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IMPROVED ROUTES TO HOMOLOGATED ISOXAZOLES

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ABSTRACT: Two carbon homologation of isoxazole-4-carbinols was performed by reaction of lithio-2,4,4-trimethyl-Δ^2-oxazoline **1** with 4-chloromethyl-isoxazole **2**, followed by trans-esterification and reduction to the isoxazole-4-propanols **5a** and **b**. Alternatively, 2,4-diketones **6** were alkylated with 1-bromo-3-chloro-propane, and the chloro ketones **7** treated with hydroxylamine to give isoxazole-4-propanols, **5a-c**.

We required an efficient two carbon homologation of isoxazole 4-carbinols for our studies on the structure, reactivity and biology of functionalized isoxazoles.[1,2] One useful tactic for the functionalization of C-4 of the isoxazole has been halogen-metal exchange of the 4-iodo-isoxazole, followed by electrophilic quenching.[3] We have found that reaction of the lithio anion of 2,4,4-trimethyl-Δ^2-oxazoline[4]

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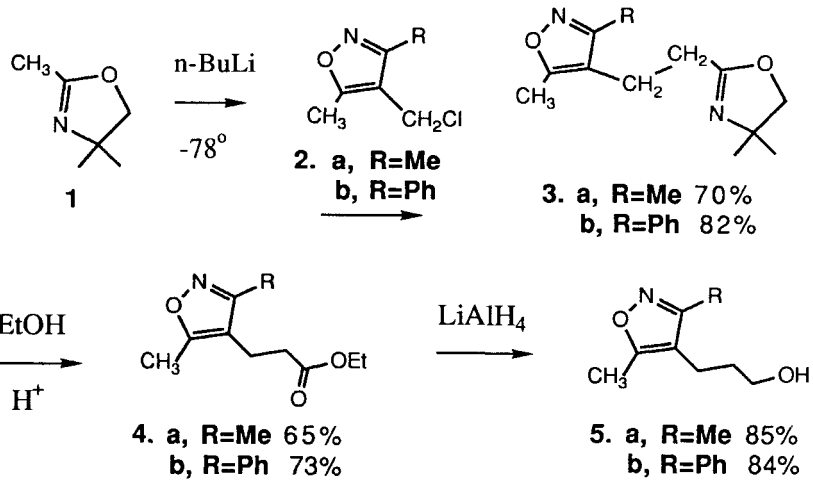

FIGURE 1

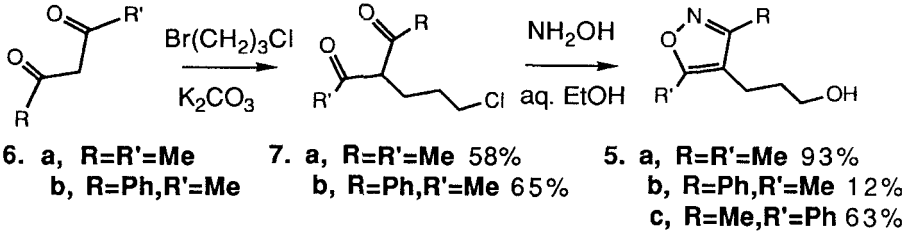

FIGURE 2

with the readily available 4-chloromethyl-isoxazoles,[5,7] followed by trans-esterification and reduction to the isoxazole-4-propanols, provides an efficient route to the desired products. The route is shown in Figure 1. In our hands this procedure was the method of choice for preparation of the 5-methyl-3-phenyl-isoxazole-4-propanol **5b** on a multi-gram scale.

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Alternatively, we have prepared the isoxazole propanols **5**, via the 2,4-diketones, as shown in Figure 2. Alkylation of the diketone **6** with 1-bromo-3-chloro-propane in the presence of base produced the chloro ketone **7**.[6] Reaction of **7** with hydroxylamine produced both isoxazole ring closure and chloride displacement to produce isoxazole carbinols **5**. The latter procedure has two advantages: (1) it can be easily run on a mole scale for 3,5-symmetrical isoxazoles, and (2) it produces the complementary 5-phenyl-3-methyl isomer, **5c**, as the major product, when R'=Ph. We have found the isoxazoles **5a-c** to be useful intermediates,[1,2] and will report on further applications in due course.

