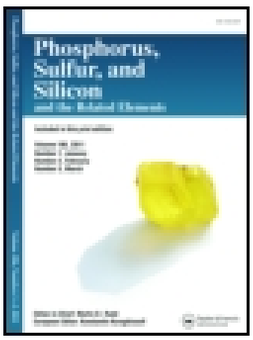

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Reaction Pathway of $POCl_3$-Mediated Knoevenagel Condensation of Bisulfite Adducts with 2,4-Thiazolidinedione

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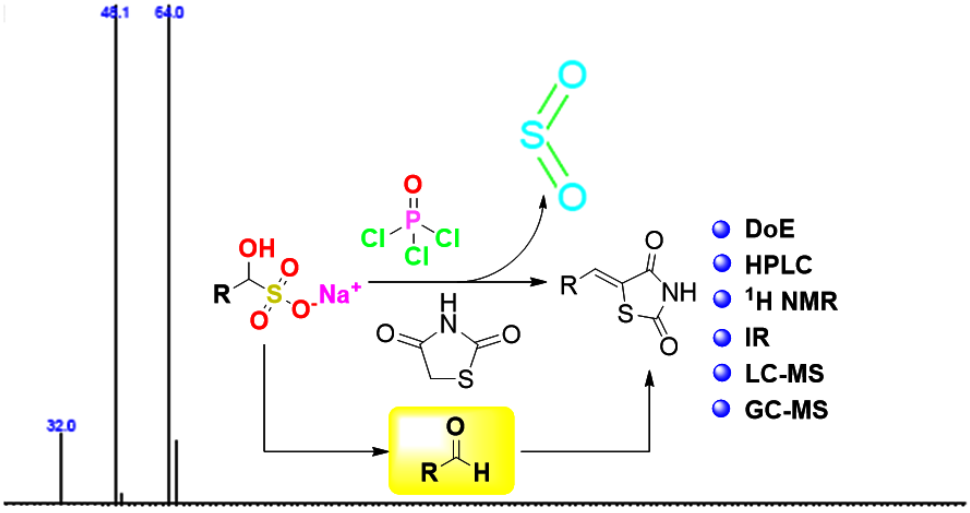
Abstract:

We investigated the $POCl_3$-mediated transformation of aromatic bisulfite adducts to the corresponding 5-arylidenethiazolidine-2,4-diones. The in situ transformation of an aromatic bisulfite adduct to the parent aldehyde in a non-aqueous non-polar solvent (toluene) was demonstrated using DoE (Design of experiment), off-line ^1H NMR, on-line ReactIR, HPLC, LC-MS, and GC-MS. By means of these analytical tools, we determined, for the first time, the structure of the intermediate species (aldehyde) prior to the carbon–carbon double bond

formation. The carbon–sulfur bond undergoes a fast cleavage, immediately after the addition of $POCl_3$, which finally affords the corresponding 5-arylidenethiazolidine-2,4-diones.



Keywords:

Knoevenagel condensation, Statistical design of experiment, ^{1}H NMR, ReactIR, LC-MS

Introduction

5-Benzylidenes with a thiazolidine-2,4-dione ring system, form the core chemical structures of many pharmacologically[1] and biologically active compounds in medicinal chemistry.[2] These compounds are synthesized via the Doebner modification of the Knoevenagel condensation reaction.[3] In general, Knoevenagel reactions[4] are carried out in the presence of weak bases; acid-catalyzed Knoevenagel reactions are rare. Recently, significant progress has been made in the heterogeneous Knoevenagel condensation using various modified catalysts.[5] Most studies use aldehydes as the starting materials. However, aldehydes are sensitive to oxygen, light, and moisture, and are known to readily polymerize and decompose during storage.[6] The conversion of aldehydes to the corresponding crystalline bisulfite adducts provides significant stability to the parent aldehyde,[7,8] and facilitates their use in the purification of aldehydes.[9] In contrast to the numerous coupling reactions between aldehydes and active methylene groups, the bisulfite adducts of aldehydes have rarely been used for direct carbon–carbon bond formation reactions.[10,11] Recently, Khosropour *et al.*,[12] reported the direct coupling of bisulfite adducts to azlactones using $POCl_3$ to facilitate carbon–carbon bond formation in polar solvents such as acetonitrile. After screening various reagents, they found that reactions with $POCl_3$ (2.0 mmol) afforded the best result (86% yield), but the authors also reported that bisulfite adducts are stable in $POCl_3$. Encouraged by this work we further explored this concept for the synthesis of a small library of 5-arylidenethiazolidine-2,4-diones from bisulfite adducts of different aromatic aldehydes (with EWG and EDG) as shown in Scheme 1.[13] Our results showed that conversions in aprotic solvents are low, and that $POCl_3$ worked more efficiently in non-polar solvents such as toluene. We suggested that the reaction of aromatic bisulfite adducts with thiazolidine-2,4-dione

3 would first involve the activation of the hydroxyl group of compound 2 by $POCl_3$ to afford intermediate 4, followed by the coupling of thiazolidine-2,4-dione 3 to give intermediate 5 and, finally, to afford 5-arylidene-2,4-thiazolidinedione 6 (Scheme 1). In the aforementioned publication[14] we also proposed a plausible pathway for the formation of 6 from the bisulfite adduct 2 of an aromatic aldehyde 1 with two labile intermediates (Scheme 1; 4 and 5). To the best of our knowledge, this type of transformation from 2 to 6 with $POCl_3$ ours was the first report. The mechanism was not well understood and therefore in order to provide a deeper understanding of the reaction pathway, we again re-examined the reaction and the intermediates. Herein, we report our preliminary results on this subject.

Results and Discussion:

In order to provide a deeper understanding of the reaction pathway, we re-examined the reaction and the intermediates with HPLC (High-performance liquid chromatography). A model condensation reaction between a bisulfite adduct 2 and 2,4-thiazolidinedione 3 was selected for this investigation (Scheme 1). We first monitored the reaction mass with HPLC at regular time intervals. Relative retention time (RRT) of bisulfite adduct 2, thiazolidine-2,4-dione 3, and of product 6 was determined by HPLC co-injection. Notably, an intermediate X (plot c, Figure 1) was found in the HPLC profile, following a parabolic pattern (plot a: bisulfite adduct 2, plot b: thiazolidine-2,4-dione 3, plot d: product 6, plot c: unknown). At temperatures lower than 60 °C, we observed an accumulation of this intermediate X; as the temperature was increased, the intermediate (plot c, Figure 1) converted into the desired product 6 (Scheme 2).

According to our earlier proposed mechanism,[14] we expected to observe two plots for intermediates 4 and 5; therefore, we reasoned that the intermediate X might be assigned to intermediates 4 or 5 or to some other unknown species. However observing only one peak in HPLC, we hypothesised that as the analysis of the reaction mass by HPLC was done offline; any intermediate with a very short lifetime would not be observed in the HPLC reaction profile. Furthermore, this reaction (Scheme 1) has multicomponent intermediates; hence, we thought of utilizing the unique capabilities of ReactIR technology to visualize the progress of the reaction online, so that information on the various transient species formed in the reaction can be obtained. As a model reaction, the coupling of bisulfite adduct 2 with thiazolidine-2,4-dione 3 was performed in toluene using 2.0 equivalents of $POCl_3$ with ReactIR probe dipped into the reaction mass. The IR spectrum of the reaction mass was recorded after every 45 s, and the obtained reaction profile is shown in Figure 2 capturing the various reaction components. Surprisingly, the bisulfite adduct 2 disappeared immediately after completion of $POCl_3$ addition to the reaction mass at RT with simultaneous formation of a curve g in Figure 2. It appears that bisulfite adduct was not stable in $POCl_3$ even at RT, this observation was in contradiction with Khosropour report. An increase in the reaction temperature from 35 °C to 110 °C resulted in reduction of curve 'g' with simultaneous increase in the concentration of product 6 represented by "curve b" as shown in Figure 2.

