamine ensured the reaction medium was basic throughout, thereby circumventing unwanted isomerization.

The yield of cycloadducts drops off significantly as steric bulk at the 5-position increases. We have previously observed that the stereochemical course of nitrile oxide cycloaddition reactions can be especially sensitive to steric influences.[10,11] In the three dipolarophile substrates (**3b**, **3f**, and **3g**), facial asymmetry gives rise to potential diastereomers. In all three cases, a selectivity of ~5:1 was observed. Not surprisingly, the major diastereomer formed from approach of the nitrile oxide to the least hindered face. This was established by nuclear Overhauser enhancement spectroscopy (NOESY). Dipolar couplings observed between the methylene protons of the isoxazoline ring and the substituent on the oxazolidinone served to ascertain the relative stereochemistry of the system. In the cases of isoxazolines **6b** and **6g**, single crystal X-ray structures were also obtained to confirm the relative stereochemistry of the cycloaddition adducts (Fig. 1 and Fig. 2, respectively).

Conclusion

Substituted 4-methylene-2-oxazolidinones have been shown to readily undergo 1,3-dipolar cycloaddition reactions with benzonitrile oxide to give the corresponding 1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one systems with complete regioselectivity. In the cases where the dipolarophile exhibited facial

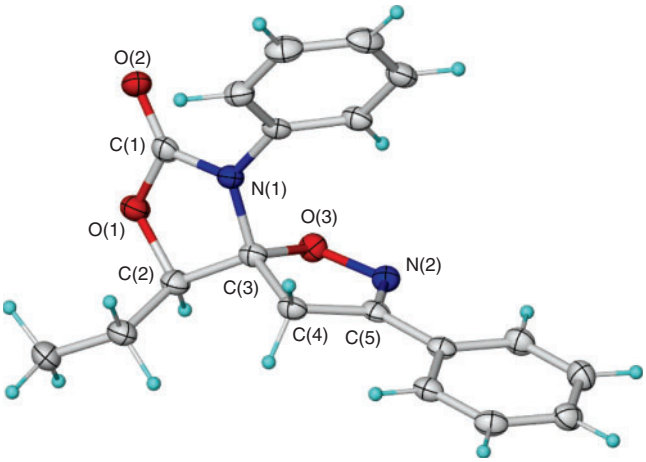


Fig. 1. Molecular diagram of (5*S**,9*S**)-9-ethyl-3,6-diphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one **6b**, shown with 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size. The molecule crystallizes in a centrosymmetric space group (P21/c), which means that the inverted structure is also present in the crystal.

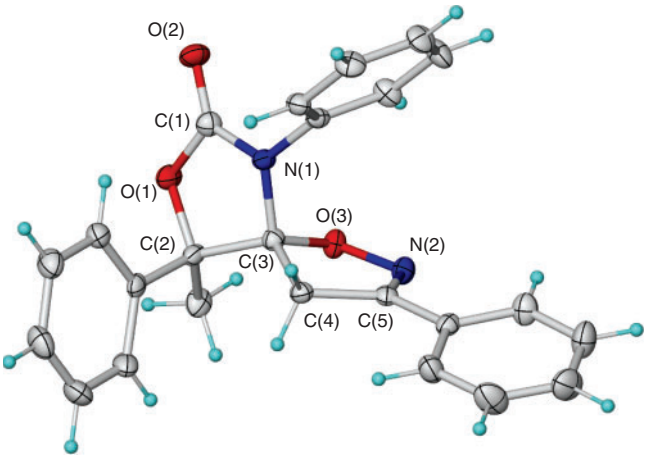


Fig. 2. Molecular diagram of (5*S**,9*S**)-9-methyl-3,6,9-triphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-ene-7-one **6g**, shown with 50% thermal ellipsoids and hydrogen atoms as spheres of arbitrary size. The molecule crystallizes in a centrosymmetric space group (P21/c), which means that the inverted structure is also present in the crystal.

asymmetry, the cycloaddition proceeded on the less-hindered face in a diastereomeric ratio of ~5:1.

Experimental

General

For general details, see ref. [3]. The Cambridge Crystallographic Data Centre contains the supplementary crystallographic data for the present paper. These data for (5*S**,9*S**)-9-ethyl-3,6-diphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one **6b** (CCDC 680920) and (5*S**,9*S**)-9-methyl-3,6,9-triphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-ene-7-one **6g** (CCDC 680921) can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html (verified 12 March 2008) or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223–336033; email: deposit@ccdc.cam.ac.uk.

General Method of Carbamate Synthesis

Phenyl isocyanate (1.3 mL, 12 mmol) was added to a solution of the appropriate acetylenic alcohol **1a**–**g** (10 mmol), triethylamine (2.1 mL, 15 mmol) and *N*,*N*-dimethylaminopyridine (146 mg, 1.2 mmol) in THF (10 mL) at room temperature. The reaction mixture was stirred for 90 h before adding 2 M HCl (25 mL) and extracting with EtOAc (3 × 25 mL). The combined organic phases were washed with saturated NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to return the crude product.[21,22] The crude products were sufficiently pure for subsequent cyclization reactions, but they could be purified by either recrystallization or flash column chromatography.

