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N-Amination of Indoles on Pilot-Plant Scale via Simultaneous and Proportional Metering of Reagents

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ABSTRACT: The *N*-amination of indoles on large scale, utilizing a portable Coriolis mass flow metering and pumping system that provides precise dispensing of two reagent streams simultaneously and proportionally, is described.

INTRODUCTION

The *N*-amination of indoles was a chemical transformation that was common in the synthesis of a series of target molecules that were in preclinical and clinical development in our company. Early batches of the *N*-aminoindoles were prepared using the method of Somei and Natsume[1] whereby indoles were treated with hydroxylamine-*O*-sulfonic acid (HOSA) in DMF in the presence of solid KOH. Several limitations were encountered upon scale up of this protocol. For example, yields were variable, often below 50%, and were dependent upon agitation efficiency and on the quality and surface area of the KOH employed as the heterogeneous base in this process. In addition, there was a tendency for the KOH to cake up and block the bottom discharge valve.

Recently, we described[2] an efficient process for preparing *N*-aminoindoles reliably in high yields (Scheme 1) by treating indoles with HOSA and 2 equiv of KO*t*Bu (based on HOSA) employed to neutralize the acidic proton in HOSA (a monobasic acid) and to generate the indolyl anion **2**,[3] the reactive species. The underlying technology of the improved *N*-amination process was the protocol for introducing the reagents because poor conversions were observed when either HOSA or KO*t*Bu was added last in a batch reaction mode.[4] For example, less than 30 A% (HPLC) conversion to **3a** was observed when **2a** was generated using 1 equiv of KO*t*Bu upfront followed by 0.5 equiv HOSA added last in a batch sequence (theory limited to 50% because of protonation of **2a** during addition of the acidic HOSA). When employing ≥2 equiv KO*t*Bu upfront, conversions remained poor, presumably because the nucleophilic *tert*-butoxide ion competed with **2a** for the aminating agent, and a large excess of base favored *N*-deamination.[1b,5] Similarly, when KO*t*Bu was charged last in batch mode, less than 5 A% conversion to **3a** was observed. These observations were consistent with a scenario whereby the desired indolyl anion was generated in equilibrium with KO*t*Bu.[6] In contrast to batch-mode processes, high conversions were achieved when the reagents were dispensed in a simultaneous and proportional fashion as a means to operate in a reaction window that avoided a large excess of KO*t*Bu, but was maintained sufficiently basic in order to neutralize the acidic proton in HOSA and to generate a sufficient concentration of indolyl anion while the feeds and the *N*-amination process proceeded.

The parameters of the improved HOSA amination process were established in lab screenings. The general procedure consisted of preparing separate solutions of HOSA (2 equiv)[7] and KO*t*Bu (4 equiv) in NMP,[8] then drawing the solutions into gastight Teflon-glass syringes. In a separate reaction flask, a solution of the indole in NMP was prepared along with an initial charge of 0.05 equiv of KO*t*Bu. Efficient *N*-amination then resulted upon simultaneous and proportional dispensing of the reagent solutions to the indole solution over 2−4 h using programmed syringe pumps while maintaining 20−40 °C in the amination vessel. In a variation, the indole was predissolved in the HOSA/NMP solution,[3] and then the resulting HOSA/indole/NMP solution and the KO*t*Bu/NMP solution were similarly transferred simultaneously and proportionally to a third vessel in which *N*-amination occurred upon mixing of the reagent solution streams.[9] The two variations provided essentially identical amination performances. However, in the former variation, it was important to ensure efficient agitation in the amination vessel so that the HOSA/NMP and KO*t*Bu/NMP streams did not quench each other by coming into direct contact prior to fully mixing with the indole/NMP.

It was important to maintain proportionality of the reagents for the duration of the feeds to ensure that the reaction stayed within the desired operating space. In a robustness study, a 2.5% deviation in the relative feed of either reagent gave unacceptable conversions to **3a** (≤91 A%).[10] On lab scale, proportionality within 1% was readily achieved by carefully weighing the materials and by using calibrated syringe pumps, affording **3a** with quality suitable for downstream chemistry (≥93 A% conversion). Therefore, the challenge was to design a dual dispensing system for use on multikilogram scale with performance analogous to lab syringe pumps. Additional pilot-plant criteria included metered flow rates adjustable to about 2.5 L/min, suitability in an explosion-proof (XP)[11] environment, and portability and ease of operation in the field because it was anticipated that the amination technology would be transferred internally and externally to several piloting facilities of varying capabilities.