From the visual comparison of HPLC plot (Figure 1) and ReactIR plot (Figure 2), it appeared that the intermediate X in Figure 1 (plot 'c') and Figure 2 (curve 'g') are representing the same component. This assumption was validated by the fact that the IR spectra of the component represented by curve 'g' matched with that of the standard reference IR spectra of 4-

ethoxybenzaldehyde (1). Hence, at first sight it can be assumed that the reaction was proceeding through the insitu formation of aldehyde 1 as shown in Scheme 2. Additionally ReactIR also helped in identifying the other $POCl_3$ related by-products of the reaction as shown in Figure 2.[14]

The outcome of the HPLC and ReactIR analysis was further substantiated by monitoring the reaction progress by ^1H NMR. Due to the poor solubility of 2 and 3 in toluene, the reaction progress was investigated by off-line ^1H NMR. The stacked plots of ^1H NMR spectrum (Figures 4) taken at different temperatures showed that the bisulfite adduct 2 was instantaneously de-protected to aldehyde 1 upon addition of $POCl_3$ at room temperature (35 °C). This was confirmed by the disappearance of the characteristic -CH proton (δ 5.59) and OH (δ 4.87) of bisulfite adduct 2 (Figure 3 and 4) with a simultaneous appearance of the characteristic aldehydic proton at δ 9.86 (Figure 4) immediately after the completion of $POCl_3$ addition. Notably, major conversion of aldehyde 1 to the final product 6 started at 75 °C and by the time the reaction temperature reached 110 °C almost all of the insitu generated aldehyde 1 converted to the desired product 6. This was confirmed by the disappearance of the aldehydic proton at δ 9.86 with simultaneous appearance of the characteristic =CH proton (Figure 4) of the product 6 at δ 7.74. These findings are in agreement with those obtained from ReactIR confirming once again that the condensation proceeds through the insitu regeneration of aldehyde rather than earlier proposed intermediates for the same type of reactions (Scheme 1; intermediate 4 and 5).

To further support our results (HPLC, ReactIR and ^1H NMR), we investigated the formation of the intermediate species for the reaction of 2 with 3 using offline LC-MS to check for the possible trace level intermediates in the reaction mass. We performed our study using an AB

SCIEX TripleTOF 4600 mass spectrometer coupled with an Agilent 1290 series LC system; the reaction mass isolated at different intervals was monitored using negative-ion mode mass spectra. The reaction produced clean spectra, which displayed cationic species at $[2a + H]^+$ *m/z* 151.0 (absolute mass 150.07) and $[1a + H]^+$ *m/z* 250 (absolute mass 249.05) for product 6 (Figure 5).

The observation of 1 in both ^1H NMR and LC-MS provides strong evidence for the in situ regeneration of 1, thus confirming our observations from HPLC and ReactIR. We reasoned that $POCl_3$ facilitates the cleavage of bisulfite adduct 2 to 1 releasing $POCl_2(OH)$ and SO_2 (g) (Scheme 3). As a result, based on our observations from the analytical tools, the modified plausible mechanism was shown in Scheme 4. We used GC-MS to confirm the evolution of SO_2 during the course of the reaction. GC-MC results clearly indicated that the *m/z* value of the gas evolved during the reaction of 2 with $POCl_3$ in consistent with that of SO_2 released from the reaction mass (Scheme 4).

In order to ascertain the effect of $POCl_3$, one-control condensation reaction of 3 was performed using free aldehyde 1. Formation of product 6 in presence of $POCl_3$ further confirm the essential role of $POCl_3$ in the transformation of 2 to 1 and subsequently to product 6 (Scheme 5).

Having recognized the role of $POCl_3$, it was decided to optimize the reaction with the help of DoE approach utilizing bisulfite adduct 2 and thiazolidine-2,4-dione 3 as a substrate for the model reaction. Three reaction parameters that were selected for DoE are captured in Table 1 along with their experimental range. A 2^3 full factorial design (= 8 experiments) was planned to

study the effect of the three variables on the formation of aldehyde 1 and the desired product 6. Results of this full factorial design are presented in Table 2.

The first step of DoE data analysis was the identification of few significant reaction variables (Table 1) that were affecting the formation of aldehyde 1 from bisulfite adduct 2. Based on Half-Normal plot (Figure 5) and Pareto analysis (Figure 6), it was clear that the formation of aldehyde 1 was only affected by $POCl_3$ equivalents while other two variables (Table 1) were having insignificant effect. This fact was also confirmed from the ANOVA analysis (Table 3) and was further augmented by the regression analysis where only $POCl_3$ appeared in the regression equation-1 and same has been depicted in 3D plot given in Figure-6. Observed and calculated values of the unknown intermediate are close enough (see residuals in Table 4) to conclude that Equation-1 explains the relationship very well. Another important observation is that the formation of 1 from 2 was facilitated by low equivalents of $POCl_3$ whereas high $POCl_3$ equivalents favored product formation (Table 2).

$$\sqrt{Unknown\ intermediate\ (1)} = 9.42 - 4.09 \times POCl_3 \qquad (1)$$

Similarly, the statistical analysis of DoE data was performed for the product 6. Based on Half normal curve (Figure 8) and Pareto chart (Figure 9), it was once again found that the product 6 formation was only influenced by the $POCl_3$ equivalents but in this case excess of $POCl_3$ was required (Compare with quantity of $POCl_3$ required for aldehyde 1 formation). This was also indicated by ANOVA (Table 5), regression analysis (equation-2) and is presented graphically in

Figure 9. Observed and calculated values of the product were close enough (Table 6) to conclude that equation-2 explains the relationship very well.

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$$Product\ (6) = -13.53 + 47.82 \times POCl_3 \qquad (2)$$

The main observation from the DoE approach was that the formation of aldehyde 1 and product 6 was influenced by the equivalent of $POCl_3$ used. Formation of aldehyde 1 from bisulfite adduct 2 is favored by low equivalents of $POCl_3$ (Equation 1) whereas the product 6 formation was favored by the high equivalents of $POCl_3$ (Equation 2), which is also evident from equation 1 and 2. Another point from the DoE data that needs to be stressed here is that the reaction with high equivalents of $POCl_3$ was not having aldehyde 1 as the high equivalents of $POCl_3$ as the high equivalents of $POCl_3$ was driving the reaction immediately to product 6. A possible explanation for this observation might be the conversion of bisulfite adduct 2 to aldehyde 1 which in turn converting to the product 6. Therefore studies with DoE approach was confirms aldehyde as an intermediate in this reaction. This is further augmented by the fact that aldehyde 1 was the major product wherein catalytic quantity of $POCl_3$ was used whereas in case of excess $POCl_3$, desired product 6 was the major component (Table 2).

