Design of New Reaction Conditions for the Sugasawa Reaction Based on Mechanistic Insights[‡]

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Abstract:

A process to prepare 2-propionyl-4-bromoaniline by ortho acylation of 4-bromoaniline under Sugasawa conditions was developed. Upon scale-up in a pilot plant, the process gave lower yields than in the laboratory in four out of five plant runs. Analysis of the pilot-plant data, in conjunction with reaction calorimetric experiments, showed that expulsion of HCl from the reaction medium was key for obtaining high product yields. New reaction conditions were subsequently developed for carrying out ortho acylation of 4-bromoaniline (1). The reaction mixture containing aniline/BCl$_3$/AlCl$_3$/C$_2$H$_5$CN was added to a refluxing solution of toluene to allow for substantial HCl expulsion and thus obtain the optimum yield of the desired product. Aniline hydrochlorides were also shown to be suitable starting materials under these conditions. Mechanistic implications of these findings are discussed. The new reaction conditions significantly increased the yield.

Introduction

Ortho acylation of anilines by condensation with a nitrile in the presence of BCl$_3$ and AlCl$_3$ is a powerful method in organic synthesis and is commonly referred to as the Sugasawa reaction.[1] This transformation has gained greater synthetic importance as *o*-acyl anilines are preferred precursors in building a variety of medicinally useful heterocycles.[2−4] In one of our antifungal projects[5] we needed an efficient synthesis for making multikilogram quantities of quinazoline **3** which was made from *o*-acyl aniline **2**.

The *o*-acyl aniline **2** has been made from 3′-bromopropiophenone (Aldrich price > $2000/kg) in two steps[2] as shown in Scheme 1. As the starting material is expensive and the reaction conditions are not conducive to large-scale manufacturing, we explored the ortho acylation of readily available 4-bromoaniline **1** using propionitrile/BCl$_3$/AlCl$_3$ and Sugasawa reaction conditions. Ortho acylation of 4-bromoaniline **1** with propionitrile mediated by BCl$_3$ with AlCl$_3$ as the auxiliary Lewis acid had been reported in the literature[6]

[‡] Dedicated to Professor Andrea Vasella on the occasion of his 60th birthday.
(1) Sugasawa, T.; Toyoda, T.; Adachi M.; Sasakura, K. *J. Am. Chem. Soc.* **1978**, *100*, 4482.
(2) Earley, J. V.; Gilman, N. W. *Synth. Commun.* **1985**, *15*, 1271−1276.
(3) Houpis, I. N.; Molina, A.; Douglas, A. W.; Xavier, L.; Lynch, J.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 6811−6814.
(4) Tabuchi, S.; Ito, H.; Sogabe, H.; Kuno, M.; Kinoshita, T.; Katumi, I.; Yamamoto, N.; Mitsui, H.; Satoh, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1−15.
(5) Nussbaumer, P. WO 9628430, 1996.
(6) Yaegashi, T.; Sawada, S.; Nagata, H.; Furuta, T.; Yokokura, T.; Miyasaka, T. *Chem. Pharm. Bull.* **1994**, *42*, 2518−2525.
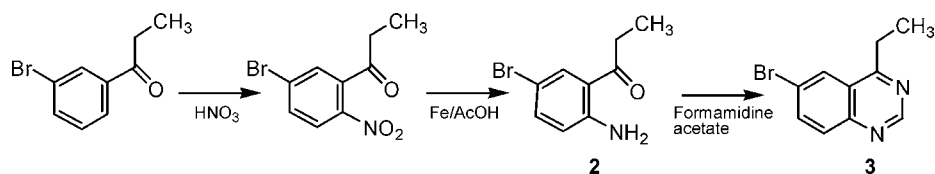
to give the acylated product in 9% yield. By switching from refluxing benzene to refluxing toluene, we improved the yield to 50%. Using this acylation as a key step, we developed a two-step process for producing 6-bromo-4-ethylquinazoline **3** in 44% isolated yield (Scheme 2; see method A in the Experimental Section); the final step, as before, comprises the reaction of **2** with formamidine acetate to give **3**.

The process based on these experiments was scaled-up by a factor of about 800 in a pilot plant, but gave the product in lower yield, on scale-up, in four out of five pilot-plant batches. The causes for the lower yields were then investigated, and these studies led to a development of modified reaction conditions that made the reaction more rugged, reproducible, and higher-yielding compared to the classical mix-reflux conditions.

Results and Discussion

Conversion of 1 to 2. Initial process development efforts focused on enhancement of the reactivity of **1** to obtain reasonable product yields. By changing the addition sequence and the stoichiometry of various reagents, and performing the reaction in xylenes at reflux (Table 1, item E), an efficient process to produce **2** in 50% yield was developed. Upon reaction of **2** with formamidine acetate, **3** was obtained in an overall yield of 44% (based on **1**). A key finding was that the order of reagent addition was not critical. Consequently, it was possible to develop a safer process wherein controlled addition of liquid reagents (see below) was performed for the highly exothermic steps vs the classical Sugasawa conditions, in which the highly exothermic addition of solid AlCl$_3$ to the aniline/BCl$_3$/nitrile mixture is performed (Table 1, item A).

Although all the initial experiments were done in refluxing xylenes, refluxing toluene gave similar yields, and the optimized procedure was developed using toluene as the solvent. At the optimal conditions, a solution of **1** in toluene at room temperature was added to a suspension of AlCl$_3$ in toluene at −10 °C. Pressurized BCl$_3$ was then added as a liquid at −10 °C, followed by propionitrile addition at about −5 °C. The reaction mixture was heated to reflux (103−107 °C) and held at reflux for 3 h to produce the cyclic precursor to product **2**. HCl evolution occurred during this process. After cooling to room temperature, the reaction mixture was poured slowly into a vessel containing water, thus hydrolyzing the cyclic precursor to give **2**. After allowing the reaction mixture to settle into two layers at 55 °C, the lower aqueous layer was removed. The desired

Scheme 1

Table 1. Initial experiments to enhance the yield of 2

molar ratio (**1**:C$_2$H$_5$CN:BCl$_3$:AlCl$_3$)	addition sequence of reactants and reagents	yield (%)
A. 1:2:1.1:1.2	Add BCl$_3$/xylene into **1**/C$_2$H$_5$CN solution, then add AlCl$_3$ & reflux	50
B. 1:4.6:1.1:1.2	Add **1**/C$_2$H$_5$CN solution into BCl$_3$/xylene then add AlCl$_3$ & reflux	44
C. 1.3:4.7:1:1.4	Same as B, but use more **1** and more AlCl$_3$ & reflux	21
D. 1:4.6:1.1:1.2	Same as B, but use **1** HCl salt	47
E. 1:4.6:1.1:1.2	Add **1**/C$_2$H$_5$CN solution into a mixture of AlCl$_3$ and BCl$_3$/xylene solution & reflux	44
F. 1:1.2:1.05:1.26	Add C$_2$H$_5$CN into BCl$_3$/xylene, add **1** at room temperature, then add AlCl$_3$ & reflux.	47