Prop-2-ynyl Phenylcarbamate ***2a***

Prepared on a 20-mmol scale to give carbamate **2a** (3.50 g, 100%) as a pale yellow solid, which was purified by flash column chromatography, eluting with 9:1 petrol/EtOAc, mp 60.6–61.8°C (lit.[23,24] 62°C), δ_H (400 MHz, $CDCl_3$) 7.41–7.06 (6H, m, Ar and NH), 4.78 (2H, d, *J* 2.3, CH_2) and 2.52 (1H, t, *J* 2.3, CH). δ_C (100 MHz, $CDCl_3$) 152.7 (C=O), 137.5 (ArC), 129.1, 123.8, 118.9 (ArCH), 77.9 (C), 75.1 (CH) and 52.8 (CH_2).

Pent-1-yn-3-yl Phenylcarbamate ***2b***

Prepared on a 20-mmol scale to give carbamate **2b** (3.43 g, 84%) as a pale yellow oil that very slowly solidified, and was subsequently purified by flash column chromatography, eluting with 9:1 petrol/EtOAc, mp 46.6–48.2°C. δ_H (400 MHz, $CDCl_3$) 7.40–7.29 (4H, m, Ar), 7.07 (1H, t, *J* 7.3, Ar), 6.71 (1H, br s, NH), 5.37 (1H, dt, *J* 2.0 and 6.4, CH_2CH), 2.49 (1H, d, *J* 2.0, C≡C*H*), 1.86 (2H, p, *J* 7.2, CH_3CH_2CH) and 1.07 (3H, t, *J* 7.4, CH_3). δ_C (100 MHz, $CDCl_3$) 152.5 (C=O), 137.7 (ArC), 129.2, 123.8, 118.8 (ArCH), 81.3 (C), 74.0 (C≡*C*H), 66.1 (CH_2*C*H), 28.2 (CH_3*C*H_2) and 9.3 (*C*H_3CH_2). Compound **2b** is referred to in a table in one literature reference[21] but no details are recorded in the experimental section.

2-Methylbut-3-yn-2-yl Phenylcarbamate ***2c***

Prepared on a 10-mmol scale and purified by flash column chromatography, eluting with 9:1 petrol/EtOAc to return carbamate **2c** (1.78 g, 88%) as a pale yellow solid, which was recrystallized from toluene to give colourless needles, mp 102°C (lit.[24] 102–103°C). δ_H (200 MHz, $CDCl_3$) 7.42–7.24 (4H, m, Ar), 7.05 (1H, t, *J* 7.2, Ar), 6.63 (1H, br s, NH), 2.58 (1H, s, C≡C*H*) and 1.75 (6H, s, 2 × CH_3). δ_C (50 MHz, $CDCl_3$) 151.7 (C=O), 137.9 (ArC), 129.1, 123.4, 118.7 (ArCH), 84.0 (*C*≡CH), 72.5 (C≡*C*H), 72.3 ($(CH_3)_2$*C*) and 29.3 (2 × CH_3).

1-Ethynylcyclopentyl Phenylcarbamate ***2d***

Prepared on a 2.5-mmol scale to return carbamate **2d** (510 mg, 89%) as a pale yellow solid, which was recrystallized from toluene to give colourless needles, mp 93.8–94.1°C. (Found: [M^+] 229.1098. $C_{14}H_{15}NO_2$ requires [M^+] 229.1103). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl) 3300, 2960, 1710, 1601, 1531, 1443, 1316, 1229, 1048. δ_H (200 MHz, $CDCl_3$) 7.41 (2H, d, *J* 8.0, Ar), 7.28 (2H, t, *J* 7.4, Ar), 7.04 (1H, t, *J* 7.3, Ar), 6.67 (1H, br s, NH), 2.60 (1H, s, C≡C*H*), 2.42–2.10 (4H, m, cyclopentyl (cp)) and 1.90–1.70 (4H, m, cp). δ_C (50 MHz, $CDCl_3$) 152.0 (C=O), 137.9 (ArC), 129.1, 123.4, 118.7 (ArCH), 84.4 and 80.9 (*CC*≡CH), 73.1 (C≡*C*H), 40.7 and 23.4 (cp).

1-Ethynylcyclohexyl Phenylcarbamate ***2e***

Prepared on a 10-mmol scale to return carbamate **2e** (2.42 g, 100%) as a pale yellow solid, which was purified by flash column chromatography, eluting with 9:1 petrol/EtOAc to give carbamate **2e** as an off-white solid, mp 94°C (lit.[24] 94–96°C). δ_H (200 MHz, $CDCl_3$) 7.38 (2H, d, *J* 8.0, Ar), 7.27 (2H, t, *J* 7.4, Ar), 7.03 (1H, t, *J* 7.3, Ar), 6.82 (1H, br s, NH), 2.61 (1H, s, C≡C*H*), 2.25–2.15 (2H, m, cyclohexyl (cy)), 2.0–1.85 (2H, m, cy), and 1.7–1.6 (6H, m, cy). δ_C (50 MHz, $CDCl_3$) 151.5 (C=O), 138.0 (ArC), 128.9, 123.2, 118.6 (ArCH), 83.9 (*C*≡CH), 75.6 and 74.5 (cy *C* and C≡*C*H), 27.3, 25.1 and 22.5 (cy).

