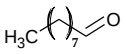
Electronic Supplementary Material (ESI) for RSC Advances

Ozonolysis of Some Complex Organic Substrates in Flow

M. D. Roydhouse, W. B. Motherwell, A. Constantinou, A. Gavriilidis, R. Wheeler, K. Down and I. Campbell.

Supporting Information

Nonanal **1b**



δ_H (400 MHz, $CDCl_3$) 0.86 (3 H, t, *J* 6.8, CH_3), 1.20 - 1.37 (10 H, m, 5xCH_2), 1.62 (2 H, quin, *J* 7.3, CH_2), 2.40 (2 H, td, *J* 7.3 & 1.9, CH_2) & 9.75 (1 H, t, *J* 1.9, CHO).

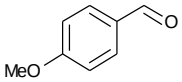
Benzophenone **2b**

δ_H (400 MHz, $CDCl_3$) 7.46 – 7.53 (4 H, m, *m*-Ph), 7.58 – 7.66 (2 H, m, *p*-Ph) & 7.83 (4 H, m, *o*-Ph).

Acetophenone **3b**

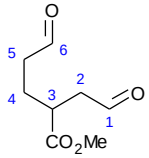
δ_H (400 MHz, $CDCl_3$) 2.61 (3 H, s, CH_3), 7.46 (2 H, dd, *J* 4.7 & 10.5, *m*-Ph), 7.51 – 7.65 (1 H, m, *p*-Ph), 7.96 (2 H, dd, *J* 3.3 & 5.2, *o*-Ph).

4-Methoxybenzaldehyde **4b**



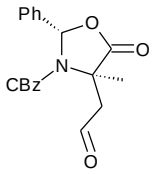
δ_H (400 MHz, $CDCl_3$) 3.90 (3 H, s, CH_3O), 6.96 – 7.04 (2 H, m, *m*-Ph), 7.77 – 7.91 (2 H, m, *o*-Ph), 9.90 (1 H, s, CHO).

Methyl 5-oxo-2-(2-oxoethyl)pentanoate **6b**



δ_H (400 MHz, $CDCl_3$) 1.74 – 1.92 (2 H, m, C(4)H_2), 2.41 – 2.59 (3 H, m, C(5)H_2 & C(3)H), 2.77 – 2.90 (2 H, m, C(2)H_2), 3.58 – 3.63 (3 H, m, CH_3O), 9.66 (1 H, s, CHO), 9.67 (1 H, s, CHO).

Benzyl (2S,4R)-4-methyl-5-oxo-4-(2-oxoethyl)-2-phenyl-1,3-oxazolidine-3-carboxylate **7b**



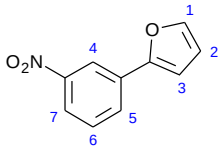
δ_H (400 MHz, $CDCl_3$) 1.78 (3 H, s, Me), 3.10 (1 H, d, *J* 19.3, CH_AH$_B$CHO), 4.07 (1 H, d, *J* 19.2, CH$_A$$H_B$CHO), 4.88 (1 H, d, *J* 12.1, PhCH_CH$_D$), 5.00 (1 H, d, *J* 12.3, PhCH$_C$$H_D$), 6.60 (1 H, s, PhCH), 6.78 – 6.89 (2 H, m, Ph), 7.16 – 7.53 (8 H, m, Ph), 9.68 (1 H, s, CHO).

Hutton, Craig A.; Bartlett, Paul A., *Journal of Organic Chemistry*, 2007, **72**, 6865 – 6872.

Benzaldehyde **8b**

δ_H (400 MHz, $CDCl_3$) 7.50 – 7.59 (2 H, m, *m*-Ph), 7.61 – 7.70 (1 H, m, *p*-Ph), 7.87 – 7.93 (2 H, m, *o*-Ph), 10.04 (1 H, s, CHO).

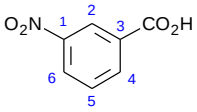
2-(3-Nitrophenyl)furan **10a**



δ_H (400 MHz, $CDCl_3$) 6.51 (1 H, dd, *J* 1.8 & 3.4, C(2)H), 6.78 (1 H, dd, *J* 0.6 & 3.5, C(3)H), 7.51 (1 H, dd, *J* 0.6 & 1.8, C(1)H), 7.52 (1 H, dd, *J* 8.0 & 8.0, C(6)H), 7.93 (1 H, ddd, *J* 1.0, 1.7 & 8.0, C(5)H), 8.06 (1 H, ddd, *J* 1.0, 1.7 & 8.0, C(7)H), 8.46 (1 H, dd, *J* 1.0 & 1.0, C(4)H).

