Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Selectivity Engineering of Meerwein Arylation in a Continuous Flow Reactor: A Modelling Approach

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Supporting Information

Reaction Mechanism

Dickerman et al. have proposed the following reaction mechanism for Meerwein Arylation.[1] In the first step aromatic amine reacts with hydrochloric acid and sodium nitrite to give corresponding diazonium salt (see Scheme 1S). The diazonium salt is unstable and decomposes to form phenol as one of the side products (Scheme 2S). The cuprous chloride dissolved in the hydrochloric acid solution forms $CuCl^{2-}$ complex which further reduces diazonium ion to generate aryl radical and cupric chloride as a by-product (Scheme 3S). The cupric chloride acts as a trapping agent for aryl radical to form Sandmeyer (Scheme 4S) and Reduction (Scheme 5S) side products. The aryl radical can react with the unsaturated substrate to form an arylated product which is the desired reaction (scheme 6S)

$$\mathrm{ArNH_2 + 2HCl + NaNO_2 \longrightarrow ArN_2^+Cl^- + NaCl + 2H_2O}$$

Scheme 1S. Diazotization of aniline substrate

$$\mathrm{ArN_2^+Cl^- + H_2O \xrightarrow{k_d} ArOH + HCl + N_2}$$

Scheme 2S. Decomposition reaction

$$\mathrm{CuCl_{(s)} + Cl^-_{(aq)} \rightleftharpoons [CuCl_2]^-_{(aq)}}$$

$$\mathrm{ArN_2^+ + CuCl_2^- \xrightarrow{k_1^*} ArN{=}N^\bullet + CuCl_2}$$

$$\mathrm{ArN{=}N^\bullet \xrightarrow{k_2^*} Ar^\bullet + N_2}$$

Scheme 3S. Aryl radical formation

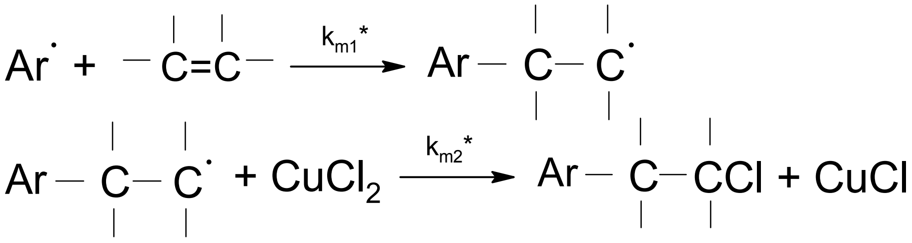
$$\mathrm{Ar^\bullet + CuCl_2 \xrightarrow{k_s^*} ArCl + CuCl}$$

Scheme 4S. Sandmeyer reaction

$$\mathrm{Ar^\bullet + CH_3COCH_3 \xrightarrow{k_{r1}^*} ArH + {}^\bullet CH_2COCH_3}$$

$$\mathrm{{}^\bullet CH_2COCH_3 + CuCl_2 \xrightarrow{k_{r2}^*} ClCH_2COCH_3 + CuCl}$$

Scheme 5S. Reduction reaction



$$\mathrm{Ar^\bullet + {-}C{=}C{-} \xrightarrow{k_{m1}^*} Ar{-}C{-}C^\bullet}$$

$$\mathrm{Ar{-}C{-}C^\bullet + CuCl_2 \xrightarrow{k_{m2}^*} Ar{-}C{-}CCl + CuCl}$$

Scheme 6S. Meerwein arylation

Batch Experiments

Batch experiments were performed to generate kinetic data. Experiments were conducted in the glass jacketed reactor with a volume of 125 mL or 50 mL with magnetic stirring. The reaction generates nitrogen gas which causes froth or foam which rises inside the reactor. Hence reaction mixture was always less than 45% of the reactor volume to avoid overflow of the reaction mixture. Temperature sensors (Pt-100) were used inside the reactor to monitor the temperature continuously for all experiments. Mixing time experiments were performed to ensure that the experiments are in the kinetically controlled regime.

Meerwein Arylation Batch Kinetics

Initially, diazotization reaction was done in semi-batch mode by adding 1.53 M sodium nitrite solution (1.1 equiv.) at a constant flow rate for ~30 min to a solution of 3, 4-dichloroaniline (1 equiv.) dissolved in 11.27 M hydrochloric acid (4 equiv.) and acetone (11 equiv.) mixture in the batch reactor. The temperature inside the reactor was maintained in the range of 0^0C – 5^0C by circulating coolant in the jacket side which was connected to the thermostat (Julabo). After the addition of sodium nitrite, methacrylic acid (3 equiv.) was added and the temperature was raised to the desired set-point value and 1.34 M CuCl solution (0.05 equiv. – 0.1 equiv.) in hydrochloric acid and water was added to the reactor in one shot. Samples were taken at regular intervals by micropipette and were immediately quenched with a solution of 0.23 M beta-Naphthol and 1.89 M sodium hydroxide. The quenched sample was further diluted with acetone and water mixture and HCl was added to adjust the pH in the range of 0.7-0.9. The sample was further analyzed using HPLC.

