A New and Convenient Synthesis of 1-Aryl-2-dimethylaminoethanols

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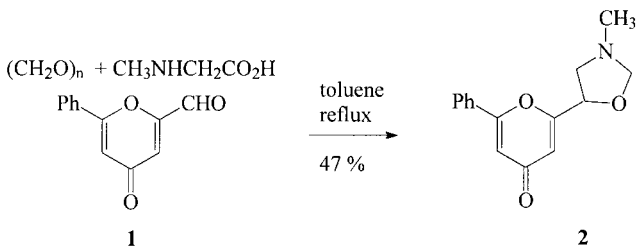
Abstract: An efficient two-step synthesis of 1-aryl-2-dimethylaminoethanols **4** is described, consisting of oxazolidine **3** generation from the cycloaddition of an azomethine ylide to an aldehyde, followed by reductive ring-opening.

Key words: aldehydes, amino alcohols, cycloadditions

The importance of β-hydroxyamines as β-blockers in medicine is well-known and some of their uses include nervous system stimulants, bronchodilators, appetite suppressants and, most significantly, combating heart disease.[1] The vicinal amino alcohol moiety is also a structural component in many naturally occurring and synthetic molecules.[2] Herein, we report a new, convenient, two-step synthesis of 1-aryl-2-dimethylaminoethanols **4**, which have a wide range of biological activities.[3] Usually the synthesis of these β-hydroxyamines consists of several steps via intermediates such as dimethylamino ketones,[4] vicinal hydroxy halides,[3a,5] oxiranes,[5] or α-ketoacetamides.[6]

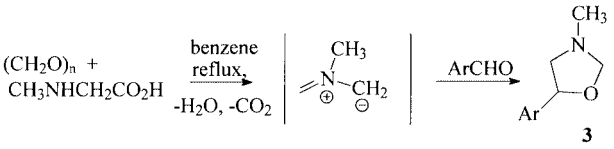
In the course of our studies directed towards the investigation of substituent effects on the 4π + 2π cycloadditions of 4*H*-pyran-4-one derivatives[7] we observed the formation of *N*-methyloxazoline **2**, in good yield, in the three component reaction of pyranone aldehyde **1**, sarcosine and paraformaldehyde (Scheme 1) and, with a view to prepare 5-aryl-3-methyloxazolidines **3**, which are valuable intermediates for further elaboration to 1-aryl-2-dimethylaminoethanols **4**, we initially studied this cycloaddition. It is known that azomethine ylides can react with C=O double bonds in 1,3-dipolar cycloadditions, and several oxazolidine-type cycloadducts have been described, but in these cases either (a) the aldehyde component of the azomethine ylide, formed in situ, was the same as the dipolarophile,[8] or (b) a stable precursor of the azomethine ylide was prepared in advance and this was followed by the cycloaddition step.[8a,9]



1 2

Scheme 1

With our new method it is possible to synthesize a variety of 5-aryl-3-methyloxazolines **3** by simple mixing of sarcosine, paraformaldehyde and an aromatic aldehyde (as the dipolarophile) in benzene and refluxing under Dean–Stark conditions (Scheme 2). In all cases only the formaldehyde served as a component for the non-stabilised azomethine ylide generation, and the cycloadduct **3** was isolated in high yield as the sole product (Table 1).



3

Scheme 2

The reaction of these cycloadducts **3** with sodium borohydride in ethanol at room temperature afforded the desired 1-aryl-2-dimethylaminoethanols **4**, with only one exception (**3i**), (Scheme 3, Table 2).

Table 1 Preparation of 5-Aryl-3-methyloxazolines **3**

Entry	Starting Aldehyde Ar	Time (h)	Product[a]	Yield (%)
1	2-nitrophenyl	1	**3a**	95
2	3-nitrophenyl	1	**3b**	98
3	4-nitrophenyl	1	**3c**	92
4	4-chlorophenyl	2	**3d**	87
5	2,4-dichlorophenyl	3	**3e**	91
6	2-bromophenyl	3	**3f**	86
7	3,4-methylene-dioxyphenyl	15	**3g**	58
8	1-naphthyl	5	**3h**	72
9	2-pyridyl	3	**3i**	77
10	2-thiophenyl	2	**3j**	87

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.3, N ±0.2.

