Electronic Supplementary Material (ESI) for Lab on a Chip


# Efficient and continuous monoacylation with superior selectivity of symmetrical diamines in microreactor

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**General:** Sylgard 184 silicone elastomer (dimethyl siloxane oligomer) and curing agent were purchased from Dow Corning (Midland, MI, USA). PFA tubing (id = 500 micron) and T-shaped micromixer were purchased from Upchurch Scientific. Unless otherwise specified, all reagents and chemicals were purchased from Sigma-Aldrich and were used as such without further any purification. Common solvents were purchased from Daejung Chemicals. $^{1}H$ NMR and $^{13}C$ NMR spectra were recorded on a JEOL JNM-AL 400 spectrometer. Proton (400 MHz) and carbon (100 MHz) chemical shifts are reported in ppm ( $\delta$ ) relative to TMS as internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet and doublet dt = doublet and triplet, m = multiplet, quint = quintet), coupling constants (Hz) and integration. PHD 2000 HARVARD infuse/withdraw syringe pumps, glass syringes, JAC Ultrasonic (330W), PFA tubing and T-shape micromixer (Upchurch Scientific) were used for experiments. All the compounds were known and were characterized by comparing their $^{1}H$ and $^{13}C$ NMR spectra with literature values.

**Continuous capillary microreactor experiments:** In our experiments, we took T- shaped micromixers where due to the channel bends the laminar flow is disturbed, vortices are generated, and first transient effects are observed, which dramatically enhance the mixing quality.[1] In order to further enhance mixing, the T-micromixer and tubing were immerged in an ultrasonic bath. The typical schematic diagram of reaction set-up in microreactor is shown in figure 1. A PFA capillary microreactor (inner diameter = 500μm) was used for this study.

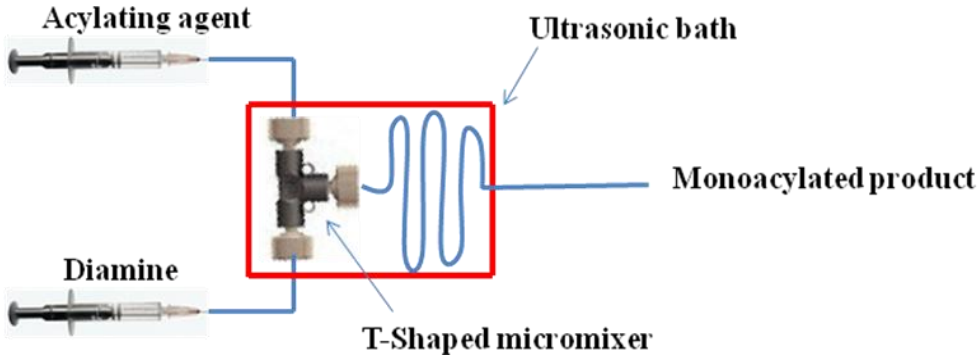



**Figure 1.** Length of capillary micrreactor dipped in ultrasonic bath(330W) = 50 cm (effective volume = 0.098 ml); length of capillary microreactor outside ultrasonic bath = 10 cm

**Fabrication of the microchannel for droplet generation and merging experiment:** The microfluidic devices for droplet generation and merging were fabricated using the facile non-lithographic embedded template method, as developed by our own group.[2] Briefly a framework for channel formation was assembled using commercially available tubing. All the tubings were purchased from Upchurch Scientific (Oak Harbor, WA). A perfluoralkoxyalkane (PFA) tubing (OD 1.5mm, ID ~508 μm) was connected to both the ends of a polyetherether ketone (PEEK) tubing with an OD of ~510 μm. For creation of the perpendicular side channels for injection, PEEK (OD 360μm, ID 100μm) were connected with the surface of PEEK tubing. This scaffold was then placed on the double sided tape (3M, St. Paul, MN) and subsequently a mixture of PDMS pre-polymer and curing agent (10:1) was poured in a Petri dish and cured at 60°C for several hours.