Table 2. Process data from scale-up reactions

	lab process	plant batches				
		1	2	3	4	5
Isolated yield of **3**, %	44	35	38	38	40	50
HPLC: area % of **2**	53.6	47.1	50.0	50.0	49.9	58.0
time to heat, h:min	1:50	1:30	2:00	1:00	1:30	2:20
reflux time, h:min	3:00	4:00	4:00	4:00	5:00	5:00
amount distilled, L	N/A	64	135	96	101	232
no. of distillate returns	total reflux	1	3	2	10	10
batch temperature, °C	105−107	103−104	102−104	103−104	104	105−107
jacket temperature,°C	107−110	103−105	104−105	104−106	105	112

Scheme 2
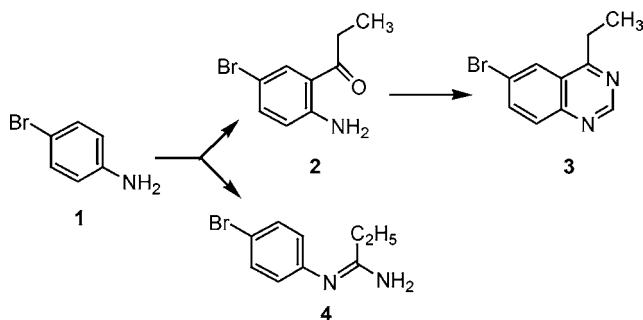
product **2** was in the organic phase, and **1** and **4** were in the aqueous phase.

Although pure **2** could be isolated by evaporation of the solvent, the process was streamlined to allow production of **3** without the isolation of **2**. First, a vacuum distillation of the organic layer was performed to remove toluene, excess propionitrile, and water. Formamidine acetate and ethylene glycol solvent were added, and the mixture was heated to reflux (105−120 °C) to give **3**. Ammonia was formed during the reaction. A vacuum distillation was then performed to remove additional toluene. Product **3** precipitated by the addition of water to the reaction mixture and cooling to 0−5 °C; the mixture was held at this temperature for 1.5 h, and **3** was isolated by filtration and drying. An overall yield of 44% of **3** was obtained.

This rather low yield was attributed primarily to low yield of the ortho acylation reaction based on (a) the near 90%

yield of **3** obtained when isolated **2** was used and (b) HPLC analyses of ortho acylation reaction mixture for **2**. The low yield of Sugasawa reaction was, in turn, related to two factors: (a) incomplete conversion of the starting material **1** and (b) formation of a competing amidine byproduct **4** as shown in Scheme 2.

Pilot-Plant Scale-Up. Five batches were prepared in the pilot plant based on the above procedure. Unlike the laboratory procedure, the ortho acylation step was not performed under total-reflux conditions. Instead, the vapors were directed to a separate vessel for condensation, the contents of which were returned to the reactor periodically. This modification was prompted by concerns over the possible breakage of the glass condenser on top of the reactor, which might result in a violent reaction between the ethylene glycol condenser coolant and BCl$_3$ and AlCl$_3$ in the reactor. Process data, including the isolated **3** yields from the pilot-plant runs, are summarized in Table 2. In comparison to the laboratory yield, the isolated yields of **3** in batches 1−4 were lower, whereas that of batch 5 was higher. HPLC analyses of the ortho acylation hydrolysis mixture, performed to allow separate determination of the yield of **2** and thus decouple the scale-up performance of the two steps, indicated that lower yields of **3** in batches 1−4 were correlated with lower yields of **2**.

Examination of the data shows that the key process variable that was changed in batch 5 was the jacket temperature at reflux (viz., 112 vs ≤ 106 °C in the first four

batches). The higher jacket temperature at reflux in batch 5 is expected to result in greater heat-input rate to the reaction mixture according to the following equation

$$Q = UA(T_j - T_r) \qquad (1)$$

where:

Q = heat input rate, W

U = overall heat transfer coefficient between jacket and

reaction mixture, $W/(m^2 \cdot °C)$

A = heat transfer area, m^2

T_j, T_r = jacket and batch temperatures, respectively, °C

With a greater heat input rate at reflux, where the batch temperature hardly changes, the boilup rate increases, as evidenced by the greater amount of condensed vapors collected in batch 5 relative to the other batches (232 vs ≤ 135 L). Heat-input rates in the plant batches were estimated for batches 4 and 5 using measured values of 375 $W/(m^2 \cdot °C)$ for the overall heat transfer coefficient U in the plant reactor.[7] Although the latter value was determined in experiments with water in the reactor, it was nevertheless useful to calculate an upper bound for U, and thus the heat-input rate. The heat transfer area (2.12 m^2) was determined from knowledge of the wetted area at two fill-volumes, viz., 1.83 m^2 at 300 L and 3.02 m^2 at 600 L, and linear interpolation at the actual reaction volume. From these results, the heat-input rates per unit mass in batches 4 and 5 were determined to be 5.7 and 15.2 W/kg, respectively. Thus, in batch 5, the heat input rate per unit mass was more than 2.5 times greater than for the previous batches. Evidently, the reaction performance depended on the heat-input rate at reflux, and hence the boilup rate.

The boilup rate per se, however, cannot account for the lower yield in the first four batches, since the rate of a reaction depends on reactant concentrations and temperature, neither of which changed appreciably in the plant batches (Table 2). However, the boilup rate could affect the concentration of a volatile component in solution that impacts product selectivity. The most obvious such component is the HCl formed as a byproduct, most of which is produced as an offgas. It was thus necessary to investigate more thoroughly the role of heat-input rate and its impact on the boilup rate, the HCl-removal rate, and the selectivity to **2** vs **4**.

Follow-up Experiments: Impact of Heat-Input Rate. Subsequent experiments were performed using a Mettler-Toledo RC1 reaction calorimeter to measure the effect of the heat-input rate on reaction selectivity. A schematic diagram of the apparatus is given in Figure 1; details are given in the Experimental Section. In the RC1, the quantity UA, comprising the product of the overall heat transfer coefficient U and the heat transfer area A, was determined as part of the experiment, and the batch and jacket temperatures were continuously data-logged. The heat-input rate could thus be calculated directly from eq 1. Additionally, the reaction mixture composition was determined using
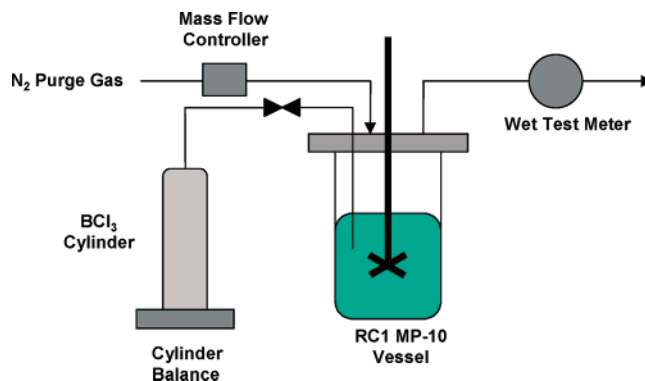
(7) Streemke, J. W.; Khan, S. Unpublished results.

