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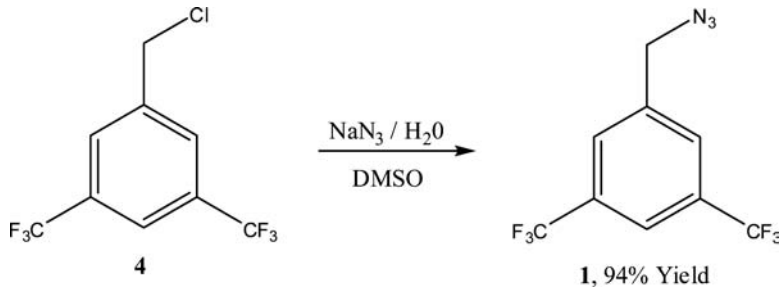

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Full Papers

Improved Synthesis of 1-(Azidomethyl)-3,5-bis-(trifluoromethyl)benzene: Development of Batch and Microflow Azide Processes

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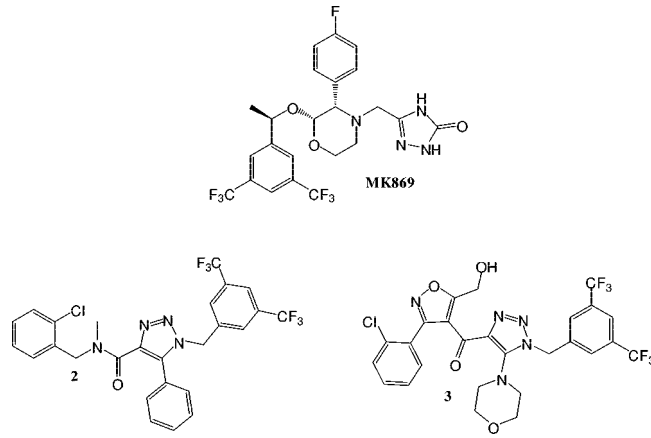
Abstract:

A batch process was developed to produce 1-(azidomethyl)-3,5-bis-(trifluoromethyl)benzene, 1, in 94% yield by an efficient nucleophilic substitution reaction between 3,5-bis-(trifluoromethyl)benzyl chloride, 4, and sodium azide. Hydrazoic acid (HN_3), a toxic volatile compound with explosive properties, can be formed in the reactor headspace during conventional batch processing that requires significant engineering controls. In order to improve the overall safety profile, the process to produce azide 1 was optimized for operation in a microcapillary tube reactor. In addition, azide 1 was prepared in a simple biphasic solvent system using phase-transfer catalysis which results in an overall low *e*-factor. The product was purified via wiped film evaporation (WFE) technology.

Introduction

In recent years there has been significant interest in therapeutic applications of NK1-antagonists, and Merck's NK1-antagonist (MK-869) has been approved for emesis treatment.[1] In addition, Eli Lilly and Company recently disclosed compounds **2** and **3** with potent NK1 antagonist activity in both *in vitro* and *in vivo* models (Scheme 1).[2] A key step in the preparation of compounds **2** and **3** is regioselective condensation of azide **1** with a β-ketoester to produce the triazole core via the method of Cottrell.[3] Thus, for these syntheses an important active pharmaceutical ingredient (API) starting material is azide **1** which

Scheme 1. **Selected NK1-II antagonists**



at present is not commercially available. A variety of methods are known in the literature for the synthesis of alkyl azides, and the most common approach is nucleophilic substitution of alkyl halides with sodium or lithium azide.[4] However, in many cases these syntheses require high temperature, long reaction times, and cumbersome workup conditions. In addition, purification of many alkyl azides via distillation is extremely hazardous and can result in an explosion.[5] Recently, a high-yielding synthesis of alkyl azides in DMSO has been reported by Alvarez,[6] and these conditions were evaluated as a starting point for production of azide **1**, a key starting material for a new phase 2 investigational drug candidate at Eli Lilly and Company.[7] Variations of the enabling technology for synthesis of azide **1** were used by two third-party suppliers for the preparation of kilogram quantities in batch mode for use in clinical pilot-plant campaigns. However, these processes produced significant amounts of waste, and two of the three lots contained more than 1.0% of 3,5-bis-

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(trifluoromethyl)benzyl alcohol, **6**, which was outside specifications. For these reasons, we endeavored to seek a more efficient preparation for azide **1**.

Results and Discussion

Process Safety Considerations. When an azide reaction is considered for production in pilot-plant or with manufacturing-scale equipment, several safety concerns must be addressed. The entire equipment set must be free of heavy metals such as lead, copper, silver, gold, mercury, etc. due to the ready formation of insoluble explosive heavy-metal azide salts.[8] These salts can settle to low points in processing equipment and detonate at a later date when they are subjected to mechanical or thermal stress. In fact, heavy-metal azides are commonly used as detonators for commercial explosives.[9] Perhaps of even greater concern are the safety issues associated with hydrazoic acid. In protic solvent systems, equilibrium concentrations of hydrazoic acid are unavoidable and can be formed in either acidic or neutral conditions. In dilute solutions hydrazoic acid is stable. However, as a neat liquid it is exceedingly sensitive to shock, with a decomposition enthalpy greater than that of trinitrotoluene (TNT).[10] Hydrazoic acid is highly volatile, with a normal boiling point of 36 °C. Therefore, azide reactions are seldom run at temperatures greater than 35 °C to minimize the volatilization of hydrazoic acid. This temperature constraint can result in long reaction times and impact process throughput. Even at low temperatures, great care must be taken to avoid cold surfaces or dead-legs in the reactor and process vent headers in which hydrazoic acid could concentrate. Ideally, the reaction system is constantly swept of heavy-metal azides and hydrazoic acid to a caustic scrubber by using an inert gas, such as nitrogen.

However, simply avoiding condensation of neat hydrazoic acid (HN_3) does not ensure process safety. Explosive gas-phase mixtures of hydrazoic acid in nitrogen have been reported at concentrations as low as 8%.[11] Extensive reactor headspace testing must therefore be performed before running azide processes at industrial scale. Complicating this testing, however, is the toxicity of HN_3. The recommended airborne limits for hydrazoic acid and sodium azide are 0.11 ppm and 0.3 g/m^3, respectively.[12] Process Analytical Technology such as near-infrared spectroscopy[13] has been applied to the online monitoring of vapor-phase hydrazoic acid concentration to avoid the need to handle analytical samples of the highly toxic hydrazoic acid mixtures. Use of this technology can alert plant personnel if the concentration approaches the lower explosive limit (LEL), but other engineering controls are required to prevent this unsafe situation from occurring. The combination of potential hazards associated with hydrazoic acid in the reactor headspace and the sometimes long reaction times necessitated by the low reaction temperatures required to minimize this headspace concentration are two of the significant barriers to the use of azide chemistry on large scale.