Young, Rodney C.; Mitchell, Robert C.; Brown, Thomas H.; Ganellin, C. Robin; Griffiths, *Journal of Medicinal Chemistry*, 1988, **31**, 656 – 671.

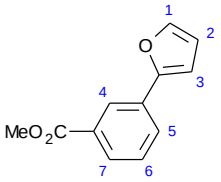
3-Nitrobenzoic acid **10b**



δ_H (400 MHz, MeOD) 7.72 (1 H, t, *J* 8.0, C(5)H), 8.33 – 8.38 (1 H, m, C(6)H), 8.42 (1 H, ddd, *J* 0.9, 2.2 & 8.2, C(4)H), 8.70 – 8.77 (1 H, m, C(2)H).

Murray, Alexander T.; Matton, Pascal; Fairhurst, Nathan W. G.; Carbery, David R.; John, Matthew P., *Organic Letters*, 2012, **14**, 3656 – 3659.

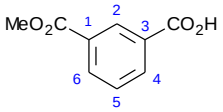
Methyl 3-(furan-2-yl)benzoate **11a**



δ_H (400 MHz, $CDCl_3$) 3.97 (4 H, d, *J* 4.1, CH_3O), 6.52 (1 H, dd, *J* 1.6, 3.3, C(2)H), 6.76 (1 H, d, *J* 3.3, C(3)H), 7.48 (1 H, dd, *J* 7.8 & 7.8, C(6)H), 7.52 (1 H, d, *J* 1.6, C(1)H), 7.88 (1 H, d, *J* 7.8, C(7)H), 7.95 (1 H, d, *J* 7.8, C(5)H), 8.36 (1 H, dd, *J* 1.6 & 1.6, C(4)H).

Kang, Suk-Ku; Kim, Jae-Sun; Yoon, Seok-Keun; Lim, Kwon-Ho; Yoon, Seung Soo, *Tetrahedron Letters*, 1998, **39**, 3011 – 3012.

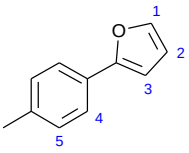
3-(Methoxycarbonyl)benzoic acid **11b**



δ_H (400 MHz, MeOD) 3.94 (3 H, s, *J* 5.4, CH_3), 7.59 (1 H, t, *J* 7.8, C(5)H), 8.22 (2 H, ddt, *J* 1.3, 7.8 & 9.1, C(6)H & C(4)H), 8.63 (1 H, t, *J* 1.6 C(2)H).

Faridoon; Hussein, Waleed M.; Vella, Peter; Schenk, Gerhard; McGeary, Ross P.; Islam, Nazar Ul; Ollis, David L., *Bioorganic and Medicinal Chemistry Letters*, 2012 , **22**, 380 – 386.

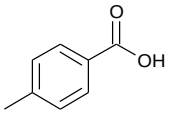
2-(4-Methylphenyl)furan **12a**



δ_H (400 MHz, $CDCl_3$) 2.37 (1 H, s, CH_3), 6.46 (1 H, dd, *J* 1.5, 3.3, C(2)H), 6.60 (1 H, d, *J* 3.3, C(3)H), 7.20 (1 H, d, *J* 8.0, 2xC(5)H), 7.45 (1 H, d, *J* 1.5, C(5)H), 7.59 (1 H, d, *J* 8.2, 2xC(4)H).

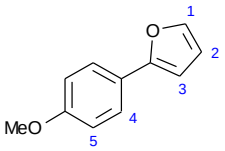
Goossen, Lukas J.; Linder, Christophe; Rodriguez, Nuria; Lange, Paul P. *Chemistry--A European Journal*, 2009, **15**, 9336 – 9349.

4-Methylbenzoic acid **12b**



δ_H (400 MHz, MeOD) 2.37 (3 H, s, CH_3), 7.24 (2 H, d, *J* 8.0, *m*-Ph), 7.84 – 7.94 (2 H, m, *o*-Ph).

