A Facile Synthesis of 3-Cyclopropyl- and 5-Cyclopropyl-isoxazoles†

Okram Mukherjee Singh, a,* H. Junjappa b and H. Ila b

a Department of Chemistry, Manipur University, Canchipur – 795003, Manipur, India
b Department of Chemistry, IIT Kanpur-208016, U.P, India

The regioselective synthesis of isomeric isoxazoles 3-(2-arylcyclopropyl)-5-methylthio- and 5-(2-arylcyclopropyl)-3-methylthio-isoxazoles is described.

Cyclopropyl ketones 1 which can be prepared in quantitative yields by the addition of dimethylsulfoxonium methylide to the corresponding z-cinnamyl ketone diithioacetals in the presence of NaOMe (4 equiv., pH 7.9) have been reported as useful precursors for functionalized cyclopentanes,2a,b cyclopropane[3]indenones3c and 11-oxosteroids.2d Their synthetic applications as 1,3-dielectrophilic intermediates to obtain various heterocycles by reacting with various nucleophiles have also been reported.3 In continuation of these studies we now report a highly regioselective synthesis of both 3-cyclopropyl and 5-cyclopropyl isoxazoles 2 and 3 by reacting cyclopropyl ketones 1 with hydroxylamine hydrochloride under different reaction conditions.

When 2-(bimethylthio)methylene cyclopropyl ketones 1a–e were reacted with hydroxylamine hydrochloride (4 equiv.) in the presence of NaOMe (4–6 equiv., pH 7–9) and refluxed in methanol, the corresponding 3-(2-arylcyclopropyl)-3-methylthioisoxazoles 3a–e were obtained in 80–90% overall yields as colourless needles (CHCl3–hexane). The structures of 3a–e were confirmed with the help of spectral and analytical data (see Experimental section). In these reactions regioisomeric products 3 were not detected even in traces. On the other hand, the 2-(bimethylthio)methylene cyclopropyl ketones 1a–e when reacted with NH2OH in sodium acetate–acetic acid–ethanol–water and refluxed with benzene (pH 2–3),5 gave the corresponding isomeric isoxazoles 5-(2-arylcyclopropyl)-3-methylthioisoxazoles 3a–e in 50–60% overall yields. In these reactions small quantities of regioisomeric isoxazoles 2 (<10%) were also detected. The isomeric isoxazoles 2 and 3 have very similar Rf values (EtOAc–hexane, 1:4) and their separation was achieved by column chromatography.

Isomers 2 and 3 were clearly distinguished by comparing their melting points, IR and NMR spectral data. However, the finest distinction between the isomers was obtained from the mass spectrum fragments arising from loss of the substituents at the 5-position of the isoxazole ring.

Experimental

All melting points are uncorrected. The IR spectra were obtained (KBr disk) on a Perkin-Elmer-297,1 HNMR spectra were measured on a Varian EM-390 spectrometer, mass on a JEOL D-300 mass spectrometer and elemental analytical data were obtained from a Heraeus CHN-O-Rapid analyzer.

3-(2-Arylcyclopropyl)-5-methylthioisoxazoles 

2a–e—Hydroxylamine hydrochloride (0.04 mol) was added to NaOCH3 (0.06 mol) in absolute methanol (30 ml) and stirred for 10 min. Cyclopropyl ketone 1 (0.01 mol) was added and the mixture was refluxed for 10–12 h. Methanol was evaporated under reduced pressure and the residue was poured into ice-cold water. It was extracted with chloroform (100 ml), washed with water (200 ml), dried (Na2SO4) and evaporated to yield the cyclopropyl isoxazoles 2 as pale coloured solids. Recrystallization from ethanol gave the analytically pure products.