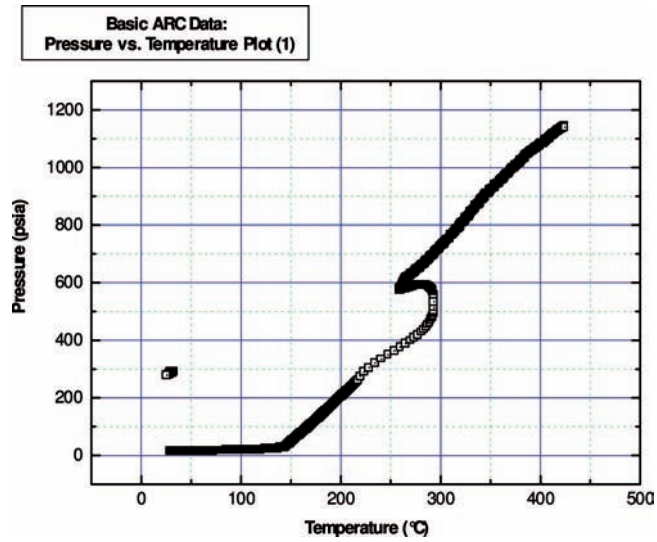

Figure 1. **ARC data for azide 1.**

Continuous-flow channel reactors offer a possible solution. Unlike a traditional flask or chemical reactor, they can be run liquid-filled without vapor-phase headspace. The reaction mixture can be quickly cooled and then quenched or pH-adjusted before exiting the flow reactor, eliminating concerns about volatile hydrazoic acid before the reaction mixture reaches a vessel with any headspace. This potentially allows these reactions to be run at temperatures which would be unsafe in traditional batch vessels. The reduced reaction times at the higher temperatures could allow the use of a reactor of much smaller volume to obtain the same throughput, and the consequences of an explosive event or overpressurization in the smaller-flow reactor system are much less severe and easier to contain when compared to those happening in a batch reactor of the same throughput capacity. These small-diameter tube reactors produce results which have been shown to scale up to larger microflow reactors, provided the length/diameter ratio of the two reactors is similar. It was with these potential safety advantages in mind that we undertook research into preparation of 1-(azidomethyl)-3,5-bis-(trifluoromethyl)benzene, **1**, in a continuous-flow thermal tube reactor.

ARC data reveal that azide **1** decomposes at 157 °C with an energy output of 586 J/g over a 10-min period. On the basis of the heat of decomposition, a maximum allowable processing temperature was determined to be 95 °C which governed the research and development (R&D) activity (Figure 1). Since many organic azides are known to be shock sensitive, azide **1** was subjected to the UN Series 1 explosivity tests and was found to be nonexplosive.[14] In the experiments that follow, typically 3−6 mg/mL of azide waste was generated in the primary aqueous waste stream and safely disposed of using a standard azide destruction protocol.[15]

First-Generation Batch Process. *Reagent Selection.* A key decision required early in the R&D was selection of either the 3,5-bis-(trifluoromethylbenzyl chloride or bromide as the pri-

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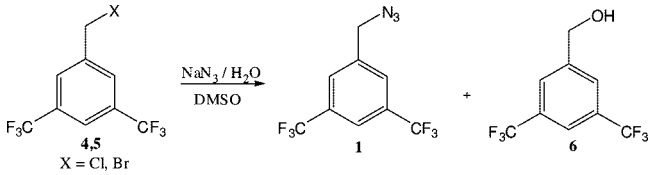
Scheme 2. **Evaluation of benzyl halides 4 and 5 as raw materials for azide 1 synthesis**



mary raw material. A head-to-head comparison of both substrates was made using a slight modification of the conditions reported by Alvarez (Scheme 2). The *in situ* purity and yield of azide **1** produced from the chloride system was 7−8% higher due to the absence of hydrolysis. In addition, a significant advantage for the chloride system was improved availability with advantageous commercial pricing.[16] For these reasons 3,5-bis-trifluoromethylbenzyl chloride, **4**, was selected as the key reactant for the azide **1** manufacturing process.

Initial development focused on improving the environmental footprint of the Alvarez conditions, which had an *e*-factor of 112 kg/kg of **1** and used the hazardous solvent diethyl ether as part of the workup.[17] The Alvarez azide alkylation process in DMSO was successfully modified by addition of a solution of benzyl chloride **4** (1.0 equiv) in 1 vol (L/kg, **4**) of DMSO to a sodium azide (1.2 equiv) solution in 5 vol of 80 wt % DMSO/water. The mixture was stirred at ambient temperature for 6 h and then quenched with water. The product was extracted into heptane, and the combined organic layers were washed with water. The solvent was removed to produce a 91% yield of azide **1**. While the yield was satisfactory, the peak volume was 25 vol, and a total of 43 vol of solvent was used for the overall process. Further improvement of the *e*-factor of the process was attempted by adding 1 vol DMSO solution of benzyl chloride **4** to a 1 vol sodium azide aqueous suspension. These conditions, however, resulted in a thick mixture. The addition of an additional volume of DMSO (2 vol total) facilitated stirring of the two liquid phases, but reaction completion in the biphasic mixture could not be achieved under these conditions at 40 °C; reaction monitoring (NMR) showed 29% starting material remaining after 1 h, and further reaction completion was not achieved by stirring overnight. The reaction could be progressed further by adding an additional 2 vol of DMSO to the mixture and stirring for an additional hour. These observations illustrate the importance of the proper DMSO/water ratio in order to achieve a productive alkylation. The minimum quantity of DMSO needed to promote the azide reaction at 23 °C was determined to be 4 vol when 0.5 vol of water were employed.

(15) In order to test for residual azide **1**, a 1 wt % solution of iron (III) chloride in deionized water is prepared and used as a qualitative test. If positive (red color and/or precipitate), the following procedure for destruction of azide waste was used: (1) adjust pH of waste stream to ∼13 with 2 N NaOH; (2) charge 0.5 M solution of $NaNO_2$; (3) carefully adjust pH to 2.0 with 4 N H_2SO_4; (4) test with 1 wt % iron (III) chloride to verify azide destruction; (5) dispose of aqueous waste.

(16) Both substrates are available from Aldrich at ∼$22/g which translates to a ∼17% lower cost of **4** on a per mol basis for small-scale quantities. Multikilogram quantities of chloride **4** are available at $200−300/kg and bromide **5** at $300−$400/kg.

