Reductive Cleavage of *N*-Substituted 2-Aryl-1,3-oxazolidines: Generation of α-Amino-Substituted Carbanions

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The behavior of several *N*-substituted 2-aryl-1,3-oxazolidines has been investigated under conditions of electron transfer from alkali metals in aprotic solvents. The reduction led to the regioselective cleavage of the benzylic carbon–oxygen bond, with formation of the corresponding *N*-substituted benzylamino alcohols in good yields. Investigation of the mechanism of this reductive cleavage, with the aid of labeling experiments, showed the intermediate formation of α-tertiary amino-substituted carbanions.

The reduction of benzyl alkyl ethers by electron transfer from alkali metals in ethereal solvents is a well-known reaction which affords regioselective cleavage of the benzylic carbon–oxygen bond and has found applications in the generation of benzyl carbanions.[1] Several papers are devoted to the investigation of the synthetic and mechanistic aspects of this reaction.[1-3] A similar regioselectivity has been observed in the reductive cleavage of aromatic acetals and ketals,[4] as well as in the reductive cleavage of aromatic epoxides.[5]

Following our interest in the reductive cleavage of derivatives of aromatic aldehydes and ketones[4] and due to the great actual interest in the generation of carbanions at the α-position to nitrogen,[6] we have investigated the reduction with alkali metals in ethereal solvents of *N*-substituted 2-aryl-1,3-oxazolidines **1**. Indeed, regioselective cleavage of the benzylic carbon–oxygen bond of such substrates should afford the corresponding *N*-substituted benzylamino alcohols **2**, important intermediates in the synthesis of several products endowed with interesting biological and pharmacological properties,[7] *via* the intermediate generation of uncommon α-tertiary amino-substituted carbanions.[8-10]

Results

Most *N*-substituted 2-aryl-1,3-oxazolidines **1** were synthesized by the reaction of the corresponding aromatic carbonyl derivatives with the appropriate amino alcohol in refluxing benzene in the presence of a catalytic amount of NH_4Cl or $MgCl_2$. A 2-alkyl-substituted derivative, namely 2-cyclohexyl-3-methyl-1,3-oxazolidine **4**, was synthesized in a similar way. 2,2-Diphenyl-3-methyl-1,3-oxazolidine (**1g**) was synthesized by the reaction of dichlorodiphenylmethane with 2-(methylamino)ethanol in dry THF in the presence of K_2CO_3.

The reductive cleavage reactions were carried out during 24 h under argon in the presence of the freshly cut metal (mostly K) in THF (Scheme I).

According to Scheme I, the reaction led to the exclusive cleavage of the benzylic carbon–oxygen bond and afforded the corresponding *N*-substituted benzylamino alcohols **2**. Cleavage of the alkyl carbon–oxygen bond was not observed; such a cleavage should lead, *via* the intermediate formation of the α-amino alcohols **3**, to the recovery of the starting carbonyl compounds. Furthermore, no evidence for the formation of products of carbon–nitrogen bond cleavage(s) was obtained.

Selected results are reported in Table I. The results of D_2O quenching experiments, carried out in order to check the formation of intermediate carbanions, are also reported in Table I.

Good yields of compounds **2** were obtained using K metal as the reducing agent. The use of Na or Li metal as electron donors (Table I, entries 2 and 3) was by far less effective in the reductive cleavage of 2-phenyl-3-methyl-1,3-oxazolidine (**1a**) (the starting material was recovered to a high extent); furthermore, with Li metal, formation of a dimeric product **5**, as a pair of diastereoisomers, was observed (Table I, entry 3).