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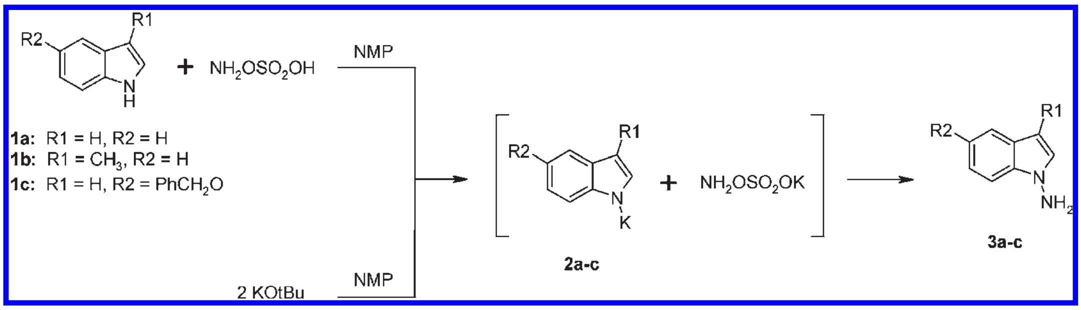
Scheme 1. *N*-Amination of indoles



EQUIPMENT DESCRIPTION, SETUP AND PERFORMANCE VERIFICATION

A compact and portable mass flow metering system was designed, assembled, and implemented in pilot-plant campaigns in the synthesis of a series of intermediates that required simultaneous and proportional dispensing of two reagent streams to effect efficient *N*-amination of indoles. The main components of the metering system were a dual pump and two mass flow meter assemblies.[12] Synchronized pumping of two separate solutions was provided by a pump with two heads driven by a single electric motor. Flow could be manually and independently adjusted between 0 to 100% of the 20-mm stroke length at each head, corresponding to rates ranging from 0 to 2.4 L/min (0−38 US gal/h). Fine tuning was feasible because the stroke lengths were adjustable in 0.02-mm increments. The pump was mounted on a portable cart and was powered (120 V) by an XP receptacle connected by flexible power cord to an XP toggle switch on the cart.

Flow was measured by Coriolis mass flow meters (MFM) in units of mass per unit time. Unlike devices that measure flow in volume per unit time, MFMs provided extremely accurate mass flows (manufacturer specifications: ±0.2% of flow rate; 0−6 kg/min through the 1/8-in diameter tubes for the MFMs utilized in this study) that were essentially unaffected by fluctuations in temperature, pressure, viscosity, or even composition (e.g., entrained bubbles). Although MFMs are often hard-piped, in this application they were mounted on portable stands. Due to background vibration in one facility, vibration isolation pads were placed under the stands during operation.

Each MFM functioned by generating a voltage output signal that was proportional to the mass flowing through it that a transmitter relayed to a flow monitoring device (FMD). The FMD digitally displayed the flow rate in kg/min units and totalized flow in kg units, both to three decimal units. The measurement of totalized flow of each reagent solution was a crucial tool that provided a real-time view of the overall progress of the reagent additions and indicated whether tweaking of relative flow rates were needed to ensure that the net stoichiometry of two reagents in the pot was proceeding within the desired operating space, namely, a slight excess of base for the duration of the feeds.

Each FMD was mounted inside an XP housing that had sealed external pushbuttons that were used to access the controls on the FMD, mainly for zeroing purposes, without opening the housing. The overall assembly was compact and portable. All components, electrical fittings, wiring, and connections in the complete pumping and MFM assemblies were consistent for use in an XP environment.

Connections to the pump, the MFMs, and the reactors were made using 3/8-in and 1/2-in NPT fittings and SS-braided PTFE tubing. All wetted components were chemically compatible with the materials used in the process.

Performance of the metering assembly was verified in the pilot plant by conducting a series of blank runs by pumping NMP through the individual MFMs and into tared receivers, and then comparing the totalized mass readings on the FMDs with the actual dispensed masses as measured on a calibrated balance at timed points. The results (Table 1) verified that target deviations for a proportional flow of less than 1% were achievable with the portable MFM dispensing system.