(17) *e*-factor = total kg of all materials per kg of active pharmaceutical ingredient (API). In this case the *e*-factor is defined by azide product **1**. See: (a) Sheldon, R. D. *Chem. Ind. (London).* **1999**, 93. (b) Sheldon, R. D. *CHEMTECH* **1994**, *24*, 38.

Table 1. **Azide 1 solvent screen**[a]

entry	solvent	temp (°C)	area % **4** 1 h	area % **4** 2 h
1	NMP	23	2.73	0.08
2	DMAC	23	0.48	0.12
3	DMSO	23	2.04	0.33
4	DMF	23	2.80	0.94
5	NMP	40	0.43	0.0
6	DMAC	40	0.0	0.0
7	acetonitrile	40	58.1	47.6[b]
8	DMF	40	0.0	0.0
9	IPA	65	N.A.	0.0[c]
10	EtOAc	40	100	100
11	toluene	40	100	100

[a] All reactions were run in Argonaut 2050 reaction tubes with a magnetic stir rate of 550 rpm and were monitored by normal phase HPLC. [b] Reaction was analyzed after 18 h, and 10.0% starting material remained. [c] 3-h time point.

Table 2. **DMSO and DMF process comparison**

Entry	solvent	temp (°C)	area % **4** 1 h	area % **4** 3 h
1	DMSO	40	3.9	0.83
2	DMSO	40	1.6	0.94
3	DMSO	23	10.7	1.2
4	DMF	23	8.7	0.73
5	DMF	40	0.91	0.76

Reaction completion (<1% 4) could be achieved within three hours using 4.5 vol of DMSO and 1 vol of water at 40 °C (see Table 1).

Ultimately, the best batch reaction conditions developed consisted of feeding a 2 vol DMSO solution of benzyl chloride **4** solution to 1.2 equiv of sodium azide suspended in 2.5 vol of DMSO and 1 vol of water. The mixture was worked up by dilution with heptane (6 vol) then addition of water (4 vol) to dissolve precipitated salts. The aqueous layer was removed and the organic layer washed with water (2 × 3 vol). Heptane was then removed via vacuum distillation to produce azide **1** in 94% yield and >99% purity on a 125-g scale with a final *e*-factor of 21.5 L/kg of **1**, an improvement of 80% relative to the original route.

Solvent Screen. A solvent screen was performed to determine if a solvent system superior to DMSO could be identified for the nucleophilic substitution reaction (Table 1). Benzyl chloride **4** was the limiting reagent and 1.2 equiv of sodium azide were used to effect the conversion. The reactions were all conducted in 5 vol (based on benzyl chloride starting material) of the chosen solvent and 0.5 vol of water. The reactions were complete within specification (<1% **4**) after 2 h in most polar aprotic solvents. Hydrolysis to the alcohol **6** was not noted during these studies, consistent with results previously observed for the benzyl chloride system. The solvents can be placed in the following reactivity order at 23 °C: DMAC > DMSO > NMP > DMF. Conversions in isopropanol and acetonitrile were sluggish and required higher temperatures. In the case of isopropanol, a new unidentified impurity was formed. No reaction was achieved in less polar solvents such as toluene and ethyl acetate. On the bases of environmental considerations, ease of workup, and cost, DMSO and DMF appeared to offer the best processing options. Both DMSO and DMF were compared head-to-head on a 250-mL scale in a mechanically stirred reactor (Table 2). The reaction stoichiometry was kept constant with that of the small-scale reactions. As the data show,

Table 3. **^{1}H NMR evaluation of impact of water on azide 1 reaction kinetics[a]**

water (vol)	temp (°C)	time (h)	% azide **1**	solids (Y or N)
2.0	70	1	87.3	N
1.5	70	1	100	Y
1.2	70	1	100	Y
0.8	70	1	100	Y
2.0	80	1	86.2	N
2.0	70	2	100	N
2.0	75	0.5	96.8	N
1.8	75	0.5	98.4	N
2.0	85	0.5	97.4	N
1.8	85	0.5	100	N
2.0	90	0.5	98.0	N

[a] Reaction conditions: 2 g scale, 1.2 equiv of NaN_3, 950 rpm.

the reaction proceeds at an equal or slightly faster rate in DMF as compared to the rate using DMSO at both 23 and 40 °C. Notably, the reaction rate is much slower with mechanical stirring, which more closely models what could be expected on pilot-plant scale where mass-transfer effects would be potentially rate limiting.

Reaction Workup. The base procedure involves the partitioning of the reaction mixture between heptane (7.5 vol) and water (5 vol). The intent is to extract the azide product **1** into the heptane layer and partition the reaction solvent into the aqueous layer along with the sodium chloride formed as the reaction byproduct. While heptane performs well in the extractive workup, long-term supply of heptane in the world market could be an issue. Isooctane has similar physical properties to heptane, is commercially available, and is broadly used by the petroleum industry. Both isooctane and heptane were screened as workup solvents with the DMSO, DMF, DMAC, and NMP solvent systems. For the isooctane system, azide **1** was fully partitioned into the organic layer and a single brine or water wash removed residual solvent from the organic layer. The results were similar with heptane, with the exception of NMP where large losses of azide **1** in the aqueous layer were observed. Overall, the results demonstrated that isooctane could potentially replace heptane as the workup solvent for azide **1** production.

Alternative Reactor Technology. In order to adapt the azide **1** chemistry to a tubular reactor, a solids free system is required. The optimized DMSO batch process operated at high concentration (4.5 vol water, 0.5 vol H_2O), but the low water level resulted in an initial suspension of sodium azide and precipitation of sodium chloride as the reaction progressed which was not amenable for a microcapillary reactor. Solubility experiments demonstrated that a "solids-free" biphasic process can be obtained if water volumes of 1.8 or more relative to benzyl chloride **4** are employed (Table 3). It is noteworthy that significant hydrolysis of the chloride to 3,5-bis-(trifluoromethyl)benzyl alcohol, **6**, was not noted even at 90 °C using 2 vol of water.

Further studies underscored the importance of water to reaction kinetics. For example, complete reaction within 0.5 h could not be achieved, even at 90 °C using 2.0 vol of water which suggests that the reaction might be mass-transfer limited at higher temperatures. However, large-scale (20 g) experiments at 60 °C in the DMSO/water system demonstrated the absence of mass-transfer effects by varying the agitation speed between 135 and 1000 rpm. From a process safety perspective, the high water/high temperature approach is not desirable for a batch process; however, there is utility in this approach in a microcapillary tube reactor environment.