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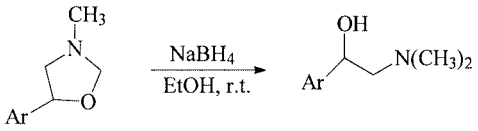

3 4

Scheme 3

Column chromatography was performed using Merck Kieselgel 60 70–230 mesh; TLC on aluminum sheets coated with Kieselgel 60 F_{254}. Plates were stained with anisaldehyde solution (100 mL glacial AcOH, 2 mL H_2SO_4 and 1 mL anisaldehyde) and heated at ca. 150 °C. IR spectra were recorded on a NICOLET FT-IR instrument. Low-resolution electron impact mass spectra were obtained on a Varian CH5-D spectrometer. NMR measurements were carried out on a Bruker 250 instrument. Chemical shifts are given relative to TMS (δ = 0.00).

5-Aryl-3-methyloxazolidines 3; General Procedure

The corresponding aryl aldehyde **1** (1 mmol), sarcosine (178 mg, 2 mmol) and paraformaldehyde (150 mg, 5 mmol) were suspended in benzene (50 mL) and the reaction mixture was then heated for the time given in Table 1 under Dean–Stark conditions. After the reaction was complete, the solvent was removed in vacuo and the residue was dissolved in acetone and filtered through a plug of silica gel. The filtrate was then evaporated under reduced pressure to give the product (Table 3).

Table 2 Preparation of 1-Aryl-2-dimethylaminoethanols **4**

Entry	Starting Material	Time (h)	Product[a]	Yield[b] (%)
1	**3a**	1	**4a**	87
2	**3b**	1	**4b**	93
3	**3c**	1.5	**4c**	94
4	**3d**	0.5	**4d**	91
5	**3e**	1	**4e**	93
6	**3f**	1	**4f**	95
7	**3g**	1	**4g**	88
8	**3h**	2	**4h**	90
9	**3j**	2	**4j**	90

[a] Satisfactory microanalyses obtained: C ±0.3, H ±0.2, N ±0.2.