EXPERIMENTAL SECTION

2-[(3',5'-Dimethylisoxazol-4'-yl)ethyl]-4,4-dimethyl-Δ^2-oxazoline, 3a. To 2,4,4-Trimethyl-Δ^2-oxazoline **1** (4.9 g, 39 mmol) in 250 mL of dry THF at -78°C was added 20 mL of n-butyllithium in hexane (2.2 M, 44 mmol) via syringe. After stirring for 1.5 hr, 4-chloromethyl-3,5-dimethyl-isoxazole **2a**[5a] (5.8 g, 40 mmol) in THF (5 mL) was added dropwise over 5 min. The mixture was allowed to warm to room temperature, and then poured into 100 mL of water. The aqueous solution was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with water, and dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to produce a yellow oil, which was purified by flash chromatography (SiO_2, CH_2Cl_2-ethyl acetate/ 1:1) or Kugelrohr

distillation (120°C, 0.45 mmHg) to produce **3a** as an oil (6.1 g, 70%). ^{1}H NMR ($CDCl_3$) δ (ppm): 3.7 (s, 2H, OCH_2); 2.3-2.5 (m, 4H, isoxazole-CH_2-CH_2-oxazoline); 2.2 (s, 3H); 2.1 (s, 3H); 1.1 (s, 6H). Mass spectrum, EI: 222 (15% rel. intensity, M^+), 207(15, M-CH_3^+), 110(100, CH_2-isoxazole$^+$).

Ethyl 3-[3',5'-dimethyl-isoxazol-4'yl]propanoate, 4a. Oxazoline **3a** (4.2 g, 19 mmol) was heated to reflux in 100 mL of 95% ethanol containing catalytic sulfuric acid for 18 h. After cooling, the solution was concentrated to about 25 mL and poured into 200 mL of diethyl ether. The ethereal solution was washed with brine(4 x 50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give **4a** as an oil (2.8 g, 76% yield), which was further purified by flash distillation on a Kugelrohr apparatus (b.p. 105°C/0.45 mmHg) to produce ester **4a** as a colorless oil (2.4 g, 65% yield), which was identical to authentic **4a** prepared as previously described.[2]

2-[(5'-Methyl-3'-phenylisoxazol-4'-yl)ethyl]-4,4-dimethyl-Δ^2-oxazoline, 3b. To 2,4,4-Trimethyl-Δ^2-oxazoline **1** (4.9 g, 43 mmol) in 50 mL of dry THF at -78°C was added 27 mL of n-butyllithium in hexane (1.9 M, 51 mmol) via syringe. After stirring for 30 min, 4-chloromethyl-5-methyl-3-phenyl-isoxazole **2b**[7] (9.1 g, 43 mmol) in THF (20 mL) was added dropwise over 10 min. The mixture was allowed to warm to room temperature, and then poured into

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100 mL of water. The aqueous solution was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with water, and dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to produce a yellow oil, which was purified by flash chromatography (SiO_2, hexane-ethyl acetate/ 1:1, R_f=0.37) or Kugelrohr distillation (120-130°C, 0.001 mmHg) to produce **3b** as an oil (15.04 g, 82%). ^1H NMR ($CDCl_3$) δ (ppm): 7.5-7.57 (m, 2H, Ar**H**); 7.35-7.45 (m, 3H, Ar**H**); 3.75 (s, 2H, OC**H**$_2$); 2.77 (t, 2H, J = 6.0 Hz, **CH**$_2$-oxazoline); 2.36 (s, 3H); 2.26 (t, 2H, J = 6.0 Hz, **CH**$_2$-isoxazole); 1.14 (s, 6H). ^{13}C NMR ($CDCl_3$) δ (ppm): 166.5, 164.3, 162.0, 129.7, 129.3, 128.8, 127.9, 111.7, 78.9, 66.9, 28.3, 28.1, 19.1, 11.2 IR (KBr): 1669.4, 1627.9 cm^{-1}. Mass spectrum calc'd for $C_{17}H_{20}N_2O_2$: 284.15247. Found: 284.15303.

Ethyl 3-[5'-methyl-3'-phenylisoxazol-4'yl]propanoate, 4b. Oxazoline **3b** (15 g, 53 mmol) was heated to reflux in 200 mL of 95% ethanol containing catalytic sulfuric acid for 16 h. After cooling, the solution was concentrated to about 25 mL and poured into 300 mL of diethyl ether. The ethereal solution was washed with brine, water and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give an oil which was purified by flash distillation on a Kugelrohr apparatus (b.p. 120°C/0.005 mmHg) to produce ester **4b** as a colorless oil (10 g, 73% yield). ^1H NMR ($CDCl_3$) δ (ppm): 7.5-7.57 (m, 2H, ArH); 7.37-7.45 (m, 3H, ArH); 4.0 (q, 2H, J = 7.12 Hz, OC**H**$_2$CH$_3$); 2.78 (t, 2H, J = 7.7 Hz, **CH**$_2$); 2.34 (s, 3H); 2.3 (t,

2H, J = 7.7 Hz,); 1.12 (t, 3H, J = 7.12 Hz, -$OCH_2\mathbf{CH_3}$). ^{13}C NMR ($CDCl_3$) δ (ppm): 172.2, 166.6, 162.1, 129.76, 129.4, 128.8, 127.9, 111.5, 60.5, 33.8, 17.9, 14.1, 11.1. IR(KBr): 1734.0 cm^{-1}. Mass spectrum, EI: m/z 259 (M^+, 51% rel. intensity). Anal. calc'd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.09; H, 6.58; N, 5.32.

