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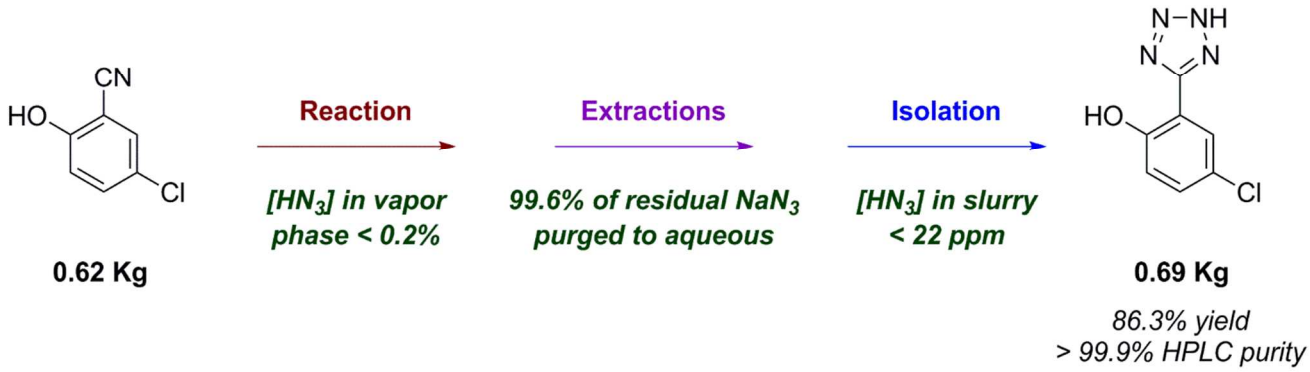


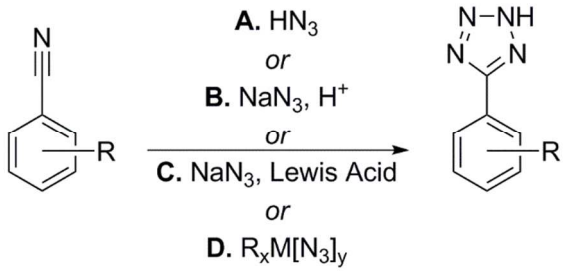
ABSTRACT: The search for a faster, safer protocol for the direct synthesis of 5-aryltetrazoles from aryl nitriles in the presence of sodium azide and an amine hydrochloride salt led to the discovery of a buffered system comprised of $BnNH_2$, $BnNH_2 \cdot HCl$, and NaN_3. After optimization of reaction conditions and a thorough investigation of reaction safety, the procedure was demonstrated for the synthesis of several hundred grams of 4-chloro-2-(2*H*-tetrazol-5-yl)phenol. The generality of the developed reaction conditions was established by a small scale reactivity screen using 16 additional aryl and heteroaryl nitrile substrates.

KEYWORDS: Tetrazole, Sodium Azide, Hydrazoic Acid, Safety

INTRODUCTION

Up until the middle of the 20th century, the most direct method to access 5-aryltetrazoles was by reacting an aryl nitrile with hydrazoic acid (Scheme 1, Eq A).[1] However, hydrazoic acid is not only toxic (Mouse LD_{50} = 22 mg/kg)[2] but also explosive. Based on calculated total energy release and measured detonation velocity, HN_3 is a superior explosive to TNT.[3] These hazards are compounded by its volatility (bp = 37 °C) and its propensity to react with metals to form extremely dangerous shock-sensitive metal azides, many of which explode at the slightest provocation.[4]

Scheme 1. Literature Methods for the Synthesis of 5-Aryltetrazoles from Aryl Nitriles



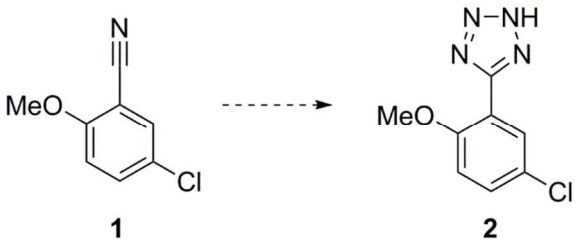
In order to avoid the use of hydrazoic acid, dozens of alternative protocols have since been developed for the conversion of an aryl nitrile to the corresponding 5-aryltetrazole.[5] In the simplest of these procedures, hydrazoic acid is generated *in-situ* by the reaction of sodium azide with a weak Brönsted acid, typically ammonium chloride or triethylamine hydrochloride (Scheme 1, Eq B).[6] Alternatively, myriad Lewis acids have been demonstrated to mediate the reaction between an aryl nitrile and sodium azide. Reported protocols use Lewis acids derived from Li,[6b] B,[7] Mg,[8] Al,[9] Si,[10] Sc,[11] Ti,[12] Fe,[13] Co,[14] Ni,[15] Cu,[16] Zn,[17] Zr,[18] Mo,[19] Ag,[20] Cd,[21] In,[22] Sb,[23] La,[24] Ce,[25] Yb,[24] W,[26] Au,[27] and Bi[19] (Scheme 1, Eq C). Furthermore, there are a number of tetrazole preparations that rely on more exotic reagents such as azides of boron,[28] aluminum,[29] silicon,[30] or tin[31] (Scheme 1, Eq D).

