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Synthesis of 1,3-oxazolidines by copper-catalyzed addition of acetone and ethyl diazoacetate to imines

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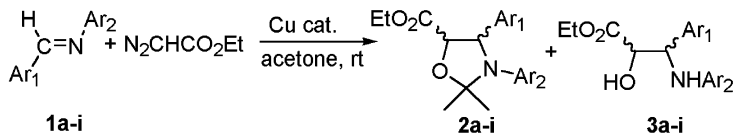
Abstract—1,3-Oxazolidines are obtained in high yields by copper-catalyzed addition of ethyl diazoacetate to imines in the presence of acetone. Hydrolysis of the oxazolidines with 6N HCl yields 1,2-amino alcohols.

1,3-Oxazolidines have been used often in organic synthesis as intermediates in preparative pathways and as chiral auxiliaries to direct diastereoselective transformations.[1] These substances are typically prepared by condensation reactions of 1,2-amino alcohols with aldehydes or nitriles,[2] [3+2]-cycloadditions of azomethine ylides and carbonyl compounds,[3] or other routes.[4] Recently a new method to prepare 1,3-oxazolidines, via metal-catalyzed addition of epoxides to imines, was described.[5] During the course of investigations into probing methods for aziridine ring construction, we observed that copper catalyzed reactions of ethyl diazoacetate with imines in the presence of acetone results in the formation of 1,3-oxazolidines and 1,2-amino alcohols (Scheme 1). A detailed study of this process has led to the development of a convenient and efficient procedure to prepare 1,3-oxazolidines. Below, we report the results of this study which demonstrates that 1,3-oxazolidines and amino alcohols can be generated in high yields by reaction of imines with ethyl diazoacetate in the presence of 10 mol% copper tetrafluoroborate or triflate.



Scheme 1.

Table 1. 1,3-Oxazolidine formation by Cu-catalyzed addition of ethyl diazoacetate to imines in the presence of acetone

Entry	Imine	Ar_1	Ar_2	Catalyst	**2** (%)[a] (*cis*/*trans*)[b]	**3** (%)	Total yield (%)
1	**1a**	*p*-MethoxyPh	Ph	$Cu(OTf)_2$	38 (2)	48	86
2	**1b**	*p*-NitroPh	*p*-MethoxyPh	$Cu(OTf)_2$	45 (3)	28	73
3	**1c**	*p*-NitroPh	Ph	$Cu(OTf)_2$	38 (2)	39	77
4	**1d**	*p*-MethoxyPh	*p*-MethoxyPh	$Cu(OTf)_2$	53 (2)	28	81
5	**1c**	*p*-NitroPh	Ph	$CuI/AgBF_4$	79 (1.5)	17	96
6	**1d**	*p*-MethoxyPh	*p*-MethoxyPh	$CuI/AgBF_4$	48 (1.3)	32	80
7	**1e**	Ph	Ph	$CuI/AgBF_4$	56 (1.1)	13	69
8	**1f**	Ph	*p*-MethoxyPh	$CuI/AgBF_4$	58 (1.7)	19	77

[a] Isolated yields.
[b] Ratios were determined by ^1H NMR analysis.

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Table 2. 1,3-Oxazolidine formation by Cu-catalyzed addition of ethyl diazoacetate to imines in the presence of acetone and molecular sieves

