Supplementary Material (ESI) for Lab on a Chip

Surface Acoustic Waves as an Energy Source for Drop-Scale Synthetic Chemistry

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General

All reactions were conducted on a Teflon coated 20 MHz lithium niobate surface acoustic wave (SAW) device. A 500 nm thick Teflon coating of the substrate was accomplished using spin coating of amorphous Teflon AF (DuPont, Wilmington, DE USA) precisely following their recommended process except for a circular region at the centre of the substrate with bare lithium niobate, 5 mm in diameter and commensurate with the reaction droplet dimension. Reaction material was placed onto this circular region thus coming into direct contact with the lithium niobate.

The SAWs were generated by applying a sinusoidal oscillating electrical signal output to an interdigital transducer (250 nm thick Ti-Al electrodes) from an RF amplifier (10W1000C, Amplifier Research, Souderton PA USA) connected to a SMD01 signal generator (Rhode and Schwarz, Munich Germany). All four electrodes (2 electrodes on each of the IDTs) were connected to the RF output of the amplifier. The signal generator was set to sine wave with a frequency of 20 MHz and amplitude of 230 mV_{rms}. The gain on the amplifier was adjusted to provide 4 Watts of power to the SAW device.

Reaction temperature was monitored using an analogue probe with an insulated type K thermocouple (HH501BJK, Omega, Stamford CT USA).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 300 MHz with a Bruker Avance DPX300 spectrometer and at 400 MHz with a Bruker Avance DRX400 spectrometer. The ^{1}H spectra were run in deuterochloroform ($CDCl_3$) with δ 7.26 (residual $CHCl_3$) used as an internal reference. Each resonance was assigned according to the following convention: chemical shift measured in parts per million (ppm), multiplicity, coupling constant (*J* Hz), number of protons, assignment. Multiplicities are denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or b (broad) and prefixed where appropriate.

Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 75 MHz with a Bruker Avance DPX300 spectrometer or at 100 MHz with a with a Bruker Avance DRX400 spectrometer and were run in deuterochloroform ($CDCl_3$) solutions with δ 77.16 ($CDCl_3$ solvent resonance) used as an internal reference. Each reference was assigned according to the following convention: chemical shift in parts per million (ppm), structural assignment.

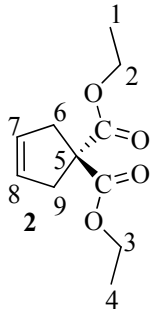
Low resolution electrospray ionisation (ESI) mass spectrometry (*m/z*) was performed and recorded on a Micromass Platform spectrometer. Only the $[M+H]^+$ and $[M+Na]^+$ peaks (*m/z*) were quoted. Accurate mass determinations were made at high resolution on an Agilent G1969A LC – TOF system with reference and mass correction at 4000V capillary voltage for ESI.

Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 FT-IR spectrophotometer and refer to solutions in chloroform ($CHCl_3$) applied as thin films to sodium chloride plates. The intensity of absorption bands for all samples have been specified as either s (strong), m (medium), w (weak) or b (broad).

Optical absorptions of phthalocyanines involved the use of rectangular quartz cuvettes with an internal width of 1 cm. 1-Chloronaphthalene was used as the solvent. The spectral absorption curves were measured at room temperature with a Cary Model 1E recording spectrophotometer (Varian).

Ring-closing metathesis[1]

*Synthesis of diethyl cyclopent-3-ene-1,1-dicarboxylate **2***



The SAW device was charged with diethyl 2,2-diallylmalonate (**1**, 18 μl, 74.5 μmol) and 5 mol % of Grubbs catalyst (3.0 mg, 3.65 μmol). To maintain the reaction temperature at 25 – 30 °C the LN substrate was cooled (by placing it on an ice-cooled aluminium block or a Peltier device). The reaction droplet was allowed to react on SAW for < 2 min as the progress of this reaction was easily monitored by observation of bubbling due to the evolution of ethylene. Following cessation of ethylene release the reaction mixture was purified (silica gel pipette column, eluting with ethyl acetate/hexane (1:5)) providing diethyl cyclopent-3-ene-1,1-dicarboxylate **2**, (17 mg) in an overall yield and of > 99%.

IR ($CHCl_3$) υ 3064w, 2983w, 2936w, 1732s, 1466w, 1447w, 1389w, 1367w, 1340w, 1256s, 1183s, 1097w, 1072m, 1017w, 952w, 914w, 861w, 733m, 696w, 668w cm^{-1}.