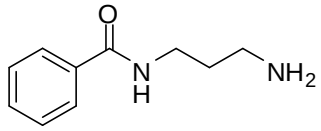
**Typical experimental procedure for monoacylation of symmetrical diamines with acid chloride in microreactor under ultrasonic irradiation in glacial AcOH:** The T-micromixer and microreactor tubing were immerged in an ultrasonic bath (330W). Acid chloride (1 mmol in 20 ml of glacial AcOH) and diamine (1 mmol in 20 ml of glacial AcOH) were taken in separate syringe and pumped through a syringe pump. The temperature of ultrasonic bath was set to 60 $^{0}$C. After completion, the reaction mixture was evaporated to dryness to yield crude. The crude was stirred with 30 ml of concentrated ammonia for 2 h then it was extracted with dichloromethane (25 ml x 6). The dichloromethane layer was dried over anhydrous $MgSO_4$ and concentrated to yield crude which was purified by silica-gel column chromatography using methanol/chloroform as eluent with increasing polarity to yield the desired monoacylated product.

**Typical experimental procedure for monoacylation of symmetrical diamines with N-hydroxy succinimide esters in microreactor under ultrasonic irradiation:** The T-micromixer and microreactor tubing were immerged in an ultrasonic bath (330W). N-hydroxy succinimide ester (1 mmol in 20 ml of methanol) and symmetrical diamine (1 mmol in 20 ml of methanol) were taken in separate glass syringes and pumped by a syringe pump with flow rate of 200 μL/min. Ultrasonic irradiation resulted to increase in the temperature of ultrasonic bath hence the temperature of ultrasonic bath was maintained below 25 $^{0}$C by addition of ice at certain intervals. The reaction mixture was collected in 20 ml of 0.1N HCl. After completion the resulting methanol-water solution was concentrated, basified with ammonia and extracted with dichloromethane (15 ml x 6). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure to yield crude which was purified by silica-gel column chromatography using methanol/chloroform as eluent in increasing polarity to yield the desired products.

**Typical experimental procedure for mono acylation of diamines with PhCOSu in flask:** Diamine (1 mmol in 20 mM in MeOH) was placed in a round bottom flask and PhCOSu (1 mmol in 20 ml MeOH) was added drop-wise to it over a period of 90 min. The reaction mixture was further stirred for 30 min at room temperature. The products were isolated and purified as aforementioned.

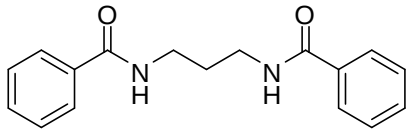
**$^{1}$H and $^{13}$C NMR data of compounds**

**N-(3-aminopropyl)benzamide (3aa):**



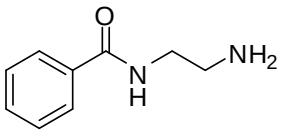
$^{1}$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.70-1.78 (m, 2H), 2.69-2.84 (m, 2H), 3.26-3.43 (m, 2H), 4.67 (bs, 2H), 7.38-7.48 (m, 3H), 7.88 (d, J = 7.32 Hz, 2H), 8.86 (s, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 31.45, 39.31, 40.71, 126.99, 128.52, 131.40, 134.34, 167.82.

**N,N'-(propane-1,3-diyl)dibenzamide (4aa):**



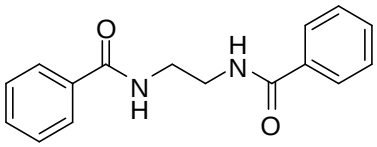
$^{1}$H NMR ($CDCl_3$ + DMSO-$d_6$, 400 MHz) δ: 1.83 (qui, J = 6.10 Hz, 2H), 3.50 (dd, J = 6.10 & 12.20 Hz, 4H), 7.40-7.51 (m, 6H), 7.90 (d, J = 7.32 Hz, 4H), 8.12 (s, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 29.59, 37.68, 127.40, 128.29, 131.08, 134.61, 166.37.

**N-(2-aminoethyl)benzamide (3ba):**



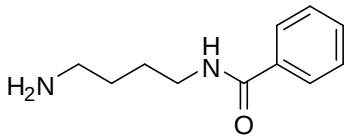
$^{1}$H NMR ($CD_3OD$, 400 MHz) δ: 2.80 (t, J = 6.59 Hz, 2H), 3.42 (t, J = 6.59 Hz, 2H), 4.79 (s, 3H), 7.37-7.50 (m, 3H), 7.79 (d, J = 7.07 Hz, 2H); $^{13}$C NMR ($CD_3OD$, 100 MHz) δ: 42.06, 43.58, 128.32, 129.54, 132.66, 135.67, 171.52.