Hence a refined methodology of one pot direct condensation of bisulfite adduct with thiazolidine-2,4-dione 3 was developed which enabled us to use bisulfite directly for the reaction. It was evident that it involved two chemical step, first step involves insitu deprotection of bisulfite adduct to parent aldehyde at room temperature and this deprotection was found to be instantaneous and catalyzed by $POCl_3$. While the second step of condensation of insitu

generated aldehyde 1 with thiazolidine-2,4-dione 3 will excess $POCl_3$ and higher temperature. This reaction proceeded through an Aldol type intermediate 7 which was captured by XIC mass spectra of the reaction mass (Figure 11). This intermediate 7 was not captured by HPLC/ReactIR or by ^{1}H NMR, probably because of very low concentration. Based on the above information, a probable reaction mechanism is shown in Scheme 3. Examining the course of the reaction with different analytical and spectroscopic tools (HPLC, ReactIR, ^{1}H NMR, LC-MS and GC-MS) confirmed that the reaction proceeds via in situ generation of aromatic aldehyde (resulting from the dissociation of bisulphite adduct in presence $POCl_3$), not the intermediates proposed earlier phosphorodichloridate 4 and sulphonate moiety 5. Significant improvement in yield was demonstrated with a single reaction. Interestingly, our investigation on $POCl_3$ mediated synthesis of 6 unfolds three important synthetic aspects of the reaction: (a) the regeneration of an aromatic aldehyde 1 from aromatic bisulphite adduct 2 in a non-polar solvent like toluene using catalytic $POCl_3$, (b) initiation of reaction at low temperature, and (c) in-situ generation of a second intermediate 7 which in turn facilitates carbon-carbon bond formation to give product 6. Based on our findings we optimized and modified version of the synthesis of $POCl_3$ mediated synthesis of 5-benzylidene at lower temperature resulting in good yield. To the best of our knowledge, this is the first report where *in situ* regeneration of intermediate aldehyde in synthesis of 5-benzylidenes was confirmed using analytical and spectroscopic tools.

Based on this new one pot methodology for the direct Knoevenagel condensation of bisulfite adducts of aldehydes with thiazolidine-2,4-dione, a small library of four compounds (8-11) were synthesized as shown in Figure 11.

The present methodology gave excellent yield of the desired product (6, 8, 9, 10 and 11) as captured in the experimental section (>77%). Inspired by these results, we carried out a reaction between pioglitazone-adduct, isolated from a pharmaceutically important aryl aldehyde intermediate of pioglitazone, and 1.33 equiv of $POCl_3$ in toluene at 90-100 ^oC to afford 5-arylidene 11 in good yield (Figure 12). In addition to the present methodology, other advantages include rapid product isolation (6, 8-11), a cleaner reaction, and better operational efficiency.

Experimental:

General Experimental Procedure:

Synthesis of (Z)-5-(4-ethoxybenzylidene)thiazolidine-2,4-dione (6)

A slurry of bisulfite adduct 2 (10 g, 39.40 mmol) with thiazolidine-2,4-dione 3 (4.6 g, 39.30 mmol) was prepared in toluene (10 mL) in a 100 mL reaction vessel. $POCl_3$ (8.0 g, 52.40 mmol) was added in one portion at 25 °C. The reaction temperature was gradually raised to 90-100 °C, and the reaction mass temperature was maintained at 90 °C for 6 h. After the visual absence of aldehyde on TLC, the reaction mass was slowly quenched by adding ice-cold water at 10 °C, and the biphasic slurry was stirred below 20 °C for 10 min. The resulting bright yellow crystalline material was filtered. The wet cake obtained was washed with toluene (2 × 10 mL) at 25 °C and dried in vacuum at 50 °C to afford product 6 in 81% yield.

Procedure for monitoring the reaction mass by ^1H NMR

The ^1H NMR spectra was recorded offline in DMSO-d_6 at 400 MHz on Bruker Avance 400MHz spectrometer. The chemical shift values were reported on ppm scale with respect to

tetramethylsilane (TMS) (0.00 ppm) as the internal standard. The reaction was performed as per optimized conditions described above. Samples for NMR were drawn via a pipette under N_2 atmosphere and the reaction mixture was concentrated by evaporation (with N_2 pressure) below 30 ^oC. 50 mg of dry sample under N_2 atmosphere was transferred to a micro-sample NMR tube for recording the spectra. Samples were drawn after the addition of $POCl_3$ at different temperatures between 35 ^oC to 110 ^oC.

Procedure for monitoring the reaction mass by ReactIR

Reaction monitoring by on-line ReactIR: ReactIR 45m (Mettler Toledo) was used for monitoring on-line reactions in our initial study. The ReactIR probe was immersed in the reaction mixture to obtain samples for the instrument. During the reaction, IR spectra were recorded in 45 s intervals for 2 h and then compared to standard reference spectra. Prior to the reaction, the IR spectra of the starting materials were recorded in DMSO. Distinct characteristic peaks in the range 1900–800 cm–1 were recorded in the IR spectra by eliminating the overlapped DMSO peaks.

Procedure monitoring the reaction by HPLC

Offline HPLC analysis was performed using Waters 2690 HPLC system. Reaction mass sampling for HPLC was drawn via a pipette under N_2 atmosphere and transferred to a 50 mL round bottom flask (RBF), and the reaction mass was concentrated by evaporation (with N_2 pressure). 20 mg of dry sample was removed and transferred to a 10.0 mL volumetric flask. The freshly prepared diluted sample was then transferred to the injection loop for analysis (sample in 5 mL of diluent). HPLC conditions required for reactions to progress include Column: Kromasil, Altima C18, 150 x 4.6, 3μm, λ_{max} 245 nm, Flow: 1.0 mL/min, Run time: 30min, and diluent

DMSO. Chromatograms were recorded for samples at different intervals over the course of the reaction.

(Z)-5-(4-ethoxybenzylidene)thiazolidine-2,4-dione (6): 80%, Yellow solid, 98.6%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.50 (s, 1H), 7.74 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 4.10 (q, *J* = 6.8 Hz, 2H), 1.3–1.36 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 167.9, 167.3, 160.0, 132.1, 131.8, 125.2, 120.0, 129.5, 115.2, 63.4, 14.4 ppm; ESI-MS: *m/z* 248.3 (M-1).

(Z)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione (8): 77%, Yellow solid, 99.0%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.50 (s, 1H), 7.75 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 167.9, 167.4, 160.9, 132.0, 131.8, 131.7, 125.5, 120.3, 114.8, 55.5 ppm; ESI-MS: *m/z* 234.0 (M-1).

(Z)-5-(4-chlorobenzylidene)thiazolidine-2,4-dione (9): 80.8%, Light brown solid, 99.2% ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.66 (s, 1H), 7.78 (s, 1H), 7.63–7.58 (m, 4H) ppm; ^{13}C NMR (400 MHz, DMSO-d_6): 172.1, 170.1, 134.1, 132.8, 131.2 (2C), 129.1, 128.2, 127.5, 127.4 ppm; ESI-MS: *m/z* 238.4 (M-1).

(Z)-5-(4-nitrobenzylidene)thiazolidine-2,4-dione (10): 81.7%, Yellow solid, 97.1%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.82 (s, 1H), 7.86 (s, 1H), 8.30–8.40 (d, *J* = 8.6 Hz, 2H), 7.60–7.80 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): 167.3, 167.0, 147.4, 139.3, 130.9, 129.1, 124.2, 116.2 ppm; ESI-MS: *m/z* 249.0 (M-1).

(Z)-5-(4-(2-(5-ethylpyridin-2-yl)ethoxy)benzylidene)thiazolidine-2,4-dione (11): ^{1}H NMR (400 MHz, DMSO-d_6): 12.5 (s, 1H), 8.3–7.0 (m, 7H), 4.40 (t, J = 6.8 Hz, 2H), 3.20 (t, J = 6.8 Hz, 2H),

2.60 (q, J = 7.4 Hz, 2H), 1.20 (d, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO d_6): 167.9, 167.4, 160.1, 155.1, 148.5, 136.7, 135.7, 132, 131, 125, 123, 120, 115.3, 67, 36.5, 24.9, 15.3 ppm; ESI-MS: m/z 355.1 (M+1).