From a safety perspective, tetrazole formation reactions represented by Equations C and D in Scheme 1 appear to be superior by circumventing hydrazoic acid formation, but it should be noted that the majority of these systems will react with adventitious water (or other protic solvents, or protic functional groups on the substrate of interest) to generate hazardous HN_3 (aqueous pK_a = 4.7).[32] Additionally, the traditional acidic aqueous workup would result in the formation of hydrazoic acid from unconsumed azide reagent.

RESULTS AND DISCUSSION

During the course of a recent synthesis of an intermediate towards a drug candidate it was necessary to produce several hundred grams of tetrazole **2** (Scheme 2). Since the corresponding nitrile (**1**) was commercially available, it was proposed that the tetrazole ring should be introduced directly via azide cycloaddition. We were thus faced with the task of deciding which of the dozens of tetrazole-forming reaction conditions to employ.[6-31] Considering ease of operation, reagent cost, and waste minimization, we decided to first investigate the simple conditions reported by Finnegan, Henry, and Lofquist in 1958: NaN_3 in the presence of NH_4Cl in DMF.[6b] While nitrile **1** was successfully transformed to **2** under these conditions, the reaction was unfortunately very sluggish, as is often the case for ortho-substituted nitriles.[6g,11,17,28] Full consumption of the nitrile starting material required >40 h at 120 °C with a significant excess of reagents (2.0 eq NaN_3, 2.5 eq NH_4Cl). From a safety perspective, we were also concerned because a sublimate was observed on the upper portions of the reaction flask, likely ammonium azide (NH_4N_3). This relatively volatile salt (vapor pressure at 80 °C is 38 mm Hg) is known to be explosive.[33]

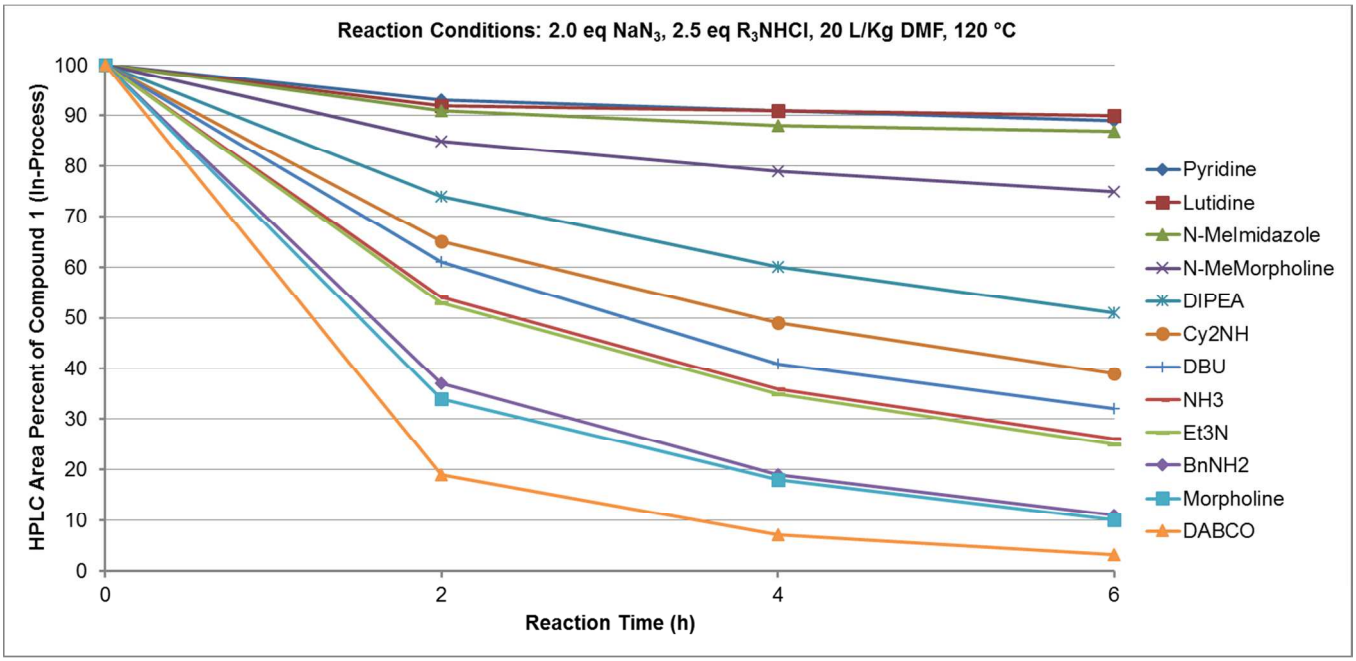
Scheme 2. Proposed Synthesis of 5-Aryltetrazole **2**



