Electronic Supplementary Material (ESI) for RSC Advances

Supporting Information for

Initiation Efficiency and Cytotoxicity of Novel Water-soluble Two-photon Photoinitiators for Direct 3D Microfabrication of Hydrogels

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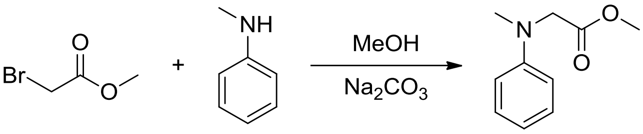
1. Synthesis of precursors for condensation

2. Processing windows of TPA PIs

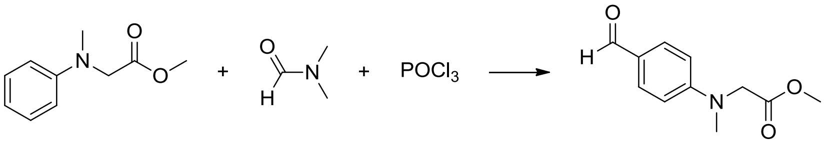
1. Synthesis of precursors for condensation

Methyl 2-(methyl(phenyl)amino)acetate[1]



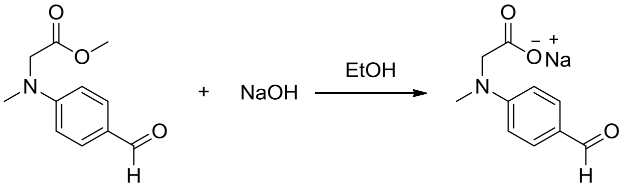
12.2 mL of ethyl bromoacetate (110 mmol), 15.9 g of sodium carbonate (150 mmol) and 10.9 mL of N-methylaniline (100 mmol) were dissolved in 150 mL of methanol. The reaction mixture was stirred under reflux until N-methylaniline was completely consumed (GC-MS analysis). Then the solution was filtered off, the solid residue was washed with ethyl acetate (2 × 50 mL) and the volatile compounds were removed in vacuum. The crude product was dissolved in 150 mL ethyl acetate and washed with water (3 × 100 mL) and brine (1 × 100 mL). The organic layer was dried over sodium sulfate, filtered and concentrated. Purification by column chromatography (PE:EE=20:1) yielded 15.2 g (85%) of the desired products as light yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$):δ (ppm) = 7.51 – 7.10 (m, 2H), 6.85 – 6.74 (m, 3H), 4.14 (s, 2H), 3.77 (s, 3H), 3.13 (s, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) = 171.6, 148.8, 129.2, 117.4, 112.3, 54.3, 51.9, 39.5. GS-MS analysis: (m/z) = 179.20, 120.16, 91.11, 77.08.

Methyl 2-((4-formylphenyl)(methyl)amino)acetate[1]



2.3 mL of phosphorous oxychloride (25 mmol) were added dropwise to 20 mL of dry DMF at 0 °C. After 30 min, 4.48 g of methyl 2-(methyl(phenyl)amino)acetate (25 mmol) were added to the reaction mixture, which was subsequently heated to 75 °C for 4h. Then the solution was cooled and poured into ice water (250 mL) with vigorous stirring overnight. The mixture was extracted with methylene chloride (3 × 50 mL) and the combined organic layers were washed with water (3 × 50 mL) and brine (1 × 50 mL) and finally dried over sodium sulfate. The solvent was evaporated and the crude product was purified by column chromatography (PE:EE=2:1) to yield 3.1 g (60%) of products as white solid. Mp: 75-78 °C. ^{1}H-NMR (200 MHz, $CDCl_3$): δ (ppm) = 9.68 (s, 1H), 7.66 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 4.09 (s, 2H), 3.66 (s, 3H), 3.07 (s, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ (ppm) = 190.39, 170.26, 153.34, 131.98, 126.34, 111.37, 53.84, 52.25, 39.65. GS-MS analysis: (m/z) = 207.28, 148.22, 118.20, 77.10.