Compound 2a. mp 99 °C; yield 78%; vmax/cm−1 (KBr): 1602, 1546, 1413; δ 14(CDC13): 1.23–1.31 (2H, m, CH2), 1.85–2.20 (2H, m, CH2), 2.40 (3H, s, SCH2), 3.65 (3H, s, OCH3), 5.72 (1H, s, 4-H), 6.70 (2H, d, J = 9 Hz, ArH), 6.95 (2H, d, J = 9 Hz, ArH); m/z: 261 (M+ 55), 214 (M− 75, 100), 156 (M− 75, 25) (Found; C, 76.6; H, 5.5; N, 6.16; C6H11NSO requires C, 76.53; H, 5.62; N, 6.06%).

Compound 2b. mp 150 °C; yield 80%; vmax/cm−1 (KBr): 1600, 1540, 1430; δ13(CDC13): 1.10–1.32 (2H, m, CH2), 1.85–2.20 (2H, m, CH2), 2.40 (3H, s, SCH2), 3.65 (3H, s, OCH3), 5.72 (1H, s, 4-H), 6.70 (2H, d, J = 9 Hz, ArH), 6.95 (2H, d, J = 9 Hz, ArH); m/z: 261 (M+ 55), 214 (M− 75, 100), 156 (M− 75, 25) (Found; C, 64.21; H, 5.74; N, 5.36%).

Compound 2c. Mp 100 °C; yield 72%; vmax/cm−1 (KBr): 1600, 1530, 1420; δ13(CDC13): 1.25–1.50 (2H, m, CH2), 2.10–2.36 (2H, m, CH2), 2.65 (3H, s, CH3), 3.85 (3H, s, OCH3), 3.90 (3H, s, OCH3), 5.90 (1H, s, 4-H), 6.75–6.85 (3H, m, ArH); (Found; C, 61.60; H, 5.72; N, 4.81; C13H15NSO requires C, 61.83; H, 5.88; N, 4.81%).

Compound 2d. Mp 105 °C; yield 70%; vmax/cm−1 (KBr): 1601, 1500, 1450; δ13(CDC13): 1.15–1.30 (2H, m, CH2), 1.87–2.26 (2H, m, CH2), 2.48 (3H, s, SCH2), 2.51 (3H, s, CH3), 5.75 (1H, s, H-4), 6.90–7.01 (4H, m, ArH); m/z: 245 (M+, 35), 198 (M− 47, 75), 170 (M− 75, 17) (Found; C, 68.42; H, 6.1; N, 5.6; C13H13NSO requires C, 68.57; H, 6.12; N, 5.71%)

Compound 2e. Mp 120 °C; yield 75%; vmax/cm−1 (KBr): 1602, 1545, 1415; δ13(CDC13): 1.21–1.45 (2H, m, CH, 2.10–2.35 (2H, m, CH2), 2.50 (3H, s, SCH2), 5.80 (1H, s, H-4), 7.05 (2H, d, J = 9 Hz, ArH), 7.25 (2H, d, J = 9 Hz, ArH); m/z: 265 (M+, 65%), 218 (M− 47, 100),190 (M− 75, 41) (Found; C, 58.82; H, 4.6; N, 5.15; C12H11NOSO requires C, 58.86; H, 4.52; N, 5.28%).

5-(2-Arylcyclopropyl)-3-methylthioisoxazoles 3a–e—Cyclopropyl ketone 1 (0.01 mol) was dissolved in a mixture containing benzene (100 ml) and acetic acid (100 ml). After stirring for 10 min, a mixture of hydroxylamine hydrochloride (0.04 mol), NaOAc (0.03 mol) in ethanol (55 ml) and water (10 ml) was added. The reaction mixture was refluxed for 8–10 h. After evaporating the organic solvents under reduced pressure, the residue was dissolved in water (100 ml). It was extracted with CHCl3 (100 ml), dried (Na2SO4) and concentrated

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* To receive any correspondence.
under reduced pressure to give crude products of 3a-e. The crude products were purified by passing through column chromatography using EtOAc-hexane (1:1) as eluent.