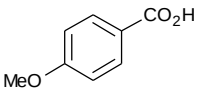
2-(4-Methoxyphenyl)furan **13a**



δ_H (400 MHz, $CDCl_3$) 3.82 (2 H, s, CH_3O), 6.42 (1 H, dd, *J* 1.5, 3.3, C(2)H), 6.49 (1 H, d, *J* 3.3, C(3)H), 6.86 – 6.93 (2 H, m, 2xC(5)H), 7.40 (1 H, d, *J* 1.5, C(1)H), 7.55 – 7.62 (2 H, m, 2xC(4)H).

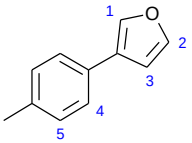
Snegaroff, Katia; L'Helgoual'ch, Jean-Martial; Bentabed-Ababsa, Ghenia; Nguyen, Tan Tai; Chevallier, Floris; Mongin, Florence; Yonehara, Mitsuhiro; Uchiyama, Masanobu; Derdour, Aicha, *Chemistry--A European Journal*, 2009, **15**, 10280 – 10290.

4-Methoxybenzoic acid **13b**



δ_H (400 MHz, MeOD) 3.85 (3 H, s, CH_3O), 6.96 (2 H, d, *J* 8.9, *m*-Ph), 7.96 (2 H, d, *J* 8.9, *o*-Ph).

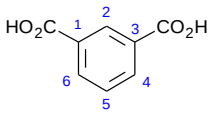
3-(4-Methylphenyl)furan **14a**



δ_H (400 MHz, $CDCl_3$) 2.37 (3 H, s), 6.69 (1 H, dd, *J* 0.8 & 1.7, C(3)H), 7.19 (2 H, d, *J* 8.0, 2xC(5)H), 7.39 (2 H, d, *J* 8.0, 2xC(4)H), 7.47 (1 H, dd, *J* 1.6 &1.7, C(2)H), 7.71 (1 H, dd, *J* 0.8, 1.6, C(1)H).

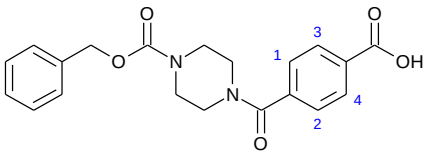
Taniguchi, Takahiko; Nagata, Hiroshi; Kanada, Regina Mikie; Kadota, Kohei; Takeuchi, Miwako; Ogasawara, Kunio, *Heterocycles*, 2000, **52**, 67 – 72.

Isophthalic Acid **15b**



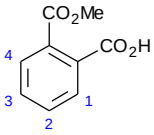
δ H (400 MHz, DMSO) 7.64 (1 H, t, *J* 7.7, C(5)H), 8.16 (2 H, dd, *J* 1.8 & 7.7, C(6)H & C(4)H), 8.48 (1 H, t, *J* 1.6, C(2)H).

4-({4-[(Benzyloxy)carbonyl]piperazin-1-yl}carbonyl)benzoic acid **16b**



δ_H (400 MHz, $CDCl_3$) 3.28 – 3.68 (8 H, m, piperazine-H), 5.13 (2 H, s, $PhCH_2$), 7.26 – 7.37 (5 H, m, Ph), 7.45 (2 H, d, *J* 8.2, C(1)H & C(2)H), 8.06 – 8.12 (2 H, m, C(3)H & C(4)H).

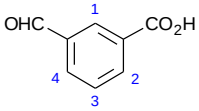
2-(Methoxycarbonyl)benzoic acid **18b**



δ_H (400 MHz, $CDCl_3$) 3.92 (3 H, s, CH_3O), 7.55 – 7.60 (2 H, m, C(2)H & C(3)H), 7.67 – 7.73 (1 H, m, C(4)H), 7.89 – 7.94 (1 H, m, C(1)H).

Hoesch, Lienhard, *Helvetica Chimica Acta*, 1981, **64**, 890 – 904.

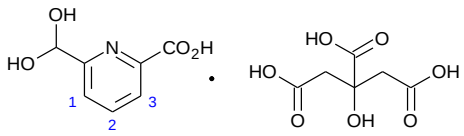
3-Formylbenzoic acid **19b**



δ_H (400 MHz, DMSO) 7.74 (1 H, t, *J* 7.7, C(3)H), 8.11 – 8.17 (1 H, m, C(2)H), 8.24 (1 H, d, *J* 7.7, C(4)H), 8.44 (1 H, s, C(1)H), 10.09 (1 H, s, CHO).