Table 3 Spectral Data for 5-Aryl-3-methyloxazolidines **3a–j**

Product	IR (film) ν (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
3a	2851, 2867, 2799, 1524, 1452, 1346, 1058	8.03 (d, 1 H, *J* = 8.2), 7.87 (d, 1 H, *J* = 8.2), 7.65 (t, 1 H, *J* = 8.2), 7.41 (t, 1 H, *J* = 8.2 Hz), 5.53 (t, 1 H, *J* = 6.7 Hz), 4.64 (d, 1 H, *J* = 5.1), 4.47 (d, 1 H, *J* = 5.1), 3.62 (dd, 1 H, dd, *J* = 11.6, 6.7), 2.80 (dd, 1 H, *J* = 11.6, 6.7), 2.49 (s, 3 H)	147.8 (quat), 139.3 (quat), 133.8 (CH), 127.6 (CH), 127.0 (CH), 124.5 (CH), 89.3 (CH_2), 73.3 (CH), 61.1 (CH_2), 41.5 (CH_3)
3b	2941, 2897, 2791, 1522, 1453, 1345, 1058	8.21 (s, 1 H), 8.11 (d, 1 H, *J* = 7.5), 7.67 (d, 1 H, *J* = 7.5), 7.52 (t, 1 H, *J* = 7.5), 5.13 (t, 1 H, *J* = 6.9), 4.59 (d, 1 H, *J* = 4.6), 4.50 (d, 1 H, *J* = 4.6), 3.40 (dd, 1 H, *J* = 11.1, 6.9), 2.80 (dd, 1 H, *J* = 11.1, 6.9), 2.51 (s, 3 H)	148.1 (quat), 145.6 (quat), 131.4 (CH), 129.2 (CH), 122.1 (CH), 120.2 (CH), 89.4 (CH_2), 75.3 (CH), 62.3 (CH_2), 41.0 (CH_3)
3c	2950, 2873, 2801, 1601, 1518, 1346, 1057	8.18 (d, 2 H, *J* = 8.3), 7.51 (d, 2 H, *J* = 8.3), 5.13 (t, 1 H, *J* = 7.0), 4.57 (d, 1 H, *J* = 4.8), 4.51 (d, 1 H, *J* = 4.8), 3.41 (dd, 1 H, *J* = 11.2, 7.0), 2.76 (dd, 1 H, *J* = 11.2, 7.0), 2.50 (s, 3 H)	149.9 (quat), 146.0 (quat), 125.9 (2 × CH), 123.5 (2 × CH), 89.4 (CH_2), 75.3 (CH), 62.3 (CH_2), 41.2 (CH_3)
3d	2949, 2871, 2798, 1666, 1489, 1457, 1087, 1056, 1011	7.31 (d, 2 H, *J* = 8.7), 7.25 (d, 2 H, *J* = 8.7), 5.00 (t, 1 H, *J* = 7.0 Hz), 4.52 (d, 1 H, *J* = 4.7 Hz), 4.47 (d, 1 H, *J* = 4.7), 3.30 (dd, 1 H, *J* = 11.1, 7.0), 2.72 (dd, 1 H, *J* = 11.1, 7.0), 2.49 (s, 3 H)	140.6 (quat), 132.9 (quat), 128.5 (2 × CH), 126.8 (2 × CH), 89.3 (CH_2), 75.8 (CH), 62.6 (CH_2), 41.3 (CH_3)
3e	2950, 2869, 2797, 1587, 1466, 1382, 1053	7.52 (d, 1 H, *J* = 8.3), 7.34 (d, 1 H, *J* = 2.0), 7.24 (dd, 1 H, *J* = 8.3, 2.0), 5.23 (t, 1 H, *J* = 6.9), 4.55 (d, 1 H, *J* = 5.1), 4.47 (d, 1 H, *J* = 5.1), 3.50 (dd, 1 H, *J* = 11.3, 6.9), 2.69 (dd, 1 H, *J* = 11.3, 6.9), 2.49 (s, 3 H)	139.2 (quat), 133.2 (quat), 130.0 (quat), 129.0 (CH), 127.3 (CH), 127.1 (CH), 89.3 (CH_2), 73.5 (CH), 61.2 (CH_2), 41.7 (CH_3)
3f	2950, 2869, 2798, 1466, 1439, 1159, 1058, 1029	7.57 (d, 1 H, *J* = 7.7), 7.49 (d, 1 H, *J* = 7.7), 7.30 (t, 1 H, *J* = 7.7), 7.10 (t, 1 H, *J* = 7.7), 5.25 (t, 1 H, *J* = 6.9), 4.58 (d, 1 H, *J* = 5.1), 4.49 (d, 1 H, *J* = 5.1), 3.56 (dd, 1 H, *J* = 11.5, 7.1), 2.70 (dd, 1 H, *J* = 11.5, 7.1), 2.48 (s, 3 H)	141.8 (quat), 132.4 (CH), 128.5 (CH), 127.5 (CH), 126.3 (CH), 120.9 (quat), 89.3 (CH_2), 75.6 (CH), 61.3 (CH_2), 41.7 (CH_3)

Table 3 Spectral Data for 5-Aryl-3-methyloxazolidines **3a–j** (continued)