3-Methylpent-1-yn-3-yl Phenylcarbamate ***2f***

Prepared on a 10-mmol scale to return carbamate **2f** (2.16 g, 100%) as a pale yellow solid, which was purified by flash column chromatography, eluting with 9:1 petrol/EtOAc to give carbamate **2f** as an off-white solid, mp 67–68°C (lit.[25] 68–69°C). δ_H (200 MHz, $CDCl_3$) 7.38 (2H, d, *J* 8.0, Ar), 7.27 (2H, t, *J* 7.4, Ar), 7.03 (1H, t, *J* 7.3, Ar), 6.71 (1H, br s, NH), 2.58 (1H, s, C≡C*H*), 2.04 and 1.92 (2H, m, *J* 7.4, CH_3CH_2) and 1.08 (3H, t, *J* 7.4, CH_3). δ_C (50 MHz, $CDCl_3$) 151.6 (C=O), 137.9 (ArC), 128.9, 124.0, 118.6 (ArCH), 83.9 (*C*≡CH), 75.9 and 73.4 (*C*C≡*C*H), 34.6 (CH_2), 26.3 (CH_3), 8.5 (CH_2CH_3).

2-Phenylbut-3-yn-2-yl Phenylcarbamate ***2g***

Prepared on a 5-mmol scale to return carbamate **2g** (980 mg, 74%) as a pale yellow solid, which was purified by flash column chromatography, eluting with with 9:1 petrol/EtOAc. A sample was recrystallized from toluene, mp 119.8–122.1°C. (Found: C 76.8, H 5.6, N 5.4. $C_{17}H_{15}NO_2$ requires C 77.0, H 5.7, N 5.3%). δ_H (200 MHz, $CDCl_3$) 7.69–7.65 (2H, m, Ar), 7.44–7.23 (7H, m, Ar), 7.05 (1H, t, *J* 7.2, Ar), 6.83 (1H, br s, NH), 2.89 (1H, s, C≡C*H*) and 1.98 (3H, s, CH_3). δ_C (50 MHz, $CDCl_3$) 151.1 (C=O), 142.3 and 137.8 (ArC), 129.0, 128.5, 128.1, 124.9, 123.4 and 118.6 (ArCH), 83.2 and 76.0 (*CC*≡CH), 75.9 (C≡*C*H) and 32.3 (CH_3).

General Method for Cyclization to Oxazolidinones ***3****[23]*

Lithium hydroxide monohydrate (21 mg, 0.5 mmol) was added to a solution of the appropriate carbamate **2a**–**g** (5.0 mmol) in DMF (5 mL) at room temperature and the reaction stirred for 1 h (unless otherwise stated). The reaction was diluted with water (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were then washed with water (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to return the oxazolidinones **3a**–**g**.

4-Methylene-3-phenyloxazolidin-2-one ***3a***

Prepared on a 5-mmol scale to return oxazolidinone **3a** (790 mg, 90%) as a pale yellow solid. δ_H (400 MHz, $CDCl_3$) 7.50–7.33 (5H, m, Ar), 5.03 (2H, d, *J* 2.0, CH_2C=CHH), 4.23 (1H, app. t, *J* 2.5, CH_2C=C*H*H) and 4.14 (1H, d, *J* 2.1, C=CH*H*). δ_C (100 MHz, $CDCl_3$) 156.1 (C=O), 141.9 (C4), 133.7 (ArC), 129.7, 128.5, 127.1 (ArCH), 82.1 (=*C*H_2) and 67.3 (C5). ^{1}H and ^{13}C NMR spectral data were in agreement with those previously reported.[23] The product was not purified further owing to concerns over *exo-endo* isomerization.

5-Ethyl-4-methylene-3-phenyloxazolidin-2-one ***3b***

Prepared on a 5-mmol scale to return oxazolidinone **3b** (960 mg, 94%) as a pale yellow solid. δ_H (400 MHz, $CDCl_3$) 7.40–7.27 (5H, m, Ar), 5.17–5.09 (1H, br m, CH_2C*H*C=CHH), 4.22–4.19 (1H, br m, C=C*H*H), 4.08–4.06 (1H, br m, C=CH*H*), 2.06–1.96 (1H, m, CH_3C*H*HCH), 1.89–1.79 (1H, m, CH_3CH*H*CH) and 1.11 (3H, t, *J* 7.4, CH_3). δ_C (100 MHz, $CDCl_3$) 155.7 (C=O), 146.1 (C4), 134.0 (ArC), 129.7, 128.5, 127.2 (ArCH), 82.2 (=*C*H_2), 79.6 (C5), 28.5 (CH_3CH_2) and 8.0 (CH_3). ^{1}H NMR spectral data were in agreement with those previously reported.[21] The product was not purified further due to concerns over *exo-endo* isomerization.