Formation of α-amino carbanions, although not evidenced in the reductive cleavage of **1a**, was shown to occur in several cases; this finding can be related to the effect of the substituents R, R^1, and R^2. Indeed, the presence of a methoxy substituent in the *ortho* (Table I, entries 4 and 5), but not in *para* position (Table I, entry 6), permitted the clear detection of benzyl carbanions. Similar results were obtained in the reductive cleavage of the derivatives of 1-naphthaldehyde **1f** and of benzophenone **1g** (Table I, entries 8 and 9, respectively), but not in the case of the derivative of acetophenone **1h** (Table I, entry 10). Increasing steric hindrance at nitrogen favored formation of

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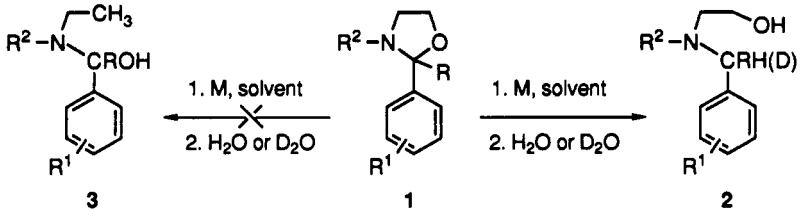
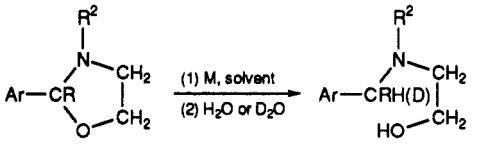
Scheme I



3 1 2

1a, 2a: R = R^1 = H, R^2 = CH_3; **1b, 2b**: R = H, R^1 = 2'-OCH_3, R^2 = CH_3; **1c, 2c**: R = H, R^1 = 2',3'-OCH_3, R^2 = CH_3; **1d, 2d**: R = H, R^1 = 4'-OCH_3, R^2 = CH_3; **1e, 2e**: R = H, R^1 = 4'-$(CH_3)_2N$, R^2 = CH_3; **1f, 2f**: R = H, R^1 = 2',3'-benzo, R^2 = CH_3; **1g, 2g**: R = C_6H_5, R^1 = H, R^2 = CH_3; **1h, 2h**: R = CH_3, R^1 = H, R^2 = CH_3; **1i, 2i**: R = R^1 = H, R^2 = C_2H_5; **1j, 2j**: R = H, R^1 = 2'-OCH_3, R^2 = C_2H_5; **1k, 2k**: R = H, R^1 = 2',3'-benzo, R^2 = C_2H_5; **1a-d_1, 2a-d_1**: R = D, R^1 = H, R^2 = CH_3.

Table I. Reductive Cleavage of Compounds 1 in THF

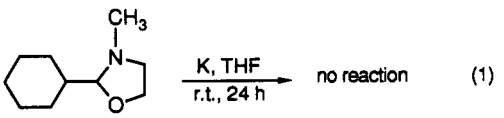


entry	compd	Ar	R	R^2	metal (equiv)	% yield[a,b]	% D[c]
1	**1a**	C_6H_5	H	CH_3	K(2.2)	80	*d*
2	**1a**	C_6H_5	H	CH_3	Na(2.2)	44	*d*
3	**1a**	C_6H_5	H	CH_3	Li(2.2)	28[e]	*d*
4	**1b**	2-$(CH_3O)C_6H_4$	H	CH_3	K(3)	68	61
5	**1c**	2,3-$(CH_3O)_2C_6H_3$	H	CH_3	K(3)	60	80
6	**1d**	4-$(CH_3O)C_6H_4$	H	CH_3	K(3)	77	*d*
7	**1e**	4-$(CH_3)_2NC_6H_4$	H	CH_3	K(3)	97	*d*
8	**1f**	1-naphthyl	H	CH_3	K(3)	62	25
9	**1g**	C_6H_5	C_6H_5	CH_3	K(3)	60	67
10	**1h**	C_6H_5	CH_3	CH_3	K(2)	75	*d*
11	**1i**	C_6H_5	H	C_2H_5	K(2)	85	*d*
12	**1j**	2-$(CH_3O)C_6H_4$	H	C_2H_5	K(3)	65	81
13	**1k**	1-naphthyl	H	C_2H_5	K(3)	89	80

[a] Based on isolated crude product, purity >95% (^{1}H NMR); no other product, unless starting material, was observed to a considerable extent. [b] Reaction time 24 h. [c] Upon D_2O quenching, as determined by ^{1}H NMR, by monitoring the percentage of deuterium in the benzylic position of recovered **2** (see Experimental Section). [d] No deuterium incorporation was detected. [e] Twenty percent of [Ph-CHN(CH_3)CH_2CH_2OH]$_2$ (**5**) (as a 40:60 mixture of diastereoisomers) was also recovered.

the carbanion, but only in the presence of the effect of other substituents (R^2 = CH_3 *vs* C_2H_5: Table I, entries 1, 4, and 8 *vs* 11–13).