Use of 5 L of DMSO/kg of benzyl chloride and 1.8 L of water/kg of benzyl chloride allowed the azide reaction to run to completion at 23−40 °C without precipitation of solids. However, under these conditions the reaction proceeded much slower, with 8−10 h required to consume >99% of the starting material, compared to about 1 h under the optimized batch conditions. At higher water levels, azide ion is presumed to be more hydrated and less reactive. Two liquid phases were present throughout the reaction in the new solvent system, and GC analysis showed that nearly all of the starting material was present in the smaller, heavier phase.

A simple system was assembled using a coil of 316 stainless steel tubing for a reactor (Figure 2). The reactor was placed in a GC oven to provide accurate temperature control. Two separate high-pressure ISCO syringe pumps were used to feed the two reaction solutions, the benzyl chloride in DMSO and the sodium azide in water. The two feed streams mixed in a T-fitting just outside the GC oven and then flowed through the tubular reactor inside. The reaction mixture was then cooled to 25 °C as it exited the oven in a tube-in-tube heat exchanger. Samples of the reaction stream were taken via a six-port sampling valve at the outlet of the heat exchanger. The reactor was subjected to back-pressure provided by a Mighty Mite diaphragm pressure regulator set at 200 psig.

Flow reactor studies were conducted using two stainless steel reactors, termed reactors and 1 and 2. The dimensions of these reactors are outlined in Table 4.

It should be noted that due to its relatively large inner diameter (2.16 mm), reactor 1 does not fit the common definition of a "microreactor" which has been generally accepted as a channel having a characteristic cross-sectional dimension of <1 mm. We began our research with a screen of temperatures, running the reaction at 50, 70, and 90 °C which had been previously tested under batch conditions (Table 5). Flow rates of the two feed streams were set to allow 1.2 mol equiv of sodium azide, and an overall residence time in the hot zone of the reactor at 60 min. Samples were taken and partitioned between heptane and water, and then the organic layer was assayed by GC.

Results from reactor 1 were somewhat unexpected based on results from the analogous batch reaction. In the continuous flow reactor, there was almost no difference in conversion to the desired product at 50 and 70 °C, and even at 90 °C where the reaction had only proceeded to 64% conversion with a 60 min residence time (Table 5).[18] These data seemed to be more evidence that phase-transfer effects were severely limiting the rate of reaction when large amounts of water were present. The phase separation of the starting material and product from the bulk of the reaction liquid would create a segmented flow in the tubular reactor, with alternating slugs of heavy and light phases. Since the two liquid phases in this system are of widely different volumes, with the starting material/product phase comprising only about 1/6 of the total volume, the interfacial

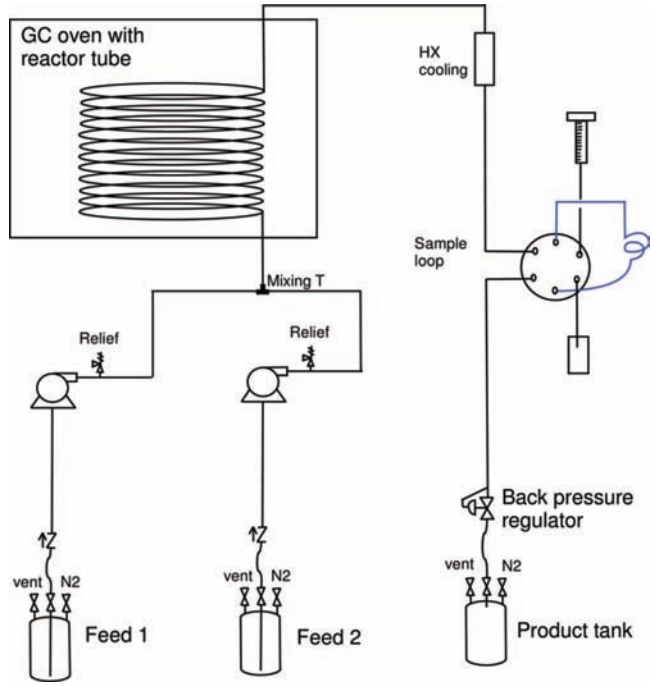


Figure 2. **Simple, high-pressure continuous-flow thermal tube reactor.**

Table 4. **Comparison of tubular reactor dimensions**

reactor	tubing o.d., in.	tubing i.d., in.	tube length, ft	tube volume, mL	*l*/*d* ratio
1	0.125	0.085	10.9	12.16	1539
2	0.0625	0.025	207	20	99360

Table 5. **Temperature screens in reactors 1 and 2**

reactor	temperature (°C)	residence time (min)	% area **4**	% area **1**
1	50	60	62.1	32.0
1	70	60	59.7	38.4
1	90	60	33.4	64.4
2	50	60	53.9	43.5
2	70	60	2.7	93.2
2	80	60	0.35	96.2
2	90	20	0.39	97.3

surface area for contact between the phases is relatively small. One way to improve the mass transfer between the two liquid phases is to use a longer, narrower channel (see reactor 2). Using a narrower reactor forces the phases into much smaller segments, thus increasing the interfacial area. In addition, the narrower channel increases the linear velocity of the liquid for a given flow rate, and this should increase mixing along the length of the tube. The Reynolds number (*Re*) is a means of characterizing mixing in a tube. It can be defined as follows:[19]

$$Re = \frac{\rho V D}{\mu} \tag{1}$$

where ρ = fluid density (kg/m^3); V = mean fluid velocity (m/s); D = pipe diameter (m); μ = dynamic viscosity of the fluid (N·s/m^2).

Where reactor 1 had a length-to-diameter ratio of only 1539:1, this ratio increased to 99360:1 for reactor 2. *Re* increases by a factor of 3.4 for the smaller i.d. tube compared to that for the larger. Linear velocity increases by a factor of 11.6 for the smaller diameter tube compared to that for the larger. Because flow is in the laminar regime, mixing is limited by rate of diffusion which is proportional to the characteristic dimension squared. Therefore, mixing time by diffusion in the radial direction for a slug of homogeneous solution is about 11.6 times faster for the smaller-diameter tube.

The results using reactor 2 were much more satisfying and seemed to confirm the predicted effect, with >99% of benzyl chloride **4** consumed at 80 °C and a 60-min residence time. The reaction could also be driven to completion in only 20 min by increasing the residence time at 90 °C. Indeed these results compare favorably to the Argonaut 2050 system, where mass-transfer effects were apparent at 90 °C. This set of conditions, with shorter residence time and higher temperature were selected to demonstrate chemical equivalence to the batch process by converting 25 g of the benzyl chloride to the benzyl azide over 3 h in 94% isolated yield which compares favorably to the yield obtained in the batch process.