Batch Equation for Meerwein Arylation Kinetics Estimation

The kinetic parameters were estimated using nonlinear regression. Equations (1S)-(4S) are the mass balance equations of the diazonium salt, methacrylic acid, Meerwein product, and the side product. These equations were solved using ode45 solver in MATLAB coupled with lsqcurvefit to estimate the kinetic parameters. The input data for the above analysis were the time vs. concentration data obtained from the kinetic experiments. The concentration of the side product was calculated according to the mass balance equation (5S).

$$\frac{dC_d}{dt} = -k_M C_d C_m - k_S C_d \tag{1S}$$

$$\frac{dC_m}{dt} = -k_M C_d C_m \tag{2S}$$

$$\frac{dC_p}{dt} = k_M C_d C_m \tag{3S}$$

$$\frac{dC_s}{dt} = k_S C_d \tag{4S}$$

$$C_{A0} = C_d(t) + \; C_P(t) + C_S(t) \tag{5S}$$

Where,

C_{A0} = Initial concentration of 3,4-dichloroaniline in mol/L

C_d = Concentration of diazonium salt in mol/L

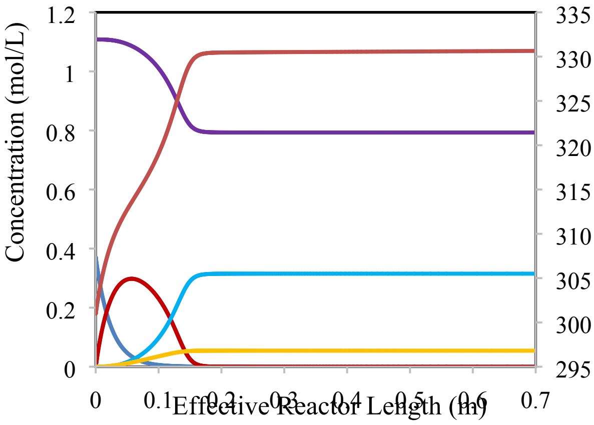
C_m = Concentration of Methacrylic acid in mol/L

C_P = Concentration of the Meerwein product in mol/L

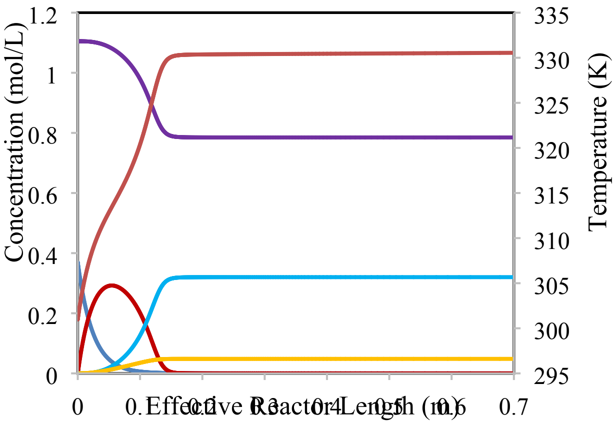
C_S = Concentration of the lumped side product in mol/L

Concentration and Temperature Profiles

The nonisothermal model was validated using experimental data. Figure 1S (a)-(i) shows the predicted concentration and temperature profiles. Simulation were performed for over a range of catalyst concentrations (1 mol% – 10 mol%), temperature (60^0C – 70^0 C) and the mole ratio of methacrylic acid (3 equiv. – 5 equiv.). It can be clearly seen from figure 1S that the temperature is nonisothermal for all the conditions. Since diazotization and Meerwein arylation are both exothermic and fast and are taking place simultaneously, the temperature does not remain isothermal. It can also be seen that for 1% CuCl, 2 % CuCl and 3 % CuCl the diazonium salt is relatively greater compared to 5% CuCl. Moreover, for 10% CuCl the diazonium salt instantaneously reacts to form Meerwein product and side products.


Concentration (mol/L)
Temperature (K)
Effective Reactor Length (m)
0
0.2
0.4
0.6
0.8
1
1.2
295
300
305
310
315
320
325
330
335
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7

(a)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Temperature (K)
Effective Reactor Length (m)
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295
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305
310
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320
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330
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0
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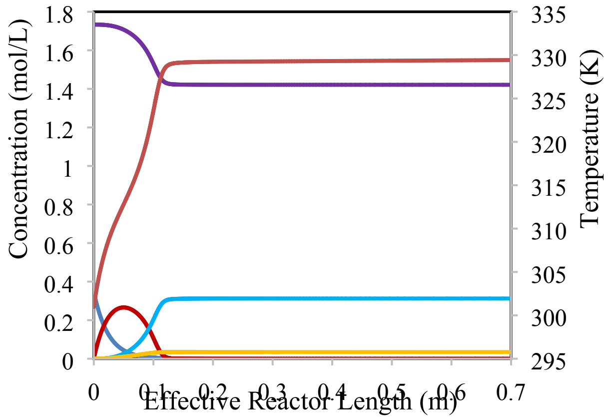
(b)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Temperature (K)
Effective Reactor Length (m)
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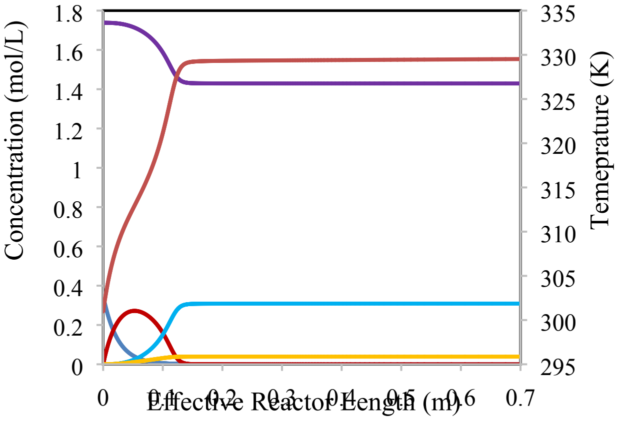
(c)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Temeprature (K)
Effective Reactor Length (m)
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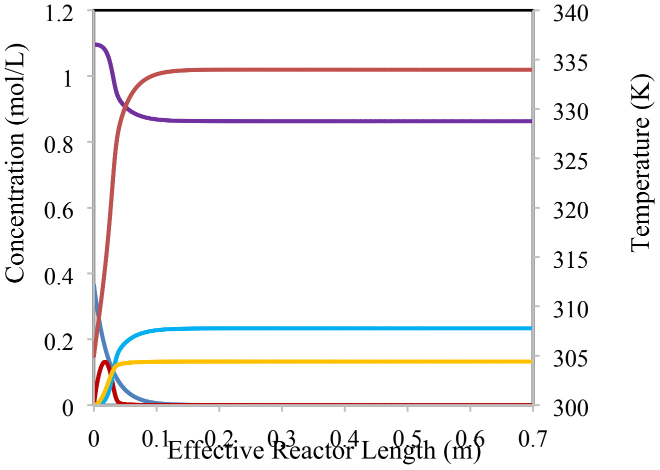
(d)