It is interesting to observe that *N*-substituted-2-alkyl-1,3-oxazolidines were unreactive under the above reported reaction conditions: as an example, 2-cyclohexyl-3-methyl-1,3-oxazolidine (**4**) was recovered quantitatively after 24 h stirring in the presence of 3 equiv of K metal (eq 1).



(1)

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Additional deuterium labeling experiments were performed to shed light on the mode(s) of formation (and, eventually, of decay) of the carbanions.

Effect of the Solvent. The reductive cleavage of **1a** and of 2-(2'-methoxyphenyl)-3-methyl-1,3-oxazolidine (**1b**) as well as of 2-phenyl-2-deuterio-3-methyl-1,3-oxazolidine (**1a**-d_1) was investigated in different solvents; the reactions were run for 24 h at room temperature, with 3 equiv of K metal. The results are reported in Table II.

Table II. Effect of Solvent on the Reductive Cleavage of Compounds 1a and 1b[a]

entry	compd	solvent	quencher	% D[b]	product (% yield[c])
1	**1a**	THF-d_8	H_2O	56	**2a** (53)
2	**1a**-d_1[d]	THF	H_2O	41	**2a**-d_1 (82)
3	**1a**	2,5-$(CH_3)_2$THF	D_2O	*e*	**2a** (32)
4	**1b**	2,5-$(CH_3)_2$THF	D_2O	27	**2b** (36)
5	**1a**	Et_2O	D_2O	50	**2a** (44)
6	**1a**	isooctane	H_2O	ND[f]	**2a** (8)

[a] Reactions were run in the presence of 3 equiv of K metal for 24 h. [b] Determined by ^{1}H NMR, by monitoring the percentage of deuterium incorporation in the benzylic position of recovered **2** (see Experimental Section). [c] Determined on isolated products. No other product, unless starting material, was observed to a considerable extent. [d] The percentage of deuteriation in the benzylic position of **1a**-d_1 was >95% (^{1}H NMR). [e] No deuterium incorporation was detected. [f] ND = Not determined.

Participation of the solvent as a source of hydrogen atoms and/or of protons was evidenced by performing the reductive cleavage of **1a** in perdeutero-THF (THF-d_8, Table II, entry 1).

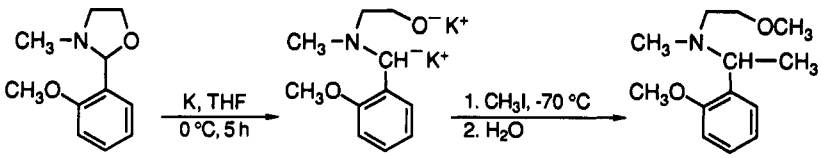
A similar exchange was observed also in the reductive cleavage of **1a**-d_1 in THF followed by H_2O quenching; indeed, recovered **2a**-d_1 showed a marked decrease of the deuterium label in the benzylic position (Table II, entry 2).

To better understand the role of the solvent, 2,5-dimethyltetrahydrofuran (2,5-$(CH_3)_2$-THF) was chosen as a better hydrogen atom donor than THF; at the same time, this solvent should also undergo proton abstraction much more slowly than THF.[11] 2,5-$(CH_3)_2$-THF was therefore employed as the solvent in the reductive cleavage of **1a** and **1b** followed by D_2O quenching (Table II, entries 3 and 4). While no deuterium incorporation was evidenced in recovered **2a**, only 27% deuteriation in the benzylic position of **2b** was evidenced. Furthermore, moderate conversion of the two substrates took place.

Low conversion was also observed when the reductive cleavage of **1a** was carried out in Et_2O or in 2,2,4-trimethylpentane (isooctane) (Table II, entries 5 and 6, respectively). Interestingly, in the reductive cleavage of **1a** in Et_2O, a solvent which should be more stable than

(11) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.

