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Controlling the Exothermicity of *O*-Arylation by Evaporative Cooling during the Process Development of Fluoxetine Hydrochloride†

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Supporting Information

ABSTRACT: This study illustrates the optimization of the *O*-arylation step of fluoxetine hydrochloride (**1**) synthesis. In the entire process, this is the most critical step that dictates the yield and quality of the product. The highlight of the process is the concept of evaporative cooling that was employed in manipulating the above highly exothermic reaction by introducing toluene as the cosolvent. The evaporative cooling not only aided in getting an efficient procedure but also increased the yield of **1** and simplified the work-up procedure. This was a protective approach adopted for process safety, considering the worst-case scenario in the plant.

INTRODUCTION

Fluoxetine hydrochloride (**1**) was originally developed by Eli Lilly[1] and is available under the trade name of "Prozac", which was introduced into the market in 1987 for the treatment of major depression. Fluoxetine is also used to treat trichotillomania where cognitive behaviour therapy is unsuccessful. Although the molecule has gone off patent in 2001, it still has paramount commercial value, which is evident by the fact that the price has increased by 10% (Table 1) even though the sales and consumption across the different geographies are going down during the same period. Although new agents have later been introduced into the market, this molecule still has remarkably consistent demand in the market. It is also marketed under the brand name "Sarafem" for premenstrual dysphoric disorder. "Symbyax" is a combination of **1** and olanzapine and was developed to treat the depressive episodes of bipolar I disorder as well as for treatment-resistant depression.

Thirty two years since the discovery of fluoxetine, many synthetic routes to it or its enantiomers have been published.[3,4] The main steps that dictate the yield and quality of **1** are *O*-alkylation step (**2** → **4**, Scheme 1) and *O*-arylation step (**11** → **13**, Scheme 2). Many base/solvent combinations have been reported for the *O*-arylation step, e.g. KOH in NMP,[5] C:18-Crown-6 as the phase-transfer catalyst in sulpholane,[6] NaOH in DMSO along with TBAB as the phase-transfer catalyst,[7] NaH in anhydrous DMA,[8a−k] *t*-BuOK in THF,[9] *O*-arylation of 1,2,3-oxathiazolidine-2,2-dioxides[10] with NaH in anhydrous DMSO.[11a−f] The above methods suffer from one or more drawbacks, but the major drawbacks are as follows: (i) The use of NaH at a large scale has its own disadvantages such as handling in commercial scale and the liberation of hydrogen gas. (ii) The reaction of a strong base with DMSO generates highly reactive sodium methylsulfinyl carbanion[12,13] (the dimsyl ion), which on decomposition at high temperatures could increase the chances of uncontrolled exothermicity and explosion. (iii) Longer reaction time is required.

Because *O*-arylation is the most critical step in the synthesis of **1**, we focused our efforts on optimizing this step. The first strategy was to screen for an alternative, compatible combination of base and solvent. In case we fail to find a suitable solution, then the second strategy was to focus on handling/controlling the exothermicity of the reaction by utilizing the concept of *evaporative cooling*. This would involve a cosolvent with a boiling point close to the reaction temperature. The heat generated in the reaction would then be absorbed by the cosolvent (as the heat of vaporization), thereby converting it into its vapour phase that then transfers the heat to the cooling fluid of the condenser (Figure 2). This concept would enable the reaction to be performed in a safe mode. The two prevailing schools of thought for providing the basis of process safety are preventive and protective approaches. Evaporative cooling is a protective approach that is used for handling the worst-case scenario, which may occur during the execution of an exothermic process.

RESULTS AND DISCUSSION

Fluoxetine Manufacturing Process (Scheme 2).[14] Benzaldehyde (**7**) was coupled with monomethylamine to afford benzylidene methylamine (**8**) followed by the reduction of imine to afford benzylmethylamine (**9**). The secondary amine (**9**) was then subjected to the classical Mannich reaction in the presence of formaldehyde and acetophenone in aqueous HCl to afford 3-(benzylmethylamino)-1-phenylpropane-1-one (**10**) as the HCl salt. *N*-debenzylation followed by the reduction of the keto group of compound **10** in one pot afforded 3-methylamino-1-phenylpropan-1-ol (**11**). The *O*-

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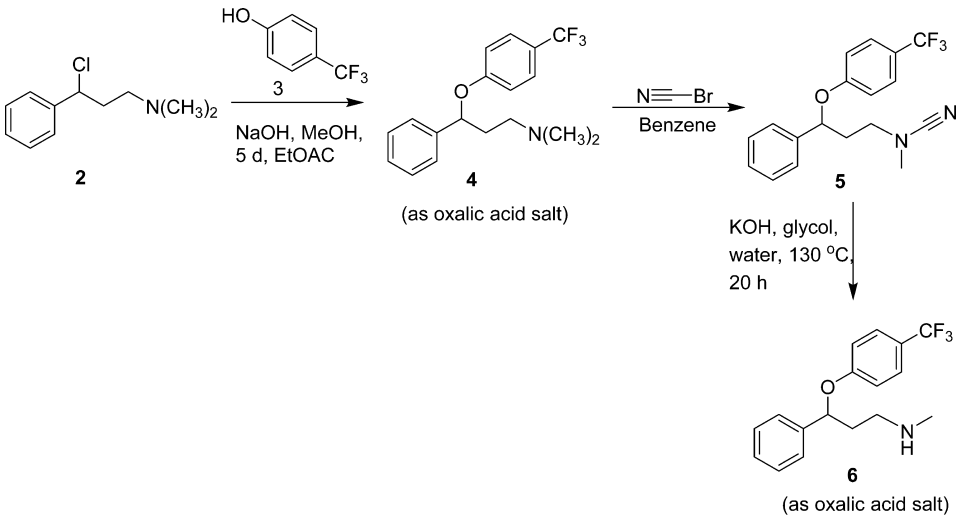
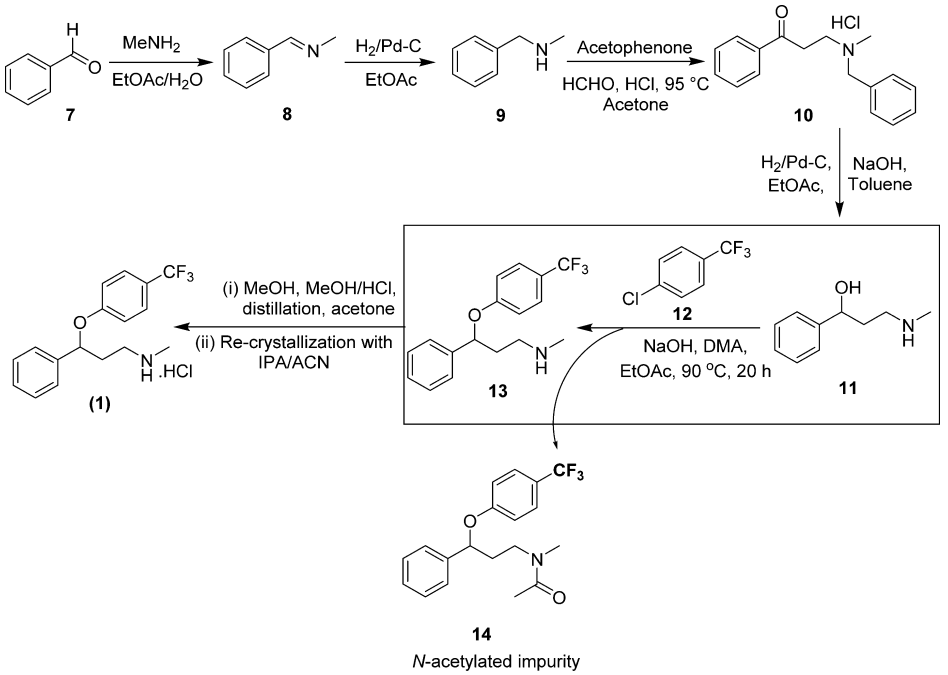
Table 1. Consumption and sales data of fluoxetine (irrespective of salt form)