Second-Generation Process Development. *Phase-Transfer Studies.* The main drawback to the first-generation DMSO approach was that heptane/isooctane with an aqueous workup was required to produce the target azide free of solvents, and the overall step *e*-factor was 22 kg/kg **1**. Phase-transfer catalysis (PTC) can be an attractive alternative in these instances.[20] For the purposes of the synthesis of azide **1**, we focused on liquid−liquid phase transfer catalysis (LLPTC) to facilitate transfer to a continuous flow reactor. A variety of different

(18) The effluent in the initial experiments was dark red, which suggests that an iron azide contaminant may have formed within the stainless steel tube reactor, and after several minutes the red coloration dissipated. Since pickling was effective at color removal, an impurity within the stainless steel tube reactor from a prior process was the likely source of the color rather than an unfavorable reaction between the tube reactor material of construction and sodium azide.

(19) *Perry's Chemical Engineers' Handbook*, 7th ed.; McGraw-Hill: New York, NY, 1997.

(20) Dozeman, G.; Fiore, P.; Puls, T.; Walker, J. J. *Org. Process Res. Dev.* **1997**, *1*, 137.

Table 6. **Preparation of azide 1 via PTC**[a]

solvent	area % **4**, 3 h	area (%) **4**, 4.2 h	area (%) **4**, 27 h	area (%) **4**, 72 h
EtOAc	3.4	0	0	0
toluene	57.2	45.9	3.3	0
heptane	97.6	90.3	75.9	0
tert-butyl alcohol	20.4	4.9	0	0

[a] Reaction conditions: 2 g scale, 5 vol solvent, 1 vol of water, 10 mol % TBAB, 1.2 equiv of NaN_3, 600 rpm stirring, 40 °C.

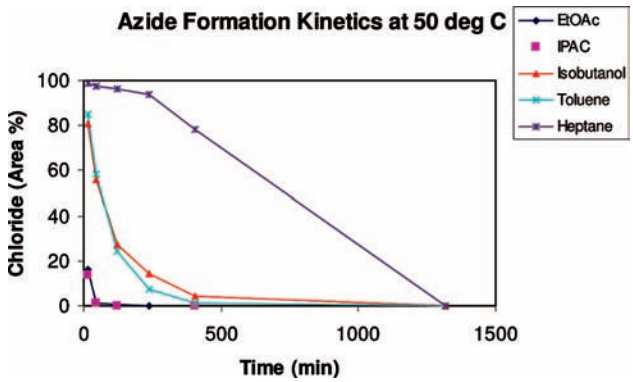


Figure 3. **Azide 1 formation kinetics with PTC.**

phase-transfer catalysts to effect this conversion have been reported in the literature. These include tetraalkylammonium salts such as Aliquat 336,[21] 18-crown-6,[22] cryptands,[23] and doped clays.[24] We focused on tetrabutylammonium bromide (TBAB) as a potential phase-transfer catalyst on the grounds of its relatively low cost, favorable toxicity profile, high water solubility, and ease of removal.

Initial kinetic studies were conducted at 40 °C in the well-mixed Argonaut 2050 system, and the expected reaction rate trends were in line with expectations (Table 6). The reaction proceeded fastest in relatively polar ethyl acetate and slowest in heptane. It is noteworthy that in these solvents, reaction is not observed in the absence of PTC (Table 1, entries 10 and 11). The reaction kinetics were tracked by comparing the area % of the azide to that of the chloride by GC. Although *tert*-butyl alcohol is fully miscible in water, it is used in the next step utilizing azide **1**, and was included in the study as a comparator. Precipitation of sodium chloride was noted during the *tert*-butyl alcohol experiment, and the kinetics of the conversion were notably slower than those observed in ethyl acetate. This is consistent with extensive hydration of azide slowing the reaction rate.

Similar studies were conducted at 50 °C using water immiscible isobutanol as a comparator. Reaction rates in ethyl acetate and isopropyl acetate were comparable, and both solvents had considerably faster reaction rates than those observed in the more polar isobutyl alcohol (Figure 3). Interestingly, initial conversion rates in isobutyl alcohol were faster than those observed in toluene, but overall completion

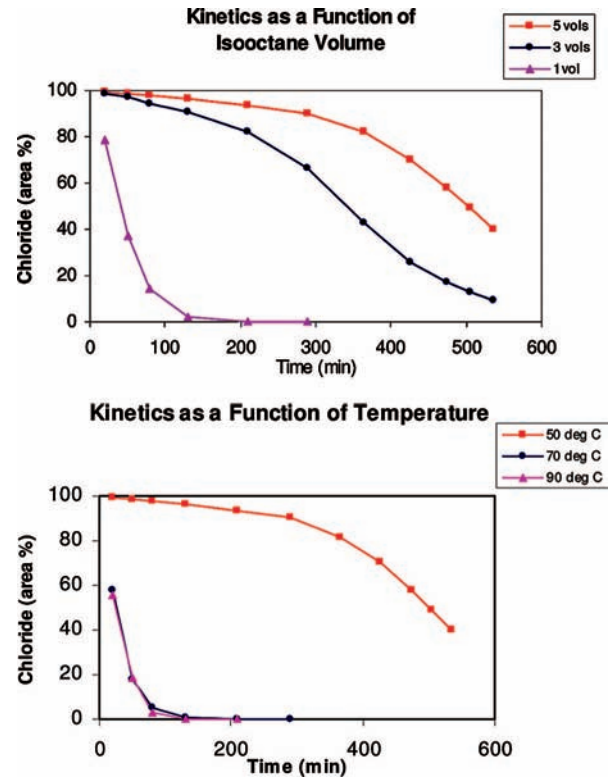


Figure 4. **Azide 1 conversion in isooctane with PTC.**

times in toluene were shorter. Similarly, conversion rates in heptane appear to accelerate as the reaction proceeds, the reaction is only 6% complete after 4 h, 22% complete after 6.75 h, and is >99% complete after 22 h.

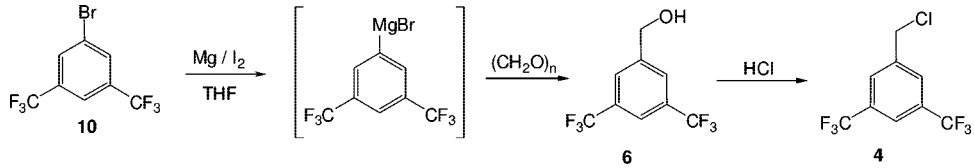
The unusual kinetics of the reaction in nonpolar heptane were interesting and were probed further in a similar solvent, isooctane (Figure 4). The reaction was conducted under variable temperatures and volumes of isooctane in an Argonaut 2050. It was noteworthy that reaction kinetics appeared to accelerate as the reaction progressed, consistent with the behavior observed in heptane. These observations are consistent with an increase in dielectric constant of the organic phase as the reaction progresses. Even in the well-mixed Argonaut 2050 system, mass-transfer effects were apparent at elevated temperatures, and acceleration of kinetics was noted going from 50 to 70 °C, whereas reaction completion times at 70 and 90 °C were similar.