1 **2**

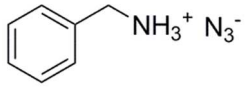
We hypothesized that an investigation of alternative amine hydrochlorides might uncover one with increased reactivity, perhaps due to improved solubility or acidity. More importantly, we hoped to introduce a higher molecular weight amine hydrochloride to decrease the volatility of the corresponding ammonium azide salt formed *in-situ*, in order to prevent deposition of a potential explosive salt. Moreover, even if sublimation and deposition were to occur, an ammonium azide salt with a higher carbon:nitrogen ratio would likely demonstrate increased thermal stability, mitigating the risk of an explosion.[34] Although there have been previous publications investigating alternative amine hydrochloride promoters, to the best of our knowledge these investigations have been focused on improving reactivity rather than process safety.[6b,c,e,h,k] We decided to evaluate 12 amine hydrochloride salts in the desired transformation and obtain rough kinetic data by HPLC analysis of the reaction mixture after 2 h, 4 h, and 6 h at 120 °C. The compiled reaction conversion data is plotted in Figure 1, where the Y-axis illustrates tracks the consumption of aryl nitrile **1**. Surprisingly, the most acidic amine hydrochloride salts employed (pyridine HCl, lutidine HCl, and N-methylimidazole HCl) exhibited poor reactivity under our conditions. Nonetheless, we found that three amine hydrochloride salts demonstrated a significantly faster reaction rate than the original NH_4Cl conditions: benzylamine hydrochloride, morpholine hydrochloride, and DABCO hydrochloride. All three of these amine hydrochloride salts have significantly higher molecular weights than ammonium chloride, suggesting that the corresponding azide salts should be much less volatile and thus safer to work with. Among the three contenders, benzylamine hydrochloride was selected for further study since it has the highest C:N ratio and is also commercially available from several vendors on multi-kilo scale.

Figure 1. Aryl nitrile consumption rates for 12 amine hydrochloride promoters



Since the combination of benzylamine hydrochloride and sodium azide should lead to the formation of benzylammonium azide *in situ*, our next step was to carefully synthesize small amounts of this salt for thermal decomposition analysis and shock/friction testing. Results are presented in Table 1. The energy released upon decomposition of **3** is large, but the high temperature threshold for this decomposition was reassuring. Use of AKTS software to estimate ADT_{24} (temperature at which time to maximum rate at adiabatic conditions is 24 h) suggests prolonged stability of **3** in the solid phase at temperatures below 137 °C. Most importantly, **3** exhibited insensitivity to shock and friction, distinguishing it from ammonium azide, hydrazoic acid, and most metal azides.[3,4,33] With this data in hand, we felt comfortable scaling the benzylamine hydrochloride system with the caveat that we still needed to understand how much free hydrazoic acid was released during the course of the reaction. Hydrazoic acid vapor in the headspace is especially dangerous because HN_3 is liquid at room temperature and can condense onto cooler parts of the equipment, potentially leading to an explosion.[4a,35] In order to monitor hydrazoic acid in the headspace, we employed an in-line mass spectrometer (MS) to sample gases from above the reaction solution under a slow flow of nitrogen (~1 headspace volume/10 minutes).

