New Synthesis of Isoxazolidines

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A new synthesis of 5-substituted isoxazolidines was developed by direct isoxazolidine ring formation of allylic hydroxylamines under acidic conditions. The cyclization process is an electrophilic S_N1 type reaction. The formed carbocation intermediate is stabilized by electron rich groups (*i.e.*, phenyl). A moiety that mediates oxonium ion formation (*i.e.*, *para*-methoxy) accelerates the rate of product formation.

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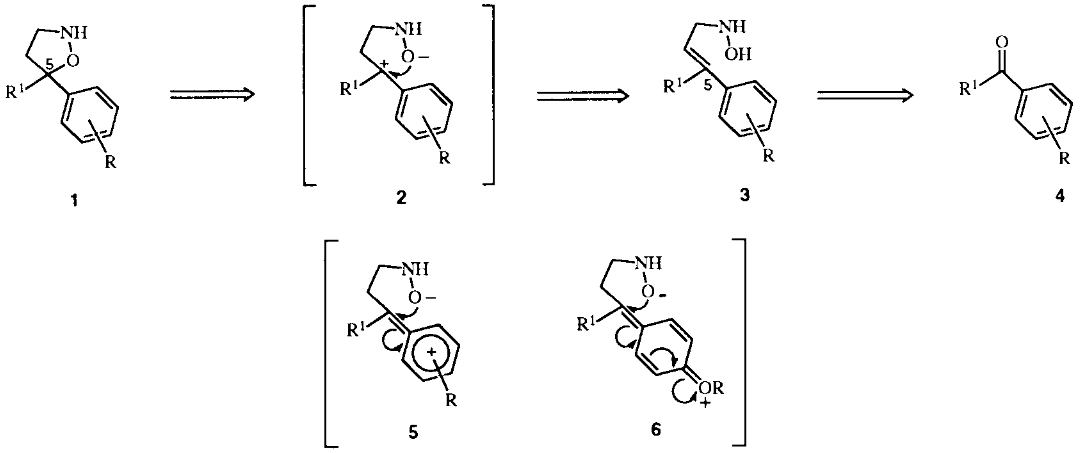
Isoxazolidines are generally prepared from nitrones or their tautomeric counterparts (*i.e.*, nitronic esters, oximes) and olefins, *via* a 3+2 dipolar cycloaddition process [1]. Preparations of 5-monosubstituted and 5-spiroisoxazolidines, where the nitrogen atom is masked with an alkyl substituent, have been previously described [2]. As part of our efforts to identify new antihyperglycemic agents, we have studied the synthesis of 5-substituted isoxazolidines **1** as the free base. We report herein a new synthesis of these isoxazolidines **1**.

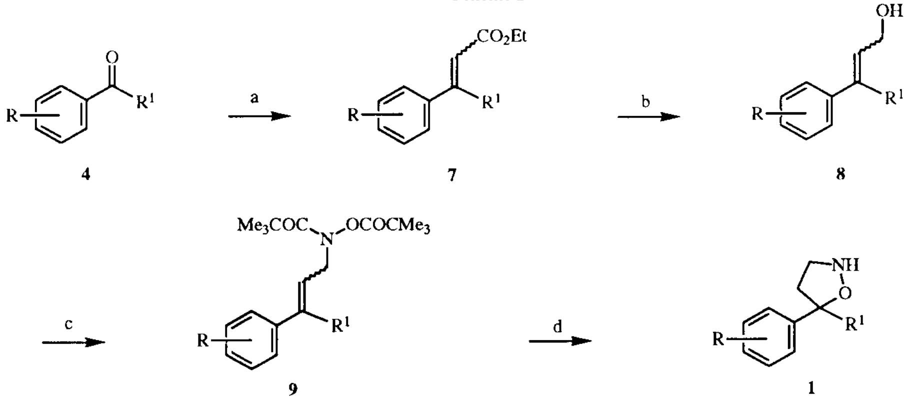
Retrosynthetic analysis of isoxazolidine **1** suggests that the isoxazolidine ring could be prepared from the hydroxylamine **3** by bond formation between carbon at position 5 and the hydroxyl group (Scheme 1). Intramolecular cyclization could be affected under acidic conditions, where the carbocation intermediate **2** could be trapped by the nucleophilic hydroxyl group. Hydroxylamines **3** could efficiently be prepared from **4**.

A general synthetic process for the preparation of 5-substituted isoxazolidines (Table 1) is described.