Entry	Imine	Ar_1	Ar_2	Catalyst	**2** (%)[a] (*cis*/*trans*)[b]	**3** (%)	Total yield (%)
1	**1a**	*p*-MethoxyPh	Ph	$Cu(OTf)_2$	68 (1.2)	10	78
2	**1b**	*p*-NitroPh	*p*-MethoxyPh	$Cu(OTf)_2$	80 (2)	13	93
3	**1c**	*p*-NitroPh	Ph	$Cu(OTf)_2$	72 (3)	23	95
4	**1d**	*p*-MethoxyPh	*p*-MethoxyPh	$Cu(OTf)_2$	85 (1.2)	14	99
5	**1e**	Ph	Ph	$Cu(OTf)_2$	53 (1.2)	13	66
6	**1f**	Ph	*p*-MethoxyPh	$Cu(OTf)_2$	80 (1.2)	12	92
7	**1g**	*p*-ChloroPh	*p*-MethoxyPh	$Cu(OTf)_2$	86 (1.5)	13	99
8	**1a**	*p*-MethoxyPh	Ph	$CuI/AgBF_4$	93 (1)	5	98
9[c]	**1a**	*p*-MethoxyPh	Ph	$CuI/AgBF_4$	63 (3)	17	80
10	**1b**	*p*-NitroPh	*p*-MethoxyPh	$CuI/AgBF_4$	80 (2)	13	93
11	**1c**	*p*-NitroPh	Ph	$CuI/AgBF_4$	82 (2.8)	15	97
12	**1d**	*p*-MethoxyPh	*p*-MethoxyPh	$CuI/AgBF_4$	73 (1.4)	11	84
13	**1e**	Ph	Ph	$CuI/AgBF_4$	78 (1.5)	6	84
14	**1f**	Ph	*p*-MethoxyPh	$CuI/AgBF_4$	85 (2.8)	10	95
15	**1g**	*p*-ChloroPh	*p*-MethoxyPh	$CuI/AgBF_4$	79 (1.6)	12	91
16	**1h**	Ph	*p*-NitroPh	$CuI/AgBF_4$	61 (1)	11	72
17	**1i**	*p*-MethoxyPh	*p*-NitroPh	$CuI/AgBF_4$	84 (1.5)	10	94
18	**1a**	*p*-MethoxyPh	Ph	$CuCl_2/AgBF_4$	74 (1.6)	16	90
19	**1c**	*p*-NitroPh	Ph	$CuCl_2/AgBF_4$	76 (2.2)	14	90
20	**1e**	Ph	Ph	$CuCl_2/AgBF_4$	61 (2.2)	19	80
21	**1f**	Ph	*p*-MethoxyPh	$CuCl_2/AgBF_4$	53 (1.7)	15	68

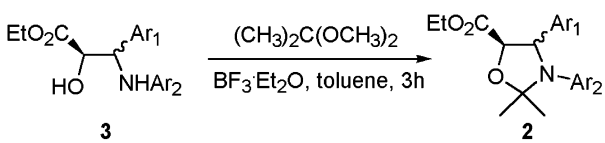
[a] Isolated yields.
[b] Ratios were determined by ^1H NMR analysis.
[c] Reaction was performed at 0°C.

A number of experiments were performed to maximize the efficiency of the 1,3-oxazolidine forming reaction (Table 1).[6] In this effort, we found that reactions of imines with ethyl diazoacetate using copper(I) iodide as catalyst were unsuccessful. However, the addition process catalyzed by copper(I) tetrafluoroborate, prepared by reaction of copper(I) iodide with silver tetrafluoroborate, afforded the oxazolidines and corresponding amino alcohols in high yields (Table 1, entries 5–8).[7] In addition, copper(II) triflate serves as an effective catalyst for this process (Table 1, entries 1–4). When the addition reactions are run in the absence of molecular sieves, large quantities of 1,2-amino alcohols are generated, presumably by hydrolysis of the initially formed 1,3-oxazolidines. Inclusion of molecular sieves in the reaction mixtures, however, prevents formation of the amino alcohols and it results in enhanced oxazolidine yields (Table 2).

The structures of 1,3-oxazolidine products were determined by using ^1H, ^{13}C NMR spectroscopy and elemental analysis. For example, the ^1H NMR spectra of the *cis*-diastereomer of oxazolidine **2e**, prepared from *N*-phenylbenzaldimine, contained two singlets (1.48 (3H) and 1.89 (3H) ppm) assigned to the methyl groups at C-2 and two doublets (4.49 (1H, $J=7.6$ Hz) and 5.05 (1H, $J=7.6$ Hz) ppm) corresponding to the vicinally disposed ring protons. The oxazolidine diastereomers were separated by column chromatography and purified by recrystallization. Since the coupling constants of ring protons in *cis*- and *trans*-oxazolidines are nearly the same, stereochemical assignments to the oxazolidines required the use of COSY spectra.

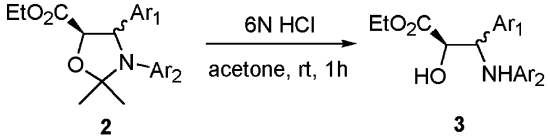
The ratios of the *cis*- to *trans*-oxazolidines produced in these reactions were found to vary from 1:1 to 3:1. As demonstrated by the addition of ethyl diazoacetate to *N*-phenylanisaldimine **1a**, reaction at 0°C versus 25°C results in an increase (3:1 versus 1:1) in the *cis*/*trans* ratio. However, the observation that the reaction does not occur at −25°C rules out the use of even lower temperatures to further enhance stereoselectivity.