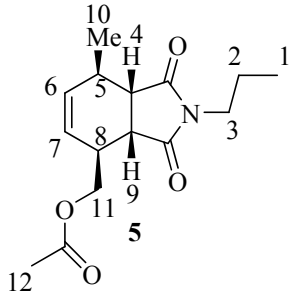
^{1}H NMR (400MHz, $CDCl_3$) δ 5.61, (s, 2H, H7 & H8); 4.20, (q, *J* 7.1 Hz, 7.1 Hz, 4H, H2 & H3); 3.01, (s, 4H, H6, H9); 1.25, (t, *J* 7.1 Hz, 6H, H1 & H4).

^{13}C NMR (100MHz, $CDCl_3$) δ 172.38, 2XC=O; 127.96, C7 & C8; 61.66, C2 & C3; 59.05, C5; 41.01 C6 & C9; 14.18, C1 & C4.

HRMS calculated for ($C_{11}H_{17}O_4^+$) *m/z* = 213.1121 found 213.1123; ($C_{11}H_{16}NaO_4^+$) *m/z* = 235.0941 found 235.0943

Diels-Alder reaction[2]

Synthesis of ((3aR,4S,7R,7aS)-7-methyl-1,3-dioxo-2-propyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)methyl acetate ***5***



The SAW device was charged with (2E,4E)-hexa-2,4-dienyl acetate (15 µl, 100.5 µmol) and 1-propyl-1H-pyrrole-2,5-dione (8.4 µl, 67.1 µmol). The reaction droplet was allowed to react on SAW for 30 min at 45°C (employing a Peltier cooling device) to afford ((3aR,4S,7R,7aS)-7-methyl-1,3-dioxo-2-propyl-2,3,3a,4,7,7a-hexahydro-1H-isoindol-4-yl)methyl acetate **5** (13.8 mg) as a thick viscous oil in an overall yield of 74% and >95% purity.

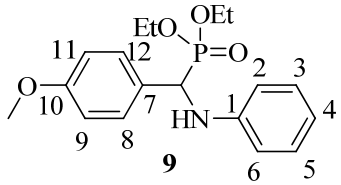
^{1}H NMR (400MHz, $CDCl_3$) δ 5.76, (s, 2H, H6, H7); 4.6, (ddd, *J* 7.7 Hz, 11.2 Hz, 19.3 Hz, 2H, H11); 3.38, (t, *J* 7.1 Hz, 2H, H3); 3.12, (ddd, *J* 6.5 Hz, 8.6 Hz, 15.6 Hz, 2H, H4 & H9); 2.64 – 2.56, (m, 1H, H8); 2.48 – 2.39, (m, 1H, H5); 2.08, (s, 3H, H12); 1.50, (dd, *J* 7.3 Hz, 14.5 Hz, 2H, H2); 1.45, (d, *J* 7.4 Hz, 3H, H10); 0.83, (t, *J* 7.5 Hz, 3H, H1).

^{13}C NMR (100MHz, $CDCl_3$) δ 177.34, N-C=O; 177.27, N-C=O; 170.98, O-C=O; 135.41, C6/C7; 129.22, C6/C7; 64.64, C11; 44.81 C4/C9; 42.44, C4/C9; 40.29, C3; 36.03, C8; 31.35, C5; 21.15, C12/C2; 21.10, C12/C2; 16.82, C10; 11.32 C1.

HRMS calculated for ($C_{15}H_{22}NO_4^+$) *m/z* = 280.1543 found 280.1549; ($C_{15}H_{21}NNaO_4^+$) *m/z* = 302.1363 found 302.1367

Kabachnik-Fields reaction[3]

*Synthesis of diethyl (4-methoxyphenyl)(phenylamino)methylphosphonate **9***



9

The SAW device was charged with p-anisaldehyde (9.4 µl, 77.3 µmol) and aniline (7.1 µl, 77.8 µmol). After 2.5 min at 75°C diethyl phosphite (10 µl, 77.5 µmol) was added to the reaction droplet and allowed to react at the same temperature on SAW for an additional 2 min to afford diethyl (4-methoxyphenyl)-(phenylamino)methylphosphonate **9** (26.7 mg) as a thick viscous pale yellow oil in an overall yield of 98% and >95% purity.

IR ($CHCl_3$) υ 3418w, 2984m, 2925w, 2909w, 2838w, 1604s, 1510s, 1463m, 1442m, 1392w, 1369w, 1304m, 1247s, 1175m, 1097w, 1027s, 976m, 908s, 837m, 791w, 732s, 692m, 649m cm^{-1}.