Figure 1. Schematic diagram of RC1 apparatus.

HPLC to quantify reactant conversion and product yields and selectivities as functions of reaction time.

An experiment was first performed in which a heat-input rate corresponding approximately to that of batch 5 was used. In the latter experiment, when the batch temperature approached 105 °C, the temperature control mode in the RC1 was changed from batch to jacket temperature control to simulate the pilot plant's temperature control method. The jacket temperature was then increased gradually to maintain an average temperature difference of about 2.5 °C between the jacket and the batch temperatures, giving an average heat-input rate of 16.5 W/kg (vs 15 W/kg in batch 5). Temperature and concentration profiles are shown Figure 2. The figure indicates that when the reaction is terminated after a 3-h hold at a batch temperature of 105−107 °C, the fractional molar yield of **2** is 0.559 (i.e., about 56%), with an amidine **4** yield of 0.222 and incomplete conversion of **1**. A good mass balance closure is obtained (96%). Furthermore, the rate of amidine **4** formation during reflux is lower than that of **2**. For example, at a reaction time of 2.3 h, the yield of **2** and amidine **4** molar yields are 0.195 and 0.120 respectively; at a reaction time of 5.1 h, the yield of **2** triples (0.557), whereas that of amidine **4** barely doubles (0.222).

To evaluate how a lower heat-input rate impacts yields relative to the base case illustrated in Figure 2, a subsequent experiment was performed using a lower jacket temperature to give a heat-input rate more similar to that in plant batch 4 (Figure 3), namely, 7 W/kg. The lower heat-input rate also resulted in a slightly lower batch temperature (<2.5 °C) during reflux. Similar lower batch temperatures were also observed at lower jacket temperatures in plant batches 1−4 (Table 2).

The lower heat-input rate did not affect the overall consumption of **1** significantly (Figure 4), but had a large impact on the molar yield of **2** (Figure 5), the latter being significantly lower (0.414 vs 0.559) at the lower heat-input rate. The yield of **2** at the lower heat-input rate is 74% that of the base case value, and the change is comparable to plant results, where batch 4 value was about 80% that of batch 5. Thus, the lower yield of **2** when using a lower heat-input rate per unit mass was replicated in the laboratory. Note that the yield comparisons are done at the same 5-h reaction time, corresponding to about 3 h at reflux. Figure 5 also shows that longer time at reflux did not impact yield of **2** significantly at lower heat-input rate.
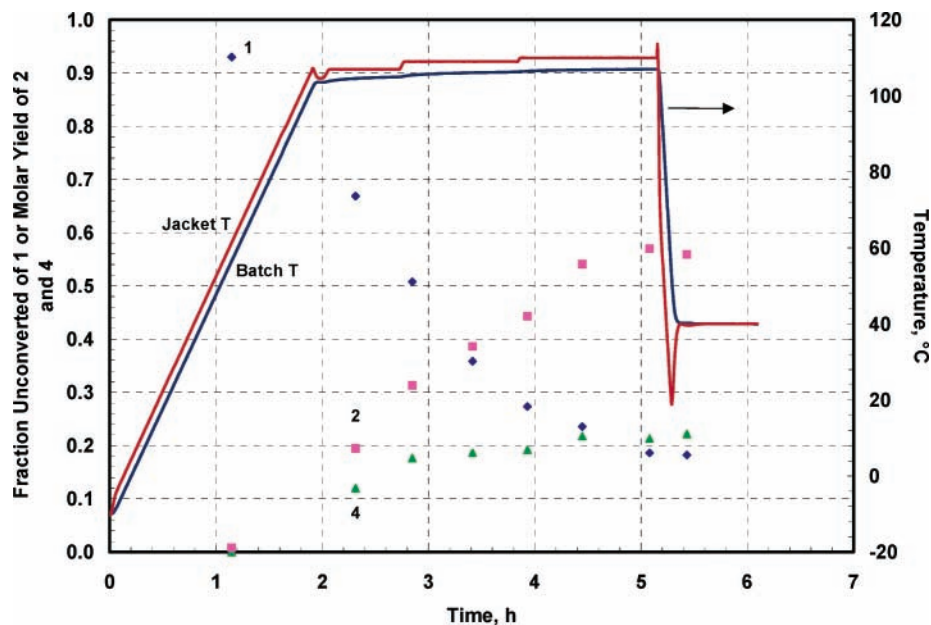
Figure 2. Temporal temperature and concentration profiles of compounds 1, 2, and 4 in experiment corresponding to same heat input rate as pilot-plant batch 5.
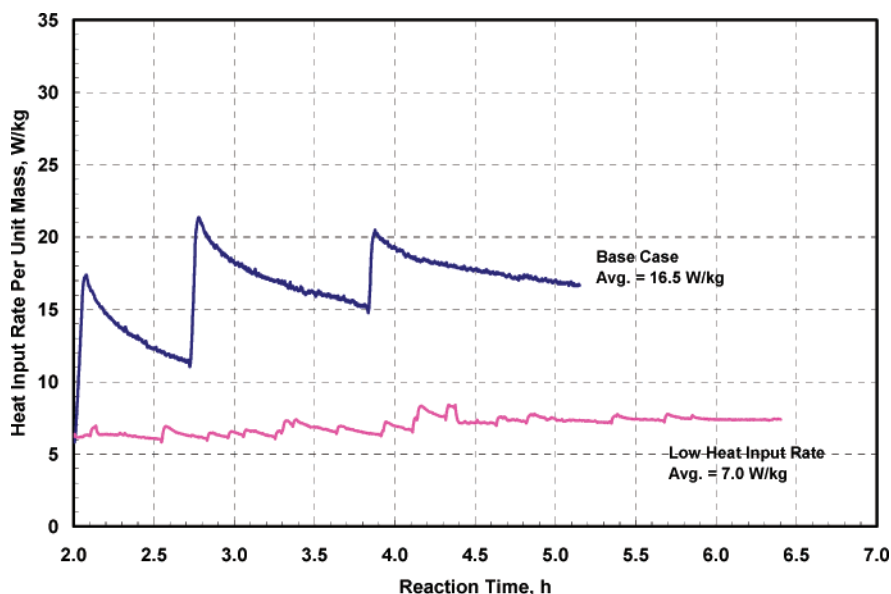

Figure 3. Heat input rate profiles in experiments to simulate pilot-plant batches 4 and 5.

