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

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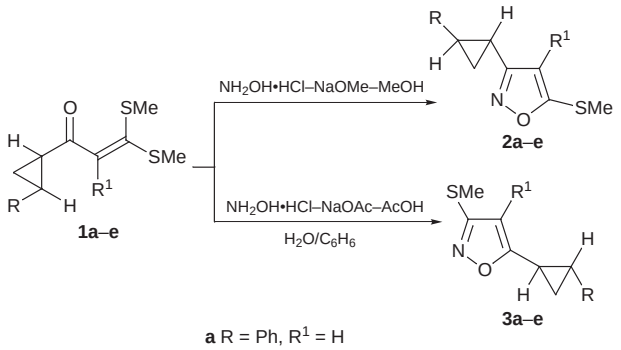
The regioselective synthesis of isomeric isoxazoles 3-(2-arylcyclopropyl)-5-methylthio- and 5-(2-arylcyclopropyl)-3-methylthio-isoxazoles is described.

Cyclopropyl ketones **1** which can be prepared in quantitative yields by the addition of dimethyloxosulfonium methylide to the corresponding α-cinnamoyl ketene dithioacetals in the presence of phase transfer catalyst[1] have been reported as useful precursors for functionalized cyclopentanones,[2a,b] cyclopent[*a*]indenes[2c] and 11-oxosteroids.[2d] Their synthetic applications as 1,3-dielectrophilic intermediates to obtain various heterocycles by reacting with various binucleophiles 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.



a R = Ph, R^1 = H
b R = 4-$MeOC_6H_4$, R^1 = H
c R = 3, 4-$(MeO)_2C_6H_3$, R^1 = H
d R = 4-MeC_6H_4, R^1 = H
e R = 4-ClC_6H_4, R^1 = H

Scheme 1

When α-bis(methylthio)methylene cyclopropyl ketones **1a–e** were reacted with hydroxylamine hydrochloride (4 equiv.) in the presence of NaOMe (4–6 equiv., pH 7–9)[4] and refluxed in methanol the corresponding 3-(2-arylcyclopropyl)-5-methylthioisoxazoles **2a–e** were obtained in 80–90% overall yields as colourless needles ($CHCl_3$–hexane). The structures of **2a–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 α-bis(methylthio)methylene cyclopropyl ketones **1a–e** when reacted with NH_2OH in sodium acetate–acetic acid–ethanol–water and refluxed with benzene (pH 2–3),[5] gave the corresponding isomeric isoxazoles 5-(2-arylcyclopropyl)-3-methyithioisoxazoles **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 R_f 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 firmest distinction between the isomers was obtained[4a] 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, ^1H NMR 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 Herraeus CHN-O-Rapid analyzer.

3-(2-*Arylcyclopropyl*)-5-*methylthioisoxazoles* **2a–e**.—Hydroxylamine hydrochloride (0.04 mol) was added to $NaOCH_3$ (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 (Na_2SO_4) and evaporated to yield the cyclopropyl isoxazoles **2** as pale coloured solids. Recrystallization from ethanol gave the analytically pure products.

Compound **2a**. Needles, mp 99 °C, yield 78%; ν_{max}/cm^{-1} (KBr); 1602, 1546, 1413; δ_H ($CDCl_3$): 1.23–1.51 (2H, m, CH_2), 2.15–2.39 (2H, m, CH), 2.50 (3H, s, SCH_3), 5.85 (1H, s, H-4), 7.20–7.40 (5H, m, ArH); *m/z*: 231 (M^+, 50%), 184 ($M^+ - 47$, 100), 156 ($M^+ - 75$, 25) (Found; C, 67.6; H, 5.5; N, 6.16. $C_{13}H_{13}NSO$ requires C, 67.53; H, 5.62; N, 6.06%).

Compound **2b**. Mp 150 °C, yield 80%; ν_{max}/cm^{-1} (KBr); 1600, 1500, 1430; δ_H ($CDCl_3$): 1.10–1.32 (2H, m, CH_2), 1.85–2.20 (2H, m, CH), 2.40 (3H, s, SCH_3), 3.65 (3H, s, OCH_3), 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^+, 65%), 214 ($M^+ - 47$, 100), 186 ($M^+ - 75$, 30) (Found; C, 64.21; H, 5.6; N, 5.52. $C_{14}H_{15}NO_2S$ requires C, 64.36; H, 5.74; N, 5.36%).