	sales (in MUSD)			consumption in kg			price USD/kg	price USD/kg	
	2012−13	2011−12	change %	2012−13	2011−12	change %	2012−13	2011−12	price change %
U.S.A.	259.6	300.3	−13.6	32,472.7	33,013.5	−1.6	125.09	109.9	**13.8**
EU top 5	87.4	101.9	−14.2	15,280.6	14,899.5	2.6	174.84	146.2	**19.6**
rest of Europe	52.3	62.3	−16.1	5437	5397.7	0.7	103.96	86.6	**20**
Latin America	120.9	131	−7.7	5781.9	5835	−0.9	47.82	44.5	**7.4**
rest of world	151.7	161	−5.8	14,182.1	13,250	7	93.49	82.3	**13.6**
worldwide	671.8	756.5	−11.2	73,154.4	72,395.7	1	108.89	95.7	**13.8**

Scheme 1. Original synthetic route by Molloy et al. (1982)[2]



Scheme 2. Synthetic route for the manufacturing of fluoxetine hydrochloride (1)



arylation of (**11**) with 1-chloro-4-(trifluoromethyl)benzene (**12**) in the presence of NaOH in DMA at 90 °C for 20 h afforded crude fluoxetine free base (**13**), which was then converted to its HCl salt (**1**) in methanolic HCl. Recrystallization from acetone and two recrystallizations from acetonitrile afforded pure **1** with 51% overall yield.

As stated earlier, the conversion of the *O*-arylation step was low along with the formation of impurities. On the basis of this information, we envisioned that resolving the above issue would result in a cleaner reaction to afford **13**, which in turn would reduce the number of recrystallizations at the final stage, thereby increasing the yield and efficiency of the process. First,

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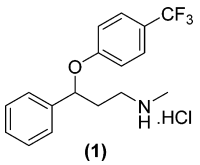

(1)

Figure 1. Fluoxetine hydrochloride (**1**).

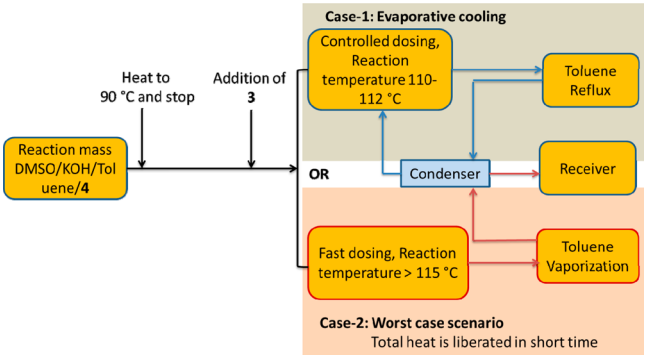

Figure 2. Concept of evaporative cooling.

a trial reaction was performed using NaOH as the base, and the reaction was maintained at 95 °C for 20 h in DMA. The HPLC analysis of the reaction mass showed ~86% conversion to the product (**13**), along with ~5% of an undesired *N*-acyl derivative (**14**).[15] Although the acetylated impurity (**14**) could be removed into the mother liquor during multiple recrystallizations, it resulted in an overall yield loss at the final stage. The process development was challenging because of the inexpensive raw materials (**12**, NaOH, and HCl) and solvents (MeOH, acetone, IPA, and ACN) used in the process, with little scope for reducing the cost further. The only way to increase the efficiency and reduce the cost was to increase the conversion at the *O*-arylation step with a cleaner profile of **13**. Herein, we report the development of an overall efficient and safe process with high conversion at the *O*-arylation step, thus avoiding the multiple recrystallizations at the final stage.

Stage 1 of the Process Development: Screening for an Alternative Solvent for *O*-Arylation. Various solvents were screened for studying the conversion at the *O*-arylation step with 10 equiv of NaOH. The reaction was monitored by HPLC, and the % conversions to (**1**) are shown in Table 2.

Evidently, a polar aprotic solvent (except DMF) was required for good conversion (Table 2). Although the conversion in DMA was the best, DMSO appeared to be a good alternative as there is no possibility for the formation of impurity **14** and also because of less reaction time (entry 3, Table 2). Other advantages of using DMSO are its ability to enhance the rate of Williamson synthesis with better solvation effect,[13] and most importantly, its safe toxicology profile.[16,17] The reactions in ACN and toluene remained incomplete, probably because of the heterogeneous nature of the reaction mass.