AMINATION PROCESS

The first reaction that was scaled (133.5 mol) using the new *N*-amination technology was the conversion of **1a** to **3a**. In one 50-gal reactor, HOSA[13] (2.15 equiv) was dissolved in 3.5 vol of NMP.[14] High agitation was avoided because it led to lumping of HOSA beneath the retreat-blade impeller.[15] The temperature was allowed to increase to 30−35 °C to facilitate dissolution, achieved after about 1 h.[16] Indole was then dissolved in the HOSA solution at 20 °C. In a second 50-gal reactor, KO*t*Bu (4.25 equiv) was dissolved in 1.8 vol of NMP. A third vessel, a 150-gal amination reactor, was charged with 2.9 vol of NMP.

The HOSA and KO*t*Bu reactors were normally elevated or located in a mezzanine area, allowing gravity feed to the pumping systems. Flows were first recycled to the source reactors via three-way valves (Figure 1) in order to purge air slugs from the loops, adjust the stroke lengths on the pump heads, and stabilize the flow rates. The target flows, scaled from lab runs, were 0.904 kg/min (1.53 mol/min HOSA, 0.71 mol/min indole) for the HOSA/indole/NMP solution and 1.000 kg/min (2.99 mol/min) for the KO*t*Bu/NMP solution, corresponding to an addition time of 187 min to completely transfer the reagents.

Once stabilized, the flows were diverted to the amination reactor by actuating three-way valves in timed sequences. The timed sequences were necessary to allow pretransfer of 0.05 equiv of the KO*t*Bu solution[17] (134 s) and to account for differences in the flow rates in filling the dead volumes in the 3/8-in lines leading from the three-way valves to the amination reactor. The pretransfer quantity of KO*t*Bu provided a slight excess of base to ensure formation of indolyl anions from the onset of the additions. The failure of one batch (66 A% conversion) was attributed to insufficient quantity of base at the onset of the reaction possibly due to minor leakage of HOSA/NMP solution through the three-way valve into the

Table 1. Performance verification[a]

min	MFM 1[b] calcd mass kg	MFM 1 dispensed[c] kg	deviation (%)	MFM 2[d] calcd mass kg	MFM 2 dispensed[c] kg	deviation (%)
5.00	4.520	4.54	0.44	5.000	4.99	0.20
10.00	9.040	9.04	0.00	10.000	9.98	0.20
15.00	13.560	–	–	15.000	15.01	0.07
20.00	18.080	18.07	0.06	20.000	20.02	0.10
25.00	22.600	22.59	0.04	25.000	25.02	0.08
30.00	27.120	27.16	0.15	30.000	30.10	0.33

[a] Simultaneous flows of NMP from reactors to pump heads and through individual MFM systems to tared receivers. [b] Flow equilibrated at 0.904 kg/min prior to trial. [c] Mass measured on a calibrated, 2-digit electronic balance. [d] Flow equilibrated at 1.000 kg/min prior to trial.