Scheme 1



Scheme 2



Reagents: (a) $(EtO)_2POCH_2CO_2Et$, NaH, toluene; (b) $[(CH_3)_2CHCH_2]_2AlH$, THF;
(c) $Me_3COCONHOCO_2CMe_3$, Ph_3P, $(CH_3)_2CHO_2CN{=}NCO_2CH(CH_3)_2$, THF; (d) CF_3CO_2H, CH_2Cl_2

Treatment of ketone **4** (Scheme 2) with the sodium salt of triethyl phosphonoacetate [3] produced ester **7**, which was reduced to allylic alcohol **8** with diisobutylaluminum hydride. Alcohol **8** was treated with *tert*-butyl *N*-(*tert*-butoxycarbonyloxy) carbamate, triphenylphosphine and diisopropyl azodicarboxylate [4] to afford diester **9**. One step conversion of the masked hydroxylamines **9** to isoxazolidines **1** was accomplished by treatment of **9** with trifluoroacetic acid. Isoxazolidines **1** were also similarly formed from analogous unmasked hydroxylamines.

Since the cyclization process is an electrophilic S_N1 type reaction, the stabilization of carbocation **2** (Scheme 1) is greatly affected by the electronic nature of adjacent substituents. This effect mandated different acid concentrations and reaction times (Table 1, footnote) for the isoxazolidine ring formation of various analogs. While the 4-methoxy analog **13** was obtained after treatment with 10% trifluoroacetic acid in dichloromethane within one hour, the 5,5-diphenyl analog **10** was produced only after treatment with concentrated trifluoroacetic acid for 24 hours. Furthermore, the dialkyl analog **16** (Table 2) did not produce any cyclized isoxazolidine under similar severely acidic conditions, even after treatment for two days. Since the *para*-methoxy substituent can stabilize the carbocation **2** *via* oxonium ion formation **6** (Scheme 1), a more effective cyclization process is anticipated.

Analog **10** under mild conditions (10% trifluoroacetic acid) produced only the hydroxylamine **17** (Table 2). Weaker stabilization of the carbocation of **17** by resonance interactions from the adjacent phenyl group, may not be sufficient to affect the cyclization process under mild conditions. Thus, stronger acidic conditions were required for the cyclization of the unsubstituted phenyl analogs. Also, the *meta*-methoxy analog **12** required similar strongly acidic conditions for the cyclization step, due to the inability of the meta substituent to stabilize the carbocation *via* oxonium ion formation. These findings support the importance of an electron rich group (*i.e.*, phenyl) or preferably a group (*i.e.*, *para*-methoxy) that can participate in oxonium ion formation (**5**, **6** Scheme 1). The 4-methoxy isoxazolidine **15** was obtained under mild acidic conditions but with an

Table 1

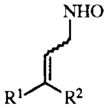
Chemical Data of Isoxazolidines

Compound	R^1	R^2 [a]	Formula	Elemental Analyses Calculated C	H	N	Found C	H	N
10	Ph	Ph [b]	$C_{15}H_{15}NO$	79.97	6.71	6.22	79.68	6.64	6.20
11	2-MeO-Ph	Ph [c]	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.32	6.71	5.44
12	3-MeO-Ph	Ph [b]	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.37	6.79	5.45
13	4-MeO-Ph	Ph [d]	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.34	6.66	5.35
14	4-MeO-Ph	CH_3 [d]	$C_{11}H_{15}NO_2$	68.37	7.82	7.25	68.13	7.93	7.21
15	4-MeO-Ph	H [c]	$C_{10}H_{13}NO_2$	67.02	7.31	7.81	66.72	7.45	7.78

[a] The reagents and reaction times for the cyclization step were: [b] CF_3CO_2H, 24 hours. [c] 10% CF_3CO_2H in CH_2Cl_2, 24 hours. [d] 10% CF_3CO_2H in CH_2Cl_2, 1 hour.

Table 2

Chemical Data of Hydroxylamines



Compound	R^1	R^2 [a]	Formula	Elemental Analyses Calculated C	H	N	Found C	H	N
16	C_8H_{17}	CH_3 [b]	$C_{12}H_{25}NO$	72.31	12.64	7.03	72.60	12.50	6.66
17	Ph	Ph [c]	$C_{15}H_{15}NO$	79.97	6.71	6.22	79.98	6.70	6.20
18	3-MeO-Ph	Ph [c]	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.30	6.87	5.43

[a] The reagents and reaction times for the formation of the hydroxylamines were: [b] CF_3CO_2H, 12 hours, [c] 10% CF_3CO_2H in CH_2Cl_2, 24 hours. No cyclization products (isoxazolidines) were obtained under these conditions.

extended period of time (24 hours). In this case, weaker stabilization of a secondary carbocation contributes to the prolonged treatment time required for isoxazolidine ring formation (**14** *vs* **15**).