Concentration (mol/L)
Temperature (K)
Effective Reactor Length (m)
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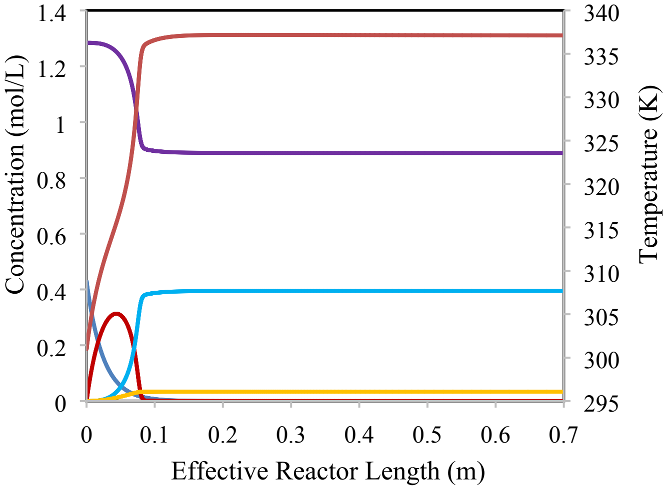
0.2
0.4
0.6
0.8
1
1.2
300
305
310
315
320
325
330
335
340
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7

(e)


Concentration (mol/L)
Temperature (K)
Effective Reactor Length (m)
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0.4
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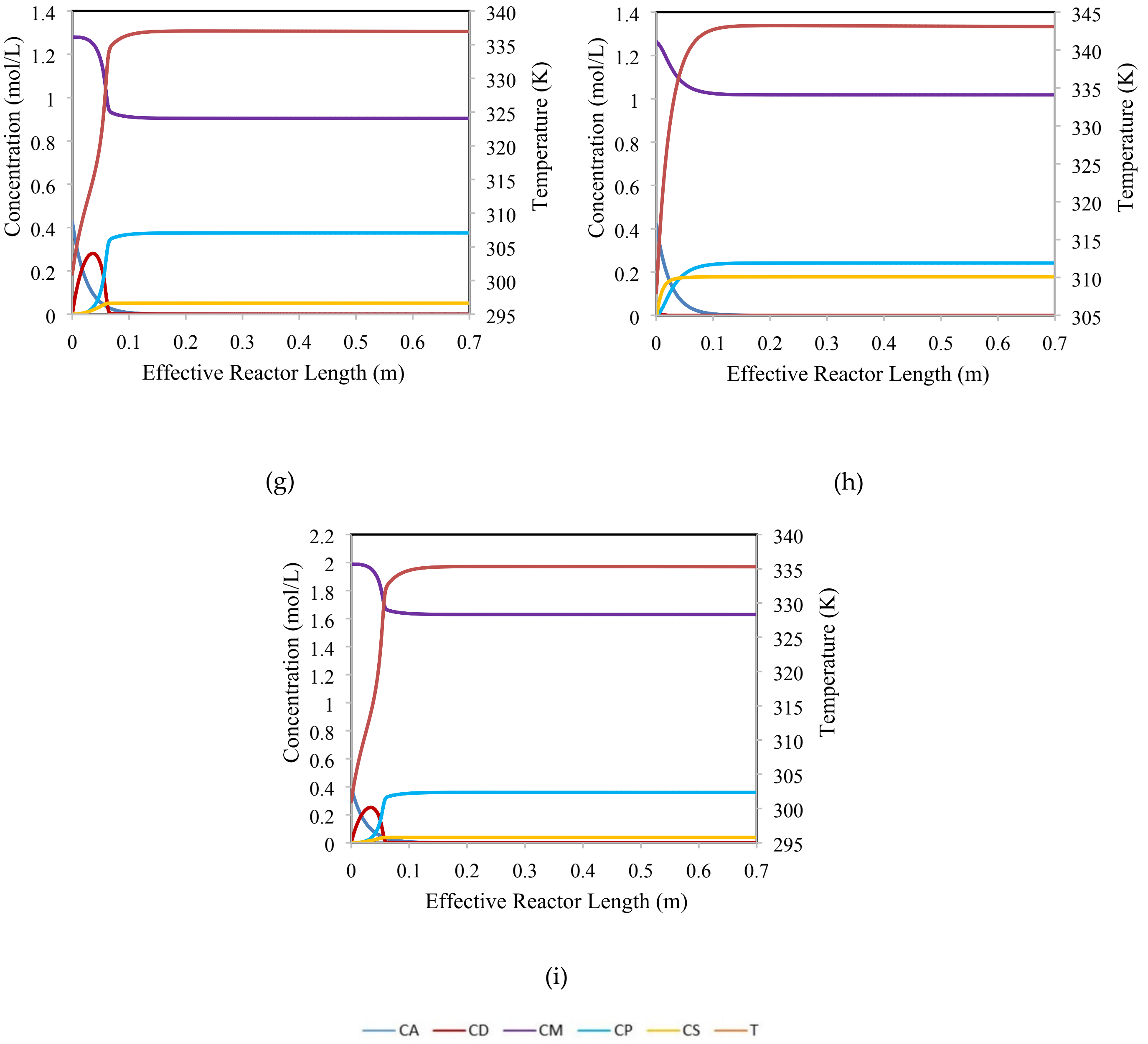
(f)