The results in Figures 4 and 5 are in agreement with the greater yields of **2** obtained in plant batch 5 relative to those in the other plant batches. As mentioned earlier, the heat input rate does not appear to impact consumption rate of **1** greatly. Thus, its impact on selectivity indicates that it must affect another factor. With a greater heat input rate, it is hypothesized that the reflux rate is greater, allowing more HCl to be evolved per unit time, and thus keeping less HCl in solution. Using a wet test meter placed at the exit of the RC1 reactor vessel, the gas-evolution rate could be determined (see Experimental Section). Figure 6 shows clearly that a greater off-gas evolution rate is obtained in the experiment at the higher heat-evolution rate. With more HCl left in the liquid phase, with conversion being minimally impacted, lower selectivity for **2** results.

Follow-up Experiments: Impact of HCl Removal Rate. To probe further the impact of HCl offgas on product selectivity, two additional experiments were performed: In the first, the reactor was closed during the reaction. Thus, any HCl gas evolved escaping from the liquid-phase accumulated in the headspace. The resulting greater pressure increases HCl concentration in the liquid-phase according to Henry's Law:[8]

$$P_i = Hx_i$$

where:

P_i = partial pressure of component i

H = Henry's Law coefficient

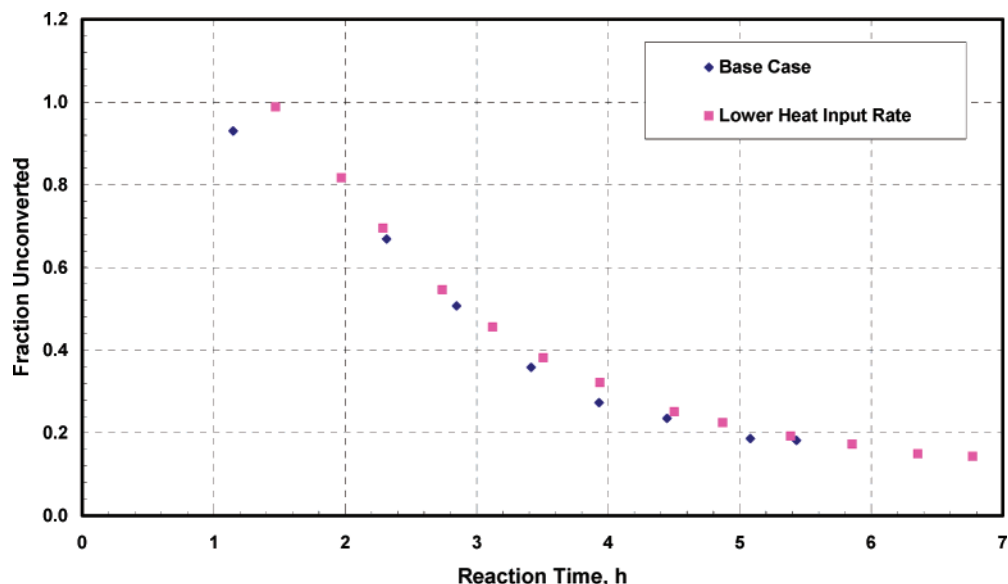x_i = liquid-phase mole fraction of component i

Figure 4. Conversion of **1** at two different heat input rates corresponding to pilot-plant batches 4 and 5.
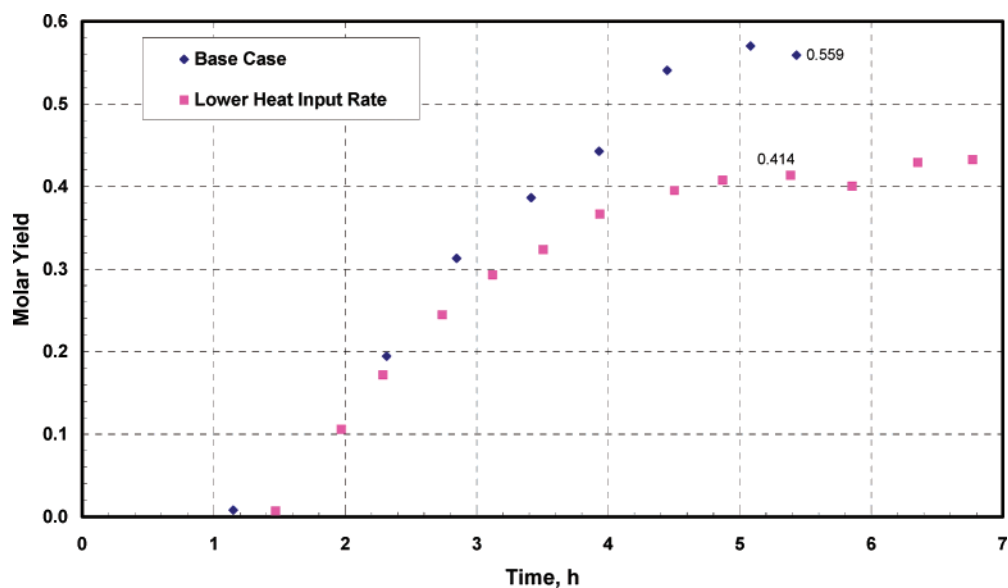

Figure 5. Yields of **2** at two different heat input rates corresponding to plant batches 4 and 5.

In the second experiment, the toluene solvent (bp 111 °C) was replaced by higher-boiling xylenes (bp 137−144 °C), and the reaction mixture was heated to 107 °C. This temperature corresponds to the upper temperature reached during the reaction in toluene. With toluene as solvent, reflux occurs at 103−107 °C because propionitrile, which boils at 97 °C, is present in the reaction mixture. Because of the higher boiling point of xylene, less reflux should occur, and therefore the HCl gas evolution rate will be diminished. In both these experiments, then, the HCl concentration in the liquid phase is expected to be greater than that in the previous set of experiments, and on the basis of the results in Figure 5, one should expect a lower selectivity of **2**.

The results from these experiments are compared in Figures 7, 8, and 9 to those from the low-heat input run. The figures indicate that a greater HCl liquid-phase concen-

tration, arising from either a sealed reactor or a lower boilup rate due to absence of reflux, does not impact conversion of **1**, but that it decreases substantially the yield of **2** and increases that of the amidine. Since conversion of **1** is hardly impacted, this means that a greater liquid-phase concentration decreases selectivity of **2** while increasing that of amidine **4**.

Mechanistic Interpretations. The published[9] reaction mechanism (Scheme 3) for the Sugasawa reaction, which was inferred on the basis of NMR spectroscopic examination of various intermediates, involves formation of a supercomplex by reaction of two initial complexes, one comprising the aniline and BCl_3 and the other the nitrile and the auxiliary Lewis acid. With $AlCl_3$ as the auxiliary acid, $HAlCl_4$ is eliminated from the supercomplex with the formation of the ortho-functionalized intermediate. Low conversions are typi-

(8) Sandler, S. I. *Chemical and Engineering Thermodynamics*; John Wiley and Sons: New York, 1977.