5-methyl-3-phenyl-4-[prop-3'-yl-1'-ol]isoxazole, 5b. To a stirred solution of ester **4b** (9.5 g, 37 mmol) in 300 mL of dry THF, under N_2 at 0°C, was added $LiAlH_4$ (pellets, 1.05 g, 28 mmol). The mixture was allowed to warm to room temperature and stirred for 10 h. The excess hydride was destroyed by the careful addition of $Na_2SO_4 \cdot 10\ H_2O$, filtered through celite, concentrated *in vacuo*, and flash distilled on a Kugelrohr apparatus (115°C/0.005 mmHg) to give the product **5b** (6.68 g, 84%). ^1H NMR ($CDCl_3$) δ (ppm): 7.28-7.56 (m, 5H, Ar**H**); 3.48 (t, 2H, J = 6.2 Hz, $\mathbf{CH_2}$OH); 2.58 (t, 2H, J = 7.4 Hz); 2.39 (s, 3H); 1.63 (m, 2H); 1.29 (br.s., 1H, OH). ^{13}C NMR ($CDCl_3$) δ (ppm): 166.3, 162.4, 130.0, 129.3, 128.7, 127.9, 112.7, 61.4, 32.4, 18.5, 11.1. IR (KBr): 3373.5 cm^{-1}. Mass spectrum, EI: m/z 217 (M^+, 35% rel. intensity). Anal. calc'd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.62; H, 6.86; N, 6.26.

1-chloro-4-acetyl-hexan-5-one 7a, A 3-liter flask was charged with 1-bromo-3-chloro-propane (0.75 mole), 2,4-pentane dione **6a**, KI (45.1 g) and anhydrous powdered K_2CO_3 (145 g, 1.05 mole). The mixture was diluted to 2 liters volume

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with anhydrous acetone, and then heated to reflux for 48 h. The resulting solution was cooled, and concentrated *in vacuo* to 1 L. Aqueous HCl (10M, 250 mL) was added dropwise, and the solution further concentrated to *ca.* 500 mL. The oily yellowish layer was separated, and the aqueous layer extracted with ethyl ether (2 x 150 mL). The combined organic layers were dried over anhydrous $CaCl_2$, filtered, concentrated and immediately distilled, **7a** is the fraction with b.p. 40-45°C at 1 mmHg (58% yield). ^1H NMR 3.96 (t, 2H); 2.58 (br. s, 1H); 2.30 (m, 2H): 2.12 (d, 6H); 1.82 (m, 2H). This intermediate **7a** was unstable even at reduced pressure under an inert atmosphere and was carried on immediately.

3,5-dimethyl-isoxazole-4-[3'-propanol] 5a, A 1 L flask was charged with chloro ketone **7a** (76.8 g, 0.44 mole), hydroxylamine hydrochloride (37.4 g, 0.54 mole), NaOAc (68 g), 500 mL ethanol and 100 mL of water. The mixture was refluxed for 18 h, concentrated *in vacuo*, and the residue extracted with CH_2Cl_2 (3 x 250 mL). The combined organic layers were washed with water (250 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and distilled to produce **5a** as the fraction with b.p. 90-110°C /0.4 mm Hg (63.61 g, 93% yield, 54% overall), which was identical in all respects to authentic **5a** prepared as previously described.[2]

4-benzoyl-1-chloro-hexan-5-one 7b. Prepared as described for **7a** above, the product chloro ketone **7b** was

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purified by flash chromatography (SiO_2, hexane-CH_2Cl_2/ 5:1, R_f= 0.55) to produce **7b** as an oil (41.36 g , 65%).

5-phenyl-3-methyl-isoxazolyl-4-[3'-propanol], 5c. Prepared as described for **5a** above, the mixture of isomers **5c** and **5b** (*ca* 5:1, respectively by ^1H NMR), were purified by distillation (100-130°C, 0.075 mmHg). The isomers were separated by HPLC (SiO_2, hexane-CH_2Cl_2/ 9:1, R_t= 14.6 min (**5c**, 23.74 g, 63%, 41% overall) and R_t=18.5 min (**5b**, 4.73 g, 12%, 8% overall). Characterization data for **5c**: ^1H NMR ($CDCl_3$) δ (ppm): 7.66 (m, 2H, Ar**H**); 7.45 (m, 3H, Ar**H**); 3.52 (t, 2H, J = 6.2 Hz, CH_2OH); 2.73 (t, 2H, J = 7.8 Hz); 2.04 (s, 3H); 1.97 (m, 2H). ^{13}C NMR ($CDCl_3$) δ (ppm): 164.1, 162.1, 129.5, 129.1, 128.1, 127.6, 112.6, 60.9, 32.1, 18.3, 10.7. IR (KBr): 3350 cm^{-1}. Mass spectrum, FAB: m/z 218 (100% rel. intensity, $M+1^+$), 172(7); 130(5.7), 104 (8.3).

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