Scheme II



1b 6, 51%

Table III. Effect of Reaction Time and Temperature on the Reductive Cleavage of Compounds 1a and 1b[a]

entry	compd	t, h	T, °C	quencher	% D[b]	product (% yield[c])
1	1a	1	25	D_2O	45	2a (25)
2	1a	2	25	D_2O	15	2a (60)
3	1a	24	25	D_2O	d	2a (80)
4	1b	2	25	D_2O	56	2b (68)
5	1b	7	25	D_2O	60	2b (83)
6	1b	24	25	D_2O	61	2b (83)
7	1b	36	25	D_2O	48	2b (85)
8	1b	72	25	D_2O	d	2b (79)
9	1a	6	-10	D_2O	53	2a (62)
10	1a	6	-20	D_2O	48	2a (20)
11	1b	5	0	D_2O	87	2b (85)

[a] Reactions were run in THF in the presence of 3 equiv of K metal. [b] Determined by ^1H NMR, by monitoring the percentage of deuterium incorporation in the benzylic position of recovered 2 (see Experimental Section). [c] Determined on isolated products. No other product, unless starting material, was observed to a considerable extent. [d] No deuterium incorporation was detected.

THF to organometallic reagents,[12] evidence of the intermediate formation of the benzylic carbanion was obtained.

Effect of Reaction Time and Temperature. The reductive cleavage of compounds **1a** and **1b** with 3 equiv of K metal was also investigated as a function of reaction time and temperature; the results are reported in Table III.

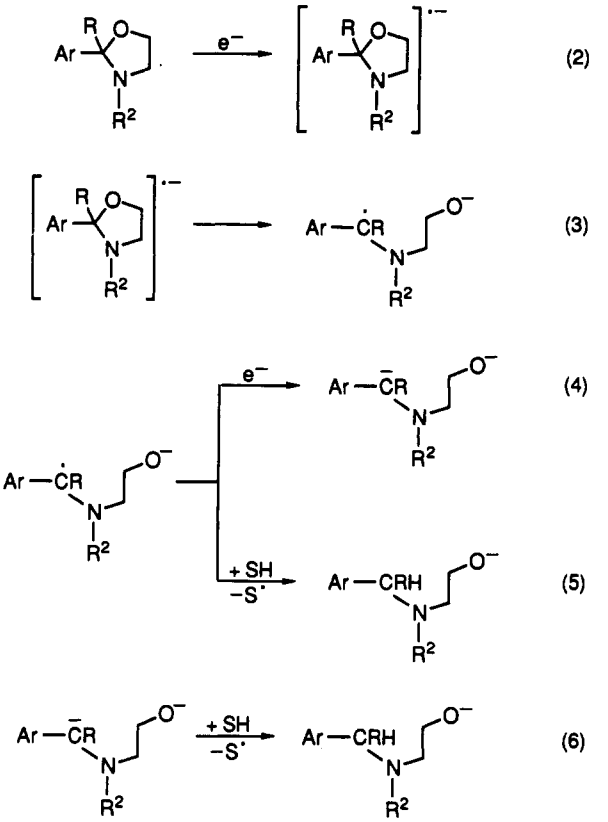
Formation and decay of the intermediate carbanions was evidenced by quenching with D_2O, at different times, the mixtures obtained by the reductive cleavage of **1a** and **1b** in THF at room temperature. This procedure permitted us to ascertain that the percentage of deuterium incorporation in the benzylic position reaches a maximum (about 50% for **2a** and 50–60% for **2b**) and, depending on the substitution pattern, decreases thereafter with time (Table III, entries 1–3 and 4–8, respectively).

Complementary results were obtained in the following D_2O-quenching experiments. Reductive cleavage of **1a** in THF at −10 and at −20 °C (Table III, entries 9 and 10, respectively) afforded about 50% deuteriation in the benzylic position of recovered **2a**, showing a relatively high stability to protonation of the intermediate carbanion at the low temperatures investigated.

A similar result was obtained when the reductive cleavage of **1b** was performed at 0 °C: indeed, 87% deuteriation in the benzylic position of recovered **2b** was observed (Table III, entry 11).