(g)

(h)

(i)

Figure 1S. Concentration and temperature profiles. (a) Experiment No: 1 (1% CuCl, T_W = 70^0C, 3 equiv. MAA & C_0 = 0.36 M), (b) Experiment No: 2 (2% CuCl, T_W = 70^0C, 3 equiv. MAA & C_0 = 0.36 M), (c) Experiment No 3 (2% CuCl, T_W = 70^0C, 5 equiv. MAA & C_0 = 0.34 M), (d) Experiment No 4 (1% CuCl, T_W = 70^0C, 5 equiv. MAA & C_0 = 0.34 M), (e) Experiment No 5 (5% CuCl, T_W = 60^0C, 3 equiv. MAA & C_0 = 0.37 M), (f) Experiment No 6 (2% CuCl, T_W = 60^0C, 3 equiv. MAA & C_0 = 0.43 M), (g) Experiment No 7 (% CuCl, T_W = 60^0C, 3 equiv. MAA & C_0 = 0.43 M), (h) Experiment No 8 (10% CuCl, T_W = 60^0C, 3 equiv. MAA & C_0 = 0.42 M) and (i) Experiment No 9 (3% CuCl, T_W = 60^0C, 5 equiv. MAA & C_0 = 0.40 M)

Effect of Initial Concentration and Inlet Temperature

The non-isothermal model was used to study the effect of inlet temperature and initial concentration on the yield of the desired product for various catalyst concentrations. Simulations were performed for the initial concentration range of 0.2 M to 0.4 M and inlet temperature range of 298 K to 308 K. The reactor wall temperature and residence time were kept constant at 333 K and 30 s for all the simulations. Figure 2S (a)-(e) shows the yield of Meerwein Arylation for various inlet temperatures, initial concentration, and catalyst quantities. The desired product yield for 1% CuCl, 2% CuCl, 3% CuCl, 5% CuCl and 10% CuCl were in the range of 21.36% – 94.35%, 25.93% – 95.01%, 32.90% – 92.15%, 13.29% – 75.67% and 4.26% – 54.89% respectively. For 1% CuCl and 2% CuCl the diazonium salt was not completely consumed for concentrations below 0.3 M at low temperatures resulting in lower yield. For 3% CuCl, the diazonium salt remained unreacted below 0.25 M initial concentration at low temperatures. Further increasing the residence time can increase the yield however selectivity will largely depend on temperature and catalyst concentration. For 5% CuCl and higher catalyst concentration the Meerwein arylation rate was much higher and diazonium salt was completely consumed even for dilute concentration i.e. 0.2 M and low temperatures. It was observed that for 1% CuCl, 2% CuCl and 3% CuCl the average deviation in the yield was 20.08, 18.60 and 15 at 298 ^{0}K inlet temperature, indicating that the yield is highly sensitive towards concentration at low temperatures. At 308 K the average deviation was 6.29, 5.56 and 7.08 respectively for 1%, 2%, and 3% CuCl indicating that the yield is relatively less sensitive towards concentration for higher temperatures. For 5% CuCl, the average deviation in yield is relatively constant (12.55 for 298 K and 11.39 for 308 K) indicating that the yield is equally sensitive towards concentration for all the temperatures. In the case of 10% CuCl, the average deviation in the yield were 8.11 and 11.42 for 298 K and 308 K respectively.