In conclusion, a new synthesis of 5-substituted isoxazolidines was developed by direct isoxazolidine ring formation of allylic hydroxyl amines under acidic conditions. The cyclization process is an S_N1 type reaction. The formed carbocation intermediate is stabilized by electron rich groups (*i.e.*, phenyl). An oxonium mediated process appears feasible in the rapid formation of the *para*-phenoxy analogs. This simple protocol for the production of isoxazolidines could also be applied using various electron rich heteroaromatic moieties, such as benzofuran and benzothiophene.

EXPERIMENTAL

Chemistry.

Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus, and are reported uncorrected ^{1}H nmr spectra were determined in the cited solvent on a Bruker AM 400 (400 MHz) instrument, with tetramethylsilane as an internal standard. Chemical shifts are given in ppm and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer as potassium bromide pellets or as films. Mass spectra were recorded on either a Finnigan model 823 or a Hewlett-Packard model 5995A spectrometer. Elemental analyses (C, H, N) were performed on a Perkin-Elmer 240 analyzer. All products, unless otherwise noted, were purified by "flash chromatography" [5] with use of 220-400 mesh silica gel. Thin-layer chromatography was done on silica gel 60 F-254 (0.25 mm thickness) plates. Visualization was accomplished with UV light and/or 10% phosphomolybdic acid in ethanol. Unless otherwise noted, all materials were obtained commercially and used without further purification. All reactions were carried out under an atmosphere of dry nitrogen.

General Procedure for the Synthesis of Isoxazolidines (**1**).

Compounds of the general structure **1** were synthesized from either commercially available or prepared ketones/aldehydes of structure **4** by the representative procedure illustrated for analog **13** (Table 1). Only the reaction conditions of the last cyclization step were modified with respect to acid concentration and reaction time for the various analogs. The acid concentrations and reaction times required for the preparation of the various analogs are listed in the footnotes of Tables 1 and 2.

3-(Methoxyphenyl)-3-phenylacrylic Acid Ethyl Ester (**7**, R is 4-methoxy and R^1 is phenyl).

Triethyl phosphonoacetate (17.9 ml, 94.9 mmoles) in toluene (50 ml) was added dropwise into a cold (0°C) suspension of sodium hydride (3.58 g, 89.7 mmoles) and toluene (500 ml). The mixture was stirred for one hour and then 4-methoxybenzophenone (10.0 g, 47.2 mmoles) in tetrahydrofuran (50 ml) was added dropwise. The mixture was allowed to come to room temperature, stirred for two days, poured into water and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation and purification by flash chromatography on silica gel (eluting solvent hexane/ethyl acetate 6:1) gave a clear oil 12.2 g (91% yield) of **7**; ^{1}H nmr (dimethyl sulfoxide-d$_6$, 400 MHz): δ (1.0, 1.05, t, t, J = 7.0 Hz, 3H, isomers, CH$_3$), (3.75, 3.78, s, s, 3H, isomers, OCH$_3$), (3.9, 3.97, q, q, J = 7.0 Hz, 2H, isomers, CH$_2$), (6.28, 6.33, s, s, 1H, isomers, CH), 6.85-7.8 (m, 9H, isomers, phenyl protons); ir (film): 1725 (CO) cm^{-1}; ms: (electron impact) m/z 282 (molecular ion).

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.88; H, 6.31.

3-(Methoxyphenyl)-3-phenylpro-2-en-1-ol (**8**, R^1 is phenyl and R is 4-methoxy).

3-(Methoxyphenyl)-3-phenylacrylic acid ethyl ester (**7**, R is 4-methoxy and R^1 is phenyl, 11.0 g, 39.0 mmoles) in tetrahydrofuran (20 ml) was added dropwise into a cold (0°C) solution of tetrahydrofuran (60 ml) and diisobutylaluminum hydride (117 ml, 117 mmoles). The mixture was stirred for one hour, quenched with acetone and methyl alcohol, poured into water, acidified with hydrochloric acid and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation and purification by flash chromatography on silica gel (eluting solvent hexane/ethyl acetate 3:1) gave a clear oil 8.4 g (89% yield) of **8**; ^{1}H nmr (dimethyl sulfoxide-d$_6$, 400 MHz): δ (3.72, 3.76, s, s, 3H, isomers, OCH$_3$), (3.95, 4.02, d, d, J = 6.9 Hz, 2H, isomers, CH$_2$), 4.8 (br, 1H, OH), 6.1 (m, 1H, CH), 6.82-7.4 (m, 9H, phenyl protons); ir (film): 3350 (OH) cm^{-1}; ms: (electron impact) m/z 240 (molecular ion).