Quenching with Methyl Iodide. This experiment was carried out to check the possibility to trap the intermediate of the reductive cleavage of compounds **1** with an electrophile different from the proton. Compound **1b** was chosen as a substrate, due to the high percentage of α-amino carbanion detected in D_2O-quenching experiments. Reductive cleavage was performed in THF with K metal at 0 °C during 5 h; subsequent addition of an excess (3 equiv) of the electrophile was performed at −70 °C. As expected for a dianion, the product of both benzylic carbon and oxygen methylation was obtained, although in moderate yield (Scheme II).

Scheme III



Discussion

Our results clearly show that the reductive cleavage of 2-aryl-substituted 1,3-oxazolidines is a highly regioselective reaction occurring, at least in part, *via* the intermediate formation of α-tertiary amino-substituted carbanions, otherwise not easily accessible.[8-10]

According to these findings and to what is already reported in the literature for similar reductions,[1-5] a likely reaction mechanism for the reductive cleavage of the benzylic carbon–oxygen bond of 2-aryl-1,3-oxazolidines can be formulated (Scheme III).

As in the case of benzyl ethers, the first step is the formation of a radical anion by electron transfer from the metal (eq 2). The lack of reactivity under the reported reaction conditions of the 2-alkyl-substituted 1,3-oxazolidine **4** suggests that such electron transfer leads to the formation of a π^* aromatic radical anion. Transfer of the electron at the orbital crossing point from the π^* orbital to the σ^* orbital of the bond to be cleaved has been postulated for several related systems.[1,13]

(12) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988.

In the next step, the radical anion undergoes fragmentation into a molecular species containing both a benzyl radical and an alkoxide anion (eq 3). This species can be further reduced to the corresponding open-chain dianion (eq 4); support for formation of a dianionic species was provided by the methyl iodide-quenching experiment described above. Decay of the benzyl radical by hydrogen atom abstraction from the solvent (eq 5), or other components of the reaction mixture, competes with the reduction to carbanion. Once formed, the carbanion could decay by proton abstraction from the solvent (eq 6).

The results obtained show that both the decay of the benzyl radical by hydrogen atom abstraction and the decay of the carbanion by proton abstraction are at work. Indeed, when a good hydrogen atom donor, such as 2,5-$(CH_3)_2$-THF, is used as a solvent, carbanion formation was evidenced to a small extent even in the reductive cleavage of **1b**.

On the other hand, the results of Table III clearly show that carbanions are always formed in the reductive cleavage of both **1a** and **1b** in THF, and that they decay with time by proton abstraction from the solvent. The last point is supported by the results obtained in the reactions run in THF at low temperatures and in Et_2O.

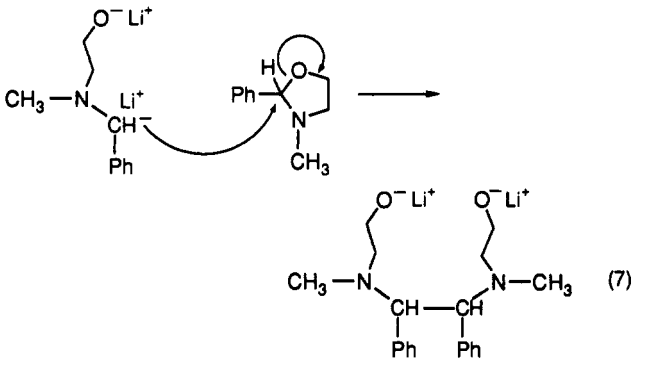
The effect of substituents R and R^1 on the relative stabilities of the carbanions affects the competition between steps 4 and 5 (Scheme III). The decay of the carbanions by proton abstraction from the solvent is, of course, affected in a similar way. This is the case of a substituent able to stabilize a benzyl carbanion by complexation, like a methoxy in the *ortho* position[14] (compounds **1b** and **1c**), or of substituents leading to further mesomeric stabilization (compounds **1d** and **1e**).

It is more difficult to rationalize the effect of the substituent at nitrogen, R^2. It seems that increasing steric hindrance at nitrogen stabilizes the α-amino carbanions, allowing formation of these intermediates in high concentrations, but only in the presence of other stabilizing effects (Table I, compounds **2a**, **2b**, and **2f** *vs* compounds **2i**, **2j**, and **2k**).

