Regiospecific Synthesis of 3-Substituted 5-Alkylisoxazoles from Oxime Dianions and *N*-Methoxy-*N*-methylalkylamides

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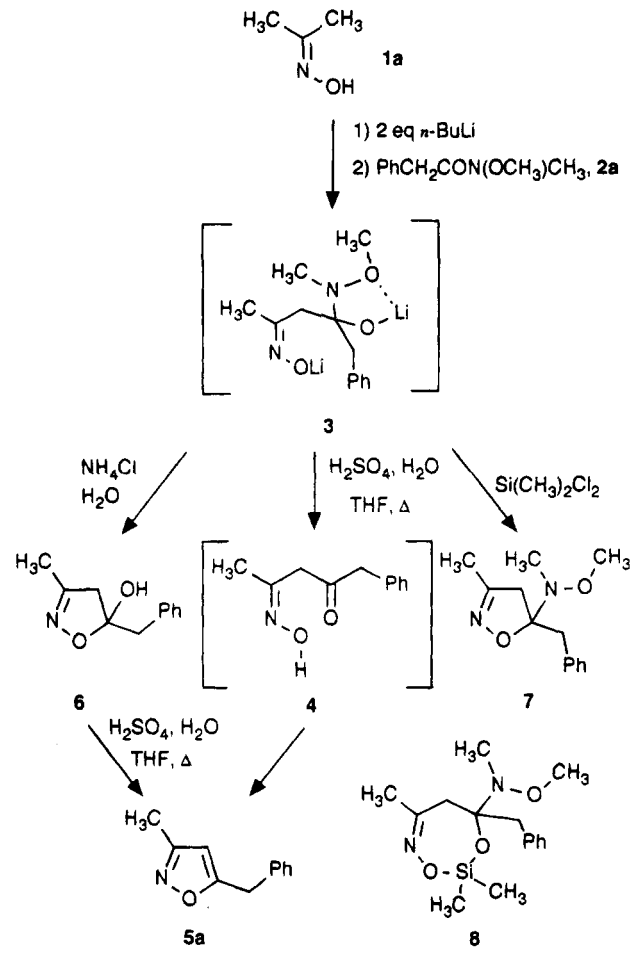
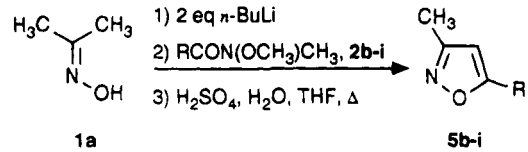
As part of our efforts directed at the synthesis of antipicornavirus agents,[1] we required a general synthesis of 3-methyl-5-alkylisoxazoles. Numerous methods are available for the synthesis of isoxazoles.[2] Barber and Olofson[3a] have described a convenient synthesis of 5-arylisoxazoles. In this method, oxime dianions[4] are acylated with *N*,*N*-dialkylarylamides to give, following acid hydrolysis, the 5-arylisoxazoles.[5] 5-Alkylisoxazoles are not obtained in this manner due to a postulated[3a] competing deprotonation of the alkylamides. A modification of this method which employs *O*-ethyl-*N*,*N*-dibutylamide carbocation salts overcomes this problem and allows for the introduction of the 5-alkyl group.[3b] Herein we report that utilization of *N*-methoxy-*N*-methylalkylamides[6] as the acylating agent offers a very simple alternative to the synthesis of 5-alkylisoxazoles from oxime dianions.

N-Methoxy-*N*-methylamides have been shown to be very effective acylating agents for a wide variety of organometallic reagents.[6,7] Reaction of *N*-methoxy-*N*-methylphenylacetamide (**2a**) (R = $PhCH_2$) with the dianion of acetone oxime **1a** provided 3-methyl-5-(phenylmethyl)isoxazole (**5a**) in 94% yield (Scheme 1). The presumed tetrahedral intermediate **3** was, without isolation, subjected to acidic hydrolysis to give β-keto oxime **4** which underwent cyclodehydration to **5a**. Quenching the reaction mixture with saturated ammonium chloride

Scheme 1



Scheme 2



allowed for the isolation of ketol **6** in 94% yield.[8] Dehydration to **5a** occurred in 84% yield. In an attempt to trap **3** with dichlorodimethylsilane, carbinolamine **7** was isolated in 69% yield after purification by silica gel chromatography. None of the expected silane **8** was observed in the crude product, as determined by MS, ^1H, and ^{13}C NMR analysis. The moderate yield for isolated, pure **7** may be due to instability on silica gel. The comparison between the crude and chromatographed ^1H and ^{13}C NMR spectra indicated that the crude product consisted mainly of **7** with only a small amount of an unidentified component. The formation of **8** cannot be ruled out as it may undergo an amine-induced fragmentation, loss of silanol, and subsequent ring closure to **7** during aqueous workup.

Application of this methodology to a variety of *N*-methoxy-*N*-methylalkylamides gave the desired 3-methyl-5-alkylisoxazoles **5b–i** (Scheme 2) in 55–94% isolated yields (Table 1) from the dianion of acetone oxime (**1a**).

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(2) (a) For a comprehensive review on isoxazoles, see: *The Chemistry of Heterocyclic Compounds*; Grünanger, P., Vita-Finzi, P., Eds.; John Wiley: New York, 1991; Vol. 49, Part 1, p 1. (b) Lang, S. A., Jr.; Lin, Y.-i. In *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: New York, 1984; Vol. 6, Part 4B, p 1. (c) For the use of nitrile oxides in the synthesis of isoxazoles, see: Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988. For an intramolecular cycloaddition of nitrile oxides to 3,5-disubstituted isoxazoles, see: Kim, H. J.; Lee, J. H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1992**, *57*, 6513. (d) The intramolecular cyclization of propargyloximes to isoxazoles has recently been reported: Short, K. M.; Ziegler, C. B., Jr. *Tetrahedron Lett.* **1993**, *34*, 75.