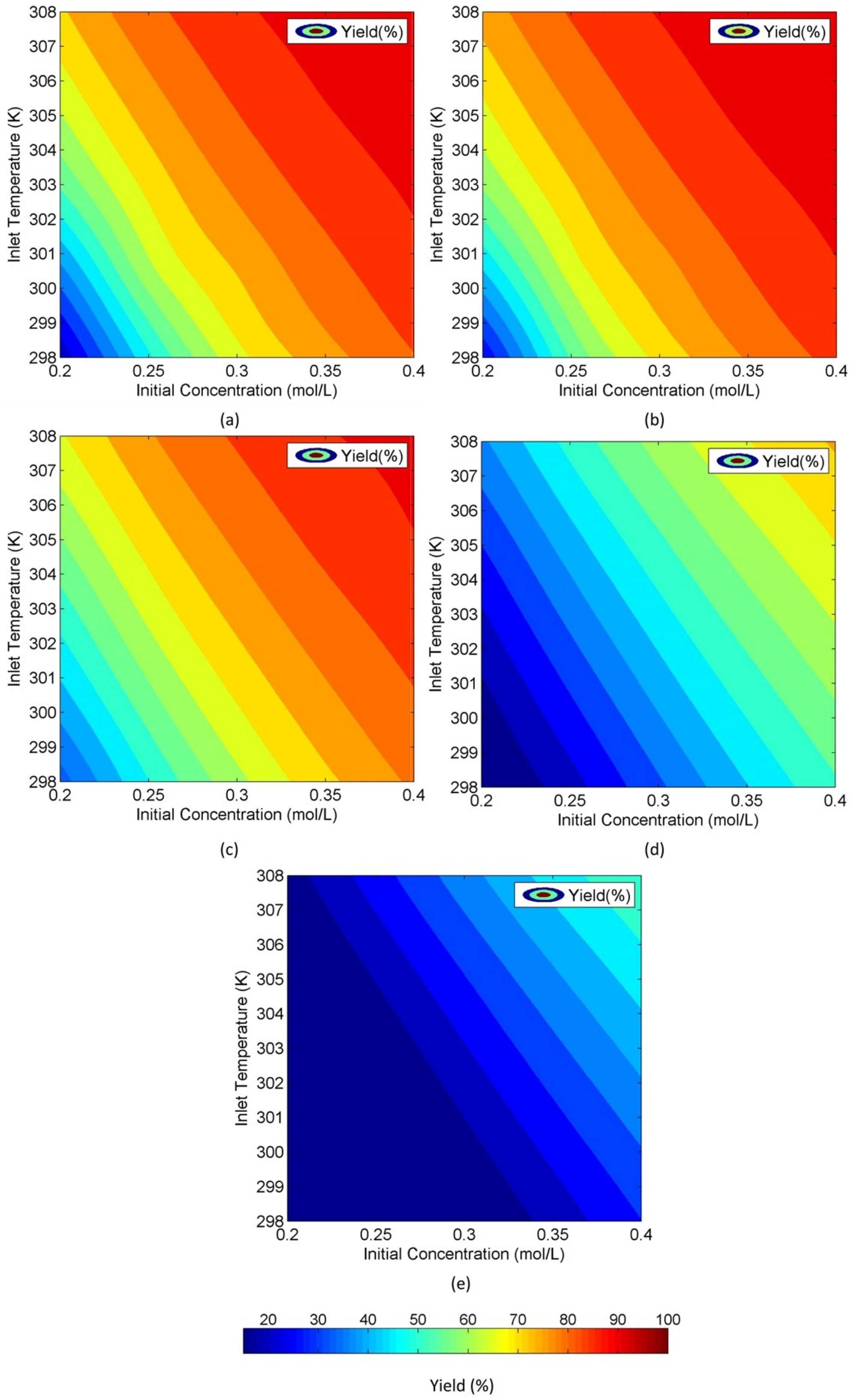
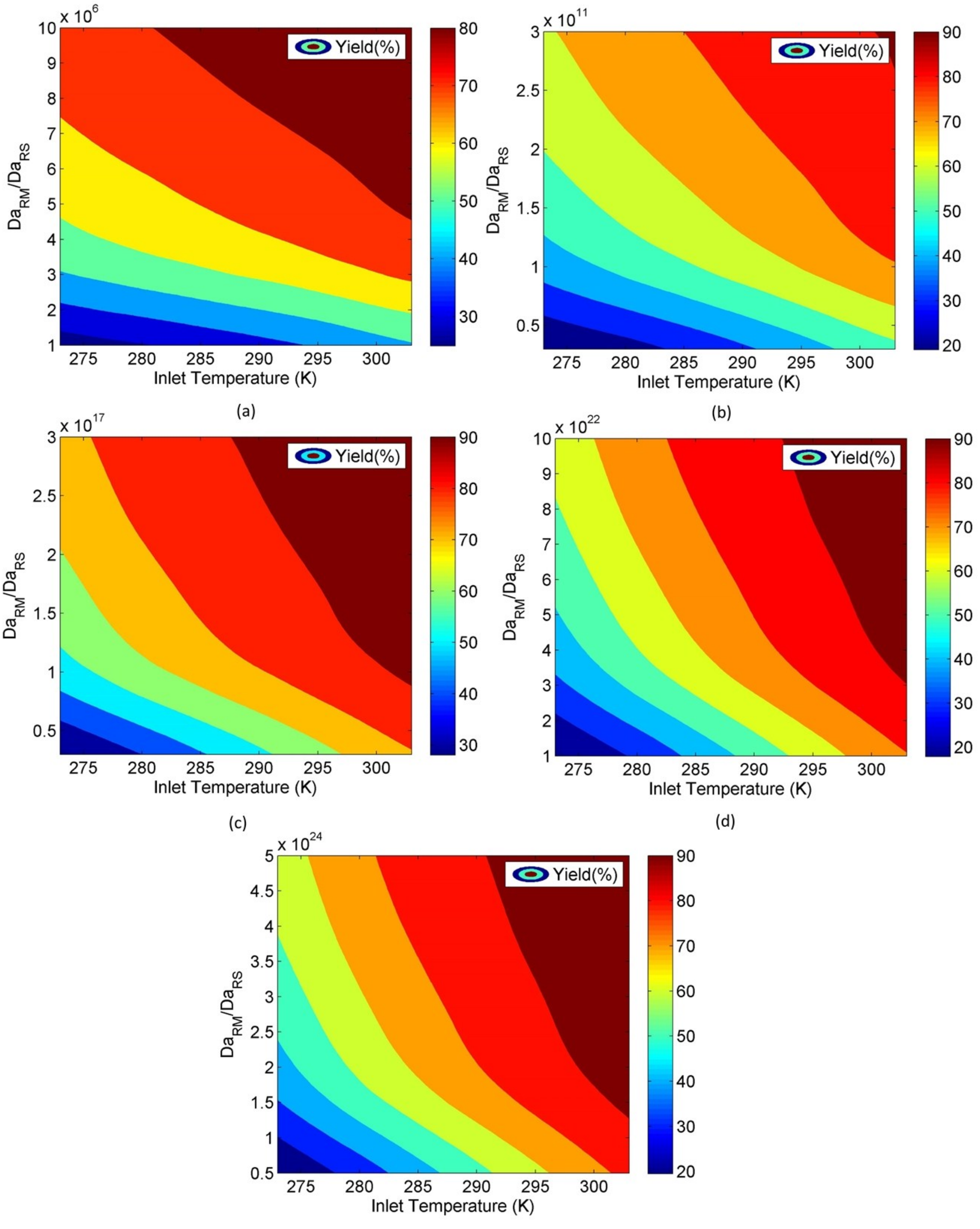


Figure 2S. Effect of initial concentration and inlet temperature on Product yield. (a) 1% CuCl, (b) 2% CuCl, (c) 3% CuCl, (d) 5% CuCl and (e) 10% CuCl.