(9) Douglas, A. W.; Abramson, N. L.; Houpis, I. N.; Karady, S.; Molina, A.; Xavier, L. C.; Yasuda, N. *Tetrahedron Lett.* **1994**, *35*, 6807−6810.
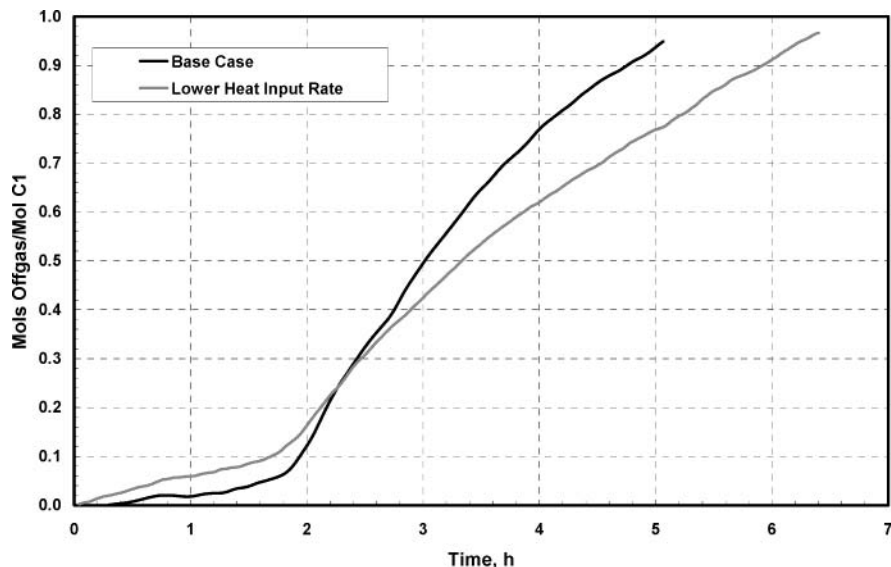
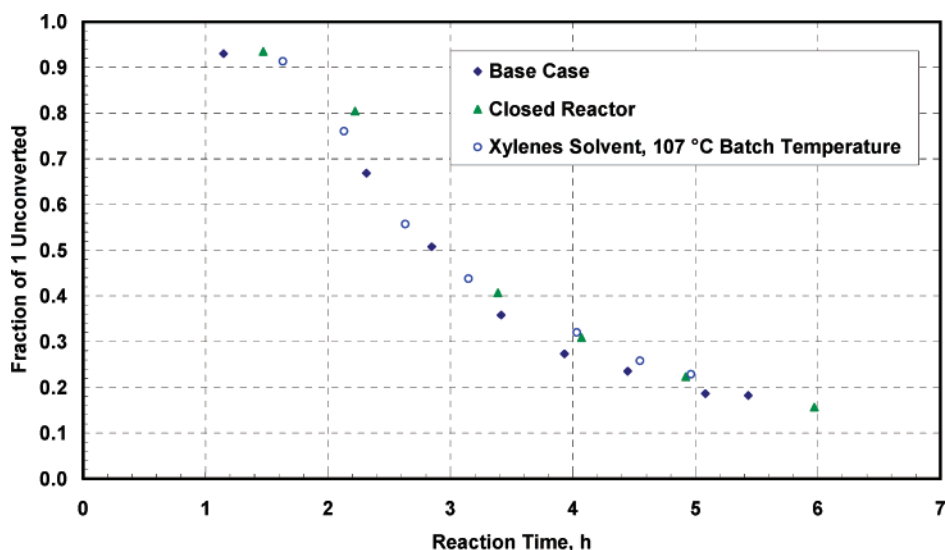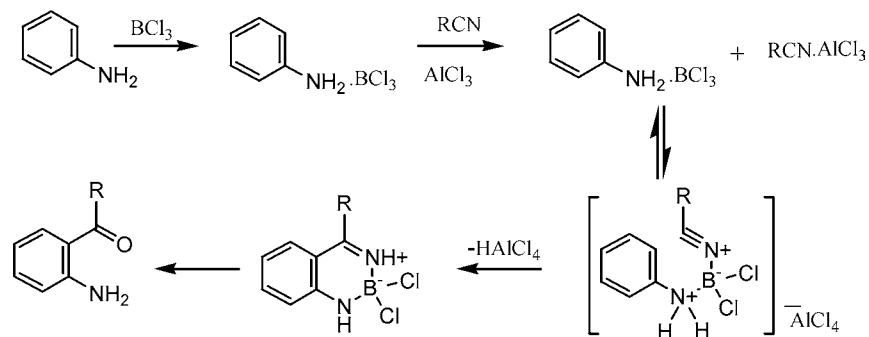**Figure 6.** Impact of heat evolution rate on HCl offgas rate.

Figure 7. Reactivity of 1 in three experiments: (a) low heat input rate, (b) sealed reactor, (c) with xylenes as solvent.

Scheme 3. Published reaction mechanism of the Sugasawa reaction[9]

cally attributed to the generation of the anilinium hydrochloride salt of the starting aniline.[3]

On the basis of the results discussed so far in our work, the following fundamental observations became clear: (a) aniline HCl salt is as effective as the corresponding aniline in the Sugasawa reaction without affecting the yield of ortho-functionalized product as evidenced by entry D in Table 1; (b) 1 equiv of HCl is liberated during these reaction conditions; (c) the formation of the supercomplex and the following ortho functionalization is independent of the order of mixing the reagents; and (d) the expulsion of HCl from the reaction mixture is required to increase the ortho acylation yield compared to the amidine formation.

