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RAPID COMMUNICATION

SHORT AND SIMPLE SYNTHESES OF 4-OXO-(*E*)-2-HEXENAL AND HOMOLOGS: PHEROMONE COMPONENTS AND DEFENSIVE COMPOUNDS OF HEMIPTERA

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Abstract—One-step syntheses of 4-oxo-(*E*)-2-hexenal and 4-oxo-(*E*)-2-octenal from commercially available 2-ethyl- and 2-butylfuran are described. A two-step synthesis of the homolog 4-oxo-(*E*)-2-decenal from furan is also reported. These compounds are common components of true bug defensive secretions, and recently have been identified as pheromone components for several species. The simple syntheses reported here will make these compounds readily available for further research.

Key Words—4-Oxo-(*E*)-2-alkenal, true bug, Hemiptera, Heteroptera, allomone, attractant

INTRODUCTION

4-Oxo-(*E*)-2-alkenals of 6, 8, and 10 carbon chain lengths are common components of the defensive secretions of true bugs (Hemiptera) (Aldrich, 1988, 1995; Millar, 2004). More recently, these compounds also have been identified as pheromone components of nymphal (Fucarino et al., 2004) and adult bugs (Innocenzi et al., 2004; Millar, 2004). Several syntheses of these compounds have been reported (e.g., Ward and van Dorp, 1969; Marques et al., 2000; Zarbin et al., 2000), but most have required at least several steps. Because of the increasing interest in these compounds, and in an effort to make them readily available to other researchers, we report here simple, one step syntheses of 4-oxo-(*E*)-2-hexenal and 4-oxo-(*E*)-2-octenal from commercially available 2-

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ethyl- and 2-butylfurans respectively, and the two step synthesis of the ten carbon analog from furan. The ready availability of these compounds should also enhance their potential for exploitation for insect pest management.

METHODS AND MATERIALS

Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under argon. ^{1}H- and ^{13}C-NMR spectra (400 and 100 MHz, respectively) were obtained in $CDCl_3$ solutions with a Varian INOVA-400 spectrometer. Mass spectra were obtained with an Hewlett-Packard 5970 (70 eV) mass selective detector interfaced to an H-P 5890 gas chromatograph fitted with a DB5-MS column (25 m × 0.20 mm id × 0.33 μm film) with helium as carrier gas (100 kPa). Products were purified by vacuum flash chromatography on silica gel (E. Merck, 230-400 mesh).

Synthesis of 2-n-Hexylfuran. Butyl lithium (2.5 M in hexanes, 5.9 ml, 14.7 mmol) was added dropwise to a stirred solution of furan (1.00 g, 14.7 mmol) in dry THF (60 ml) at −20°C under argon atmosphere. The resulting mixture was stirred for 3 hr, then 1-iodohexane (3.12 g, 14.7 mmol) in dry THF (8 ml) was added dropwise. The solution was stirred at −20°C for 2 hr and room temperature for 1 hr, then quenched with water. The mixture was extracted with 1:1 ether-pentane (3 × 20 ml). The combined organic layers were washed with aqueous 5% sodium bisulfite solution (2 × 30 ml), water (2 × 50 ml), and brine (2 × 50 ml), then dried over Na_2SO_4 and concentrated. The crude product was purified by vacuum flash chromatography over silica gel eluting with pentane to afford 2.01 g of the product (89.8% yield). ^{1}H NMR δ 0.89 (*t*, 3H, J = 7.0 Hz), 1.24–1.44 (*m*, 6H), 1.63 (quint, 2H, J = 7.6 Hz), 2.62 (*t*, 2H, J = 7.6 Hz), 5.95–5.98 (*m*, 1H), 6.27 (dd, 1H, J = 2.0 and 3.1 Hz), 7.29 (dd, 1H, J = 0.8 and 2.0 Hz). ^{13}C NMR δ 14.31, 22.81, 28.22, 28.24, 29.10, 31.82, 104.71, 110.24, 140.84, 156.87 ppm. MS (*m/z*, rel. intensity): 152 (M^+, 13), 123 (5), 109 (3), 95 (14), 81 (100), 67 (6), 53 (20), 43 (8).

Synthesis of 4-Oxo-(E)-2-hexenal. N-bromosuccinimide (2.72 g, 15.3 mmol, 1.5 eq.) and pyridine (1.61 g, 20.4 mmol, 2 eq.) were sequentially added to a solution of 2-ethylfuran (1.00 g, 10.2 mmol, 1 eq.; Lancaster Synthesis, Pelham, NH, USA) in THF/acetone/water (5:4:2, 22.0 ml) at −15°C. The resulting mixture was stirred for 3 hr at −15° and then warmed to room temperature and stirred overnight. The mixture was poured into aqueous HCl (0.5 M, 20 ml) and extracted with ether (3 × 20 ml). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and the solvent was removed by distillation. The crude product was purified by vacuum flash chromatography over silica gel (ether: pentane, 15:85) to afford 4-oxo-(*E*)-2-hexenal (0.55 g, 48%). ^{1}H NMR δ 1.15 (*t*, 3H, J = 7.2 Hz), 2.73 (*q*, 2H, J = 7.2 Hz), 6.77 (dd, 1H, J = 7.2 and 16.2