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(4) (a) Henoch, F. E.; Hampton, K. G.; Hauser, C. R. *J. Am. Chem. Soc.* **1969**, *91*, 676. (b) Beam, C. F.; Dyer, M. C. D.; Schwarz, R. A.; Hauser, C. R. *J. Org. Chem.* **1970**, *35*, 1806. (c) Kofron, W. G.; Yeh, M.-K. *J. Org. Chem.* **1976**, *41*, 439. (d) Jung, M. E.; Blair, P. A.; Lowe, J. A. *Tetrahedron Lett.* **1976**, *18*, 1439.

(5) 5-Arylisoxazoles can be prepared by treatment of oxime dianions with substituted benzoates: (a) Beam, C. F.; Shealy, K. D.; Harris, C. E.; Shealy, N. L.; Dasher, L. W.; Hollinger, W. M.; Sandifer, R. M.; Reames, D. C. *J. Pharm. Sci.* **1976**, *65*, 1408. (b) Fos, E.; Borràs, L.; Gasull, M.; Mauleón, D.; Carganico, G. *J. Heterocycl. Chem.* **1992**, *29*, 203.

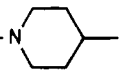
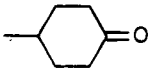
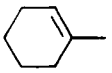
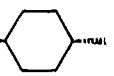
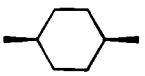
(6) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(7) For a recent review concerning the synthesis and chemistry of *N*-methoxy-*N*-methylamides, see: Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.

(8) For discussions concerning ring–chain equilibration of 2-isoxazolin-5-ols, see: (a) Castells, J.; Colombo, A. *J. Chem. Soc., Chem. Commun.* **1969**, 1062. (b) Escale, R.; Jacquier, R.; Ly, B.; Petrus, F., Verducci, J. *Tetrahedron* **1976**, *32*, 1369.

0022-3263/94/1959-5828$04.50/0

Table 1. Isoxazoles Prepared from Acetone Oxime Dianion and *N*-Methoxy-*N*-methylalkylamides

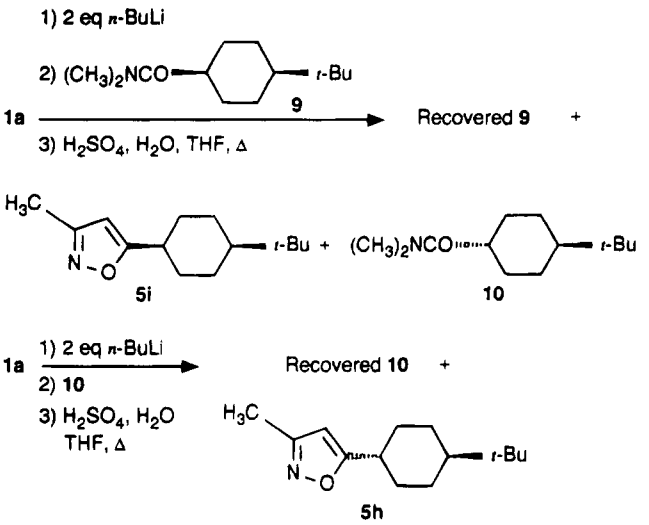
entry	amide, R	isoxazole, % yield[a]
1	**2a**, $PhCH_2$	**5a**, 94
2	**2b**, $(CH_3)_2CHCH_2$	**5b**, 72
3	**2c**, $(CH_3CH_2)_2CH$	**5c**, 62
4	**2d**, 	**5d**, 75
5	**2e**, *t*-BOC—N 	**5e**, 38[b]
6	**2f**, 	**5f**, 55, R= 
7	**2g**, 	**5g**, 85
8	**2h**, *t*-Bu 	**5h**, 90
9	**2i**, *t*-Bu 	**5i**, 80

[a] Isolated yields. [b] 61% based on recovered **2e**.

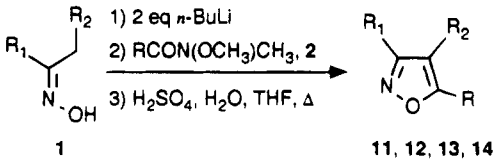
5-Alkylisoxazoles were obtained from the amides derived from primary (entries 1 and 2), secondary (entry 3), and cyclic (entries 4–6, 8, and 9) carboxylic acids. The cyclohexenylisoxazole **5g** was obtained in 85% yield from the α,β-unsaturated amide **2g**. Conditions for hydrolysis and ring closure are such that the *t*-BOC protecting group of **2e** remains intact. However, the dioxolane of **2f** underwent deketalization during hydrolysis and ring closure to give the ketone **5f**. Isoxazole formation from either **2h** or **2i** was completely diastereospecific, giving isoxazoles **5h** and **5i** in 90 and 80% yields, respectively, free of the other diastereomer, as determined by ^1H NMR analysis of the crude reaction product. When *cis*-dimethylamide **9** was employed as the acylating agent, GC analysis of the crude product revealed that a 1.5:1.0:1.5 mixture of recovered **9**, *cis*-isoxazole **5i**, and *trans*-dimethylamide **10** had been realized (Scheme 3). A trace (<5%) amount of **5h** was observed by GC and ^1H NMR. The formation of **10** probably arises through protonation of the enolate of **9** to give the thermodynamically more stable *trans*-isomer. The *trans*-dimethylamide **10** gave a 1.5:1 mixture of recovered **10** and *trans*-isoxazole **5h** under the same reaction conditions. This result supports the finding that *N*,*N*-dialkylalkylamides preferentially undergo proton abstraction with oxime dianions rather than act as acylating agents.[3]

This methodology has been expanded to include the synthesis of isoxazoles from a variety of oximes (Scheme 4). Phenyl (**11a** and **11b**), phenethyl (**12**), and fused isoxazoles (**13a–c**, **14**) were obtained in 38–69% yield (Table 2). For **1b**, **1c**, and **1f**, a mixture of *syn*- and *anti*-oximes was employed. For comparison purposes, the yields obtained from the *O*-ethyl-*N*,*N*-dibutylalkylamide carbocation salt route[3b] are given in parentheses. The use of *N*-methoxy-*N*-methylalkylamides generally affords superior yields of isoxazoles and avoids the lithium aluminum hydride workup which is required in removal of the amide contaminate when the carbocation salts are