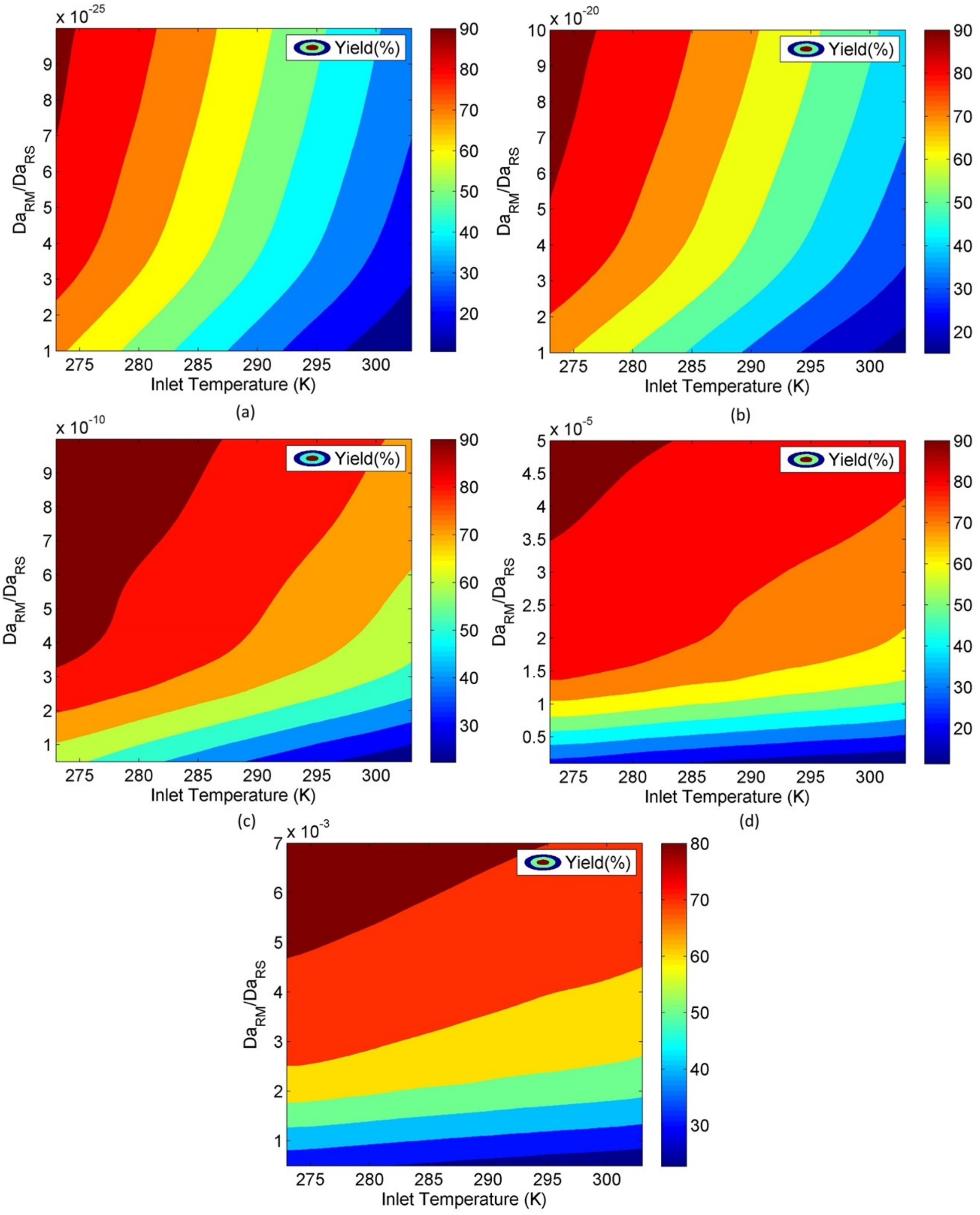
Application for Non-isothermal Model for Generalized Meerwein Arylation