Screening for a Suitable HCl Scavenger for *O*-Arylation. After selecting DMSO as the solvent, we screened for a suitable base for the reaction in order to increase the conversion beyond 72% (entry 3, Table 2). The results are summarized in Table 3.

Table 3. Screening of HCl scavenger for *O*-arylation (all the reactions were carried out at ~100−110 °C)

			HCl scavenger			
entry	solvent	dilution (×)	base	equiv	time (h)	product (**2**)
1	DMSO	2	Na_2CO_3	5	3	2.77
2	DMSO	2	K_2CO_3	5	3	4.35
3	DMSO	5	NaOH	5	3	82.03
4	DMSO	2	KOH	5	3	91.36

The reaction was found to be sluggish with Na_2CO_3 and K_2CO_3, whereas KOH afforded the best conversion at 110 °C (entry 4, Table 3) in DMSO. Therefore, the temperature range 110−115 °C was the optimal reaction temperature for the best conversion. It is important to mention here that the reaction initiates at 85−90 °C and completes at the temperature range 110−115 °C. Therefore, the reaction mass was required to be heated to 85−90 °C using an external heat source prior to the addition of **12**. The addition of **12** results in uncontrolled exothermicity, and the temperature of the reaction mass rapidly increased to ~135−145 °C in the absence of a controlled addition of **12** (entry 1, Table 5). The reactions shown in Table 3 were performed at 5 g scale, and even at this small scale, it was highly exothermic. This prompted us for the safety evaluation of this reaction.

To check the exothermicity, a test reaction was performed in a reaction calorimeter by employing all safety measures. KOH was added to the solution of **11** in DMSO under nitrogen atmosphere, and the reaction mass was heated to 85−90 °C (reaction initiation temperature). Later, external heating was stopped, and **12** was added slowly over a period of 45 min (a slower addition slows down the reaction as the temperature of the reaction mass falls below 85 °C). During this addition period, the temperature of the reaction mass increased up to >135 °C. The amount of heat generated from the calorimeter was calculated and extrapolated for a 70 kg batch (Table 4). *This exothermicity study was also attempted using differential scanning calorimetry (DSC); however, in the absence of mixing in a crucible, no data could be obtained* (Supporting Information*SI*).

The RC1e data shown in Figure 3 indicate that the heat release was instantaneous; however, the reaction could also be

Table 2. Product conversion in various solvents

entry	solvent	polarity index (water 10.2)	bp (°C)	time (h)	temp (°C)	% product (**1**)[a]	% N-acylated impurity
1	DMA[b]	6.5	165	20	90	86.44	5
2	DMA[b]	6.5	165	7	165[b]	85.39	4.5
3	DMSO	7.2	189	3	90−110	72.53	ND
4	DMF	6.4	154	8	153	3.31	ND
5	ACN	5.8	81.6	20	80	3.08	ND
6	toluene	2.4	110.6	12	90−110	9.42	ND

[a]Reaction monitoring by HPLC. [b]*N*-acyl impurity (**14**) formation in DMA due to the hydrolysis of DMA, ND = not detected.

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Table 4. Heat of reaction extrapolated for 70.0 kg DMSO process

	heat input		remarks
A	total enthalpy observed during the addition in RC1e	52.47 kg	from Figure2
B	batch size in RC1e	50.00 G	
C	heat of reaction per kg of KSM as per the RC1e data	1049.40 kJ/kg	= $(A \times B) \times 1000$
	pilot run batch details		
D	batch size	70.00 kg	
E	total heat liberated (kJ)	73458.00 kJ	$C \times D$
F		17574.00 kcal	= $E/4.18$
G	time duration for heat release	45.00 min[a]	
H	rate of heat release	23431.58 kcal/h	= $(D \times 60)/E$

[a]Addition time of **12**. Heat release was found to be the function of addition/dosing rate.

controlled by a slow dosing of compound **12**. During the addition of the remaining compound **12**, the heat release was not instantaneous, indicating delayed exothermicity.

The data in Table 4 show that the rate of heat release was too high to be handled by any normal jacketed reactor cooling system, posing a threat of a runaway reaction.[18] Because the total energy release occurs in 45 min, this reaction is classified as a reaction with 'significant energy release potential' or an extremely high hazardous reaction[19] and is not suitable for scale-up as such.

Stage 2 of the Process Development: Controlling the Exothermicity by Evaporative Cooling at the *O*-Arylation Step. Many excellent articles are available on controlling the exothermicity of chemical reactions.[20] The concept of evaporative cooling prevails in the polymer industry, where it is used extensively for controlling the heat of the reaction.[21] However, the most common use of evaporative cooling is evident when any reaction is performed at the boiling point of the solvent. Thus, the heat of the reaction is immediately transferred to the heat exchanger/condenser by the vaporized solvent. However, the above method is only suitable for the 'low-energy release potential' reactions.[18] In this case, the rate of energy release was 23431.58 kcal/h (Table 4) that was too high to be handled by the above methods. Therefore, to overcome this problem, we thought of employing a cosolvent that will serve as the internal coolant, which would immediately transfer the heat of the reaction to the condenser as shown in Figure 2. We selected toluene as the cosolvent because its boiling point is 110 °C, and our desired reaction temperature was also ~110 °C. If this thought process works, then it could also act as a protective safety mechanism in worst-case scenarios in the plant. The other advantage of using toluene in this case was to simplify the downstream process after the aqueous work-up. The experiments with different volumes of toluene as the cosolvent were carried out at 5 g scale (Table 5).[22]

The experimental data shown in Table 5 proved our assumption that toluene could control the exothermicity of the reaction by evaporative cooling as the temperature of reaction mass did not exceed 110 °C. Notably, the volume of toluene required for best heat transfer and conversion at 5 g scale was more than ~3 volumes (entries 4, 5, and 6, Table 5).