The amino alcohols **3**, formed as minor products in these processes, were separated and converted to the oxazolidines by acid catalyzed (*p*-toluenesufonic acid or $BF_3{\cdot}Et_2O$)[8] reaction with acetone or 2,2-dimethoxypropane (Scheme 2). It is interesting that the *trans*-oxazolidines are formed as major products (*trans* to *cis* ratios ca. 1.5:1). In addition, the amino alcohols are formed in moderate to high yields (60–97%) by hydrolysis of 1,3-oxazolidines with 6N HCl (Scheme 3 and Table 3).[9]



3 **2**

Scheme 2.



2 **3**

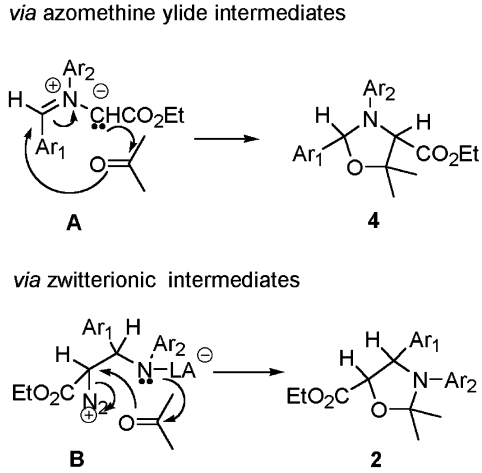
Scheme 3.

Table 3. Amino alcohols by hydrolysis of 1,3-oxazolidines

Entry	Oxazolidine	Ar_1	Ar_2	Yield (%)[a]
1	*cis*-**2a**	*p*-MethoxyPh	Ph	71
2	*cis*-**2c**	*p*-NitroPh	Ph	75
3	*cis*-**2d**	*p*-MethoxyPh	*p*-MethoxyPh	97
4	*cis*-**2e**	Ph	Ph	71
5	*cis*-**2f**	Ph	*p*-MethoxyPh	84
6	*cis*-**2h**	Ph	*p*-NitroPh	61
7	*cis*-**2i**	*p*-MethoxyPh	*p*-NitroPh	65
8	*trans*-**2a**	*p*-MethoxyPh	Ph	58
9	*trans*-**2d**	*p*-MethoxyPh	*p*-MethoxyPh	94
10	*trans*-**2e**	Ph	Ph	77
11	*trans*-**2f**	Ph	*p*-MethoxyPh	90
12	*trans*-**2h**	Ph	*p*-NitroPh	61

[a] Isolated yield.

It is interesting to speculate about the mechanism of this 1,3-oxazolidine ring forming reaction. It has been proposed that formation of aziridines in copper catalyzed reactions of diazoacetates with imines involves the intermediacy of carbene complexes and azomethine ylides, or zwitterionic (Lewis acid catalyzed) species.[10] In reactions proceeding via carbene complexes, fumarate and/or maleate esters are commonly formed as side products.[11] However, reaction mixtures generated in the oxazolidine forming processes described above were found not to contain either diethyl maleate or diethyl fumarate. Thus, it is likely that this reaction does not proceed via the intermediacy of metal carbene complexes. Also, oxazolidines are known to be produced by cycloaddition reactions of carbonyl compound such as ketene with azomethine ylides, generated by thermal electrocyclic ring opening of aziridines.[3b] But, if the above reactions were to proceed through azomethine ylide intermediates **A**, it is expected that ethyl 5,5-dimethyl-2,3-diphenyl-4-oxazolidinecarboxylate **4** (Scheme 4) would be formed. The ^1H NMR spectra of these substances, which are structural isomers of the oxazolidines actually generated in the copper catalyzed reactions of acetone, imines and the diazoacetate ester, would characteristically contain two singlets corresponding to the ring protons. Also, we have prepared aziridines, representative of those that are possible intermediates in the oxazolidine forming reactions. Treatment of these aziridines with acetone under the copper catalyzed reaction conditions did not lead to generation of oxazolidine products. Recently, 1,3-oxazolidines were synthesized by using SmI_2 or Pd(0) catalyzed reactions between epoxides and imines.[5] To determine if epoxides are intermediates in the reactions described above, we treated acetone with ethyl diazoacetate in the presence of copper catalyst and then with imines. Here again, no oxazolidines were obtained. The combined results suggest that the likely mechanism for oxazolidine formation in copper catalyzed reactions between ethyl diazoacetate, imines and acetone involves formation of the zwitterionic (Lewis acid catalyzed) intermediate **B** followed by acetone addition (Scheme 4).