A final remark concerns the result obtained in the reductive cleavage of **1a** with Li metal, which afforded, besides **2a**, a dimeric product, namely *N,N'*-dimethyl-*N,N'*-bis(2-hydroxyethyl)-1,2-diphenylethylenediamine (**5**) as a pair of diastereoisomers. Formation of this product can be attributed to dimerization of the intermediate benzyl radical alkoxide; nucleophilic attack of the α-amino carbanion to unreacted starting material can also be considered (eq 7).

Indeed, the reactivity of 1,3-oxazolidines toward organolithium (and -magnesium) reagents is well known, as well as their inertness toward organosodium and -potassium reagents.[15-17]

In conclusion, with suitable substrates, our procedure allows the generation of α-tertiary amino-substituted carbanions by the reductive cleavage of 2-aryl-1,3-oxazolidines; in view of the result obtained in the methyl iodide-quenching experiment, trapping of these carbanions with electrophiles could find wider use. Synthetic exploitation of this reaction is under investigation.



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Experimental Section

General Procedures. Boiling and melting points are uncorrected. All products and reagents were of the highest commercial quality and were further purified by distillation. Deuterium oxide was 99.8% isotopic purity. Solvents were distilled from Na/K alloy under N_2 immediately prior to use. Benzaldehyde-α-d_1 was synthesized according to a literature procedure.[18] ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra at 75 MHz in $CDCl_3$ solution with $SiMe_4$ as internal standard. Deuterium incorporation was calculated by monitoring the ^1H NMR spectra of compounds **2** and comparing the integration of the signal corresponding to the proton(s) in the benzylic position with the integrals of the CH_2O and CH_2N protons. Elemental analyses were performed by the Microanalytical Laboratory of the Dipartimento di Chimica, Università di Sassari.

Preparation of 1,3-Oxazolidines 1a–f, 1i–k, 1a-d_1, and 4. A solution of the appropriate carbonyl compound (0.1 mol) and the amino alcohol (0.2 mol) in 100 mL of dry benzene was distilled with fractionation under nitrogen in the presence of NH_4Cl (100 mg, 1.9 mmol) (compounds **1a–d**, **1f**, **1i–1k**, and **1a–d_1**), or $MgCl_2$ (100 mg, 1 mmol) (compound **1h**), or a mixture of both (compound **1e**) until the azeotrope benzene–water was distilled away. The reaction mixture was chilled to 0 °C and triethylamine (2 mL, 14 mmol) was added at once. The mixture was then filtered, washed with saturated $NaHCO_3$ (1 × 50 mL) and water (2 × 50 mL), and dried (K_2CO_3). Evaporation of the solvent and vacuum distillation afforded pure compounds in good to high yields (60–90%).

2-Phenyl-3-methyl-1,3-oxazolidine (1a): bp 64–65 °C (1 Torr) (lit.[19] bp 129 °C (30 Torr)); ^1H NMR δ 2.31 (s, 3 H), 2.62–2.80 (m, 1 H), 3.24–3.42 (m, 1 H), 3.96–4.20 (m, 2 H), 4.76 (s, 1 H), 7.36–7.50 (m, 5H).

2,2-Diphenyl-3-methyl-1,3-oxazolidine (1g). A mixture of dichlorodiphenylmethane (2 g, 8.4 mmol), K_2CO_3 (9.3 g, 67 mmol), and 2-(methylamino)ethanol (1.4 mL, 17 mmol) in 20 mL of dry THF was stirred at reflux temperature under nitrogen for 24 h. The reaction mixture was chilled to rt and filtered. The filtrate was washed with saturated $NaHCO_3$ (2 × 20 mL) and water (20 mL) and dried (K_2CO_3). Evaporation of the solvent and vacuum distillation afforded pure **1g** (1.26 g, 5.3 mmol, 63%) as a colorless oil which solidified upon standing: bp 178–180 °C (1 Torr); ^1H NMR δ 2.14 (s, 3 H), 3.07 (t, J = 7.0 Hz, 2 H), 3.90 (t, J = 7.0 Hz, 2 H), 7.16–7.34 (m, 6H), 7.50–7.58 (m, 4 H); ^{13}C NMR δ 39.4, 54.1, 62.2, 126.9, 127.2, 127.9, 128.2, 142.9.