Product	IR (film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
3g	2880, 2798, 1487, 1442, 1245, 1036	6.90 (s, 1 H), 6.76 (s, 2 H), 5.92 (s, 2 H), 4.95 (t, 1 H, *J* = 6.9), 4.50 (d, 1 H, *J* = 4.6), 4.44 (d, 1 H, *J* = 4.6), 3.25 (dd. 1 H, *J* = 11.0, 6.9), 2.73 (dd, 1 H, *J* = 11.0, 6.9), 2.48 (s, 3 H)	147.7 (quat), 146.8 (quat), 135.9 (quat), 118.9 (CH), 108.0 (CH), 106.1 (CH), 100.9 (CH), 96.9 (CH_2), 89.2 (CH_2), 76.5 (CH), 62.6 (CH_2), 41.3 (CH_3)
3h	2949, 2870, 2797, 1674, 1596, 1510, 1455, 1329, 1234, 1169, 1065, 1015	7.89–7.75 (m, 4 H), 7.53–7.46 (m, 3 H), 5.76 (t, 1 H, *J* = 7.0), 4.64 (d, 1 H, *J* = 5.0), 4.59 (d, 1 H, *J* = 5.0), 3.62 (d, 1 H, *J* = 7.0, 11.1), 2.83 (d, 1 H, *J* = 7.0, 11.1), 2.54 (s, 3 H)	137.9 (quat), 133.5 (quat), 129.9 (quat), 128.7 (CH), 127.3 (CH), 125.8 (CH), 125.5 (CH), 125.3 (CH), 122.7 (CH), 121.2 (CH), 88.7 (CH_2), 73.8 (CH), 61.8 (CH_2), 41.6 (CH_3)
3i	2953, 2876, 2791, 1666, 1479, 1456, 1087, 1052, 1011	8.53 (d, 1 H, *J* = 3.8), 7.67 (t, 1 H, *J* = 7.7), 7.50 (d, 1 H, *J* = 7.6), 7.16 (dd, 1 H, *J* = 7.6, 3.8), 5.13 (t, 1 H, 6.9), 4.57 (d, 1 H, *J* = 4.9), 4.49 (d, 1 H, *J* = 4.9), 3.42 (dd, 1 H, *J* = 11.2, 6.9), 3.01 (dd, 1 H, *J* = 11.2, 6.9), 2.48 (s, 3 H)	161.7 (quat), 148.7 (CH), 136.4 (CH), 121.8 (CH), 119.4 (CH), 89.2 (CH_2), 76.5 (CH), 60.8 (CH_2), 41.3 (CH_3)
3j	2950, 2861, 1588, 1461, 1342, 1053	7.25 (d, 1 H, *J* = 8.9), 6.94 (m, 2 H), 5.25 (t, 1 H, *J* = 7.0), 4.49 (d, 1 H, *J* = 4.9), 4.40 (d, 1 H, *J* = 4.9), 3.31 (dd, 1 H, *J* = 11.3, 7.0), 2.93 (dd, 1 H, *J* = 11.3, 7.0), 2.49 (s, 3 H)	145.3 (quat), 126.6 (CH), 124.7 (CH), 124.1 (CH), 88.6 (CH_2), 72.5 (CH), 62.4 (CH_2), 41.3 (CH_3)