Table 1. Stability Data for Benzylamine Hydrazoic Acid Salt **3**

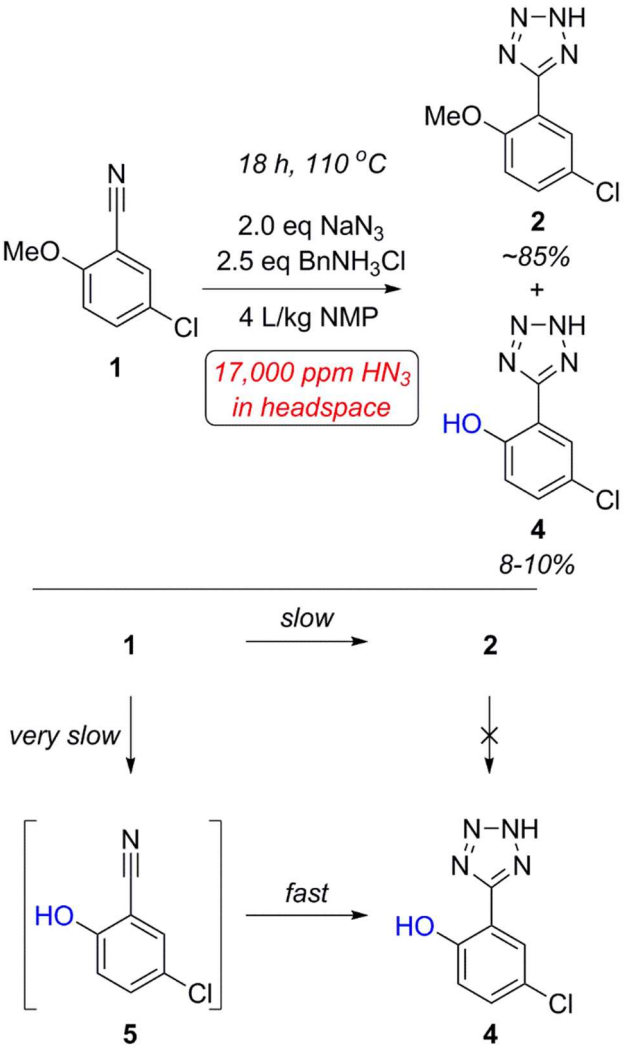


3

Test	Property Measured	Value
DSC	Onset of Exotherm	172 °C
DSC	ΔH_{Decomp}	1782 J/g
DSC	ADT_{24}	137 °C
MP-3 Impact Test	Impact Sensitivity	> 60 J
BAM Friction Test	Friction Sensitivity	> 360 N

In-line MS Analysis of the reaction of **1** to **2** under newly optimized conditions revealed that headspace HN_3 peaked early in the reaction at approximately 17,000 ppm (See Scheme 3). This level is below hydrazoic acid's reported lower decomposition limit (120,000 ppm at 100 °C)[3b] by less than an order of magnitude. Any disruption in headspace nitrogen flow or areas of low flow could allow for condensation of these vapors to form an explosion hazard. Additionally, the in-line mass spectrometer detected around 1,000 ppm of methyl azide in the headspace, which was corroborated by the observation of a demethylated phenol impurity (**4**) formed at low levels (~10% by HPLC area percent). Methyl azide in the reaction effluent is especially dangerous because this volatile explosive compound, in contrast to hydrazoic acid, cannot be trapped by a basic aqueous scrubber solution.[4a]

Scheme 3. Optimized Conditions for the Conversion of **1** to **2**, with a Kinetic Description Accounting for the Formation of **4**



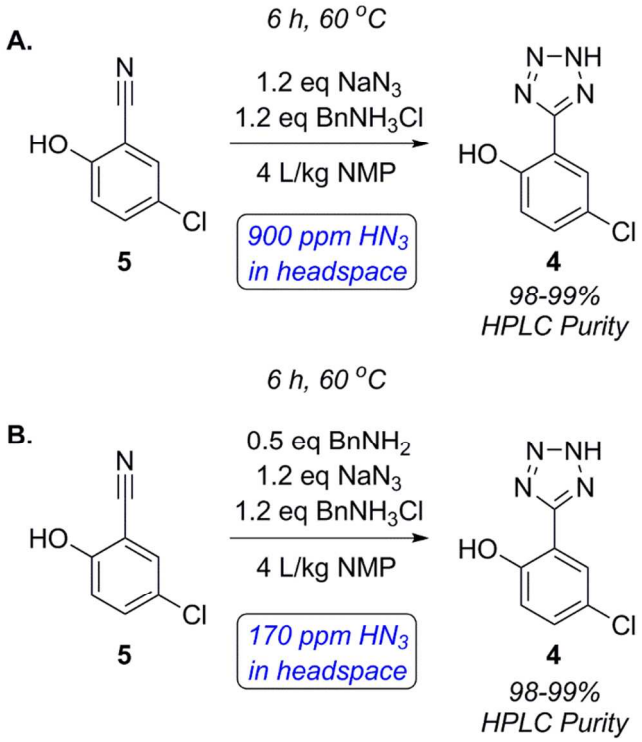
A brief investigation of the demethylation pathway yielded two key observations: 1) **2** does not convert to **4** under the reaction conditions and 2) the corresponding demethylated nitrile **5** cannot be observed by HPLC at any point during the course of the reaction. Taken together, these two observations are consistent with the simplified kinetic model at the bottom of Scheme 3, wherein very slow demethylation of **1** to afford phenol **5** is followed by rapid formation of **4**.

In order to test our hypothesis that phenol substrate **5** reacts significantly faster than methoxy substrate **1**, we subjected commercially available **5** to our reaction conditions. To our delight, >99.8% of **5** was converted to **4** after only 30 minutes at 100 °C. Subsequent experiments established that the rate of conversion of **5** to **4** was approximately two orders of magnitude faster than the rate of conversion of **1** to **2**. Fortunately, at a later step in our synthetic sequence the phenol moiety could be conveniently methylated to afford the desired methoxy group; as such we decided to change our initial synthetic target from **2** to **4**.