The reaction rates for azide **1** formation in ethyl acetate and isopropyl acetate were comparable, but as residual catalyst levels in the organic phase after aqueous extraction were significantly lower in isopropyl acetate, it was decided to pursue scaling the process to 20-g scale in isopropyl acetate. Two volumes of water were used for the scale-up run rather than the 1 vol used for the Argonaut screen. It was found that the level of water had a significant impact on reaction kinetics; reaction completion took approximately 3 h using 2 vol of water, whereas reaction completion was noted after 2 h in the Argonaut 2050 utilizing 1 vol of water. Reaction kinetics are most favorable when running the process under "near-saturation" conditions with respect to sodium azide and the byproduct, sodium chloride.

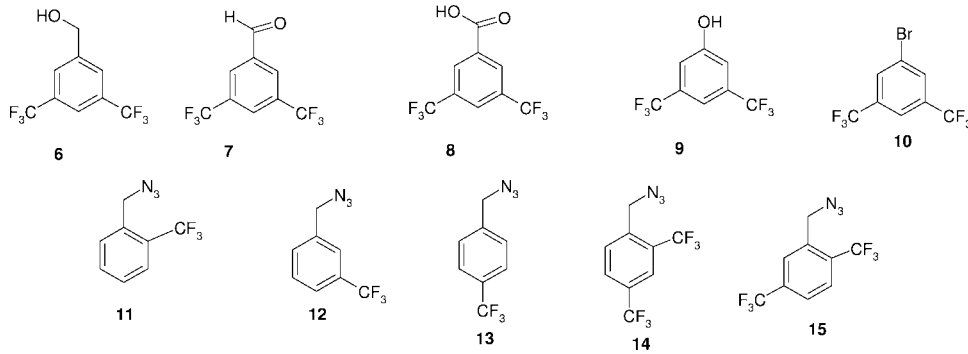
The isopropyl acetate system has notable advantages over the DMSO/water system; its kinetics are intrinsically faster, and the solvent usage is considerably lower. Only 9 vol of solvent was required to effect complete conversion versus >20 vol

(21) Reeves, W. P.; Bahr, M. L. *Synth. Commun.* **1976**, 823, and references therein.
(22) Nakajima, Y.; Kinishi, R.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1997**, *50*, 2025.
(23) Landini, D.; Maia, A. *J. Am. Chem. Soc.* **1984**, *106*, 2917.
(24) Varma, R. S.; Naicker, K. P.; Aschberger, J. *Synth. Commun.* **1999**, *29*, 2823.

Scheme 3. **Miteni's manufacturing process for production of 4**



Scheme 4. **Azide 1 potential impurities**



required for the DMSO/water system. The yield (96%) and quality (>98.5% purity by GC/LC) in the system were comparable to the DMSO/water system. The volume of water employed had a more marked effect on reaction rate in isooctane with reaction completion observed at 50 °C within 4 h when 1 vol of isooctane was employed. When the reaction was conducted at 100-mL scale in conventional glassware using 2 vol of water, the reaction was only ~25% complete after 4 h, but was complete after 48 h at 70 °C. Conducting the reaction at similar scale in the same equipment set using 1 vol of water gave kinetics similar to those of the Argonaut 2050 system. The *e*-factor in the isooctane system was even more favorable: only 7 vol of solvent (5 organic, 2 aqueous) was required to effect the transformation, purification, and isolation. The evaluation of the improved phase-transfer system in a capillary reactor will be evaluated in due course.

Azide 1 Impurity Control Strategy. The principal route of manufacture of benzyl chloride **4** has been recently described in the patent literature by Miteni, one of the main global suppliers of both **4** and **5**.[25] By Miteni's approach 3,5-bis-(trifluoromethyl)bromobenzene, **7**, the key alpha raw is converted to a Grignard reagent and then quenched with paraformaldehyde to produce benzyl alcohol **5**. Acidification with conc. HCl produces **4**, and when HBr is substituted for HCl, this route produces **5**, the other potential alpha raw material for the azide **1** synthesis (Scheme 3).

The potential impurities from Miteni's route were purchased from Aldrich and the presence of these impurities in vendor samples was assessed by HPLC. The purity of the samples ranged from 96.4−100% (Scheme 4 and Table 7).[26] The main potential impurity was alcohol **6** which is both an intermediate in Miteni's process and is a direct hydrolysis byproduct of the benzyl chloride or benzyl bromide starting materials. Fortunately, this impurity was shown to be completely removed in levels as high as 25% from the crude azide displacement reaction mixture with an aqueous wash. Other impurities potentially related to this manufacturing process include 3,5-bis-(trifluoromethyl)benzaldehyde **7**, acid **8**, phenol **9**, and unreacted bromobenzene **10** starting material. In addition, azide $(CF_3)_n$ positional isomers **11**−**15** are possible based on the quality of the 3,5-bis-(trifluoromethyl)bromobenzene feedstock.[27] The main impurities identified in a majority of the vendor lots were aldehyde **7** and acid **8**, which in the worst cases combined for 2% total impurities. Notably, the vendor samples of **4** did not contain hydrolysis byproduct **6**.

Table 7. **Benzyl chloride 4 vendor lot analysis**

supplier	**8** (area %)	**9** (area %)	**7** (area %)	**4** (area %)
1	0.59	0.11	0.28	97.0
2	0.51	0.00	0.36	98.9
3	0.0	0.0	0.0	100
4	1.00	0.0	1.17	97.0
5	0.55	0.07	1.57	96.4
6	0.19	0.03	0.05	99.6
7	0.50	0.00	0.24	98.5

Since azide **1** is a potential API starting material, an analytical method for batch release was developed that could resolve the aldehyde, phenolic byproduct, as well as bis-positional isomers **14** and **15**. Ultimately, a GC method was developed using an RTX 0.5 capillary column with temperature-control programming. The peaks of interest were quantitated by a percent normalization method using FID detection. Multiple lots of benzyl chloride, **4**, purchased from different suppliers were use tested under the optimized DMSO/water batch conditions (Table 8, batch preparation A). Analysis of all azide **1** lots revealed that the primary impurities that carried

(25) Nardello, A.; Pretto, M.; Faccin, A. Process for the Preparation 3,5-Bis(trifluoromethyl)benzyl alcohol. (Miteni, S.p.A.). WO/2005/035472A, 2005.