Scheme 3



Scheme 4



employed. Particularly noteworthy is the ease in which a methyl group can be introduced into the 5-position (Table 2, **13c**). It should be noted that the dianions of diphenylacetone oxime and β-tetralone oxime failed to give any of the desired isoxazole when treated with **2l**. A mixture of recovered oxime and ketone was obtained. The lack of reactivity of these stabilized dianions has previously been noted for arylamides.[3a] The more electrophilic carbocation salts have been shown to provide isoxazoles from β-tetralone oxime dianion.[3b] Finally, the synthesis of isoxazole **15** was achieved in 70% yield by *in situ* preparation of the dianion derived from **1a** and benzyl chloride and reaction with **2n** (Scheme 5). This result is a significant improvement over the 18% yield obtained by the carbocation salt route.

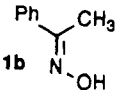
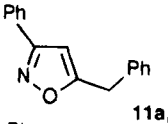
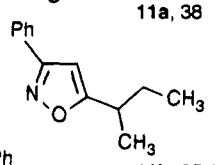
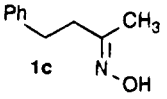
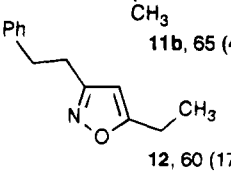
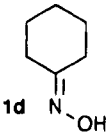
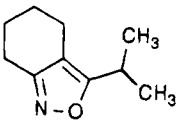
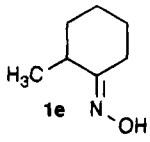
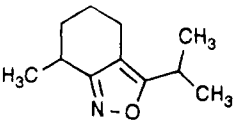
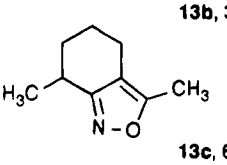
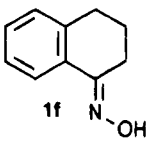
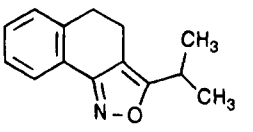
In summary, we have demonstrated that *N*-methoxy-*N*-methylalkylamides act as very efficient acylating agents for oxime dianions and provide for a very simple and direct regiospecific synthesis of 5-alkylisoxazoles. The application of this methodology to the synthesis of other heterocycles is being pursued.

Experimental Section

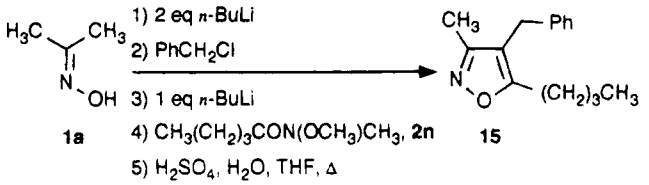
General. Melting points are uncorrected. THF was distilled from sodium benzophenone ketyl immediately prior to use. $CHCl_3$ was filtered through a column of silica gel 60 and dried with Na_2SO_4 immediately prior to use. Pyridine, TEA, and CH_2Cl_2 were dried over 4-Å molecular sieves. All other reagents and solvents were used as received from commercial sources without further purification unless otherwise noted. Oximes used in this study were prepared by standard methods.[9] Organic extracts were dried with anhydrous $MgSO_4$ following aqueous workup. Flash[10] and medium-pressure liquid chromatography (MPLC) were performed with E.M. Science silica gel 60 (40–63 μm, 230–400 mesh). Dry flash chromatography[11] was performed with E.M. Science silica gel 60H. NMR spectra were recorded as $CDCl_3$ solutions with TMS as internal standard on a Bruker-

(9) See ref 3a and pertinent references cited therein.
(10) Still, C. W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(11) Harwood, L. M. *Aldrich Chim. Acta* **1985**, *18*, 25.

Table 2. Isoxazoles Prepared from the Dianion of Oximes 1b–f and *N*-Methoxy-*N*-methylalkylamides 2

oxime	amide, R	isoxazole, %
 **1b**	**2a**, $PhCH_2$	 **11a**, 38
1b	**2j**, $CH_3CH_2CHCH_3$	 **11b**, 65 (41)
 **1c**	**2k**, CH_3CH_2	 **12**, 60 (17)
 **1d**	**2l**, $(CH_3)_2CH$	 **13a**, 69 (65)
 **1e**	**2l**	 **13b**, 38 (27)
1e	**2m**, CH_3	 **13c**, 62 (0)
 **1f**	**2l**	 **14**, 42

Scheme 5



AC200 FTNMR instrument at 200 (^{1}H) and 53 (^{13}C) MHz or on a GE QE-300 instrument at 300 (^{1}H) and 75 (^{13}C) MHz; *J* values are given in Hz. IR spectra were recorded on a Nicolet 20SX FTIR. Data are given in cm^{-1}. Elemental analyses were performed by Quantitative Technologies, Inc., Whitehouse, NJ. Low-resolution mass spectral analyses were obtained on a Nermag R10-10c quadrapole mass spectrometer. Gas chromatography analyses were conducted on a Hewlett-Packard HP 5890 instrument equipped with an Alltech AT-5 5% phenylmethylsilicone column. All moisture sensitive reactions were performed in oven-dried glassware under a nitrogen or argon atmosphere.

Amides. *N*-Methoxy-*N*-methylamides **2b**, **2c**, **2d**, **2j**, **2k**, **2l**, **2m**, and **2n** were prepared by the procedure of Nahm and Weinreb[6] with little modification; **2a**, **2f**, **2g**, **2h**, and **2i** and dimethylamides **9** and **10** were prepared by treating the appropriate carboxylic acid with 1,1′-carbonyldiimidazole (CDI) followed by the amine hydrochloride;[12] **2e** was prepared from the appropriate ester with *N*,*O*-dimethylhydroxylamine via the trimethylaluminum methodology of Levin, Turos, and Weinreb.[13] Representative experimental details follow.

