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# Microwave assisted synthesis of chiral imidazolyl and pyrazolyl alcohols

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**Abstract**

Microwave assisted ring opening of (*R*)-styrene epoxide with pyrazole and imidazole gives the corresponding (*R*)-configurated (1-phenyl)(2-azolyl)ethanols in high yields. In the case of pyrazole, the application of microwave heating increases both, chemo- and regioselectivity compared to conventional heating methods.


*Keywords: microwave heating, amino alcohols, imidazoles, pyrazoles*

Epoxide opening products of pyrazoles/imidazoles have been of interest for medicinical applications [1] and as ligands for catalytic reactions [2,3]. Kotsuki et al. recently published the ring opening of (*R*)-styrene epoxide with a variety of nitrogen nucleophiles performed under high pressure (10 kbar) or in the presence of silica gel [2-4], which proceeds at low temperatures but still requires long reaction times. Parallely, we found that epoxicyclohexane reacts with pyrazoles under reflux conditions [5] to give the corresponding pyrazolyl cyclohexanols. Performing the reaction in a pressure tube reduces the reaction time by a factor of 4 [6]. However, the opening of (*R*)-styrene epoxide with pyrazole under these conditions gives low yields of the desired alcohol due to decomposition and side reactions. In the present paper we describe a facile, short term and high yield synthesis of chiral imidazolyl/pyrazolyl alcohols derived from (*R*)-styrene epoxide under microwave conditions [7,8].

Heating a 1:1 mixture of imidazole and (*R*)-styrene epoxide in a pressure tube for 3 minutes in a microwave oven at 360 W gives (1*R*)-2-(1-imidazolyl)-1-phenylethanol (**1**) in about 90% yield (Scheme 1) [9]. The synthesis of the corresponding (1*R*)-2-(1-pyrazolyl)-1-phenylethanol (**2**) requires an increased irradiation power (510 W) and prolonged irradiation times (6 min) for complete conversion of the starting material. The regioisomer (2*S*)-2-(1-pyrazolyl)-2-phenylethanol (**3**) can be detected only in traces by GC-MS.

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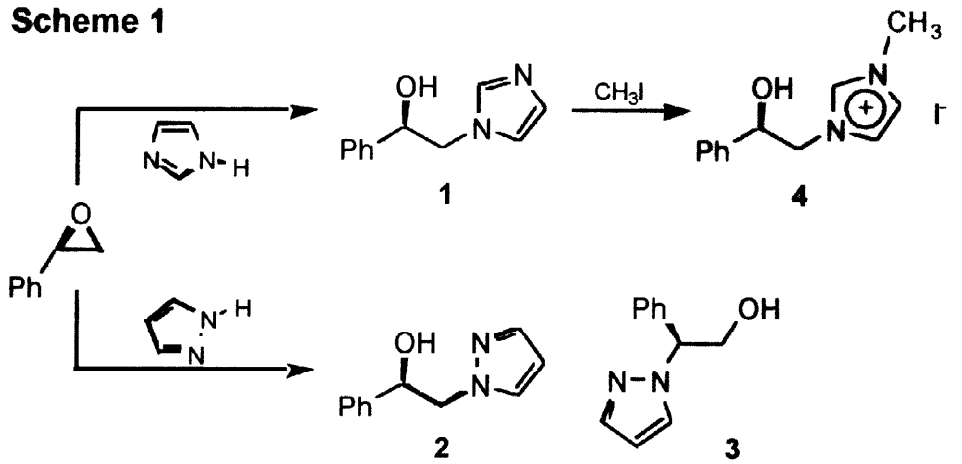
**Scheme 1**




Alkylation of **1** with $CH_3I$ leads to the formation of the corresponding imidazolium salt **4** in quantitative yield, a versatile starting material for the synthesis of chiral transition metal carbene complexes [10], which presently is under investigation in our group.

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9. Spectroscopic data of compounds **1** and **2** are given in ref. 1-3. (1*R*)-2-(1-Imidazolyl)-1-phenylethanol (**1**) and (1*R*)-2-(1-pyrazolyl)-1-phenylethanol (**2**): Imidazole/pyrazole (1.00 g, 14.7 mmoles) and (*R*)-styrene oxide (1.95 g, 16.2 mmoles) are heated for 3/6 min in a pressure tube (Aldrich, Z18,108-0) under microwave irradiation (360/510 W). After cooling to room temperature, the resulting solids are recrystallized from ethylacetate giving analytically pure **1** (2.61 g, 90%) and **2** (2.55 g, 88%). 1-{1-[(2*R*)-2-Hydroxy-2-phenyl]ethyl}-3-methylimidazolium iodide (**4**): A mixture of **1** (0.35 g, 1.86 mmoles), $CH_3I$ (1.06 g, 7.44 mmoles) and acetonitrile (15 ml) is heated to 80°C in a pressure tube. After 40 min of heating the solvent is removed in vacuo and the resulting solid is recrystallized from methanol giving analytically pure **4** (0.51 g, 83%). - mp. > 200°C. - IR (KBr, $cm^{-1}$): $\nu$ = 3282 (OH), 1167 (C-O). - $^1H$ NMR (400.13 MHz, 25°C, DMSO-$d_6$): $\delta$ = 9.11 (s, 1H, NCHN), 7.72, 7.69 (2×s, 3H, NCHCHN), 7.43-7.28 (m, 5H, $C_6H_5$), 5.94 (d, 1H, $^3J$ = 4.5 Hz, OH), 4.97 (m, 1H, C*H*OH), 4.42 (dd, 1H, $^2J$ = 13.6 Hz, $^3J$ = 3.0 Hz, $CH_2$), 4.21 (dd, 1H, $^3J$ = 8.5 Hz, $CH_2$), 3.87 (s, 3H, $CH_3$). - $^1H$ NMR (100.25 MHz, 25°C, DMSO-$d_6$): $\delta$ = 141.1 (C-i), 136.9 (NCHN), 128.2 (C-o), 127.7 (C-p), 125.9 (C-m), 123.0, 123.0 (2×NCHCHN), 70.5 (CHOH), 55.6 ($CH_2$), 35.8 ($CH_3$). - correct elemental analysis.
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