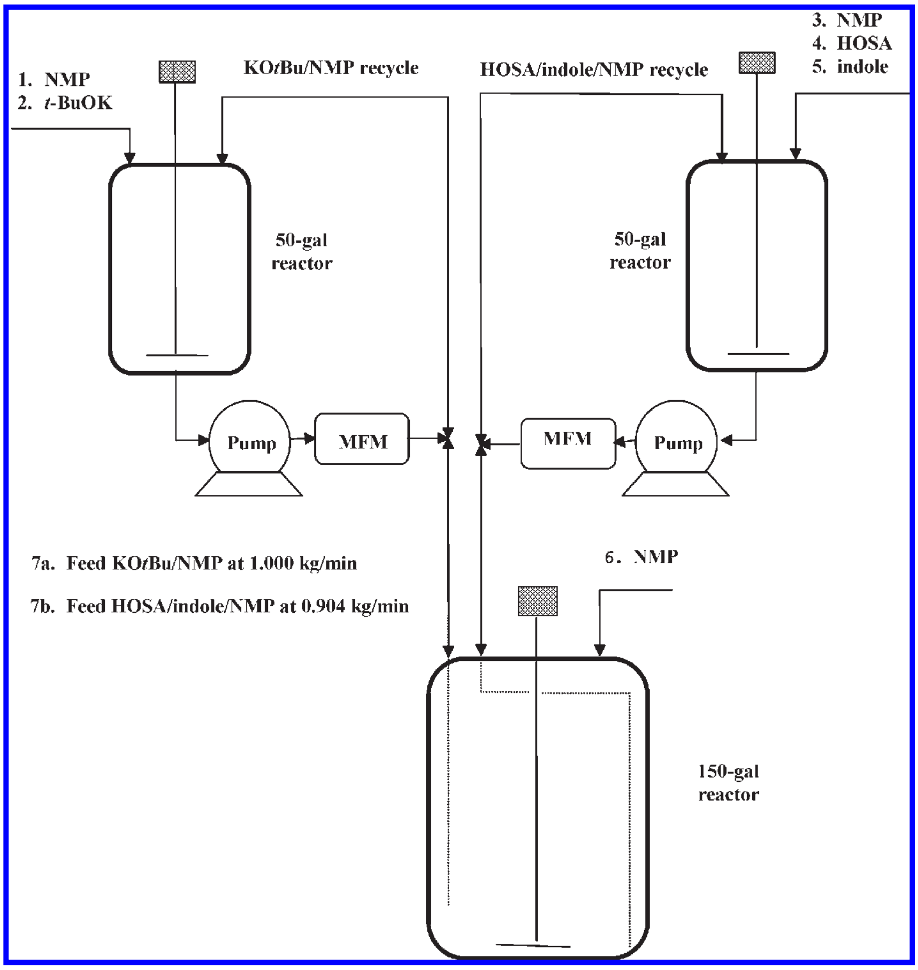


Figure 1. Process flow scheme.

amination vessel while the pumping system was being stabilized in recycle mode.[18,19]

The dead volumes in the lines corresponded to 21 s at 1.000 kg/min for the KO*t*Bu/NMP solution and 30 s at 0.907 kg/min for the HOSA/NMP solution. Thus, the timed sequence was most conveniently performed as follows (Figure 1). The KO*t*Bu/NMP solution loop was switched from the recycle vessel to the amination vessel for a total of 155 s to fill dead volume and dispense 0.05 equiv of base, then was returned to recycle mode. The HOSA/indole/NMP solution loop was switched from the recycle vessel to the amination for 30 s to fill dead volume and then was returned to recycle mode. Simultaneously, the flows from the two solutions were then switched from recycle mode to the amination vessel, and both FMDs were zeroed. The reagents were thereby being dispensed to the amination vessel proportionally, and flow rate and totalized mass flow of each reagent solution were being indicated by their respective FMDs. The coordination of valve switching and zeroing activities was facilitated by the compact design of the MFM pumping system and the proximity of its major components.

In the variation where HOSA/NMP and KO*t*Bu/NMP were simultaneously added to the indole in NMP, highest conversions were observed when the amination vessel was under high agitation and when the reagents were fed subsurfacely via sparging tubes that were oriented 180° apart[20] to ensure that the reagents did not come in direct contact and quench each

Table 2. Target totalized mass flow and conversion[a]

time (min)	HOSA (equiv)	HOSA/NMP (kg)	KO*t*Bu/NMP (kg)	conversion[b] (%)
43.6	0.5	35.8	43.6	34
87.2	1.0	71.6	87.2	66
130.7	1.5	107.4	130.7	88
174.3	2.0	143.3	174.3	95
187.5	2.15	154.0	187.5	96

[a] 133.5 mol batch where HOSA/NMP (0.904 kg/min) and KO*t*Bu/NMP (1.000 kg/min) were added to indole/NMP. See the Experimental Section for additional details. [b] A% conversion to **2a** by HPLC assay (normalized for substrate and product).

Table 3. *N*-Amination of indoles

substrate	product	scale (mol)	yield (kg)	yield (%)
1a	**3a**	133.2	15.9	88.0[a]
1b	**3b**	34.3	4.5	89.7[b]
1c	**3c**	21.0	3.9	77.4[b]

[a] Weight % yield (external standard HPLC assay). [b] Isolated yield.

other prior to mixing with the indole. Conversions were lower and less consistent when the feeds were supersurface or when they were oriented 90° apart.

The temperature of the mildly exothermic amination reaction was allowed to increase to 25−30 °C and was held in this range for the duration of the reagent feeds.[21] Samples of the reaction mixture were withdrawn for HPLC assays at intervals of 0.5 equiv of HOSA.[9] If necessary, slight adjustments of pump stroke lengths were made in order to maintain calculated totalized mass flows and proportionality within ∼1%, most conveniently at each in-process sampling point. Amination conversions leveled off at ≥95 A% after charging about 2 equiv of HOSA (Table 2).[22] The technology was successfully applied to the preparation of three different *N*-aminoindoles that were obtained in >77% yield (Table 3).