Using nondimensional numbers is advantageous in finding suitable operating conditions for any reactions. Since the dimensionless numbers are the ratios of relative time scales like mixing, heat transfer, reaction time scale, etc. the generalized results can be extended for any reactive systems. Here we have used the non-isothermal model for studying the effect of various parameters and/or operating variables, viz. inlet temperatures, the ratio of Damkholer numbers of the desired and undesired reactions, mole ratio, and the relative values of the activation energies on the yield of the desired product. The simulation results are shown as a contour plot, which can be further used for identifying suitable operating conditions for any Meerwein arylation reaction. Since the selectivity of any reaction and the favourable choice of operating conditions will depend on the relative values of the kinetic parameters (activation energy and frequency factor) of the desired and undesired reactions, we have divided our study into three categories viz. (1) $E_M > E_S$ (Figure 3S), (2) $E_M < E_S$ (Figure 4S) and (3) $E_M \approx E_S$ (Figure 5S). In the case study section, two examples were discussed for $E_M > E_S$. If the ratio of E_M/E_S is different than the simulated results given in Figure 3S (i.e. 3.5, 3, 2, 1.5 and 1.25) one can select the average value of the operating conditions or refer the contour plot for higher E_M/E_S ratio. Figure 4S shows the yield contour plots for the case of $E_M<E_S$. Since the activation of Meerwein arylation is lower than the lumped side reactions, the side reaction rate is more sensitive towards temperature. In such cases (Figure 4S), lower temperature is favorable for the better selectivity of Meerwein arylation. Figure 5S shows the yield contour plot for the case $E_M = E_S$. In such cases, the temperature will have a negligible impact on selectivity as both reaction rates are equally sensitive towards temperature. Enhancing the selectivity for such reaction will depend on the monomer mole ratio and Da_{RM}/Da_{RS} ratio (i.e. catalyst quantity and initial aniline concentration).



(a) (b) (c) (d) (e)

Figure 3S. Yield contour plots for $E_M>E_S$, E_M = 200 kJ/mol, Da_M = 5.49, Da_{RM} = 10^{35}, ΔH = -125 kJ/mol, h = 150 W/(m.K), τ = 5.5 min, L_{eff} = 1 m, d = 0.002 m, mole ratio = 3, T_0 = T_W. (a) E_M/E_S = 1.25, (b) E_M/E_S = 1.5, (c) E_M/E_S = 2, (d) E_M/E_S = 3 and (e) E_M/E_S = 3.5.



(a) (b) (c) (d) (e)

Figure 4S. Yield contour plots for $E_M<E_S$ and E_M = 57 kJ/mol, Da_M = 5.49, Da_{RM} = 10^{35}, ΔH = -125 kJ/mol, h = 150 W/(m.K), τ = 5.5 min, L_{eff} = 1 m, d = 0.002 m, mole ratio = 3, T_0 = T_W. (a) E_M/E_S =0.28, (b) E_M/E_S = 0.33, (c) E_M/E_S = 0.5, (d) E_M/E_S = 0.66 and (e) E_M/E_S = 0.8.

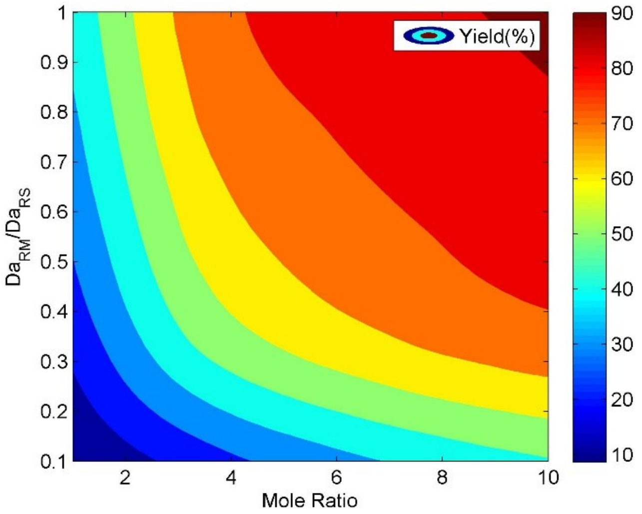


Figure 5S. Yield contour plots for $E_M = E_S$ and $E_M = 57$ kJ/mol, $Da_M = 5.49$, $Da_{RM} = 10^{35}$, $\Delta H = -125$ kJ/mol, h = 150 W/(m.K), $\tau = 5.5$ min, $L_{eff} = 1$ m, d = 0.002 m, $T_0 = T_W = 273$ K

HPLC Method

HPLC analysis was used for the quantification of analytes for the kinetics experiments. Gradient method was used for quantifying methacrylic acid, Meerwein product and azo dye product (obtained after quenching diazonium salt with beta-naphthol & sodium hydroxide). Phosphate buffer with pH = 6.9 (sodium dihydrogen phosphate dehydrate & disodium hydrogen phosphate dodecahydrate), acetonitrile and water were used as mobile phase in a C18 column. The gradient method is given below in table 1S. Figure 6S shows the calibration plot for the analytical substrates.

Table 1S. Gradient method for HPLC

Time (min)	**Volume %** **Buffer: Acetonitrile: Water**	**Wavelength (nm)**
0-5	62:38:0	225
6	0:20:80	450
8-17	0:100:0	
18	0:50:50	
20	62:38:0	

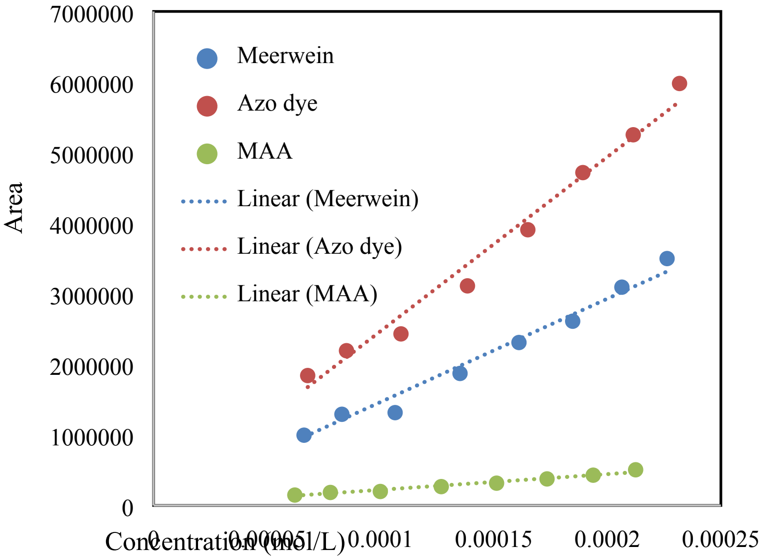


Figure 6S. Calibration chart for methacrylic acid, Meerwein product and azo dye of 3, 4 dichloroaniline.