**N,N'-(ethane-1,2-diyl)dibenzamide (4ba):**



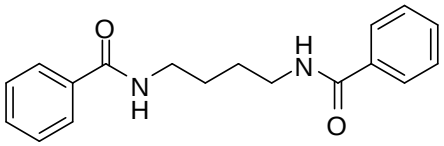
$^{1}$H NMR (DMSO-$d_6$, 400 MHz) δ: 3.44 (s, 4H), 7.37-7.52 (m, 6H), 7.84 (d, J = 7.01 Hz, 4H), 8.61 (s, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 38.99, 127.16, 128.23, 131.11, 134.46, 166.51.

**N-(4-aminobutyl)benzamide (3ca):**



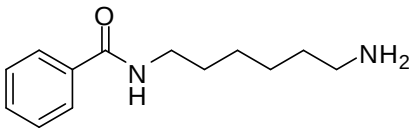
$^{1}$H NMR (DMSO-$d_6$, 400MHz) δ: 1.41-1.58 (m, 4H), 2.62 (t, J = 6.83 Hz, 2H ), 3.23-3.28 (m, 2H) 3.49 (bs, 2H), 7.42-7.53 (m, 3 H), 7.83-7.86 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 25.41, 26.42, 29.00, 40.52, 127.05, 128.13, 130.89, 134.60, 165.97.

**N,N'-(butane-1,4-diyl)dibenzamide (4ca):**



$^{1}$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.54-1.63 (m, 4H), 3.23-3.36 (m, 4H), 7.43-7.54 (m, 6H), 7.83-7.86 (m, 4H), 8.50 (s, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 26.67, 39.62, 127.04, 128.14, 130.92, 134.59, 166.05.

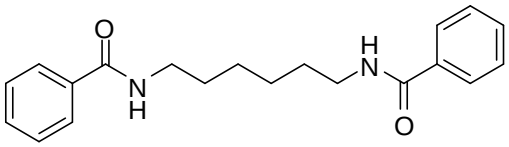
**N-(6-aminohexyl)benzamide (3da):**



$^{1}$H NMR ($CD_3OD$, 400 MHz) δ: 1.24-1.60 (m, 6H), 2.57-2.60 (m, 2H), 3.32-3.35 (m, 2H),

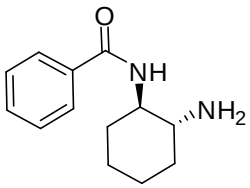
7.37-7.42 (m, 2H), 7.44-7.49 (m, 1H), 7.75-7.78 (m, 2H); $^{13}$CNMR ($CD_3OD$, 100 MHz) δ: 27.69, 27.91, 30.49, 33.64, 40.94, 42.44, 128.24, 129.54, 132.53, 135.92, 170.15.

**N,N'-(hexane-1,6-diyl)dibenzamide (4da):**



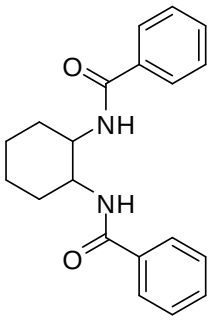
$^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.21-1.36 (m, 4H), 1.40-1.55 (m, 4H), 3.22-3.32 (m, 4H), 7.41-7.52 (m, 6H), 7.81-7.83 (m, 4H), 8.45 (s, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 26.18, 29.06, 39.42, 127.03, 128.14, 130.89, 134.64, 166.00.

**N-2-aminocyclohexyl)benzamide (3ea):**



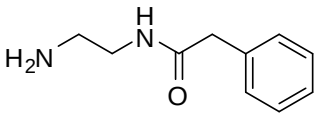
$^1$H NMR ($CDCl_3$, 400MHz) δ: 1.19-1.41 (m, 4H), 1.71-1.83 (m, 2H), 1.85 (s, 2H), 1.96-2.13 (m, 2H), 2.46-2.53 (m, 1 H), 3.67-3.75 (m, 1H), 6.43 (d, J = 8.04 Hz, 1H), 7.40-7.51 (m, 3 H), 7.80 (d, 7.07 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz,) δ: 25.06, 32.52, 35.50, 55.48, 56.63, 126.98, 128.52, 131.43, 134.71, 167.90.

**N,N'-(cyclohexane-1,2-diyl)dibenzamide (4ea):**



$^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 1.37-2.04 (m, 8H), 3.93-4.01 (m, 2H), 7.37-7.51 (m, 6H), 7.69-7.72 (m, 2H), 7.84-7.85 (m, 2H), 8.23 (s, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 24.91, 31.82, 53.30, 117.35, 128.74, 131.13, 135.10, 166.73.