^{1}H NMR (400MHz, $CDCl_3$) δ 7.38, (dd, *J* 2.3 Hz, 8.4 Hz, 2H, H8, H12); 7.1, (dd, *J* 7.4 Hz, 8.7 Hz, 2H, H3, H5); 6.86, (d, *J* 8.4 Hz, 2H, H9, H11); 6.69, (tt, *J* 1.0 Hz, 7.4 Hz, 1H, H4); 6.60, (dd, *J* 1.0 Hz, 8.7 Hz, 2H, H2, H6); 4.72, (brs, 1H, NH); 4.71, (d $J_{P\text{-}H}$= 23.8 Hz, 1H, CHNH); 4.19 – 4.05, (m, 2H, OCH_2CH_3); 4.00 – 3.87, (m, 1H, OCH_2CH_3); 3.77, (s, 3H, OCH_3); 3.76 – 3.67, (m, 1H, OCH_2CH_3); 1.28, (t, *J* 7.1 Hz, 3H, OCH_2CH_3); 1.14, (t, *J* 7.1 Hz, 3H, OCH_2CH_3).

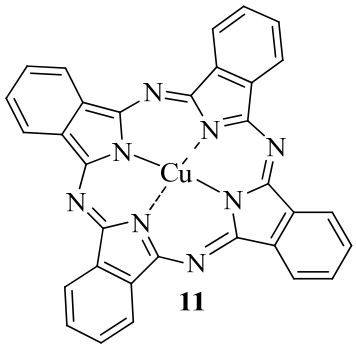
^{13}C NMR (100MHz, $CDCl_3$) δ 159.47, C10; 146.53, (d, *J* 14.7 Hz, C1); 129.28/129.14, C3/C5; 129.08, C7; 127.84/127.81, C12/C8; 118.49, C4; 114.23/114.20, C9/C11; 114.06, C2 & C6; 63.44, OCH_2CH_3; 63.37, OCH_2CH_3; 55.55, (d, *J* 152.4 Hz, CHNH); 55.37, OCH_3; 16.58, (d, *J* 5.8 Hz, OCH_2CH_3); 16.39, (d, *J* 5.8 Hz, OCH_2CH_3).

HRMS calculated for ($C_{18}H_{25}NO_4P^+$) *m/z* = 350.1516 found 350.1518

($C_{14}H_{14}NO^+$) *m/z* = 212.1070 found 212.1069 (intermediate imine)

Tetramerisation[4]

*Synthesis of copper phthalocyanine **11***



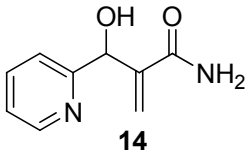
11

The SAW device was loaded with phthalonitrile (10 mg, 78 μmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (35 μl, 234 μmol) and $CuCl_2$ (2.7 mg, 20.1 μmol) in diethylene glycol (40 μl) as the solvent. The reaction droplet was allowed to react on SAW for 15 min with the device and droplet temperature reaching 80 °C to afford, after collection by filtration and washing with ethanol, copper phthalocyanine **11** (5.8 mg) in an overall yield of 52%.

UV-Vis Absorption Bands (solvent: 1-chloronaphthlene) λ_{max} 6780, 6480, 6110, 5880, 5640, 4560, 4270, 4140 Å.

Baylis Hillman reaction[5]

Synthesis of 2-(hydroxy(pyridin-2-yl)methyl)acrylamide



14

2-Pyridinecarboxaldehyde (**13**, 9.5 μl, 99.9 μmol), acrylamide (7.1 mg, 99.9 μmol) and quinuclidine (11.1 mg, 99.8 μmol) were mixed together in 10 μl of methanol and loaded onto the SAW device. The reaction droplet was allowed to react on SAW for 15 min with the device and droplet temperature reaching 70 °C to afford 2-(hydroxy(pyridin-2-yl)methyl)acrylamide as a colourless oil **14** (14.5mg) in an isolated yield (silica gel pipette column, eluting with ethyl acetate) of 86%.

^{1}H NMR (400MHz, $CDCl_3$) δ 8.58 – 8.54, (m, 1H, pyridine); 7.72, (dt, *J* 1.7 Hz, 7.7 Hz, 1H, pyridine); 7.37, (dd, *J* 0.8 Hz, 7.9 Hz, 1H, pyridine); 7.28 - 7.24, (m, 1H, pyridine); 6.75, (brs, 1H, O<u>H</u>); 6.24, (d, *J* 1.0 Hz, 1H, alkene); 5.70, (s, 1H, alkene); 5.52, (s, 1H, CHOH); 5.35, (brs, 2H, N<u>H</u>$_2$).

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