***N*-Methoxy-*N*-methylphenylacetamide (2a).** To a solution of phenylacetic acid (6.81 g, 50.0 mmol) in $CHCl_3$ was added CDI (9.73 g, 60.0 mmol) in portions over 4 min. After the evolution of CO_2 had ceased, the solution was stirred for an additional 15 min, and *N*,*O*-dimethylhydroxylamine hydrochloride (5.85 g, 60.0 mmol) was added. After 18 h at rt, the reaction mixture was partitioned between ether (150 mL) and water (50 mL). The organic phase was separated and washed with 10% NaOH (2 × 25 mL), 10% HCl (2 × 25 mL), and brine, dried, and concentrated in vacuo. The yellow oil obtained was filtered through a short column of Florisil (CH_2Cl_2) and subjected to MPLC (30% ethyl acetate in hexanes) to provide 8.14 g (90.8%) of pure **2a** as a colorless oil: ^{1}H NMR δ 7.29 (m, 5H), 3.77 (s, 2H), 3.59 (s, 3H), 3.18 (s, 3H); ^{13}C NMR δ 172.39, 134.96, 129.30, 128.50, 126.77, 61.28, 39.43, 32.28; IR (NaCl film) 1668; MS CI *m/z* 180 (MH^+).

***N*-Methoxy-*N*-methyl-1,4-dioxaspiro[4.5]decane-8-carboxamide (2f).** A mixture of 4-oxocyclohexanecarboxylic acid[14] (25.9 g, 180 mmol), benzene (200 mL), ethylene glycol (25.0 mL, 450 mmol), and *p*-toluenesulfonic acid monohydrate (catalytic) was refluxed for 24 h with continuous removal of water (Dean-Stark trap). The reaction mixture was concentrated in vacuo and partitioned between water and ethyl acetate. The organic phase was washed with water and brine, dried, and concentrated in vacuo to provide a yellow oil (31.1 g) which consisted of a mixture of acid and hydroxyethyl ester. The oil was dissolved into methanol (30 mL) and water (100 mL), and lithium hydroxide (7.19 g, 300 mmol) was added. A mild exotherm ensued. After the exotherm had subsided, the mixture was filtered and the filtrate was treated with 6 N HCl (50 mL) and twice extracted with CH_2Cl_2. The combined organic phases were washed with water and brine, dried, and concentrated in vacuo to dryness to give 19.5 g (57.5%) of 1,4-dioxaspiro[4.5]decane-8-carboxylic acid. This acid (19.2 g, 103 mmol) was treated as described for **2a**. Following MPLC (50% ethyl acetate in hexanes) there was obtained 19.5 g (82.3%) of pure **2f** as a colorless oil which solidified upon standing: mp 45–6 °C (*i*-PrOAc and hexanes); ^{1}H NMR δ 3.95 (s, 4H), 3.71 (s, 3H), 3.18 (s, 3H), 2.70 (m, 1H), 1.86–1.78 (m, 6H), 1.59–1.55 (m, 2H); IR (NaCl film) 1659. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.58; H, 8.50; N, 6.24.

***N*-Methoxy-*N*-methyl-1-cyclohexenecarboxamide (2g).** From 1-cyclohexenecarboxylic acid (3.15 g, 25.0 mmol) there was obtained 3.01 g (71.1%) of pure **2g** as a colorless oil following MPLC (30% ethyl acetate in hexanes): ^{1}H NMR δ 6.17 (m, 1H), 3.67 (s, 3H), 3.23 (s, 3H), 2.26 (m, 2H), 2.15 (m, 2H), 1.66 (m, 4H); ^{13}C NMR δ 171.78, 133.69, 130.85, 60.83, 33.59, 25.41, 24.86, 22.06, 21.51; IR (NaCl film) 1656, 1642. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.62; H, 8.92; N, 8.16.

***cis*- and *trans*-4-(Dimethylethyl)cyclohexanecarboxylic Acids.** The procedure described by van Bekkum and coworkers[15] was followed starting from commercial 4-(dimethylethyl)cyclohexanecarboxylic acid (Fluka, ~1:1 *cis*/*trans*, 25.0 g). There was obtained 11.2 g (44.7%) of pure *trans*-acid, mp 174–7 °C (acetone), and 8.78 g (35.1%) of pure *cis*-acid, mp 117–9 °C (hexanes).

***N*-Methoxy-*N*-methyl-*trans*-4-(dimethylethyl)cyclohexanecarboxamide (2h).** From *trans*-4-(dimethylethyl)cyclohexanecarboxylic acid (4.61 g, 25.0 mmol) there was obtained 4.92 g (86.6%) of pure **2h** as a colorless oil following MPLC (10–20% ethyl acetate in hexanes): ^{1}H NMR δ 3.70 (s, 3H), 3.18 (s, 3H), 2.61 (m, 1H), 1.84 (m, 4H), 1.58–1.40 (m, 2H), 1.05 (m, 3H), 0.86 (s, 9H); ^{13}C NMR δ 177.49, 61.51, 47.29, 40.03, 32.43, 32.29, 29.42, 27.49, 26.67; IR (NaCl film) 1664. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.42; H, 11.09; N, 6.13.

(12) (a) Theisen, P. D.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 2374. (b) Graham, S. L.; Scholz, T. H. *J. Org. Chem.* **1991**, *56*, 4260.
(13) Levin, J. I.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989.
(14) Prepared by catalytic reduction of the sodium salt of 4-hydroxybenzoic acid with 5% rhodium on alumina in water followed by Jones oxidation of the resulting hydroxy acid. For example, see: Ledford, N. D.; Cutcliff, C. R.; Wood, H. B., Jr. *Org. Prep. Proced. Int.* **1987**, *19*, 209.
(15) van Bekkum, H.; van de Graaf, B.; van Minnen-Pathuis, G. *Rec. Trav. Chim.* **1970**, *89*, 521.