5,5-Dimethyl-4-methylene-3-phenyloxazolidin-2-one ***3c***

Prepared on a 5-mmol scale (reaction stirred at room temperature for 16 h) to return oxazolidinone **3c** (1.02 g, 100%) as a colourless solid, which was recrystallized from ethanol, mp 119.3–122.6°C (lit.[26] 121–123°C). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1751, 1654. δ_H (400 MHz, $CDCl_3$) 7.50–7.30 (5H, m, Ar), 4.14 (1H, d, *J* 2.7, C=C*H*H), 4.04 (1H, d, *J* 2.7, C=CH*H*) and 1.63 (6H, s, 2 × CH_3). δ_C (100 MHz, $CDCl_3$) 154.6 (C=O), 152.0 (C4), 134.2 (ArC), 129.7, 128.4, 127.2 (ArCH), 82.6 (C5), 81.3 (=*C*H_2) and 28.2 (2 × CH_3). ^{1}H NMR spectral data were in agreement with those previously reported.[26] Oxazolidinone **3c** was typically used for further reactions without purification.

4-Methylene-3-phenyl-1-oxa-3-azaspiro[4.4]nonan-2-one ***3d***

Prepared on a 5-mmol scale (reaction stirred at room temperature for 16 h) to return oxazolidinone **3d** (1.15 g, 100%) as a colourless solid, which was recrystallized from ethanol, mp 150.8–151.0°C. (Found: C 73.2, H 6.6, N 6.1, [M^+] 229.1097. $C_{14}H_{15}NO_2$ requires C 73.3, H 6.6, N 6.1%, [M^+] 229.1103). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1760, 1648. δ_H (400 MHz, $CDCl_3$) 7.49–7.34 (5H, m, Ar), 4.15 (1H, d, *J* 2.8, C=C*H*H), 4.07 (1H, d, *J* 2.8, C=CH*H*), 2.36–2.19 (2H, m, cp) and 2.10–1.80 (6H, m, cp). δ_C (50 MHz, $CDCl_3$) 154.8 (C=O), 150.7 (C4), 134.3 (ArC), 129.6, 128.4, 127.2 (ArCH), 92.5 (C5), 81.2 (=CH_2), 41.3 and 24.5 (cp). Oxazolidinone **3d** was typically used for further reactions without purification.

4-Methylene-3-phenyl-1-oxa-3-azaspiro[4.5]decan-2-one ***3e***

Prepared on a 10-mmol scale (reaction stirred at room temperature for 16 h) and purified by flash column chromatography, eluting with 9:1 petrol/EtOAc to return oxazolidinone **3e** (1.95 g, 80%) as a pale yellow solid, which was recrystallized from ethanol, mp 168.6–168.7°C (lit.[18] 167–167.5°C). (Found: C 74.0, H 7.1, N 5.8, [M^+] 243.1246. $C_{15}H_{17}NO_2$ requires C 74.1, H 7.0, N 5.8%, [M^+] 243.1259). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1761, 1645. δ_H (200 MHz, $CDCl_3$) 7.53–7.28 (5H, m, Ar), 4.11 (1H, d, *J* 2.7, C=C*H*H), 4.00 (1H, d, *J* 2.7, C=CH*H*), 2.12–1.96 (2H, m, cy), 1.94–1.51 (7H, m, cy) and 1.47–1.16 (1H, m, cy). δ_C (50 MHz, $CDCl_3$) 154.9 (C=O), 152.0 (C4), 134.2 (ArC), 129.6, 128.4, 127.2 (ArCH), 84.3 (C5), 81.5 (=CH_2), 37.2, 24.8 and 21.8 (cy).

5-Ethyl-5-methyl-4-methylene-3-phenyloxazolidin-2-one ***3f***

Prepared on a 10-mmol scale (reaction stirred at room temperature for 90 h) to return oxazolidinone **3f** (2.00 g, 92%) as a pale yellow solid, which was recrystallized from ethanol, mp 80–86°C (lit.[24] 87–89°C). (Found: [M^+] 217.1098. $C_{13}H_{15}NO_2$ requires [M^+] 217.1103). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl

disc) 1751, 1645. δ_H (400 MHz, $CDCl_3$) 7.49–7.31 (5H, m, Ar), 4.16 (1H, d, *J* 2.7, C=C*H*H), 3.99 (1H, d, *J* 2.7, C=CH*H*), 1.94 (1H, dq, *J* 14.5 and 7.3, CH_3CHH), 1.79 (1H, dq, *J* 14.5 and 7.3, CH_3CHH), 1.59 (3H, s, CCH_3) and 1.02 (3H, t, *J* 7.3, CH_3CH_2). δ_C (50 MHz, $CDCl_3$) 155.0 (C=O), 150.4 (C4), 134.2 (ArC), 129.7, 128.4, 127.2 (ArCH), 85.3 (C5), 81.4 (=CH_2), 34.0 (CH_2CH_3), 26.7 (CCH_3) and 7.5 (CH_2CH_3). ^{1}H NMR spectral data are in agreement with those previously reported.[26]