Wang, Zhi-Lin; Luo, Qin-Hui; Duan, Chun-Ying; Shen, Cheng-Yu; Li, Yi-Zhi, *Dalton Transactions*, 2004, 1104 – 1112.

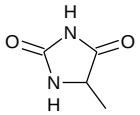
6-Formylpyridine-2-carboxylic acid citric acid (salt) hemiacetal **20b**



δ_H (400 MHz, MeOD) 2.80 (2 H, d, *J* 15.7, 2xCH_AH$_B$), 2.91 (2 H, d, *J* 15.7, 2xCH$_A$$H_B$), 5.62 (1 H, s, CH(OH)$_2$), 7.79 (1 H, dd, *J* 0.9 & 7.8, C(2)H), 8.03 (1 H, t, *J* 7.8, C(1)H), 8.12 (1 H, dd, *J* 1.0 & 7.7, C(3)H).

Jew, Sang-sup; Park, Boon-saeng; Lim, Doo-yeon; Kim, Myoung Goo; Chung, In Kwon; Kim, Joo Hee; Hong, Chung Il; Kim, Joon-Kyum; Park, Hong-Jun; Lee, Jun-Hee; Park, Hyeung-geun, *Bioorganic & Medicinal Chemistry Letters*, 2003, **13**, 609 – 612.

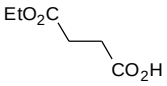
5-Methylimidazolidine-2,4-dione **21b**



δ_H (400 MHz, MeOD) 1.36 (3 H, d, *J* 6.9, CH$_3$), 4.04 – 4.15 (1 H, q, *J* 6.9, CH).

Rosa, Michael De; Freyer, Alan J., *Journal of Heterocyclic Chemistry*, 1995, **32**, 1661 – 1664.

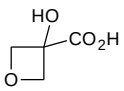
4-Ethoxy-4-oxobutanoic acid **22b**



δ_H (400 MHz, MeOD) 1.18 – 1.32 (3 H, m, CH$_3$), 2.53 – 2.64 (4 H, m,), 4.15 (2 H, m, CH$_2$).

Monsalve, Leandro N.; Rada, Mayra Y. Machado; Ghini, Alberto A.; Baldessari, Alicia, *Tetrahedron*, 2008, **64**, 1721 – 1730.

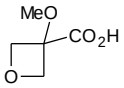
3-Hydroxyoxetane-3-carboxylic acid **23b**



Furan **23a** 0.2 M (0.54 cm^3/min, 10 min, 1.080 mmol) in ethyl acetate and ozone 0.0041 M (66 cm^3/min, 10 min, 2.71 mmol) in oxygen were mixed in a Vapourtec cooled reaction module at r.t. All streams were equilibrated prior to the reactor output being switched from waste to collect. 10 min of the equilibrated reaction flow was collected after which the output was switched back to waste. After 4.0 min the pumps

were stopped and pure oxygen was flowed through the reactor set up for at least 10 min to purge any excess ozone. The solvent was removed via evaporation and the crude material was dissolved in a minimal amount of methanol and placed on to a 5g NH_2 functionalised column (Isolute). The column was washed with methanol (30 cm^3) and then the product was eluted with 5 % AcOH in methanol (50 cm^3) to yield after evaporation of the solvent and freeze-drying 13.6 mg mg (24.4 %) of a white solid. δ_H (400 MHz, $CDCl_3$) 4.81 (2 H, d, *J* 8.0, 2xCH_AH_B), 5.10 (2 H, d, *J* 8.0, 2xCH_AH_B), 7.76 – 8.27 (2 H, m, OH, CO_2H).

3-Methoxyoxetane-3-carboxylic acid **24b**



Small scale synthesis:

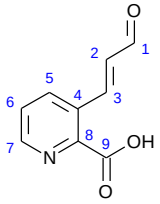
Furan **24a** 0.2 M (0.54 cm^3/min, 10 min, 1.080 mmol) in ethyl acetate and ozone 0.0041 M (66 cm^3/min, 10 min, 2.71 mmol) in oxygen were mixed in a Vapourtec cooled reaction module at r.t. All streams were equilibrated prior to the reactor output being switched from waste to collect. 10 min of the equilibrated reaction flow was collected after which the output was switched back to waste. After 4.0 min the pumps were stopped and pure oxygen was flowed through the reactor set up for at least 10 min to purge any excess ozone. The solvent was removed and the crude material was dissolved in a minimal amount of methanol and placed on to a 5g ISOLUTE SPE COLUMN, NH_2 functionalised and the column wash with 30 ml methanol, the product was then eluted with 50 ml 5 % AcOH in methanol to yield after evaporation of the solvent a clear oil that proved to be a ~1:1 mixture of AcOH and the desired product (47.2%). Attempts to remove the 1 eq. of AcOH by evaporation resulted in loss of material.