■ CONCLUSIONS

A scaleable process for *N*-amination of indoles was described. A dispensing system consisting of portable Coriolis mass flow meters and a dual pump was assembled and demonstrated to provide simultaneous and proportional dispensing of two reagent streams in a precise manner, essential for achieving high amination conversions. The versatility and portability of the equipment provided additional value because the equipment was used in the preparation of three different *N*-aminoindoles in pilot plants of varying capabilities at three different sites without the need for extensive equipment or facility upgrades to accommodate the specific dispensing requirements.

■ EXPERIMENTAL SECTION[13,14]

General. The HPLC methods that were used to monitor reactions and analyze products were as follows: **3a**: Phenomenex IB-SIL 5 Phenyl, 150 mm × 4.6 mm, 5 μ, 65:35 0.1 N ammonium formate/acetonitrile, 1.5 mL/min, 275 nm; retention times: **1a**, 5.9 min; **3a**, 4.1 min; **3b**: Waters Symmetry C_{18}, 150 mm × 4.6 mm, 5 μ, 55:45 acetonitrile/0.1 N ammonium formate, 1.0 mL/min, 280 nm; retention times: **1b**, 3.3 min; **3b**, 2.6 min; **3c**: Phenomenex IB-SIL 5 Phenyl, 150 × 4.6 mm, 5 μ, 50:50 acetonitrile/1 N ammonium formate, 1.0 mL/min, 255 nm; retention times: **1c**, 5.7 min; **3c**, 4.8 min.

1*H*-Indol-1-amine (3a). *Part 1. Preparation of the HOSA/Indole/NMP Solution.* A 50-gal reactor was charged with NMP (120.2 kg). Under a nitrogen purge and moderate agitation, HOSA was charged (33.8 kg, 32.5 kg total corrected for 97% purity,[23] 287.0 mol, 2.15 equiv) in three portions (15.8 kg, 9.0 and 9.0 kg) 15−30 min apart while allowing the temperature to rise to 30−35 °C to facilitate dissolution (achieved after ∼1 h). The solution was cooled to about 20 °C, and indole (15.8 kg, 15.6 kg corrected for 99% purity, 133.5 mol) was charged.[24] After dissolution (several minutes), the solution was cooled and maintained at 0 °C under low agitation for the remainder of the process.

Part 2. Preparation of the KOtBu/NMP Solution.[25] NMP (122.6 kg) was charged to a 50-gal reactor. KO*t*Bu (67.0 kg, 63.7 kg corrected for 95% purity, 567.4 mol, 4.25 equiv) was charged under nitrogen. A minor exotherm was controlled at 20−25 °C. After dissolution (within 15−60 min), the solution was maintained at 17−25 °C with low agitation for the remainder of the process.

Part 3. Amination. A 150-gal reactor was charged with NMP (47.0 kg) under nitrogen, and cooled to 10−22 °C. An initial amount of 0.05 equiv of KO*t*Bu[19] solution from Part 2 (6.7 mol, total 2.23 kg of the solution) was pumped into the amination vessel. The two reagent solutions prepared above were then simultaneously and proportionally pumped to the amination vessel (HOSA/indole solution at 0.904 kg/min and the remaining KO*t*Bu solution at 1.000 kg/min) over a period of 187.4 min through subsurface sparging tubes[20] positioned at opposite sides (about 180° apart) of the amination vessel while maintaining high agitation and a temperature of 25−30 °C with jacket cooling (10 °C).[21] The progress of the reaction was monitored by HPLC assay by withdrawing samples at 0.5 equiv intervals of HOSA charged (about every 43.5 min during the simultaneous reagent feeds). At the end of the feeds, the batch contained 15.4 kg (88% yield, external standard HPLC assay) of **3a,** and was used as is in a subsequent step of a synthesis.