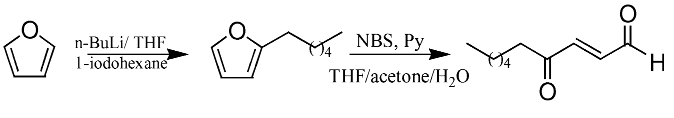
Hz), 6.88 (d, 1H, J = 16.2 Hz), 9.77 (d, 1H, J = 7.2 Hz). ^{13}C NMR δ 7.76, 34.75, 137.51, 144.98, 193.65, 200.59 ppm. MS: *m/z* 112 (M^+, 16), 97 (2), 84 (15), 83 (100), 57 (18), 55 (77), 53 (10).

Syntheses of 4-Oxo-(E)-2-octenal and 4-Oxo-(E)-2-decenal. In the same manner, 2-*n*-butylfuran (0.50 g, 4.0 mmol, Lancaster Synthesis) was converted to 4-oxo-(*E*)-octenal (0.28 g, 50% yield), and 2-*n*-hexylfuran (1.00 g, 6.6 mmol) gave 4-oxo-(*E*)-2-decenal in 56% yield (0.62 g). 4-Oxo-(*E*)-2-octenal: ^{1}H NMR δ 0.92 (*t*, 3H, J = 7.2 Hz), 1.30–1.40 (*m*, 2H), 1.58–1.68 (*m*, 2H), 2.69 (*t*, 2H, J = 7.2 Hz), 6.76 (dd, 1H, J = 7.2 and 16.2 Hz), 6.87 (d, 1H, J = 16.2 Hz), 9.77 (d, 1H, J = 7.2 Hz). ^{13}C NMR δ 14.03, 22.44, 25.93, 41.15, 137.54, 145.17, 193.66, 200.36 ppm. MS: *m/z* 140 (M^+, 1), 125 (7), 111 (39), 98 (46), 97 (13), 83 (53), 70 (40), 57 (28), 56 (15), 55 (100). 4-Oxo-(*E*)-2-decenal: ^{1}H NMR δ 0.88 (*t*, 3H, J = 6.9 Hz), 1.20–1.38 (m, 6H), 1.60–1.70 (*m*, 2H), 2.69 (*t*, 2H, J = 7.2 Hz), 6.77 (dd, 1H, J = 7.2 and 16.2 Hz), 6.87 (d, 1H, J = 16.2 Hz), 9.78 (d, 1H, J = 7.2 Hz). ^{13}C NMR δ 14.23, 22.68, 23.84, 28.98, 31.75, 41.45, 137.54, 145.19, 193.66, 200.38 ppm. MS: *m/z* 168 (M^+, 1), 153 (1), 139 (41), 125 (12), 111 (9), 98 (54), 83 (56), 70 (49), 55 (100), 43 (90).

RESULTS AND DISCUSSION

4-Oxo-(*E*)-2-alkenals were readily prepared from 2-alkylfurans, using aqueous *N*-bromosuccinimide (NBS) to promote oxidative ring opening under mild conditions (Kobayashi et al., 1998). The reaction initially produces 4-oxo-(*Z*)-2-alkenals, which are completely isomerized to the (*E*)-2-isomers after several hours at room temperature in the reaction flask. 4-Oxo-(*E*)-2-hexenal and 4-oxo-(*E*)-2-octenal were obtained in one step from commercially available starting materials in 48 and 50% isolated yields, respectively. 4-Oxo-(*E*)-2-decenal was obtained in two steps, starting from furan. Thus, treatment of furan with *n*-butyl lithium, followed by addition of one equivalent of 1-iodohexane, afforded 2-*n*-hexylfuran in 89.8% yield, which was then oxidized to 4-oxo-(*E*)-2-decenal with aqueous NBS in 56% isolated yield (Scheme 1).

Several methods have been published for the syntheses of geometrical isomers of 4-oxo-2-alkenals. For example, the routes described by Ward and van Dorp (1969), Marques et al. (2000), and Zarbin et al. (2000) furnish



SCH. 1. Synthesis of (*E*)-4-oxo-2-decenal.

stereochemically pure 4-oxo-(*E*)-2-alkenals, but both routes involve multiple steps. During the course of our work, another short synthesis was reported: thus, Fernandes and Kumar (2003) found that under appropriate reaction conditions, homoallylic alcohols react with pyridinium chlorochromate to afford 4-oxo-(*E*)-2-alkenals. This reaction was proposed to proceed by the initial oxidation of the alcohol, followed by double bond migration and subsequent allylic oxidation. However, only a limited number of the homoallylic alcohol precursors are commercially available.

In summary, the short and simple syntheses of 4-oxo-(*E*)-2-alkenals described in this communication should make these compounds readily accessible to researchers. Furthermore, the route can be readily adapted to produce homologs of any desired chain length by the straightforward alkylation of furan with an alkyl halide of the appropriate chain length.

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