To understand the basics of this ortho acylation process and to facilitate the design of proper reaction conditions, we performed a series of experiments listed in Table 3, varying
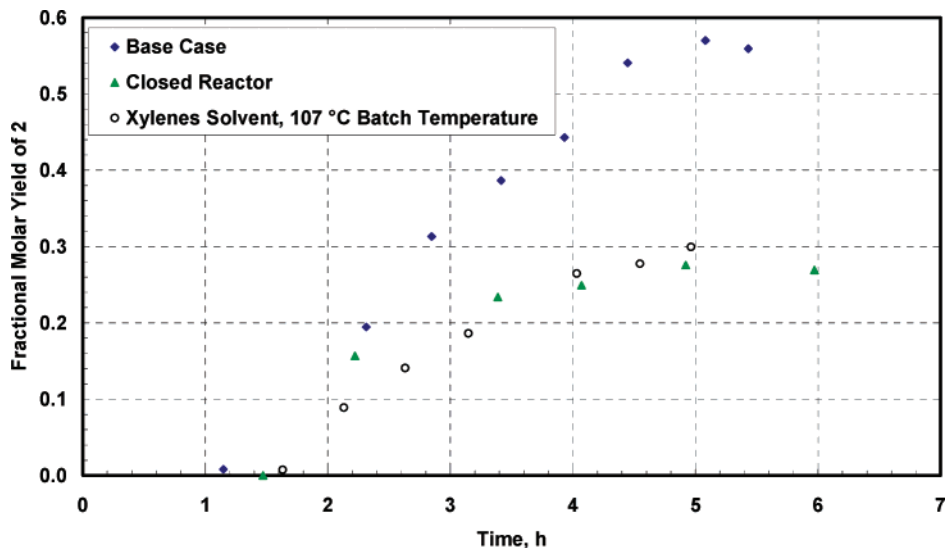
Figure 8. Molar yield of **2** in three experiments:: (a) base case, (b) closed reactor, (c) with xylenes as solvent.
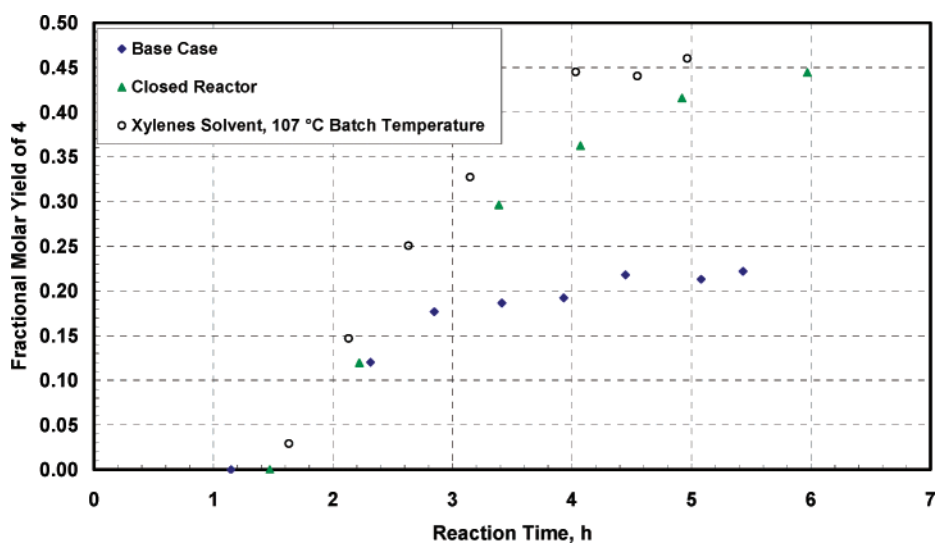

Figure 9. Amidine (**4**) yield in three experiments: (a) base case, (b) closed reactor, (c) with xylenes as solvent.

Table 3. Role of AlCl₃ and BCl₃ in ortho acylation of 4-bromoaniline **1**

reaction conditions	**1** [%]	**2** [%]	amidine **4** [%]
no BCl₃, no AlCl₃, reflux, 3 h	99.8	0	0
no BCl₃, 100 °C, 5 min	0	0	100
no AlCl₃, 101 °C, 0.5 h	62	16	22
no AlCl₃, 101 °C, 3 h	45	15	40

Table 4. Effect of time from 80 °C to reflux on the yield of **2**

heating time from 80 °C to reflux, [min]	yield, of **2** after 3-h hold at reflux [%]
5	61
30	56
60	48

the described process conditions. In the absence of BCl₃ and AlCl₃ (entry 1) aniline **1** and propionitrile are quite stable to refluxing toluene conditions. When BCl₃ was excluded from the reaction mixture, amidine formation was almost quantitative by the time internal temperature reached 100 °C. In the absence of AlCl₃, amidine formation predominated over ortho acylation. At 3 h refluxing, amidine **4** was formed in 44% yield compared to the ortho-acylated **2** formed in 15% yield. It is interesting to see that the combination of BCl₃ and AlCl₃ in fact suppresses the amidine **4** formation. In addition, we observed that in a mixture of aniline **1**, propionitrile, BCl₃, and AlCl₃ when heated at 80 °C in toluene (nonrefluxing

conditions) there is no noticeable ortho acylation or amidine formation.

Knowing that there is no significant formation of ortho acylation or amidine formation up to 80 °C, experiments were performed in which the time from 80 °C to reflux was increased (Table 4). The reaction mixture was held for 3 h in each case. The results in Table 4 show clearly that as the time to reach reflux is prolonged, the yield of **2** decreases, implying further that the fast HCl removal is critical for higher yield of ortho acylation and for a reproducible process.

The New Process. With this information in hand and knowing that the expulsion of HCl from the reaction mixture and the time needed to take the reaction mixture to reflux
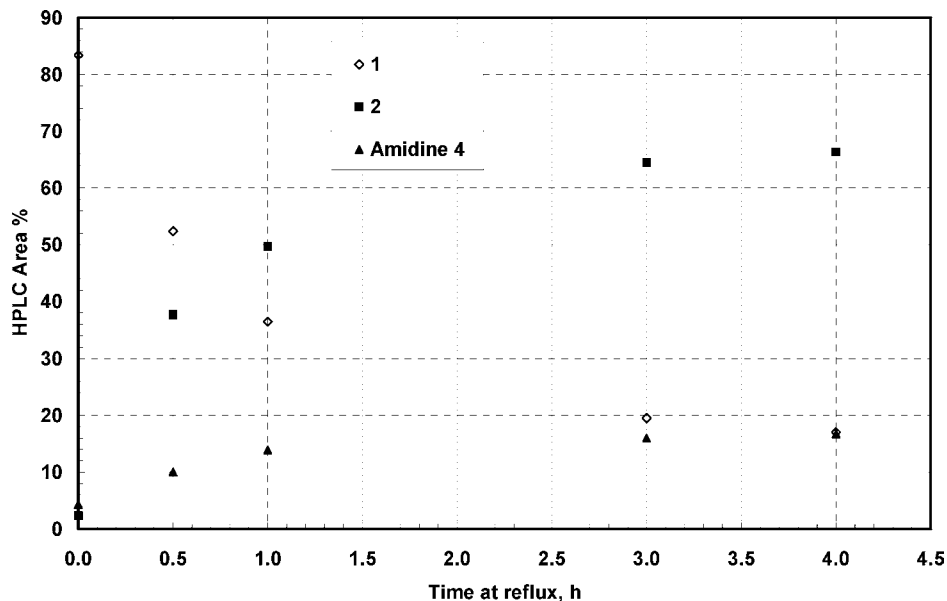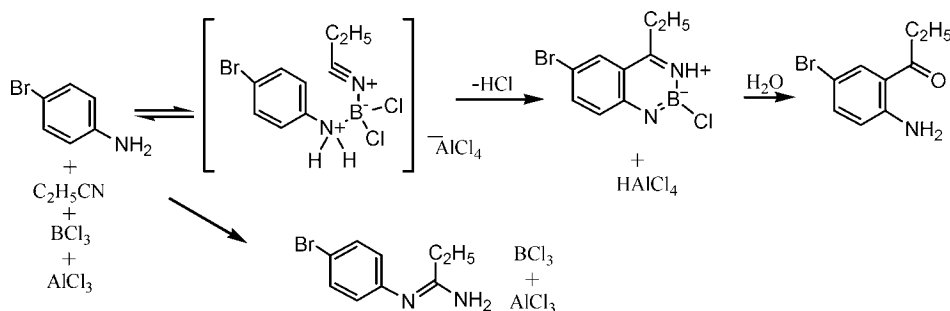
Figure 10. Relative product composition as a function of reflux time.