Recovered acid (0.47 g, 10%) was obtained by acidification of the basic aqueous washes.

N-Methoxy-N-methyl-*cis*-4-(dimethylethyl)cyclohexanecarboxamide (2i). From *cis*-4-(dimethylethyl)cyclohexanecarboxylic acid (4.61 g, 25.0 mmol) there was obtained 5.55 g (97.7%) of pure **2i** as a colorless oil following MPLC (10% ethyl acetate in hexanes): ^{1}H NMR δ 3.67 (s, 3H), 3.18 (s, 3H), 2.92 (m, 1H), 1.98 (m, 2H), 1.59–1.45 (m, 6H), 0.96 (m, 1H), 0.84 (s, 9H); ^{13}C NMR δ 177.47, 61.09, 47.94, 34.06, 32.54, 32.31, 28.29, 27.54, 23.21; IR (NaCl film) 1666. Anal. Calcd for $C_{13}H_{25}NO_2$: C, 68.68; H, 11.08; N, 6.16. Found: C, 68.56; H, 11.11; N, 6.07.

N,N-Dimethyl-*trans*-4-(dimethylethyl)cyclohexanecarboxamide (9). From *trans*-4-(dimethylethyl)cyclohexanecarboxylic acid (1.84 g, 10.0 mmol) and dimethylamine hydrochloride (0.98 g, 12 mmol) there was obtained 1.75 g (82.9%) of pure **9** as a white, flaky solid following MPLC (35% ethyl acetate in hexanes): mp 85–6 °C (pentane); ^{1}H NMR δ 3.04 (s, 3H), 2.93 (s, 3H), 2.42 (dt, J = 11.8 and 3.2 Hz, 1H), 1.61–1.43 (m, 2H), 1.04 (m, 3H), 0.85 (s, 9H); ^{13}C NMR δ 176.12, 47.28, 40.72, 37.03, 35.48, 32.40, 29.49, 27.46, 26.71; IR (1% KBr) 1626. Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 74.12; H, 11.89; N, 6.64.

N,N-Dimethyl-*cis*-4-(dimethylethyl)cyclohexanecarboxamide (10). From *cis*-4-(dimethylethyl)cyclohexanecarboxylic acid (1.84 g, 10.0 mmol) and dimethylamine hydrochloride (0.98 g, 12 mmol) there was obtained 1.83 g (86.7%) of pure **10** as a colorless oil following MPLC (25% ethyl acetate in hexanes) which slowly solidified upon standing: mp 50–1 °C (pentane); ^{1}H NMR δ 3.01 (s, 3H), 2.92 (s, 3H), 2.82 (m, 1H), 1.94 (m, 2H), 1.60–1.47 (m, 6H), 0.95 (m, 1H), 0.84 (s, 9H); ^{13}C NMR δ 176.08, 48.01, 37.48, 35.46, 34.22, 32.52, 28.33, 27.56, 23.22; IR (1% KBr) 1633. Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 74.09; H, 12.11; N, 6.61.

Dimethylethyl 4-(N-Methoxy-N-methylcarbamoyl)-1-piperidinecarboxylate (2e). To a chilled (0 °C) solution of ethyl isonipecotate (30.5 g, 194 mmol) in *p*-dioxane/water 2:1 (600 mL) and 1 N NaOH (194 mL) was added di-*tert*-butyl dicarbonate (46.1 g, 211 mmol). After 4 h at rt, the mixture was concentrated in vacuo and extracted with ethyl acetate. The combined organic extracts were dried and concentrated in vacuo to give 29.5 g (60%) of 1-dimethylethyl 4-ethyl 1,4-piperidinedicarboxylate which was used without further purification. An analytical sample was obtained by flash chromatography (20% ethyl acetate in hexanes): colorless oil; ^{1}H NMR δ 4.14 (q, J = 7.5 Hz, 2H), 4.04 (m, 2H), 2.84 (m, 2H), 2.44 (m, 1H), 1.87 (m, 2H), 1.70–1.50 (m, 2H), 1.46 (s, 9H), 1.28 (t, J = 7.5 Hz, 3H); IR (NaCl film) 1733, 1696. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.95; H, 9.02; N, 5.32.

To a solution of *N,O*-dimethylhydroxylamine[16] (2.32 g, 38.0 mmol) in CH_2Cl_2 (500 mL) was added 2 M trimethylaluminum (19 mL, 38.0 mmol). After 15 min, the ethyl ester (3.30 g, 12.8 mmol) was added. The mixture was refluxed for 24 h and chilled (0 °C), and 1 N HCl (30 mL) was added dropwise with rapid stirring. The resulting milky suspension was partitioned between water and CH_2Cl_2. The aqueous phase was separated, neutralized with $NaHCO_3$, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with water and brine, dried, and concentrated in vacuo. Purification by dry flash chromatography (CH_2Cl_2 to ethyl acetate) provided 2.40 g (72%) of pure **2e** as a colorless oil: ^{1}H NMR δ 4.12 (m, 2H), 3.68 (s, 3H), 3.16 (s, 3H), 2.78–2.67 (m, 3H), 1.71–1.60 (m, 4H), 1.43 (s, 9H); ^{13}C NMR δ 174.50, 154.58, 79.36, 61.46, 43.18, 38.00, 32.19, 28.33, 27.88; IR (NaCl film) 1694, 1662. Anal. Calcd for $C_{13}H_{24}N_2O_4$: C, 57.33; H, 8.88; N, 10.29. Found: C, 57.32; H, 8.88; N, 10.15.