(26) (a) 3,5-Bis-(trifluoromethyl)benzyl alcohol, **6**, CAS # 32707-89-4; Aldrich catalog number 263370. (b) 3,5-Bis-(trifluoromethyl)benzyaldehyde, **7**, CAS # 401-95-6; Aldrich catalog number 290130. (c) 3,5-Bis-(trifluoromethyl)benzoic acid, **8**, CAS # 725-89-3; Aldrich catalog number 232882. (d) 3,5-Bis-(trifluoromethyl)phenol, **9**, CAS # 349-58-6; Aldrich catalog number 247081. (e) 1,3-Bis-(trifluoromethyl)-5-bromobenzene, **10**,: CAS # 328-70-1; Aldrich catalog number 290157.

(27) Amegadzie, A. K.; Gardinier, K. M.; Hembre, E. J. Hong, J. E.; Jungheim, L. N.; Nickolaus, N,; Muehl, B. S.; Remick, D. M.; Robertson, M.; Savin, K. (Eli Lilly and Company). PCT Publication WO/2005/000821A1, 2005.

Table 8. **GC analysis of azide 1[a]**

entry	scale (g)	yield (%)	heptane (%)	**7** (%)	**1** (%)	**14** (%)
1	125.4	95.1	3.2	0.23	96.3	0.0
2	19	91.0	0.92	0.33	98.2	0.25
3	20	92.5	0.0	0.0	99.8	0.0
4	20	88.9	0.75	0.21	97.9	0.0
5	19	90.0	1.07	0.0	98.7	0.0
6	20	92.8	0.71	0.0	99.0	0.0
7	20.6	94.4	2.40	0.12	97.3	0.0
8	252.5	94.2	1.0	0.24	97.7	0.24
9	255	94.5	0.98	0.0	98.8	0.0

[a] Reaction conditions: DMSO/water process (batch preparation A).

through the process were aldehyde **7** and 2,4-bis-trifluoromethyl positional isomer **14** which were present up to 0.23 and 0.30%, respectively. The heptane level varied from 0 to 3%, with a typical level of ~1%. The variance was a function of the duration of the distillation operation, and it was easy to adjust the residual heptane levels up or down based on length of time of distillation. For these studies a maximum jacket temperature of 50 °C was used for all vacuum distillations on scales less than 25 g, which was well below the recommended 95 °C maximum temperature range. For the lots run on a 5-L/250-g scale the distillation was run with a jacket setpoint of 85 °C and vacuum sufficient to maintain a distillate head temperature of 55−60 °C. The final process was run on a 5-L/250-g scale of benzyl chloride **4**; the distillation was stopped at 61 and 51 wt % azide in heptane, respectively. The bulk azide solutions were then purified via WFE technology.

The data collected on the vendor benzyl chloride **4** and azide **1** revealed that some purity upgrade was achieved during the azide synthesis (Tables 7 and 8). For example, 50−75% reductions in aldehyde **7** levels were typically observed. Since aldehyde **7**, and 2,4-bis-trifluoromethyl positional isomer **14** were the main impurities identified in azide **1**, two experiments were carried out to assess how well the aforementioned impurities were rejected under standard processing conditions by spiking at 5 and 10 mol % levels, respectively. Predictably, positional isomer **14** was not rejected under the standard processing conditions and needed to be controlled by the quality of benzyl chloride **4**. However, partial reduction of the aldehyde impurity was observed, and it was suspected that aldehyde **7** might be converting to acid **8** under standard processing conditions. This was confirmed with an experiment where 0.70% acid **8** was observed in the final product when there were nondetectable amounts in the starting material. In fact, the in-process HPLC data revealed a slow conversion from aldehyde to acid over 20 h at 40 °C with 1.6% acid **8**, 6.1% aldehyde **7**, and 92.3% azide **1** present at the end of the stir time. After the aqueous washes, the acid level was reduced to 0.70%, and the aldehyde level, to 4.20%.

Azide 1 Wiped Film Evaporation (WFE) Purification. An attractive option for purification of azide **1** was identified as wiped film evaporation (WFE) using a Pope Scientific 2-in. diameter wiped film still (Figure 5). The main objective was to demonstrate successful proof-of-concept that a ~50 wt % azide **1**/heptane mixture could be purified to a target 2% or less residual heptane using WFE with minimal yield loss. It was envisioned that a partial vacuum distillation followed by WFE

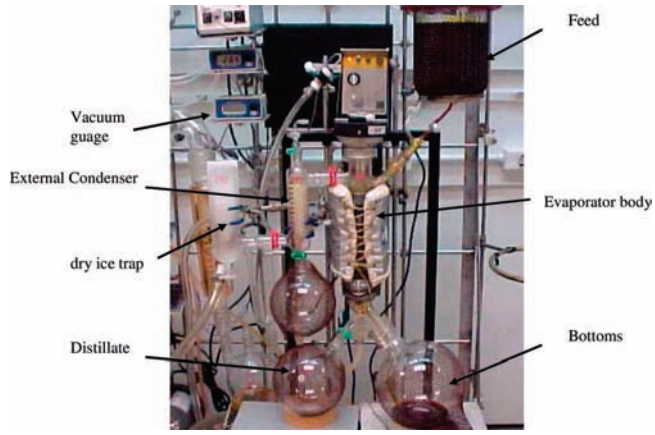


Figure 5. **Purification via WFE.**

might be employed in commercial manufacturing as a safe and efficient method to produce azide **1** with the appropriate quality attributes. During the WFE studies, the azide **1** composition was varied from 51−61 wt %. The WFE was operated over a feed rate range of 0.6−14.4 kg/h, a pressure range of 0.1−42 mmHg, and jacket temperature range of 17−92 °C (Table 9). The best operating conditions within these parameters consisted of an azide **1** feed rate of 0.89 kg/h, a jacket temperature of 64−89 °C, and a pressure of 32−35 mmHg. In this case, the bottoms phase contained 98.0% azide **1** and 1.8% heptane with an overall yield of 94% (Table 9, entry 6).

Since benzyl chloride **4** was selected as the principal starting material for the manufacture of azide **1**, there was interest in determining if the WFE was capable of reducing the levels of benzyl chloride **4** in the azide **1** crude mixture. The boiling point of azide **1** was determined to be greater than 87.5 °C at 16 mmHg, which was slightly higher than the reported literature boiling point of 68 °C for benzyl chloride **4** at the same pressure. On the basis of the boiling point data, benzyl chloride **4** was expected to be enriched in the distillate and azide **1** to be contained in the bottoms when operating the WFE. In order to test this hypothesis, a WFE experiment was performed with 0.83% benzyl chloride **4** spiked into azide **1**, with a feed rate of 2.9 kg/h, jacket temperature of 35−42 °C, and WFE pressure of 0.25−0.33 mmHg (Table 9, entry 4). Under these operating conditions, the WFE was only partially effective, with 0.61% of benzyl chloride **4** retained in the bottoms. Thus, the control strategy for the reduction of benzyl chloride **4** is required primarily in the chemical step rather than the final purification.