Compound **2c**. Mp 100 °C, yield 72%; ν_{max}/cm^{-1} (KBr); 1600, 1530, 1420; δ_H ($CDCl_3$): 1.25–1.50 (2H, m, CH_2), 2.10–2.36 (2H, m, CH), 2.65 (3H, s, SCH_3), 3.85 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.90 (1H, s, 4-H), 6.75–6.85 (3H, m, ArH); (Found; C, 61.60; H, 5.72; N, 4.81. $C_{15}H_{17}NO_3S$ requires C, 61.83; H, 5.88; N, 4.81%).

Compound **2d**. Mp 105 °C, yield 70%; ν_{max}/cm^{-1} (KBr); 1601, 1500, 1450; δ_H ($CDCl_3$): 1.15–1.30 (2H, m, CH_2), 1.87–2.26 (2H, m, CH), 2.48 (3H, s, SCH_3), 2.51 (3H, s, CH_3), 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, 5.65. $C_{14}H_{15}NSO$ requires C, 68.57; H, 6.12; N, 5.71%).

Compound **2e**. Mp 120 °C, yield 75%; ν_{max}/cm^{-1} (KBr); 1602, 1545, 1415; δ_H ($CDCl_3$): 1.21–1.45 (2H, m, CH_2), 2.10–2.35 (2H, m, CH), 2.50 (3H, s, SCH_3), 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. $C_{13}H_{12}ClNOS$ 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 $CHCl_3$ (100 ml), dried (Na_2SO_4) and concentrated

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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 °C, yield 58%; ν_{max}/cm^{-1} (KBr); 1620, 1537, 1400; δ_H ($CDCl_3$): 1.32–1.51 (2H, m, CH_2), 2.15–2.39 (2H, m, CH), 2.50 (3H, s, SCH_3), 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. $C_{13}H_{13}NSO$ requires C, 67.53; H, 5.62; N, 6.06%).

Compound **3b**. Mp 100 °C, yield 60%; ν_{max}/cm^{-1} (KBr); 1612, 1520, 1430; δ_H ($CDCl_3$): 1.10–1.32 (2H, m, CH_2), 1.85–2.20 (2H, m, CH), 2.35 (3H, s, SCH_3), 3.60 (3H, s, OCH_3), 5.85 (1H, s, 4-H); 6.70 (2H, d, $J = 9$ Hz, ArH), 6.90 (2H, d, $J = 9$ Hz, ArH); *m/z*: 261 (M^+, 70), 135(100) (Found; C, 64.61; H, 5.0; N, 5.6. $C_{14}H_{15}NO_2S$ requires C, 64.36; H, 5.74; N, 5.36%).

Compound **3c**. Mp 70 °C, yield 52%; ν_{max}/cm^{-1} (KBr); 1613, 1540, 1420; δ_H ($CDCl_3$): 1.35–1.50 (2H, m, CH_2), 2.10–2.36 (2H, m, CH), 2.55 (3H, s, SCH_3), 3.80 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.80 (1H, s, 4-H), 6.70–6.80 (3H, m, ArH); (Found; C, 61.45; H, 5.86; N, 4.9. $C_{15}H_{17}NO_3S$ requires C, 61.83; H, 5.88; N, 4.81%).

Compound **3d**. Mp 60 °C, yield 50%; ν_{max}/cm^{-1} (KBr); 1615, 1532, 1435; δ_H ($CDCl_3$): 1.25–1.30 (2H, m, CH_2), 1.87–2.20 (2H, m, CH), 2.40 (3H, s, CH_3), 2.55 (3H, s, SCH_3), 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. $C_{14}H_{15}NSO$ requires C, 68.57; H, 6.0; N, 5.71%).

Compound **3e**. Mp 67 °C, yield 57%; ν_{max}/cm^{-1}; 1615, 1535, 1425; δ_H ($CDCl_3$): 1.15–1.25 (2H, m, CH_2), 2.05–2.20 (2H, m, CH), 2.46 (3H, s, SCH_3), 5.85 (1H, s, 4-H), 7.0 (2H, d, $J = 9$ Hz, ArH), 7.20 (2H, d, $J = 9$ Hz, ArH); *m/z*: 265 (M^+, 75), 139(100) (Found; C, 58.6; H, 4.75; N, 5.0. $C_{13}H_{12}ClNOS$ requires C, 58.86; H, 4.52; N, 5.28%).

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