3-Methyl-5-(phenylmethyl)isoxazole (5a). The following procedure was used to prepare the isoxazoles listed in Tables 1 and 2: To a chilled (0 °C) solution of **1a** (439 mg, 6.00 mmol) in THF (12 mL) was added dropwise over 5 min 2.5 M *n*-butyllithium (*n*-BuLi) in hexanes (4.8 mL, 12 mmol). The initially formed white suspension gave a colorless solution after all of the *n*-BuLi had been added. After an additional 30 min, **2a** (896 mg, 5.00 mmol) in THF (20 mL) was added dropwise over 20 min. After 30 min, the pale yellow solution was poured into a solution of concentrated H_2SO_4 (1.0 mL) in THF/water 4:1 (14 mL) and refluxed for 1 h. The chilled (ice bath) reaction mixture was carefully neutralized with $NaHCO_3$, sufficient water was added to dissolve the salts, and the mixture was extracted with ether (2 × 25 mL). The combined ethereal extracts were washed with brine, dried, and concentrated in vacuo to a yellow oil which was purified by filtration through a short column of Florisil (CH_2Cl_2) to give 892 mg (94.3%) of pure **5a** as a colorless oil: ^{1}H NMR δ 7.35–7.18 (m, 5H), 5.74 (s, 1H), 4.04 (s, 2H), 2.24 (s, 3H); ^{13}C NMR δ 171.88, 159.88, 136.40, 128.79 (two overlapping peaks), 127.07, 102.57, 33.16, 11.39; IR (NaCl film) 1603, 1420, 724. An analytical sample was obtained by MPLC (5% ethyl acetate in hexanes). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 75.95; H, 6.40; N, 8.05.

3-Methyl-5-(2-methylpropyl)isoxazole (5b). From **1a** (1.10 g, 15.0 mmol) and **2b** (2.61 g, 18.0 mmol) there was obtained 1.50 g (71.8%) of pure **5b** as a colorless oil following MPLC (20% ethyl acetate in hexanes): ^{1}H NMR δ 5.80 (s, 1H), 2.58 (d, J = 7.0 Hz, 3H), 2.26 (s, 3H), 2.02 (m, 1H), 0.96 (d, J = 6.5 Hz, 6H); ^{13}C NMR δ 172.34, 159.48, 102.05, 35.49, 27.50, 22.12, 11.22; IR (NaCl film) 1605, 1419; MS CI *m/z* 140 (MH^+).

5-(1-Ethylpropyl)-3-methylisoxazole (5c). From **1a** (1.19 g, 16.3 mmol) and **2c** (3.12 g, 19.6 mmol) there was obtained 1.55 g (62.1%) of pure **5c** as a colorless oil following MPLC (10% ethyl acetate in hexanes): ^{1}H NMR δ 5.80 (s, 1H), 2.65 (m, 1H), 2.27 (s, 3H), 1.66 (m, 4H), 0.85 (t, J = 7.4 Hz, 6H); ^{13}C NMR δ 176.39, 159.42, 101.21, 41.38, 26.38, 11.53, 11.41; IR (NaCl film) 1600; MS CI *m/z* 154 (MH^+).

5-Cyclopropyl-3-methylisoxazole (5d). From **1a** (1.04 g, 14.2 mmol) and **2d** (2.10 g, 17.0 mmol) there was obtained 1.31 g (74.9%) of pure **5d** as a colorless oil following MPLC (10% ethyl acetate in hexanes): ^{1}H NMR δ 5.73 (s, 1H), 2.23 (s, 3H), 1.98 (m, 1H), 1.08–0.88 (m, 4H); ^{13}C NMR δ 174.32, 159.66, 99.25, 11.12, 7.96, 7.77; IR (NaCl film) 1608, 1421, 991. Anal. Calcd for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.00; H, 7.55; N, 11.37.

Dimethylethyl 4-(3-Methyl-5-isoxazolyl)piperidinecarboxylate (5e). From **1a** (220 mg, 3.00 mmol) and **2e** (641 mg, 2.46 mmol) there was obtained 250 mg (38.2%) of pure **5e** as a colorless oil and 240 mg (37.4%) of recovered **2e** following dry flash chromatography (hexanes–ethyl acetate). For **5e**: ^{1}H NMR δ 5.78 (s, 1H), 4.09 (m, 2H), 2.85 (m, 3H), 2.23 (s, 3H), 1.95 (m, 2H), 1.61 (m, 2H), 1.44 (s, 9H); ^{13}C NMR δ 175.42, 159.56, 154.66, 100.16, 79.64, 43.25, 34.45, 30.00, 28.39, 11.37; IR (NaCl film) 1693, 1601, 1419, 1169. Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52. Found: C, 62.83; H, 8.37; N, 10.35.

4-(3-Methyl-5-isoxazolyl)cyclohexanone (5f). From **1a** (2.56 g, 35.0 mmol) and **2f** (6.92 g, 30.0 mmol) there was obtained 3.00 g (55.5%) of pure **5f** as a white solid following MPLC (50% ethyl acetate in hexanes): mp 111–113 °C; ^{1}H NMR δ 5.89 (s, 1H), 3.23 (m, 1H), 2.61–2.32 (m, 6H), 2.32 (s, 3H), 2.08–1.88 (m, 2H); IR (1% KBr) 1715, 1704, 1601, 1417. Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.34; N, 7.82. Found: C, 66.87; H, 7.34; N, 7.75.

5-(1-Cyclohexenyl)-3-methylisoxazole (5g). From **1a** (877 mg, 12.0 mmol) and **2g** (1.69 g, 10.0 mmol) there was obtained 1.38 g (84.7%) of pure **5g** as a colorless oil following MPLC (25% ethyl acetate in hexanes): ^{1}H NMR δ 6.55 (m, 1H), 5.90 (s, 1H), 2.32–2.21 (m, 4H), 2.27 (s, 3H), 1.80–1.62 (m, 4H); ^{13}C NMR δ 170.83, 159.77, 129.64, 125.64, 98.91, 25.36, 25.16, 22.09, 21.73, 11.51; IR (NaCl film) 1651, 1579, 1416, 784. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.55; H, 7.97; N, 8.59.