5-Methyl-4-methylene-3,5-diphenyloxazolidin-2-one ***3g***

Prepared on a 5-mmol scale (reaction stirred at room temperature for 90 h) to return oxazolidinone **3g** (1.33 g, 100%) as a pale yellow solid, which was recrystallized from ethanol, mp 88.8–90.0°C. (Found: C 76.3, H 5.8, N 5.3, $[M^+]$ 265.1103. $C_{17}H_{15}NO_2$ requires C 77.0, H 5.70, N 5.3%, $[M^+]$ 265.1103). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1767, 1658. δ_H (400 MHz, $CDCl_3$) 7.61–7.35 (10H, m, Ar), 4.31 (1H, d, *J* 2.8, C=C*H*H), 4.21 (1H, d, *J* 2.8, C=CH*H*) and 2.01 (3H, s, CH_3). δ_C (50 MHz, $CDCl_3$) 154.4 (C=O), 150.7 (C4), 141.3 and 134.3 (ArC), 129.6, 128.7, 128.6, 128.4, 127.1 and 124.9 (ArCH), 84.9 (C5), 84.3 (=CH_2) and 27.7 (CH_3). Oxazolidinone **3g** was typically used for further reactions without purification.

General Method for Benzonitrile Oxide Cycloaddition Reactions

A solution of benzhydroximoyl chloride[17] (389 mg, 2.5 mmol) in dichloromethane (5 mL) was slowly added dropwise to a solution of the appropriate oxazolidinone **3a**–**g** (2.5 mmol) and triethylamine (385 μL, 2.75 mmol) in dichloromethane (2.5 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h before being diluted with dichloromethane (20 mL) and washed with HCl (2 M, 20 mL), saturated $NaHCO_3$ (20 mL), and saturated NaCl (20 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to return the crude product, which was purified as stated.

3,6-Diphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-ene-7-one ***6a***

Prepared on a 2.5-mmol scale and purified by flash column chromatography, eluting with 4:1 → 1:1 petrol/EtOAc gradient to return isoxazoline **6a** (630 mg, 86%) as a colourless solid, which was recrystallized from ethanol, mp 160.5–161.1°C. (Found: C 69.2, H 4.8, N 9.6, $[M^+]$ 294.1000. $C_{17}H_{14}N_2O_3$ requires C 69.4, H 4.79, N 9.5%, $[M^+]$ 294.1004). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1757, 1720, 1500, 1448, 1400, 1219. δ_H (400 MHz, $CDCl_3$) 7.48–7.26 (10H, m, Ar), 4.85 (1H, d, *J* 10.1, C9–Ha), 4.60 (1H, d, *J* 10.1, C9–Hb), 3.51 (1H, d, *J* 18.2, C4–Ha) and 3.37 (1H, d, *J* 18.2, C4–Hb). δ_C (125 MHz, $CDCl_3$) 156.6 (C=N), 155.1 (C=O), 133.5 (ArC), 130.9, 129.7, 129.0, 128.7 (ArCH), 128.2 (ArC), 127.4, 126.5 (ArCH), 100.0 (C5), 73.9 (C8), and 41.0 (C4).

(5S,9S*)- and (5S*,9R*)-9-Ethyl-3,6-diphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-en-7-one* ***6b***

Prepared on a 2.5-mmol scale to return the crude product (diastereomeric ratio (*dr*) 5:1), which was purified by flash column chromatography, eluting with 4:1 → 1:1 petrol/EtOAc gradient to return isoxazoline **6b** (600 mg, 75%, *dr* 4.4:1) as a colourless solid. Recrystallization from ethanol returned the major diastereomer (5*S**,9*S**)-**6b**, mp 159.6–161.3°C. (Found: C 70.8, H 5.7, N 8.8, $[M^+]$ 322.1314. $C_{19}H_{18}N_2O_3$ requires C 70.8, H 5.6, N 8.7%, $[M^+]$ 322.1317). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1764, 1658, 1641, 1382. δ_H (200 MHz, $CDCl_3$) 7.52–7.20 (10H, m, Ar), 4.79 (1H, dd, *J* 8.7 and 4.1, C8–H), 3.49 (1H, d, *J* 18.3, C4–Ha), 3.20 (1H, d, *J* 18.3, C4–Hb), 2.06–1.67 (2H, m, CH_3CH_2CH) and 1.16 (3H, t, *J* 7.3, CH_3CH_2). δ_C (50 MHz, $CDCl_3$) 156.6 (C=N), 154.7 (C=O), 133.7 (ArC), 130.8, 129.6, 128.9, 128.7 (ArCH), 128.2 (ArC), 127.8, 126.4 (ArCH), 103.0 (C5), 83.1 (C8), 36.8 (C4), 25.1 (CH_3CH_2), and 9.1 (CH_3).