Large Scale Synthesis:

2-(3-methoxyoxetan-3-yl)furan 0.2 M (0.54 ml/min, 40 min, 8.64 mmol) in ethyl acetate and ozone 0.0044 M (66 ml/min, 40 min, 23.23 mmol) in oxygen were mixed in a Vapourtec cooled reaction module at -10 °C. All streams were equilibrated prior

to the reactor output being switched from waste to collect. 40 min of the equilibrated reaction flow was collected after which the output was switched back to waste. For exact timings see the Flow readings section. After 4.0 min the pumps were stopped and pure oxygen was flowed through the reactor set up for at least 10 mins. The crude material was found to contain ~20 mg/L peroxides as determined by Quantofix Peroxide 25 strips. To this solution was added solid sodium metabisulphide and the slurry stirred overnight. The solution was tested again and was found to contain ~0.5 mg/L, this was determined to be low enough to rotary evaporate the solution. After removal of most of the solvent (30 degrees, 50 mbar) the residue was place in a Krugelrohr bulb and the remaining solvent evaporated down to a vacuum of 27 mbar at 35 degrees. Any attempts to purify further resulted in decomposition of the product. The product was obtained as a yellow viscous oil (1.0551g, (~85% pure, NMR estimate), 79 %).δ_H (400 MHz, $CDCl_3$) 3.42 (3 H, s, CH_3), 4.76 (2 H, d, *J* 7.3, 2xCH_AH_B), 4.93 (2 H, d, *J* 7.3, 2xCH_AH_B), 10.82 (1 H, s, CO_2H); δ_C (151 MHz, DMSO) 53.7 (CH_3), 77.6 (2xCH_2), 79.5 (C*) & 174.4 (COOH); *m/z* (CI) 87 [100 %, $(C_4H_7O_2)^+$], 133 [14 %, (M+H)] [Found: $(MH)^+$, 133.0488. $C_5H_9O_4$ requires 133.0495].

3-[(1E)-3-Oxoprop-1-en-1-yl]pyridine-2-carboxylic acid **26**



8-hydroxyquinoline 0.2 M (0.54 ml/min, 5 min, 0.540 mmol) in Methanol and ozone 0.0043 M (40 ml/min, 5 min, 0.860 mmol) in Oxygen were mixed in a Vapourtec cooled reaction module at 20°C. The quench stream was dimethylsulphide 0.3 M (1.08 ml/min, 3.0 eq.) in Methanol. All streams were equilibrated prior to the reactor output being switched from waste to collect. 5 min of the equilibrated reaction flow was collected after which the output was switched back to waste. After 5.0 min the pumps were stopped and pure oxygen was flowed through the reactor set up for at least 10 mins. The reaction mixture was evaporated and ethanol (c.a. 5ml) added, The mixture was filtered and the solids washed with cold ethanol (2x 5ml) and ether (2x 5ml) (Yield of 21%);.δ_H (400 MHz, DMSO) 6.89 (1 H, dd, *J* 7.6 & 15.9, C(2)H), 7.67

(1 H, dd, *J* 4.7 & 8.0, C(6)H), 8.15 (1 H, d, *J* 15.9, C(3)H), 8.37 (1 H, dd, *J* 1.4 & 8.0, C(5)H), 8.69 (1 H, dd, *J* 1.4 & 4.7, C(7)H), 9.74 (1 H, d, *J* 7.6, CHO); δ_C (151 MHz, DMSO) 126.3 (C6), 129.2 (C4), 131.8 (C2), 136.1 (C5), 147.9 (C3), 149.15 (C8), 150.55 (C7), 167.12 (COOH) & 194.64 (CHO); *m/z* (CI) 148 [100 %, $(C_8H_6O_2N)^+$], 178 [44 %, (M+H)] [Found: $(MH)^+$, 178.0498. $C_9H_8O_3N$ requires 178.0499].