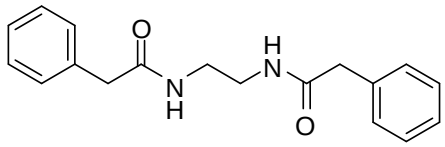
**N-(2-aminoethyl)-2-phenylacetamide (3bb):**



$^1$H NMR (DMSO-$d_6$, 400 MHz) δ 2.87-3.22 (m, 4H), 3.39 (s, 2H), 7.18-7.30 (m, 5H), 8.11 (s,

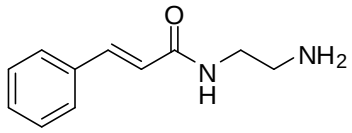
1H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 38.62, 41.34, 42.52, 126.42, 128.29, 129.12, 136.45, 169.50.

**N,N'-(ethane-1,2-diyl)bis(2-phenylacetamide) (4bb):**



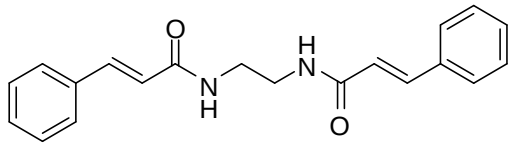
$^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 3.09 (d, J = 5.12 Hz, 4H), 3.38 (s, 4H), 7.19-7.31 (m, 10H), 8.07 (s, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 38.38, 42.32, 126.25, 128.12, 128.94, 136.26, 170.24.

**N-(2-aminoethyl)cinnamamide (3bc):**



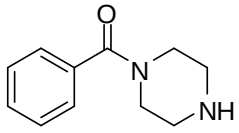
$^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.61 (bs, 2H), 2.89 (t, J = 5.85 Hz, 2H); 3.42 (dd, J = 5.85 & 11.70 Hz, 2H), 6.47 (d, J = 15.61 Hz, 1H), 6.73 (s, 1H), 7.31-7.35 (m, 3H), 7.45-7.50 (m, 2H), 7.60 (d, J = 15.61 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ , 37.51, 52.22, 120.37, 127.77, 128.71, 129.64, 134.65, 141.03, 165.94.

**(2E,2'E)-N,N'-(ethane-1,2-diyl)bis(3-phenylacrylamide) (4bc):**



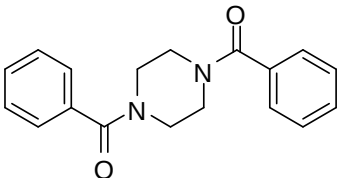
$^1$H NMR (DMSO-$d_6$, 400 MHz) δ: 3.37 (s, 4H), 6.58 (d, J = 15.61 Hz, 1H), 6.73 (s, 1H), 7.31-7.35 (m, 3H), 7.43-7.50 (m, 2H), 7.60 (d, J = 15.61 Hz, 1H), 8.28 (s, 2H); $^{13}$C NMR ($CDCl_3$ + DMSO-$d_6$, 100 MHz) δ: 28.33, 122.42, 127.86, 129.54, 129.67, 135.37, 139.41, 166.22.

**Phenyl(piperazin-1-yl)methanone (3fa):**



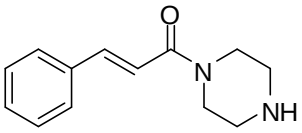
$^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.74 (s, 1H); 2.80-2.94 (m, 4H), 2.39-2.76 (m, 4H), 7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 43.15, 45.93, 46.44, 48.95, 126.97, 128.65, 129.61, 135.82, 170.41.

**piperazine-1,4-diylbis(phenylmethanone) (4fa):**



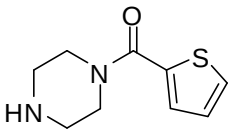
$^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 3.40-3.90 (m, 8H), 7.37-7.50 (m, 10H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 41.50, 47.45, 127.00, 128.59, 130.00, 135.10, 170.55..

**(E)-3-phenyl-1-(piperazin-1-yl)prop-2-en-1-one (3fe):**



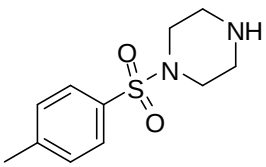
$^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1.94 (s, 1H); 2.87-2.91 (m, 4H), 3.63-3.71 (m, 4H), 6.87 (d, J = 15.4 Hz, 1H), 7.33-7.40 (m, 3H), 7.52-7.54 (m, 2H), 7.66 (d, J = 15.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 43.29, 45.89, 46.54, 47.09, 117.10, 127.70, 128.76, 129.56, 135.24, 142.64, 165.46.