**Compound 3a.** Mp 60-8°C, yield 58%; \( \nu_{\text{max}} \text{cm}^{-1} \) (KBr): 1620, 1537, 1400; \( \delta_{\text{H}} \) (CDCl3): 1.32–1.51 (2H, m, CH2), 2.15–2.39 (2H, m, CH), 2.50 (3H, s, SCH3), 5.88 (1H, s, H-4), 7.30–7.50 (5H, m, ArH); m/z: 231 (M+ 75), 105(100) (Found: C, 67.3; H, 5.7; N, 6.01. \( \text{C}_{13}\text{H}_{13}\text{NSO} \) requires C, 67.53; H, 5.62; N, 6.06%).

**Compound 3b.** Mp 100-8°C, yield 60%; \( \nu_{\text{max}} \text{cm}^{-1} \) (KBr): 1612, 1520, 1430; \( \delta_{\text{H}} \) (CDCl3): 1.10–1.32 (2H, m, CH2), 1.85–2.20 (2H, m, CH), 2.35 (3H, s, SCH3), 3.60 (3H, s, OCH3), 3.80 (3H, s, OCH3), 3.85 (3H, s, OCH3), 5.85 (1H, s, 4-H); 6.70 (2H, d, \( J = 9 \text{ Hz} \), ArH), 6.90 (2H, d, \( J = 9 \text{ Hz} \), ArH); m/z: 261 (M+ 70), 135(100) (Found: C, 64.61; H, 5.0; N, 5.6. \( \text{C}_{14}\text{H}_{15}\text{NO}_{2}\text{S} \) requires C, 64.36; H, 5.74; N, 5.36%).

**Compound 3c.** Mp 70-8°C, yield 52%; \( \nu_{\text{max}} \text{cm}^{-1} \) (KBr): 1613, 1540, 1420; \( \delta_{\text{H}} \) (CDCl3): 1.35–1.50 (2H, m, CH2), 2.10–2.36 (2H, m, CH), 2.55 (3H, s, SCH3), 3.80 (3H, s, OCH3), 3.85 (3H, s, OCH3), 5.80 (1H, s, 4-H), 6.70–6.80 (3H, m, ArH); (Found: C, 61.45; H, 5.86; N, 4.9. \( \text{C}_{15}\text{H}_{17}\text{NO}_{3}\text{S} \) requires C, 61.83; H, 5.88; N, 4.81%).

**Compound 3d.** Mp 60-8°C, yield 50%; \( \nu_{\text{max}} \text{cm}^{-1} \) (KBr): 1615, 1532, 1435; \( \delta_{\text{H}} \) (CDCl3): 1.25–1.30 (2H, m, CH2), 1.87–2.20 (2H, m, CH), 2.40 (3H, s, CH3), 2.55 (3H, s, SCH3), 5.85 (1H, s, 4-H), 6.90–7.0 (4H, m ArH); m/z: 245 (M+ 70), 119(100) (Found: C, 68.30; H, 5.9; N, 5.66. \( \text{C}_{14}\text{H}_{15}\text{NSO} \) requires C, 68.57; H, 5.8; N, 5.71%).

**Compound 3e.** Mp 67-8°C, yield 57%; \( \nu_{\text{max}} \text{cm}^{-1} \) (KBr): 1615, 1535, 1425; \( \delta_{\text{H}} \) (CDCl3): 1.15–1.25 (2H, m, CH2), 2.05–2.20 (2H, m, CH), 2.46 (3H, s, SCH3), 5.85 (1H, s, 4-H), 7.0 (2H, d, \( J = 9 \text{ Hz} \), ArH), 7.20 (2H, d, \( J = 9 \text{ Hz} \), ArH); m/z: 265 (M+ 75), 139(100) (Found: C, 58.6; H, 4.75; N, 5.0. \( \text{C}_{13}\text{H}_{12}\text{ClNOS} \) requires C, 58.86; H, 4.52; N, 5.28%).

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