As depicted in Scheme 4 Eq A, the much higher intrinsic reactivity of the phenol substrate allowed for significant reductions in reaction temperature, reaction time, and reagent loadings. These modifications in turn led to a large reduction in peak headspace hydrazoic acid detected by our in-line MS, down to 900 ppm. Furthermore, it was

found that buffering the reaction mixture with 0.5 equivalents of added benzylamine resulted in an additional 5-fold reduction in peak headspace hydrazoic acid without compromising on reactivity (Scheme 4, Eq B).[a]

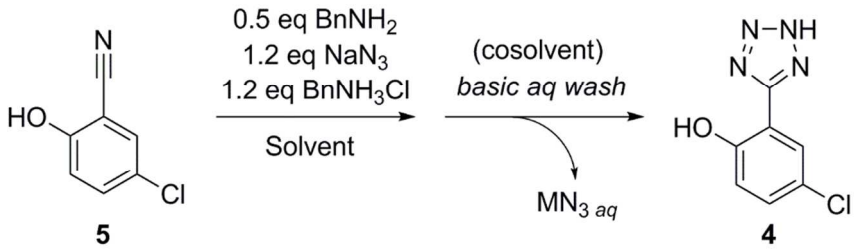
Scheme 4. Further Optimization of the Tetrazole Formation Reaction Starting from Substrate **5**



Having devised safer reaction conditions for the tetrazole formation step, we then focused on making the workup safer as well. Specifically, we took advantage of the fact that N-methyl-2-pyrrolidone (NMP) will phase-split with concentrated aqueous NaOH solutions, allowing for the aqueous extraction of residual azide prior to acidification of the reaction stream for isolation.[36] An HPLC method was developed to quantify the concentration of azide in basic aqueous solutions (λ = 245 nm). Using this method, we determined that aqueous extraction of sodium azide from the reaction stream in NMP was surprisingly inefficient, with less than 50% of the azide ion removed to the aqueous layer with each wash. As shown in Table 2, a survey of other polar aprotic solvents revealed a similar trend. Gratifyingly, reducing the polarity of the organic layer by introducing tetrahydrofuran (THF) as a cosolvent improved the purge of sodium azide to the aqueous layer. Additional screening revealed that increasing the number of aqueous NaOH washes was the most successful approach to residual azide reduction. Based on a previously published analysis of azide safety, we decided to reduce the level of azide in our organic stream to <50 ppm prior to acidification.[35c] With 1.1 – 1.2 equivalents of sodium azide added up front, we could thus calculate that four aqueous washes would be necessary to purge the unreacted NaN_3 to the appropriate level. Fortunately, product losses to the aqueous washes were minimal (~2% per wash), and upon dilution of the washed NMP/THF layer with water and acidification with HCl or citric acid, compound **4** crystallized out of solution and could be isolated in 85-90% yield with >99.5% purity by HPLC.

Table 2. Optimizing Aqueous Extraction of Azide from the Reaction Stream

[a] The apparent pH of the reaction (measured by diluting 1 part reaction mixture with 3 parts water) was increased from ~5 to ~9 by the addition of 0.5 eq benzylamine.



5 **4**

Entry	Reaction Solvent	Cosolvent	Basic Aqueous Wash	Residual N_3 Removed
1	NMP (4 L/kg)	-	25 wt% NaOH (10 L/kg)	43%
2	DMAc (4 L/kg)	-	25 wt% NaOH (10 L/kg)	50%
3	DMF (4 L/kg)	-	25 wt% NaOH (10 L/kg)	46%
4	NMP (3 L/kg)	THF (3 L/kg)	25 wt% NaOH (10 L/kg)	58%
5	NMP (3 L/kg)	THF (6 L/kg)	25 wt% NaOH (10 L/kg)	70%
6	NMP (3 L/kg)	THF (9 L/kg)	25 wt% NaOH (10 L/kg)	74%
7	NMP (2 L/kg)	THF (6 L/kg)	25 wt% NaOH (8 L/kg)	74%
8	NMP (2 L/kg)	THF (6 L/kg)	40 wt% NaOH (8 L/kg)	*emulsion*
9	NMP (2 L/kg)	THF (6 L/kg)	40 wt% K_3PO_4 (8 L/kg)	71%
10	NMP (2 L/kg)	THF (6 L/kg)	40 wt% K_2HPO_4 (8 L/kg)	23%
11	NMP (2 L/kg)	THF (6 L/kg)	2 x 25 wt% NaOH (8 L/kg)	90.5%
12	NMP (2 L/kg)	THF (6 L/kg)	3 x 25 wt% NaOH (8 L/kg)	96.9%
13	NMP (2 L/kg)	THF (6 L/kg)	4 x 25 wt% NaOH (8 L/kg)	98.9%
14	NMP (2 L/kg)	THF (6 L/kg)	5 x 25 wt% NaOH (8 L/kg)	99.6%