3-Methyl-5-[*trans*-4-(dimethylethyl)cyclohexyl]isoxazole (5h). From **1a** (877 mg, 12.0 mmol) and **2h** (2.27 g, 10.0 mmol) there was obtained 1.38 g (84.7%) of pure **5h** as a white solid following MPLC (2.5% ethyl acetate in hexanes): ^{1}H NMR δ 5.75 (s, 1H), 2.62 (dt, J = 12.0 and 3.5 Hz, 1H), 2.25 (s, 3H), 2.15 (m, 1H), 2.08 (m, 1H), 1.98 (m, 1H), 1.90 (m, 1H), 1.46–1.28 (m, 2H), 1.21–1.03 (m, 3H), 0.87 (s, 9H); ^{13}C NMR δ 177.58, 159.47, 99.48, 47.47, 36.45, 32.44, 31.67, 27.50, 26.81, 11.47; IR (1% KBr) 1597. Sublimation (0.05 mm, 55 °C) provided an analytical sample: mp 62–3 °C. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.12; H, 10.60; N, 6.27.

3-Methyl-5-[*cis*-4-(dimethylethyl)cyclohexyl]isoxazole (5i). From **1a** (877 mg, 12.0 mmol) and **2i** (2.27 g, 10.0 mmol) there was obtained 1.38 g (84.7%) of pure **5i** as a white solid following MPLC (2.5% ethyl acetate in hexanes): ^{1}H NMR δ 5.87 (s, 1H),

(16) Garigipati, R. S.; Tschaen, D. M.; Weinreb, S. M. *J. Am. Chem. Soc.* **1990**, *112*, 3475.

3.11 (m, 1H), 2.28 (s, 3H), 2.24 (m, 1H), 2.18 (m, 1H), 1.74–1.57 (m, 4H), 1.15–1.01 (m, 3H), 0.81 (s, 9H); ^{13}C NMR δ 176.10, 159.59, 101.77, 48.03, 32.50, 32.22, 29.14, 27.42, 22.92, 11.53; IR (1% KBr) 1589, 1416, 1364. Sublimation (0.05 mm, 65 °C) provided an analytical sample: mp 66–7 °C. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.14; H, 10.57; N, 6.30.

4,5-Dihydro-3-methyl-5-(phenylmethyl)isoxazol-5-ol (6) was prepared as described for **5a** except the reaction mixture was treated with saturated NH_4Cl instead of H_2SO_4/water/THF. There was obtained 901 mg (94.3%) of **6** as a light yellow viscous oil: ^{1}H NMR δ 7.30 (m, 5H), 3.73 (br s, 1H), 3.20 (s, 2H), 2.91 (d, J = 17.7 Hz, 1H), 2.75 (d, J = 17.7 Hz, 1H), 1.94 (s, 3H); ^{13}C NMR δ 156.90, 135.42, 130.35, 128.50, 127.13, 107.32, 47.93, 44.09, 13.46; IR (NaCl film) 3680–2950, 1431, 1334, 1098; MS CI m/z 192 (MH^+), 174 (MH^+-H_2O).

A solution of **6** (841 mg, 4.40 mmol), THF/water 4:1 (40 mL), and concd H_2SO_4 (0.52 mL) was refluxed for 1 h. Workup as described for **5a** provided 640 mg (84.0%) of pure **5a**.

***N*-Hydroxy-*N*,*O*-dimethyl-4,5-dihydro-3-methyl-5-(phenylmethyl)isoxazol-5-amine (7)** was prepared as described for **6** except the reaction mixture was treated with dichlorodimethylsilane (0.91 mL, 7.5 mmol). After 18 h at rt, the mixture was diluted with water (100 mL) and extracted with ether (2 × 25 mL). The combined ethereal extracts were washed with brine, dried, and concentrated in vacuo to a red oil (1.51 g). MPLC (25% ethyl acetate in hexanes) provided 807 mg (69.0%) of pure **7** as a colorless oil: ^{1}H NMR δ 7.28 (m, 5H), 3.54 (s, 3H), 3.36 (d, J = 14.2 Hz, 1H), 2.98 (d, J = 14.2 Hz, 1H), 2.69 (s, 2H), 2.68 (s, 3H), 1.76 (s, 3H); ^{13}C NMR δ 155.45, 136.31, 130.47, 128.31, 126.76, 103.76, 60.76, 43.04, 40.19, 35.80, 13.18; IR (NaCl film) 1497, 1437, 1386, 1336; MS CI m/z 235 (MH^+), 174 ($MH^+ - C_2H_7NO$).

3-Phenyl-5-(phenylmethyl)isoxazole (11a). From **1b** (1.38 g, 10.2 mmol) and **2b** (1.52 g, 8.50 mmol) there was obtained 0.77 g (38.5%) of pure **11a** as a white solid following MPLC (10% ethyl acetate in hexanes): mp 82.5–83 °C (ether and hexanes); ^{1}H NMR δ 7.75 (m, 2H), 7.43–7.25 (m, 8H), 6.21 (s, 1H), 4.13 (s, 2H); ^{13}C NMR δ 172.69, 162.46, 135.93, 129.84, 129.19, 128.87, 128.81, 127.18, 126.75, 99.99, 33.32; IR (1% KBr) 1597, 1577, 1468, 1408. Anal. Calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.74; H, 5.42; N, 5.90.

3-(1-Methylpropyl)-5-phenylisoxazole (11b). From **1b** (1.35 g, 10.0 mmol) and **2j** (1.74 g, 12.0 mmol) there was obtained 1.30 g (64.7%) of pure **11b** as a pale yellow oil following MPLC (1% ethyl acetate in hexanes): ^{1}H NMR δ 7.82 (m, 2H), 7.42 (m, 3H), 6.27 (s, 1H), 2.92 (hex, J = 6.9 Hz, 1H), 1.91–1.60 (m, 2H), 1.34 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ 178.41, 162.12, 129.71, 129.50, 128.79, 126.72, 97.65, 34.01, 28.41, 18.38, 11.42; IR (NaCl film) 1598, 1579, 1472, 1408; MS CI m/z 202 (MH^+).