Conclusion

Analysis of the data obtained from various PAT tools and DoE helped in understanding the reaction pathway of $POCl_3$ mediated of one pot direct condensation of bisulfite adduct with thiazolidine-2,4-dione. Based on the experimental evidence, the above reaction could be exploited in two different ways. If the desired output is only the de-protections of bisulfite adduct to aldehyde then catalytic quantity of $POCl_3$ is to be used at room temperature. On the other hand if condensation product is desired than excess $POCl_3$ is to be used and reaction is to be performed at high temperature. The yield obtained from the current methodology was much higher than the yield obtained from the direct condensation of free aldehyde.

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Table 1. Reaction variables (factors) considered for the optimization of product 6.

Factor	Name	Unit	Min. (-1)	Max. (+1)
A	$POCl_3$	Equiv.	0.33	2.0
B	Reaction time	h	2.0	8.0
C	Reaction temperature	^oC	60	110

Table 2. Results of 2^3 full factorial design

Std. run	$POCl_3$ equiv.	Time (h)	Temperature (^oC)	Aldehyde (1)	Product (6)
1	0.33	2	60	59.30	0.32
2	2.0	2	60	0.29	83.70
3	0.33	8	60	78.57	3.70
4	2.0	8	60	0.23	82.07
5	0.33	2	110	83.04	2.29
6	2.0	2	110	3.74	80.58
7	0.33	8	110	49.93	2.71
8	2.0	8	110	4.10	82.17

$POCl_3$ equivalents favored product formation (Table 2).

Table 3. ANOVA Table for Unknown intermediate ($\sqrt{1}$).

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob >F
Model	93.35	1.00	93.35	91.81	< 0.0001
$POCl_3$	93.35	1.00	93.35	91.81	< 0.0001
Residual	6.10	6.00	1.02		
Cor Total	99.46	7.00			

Table 4: Observed and predicted values of aldehyde 1

Observed (1_o)	Observed $\sqrt{1_o}$	Predicted $\sqrt{1_p}$	Residual $\sqrt{1_o} - \sqrt{1_p}$
59.3	7.70	8.08	-0.38
0.29	0.54	1.24	-0.71
78.57	8.86	8.08	0.79
0.23	0.48	1.24	-0.76
83.04	9.11	8.08	1.04
3.74	1.93	1.24	0.69
43.93	6.63	8.08	-1.45
4.1	2.02	1.24	0.78

Table 5. ANOVA table for product 6 formation.

Source	Sum of squares	Df	Mean square	F Value	p-value Prob >F
Model	12760.03	1.00	12760.03	7015.44	< 0.0001
$POCl_3$ Equiv.	12760.03	1.00	12760.03	7015.44	< 0.0001
Residual	10.91	6.00	1.82		
Cor Total	12770.94	7.00			

Table 6: Observed and predicted values of Product (6)

Observed product	Predicted Product	Residual
0.32	2.255	-1.935
83.70	82.13	1.57
3.70	2.255	1.445
82.07	82.13	-0.06
2.29	2.255	0.035
80.58	82.13	-1.55
2.71	2.255	0.455
82.17	82.13	0.04

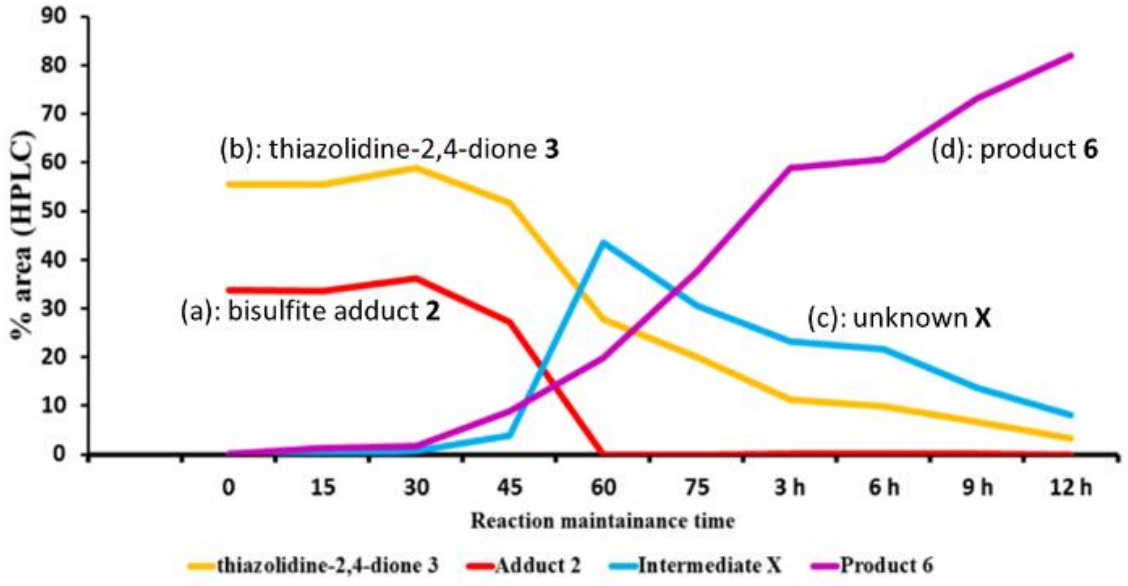


Figure 1. Conversion of 2 to 6 by HPLC (area %).

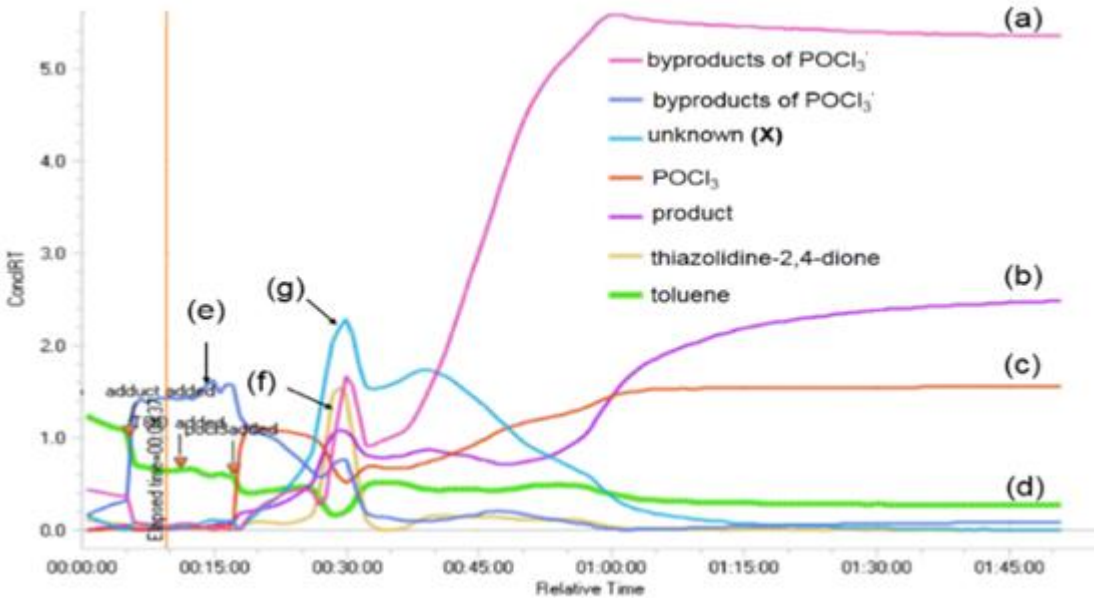


Figure 2. On-line ReactIR plot for $POCl_3$-mediated coupling of 2 with 3: (a) By-product of $POCl_3$ (b) product 6 (c) $POCl_3$ (d) toluene (e) By-product of $POCl_3$ (f) thiazolidine-2,4-dione (3) (g) intermediate X