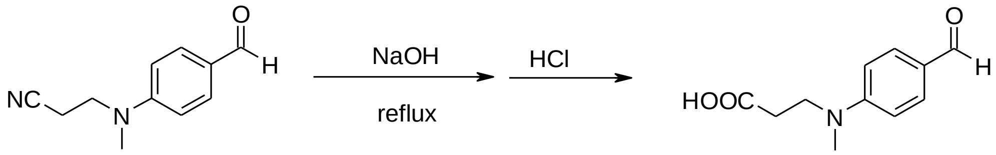
Sodium 2-((4-formylphenyl)(methyl)amino)acetate[2]



A mixture of 1 g of methyl 2-((4-formylphenyl)(methyl)amino)acetate (4.82 mmol) and 0.6 g of NaOH powder (15 mmol) in 20 mL of EtOH was stirred overnight at room temperature. The solvent was removed in vacuum and the crude product was used directly for the next step without further purification. ^{1}H-NMR (200 MHz, D_2O): ^{1}H NMR (200 MHz , D_2O) δ (ppm) = 9.29 (s, 1 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 6.53 (d, *J* =

8.8 Hz, 2 H), 3.82 (s, 2 H), 2.93 (s, 3 H) . ^{13}C NMR (50 MHz , D_2O) δ (ppm) = 193.4, 177.6, 154.7, 132.8, 123.5, 111.0, 56.0, 38.9.

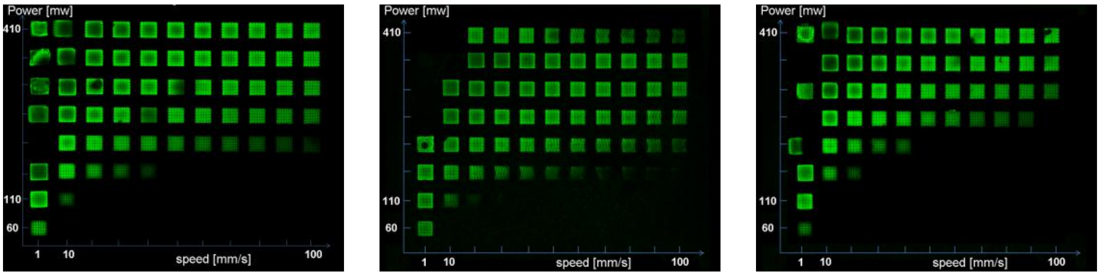
3-[(4-Formyl-phenyl)-methyl-amino]-propionic acid[3]



Sodium hydroxide (140 mmol, 5.6 g) and 3-((4-formylphenyl)-(methyl)-amino) propanenitrile (47.8 mmol, 9 g) were dissolved in 200 mL of water. The reaction mixture was refluxed for 5 h, then cooled and filtrated. A dilute HCl solution was added dropwise into the filtrate under stirring until no precipitate formed. Precipitate was collected, washed with water (3 × 150 mL) and dry to yield the product (90%) as orange solid. Mp: 125-127 °C. ^{1}H NMR (200MHz, DMSO-d_6) δ = 12.35 (bs, 1H), 9.66 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 2 H), 3.68 (t, *J* = 7.1 Hz, 2 H), 3.00 (s, 3 H). The peak of two protons in CH_2 overlaps with that of DMSO. ^{13}C NMR (50MHz, DMSO-d_6) δ = 188.7, 171.8, 151.8, 130.5, 123.5, 109.9, 46.3, 36.9, 30.2.

The sodium salt precursor was obtained by neutralizing the propionic acid with NaOH aqueous solution before starting the aldol condensation.

2. Processing Windows of TPA PIs



(a) (b) (c)

Figure S1. Processing Windows of PIs with different feed rate and laser power. (a) **E2CK**; (b) **G2CK**; (c) **P2CK**

References

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(2) Kim, H. M.; Choo, H. J.; Jung, S. Y.; Ko, Y. G.; Park, W. H.; Jeon, S. J.; Kim, C. H.; Joo, T. H.; Cho, B. R. *Chembiochem* **2007**, *8*, 553-559.

(3) Yang, W.; Zou, Q. L.; Zhou, Y.; Zhao, Y. X.; Huang, N. Y.; Gu, Y.; Wu, F. P. *Journal of Photochemistry and Photobiology a-Chemistry* **2011**, *222*, 228-235.