The minor diastereomer (5*S**,9*R**)-**6b** could not be isolated from the major diastereomer and the NMR spectra were assigned by subtraction. δ_H (200 MHz, $CDCl_3$) 7.52–7.20 (10H, m, Ar), 4.53 (1H, dd, *J* 8.7 and 4.1, C8–H), 3.49 (1H, d, *J* 18.3, C4–Ha), 3.25 (1H, d, *J* 18.3, C4–Hb), 2.20–1.90 (2H, m, CH_3CH_2) and 1.16 (3H, t, *J* 7.3, CH_3CH_2). δ_C (50 MHz, $CDCl_3$) 156.6 (C=N), 154.7 (C=O), 133.7 (ArC), 130.8, 129.5, 128.9, 128.8 (ArCH), 128.3 (ArC), 127.2, 126.4 (ArCH), 101.1 (C5), 85.1 (C8), 40.7 (C4), 21.8 (CH_3CH_2), and 10.0 (CH_3).

9,9-Dimethyl-3,6-diphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-ene-7-one ***6c***

Prepared on a 5.0-mmol scale and purified by flash column chromatography, eluting with 1% diethyl ether in dichloromethane, gave isoxazoline **6c** (1.03 g, 64%) as a colourless solid, which was recrystallized from ethanol, mp 175.2–176.4°C. (Found: C 70.7, H 5.7, N 8.8, $[M^+]$ 322.1316. $C_{19}H_{18}N_2O_3$ requires C 70.8, H 5.6, N 8.7%, $[M^+]$ 322.1317). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1759, 1599, 1498, 1393, 1372, 1119. δ_H (400 MHz, $CDCl_3$) 7.48–7.26 (10H, m, Ar), 3.41 (1H, d, *J* 18.3, C4–Ha), 3.29 (1H, d, *J* 18.3, C4–Hb), 1.64 (3H, s, CH_3) and 1.62 (3H, s, CH_3). δ_C (100 MHz, $CDCl_3$) 156.1 (C=N), 155.0 (C=O), 134.2 (ArC), 130.8, 129.7, 128.9, 128.7 (ArCH), 128.3 (ArC), 127.8, 126.5 (ArCH), 104.9 (C5), 84.5 (C8), 37.1 (C4), 25.7, and 21.2 (2 × CH_3).

3,6-Diphenyl-1,8-dioxa-2,6-diazadispiro[4.3.4.0]tridec-2-ene-7-one ***6d***

Prepared on a 5.0-mmol scale to return the crude product, which was purified by flash column chromatography, eluting with 1% diethyl ether in dichloromethane to return isoxazoline **6d** (1.10 g, 63%) as a colourless solid, which was recrystallized from ethanol, mp 175.9–176.4°C. (Found: C 72.3, H 5.8, N 8.0, $[M^+]$ 348.1469. $C_{21}H_{20}N_2O_3$ requires C 72.4, H 5.79, N 8.0%, $[M^+]$ 348.1471). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1758, 1641, 1498, 1373. δ_H (400 MHz, $CDCl_3$) 7.34–7.24 (10H, m, Ar), 3.42 (1H, d, *J* 18.3, C4–Ha), 3.32 (1H, d, *J* 18.3, C4–Hb), 2.40–2.20 (1H, m, cp) and 2.15–1.70 (7H, m, cp). δ_C (50 MHz, $CDCl_3$) 156.0 (C=N), 155.1 (C=O), 134.1 (ArC), 130.7, 129.5, 128.9, 128.6 (ArCH), 128.3 (ArC), 127.8, 126.4 (ArCH), 104.5 (C5), 95.0 (C8), 37.3, 37.0, 32.6, 24.5, and 23.3 (C4 and cp).

3,6-Diphenyl-1,8-dioxa-2,6-diazadispiro[4.3.5.0]tetradec-2-ene-7-one ***6e***

Prepared on a 5.0-mmol scale to return the crude product, which was purified by flash column chromatography, eluting with 1% diethyl ether in dichloromethane followed by recrystallization from ethanol to give isoxazoline **6e** (910 mg, 50%) as a colourless solid, mp 186.7–187.6°C. (Found: C 72.8, H 6.2, N 7.8, $[M^+]$ 362.1618. $C_{22}H_{22}N_2O_3$ requires C 72.9, H 6.12, N 7.7%, $[M^+]$ 362.1630). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1743, 1708,

1662, 1599, 1391. δ_H (400 MHz, $CDCl_3$) 7.52–7.20 (10H, m, Ar), 3.47 (1H, d, *J* 18.3, C4–Ha), 3.23 (1H, d, *J* 18.3, C4–Hb), 2.50–2.35 (1H, m, cy), 2.10–1.95 (1H, m, cy), 1.95–1.60 (6H, m, cy), 1.55–1.40 (1H, m, cy) and 1.40–1.10 (1H, m, cy). δ_C (50 MHz, $CDCl_3$) 156.2 (C=N), 155.0 (C=O), 134.1 (ArC), 130.7, 129.5, 128.8, 128.7 (ArCH), 128.3 (ArC), 128.0, 126.4 (ArCH), 105.0 (C5), 85.5 (C8), 37.0, 33.9, 29.3, 24.9, 21.9, and 21.8 (C4 and cy).