Scheme 4. Modified mechanism involving the expulsion of HCl

were crucial for the preferred ortho acylation, we designed new reaction conditions by combining all the reagents and reactants below 70 °C and adding this mixture to refluxing toluene[10] (see Method B in the Experimental Section). Time taken for the addition is not critical, but it is important to maintain refluxing conditions inside the reactor throughout the addition period.

Under these new reaction conditions, **2** was isolated in a 60% yield, the best result thus far using **1**. Figure 10 shows the results of such an experiment (HPLC area as a function of time at reflux).

On the basis of our observations that the elimination of HCl from the medium is crucial for the progress of ortho acylation, and that the order of mixing the reagents and reactants was not critical for the formation of the supercomplex, and taking into account the earlier NMR studies from the literature,[9] we propose a modified mechanism (Scheme 4).

Application of New Procedure to the Acylation of Other Anilines. The new procedure for ortho propionylation described above was tested with other anilines. These results were compared with the literature yields, and in each case the yields with the new conditions are superior (Table 5).

(10) Sparging with an inert gas such as nitrogen could be an alternative way for HCl expulsion, but it was not tried during this study.

Table 5. Propionylation of other nilines

X	yield using our new process [%]	lit. yield [%]
3-Br	72	46
2-Br	71	–
4-Cl	62	10
4-Cl, 5-Cl	36	4
4-CH₃	71	60
4-CH₃ (HCl salt)	71	–

Conclusions

The ortho acylation of 4-bromoaniline was studied in great detail with respect to optimization of yields and mechanistic details. The order of mixing of BCl₃, AlCl₃, C₂H₅CN, and aniline in toluene has no effect in the formation of supercomplex and the subsequent yield of the acylation product. Analysis of pilot-plant data following process scale-up and subsequent RC1 experiments showed that a higher jacket temperature at reflux, and thus a higher heat input rate, gave substantially higher product yield. These results, coupled with additional experiments in which greater liquid-phase HCl concentrations were obtained by either sealing the reactor

Table 6. Sources and purities of materials used

compound	purity (%)	source
4-bromoaniline	98	GIC
aluminum trichloride	99	Aldrich
boron trichloride	99.9	Scott Specialty Gases
propionitrile	97, water <0.2	Aldrich
toluene	99	Aldrich
formamidine acetate	99	SKW Trostberg
ethylene glycol	99	Aldrich

or using a higher-boiling solvent, demonstrated that expulsion of HCl from the reaction medium was of critical importance for achieving higher and reproducible acylation yields. On the basis of these findings, a new procedure involving the addition of mixture of reagents and reactants to refluxing toluene with a specific heat input was designed, and higher yields were achieved compared to those from the previous methods. A modified mechanism incorporating the expulsion of HCl was also proposed.

Experimental Section

Equipment and Materials. Reaction experiments were performed using laboratory glassware or a Mettler-Toledo RC1 reaction calorimeter. The RC1 reaction calorimeter was equipped with a 1.0-L glass MP-10 vessel and pitched-blade agitator (Figure 1). Calorimeter principles are discussed elsewhere.[11] All metallic inserts in the vessel were made of Hastelloy C. Liquid BCl_3, obtained as a pressurized liquid in a stainless steel cylinder at 50 psig initial pressure under He, was metered into the reaction mixture by placing the cylinder on a balance and controlling the addition to the reactor with a metering valve. The reactor outlet was attached to a condenser. The volume of HCl gas formed in the reaction was measured using a Ritter model TG05 wet test meter connected after the condenser. The wet test meter was filled with paraffinic white oil (Aldrich mineral oil, white, light, catalog no. 33,077-9) to minimize dissolution of HCl and thus measure gas volume accurately. The outlet of the test meter was directed to two scrubbers containing aqueous NaOH and attached in series. The wet test meter was attached to a data-logging system to allow automatic data collection.

The offgas rate during reaction was calculated as follows. Prior to the experiment, the rate of N_2 purge gas, which was set to constant value with a mass flow controller (Brooks model 5850i), was determined by numerical differentiation of the wet test meter output, which measures the cumulative gas volume. During the experiment, which was performed with N_2 purge gas, the rate of HCl offgas was determined by taking the difference of the total offgas flow rate during reaction (viz., N_2 + HCl) and that of the purge gas. The total offgas rate was also determined by numerical differentiation. The cumulative HCl volume was subsequently determined by numerical integration of the HCl flow rate. Sources and purities of all materials used are given in Table 6. All materials were used as received.

(11) Girgis, M. J.; Kiss, K.; Ziltener, C. A.; Prashad, M.; Har, D.; Yoskowitz, R. S.; Basso, B.; Repič, O.; Blacklock. T. J.; Landau, R. N. *Org. Process Res. Dev.* **1997**, *1*, 339−349.

Procedure. *6-Bromo-4-ethylquinazoline, 3 (Method A).* Thoroughly flush the 1-L vessel with dry nitrogen. Charge the reactor under nitrogen with 52.06 g of aluminum chloride and add (not exothermic) 148.79 g of toluene. Cool the slurry to ~10 °C and add (slightly exothermic, 20 W/kg) a solution (22 °C) of 55.23 g of 4-bromoaniline in 168.25 g of toluene at a rate of 4.47 g/min into the mixture at ~10 °C over 50 min. Rinse the addition funnel with 28.00 g of toluene. Add (not exothermic) 45.00 g of boron trichloride to the mixture at ~10 °C over 5 min, and purge the gas line with dry nitrogen through the scrubber. Add (exothermic, 50 W/kg) at a rate of 0.82 g/min, 73.88 g (95.70 mL) of propionitrile at ~10 °C over 90 min. Heat the contents at 1 C/min to 107 °C, under reflux and constant flow of nitrogen. As the batch temperature approaches 100 °C, gas evolution increases with a maximum rate of 150 mL/min, accompanied by an endotherm. Hold the reaction mixture at 107 °C for 3 h at reflux to obtain a yellow-brown homogeneous mixture. The cumulative amount of off-gas formed is 7.57 L. Cool the reaction mixture to 60 °C, stop the agitator, and let the reaction mixture separate into two layers. Take a sample of the bottom layer for analysis. Empty the reactor into a 2-L Erlenmeyer flask and rinse the reactor with 14.20 g of toluene.