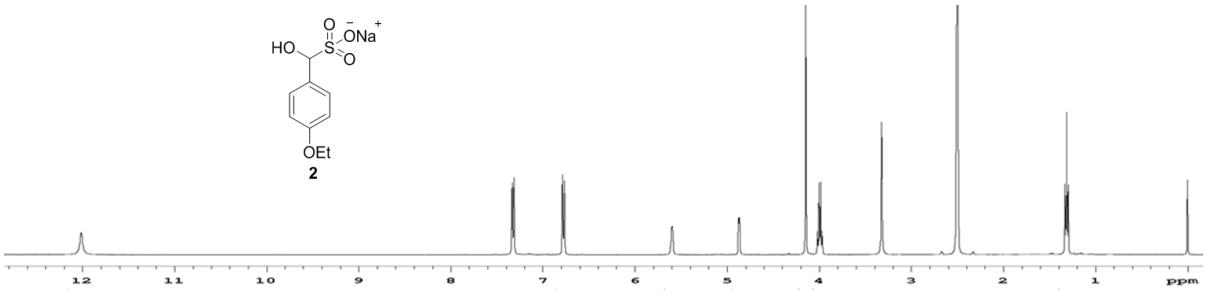


Figure 3. ^{1}H NMR of bisulfite adduct before $POCl_3$ addition

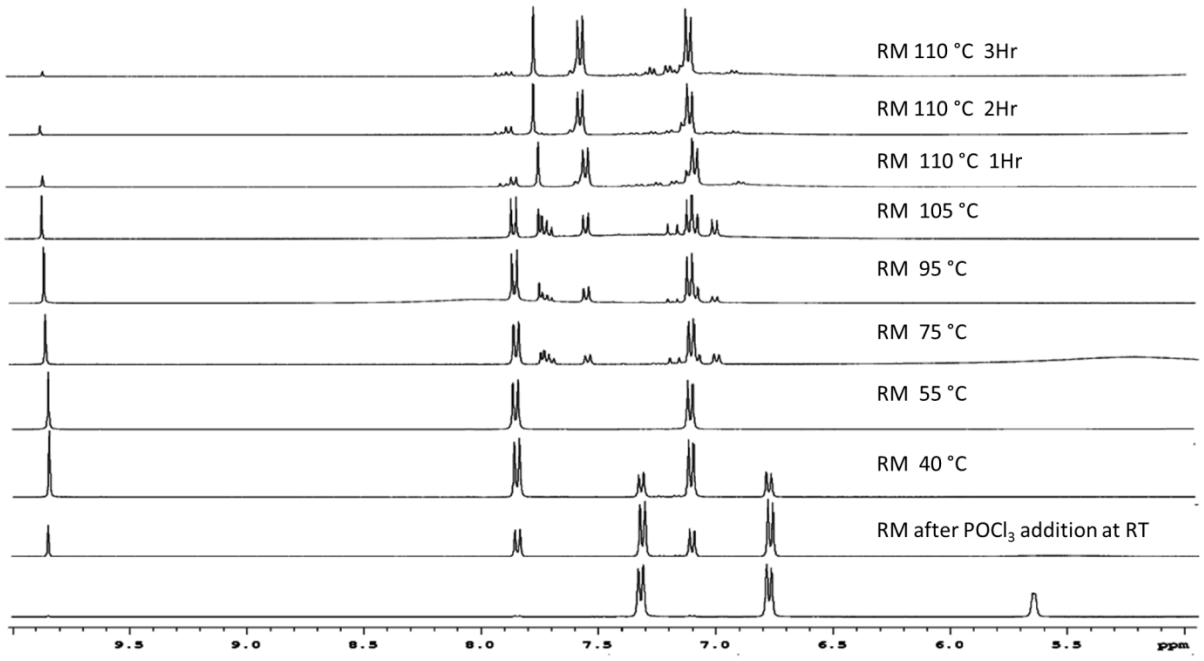


Figure 4. ^{1}H NMR plots for the reaction of (2) with (3) in the presence of 2.0 equivalents of $POCl_3$.

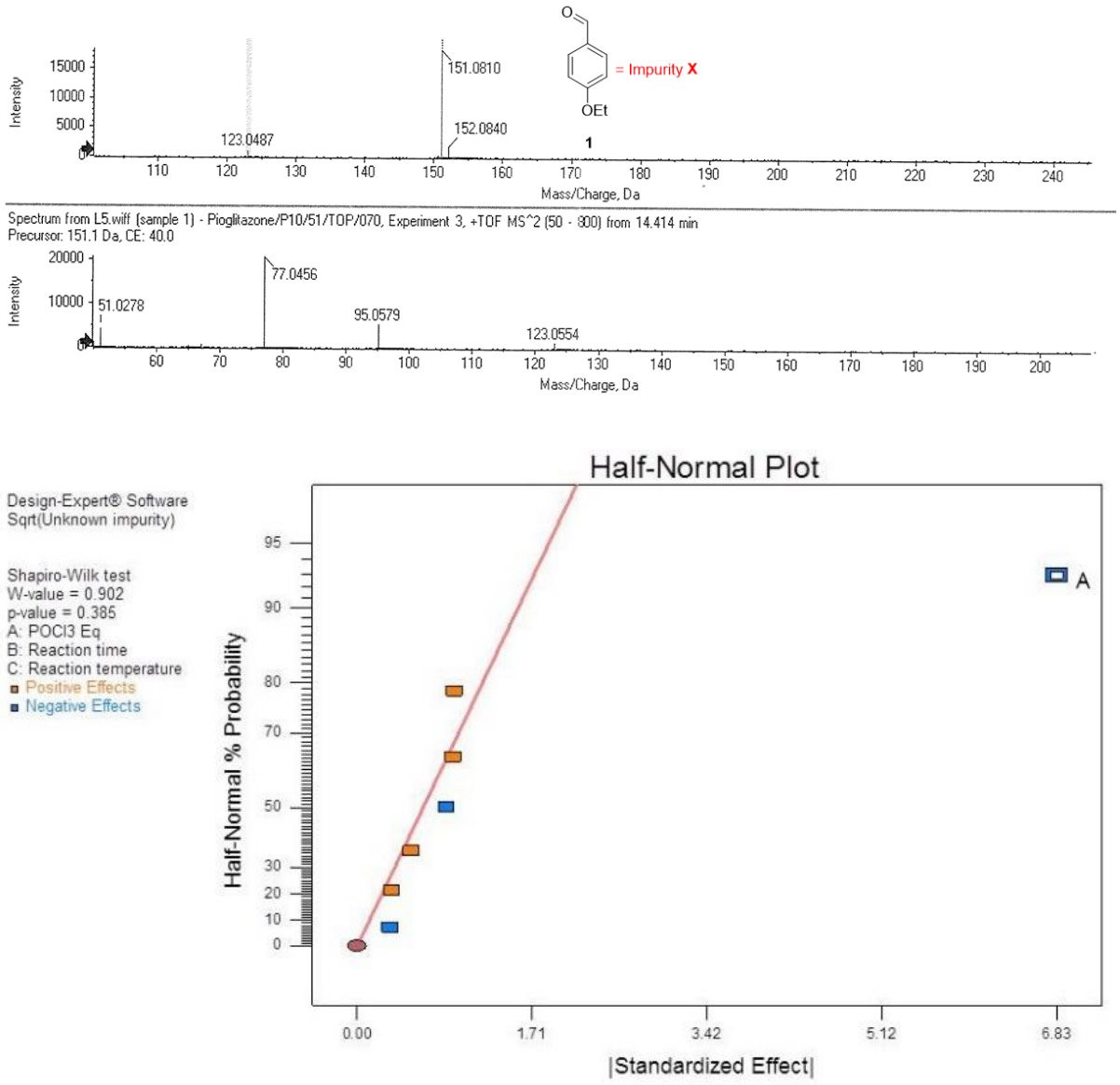


Figure 5: (a)LC-MS chromatogram for aldehyde 1 during the transformation of 2 to 6. (b)Relative effect of various reaction variables on Unknown intermediate ($\sqrt{1}$).