All 1,3-oxazolidines were further characterized by acidic hydrolysis (1 N HCl/THF = 1:1, rt, 3 h) to the corresponding carbonyl derivatives.

General Procedure for the Reductive Cleavage of 1. A solution of **1** (6 mmol) in anhydrous THF (5 mL) was added

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dropwise to a suspension of the freshly cut metal (12–18 mg atom) in anhydrous THF (30 mL) under nitrogen or argon.

The mixture was stirred at rt for 24 h, chilled to 0 °C, and quenched by slow dropwise addition of H_2O (10 mL) (*caution*!); 20 mL of brine was then added, and the mixture was extracted with Et_2O (4 × 20 mL). Aliquots of the organic layer were dried (K_2CO_3) and checked (^1H NMR, IR) for the absence of carbonyl compounds. The organic phase was stirred with 1 N HCl for 2 h and then extracted with 1 N HCl (3 × 20 mL). The acidic aqueous layers were collected and made alkaline by addition of solid NaOH and then extracted with Et_2O (4 × 20 mL); the organic phase was dried (K_2CO_3) and the solvent evaporated.

Deuterium oxide-quenching was performed by slow dropwise addition of 2 mL of D_2O to the reaction mixture chilled to 0 °C, followed by stirring of the mixture for 2 h at rt and workup as above.

2-[*N*-Methyl-*N*-(phenylmethyl)amino]ethanol (2a): bp 103 °C (1 Torr) (lit. bp 85–91 °C (0.55–0.57 Torr); see ref 23 of supplementary material); ^1H NMR δ 2.35 (s, 3 H), 2.61 (t, J = 5.1 Hz, 2 H), 2.82 (br s, 1 H), 3.57 (s, 2 H), 3.62 (t, J = 5.1 Hz, 2 H), 7.28–7.36 (m, 5 H); IR (KBr) = 3400 cm^{-1}.

2-[*N*-Methyl-*N*-[1-(2′-methoxyphenyl)ethyl]amino]ethyl Methyl Ether (6). A solution of **1b** (0.58 g, 3 mmol) in anhydrous THF (5 mL) was added dropwise to a suspension of freshly cut K (6 mg atom, 240 mg) in anhydrous THF (30 mL) chilled to 0 °C under argon. The mixture was stirred for 6 h and then chilled to −70 °C, and 3 equiv of CH_3I (1.3 g, 9 mmol) were added with a syringe. The mixture was stirred at −70 °C for 1 h and then quenched by slow dropwise addition of water (10 mL) (*caution*!); 20 mL of brine were then added, the mixture was extracted with Et_2O (4 × 20 mL), and the organic phase was dried (K_2CO_3). The solvent was then evaporated to afford the crude product which was purified by flash chromatography. Elution with a gradient of AcOEt/CH_2Cl_2 containing triethylamine (4%) afforded pure **6** (0.34 g, 1.53 mmol, 51% yield): bp 215 °C/1 Torr; ^1H NMR δ 1.32 (d, J = 6.9 Hz, 3H), 2.27 (s, 3 H), 2.38–2.50 (m, 1H), 2.62–2.74 (m, 1H), 3.31 (s, 3 H), 3.40–3.54 (m, 2 H), 3.81 (s, 3 H), 4.15 (q, J = 6.9 Hz, 1H), 6.86 (dd, J = 7.5 Hz, J = 1.2 Hz, 1 H), 6.93 (td, J = 7.5 Hz, J = 1.2 Hz, 1 H), 7.16–7.23 (m, 1H), 7.38 (dd, J = 7.5 Hz, J = 1.8 Hz, 1H). Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.90, H, 9.50, N, 6.27. Found: C, 69.61, H, 9.37, N, 5.89.

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Supplementary Material Available: Characterization data (boiling point, melting point, IR, ^1H NMR, and ^{13}C NMR) for compounds **1a-d_1**, **1b–f**, **1i–k**, **2b–k**, **4**, **5** (5 pages). This material is available on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.