1*H*-3-Methylindol-1-amine (3b). A 36.1% (w/w) solution of KO*t*Bu/NMP (enough for two amination batches, plus ∼10% excess[26]) was prepared by charging a 30-gal Hastelloy reactor under nitrogen with NMP (63.1 kg) and potassium *tert*-butoxide (35.6 kg, 317.2 mole), and then stirring at 20−25 °C for 30 min. A 19.0% (w/w) solution of HOSA/NMP (enough for two amination batches, plus ∼10% excess) was prepared by charging a 30-gal Hastelloy reactor under nitrogen with NMP (75.4 kg) and HOSA (17.7 kg added in three portions over a period of about 45 min, 156.5 mol), stirring at 30−35 °C for 40 min (until dissolution occurred), then cooling to 10 °C. An amination vessel was prepared by charging a 30-gal glass-lined reactor under nitrogen with 3-methylindole (4.5 kg, 34.3 mol), NMP (10.0 L), and KO*t*Bu (385 g, 3.4 mol, 0.1 equiv). The reagent solutions were then simultaneously transferred (HOSA solution at 0.470 kg/min, KO*t*Bu solution at 0.490 kg/min) to the amination reactor (through subsurface sparging tubes in the amination vessel) while maintaining 25−35 °C with jacket cooling (5−10 °C). The feeds were stopped after 90 min, at which time a total of 43.9 kg of the KO*t*Bu solution (4.1 equiv) and 42.0 kg of the HOSA solution (2.1 equiv) had been charged, and a 97 A% conversion to **3b** was achieved. The workup was performed in two portions. One half of the batch was transferred to a 30-gal reactor that contained cold water (48 L) and toluene (12 L). After stirring for 10 min at 20−25 °C, the phases were separated. The aqueous phase was extracted with toluene (3 × 12 L). The combined organic phase was washed with water (2 × 16 L). The other half of the batch was worked up similarly. The organic phases from each portion of the workup were combined and concentrated (60 °C, <50 mbar) to give 5.2 kg (4.5 kg of product corrected for 3.4 wt % toluene and 6.9 wt % NMP as determined by NMR and 96 A% HPLC purity, 89.7% yield) of **3b** as an oil that solidified upon standing. Similarly, a second amination was performed on the same scale to give **3b** in 91.1% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 2.28 (s, 3H), 4.45 (br s, 2H), 6.85 (s, 1H), 7.09 (apparent t, *J* = 7.5 Hz, 1H), 7.20 (apparent t, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, δ): 9.4, 108.0, 108.1, 118.8, 118.9, 121.7, 126.6, 127.1, 136.9.

5-Benzyloxy-1*H*-indol-1-amine (3c). A solution of HOSA (5.3 kg, 5.1 kg corrected for purity, 45.1 mol, 2.15 equiv) in NMP (19.1 kg) was prepared as described above and chilled to 0−5 °C. A second solution was prepared from KO*t*Bu (10.1 kg corrected for 95% purity, 90.0 mol, 4.3 equiv) and NMP (19.3 kg). An amination vessel was charged with benzyloxyindole (5.0 kg, 4.7 kg corrected for 94% purity, 21.0 mol), NMP (15.5 kg), and an initial charge of the KO*t*Bu/NMP solution (0.37 kg, 0.05 equiv). The HOSA/NMP solution and the remaining KO*t*Bu/NMP solution were then simultaneously and proportionally metered (0.142 kg/min and 0.172 kg/min, respectively) into the amination vessel over a period of 172 min while maintaining a reaction temperature of 14−29 °C with jacket cooling (10 °C) to afford a solution containing a 98.6:1.4 mixture (HPLC assay) of **3c:1c**. The reaction mixture was then added over a period of 16 min to 116 L of water while maintaining a temperature of 13−26 °C. The resulting suspension was cooled to 0−5 °C and filtered. The filter cake was rinsed with water (2 × 21 L) and then was partitioned with *n*-butyl acetate (63 L) and water (8.5 L). The resulting mixture was filtered and rinsed with *n*-butyl acetate (10 L). The organic phase of the filtrate was separated, washed with water (4.2 L), and dried over K_2CO_3 (3 kg) and then was filtered, concentrated under reduced pressure, and air-dried to give 4.7 kg of **3c** as a brown solid (3.9 kg by wt/wt HPLC assay, 77.4% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 4.70 (br s, 2H), 5.09 (s, 2H), 6.25−6.37 (m, 1H), 6.93−7.56 (m, 9H).

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Notes

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(2) Weiberth, F. J.; Lee, G. E.; Hanna, R. G.; Mueller-Lehar, J.; Dubberke, S.; Utz, R. U.S. Patent 7,112,682, September 26, 2006 (CAN 142:411224).

(3) Indoles are not sufficiently nucleophilic to react directly with HOSA.

(4) No desired product would be expected if solutions of the incompatible reagents HOSA and KO*t*Bu were mixed prior to the addition of indole.