Table 4 Spectral Data for 1-Aryl-2-dimethylaminoethanols **4**

Product	IR (film) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
4a	3420, 2923, 2856, 2830, 1526, 1459, 1345, 1261, 1101, 1030	7.92 (d, 1 H, *J* = 7.5), 7.89 (d, 1 H, *J* = 7.5), 7.61 (t, 1 H, *J* = 7.5), 7.37 (t, 1 H, *J* = 7.5), 5.32 (br d, 2 H, *J* = 9.4), 2.70 (dd, 1 H, *J* = 9.4, 11.7), 2.39 (m, 7 H)	147.6 (quat), 138.0 (quat), 133.6 (CH), 128.4 (CH), 128.0 (CH), 124.2 (CH), 65.9 (CH_2), 65.3 (CH), 45.0 (2 × CH_3)
4b	3424, 2919, 2851, 1536, 1452, 1346, 1111, 1039	8.30 (s, 1 H), 8.17 (d, 1 H, *J* = 7.9), 7.78 (d, 1 H, *J* = 7.9), 7.56 (t, 1 H, *J* = 7.9), 4.87 (br t, 1 H, *J* = 6.4), 4.15 (br s, 1 H), 2.51 (d, 2 H, *J* = 6.4 Hz), 2.43 (s, 6 H)	148.1 (quat), 144.6 (quat), 131.9 (CH), 129.2 (CH), 122.2 (CH), 120.7 (CH), 68.5 (CH), 67.0 (CH_2), 45.1 (2 × CH_3)
4c	3427, 2921, 2530, 1525, 1453, 1352, 1262, 1037	8.18 (d, 2 H, *J* = 8.7), 7.56 (d, 2 H, *J* = 8.7), 4.80 (t, 1 H, *J* = 7.0), 4.50 (br s, 1 H), 2.43 (d, 2 H, *J* = 7.0), 2.36 (s, 6 H)	150.0 (quat), 147.0 (quat), 126.4 (2 × CH), 123.3 (2 × CH), 68.6 (CH), 66.9 (CH_2), 45.1 (2 × CH_3)
4d	3421, 3203, 2550, 1588, 1468, 1383, 1084, 1045	7.18 (m, 4 H), 5.59 (br s, 1 H), 4.92 (t, 1 H, *J* = 6.7), 2.75 (d, 2 H, *J* = 6.7), 2.59 (s, 6 H)	139.9 (quat), 133.3 (quat), 128.4 (2 × CH), 127.3 (2 × CH), 67.9 (CH), 65.1 (CH_2), 44.3 (2 × CH_3)
4e	3346, 2869, 2797, 1587, 1466, 1382, 1053	7.65 (d, 1 H, *J* = 8.2), 7.30 (s, 1 H), 7.27 (d, 1 H, *J* = 8.2), 6.45 (br s, 1 H), 5.28 (br d, 1 H, *J* = 9.0), 2.67 (m, 8 H)	137.2 (quat), 133.7 (quat), 131.6 (quat), 128.7 (CH), 128.5 (CH), 127.5 (CH), 65.3 (CH), 64.0 (CH_2), 44.5 (2 × CH_3)
4f	3416, 2981, 2826, 2781, 1466, 1398, 1169, 1118, 1089, 1014	7.65 (d, 1 H, *J* = 7.6), 7.47 (d, 1 H, *J* = 7.6), 7.28 (t, 1 H, *J*= 7.6), 7.10 (t, 1 H, *J* = 7.6), 5.03 (br d, 1 H, *J* = 8.5), 2.58 (m, 2 H), 2.35 (s, 6 H)	141.0 (quat), 132.1 (CH), 128.5 (CH), 127.4 (CH), 127.3 (CH), 121.3 (quat), 68.5 (CH_2), 65.3 (CH), 45.0 (2 × CH_3)
4g	3428, 2950, 1467, 1389, 1084, 1041	6.94 (s, 1 H), 6.84 (d, 1 H, *J* = 6.8), 6.69 (d, 1 H, *J* = 6.8), 5.98 (s, 2 H), 4.92 (dd, 1 H, *J* = 6.8, 2.5), 2.64 (m, 2 H), 2.50 (s, 6 H)	147.6 (quat), 135.7 (quat), 119.3 (CH), 108.3 (CH), 108.0 (CH), 100.9 (CH_2), 67.1 (CH), 65.9 (CH_2), 45.0 (2 × CH_3)
4h	3362, 2528, 1596, 1445, 1375, 1271, 1033	8.00 (d, 1 H, *J* = 7.8), 7.98–7.70 (m, 3 H), 7.50–7.40 (m, 3 H), 5.62 (br t, 1 H, *J* = 5.6), 5.50 (br s, 1 H), 2.64 (d, 2 H, *J* = 5.6), 2.40 (s, 6 H)	137.5 (quat), 133.3 (quat), 130.0 (quat), 128.7 (CH), 127.6 (CH), 125.8 (CH), 125.4 (CH), 125.1 (CH), 123.0 (CH), 122.4 (CH), 66.2 (CH), 65.9 (CH_2), 44.9 (2 × CH_3)
4j	3299, 2950, 1660, 1454, 1400, 1264, 1166, 1034	7.26 (d, 1 H, *J* = 4.9), 7.00 (m, 2 H), 5.82 (br s, 1 H), 5.21 (br d, 1 H, *J* = 9.0), 2.87 (m, 2 H), 2.55 (s, 6 H)	145.3 (quat), 126.6 (CH), 124.4 (CH), 123.8 (CH), 66.1 (CH_2), 65.4 (CH), 44.8 (2 × CH_3)

1-Aryl-2-dimethylaminoethanols 4; General Procedure

The 5-aryl-3-methyloxazolidine **3** (1 mmol) was dissolved in EtOH (15 mL) and $NaBH_4$ (114 mg, 3 mmol) was added in portions at r.t. After stirring at r.t. for the appropriate time given in Table 2, sat. aq NH_4Cl solution (10 mL) was added, and the EtOH was removed in vacuo. The residue was extracted with CH_2Cl_2 (3×10 mL) and the organic layer was washed with brine (10 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to obtain the crude product, which was purified by flash chromatography (acetone–hexane, 1:1) (Table 4).

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