With small scale optimization complete and a thorough safety understanding in place, we began scaling up the tetrazole formation reaction (all previous data had been collected on <5 g scale as a safety precaution). Unfortunately, upon transitioning to jacketed glass reactors with overhead stirring, we discovered that the reaction no longer reached completion under our previously optimal conditions. After investigating a number of potential variables including water content, reagent source, and rate of headspace nitrogen flow, we determined that the method and rate of stirring was likely responsible for the discrepancy. With overhead stirring, even at very vigorous rates, the reaction consistently failed to reach completion. Since the reaction is heterogeneous, it appears that the grinding action of a magnetic stirbar was necessary to facilitate complete conversion as observed on small scale. As further corroboration, small-scale experiments with magnetic stirring at very slow rates were observed to be much slower, but the reaction rate could be restored by using finely ground sodium azide[b] or increasing the stir rate. As for the larger-scale reactions with overhead stirring, it was found that a kicker charge of sodium azide could increase conversion, but this would in turn require additional aqueous extractions to remove the large excess of reagent present at the end of the reaction prior to acidification.

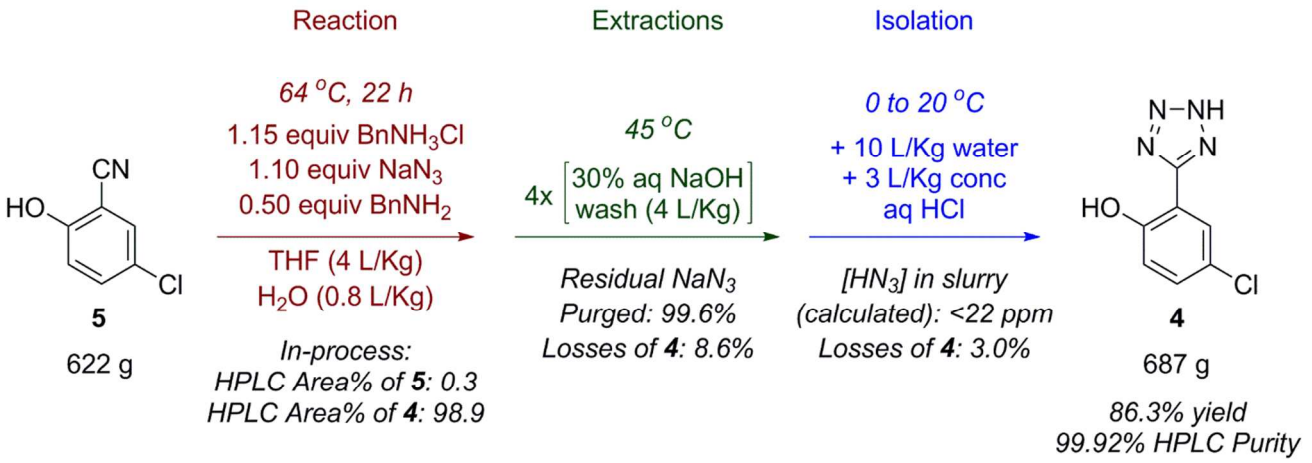
Ultimately it was observed that added water could re-start a stalled reaction, presumably by increasing the solubility of sodium azide. Building on this, a scalable process was designed by incorporating 15 – 20% water as a cosolvent into the reaction mixture. Reactions conducted in either 5:1 NMP:water or 5:1 THF:water reached complete conversion without introducing new impurities, albeit reaction times were noticeably longer (using 1.10 equivalents of NaN_3, reaction time was ~10 h at 75 °C using NMP/water or ~20 h at reflux [64 °C] using THF/water). Using in-line mass spectrometry to evaluate the headspace azide concentrations in the NMP/water

[b] Not recommended for scale-up, due to safety concerns.

system,[c] we found that compared to the pure NMP system there was a 40% increase in the concentration of HN_3 in the headspace, but overall values were still more than two orders of magnitude below the lower decomposition limit and thus considered safe. We ultimately decided to scale up the THF/water procedure, rationalizing that THF is much more volatile than NMP, such that any condensates observed should consist of mostly THF and not present an explosion hazard.[3b] This strategy was vindicated by diverting samples of the distillate for analysis as the refluxing reaction proceeded, allowing for direct measurement of [N_3] in the condensate by HPLC. By this method we determined that the distillate was >99.8% THF (the concentration of azide in the distillate peaked at the beginning of the reaction at 1700 ppm and quickly dropped below 1000 ppm as the reaction proceeded). Upon workup, an additional benefit of the THF/water system was reduction in both the number of solvents and the total solvent volumes, since the NMP/water procedure required added THF during workup to facilitate azide purge (*vida supra*).