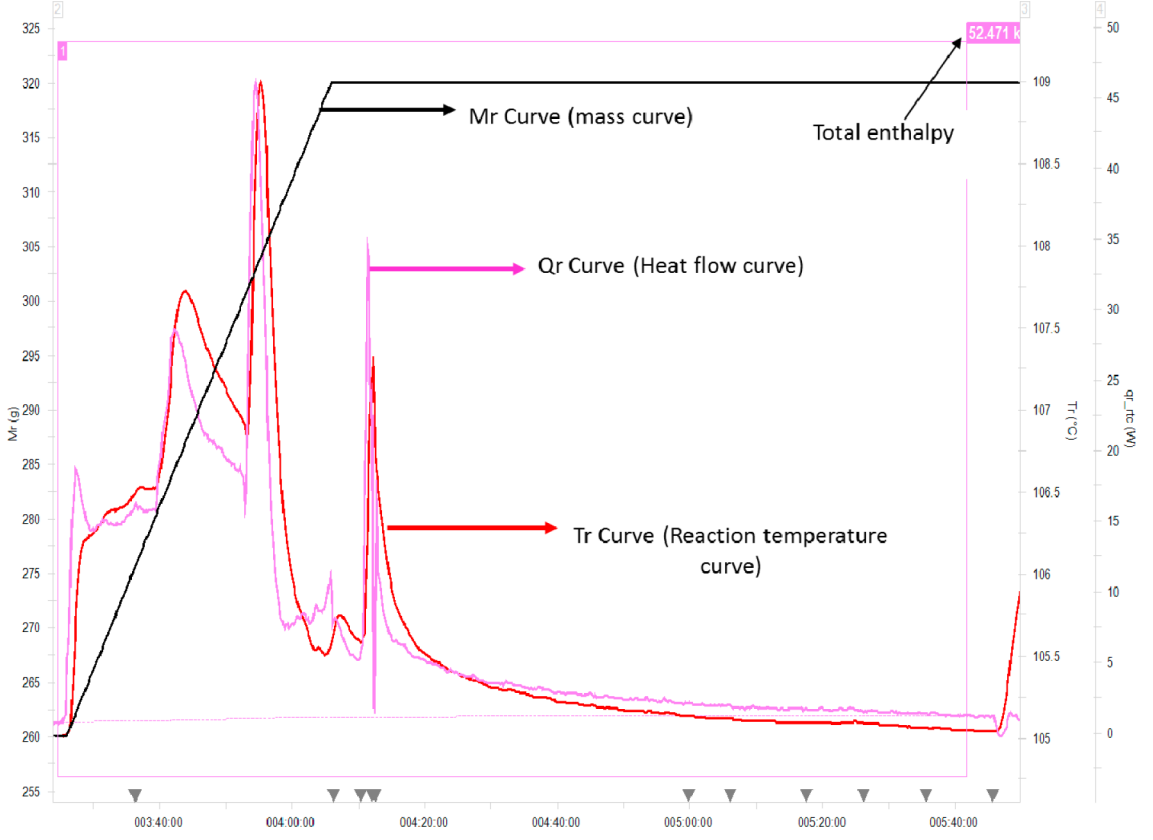

Figure 3. RC1e graph for DMSO/KOH process.

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Table 5. Effect of toluene volume (toluene as the co-solvent)

entry	solvent	dilution (×)	temperature of reaction mass (°C) step 1[a]	step 2[b]	step 3[c]	time (min)	% conversion in HPLC product (**2**)
1	DMSO	2	80	100	>135	45	91.36
2	DMSO/toluene	2:1	80	90	110	90	88.31
3	DMSO/toluene	2:2	80	90	110	90	91.6
4	DMSO/toluene	2:3	80	90	110	90	91.80
5	DMSO/toluene	2:4	80	90	110	90	93.90
6	DMSO/toluene	2:5	80	90	110	90	94.20

[a]Temperature of the reaction mass before the addition of **12**. [b]External heating to the reaction mass was stopped. [c]Final temperature of the reaction mass.

To understand the effect of various reaction components (DMSO, toluene, and KOH) on the conversion and unknown impurity, we planned a 2^3 full factorial design of experiments (DoE) with three centre points as shown in Table 6, and results of the experiments are shown in Table 7.[23]

Table 6. Variables used for DoE studies and their ranges

	variables	units	low level (−)	high level (+)
1	DMSO volumes wrt[a] the weight of (**4**)	mL/g	1	3
2	toluene volumes wrt[a] the weight of (**4**)	mL/g	1	6
3	KOH equiv wrt[a] (**4**)	equiv	2	5

[a]wrt = with respect to.

Table 7. A 2^3 full factorial experiment (all the experiments were conducted with 5 g batch size)

	entry	Reaction variables A: DMSO	B: Toluene	C: KOH	Responses % conversion	% impurity
factorial points	1	1	1	2	87.97	0.98
	2	3	1	2	88.53	2.36
	3	1	6	2	76.07	0.24
	4	3	6	2	81.7	0.61
	5	1	1	5	93.5	3.4
	6	3	1	5	85.41	8.01
	7	1	6	5	92.89	0.84
	8	3	6	5	95.55	1.90
centre points	9	2	3.5	3.5	91.29	1.38
	10	2	3.5	3.5	83.39	1.42
	11	2	3.5	3.5	88.41	1.43

Observations from DoE Studies on % Conversion. The initial ANOVA analysis including the centre points showed that the curvature was not significant for % conversion. Therefore, the ANOVA was once again calculated by ignoring the centre points, and the results are shown in Table 8. The % conversion was influenced by the equivalents of KOH (p-value 0.0119) used, and it was also affected by the two-factor interaction of toluene and KOH (p-value 0.0236); i.e., toluene itself has no role in increasing the % conversion, but along with KOH, it affected the conversion. The same has been expressed in the form of regression eq 1 and as a contour plot in Figure 4. Surprisingly, the ANOVA table does not contain the DMSO, indicating that the 1−3 volumes DMSO do not affect the conversion. It is evident from Figure 4 that the optimum condition for obtaining >90% conversion requires >4.5 equiv of KOH and >3 volumes of toluene with respect to **11**. *Caution: in case of highly exothermic reactions, determine the batch size that can be handled safely in the lab before conducting any experiments.*

Table 8. ANOVA for factorial model for % conversion (after removing the centre points) at α = 0.05

source	sum of squares	df	mean square	F value	p-value prob > F	
model	247.19	3.00	82.40	6.85	0.0173	significant
B-toluene	10.58	1.00	10.58	0.88	0.3796	
C-KOH	136.79	1.00	136.79	11.37	0.0119	
BC	99.83	1.00	99.83	8.30	0.0236	
residual	84.24	7.00	12.03			
lack of fit	52.27	5.00	10.45	0.65	0.6967	not significant
pure error	31.97	2.00	15.98			
cor total	331.43	10.00				

$$\%\text{conversion} = 91.2 - 3.76 \times \text{toluene} - 0.54 \times \text{KOH} + 0.94 \times \text{toluene} \times \text{KOH} \quad (1)$$

Observations on % Impurity Formation from DoE Studies. The ANOVA analysis (Table 9) showed that the % impurity is affected by all three reaction parameters, and their relationship is expressed by eq 2. Notably, the % impurity increased with increasing DMSO quantity, whereas it decreased with increasing toluene quantity. The same has been shown in the contour plot of Figure 5.

$$\ln(\%\text{impurity}) = -0.97 + 0.44 \times \text{DMSO} - 0.28 \times \text{toluene} + 0.4 \times \text{KOH} \quad (2)$$

Optimisation Plan. From the above discussion, it is clear that increasing the toluene volume not only controlled the exothermicity but also reduced the formation of the impurity.