(5S,9S*)- and (5S*,9R*)-9-Ethyl-9-methyl-3,6-diphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-ene-7-one* ***6f***

Prepared on a 2.5-mmol scale to return the crude product (*dr* 5:1), which was purified by flash column chromatography, eluting with 4:1 → 1:1 petrol:EtOAc gradient to return isoxazoline **6f** as a colourless solid (980 mg, 58% as a mixture of diastereomers). Recrystallization from ethanol returned the major diastereomer (5*S**,9*S**)-**6f** as colourless crystals, mp 135.8–137.8°C. (Found: C 71.2, H 6.0, N 8.4, [M^+] 336.1467. $C_{20}H_{20}N_2O_3$ requires C 71.4, H 6.0, N 8.3%, [M^+] 336.1474). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1757, 1599, 1498, 1371. δ_H (200 MHz, $CDCl_3$) 7.50–7.20 (10H, m, Ar), 3.45 (1H, d, *J* 18.2, C4–Ha), 3.24 (1H, d, *J* 18.2, C4–Hb), 1.95–1.73 (2H, m, CH_3CH_2), 1.58 (3H, s, CH_3) and 1.15 (3H, t, *J* 7.3, CH_3CH_2). δ_C (50 MHz, $CDCl_3$) 156.2 (C=N), 155.0 (C=O), 134.0, 130.6, 129.5, 128.8, 128.5, 128.3, 127.6, 126.3 (Ar), 104.6 (C5), 86.5 (C8), 37.8 (C4), 31.2 (CH_3), 18.8 (CH_2CH_3), and 8.0 (CH_2CH_3).

The minor diastereomer (5*S**,9*R**)-**6f** could not be isolated from the major diastereomer and the NMR spectra were assigned by subtraction. δ_H (200 MHz, $CDCl_3$) 7.50–7.20 (10H, m, Ar), 4.16 (1H, d, *J* 2.8, C4–Ha), 4.00 (1H, d, *J* 2.8, C4–Hb), 2.20–2.00 (2H, m, CH_3CH_2), 1.56 (3H, s, CH_3) and 1.03 (3H, t, *J* 7.3, CH_3CH_2). δ_C (50 MHz, $CDCl_3$) 156.1 (C=N), 155.0 (C=O), 134.0, 130.7, 129.5, 128.9, 128.6, 128.2, 127.8, 126.4 (Ar), 104.1 (C5), 86.5 (C8), 37.8 (C4), 27.3 (CH_3), 22.0 (CH_2CH_3), and 8.1 (CH_2CH_3).

(5S,9S*)- and (5S*,9R*)-9-Methyl-3,6,9-triphenyl-1,8-dioxa-2,6-diazaspiro[4.4]non-2-ene-7-one* ***6g***

Prepared on a 5.0-mmol scale to return the crude product, which was purified by flash column chromatography, eluting with 1% diethyl ether in dichloromethane to return isoxazoline **6g** (1.01 g, 53%, *dr* 5:1) as a colourless solid. Recrystallization from ethanol gave the major diastereomer (5*S**,9*S**)-**6g**, mp 161.5–162.7°C. (Found: C 74.8, H 5.3, N 7.4, [M^+] 322.1314. $C_{24}H_{20}N_2O_3$ requires C 75.0, H 5.2, N 7.3%, [M^+] 322.1317). ν_{max}/cm^{-1} ($CHCl_3$ solution, NaCl disc) 1767, 1497, 1369, 1236. δ_H (200 MHz, $CDCl_3$) 7.55–7.20 (15H, m, Ar), 3.04 (1H, d, *J* 18.8, C4–Ha), 2.83 (1H, d, *J* 18.8, C4–Hb) and 2.05 (3H, s, CH_3). δ_C (50 MHz, $CDCl_3$) 156.8 (C=N), 155.2 (C=O), 140.0, 133.8 (ArC), 130.7, 129.5, 129.2, 129.0, 128.8, 128.7 (ArCH), 128.0 (ArC), 127.8, 126.4, 125.2 (ArCH), 105.3 (C5), 87.2 (C8), 38.7 (C4), and 21.6 (CH_3).

The minor diastereomer (5*S**,9*R**)-**6g** could not be isolated from the major diastereomer and the NMR spectra were assigned by subtraction. δ_H (200 MHz, $CDCl_3$) 7.55–7.20 (15H, m, Ar), 3.75 (1H, d, *J* 18.8, C4–Ha), 3.44 (1H, d, *J* 18.8, C4–Hb) and 2.00 (3H, s, CH_3). δ_C (50 MHz, $CDCl_3$) 156.7 (C=N), 155.2 (C=O), 140.0, 133.8, 130.7, 129.6, 129.1, 129.0, 128.8, 128.6, 128.4, 127.7, 126.3, 124.9 (Ar), 105.1 (C5), 87.4 (C8), 37.7 (C4), and 25.9 (CH_3).