The final optimized procedure was scaled up (622 g of **5**) in a 20 L jacketed glass reactor inside a walk-in hood (see Scheme 5). Throughout the course of the reaction, a slow above-surface nitrogen purge was employed (500 mL/min; ~1.5 headspace volumes/hr) as an additional precaution against hydrazoic acid buildup in the headspace. The effluent gas exiting the condenser was bubbled through a trap containing 2.5 wt% aqueous sodium hydroxide to remove any HN_3 prior to venting into the hood baffles. *Prior to reaction start the metal thermocouple was removed from the reaction solution in order to mitigate the risk of forming dangerous metal azides*.[d] During the workup, extractions were performed at elevated temperature (45 °C) to improve the rate of layer separation. The concentration of azide in each aqueous wash was quantified by HPLC; the calculated amount of residual azide remaining at the end of the reaction minus the measured amount of azide purged allowed for determination of the maximum [HN_3] in the aqueous THF layer upon acidification for isolation.[e] This calculated maximum value (22 ppm) was safely below our already conservative limit of 50 ppm. Ultimately, this scale-up effort afforded nearly 700 grams of desired aryltetrazole **4** in very good yield and excellent purity.

Scheme 5. 20 L Batch Procedure for the Synthesis of Aryl Tetrazole **4**



[c] The THF/water system was not compatible with the in-line MS instrument because THF has a large ion fragment at 43 amu that obscures the HN_3 signal.

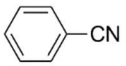
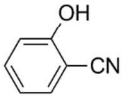
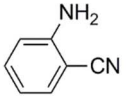
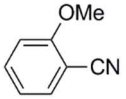
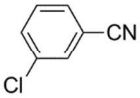
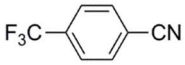
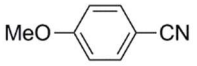
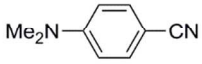
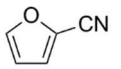
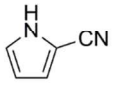
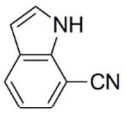
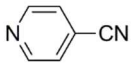
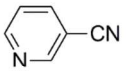
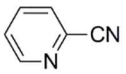
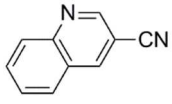
[d] Reaction temperature could be measured using a glass thermometer instead.

[e] The HPLC method developed to quantify azide levels could not be used to directly measure the azide level of the reaction stream because the small N_3 peak is obscured by other signals in the crude reaction mixture. The method could only be used for quantification of azide levels in aqueous washes and distillate.

Upon completion of our scale-up activities to prepare triazole **4**, a brief screen was undertaken to investigate the substrate scope amenable to our new reaction conditions. For each of 16 commercially available aromatic nitriles, two small scale reactions were carried out: one in 5:1 THF:water at 65 °C (Table 3, Procedure A) and one in 5:1 NMP:water at 90 °C (Table 3, Procedure B). Reactions were followed exclusively by HPLC with product identity confirmed by LC/MS; reaction aliquots were pulled after 1.5 h, 4 h, 8 h, 24 h, and 48 h, or until the conversion by HPLC area % was >98. All data in Table 3 are based on in-process uncorrected HPLC area percent. Since the purpose of this study was only to get a sense of how broadly applicable the developed conditions were, no products were isolated and no yields are given.

As evident from the results in Table 3, our developed reaction conditions proved general. The reaction rate appears predictable based on the steric and electronic properties of the substrate. For example, electron-deficient 4-triflouromethylbenzonitrile (entry 6) reacted faster than benzonitrile (entry 1), which in turn reacted faster than electron-rich 4-methoxybenzonitrile (entry 8). The least reactive substrate was electron-rich and sterically hindered 2-methoxybenzonitrile (entry 4). Among the substituted benzonitriles, 2-hydroxybenzonitrile (entry 2) stands out as an anomaly, exhibiting significantly higher reactivity than both benzonitrile (entry 1), which is less electron-rich, and 4-hydroxybenzonitrile (entry 7), which is less sterically hindered. This rate acceleration is analogous to what was observed in the synthesis of our desired intermediate, where the conversion of **1** to **2** was much slower than the conversion of **5** to **4** under the same reaction conditions. The kinetic enhancement of the ortho-phenol substrates may be attributable to an entropy-reducing directing effect, perhaps via a hydrogen bonding interaction with the azide moiety. An alternative explanation invokes hydrogen-bond stabilization of a partial negative charge that builds up on the nitrile nitrogen during the transition state. It is worth noting that this acceleration was not observed with other, less acidic, protic functional groups in the 2-position (i.e. – entries 3 and 12). Among the heteroaromatic nitriles screened, only the highly electron-rich indole and pyrrole substrates failed to reach full conversion within the allotted 48 h reaction time.