Virtual Optimisation. At this point of development, it became important for us to validate the model experimentally. We decided to work with 2−2.5 volumes of DMSO,[24] 3 volumes of toluene, and 4.5 equiv of KOH (Table 10). As per eq 1, the predicted conversion was >91%, and the predicted undesired impurity was <2% at 95% confidence level. On the basis of the above-defined constraints, an experiment was conducted at lab scale, where 93% conversion was observed with <2% impurity. The predicted and observed values (Table 10) are close enough to say that this model holds good.

Process Scale-up. It was felt necessary to evaluate the condenser design and cooling fluid before the process was scaled up. A shell and tube type condenser was selected, and the various scenarios evaluated (using ASPEN) for selecting a suitable cooling fluid for the condenser are shown in Table 11.

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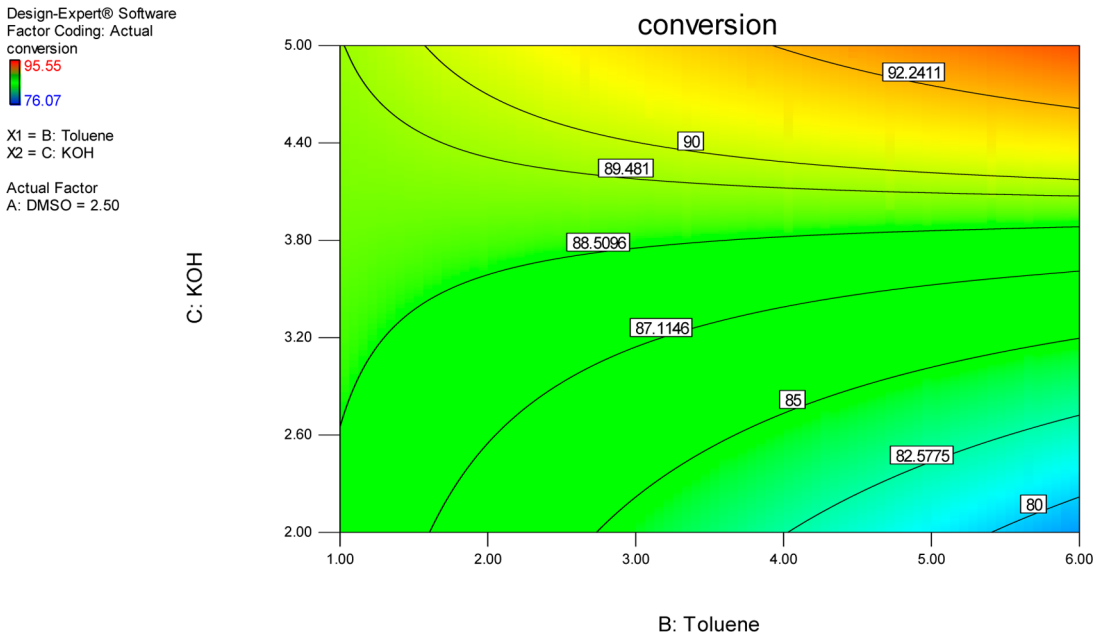

Figure 4. Contour plot for % conversion with two volumes of DMSO in reaction mass.

Table 9. ANOVA for factorial model for % impurity

source	sum of squares	df	mean square	*F*-value	*p*-value Prob > *F*	
model	8.380	3	2.79	3124.49	<0.0001	significant
A-DMSO	1.518	1	1.52	1697.98	<0.0001	
B-toluene	3.916	1	3.92	4379.86	<0.0001	
C-KOH	2.946	1	2.95	3295.63	<0.0001	
residual	0.006	7	0.00			
lack of fit	0.004	5	0.00	0.87	0.6120	not significant
pure error	0.002	2	0.00			
cor total	8.386	10				

Table 10. Validating the model

reaction variables			response			
			% conversion		% impurity	
A: DMSO	B: toluene	C: KOH	observed	predicted[a]	observed	predicted[a]
2.5	5	4.5	93.45	87–94	1.4	1.6–1.7
2.5	3	4.5	91.5	87–93.4	1.95	2.9–3.1

[a]95% confidence interval.

The basis of selecting a proper cooling fluid was to make the evaporative cooling more effective, i.e., the reaction mass temperature should not fall below 110 °C by refluxing toluene. Therefore, the toluene needed to be condensed at ∼110 °C itself, and the easiest way to achieve this was to use cooling