3-(1-Phenylethyl)-5-ethylisoxazole (12). From **1c** (1.63 g, 10.0 mmol) and **2k** (1.41 g, 12.0 mmol) there was obtained 1.19 g (59.5%) of pure **12** as a pale yellow oil following MPLC (1% ethyl acetate in hexanes): ^{1}H NMR δ 7.34–7.17 (m, 5H), 5.76 (s, 1H), 2.96 (s, 4H), 2.72 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR δ 174.52, 163.17, 140.77, 128.42, 128.30, 126.18, 99.79, 34.42, 27.92, 20.14, 11.68; IR (NaCl film) 1603, 1453, 1424; MS CI m/z 202 (MH^+).

3,4,5,6-Tetrahydro-7-(methylethyl)benzisoxazole (13a). From **1d** (1.54 g, 12.1 mmol) and **2l** (1.90 g, 14.5 mmol) there was obtained 1.38 g (69.0%) of pure **13a** as a colorless oil following MPLC (10% ethyl acetate in hexanes): ^{1}H NMR δ 3.07 (heptet, J = 7.1 Hz, 1H), 2.70 (dd, J = 6.3 and 6.1 Hz, 2H), 2.49 (dd, J = 6.2 and 5.8 Hz, 2H), 1.74 (m, 4H), 1.29 (d, J = 7.1 Hz, 6H); ^{13}C NMR δ 170.67, 160.98, 108.35, 26.91, 22.77, 21.80, 20.38, 19.26; IR (NaCl film) 1632, 1450; MS CI m/z 166 (MH^+).[17]

3,4,5,6-Tetrahydro-3-methyl-7-(methylethyl)benzisoxazole (13b). From **1e** (1.68 g, 13.2 mmol) and **2l** (1.45 g, 11.0 mmol) there was obtained 0.77 g (38%) of pure **13b** as a colorless oil following MPLC (2% ethyl acetate in hexanes): ^{1}H NMR δ 3.06 (heptet, J = 7.0 Hz, 1H), 2.85 (m, 1H), 2.62–2.31 (m, 2H), 1.89 (m, 3H), 1.69–1.50 (m, 1H), 1.35 (d, J = 6.9 Hz, 3H), 1.28 (d, J = 7.0 Hz, 6H); ^{13}C NMR δ 170.56, 165.36, 108.10, 31.54, 28.85, 26.99, 21.81, 20.42, 20.38, 19.49, 19.37; IR (NaCl film) 1635, 1448; MS CI m/z 180 (MH^+).[17]

3,4,5,6-Tetrahydro-3,7-dimethylbenzisoxazole (13c). From **1e** (0.84 g, 6.6 mmol) and **2m** (0.82 g, 8.0 mmol) there was obtained 0.62 g (62%) of pure **13c** as a colorless oil following MPLC (1% ethyl acetate in hexanes): ^{1}H NMR δ 2.92–2.75 (m, 1H), 2.64–2.32 (m, 3H), 2.30 (s, 3H), 2.01–1.82 (m, 2H), 1.68–1.42 (m, 1H), 1.32 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 165.36, 162.83, 110.07, 31.57, 28.75, 21.69, 19.34, 19.06, 10.95; IR (NaCl film) 1641, 1452; MS CI m/z 152 (MH^+).[17]

4,5-Dihydro-3-methylethylnaphth[1,2-c]isoxazole (14). From **1f** (2.27 g, 14.1 mmol) and **2l** (1.54 g, 11.7 mmol) there was obtained 1.05 g (42.0%) of pure **14** as a pale yellow oil following MPLC (15% ethyl acetate in hexanes): ^{1}H NMR δ 7.93 (m, 1H), 7.30 (m, 3H), 3.16 (heptet, J = 7.0 Hz, 1H), 2.94 (m, 2H), 2.73 (m, 2H), 1.35 (d, J = 7.0 Hz, 6H); ^{13}C NMR δ 170.39, 159.15, 137.86, 129.75, 128.56, 127.06, 126.27, 124.33, 108.63, 29.22, 26.99, 20.68, 17.92; IR (NaCl film) 1638, 1609, 1478, 1417. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.48; H, 6.98; N, 6.47.

5-Butyl-3-methyl-4-(phenylmethyl)isoxazole (15). To a chilled (0 °C) solution of **1a** (0.88 g, 12 mmol) in THF (20 mL) was added dropwise over 5 min 2.5 M n-BuLi in hexanes (9.6 mL, 24 mmol). The initially formed white suspension gave a colorless solution after all of the n-BuLi had been added. After an additional 30 min, a THF (5 mL) solution of benzyl chloride (1.38 mL, 12.0 mmol) was added dropwise over 5 min at which time the solution became a deep golden color. After 15 min chilled and 1 h at rt, the faintly yellow solution was chilled (0 °C) and n-BuLi (4.8 mL, 12 mmol) was added dropwise. The solution became orange and finally deep brown. After 30 min, a THF (5 mL) solution of **2n** (1.45 g, 10.0 mmol) was added, and the mixture was stirred for 15 min chilled and 90 min at rt. Workup as described for **5a** provided an orange oil (2.74 g) which was purified by MPLC (2.5% ethyl acetate in hexanes). There was obtained 1.61 g (70.3%) of pure **15** as a colorless oil: ^{1}H NMR δ 7.25 (m, 3H), 7.11 (m, 2H), 3.68 (s, 2H), 2.65 (t, J = 7.5 Hz, 2H), 2.06 (s, 3H), 1.62 (pentet, 2H), 1.32 (hextet, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 169.30, 159.94, 138.91, 128.58, 128.03, 126.41, 111.79, 29.78, 28.05, 25.29, 22.32, 13.68, 10.35; IR (NaCl film) 1634, 1604, 1454; MS CI m/z 230 (MH^+).

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(17) We were unable to obtain acceptable analytical data for these compounds due to chemical instability.