(5) Hynes, J., Jr.; Doubleday, W. W.; Dyckman, A. J.; Godfrey, J. D., Jr.; Grosso, J. A.; Kiau, S.; Leftheris, K. *J. Org. Chem.* **2004**, *69*, 1368.

(6) (a) The pK_a of the N−H proton in indole is reported to be ∼17. See: Remers, W. A. Properties and Reactions of Indoles, Isoindoles, and Their Hydrogenated Derivatives. In *Indoles, Part I*; Houlihan, W. J., Ed.; The Chemistry of Heterocyclic Compounds; Wiley & Sons, Inc.: New York, 1972; p 14. (b) The pK_a of *t*-BuOH is commonly reported to be within the range of 17−19, depending on the specific literature source.

(7) Conversions to **3a** were typically 60−68 A% when only 1.0 equiv of HOSA was dispensed simultaneously with 2.0 equiv of KO*t*Bu.

(8) Dipolar aprotic solvents were preferred because they solubilized both HOSA and KO*t*Bu. NMP was especially preferred because it was also suitable for downstream chemistry (telescoping).

(9) The *N*-amination was a very fast reaction (e.g., 1 min stirring was sufficient to provide representative conversion assays after feeds were momentarily interrupted for in-process sampling). Consequently, this latter charging regimen has shown potential to be adapted into a flow reaction, although the advantage may be limited because reagent solutions will need to be prepared freshly in batch mode just prior to processing (see ref 16), and an amination vessel would still be needed to collect the product stream.

(10) As determined by HPLC assay. The balance of material was mostly unreacted indole.

(11) In this discussion, XP refers to Class 1, Division 1, Group C/D processing environments.

(12) Major components: Bran & Luebbe duplex metering plunger pump model N-P32 with pulsation dampener SG-TW-25 and back-pressure valve 14010-2300; Micro Motion mass flow sensor D12H205SU (1/8-in tubes); Micro Motion transmitter model RFT9739E1SU; Micro Motion flow monitoring device model FMS1NA0EA.

(13) All materials should be handled while minimizing exposure and while wearing proper protective equipment, most importantly when handling HOSA and KO*t*Bu, both of which can cause burns on skin and in the eyes and are extremely destructive to mucous membranes and the upper respiratory tract.

(14) All materials, including NMP, were accurately preweighed.

(15) HOSA was charged in 3 portions over about 15 min to minimize formation of clumps of the solid that were then difficult to dissolve.

(16) Iodometric titrations established that HOSA dissolved in NMP solutions was stable for 18 h at ≤10 °C and 1 h at 35 °C. At 40 °C, the activity of HOSA dissolved in NMP decreased from 95% to 88% after 1 h.

(17) Alternatively, a separately weighed charge of KO*t*Bu could be added directly into the amination reactor.

(18) This failed batch was salvaged by isolating the product (extractive workup), then reprocessing the resulting mixture of **3c:1c** by treatment with additional HOSA/NMP and KO*t*Bu/NMP in a simultaneous manner to give a 98 A% conversion to **3c**.

(19) In later campaigns, it was found that a precharge of 0.07−0.10 equiv of KO*t*Bu resulted in more robust performance.

(20) The sparging tubes were fabricated from 3/8-in SS tubing by drilling a series of twenty 1/16-in. diameter holes in the submersed and

plugged end of the tubing. The tubes were secured within the reactor through a 1-in dip pipe or by clamping to a baffle.

(21) The amination was a fast reaction with no apparent accumulation of reagents (see ref 9). On a 133.5-mol scale (150-gal reactor) and while feeding the reagents over a 187-min duration, a reaction temperature of 25−30 °C was readily maintained by circulating 10 °C coolant through the jacket.

(22) The efficiency of the amination decreased as the reaction neared completion. Additional charges of HOSA and KO*t*Bu only incrementally improved the overall conversion.

(23) In some batches, up to 1% of the HOSA charge remained in the feed vessel (undissolved chunks). An in-line, polypropylene Y-strainer prevented any loose chunks of solid from reaching the pump.

(24) Alternatively, indole can be dissolved in NMP in the amination vessel prior to the simultaneous feeds of the HOSA/NMP and KO*t*Bu/NMP solutions.

(25) KO*t*Bu and its solutions should be protected from moisture.

(26) The reagents were sometimes prepared in excess as a precaution, e.g., in case they were needed to further drive the amination towards completion.