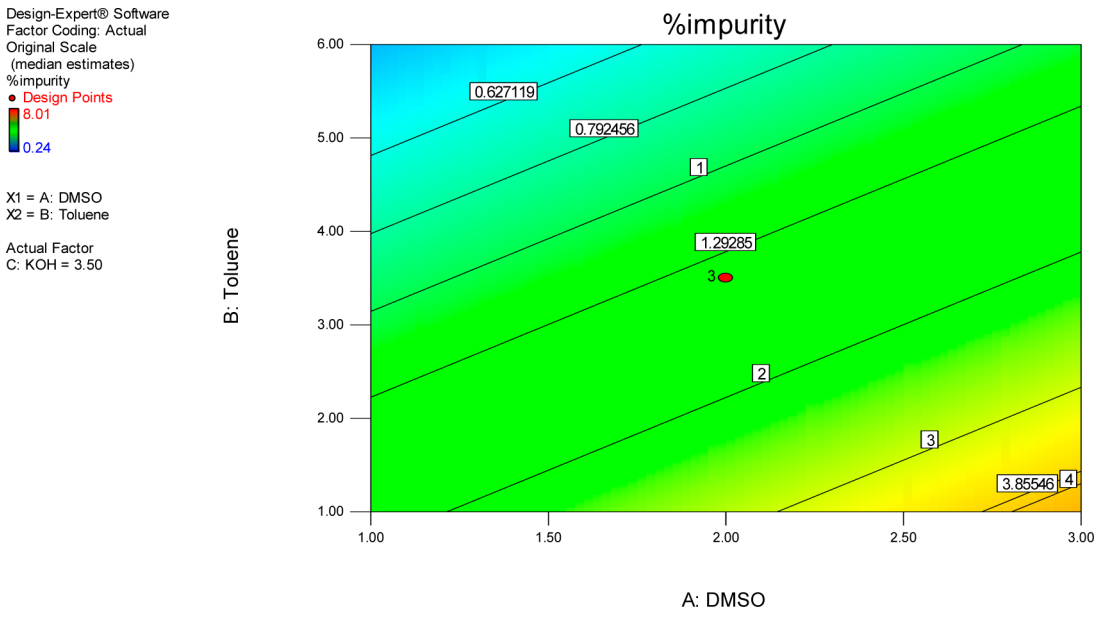

Figure 5. % Impurity formation.

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Table 11. Selection of the type of cooling fluid for the condenser

			batch size, kg			
			70		225	
		UOM	I	II	III	IV
hot fluid from the reactor	boil up	kg/h	220	220	700	700
	inlet T	C	110	110	110	110
	outlet T	C	110	110	110	110
cold fluid in the condenser	type	–	chilled brine	CT water	chilled brine	CT water
	flow rate	kg/h	5745	5257	18 230	16 271
	inlet T	C	−8	30	−8	30
	outlet T	C	−4	34	−4	34
condenser details	type	shell and tube				
	heat exchanged/h[a]	kcal/h	19 471	19 471	61 952	61 952
	calculated Area	m^2	3.5	3.5	3.5	3.5
	considered area	m^2	5	5	5	5

[a]Calculations are shown in Table 12

tower (CT) water in the condenser with different flow rates for different combinations of batch size and addition time (Table 11). Also CT water was more economical than chilled brine on a commercial scale. However, a provision was made for a secondary condenser with chilled brine for avoiding the toluene loss from the system.

After selecting the condenser and cooling fluid, a pilot trial of 70 kg was planned. As per calculations, 2.6 L of toluene was used per kg of compound **11** (Tables 10 and 12). Some part of the total heat liberated by the reaction (17574 kcal, Table 4) would be used to raise the temperature of reaction mass from 90 to 110 °C (3644 kcal, Table 12), and the rest of the excess heat would be absorbed by the toluene at 110 °C for its vaporization (13930 kcal, Table 12), thereby controlling the exothermicity. The reflux rate of toluene required for this heat removal was ∼216 kg/h. To maintain this rate, a calculated condenser area of 3.5 m^2 for CT water with a flow rate of 5257 kg was required (Table 12). The condenser area was 5 m^2, and the CT water flow rate was maintained as per the calculation. As stated above that 2.6 L of toluene was to be used as per calculation, however, a slightly higher quantity of toluene (3 L per kg of **11**) was used as per DoE optimization.

The temperature profile of 70 kg batch is shown in Figure 6, and it is evident that the above concept of evaporative cooling worked well in controlling the exothermicity at 70 kg scale. The temperature trend of 70 kg batch without toluene is also shown in Figure 7, indicating that the exothermicity could also be controlled by controlling the dosing rate of compound **12**.[25] This information proved very useful during the planning for the 225 kg batch.

Other Advantages of Using Toluene As the Cosolvent. *Ease of Work-up.* As per the reported procedure, fluoxetine base (**13**) obtained after the *O*-arylation was extracted with EtOAc, followed by three water washings and distillation of EtOAc under vacuum below 90 °C. Prolonged distillation of EtOAc also results in the formation of impurity **14**, which further contributes towards the yield drop. Fluoxetine base **13** was converted to its HCl salt with methanolic HCl in methanol. The distillation of methanol and recrystallization from acetone afforded crude **1**. Crude HCl salt **1** required two recrystallizations from acetonitrile/IPA mixture to afford pure **1**.

In this process, the reaction mass was quenched with water after the completion of the reaction. The upper toluene layer (already present in the reaction as the cosolvent) containing the product was separated and washed with water to remove the inorganic impurities. This toluene layer was directly used for HCl salt formation using IPA·HCl, resulting in crude **1**, which was then recrystallized from acetonitrile to afford pure **1**. The process is summarized in Scheme 3 and Table 13, resulting in an increased yield (from 55% to 71%) with reduced number of isolation and recrystallization steps.

CONCLUSION

This article reports a protective approach for process safety, wherein both evaporative cooling and dosing control worked together in controlling the exothermicity of the reaction. This process also eliminates the need for additional recrystallization at the final stage, thereby increasing the yield. Later, the DoE and lab optimisation at 5 g scale complemented the findings from the energy calculations and helped us in developing a robust process, which was scaled up in-plant without any safety or quality issues.

EXPERIMENTAL SECTION

Preparation of Fluoxetine Hydrochloride (1): 70 kg Batch. DMSO (140−155 L) and toluene (210−220 L) were charged into a 2 kL SS reactor equipped with a propeller-type agitator. This was followed by the slow addition of KOH flakes (140 kg, 2.5 kmol) under stirring, and finally compound **11** (69.7 kg, 0.42 kmol) was added to reactor slowly. Once the addition was completed, hot water (90−95 °C) was circulated in the jacket, and the reaction mass was heated to 85−90 °C. After reaching this temperature, the reactor jacket was emptied. To this reaction mass, compound **12** (83.7 kg, 0.46 kmol) was added slowly in ∼30 min; the reaction mass temperature was increased to ∼110 °C. At this point, hot water was recirculated in the jacket to control the temperature at ∼100−110 °C for another 45 min. The reaction was completed in 30−45 min. The reaction mass was then cooled to 60 °C and quenched with water (400−420 L), and another lot of toluene (420 L) was added. The reaction mass was stirred for another 30 min. After settling, the lower aqueous layer was discarded, and the toluene layer containing the product (**13**) was washed with water (3 × 100 L). The toluene layer was separated, and the moisture in the organic mass was removed by azeotropic distillation in the same reactor. The reaction mass was then cooled to 0−5 °C using chilled brine, and the pH of the