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.67, H, 6.66.

N-tert-Butoxycarbonyloxy-*N*-[3-(4-methoxyphenyl)-3-phenylallyl]carbamic Acid *tert*-Butyl Ester (**9**, R^1 is phenyl and R is 4-methoxy).

Diisopropyl azodicarboxylate (3.6 ml, 18.5 mmoles) in tetrahydrofuran (20 ml) was added dropwise into a cold (-20°C) solution of 3-(methoxyphenyl)-3-phenylpro-2-en-1-ol (**8**, R is 4-methoxy and R^1 is phenyl, 3.7 g, 15.4 mmoles), *tert*-butyl *N*-(*tert*-butoxycarbonyloxy) carbamate (4.3 g, 18.5 mmoles), triphenylphosphine (4.85 g, 18.5 mmoles) and tetrahydrofuran (50 ml). The mixture was stirred at -20°C for 20 minutes then allowed to come to room temperature. The mixture was poured into water and extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate. Evaporation and purification by flash chromatography on silica gel (eluting solvent hexane/ethyl acetate 10:1) gave a light yellow oil 6.2 g (88% yield) of **9**; ^{1}H nmr (dimethyl sulfoxide-d$_6$, 400 MHz): δ (1.36, 1.37, s, s, 18H, isomers, [C(CH$_3$)$_3$]$_2$), (3.75, 3.8, s, s, 3H, isomers, OCH$_3$), 4.2 (m, 2H, CH$_2$), 6.0 (m, 1H, CH), 6.83-7.42 (m, 9H, phenyl protons); ir (film): 1785 (CO), 1725 (CO) cm^{-1}; ms: (electron impact) m/z 455 (molecular ion).

Anal. Calcd. for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.18; H, 7.29; N, 3.05.

5-(4-Methoxyphenyl)-5-phenylisoxazolidine (**13**).

Trifluoroacetic acid (5 ml) was added into a solution of *N-tert*-butoxycarbonyloxy-*N*-[3-(4-methoxyphenyl)-3-phenylallyl]carbamic acid *tert*-butyl ester (**9**, R is 4-methoxy and R^1 is phenyl, 3.5 g, 7.6 mmoles) and dichloromethane (50 ml). The mixture was stirred at room temperature for one hour. The volatiles were removed *in vacuo* and the residue was taken into ethyl ether and sodium hydroxide (two normality). The organic layer was separated and dried over magnesium sulfate. Evaporation and purification by flash chromatography on silica gel (eluting solvent hexane/ethyl acetate 1:2) gave a brownish solid 1.1 g (56% yield) of **13**, 65-66°C; ^{1}H nmr (dimethyl sulfoxide-d$_6$, 400 MHz): δ 2.7 (br, 2H, CH$_2$), 3.1 (br, 2H, CH$_2$), 3.7 (s, 3H, OCH$_3$), 6.3 (br s, 1H, NH), 6.84 (d, J = 8.78 Hz, 2H, phenyl proton), 7.2-7.4 (m, 7H, phenyl protons); ir (potassium bromide): 3450 (NH) cm^{-1}; ms: (electron impact) m/z 255 (molecular ion).

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.34; H, 6.66; N, 5.35.

Preparation of *N*-(3,3-Diphenylallyl)hydroxylamine (**17**).

Trifluoroacetic acid (5 ml) was added into a solution of *N*-*tert*-butoxycarbonyloxy-*N*-[3,3-diphenylallyl]carbamic acid *tert*-butyl ester (**9**, R and R^1 are phenyl, 3.0 g, 7.0 mmoles) and dichloromethane (50 ml). The mixture was stirred at room temperature for 24 hours. The volatiles were removed *in vacuo* and the residue was taken in ethyl ether and sodium hydroxide (two normality). The organic layer was separated and dried over magnesium sulfate. Evaporation and purification by flash chromatography on silica gel (eluting solvent methyl alcohol/ethyl acetate 1:20) gave a yellow oil 1.45 g (95 % yield) of **17**; ^{1}H nmr (dimethyl sulfoxide-d$_6$, 400 MHz): δ 3.38 (d, J = 6.8 Hz, 2H, CH$_2$), 5.8 (br, 1H, NH), 6.2 (t, J = 6.8 Hz, 1H, CH), 7.2-7.4 (m, 11H, phenyl protons, OH); ir (potassium bromide): 3300 (NH), 2800 (OH) cm^{-1}; ms: (electron impact) m/z 225 (molecular ion).

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.98; H, 6.70; N, 6.20.

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