**piperazin-1-yl(thiophen-2-yl)methanone (3ff):**



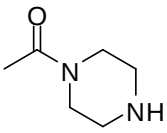
$^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1.96 (s, 1H), 2.86-2.88 (m, 4H), 3.68-3.71 (m, 4H), 7.02 (dd, J= 3.66 & 5.12 Hz, 1H), 7.26 (dd, J = 0.98 & 3.66 Hz, 1H), 7.37 (dd, J = 1.22 & 5.12 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 46.14, 126.61, 128.41, 129.16, 137.06, 163.41.

**1-tosylpiperazine (3fg):**



$^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (s, 1H), 2.43 (s, 3H), 2.90-3.08 (m, 8H), 7.32-7.35 (m, 2H), 7.59-7.65 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) δ: 21.50, 45.31, 46.88, 127.83, 129.60, 132.41, 143.61.

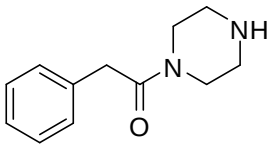
**1-(piperazin-1-yl)ethanone (3ff):**



$^{1}$H NMR ($CDCl_3$, 400 MHz) δ: 1.83 (s, 3H), 2.52 (s, 1H), 3.15-3.42 (m, 8H); $^{13}$C NMR

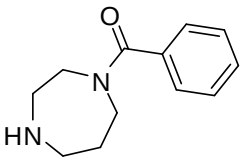
($CDCl_3$, 100 MHz) δ: 21.33, 42.18, 45.52, 46.13, 47.22, 169.17.

**2-phenyl-1-(piperazin-1-yl)ethanone (3fi):**



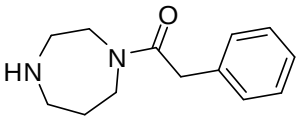

$^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.84 (s, 1H); 2.58-2.61 (m, 2H), 2.73-2.75 (m, 2H), 3.34-3.37 (m, 2H), 3.53-3.57 (m, 2H), 3.69 (s, 2H), 7.18-7.23 (m, 3H), 7.26-7.31 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 40.76, 42.82, 45.68, 46.00, 47.28, 126.61, 128.52, 135.12, 169.27.

**(1,4-diazepan-1-yl)(phenyl)methanone (3gd):**



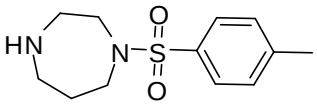

$^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.66 (m, 1H), 1.79-1.92 (m, 2H), 2.79-3.01 (m, 4H), 3.38-3.45 (m, 2H), 3.72-3.79 (m, 2H), 7.33-7.38 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 31.54, 45.15, 47.70, 48.40, 50.59, 126.36, 128.35, 129.15, 136.99, 171.58.

**1-(1,4-diazepan-1-yl)-2-phenylethanone: (3gi):**




$^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.65-1.78 (m, 2H), 2.32 (s, 1H), 2.73-2.92 (m, 4H), 3.36-3.63 (m, 4H), 3.72 (s, 2H), 7.21-7.33 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 30.80, 40.91, 44.91, 48.40, 49.91, 51.18, 126.68, 128.60, 128.71, 135.20, 170.63.

**1-tosyl-1,4-diazepane (gg):**




$^1$H NMR ($CDCl_3$, 400 MHz) δ: 1.79-1.89 (m, 2H), 2.42 (s, 3H), 2.83-2.96 (m, 4H), 3.29-3.39 (m, 4H), 7.29-7.31 (m, 2H), 7.63-7.69 (m, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ: 21.48, 31.13, 47.26, 50.08, 50.97, 51.50, 126.83, 129.82, 135.97, 143.52.

## References:

[1]. a) D. Bothe, C. Stemich and H.-J. Warnecke, *Chem. Eng. Sci*. 2006, **61**, 2950-2958;
(b) M. Hoffmann, M. Schluter and N. Rabiger, *Chem. Eng. Sci*. 2006, **61**, 2968-2976.

[2]. (a) A. Asthana, K. O. Kim, J. Perumal, D. M. Kim and D. P. Kim, *Lab Chip*, 2009, **9**, 1138–1142; (b) P. H. Hoang, C. T. Nguyen, J. Perumal, and Dong-Pyo Kim, *Lab Chip*, 2011, **11**, 329-335.