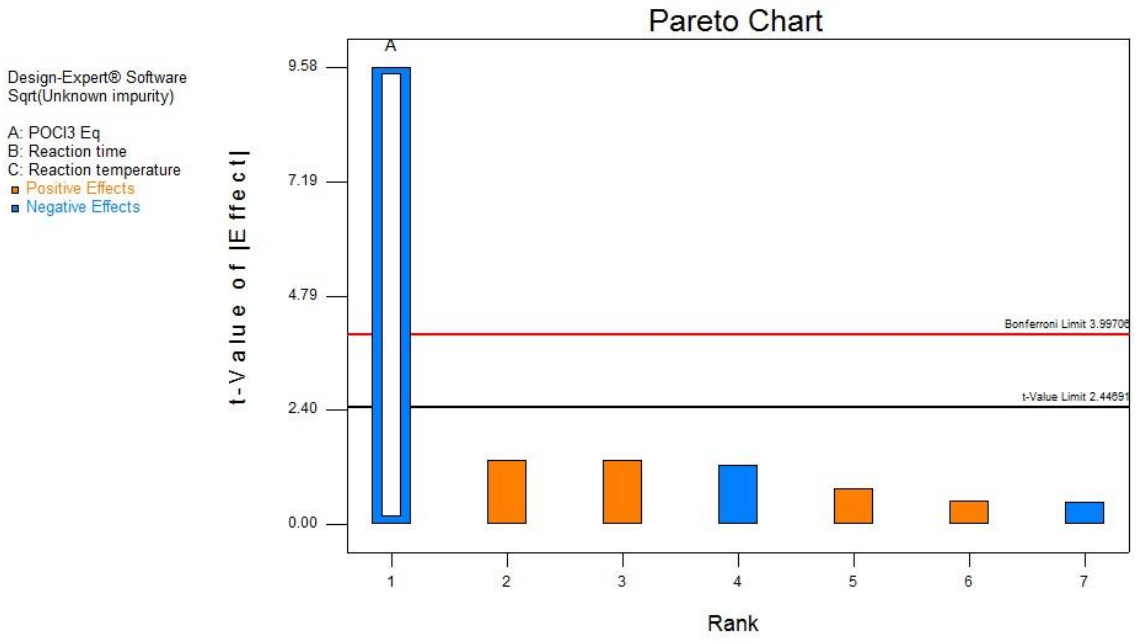


Figure 6. Pareto Chart for identification of important reaction variables affecting aldehyde ($\sqrt{1} = 1$).

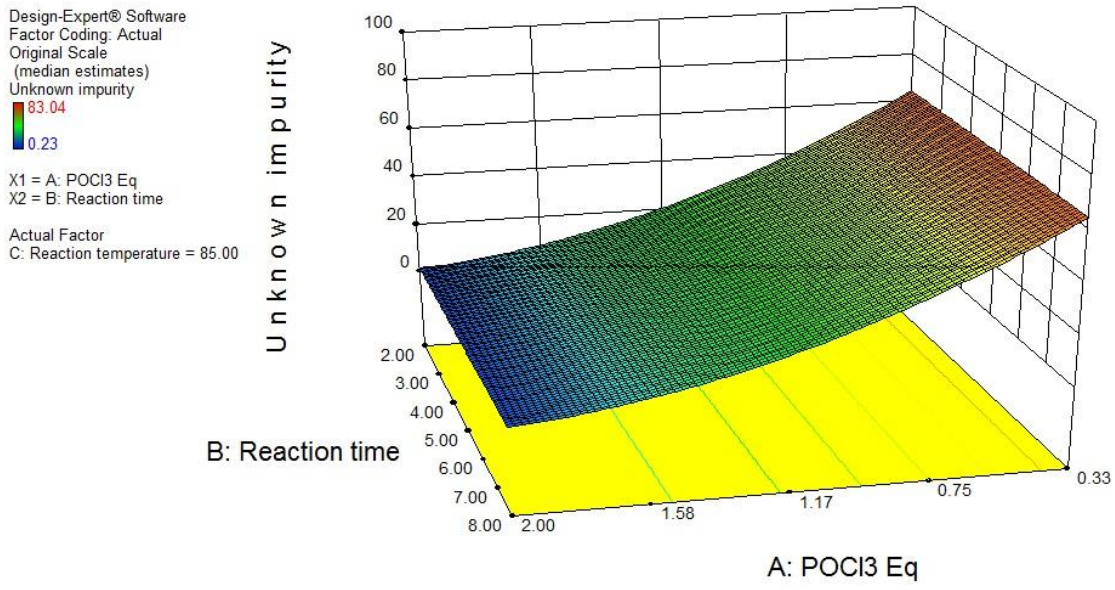


Figure 7. Contour plots of % aldehyde ($\sqrt{1}$) with respect to $POCl_3$ at 85 °C