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Table 12. Toluene volume required for (a) worst-case scenario (all the heat is liberated suddenly) and (b) evaporative cooling during the controlled addition of compound 11

				batch size, kg				
				70	225			
	heat of reaction (DMSO)	UOM	basis of calculation	45 min addition time	46 min addition time	160 min addition time	180 min addition time	
A	batch size considered in RC1e	g			50			
B	total enthalpy observed during addition in RC1e	kJ	from RC1e		52			
C	heat of reaction per kg of KSM (RC1e)	kJ/kg	= B/A × 1000		1049			
D		kcal/kg	= C/4.18		251			
E	**Batch size**	**kg**		**70**		**225**		
F	total heat liberated	kcal	= D × E	17 574		56 487		
G	time duration for the heat release	min		45	45	160	180	
H	heat of the reaction released per hour	kcal/h	= F × 60/G	23 432	75 316	21 183	18 829	
I	specific heat of reaction mass (from RC1e)	kJ/kg °C		1.70	1.70	1.70	1.70	
J		kcal/kg °C	from RC1e	0.41	0.41	0.41	0.41	
K	total mass	kg		448.00	1440.00	1440.00	1440.00	
L	ΔT (required to raise the temperature of the reaction mass from 90 →110 °C)	°C		20.00	20.00	20.00	20.00	
M	heat required to raise the temperature 90 →110 °C	kcal	= J × K × L	3644.02	11712.92	11712.92	11712.92	
	toluene required for excess heat removal							
N	net heat to be removed from the reactor by toluene	kcal	= H − M	13929.67	44773.92	44773.92	44773.92	
O	latent heat of toluene	kcal/kg	from literature	86.10	86.10	86.10	86.10	
P	toluene required to remove total heat	kg	= N/O	161.78	520.02	520.02	520.02	**worst-case scenario:** assuming all the heat is liberated at once because of the addition of compound **12**
Q	toluene required per kg of KSM	kg	= P/E	2.31	2.31	2.31	2.31	
R	volume of toluene required per kg of KSM	L	= Q/0.866	2.67	2.67	2.67	2.67	
S	time duration for heat release	h		0.75	0.75	2.67	3.00	
T	rate of heat release	kcal/h	= N/S	18 573	59 699	16 790	14 925	**evaporative cooling:** It is the case where compound **12** was added gradually. The heat was liberated in a controlled manner and removed by refluxing toluene.
U	toluene boil up rate	kg/h	= T/O	216	693	195	173	
V	toluene reflux rate (10% loss considered)	kg/h	from condenser	216	693	195	173	
W	condenser area required (Shell and Tube)	m^2		3.5	3.5	3.5	3.5	calculated based on toluene reflux rate
X	actual condenser area used (Shell and Tube)	m^2		5	5	5	5	~40% excess area

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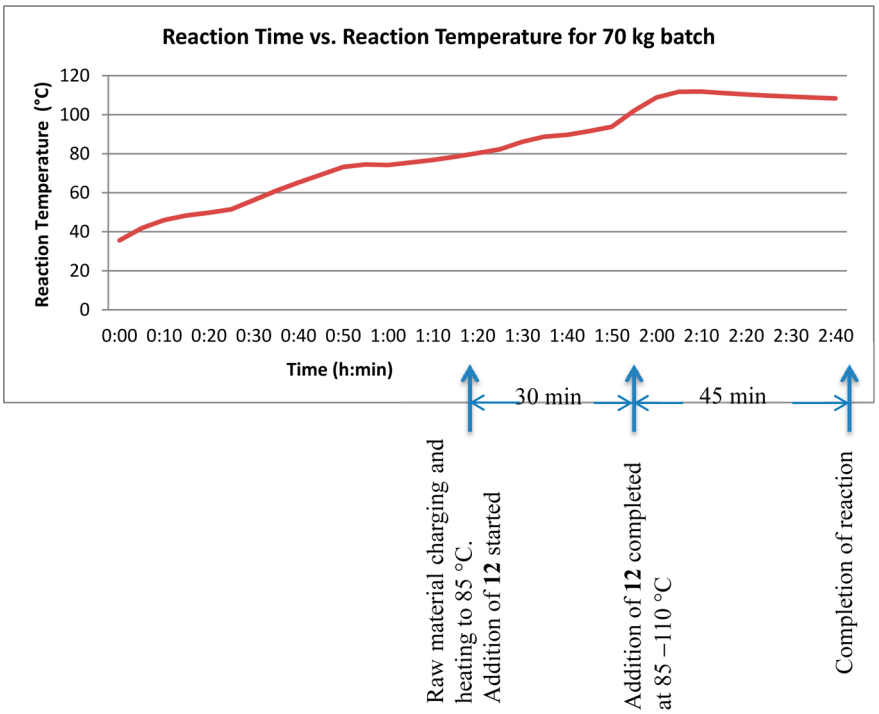


Figure 6. Detail of reaction temperature profile of 70 kg batch.