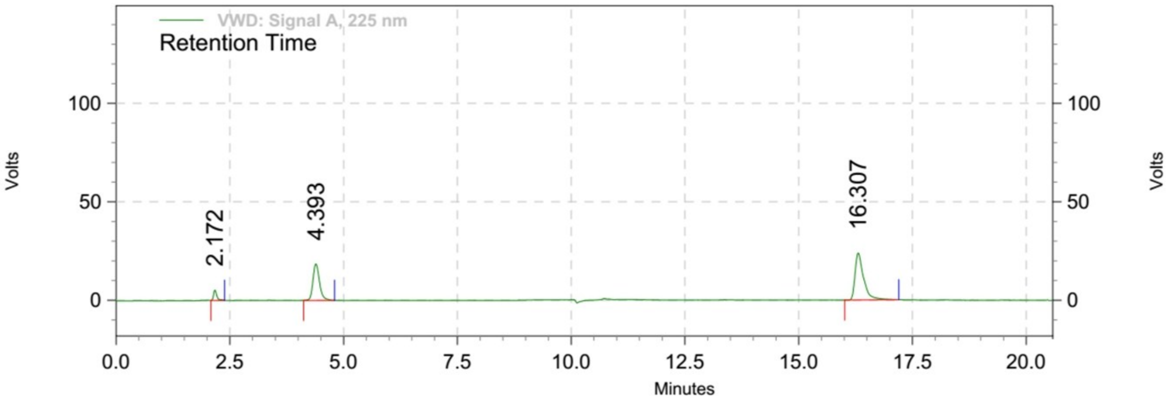
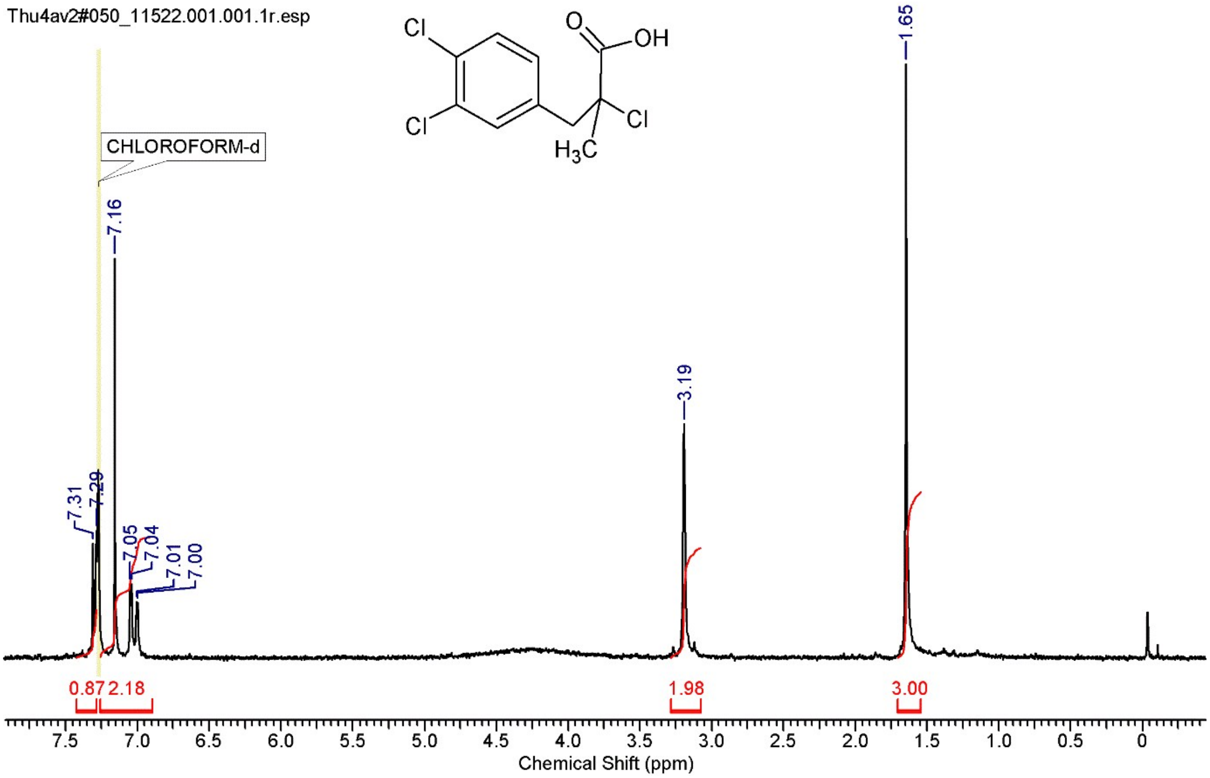


Figure 7S. HPLC results for methacrylic acid, Meerwein product and azo dye of 3, 4 dichloroaniline.

Product NMR Spectra



Spectral Data of (2-(3,4-dichlorobenzyl)-2-chloropropanoic acid)

Orange colour- ^{1}H -NMR (200 MHz, $CDCl_3$)-delta ppm; 1.65 (s,3H); 3.19 (s,2H); 7.2 (m,3H).

References

1. S. Dickerman, K. Weiss and A. Ingberman, *J. Org. Chem.*, 1956, **21**, 380-381.