Scheme 4.

Acknowledgements

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6. Acetone distilled from anhydrous K_2CO_3 under N_2 was used.

7. General procedure for the three-component 1,3-oxazolidine-forming reaction. To a stirred solution of $AgBF_4$ (0.08 mmol, 0.1 equiv.) in acetone (5 mL), containing suspended molecular sieves 4 Å, at 25°C was added CuI (0.08 mmol, 0.1 equiv.). After a white precipitate formed, imine (0.8 mmol, 1.0 equiv.) and ethyl diazoacetate (0.8 mmol, 1.0 equiv.) were added. After stirring for 30 min, the mixture was concentrated, diluted with ether, and filtered through silica gel. The ethereal filtrate was concentrated in vacuo and the residue was subjected to chromatography on silica gel (EA:hexane = 1:5) to give the oxazolidine product. Representative spectroscopic properties of the oxazolidines. **Ethyl 3-*p*-methoxyphenyl-2,2-dimethyl-4-*p*-nitrophenyl-5-oxazolidine carboxylate (*cis*-2b)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 6.74 (d, J = 9.3 Hz, 2H), 5.28 (d, J = 7.8 Hz, 1H), 4.96 (d, J = 7.8 Hz, 1H), 3.83 (dq, J = 14.4, 7.2 Hz, 1H), 3.71 (s, 3H), 3.58 (dq, J = 14.4, 7.2 Hz, 1H), 1.87 (s, 3H), 1.29 (s, 3H), 0.86 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 155.7, 147.5, 145.0, 135.6, 129.1, 123.7, 123.3, 114.3, 97.7, 78.1, 64.9, 60.8, 55.3, 29.1, 22.9, 13.7; IR (KBr) 2981, 2927, 2836, 1753 cm^{-1}. Anal. calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 63.04; H, 6.13; N, 6.93. **Ethyl 3-*p*-methoxyphenyl-2,2-dimethyl-4-*p*-nitrophenyl-5-oxazolidine carboxylate (*trans*-2b)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 5.05 (d, J = 7.8 Hz, 1H), 4.38 (d, J = 8.1 Hz, 1H), 4.29–4.25 (m, 2H), 3.70 (s, 3H), 2.04 (s, 3H), 1.71 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); IR (KBr) 2981, 2933, 2830, 1750 cm^{-1}.

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9. General procedure for the 1,3–oxazolidine hydrolysis. A solution of 1,3-oxazolidine (1.0 mmol) in acetone (3 mL) and 6N HCl (1 mL) was stirred at 25°C for 1 h, concentrated, washed with saturated aq. $NaHCO_3$, and extracted with dichloromethane. The dichloromethane extracts were concentrated and the residue was subjected to chromatography on silica gel (ethyl acetate: hexane = 3:1) to give the amino alcohol products. Representative ^{1}H NMR spectroscopic properties of the amino alcohols. **Ethyl 2-hydroxy-3-(*p*-nitrophenyl)amino-3-phenylpropanoate (3h from *cis*-oxazolidine)**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.04–7.96 (m, 2H), 7.36–7.25 (m, 5H), 6.57–6.49 (m, 2H), 5.73 (d, J = 7.5 Hz, 1H), 4.89 (dd, J = 7.9, 3.4 Hz, 1H), 4.69 (dd, J = 7.1, 3.4 Hz, 1H), 4.28–4.12 (m, 2H), 2.99 (d, J = 7.4 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); IR (KBr) 3498, 3380, 3031, 2982, 1736, 1600, 1504, 1475, 1312, 1112 cm^{-1}. **Ethyl 2-hydroxy-3-(*p*-nitrophenyl)amino-3-phenylpropanoate (3h from *trans*-oxazolidine):** ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10–7.97 (m, 2H), 7.38–7.30 (m, 5H), 6.57–6.49 (m, 2H), 5.55 (d, J = 6.2 Hz, 1H), 5.01 (d, J = 5.8 Hz, 1H), 4.55 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.20 (s, 1H), 1.24 (t, J = 7.1 Hz, 3H); IR (KBr) 3483, 3375, 3030, 2981, 1733, 1600, 1504, 1476, 1310, 1112 cm^{-1}.

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