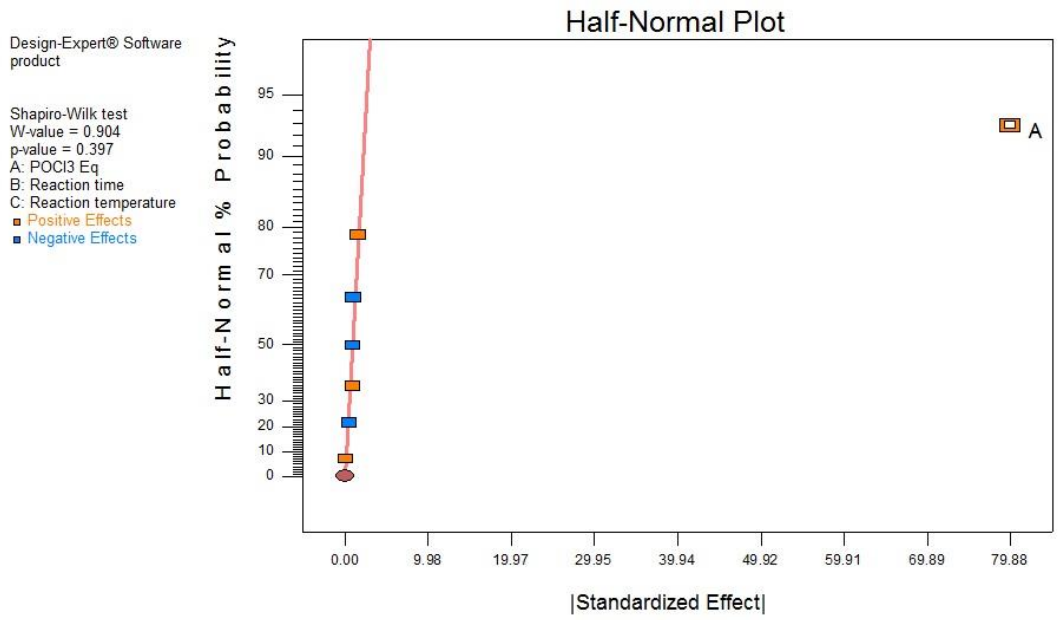


Figure 8: Relative effect of various reaction variables on product 6 formation

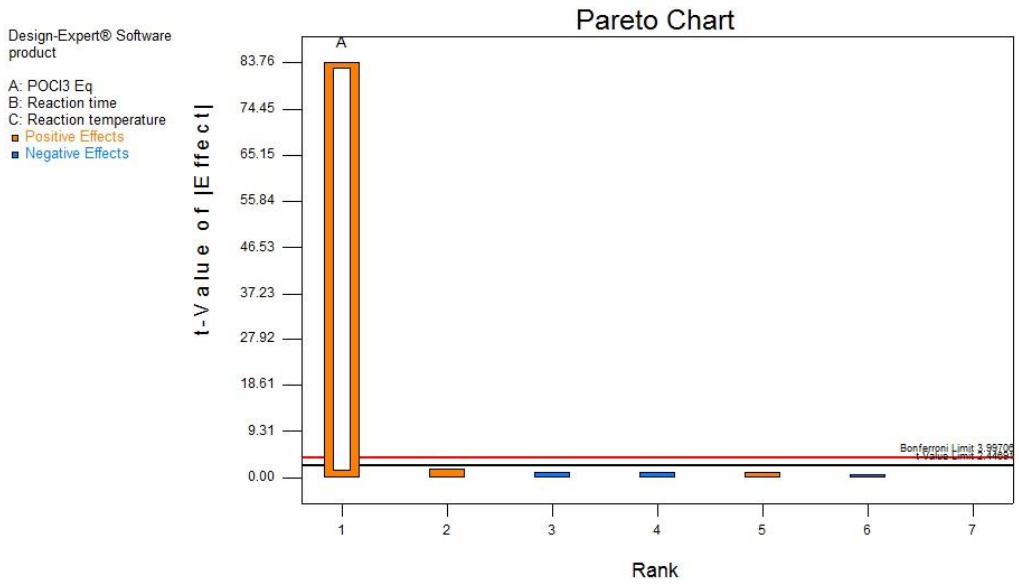


Figure 9. Pareto Chart for identification of important reaction variables for product formation

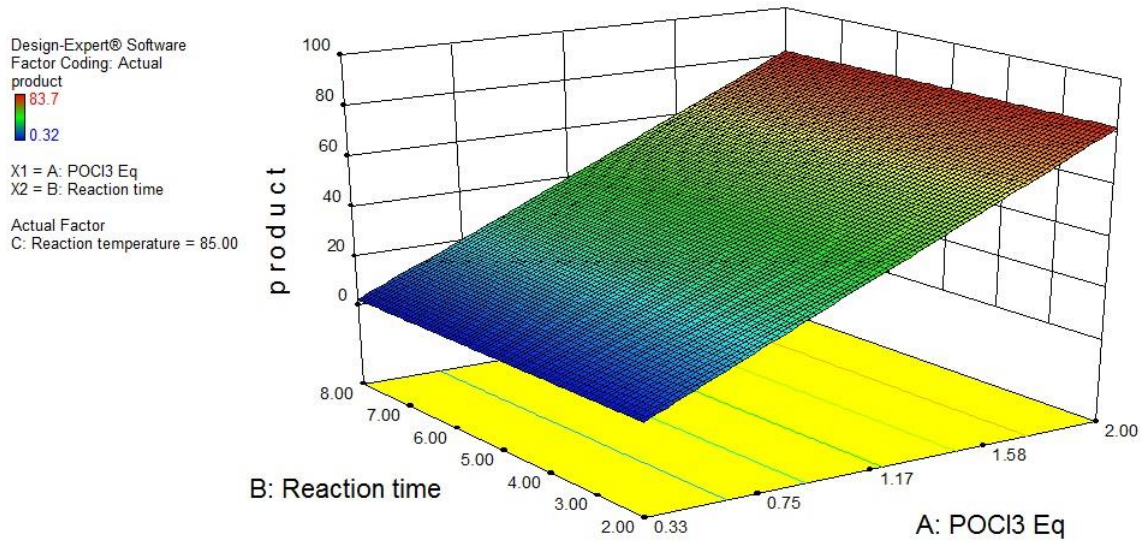


Figure 10. Contour plots of the amount (%) of product 6 wrt $POCl_3$ at 85 °C

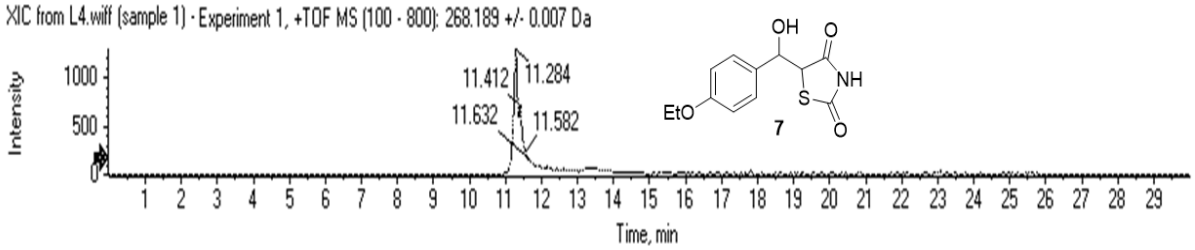


Figure 11. Extracted-ion chromatogram (XIC or EIC) for intermediate 7

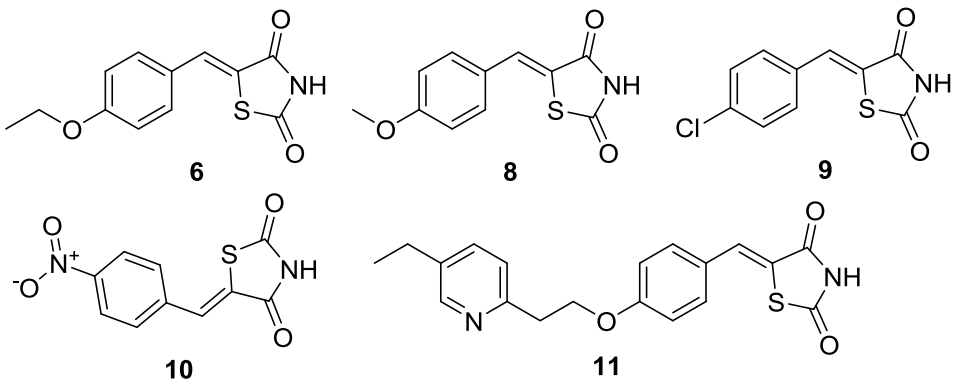
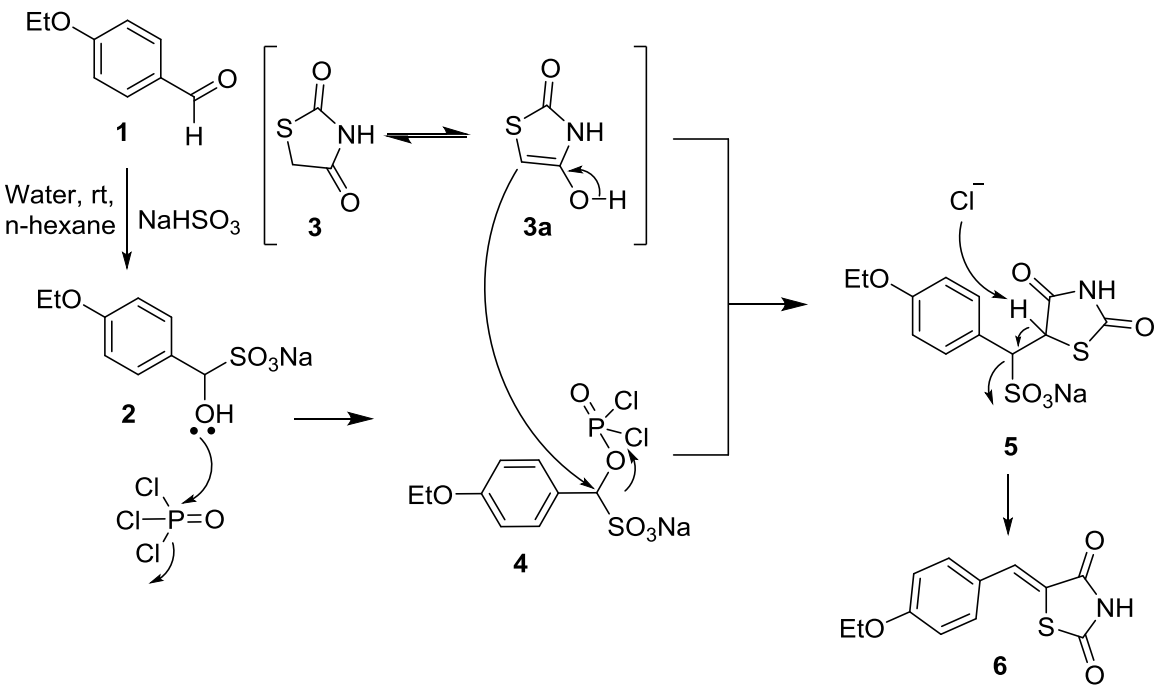
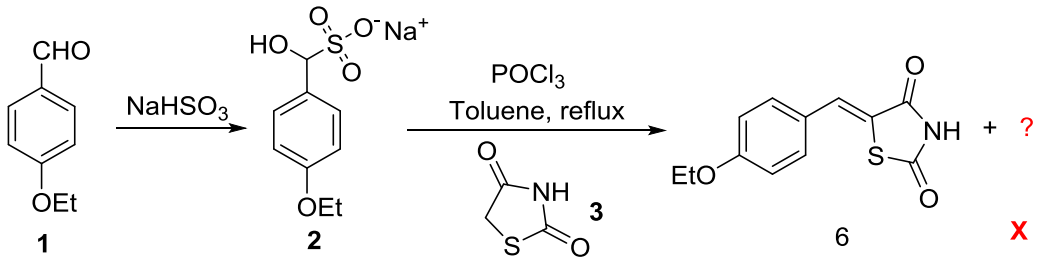