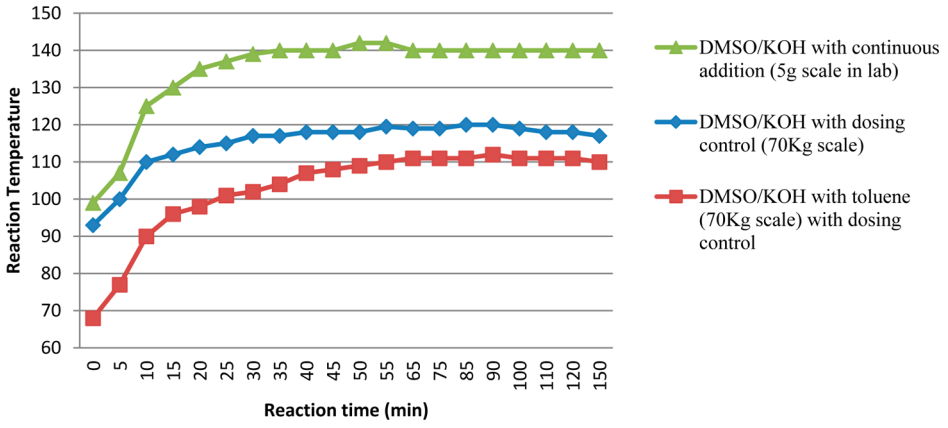
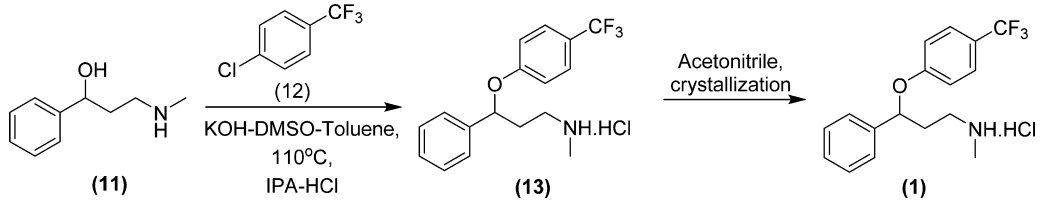


Figure 7. Reaction temperature trend during addition (with and without toluene). Note: In both DMSO/KOH and DMSO/KOH/toluene systems, the addition time was the same (150 min).

Scheme 3. Improved process for 1



reaction mass was adjusted to 2 to 3 using IPA/HCl (200 L). The resulting suspension was stirred for another 2 h, followed by the distillation of 20% (~124 L) of the toluene below 75 °C under vacuum. The concentrated reaction mass was cooled to 0–5 °C, and the precipitated solid was filtered off using an ANF and washed with toluene (310 L) to afford crude **1**. The crude product **1** was recrystallized from acetonitrile (700 L) in a 1 kL SS reactor to obtain 46.5 kg (71.7%) of **1** as a white powder with a HPLC purity of 99.94%.

^{1}H NMR (200 MHz, DMSO-d_6): δ ppm 2.54 (s, 3H), 9.32 (s, NH), 3.01 (t, J = 7.16 Hz, 3H), 2.24–2.29 (m, 2H), 5.74 (d, J = 4.9, 2.8, 1H), 7.1 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.2–7.5 (5H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 32.4, 34.2, 45.23, 76.55, 116.37, 126.02, 121.57, 126.02, 116.37, 124.39, 140.07, 126.67, 128.72, 128; MS: calcd for $C_{17}H_{18}F_3NO$ 309.1340 (M^+), found 310.1354 (M + H^+); IR (KBr) 2961, 2783, 2732 cm^{-1} (aliphatic CH), 2490, 2451, 2361 cm^{-1} (N^+H), 1616, 1518 cm^{-1} (aromatic C═C), 1476, 1429

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Table 13. Yield comparison between the previous and current processes

		process 1: $AcNMe_2$–NaOH		process 2: DMSO–toluene–KOH			
entry	input (g)	output (g)	yield (%)	crop-1 (g)	crop-1 yield (%)	crop-2 (g)	crop-2 yield (%)
1	100	115	55	150	71.77	24	7.00
3	100	115	55	151	72.2	23	6.6
4	100	116	55.5	149	71.2	25	7.2

cm^{-1} (aliphatic CH), 1330, 1244, 1109 cm^{-1} (C–O), 1164 cm^{-1} (C–N), 844, 699 (CH aromatic).

***N*-Methyl-*N*-(3-phenyl-3-(4-(trifluoromethyl)-phenoxy)propyl)acetamide (14):** ^1H NMR (400 MHz, DMSO-d_6): δ ppm 2.1 (t, J = 8.4 Hz, 2H), 2.8 (s, 3H), 2.9 (s, 3H), 3.5 (m, 2H), 5.5 (m, 1H), 7.1 (d, J = 7.2, 2H), 7.25 (t, J = 9.2 Hz, 2H), 7.4 (d, J = 7.2 Hz, 2H), 7.45 (t, J = 9.2 Hz, 1H), 7.56 (d, J = 6.8 Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6): δ ppm 43.7, 46.49, 76.5, 77.3, 116.1, 126.8, 127.7, 128.6, 140.7, 160.4, 169.6; MS: calcd for $C_{19}H_{20}F_3NO_2$ 351.1446 (M^+), found 352.1450 (M + H^+); IR (KBr) 3063 (aromatic CH), 1650, 1643 (C=O), 2928.68 cm^{-1} (aliphatic CH), 2490, 2451, 2361 cm^{-1} (N^+H), 1614, 1516 cm^{-1} (aromatic C=C), 1454, 1425 cm^{-1} (aliphatic CH), 1326, 1240, 1050 cm^{-1} (C–O), 836, 702 (CH aromatic).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Notes

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■ ABBREVIATIONS

ACN	acetonitrile
ANF	agitated Nutsche filter
ANOVA	analysis of variance
CT water	cooling tower water
d	day
DMA	*N*,*N*-dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DoE	design of experiment
equiv	equivalent
EtOAc	ethyl acetate
h	hour
HCl	hydrochloride
HPLC	high-performance/pressure liquid chromatography
IPA	isopropanol
kcal	kilocalorie
kJ	kilojoules
kL	kilolitre
kmoles	kilomoles
KOH	potassium hydroxide
KSM	key starting material (compound **11**)
MeOH	methanol
Mr	mass curve
MUSD	million U.S. dollars
NaH	sodium hydride
NaOH	sodium hydroxide
ND	not detected
NMP	methylpyrrolidone
Qr	heat flow curve
RC1e	reaction calorimetry
RT	room temperature (25–30 °C)
SS	stainless steel
TBAB	tetrabutylammonium bromide
t-BuOK	Potassium *tert*-butoxide
Temp	temperature
THF	tetrahydrofuran
Tr	reaction temperature curve
wrt	with respect to
UOM	unit of measurement
USD	U.S. dollars

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(24) Although equation 2 indicates to reduce the DMSO volumes in order to minimize the impurity, we proposed 2−2.5 volumes for the reaction to make sure that in the worst-case scenario (evaporation of all toluene) some solvent is present in the system.
(25) Figure 7 shows that the maximum heat is liberated during the addition of compound **12**. Therefore, a slow addition helped in controlling the exothermicity of the reaction.