Charge the MP10 reactor with 332.40 g of water. Heat the water to 55 °C and hold. Add the reaction mixture with stirring over a 2-h period from the 2-L Erlenmeyer flask into the MP10 reactor containing water under efficient stirring conditions. Maintain the batch temperature at 55 °C. The quench is exothermic and produces 0.47 L of HCl off-gas. Withdraw the contents of the MP-10 reactor and rinse the reactor and the dosing line thoroughly with 47.63 g of toluene and 110 g of water for 5 min. Transfer the reactor contents and toluene/water rinse into a 2-L LabMax glass reactor. Stir the mixture at 55 °C for 15 min. Stop the agitator to obtain two layers. Discard the bottom aqueous layer in a proper fashion. Take a sample from top layer. Wash the top organic layer three times with a total of 330 g of water. Transfer the organic layer to a 500-mL, four-necked, round-bottomed flask. Concentrate at 60−65 °C (20−100 mbar) to a final volume of 165 mL to obtain a light brown viscous oil (~37 g of **2** and 100 g of toluene). Cool to room temperature. Add 44.2 g of formamidine acetate and 128 g of ethylene glycol under nitrogen. Heat the suspension to 105 °C over 1 h to obtain a two-layer mixture, then distill off water, ammonia (byproduct) and toluene under atmospheric pressure to raise the internal temperature from 105 to 120 °C over 0.5 h. Ammonia evolution occurs when the batch temperature reaches about 70 °C. The cumulative amount of ammonia evolved is 10.79 L. The maximum flow rate of ammonia is about 210.6 mL/min, and occurs at a batch temperature of about 110 °C.

Reflux the homogeneous mixture at 119−120 °C by distilling off the azeotropic mixture of toluene, water and ethylene glycol, using a Dean−Stark trap continuously and maintain at 120 °C for 3 h. Take a sample when the reaction mixture is at 110 °C and analyze by HPLC. Add 15 mL of ethylene glycol into the pot containing a two-layer mixture

(top layer is **3** in toluene and bottom layer is ethylene glycol). Concentrate the contents at 60 °C (40−50 mbar) to distill off 45 mL of toluene. Cool the mixture to 20 °C and stir at room temperature to obtain a hazy mixture. Add 27 mL of water into the pot, then cool the suspension to 2 °C and maintain at 0−5 °C for 1.5 h. Filter off the solids at 0−5 °C through a polypropylene pad on a Büchner funnel. Rinse the flask with one-third of the cold filtrate, then wash the filter cake four times with a total amount of 240 mL of water. Hold the filter cake under vacuum (200 mbar) to dry for 2 h, then dry at 35 °C (30 mbar) for 2 days to afford 32.7 g of **3** (44% yield based on **1**) as a straw-yellow granular solid, mp 61.5−62.5 °C.

6-Bromo-4-ethylquinazoline, 3 (Method B). Charge a 1-L, three-necked, round-bottom flask (reactor A) under nitrogen with 49.00 g of aluminum chloride, then add 250 g of toluene. Cool the slurry to −10 °C and add 64.37 g of 4-bromoaniline **1** in portions (exothermic addition). Add (not exothermic) 47.23 g of boron trichloride to the mixture at −10 to −5 °C over 5 min and purge the gas line with dry nitrogen through the scrubber. Add (very exothermic!) 92.60 g (120 mL) of propionitrile into the reactor A (containing **1**/AlCl$_3$/BCl$_3$/toluene mixture) and allow the temperature to rise to no greater than 45 °C. Heat the reaction mixture to 63 °C over 10 min and maintain at 60−65 °C for 5 min to give a homogeneous solution.

Charge 213 g of toluene into reactor B under dry nitrogen. Heat to reflux (112 °C), distill off 24 mL (21 g) of solvent (toluene and water), and maintain the toluene solution at reflux. Add the solution from reactor A to the refluxing toluene over 45 min. Reflux the mixture vigorously at 106 °C for an additional 4 h to obtain a yellow-brown homogeneous mixture. It is important to maintain heat input rate at a value of 116 ± 10 W/kg of reaction mixture during hold period to remove HCl gas which is generated as a reaction byproduct (Figure 5). Total amount of HCl gas generated was estimated to be 7.23 L.

Add the reaction mixture to a 2-L reactor containing 500 g of water under efficient stirring over 0.5 h. Allow the temperature of the reaction mixture to rise to 45 °C from the heat released during the quenching procedure. Rinse the first reactor with 225 g of toluene and add to the quench mixture. Heat the mixture to 55 °C and stir the batch at 50−55 °C for 15 min. Some HCl gas (∼1.5 L) is also released during this step. Stop the agitation and allow the mixture to separate into two layers. Wash the top organic layer three times with a total of 360 g of water. Transfer the organic layer to a 500-mL, four-necked, round-bottomed flask and concentrate at 60−65 °C (20−100 mbar) to a final volume of 165 mL to obtain a light-brown viscous oil. Add 63.60 g of formamidine acetate and 173 g of ethylene glycol. Heat the suspension to 112 °C over 1 h to obtain a two-layer mixture, then distill off water, ammonia (byproducts), and toluene under atmospheric pressure to raise the internal temperature from 112 to 127 °C over 1 h. Reflux the homogeneous mixture at 127−131 °C by distilling off the azeotropic mixture of toluene, water, and ethylene glycol using a Dean−Stark trap and maintain at this temperature for 2 h. Cool the reaction mixture to 60 °C. Add 22 g (20 mL) of ethylene glycol and concentrate the contents at 60−70 °C (40−50 mbar) to distill off the toluene. Cool the mixture to 20 °C and add (slightly exothermic) 40 mL of water. Add seeds of **3**, cool the suspension to 2 °C, and maintain at 0−5 °C for 1.5 h. Filter off the solids at 0−5 °C through a polypropylene pad on a Büchner funnel. Rinse the flask with one-third of the cold filtrate (5 °C), then wash the filter cake four times with a total amount of 325 mL of water. Dry the filter cake at 40−45 °C (30 mbar) to afford 47.8 g of **3** (54% yield over two steps) as a straw-yellow solid; mp 61.5−62.5 °C.

Analytical Chemistry. The ortho acylation reaction mixture was analyzed using a Hewlett-Packard 1100 series HPLC. Known amounts of samples (by weight) were withdrawn periodically during the reaction and quenched immediately in a 50:50 mixture of methanol:water. The quenched mixture was diluted and then injected in the HPLC. The concentrations of **1**, **2**, and **4** in the sample were determined from the peak area and measured response factors of **1**, **2**, and **4**, determined using external reference standards. The amounts of **1**, **2**, and **4** in the reaction mixture were calculated by multiplying the concentrations with the total weight of the reaction mixture. From the latter and the amount of **1** charged to the reactor, conversion of **1** and molar yields of **2** and **4** were calculated.

After gaining more experience using this analytical technique, it was found that the HPLC area-% values of **1**, **2**, and **4** obtained from direct analysis of crude ortho acylation reaction mixture were also a good measure of reaction performance as these values correlated well with the isolated yield of **2**.