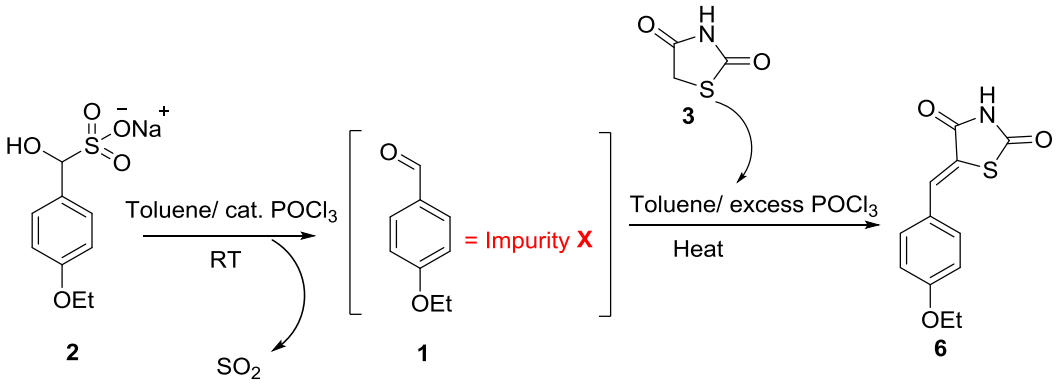
Figure 12: Four compounds prepared using current methodology



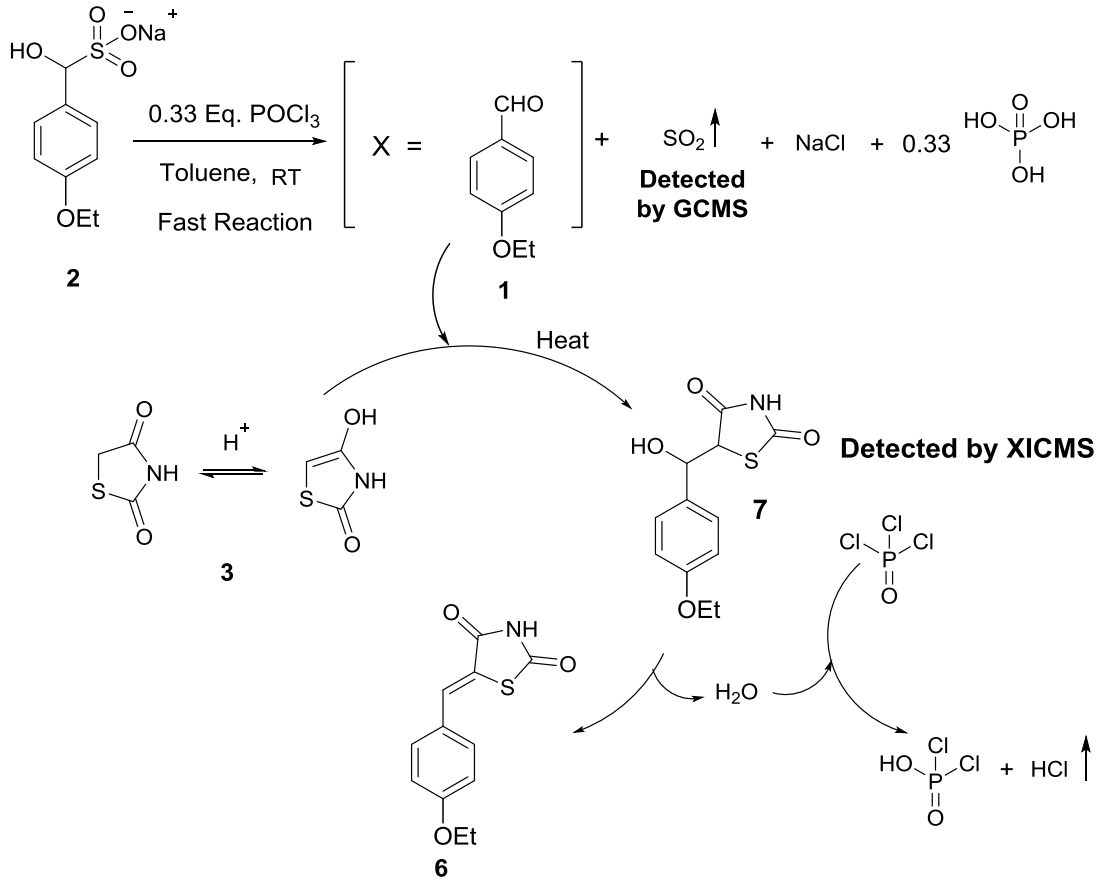
Scheme 1. Proposed reaction mechanism for conversion of 2 to 6.



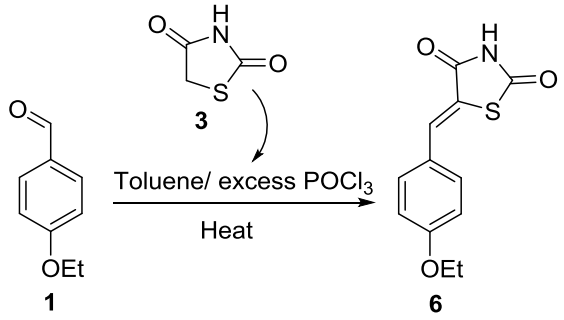
Scheme 2. Condensation of bisulfite adduct (2) with thiazolidine-2,4-dione (3) in presence of $POCl_3$.



Scheme 3: Reaction pathway for condensation of bisulfite adduct with thiazolidine-2,4-dione



Scheme 4: Plausible pathway for the $POCl_3$-mediated condensation of 3 with bisulfite adduct 2 of the aryl aldehyde 1



Scheme 5: Condensation of free aldehyde with thiazolidinedione in presence of excess $POCl_3$