Conclusions

A batch process was developed and scaled to produce azide **1** in high yield (94%) in a DMSO/water solvent system. Purification of the resulting product was accomplished by a combination of vacuum distillation and WFE. Proof-of-concept studies were also successfully completed for two alternate batch process preparations of azide **1** using PTC in isopropyl acetate and isooctane, respectively, in the same overall yield as the DMSO process. The main benefit derived from the PTC approach was the ability to perform the azide chemistry with an overall *e*-factor of <10 kg/kg of **1**, a significant improvement over the prior art. In addition, a microcapillary tube reactor process was demonstrated for efficient production of azide **1**

Table 9. **GC analysis of azide 1; WFE results**

entry	WFE feed (g)	% **1**	feed rate(kg/h)	jacket (°C)	pressure (mmHg)	bottoms (% **1**)	bottoms (% heptane)	distillate (% **1**)	distillate (% heptane)	yield (%)
1	1006	55	0.96	51−89	32−36	97.5	2.5	9.1	90.9	97
2	966	58	0.82	68−88	30−38[a]	97.2	2.8	11.4	88.7	92
3	488	58	0.84	63−92	22−27[b]	98.0	1.7	25.2	74.8	92
4	720	99	2.9	35−42	0.25−0.33	99.2	0.0	97.7	0.0	80
5	370	61	0.60	76−83	32−35	97.3	1.8	21.5	78.1	92
6	462	51	0.89	64−89	32−35	98.0	1.8	13.0	86.8	94

[a] Excursion to 22−27 mmHg observed. [b] Excursion to 38 mmHg observed.

which minimizes potential hazards associated with hydrazoic acid condensation in the reactor headspace. The alternative reactor configuration also allows for safe operation at higher processing temperatures than in analogous batch processing systems.

Experimental Section

1-(Azidomethyl)-3,5-bis-(trifluoromethyl)benzene, 1. Batch Preparation A. Sodium azide (74.3 g, 1.14 mol) was suspended in water (125 mL), and then DMSO (625 mL) was added. After stirring 0.5 h, a 3,5-bis-(trifluoromethyl)benzyl chloride, **4** (255.3 g 0.97 mol), solution in DMSO (500 mL) was fed over 0.5 h. The reaction mixture was warmed to 40 °C, stirred for 1 h, sampled, and then cooled to 23 °C. Reaction completion was verified by GC analysis (<1% benzyl chloride **4**). The mixture was diluted with heptane (1500 mL), and some thickening of the white solids was observed. Water (1000 mL) was added, and the mixture was stirred for 0.5 h. Stirring was stopped, and the aqueous layer (2200 mL) was removed. The organic phase (1700 mL) was washed with water (750 mL). The combined aqueous layers (2950 mL) were subjected to the azide destruction protocol and discarded once azide was verified as nondetectable.[15] Solvent was removed from the organic layer via vacuum distillation using a jacket setpoint of 85 °C and a distillate head temperature of 50−55 °C to produce 485 g of azide **1** as a 51 wt % solution in heptane as a clear liquid. WFE was used to produce azide **1** in the bottoms phase in 94% yield with a GC purity of 98.0% and 1.8% residual heptane. See ref 7a for characterization data.

Alternate Batch Preparation B of Azide 1. In a 250-mL three-necked flask were combined 3,5-bis-(trifluoromethyl)benzyl chloride, **4** (20.0 g, 76.21 mmol), isopropyl acetate (100 mL), an aqueous solution of tetrabutylammonium bromide (34.7 wt %, 6.9 mL, 7.62 mmol), and a solution of sodium azide in water (2.42 M, 37.5 mL, 90.8 mmol). The biphasic mixture was warmed to 50 °C and stirred for 4 h with periodic sampling. Once reaction completion was confirmed by GC analysis, the clear biphasic mixture was allowed to cool and was transferred to a separatory funnel. The layers were separated, and the organic phase was washed with water (2 × 20 mL). The organic phase was concentrated to a mass of 25.42 g (96.5% yield). GC purity = 98.7%.

Alternate Batch Preparation C of Azide 1. Analogous conditions were used as described in batch preparation B of azide **1** except that isooctane was used as the solvent rather than isopropyl acetate. Yield = 91.4%, GC purity = 97.6%.

Microcapillary Tube Reactor Preparation of Azide 1. 3,5-Bis-(trifluoromethyl)benzyl chloride, **4** (25.16 g, 0.096 mol), was dissolved in DMSO (126 mL) to form a 0.658 M solution. In a separate container, sodium azide (7.49 g, 0.115 mol, 1.2 equiv) was dissolved in 45.3 mL of deionized water to form a 2.32 M solution. The reaction apparatus pictured in Figure 2 was equipped with a 316-stainless steel reactor made of tubing measuring 0.0625 in. (2.16 mm) o.d., 0.025 in. (0.64 mm) i.d., and 207 ft (63.1 m) long. The internal volume of this reactor was 20 mL. With the GC oven containing the reactor heated to 90 °C and 200 psig of nitrogen pressure applied to the outlet of the reaction system, the two solutions were pumped into a T-shaped fitting just outside the oven, combined, and then flowed through the hot reactor. The flow rate of the benzyl chloride **4** solution was 0.745 mL/min, and the sodium azide solution flow rate was 0.255 mL/min, for a stoichiometry of 1.2 equiv of sodium azide and a combined flow rate of 1.00 mL/min. This resulted in a 20-min residence time in the 20-mL reactor tube. The reaction stream was cooled to 25 °C at the outlet of the reactor using a tube-in-tube heat exchanger, and the product solution was collected in a glass bottle for batch workup. The entire collected product solution was partitioned between *n*-heptane (120 mL) and water (120 mL). The *n*-heptane layer was then washed with water (2 × 120 mL) and concentrated to a clear, colorless oil (24.13 g, 0.0897 mol, 94%).

Acknowledgment

We dedicate this manuscript to the memory of Chris Schmid, a friend, former colleague, and great poker player who was three-time winner at the Dead Money Invitational Casino. We also acknowledge the contribution of Steve Bandy and Amy Hargis for the development of a GC method for azide **1**, Jeff Vicenzi and Amanda Mcdaniel for WFE assistance, and Jeff Niemeier for providing process safety support. In addition, we are grateful for the assistance provided by Martin Johnson and Paul Milenbaugh in the Lilly Alternate Reactor Technology laboratory.

Supporting Information Available

Release GC data, in process GC data, and HPLC analytical methods for azide **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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