Accessory Publication

The supplementary crystallographic data for the present paper is available from the authors, or until June 2013, the *Australian Journal of Chemistry*.

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References

[1] C. J. Easton, C. M. M. Hughes, G. P. Savage, G. W. Simpson, *Adv. Heterocycl. Chem.* **1994**, *60*, 261.
[2] C. J. Easton, C. M. M. Hughes, E. R. T. Tiekink, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.* **1995**, *36*, 629. doi:10.1016/0040-4039(94)02321-2
[3] C. J. Easton, C. M. M. Hughes, E. R. T. Tiekink, C. E. Lubin, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.* **1994**, *35*, 3589. doi:10.1016/S0040-4039(00)73248-5
[4] G. P. Savage, G. T. Wernert, *Aust. J. Chem.* **2005**, *58*, 877. doi:10.1071/CH05189
[5] S. J. Barrow, C. J. Easton, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.* **1997**, *38*, 2175. doi:10.1016/S0040-4039(97)00275-X
[6] C. J. Easton, G. A. Heath, C. M. M. Hughes, C. K. Y. Lee, G. P. Savage, G. W. Simpson, E. R. T. Tiekink, G. J. Vuckovic, R. D. Wesbster, *J. Chem. Soc., Perkin Trans. 1* **2001**, 1168. doi:10.1039/B008081K
[7] C. J. Easton, C. M. M. Hughes, K. D. Kirby, G. P. Savage, G. W. Simpson, E. R. T. Tiekink, *Chem. Commun.* **1994**, *18*, 2035.
[8] J. Anderson-McKay, G. P. Savage, G. W. Simpson, *Aust. J. Chem.* **1996**, *49*, 163.
[9] B. M. Kelly-Basetti, I. Krodkiewska, W. H. F. Sasse, G. P. Savage, G. W. Simpson, *Tetrahedron Lett.* **1995**, *36*, 327. doi:10.1016/0040-4039(94)02242-4
[10] C. K. Y. Lee, C. J. Easton, G. P. Savage, G. W. Simpson, *Arkivoc* **2006**, *3*, 175.
[11] B. M. Kelly-Basetti, M. F. Mackay, S. M. Pereira, G. P. Savage, G. W. Simpson, *Heterocycles* **1994**, *37*, 529.
[12] S. M. Pereira, G. P. Savage, G. W. Simpson, R. J. Greenwood, M. F. Mackay, *Aust. J. Chem.* **1993**, *46*, 1401.
[13] E. Toth, J. Torley, B. Hegedus, L. Szporny, B. Kiss, E. Palosi, D. Groo, I. Laszlovszky, E. Lapis, F. Auth, L. Gaal, *US Patent 5 157 038* **1992**.
[14] E. Toth, B. Kiss, A. Gere, E. Karpati, J. Torley, E. Palosi, A. Kis-Varga, M. Paroczai, S. Szabó, D. Groó, I. Laszlovszky, E. Lapis, K. Csomor, L. Szporny, *Eur. J. Med. Chem.* **1997**, *32*, 27. doi:10.1016/S0223-5234(97)84359-0
[15] M. C. Aversa, G. Cum, P. D. Giannetto, G. Romeo, N. Uccella, *J. Chem. Soc., Perkin Trans. 1* **1974**, 209. doi:10.1039/P19740000209
[16] Y. Horino, M. Kimura, S. Tanaka, T. Okajima, Y. Tamaru, *Chem. Eur. J.* **2003**, *9*, 2419. doi:10.1002/CHEM.200304586
[17] A. Werner, H. Buss, *Chem. Ber.* **1894**, *27*, 2193.
[18] K.-C. Liu, B. R. Shelton, R. K. Howe, *J. Org. Chem.* **1980**, *45*, 3916. doi:10.1021/JO01307A039
[19] K. Sisido, K. Hukuoka, M. Tuda, H. Nozaki, *J. Org. Chem.* **1962**, *27*, 2663. doi:10.1021/JO01054A522
[20] S. L. Shapiro, V. Bandurco, L. Freedman, *J. Org. Chem.* **1961**, *26*, 3710. doi:10.1021/JO01068A021
[21] N. R. Easton, D. R. Cassady, R. D. Dillard, *J. Org. Chem.* **1962**, *27*, 2927. doi:10.1021/JO01055A510
[22] Y. Tamaru, M. Kimura, S. Tanaka, S. Kure, Z. Yoshida, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2838. doi:10.1246/BCSJ.67.2838
[23] I. Fleming, K. Takaki, A. P. Thomas, *J. Chem. Soc., Perkin Trans. 1* **1987**, 2269. doi:10.1039/P19870002269
[24] R. Ramesh, Y. Chandrasekaran, R. Megha, S. Chandrasekaran, *Tetrahedron* **2007**, *63*, 9153. doi:10.1016/J.TET.2007.06.066
[25] N. Shachat, J. J. Bagnell, Jr, *J. Org. Chem.* **1963**, *28*, 991. doi:10.1021/JO01039A028
[26] H. Martin, G. Pissiotas, O. Rohr, *US Patent 3 800 037* **1974**.