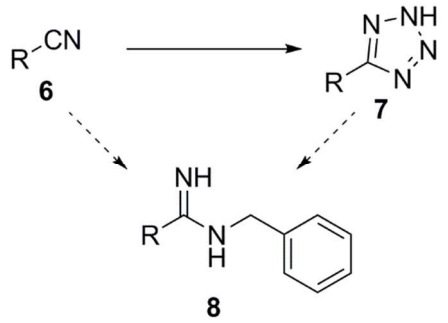
Table 3. Substrate Scope Investigation

Entry	Substrate	Procedure[a] [Rxn Time (h)]	% Product [% Conversion]
1		**A** [48] **B** [24]	93 [97] 89 [99]
2		**A** [8] **B** [1.5]	99 [99] 98 [99]
3		**A** [48] **B** [48]	17 [22] 56 [68]
4		**A** [48] **B** [48]	5 [8] 18 [32]
5		**A** [8] **B** [1.5]	99 [99] 98 [99]
6		**A** [8] **B** [1.5]	99 [99] 98 [99]
7		**A** [48] **B** [48]	21 [23] 61 [69]
8		**A** [48] **B** [48]	40 [42] 75 [82]
9		**A** [48] **B** [48]	34 [41] 69 [82]
10		**A** [8] **B** [1.5]	96 [100] 94 [100]
11		**A** [48] **B** [48]	63 [67] 78 [92]
12		**A** [48] **B** [48]	78 [86] 81 [98]
13		**A** [8] **B** [1.5]	99 [100] 97 [100]
14		**A** [24] **B** [4]	99 [100] 98 [99]
15		**A** [8] **B** [1.5]	86 [99] 79 [98]
16		**A** [24] **B** [8]	96 [99] 93 [99]

[a] $BnNH_2$ HCl (1.15 eq), NaN_3 (1.10 eq), $BnNH_2$ (0.5 eq), 1.5 M in 5:1 THF:water at 65 °C (**A**) or 5:1 NMP:water at 90 °C (**B**).

In most cases, for both heteroaryl and aryl substrates, a single byproduct accounts for the discrepancy between product area percent and conversion: benzyl amidine **8** (see Scheme 6). Formation of this impurity was accelerated at higher temperatures, globally resulting in lower levels of this impurity when using Procedure A. By HPLC, growth of the benzyl amidine byproduct **8** continued after starting material was consumed at the expense of product, suggesting that loss of N_3 from the tetrazole might be possible under the reaction conditions.

Scheme 6. Benzyl Amidine Byproduct



CONCLUSION

A safer procedure for acid-mediated tetrazole synthesis from aryl nitriles and sodium azide was developed. Thermal stability experiments, analysis of headspace gases and condensates, and quantification of azide levels in waste streams were employed to better understand the safety aspects of the newly developed reaction conditions. After ensuring that a safe procedure was in place, the protocol was scaled up to afford ~0.7 kg of aryl tetrazole **4**, an early intermediate in the synthesis of a drug candidate. In addition, the generality of the developed reaction procedure in aqueous THF (65 °C) and aqueous NMP (90 °C) was demonstrated using an array of 16 commercially available aryl and heteroaryl nitriles.

EXPERIMENTAL SECTION

General. ***All tetrazole formation reactions and other investigations using azide reagents were carried out in a fume hood behind a blast shield, on small scale (<2.5 g substrate) unless larger amounts were absolutely necessary. No metal tools or reactor components (i.e. - metal thermocouples, metal spatulae, metal needles, etc.) were used to avoid the formation of shock-sensitive metal azides. Halogenated solvents were strictly avoided to prevent formation of highly unstable polyazidoalkanes.[37] All azide-containing waste streams were segregated and diluted with aqueous sodium hydroxide. It is recommended that all attempts to replicate this chemistry include a careful, holistic evaluation of safety prior to scale-up.*** Compounds **1** and **5** were purchased from Ark Pharm and Parchem, respectively, and used as received. Benzylamine, benzylamine hydrochloride, and sodium azide were purchased from Sigma-Aldrich and used as received. Tetrahydrofuran (THF) and N-methyl-2-pyrrolidone (NMP) were purchased from Sigma-Aldrich ("anhydrous" grade) and used as received. All reactions were run under a nitrogen atmosphere, with a slow nitrogen flow through a basic aqueous trap employed in larger scale reactions to prevent headspace HN_3 accumulation. Reverse phase HPLC was used to monitor reaction progress and assess product purity. Reverse phase HPLC was also used to quantify the azide content of aqueous washes, distillates, and sublimates. Headspace hydrazoic acid concentration was monitored via in-line mass spectrometry (Ametek® ProMaxion™ process mass spectrometer); the instrument was set to intermittently draw up headspace gas samples at a flow rate of approximately 9 mL/minute; relative concentrations of HN_3 were derived from the ratio of the HN_3 and N_2 ion counts; this method of quantification was corroborated by calibration with dilute samples of known hydrazoic acid concentration.

5-(5-chloro-2-methoxyphenyl)-2*H*-tetrazole (2). In a 100 mL round-bottomed flask equipped with a magnetic stirbar, 5-chloro-2-methoxy-benzonitrile (**1**, 2.00 g, 11.9 mmol, 1.0 equiv) and benzylamine hydrochloride (4.28 g, 29.8 mmol, 2.5 equiv) were combined and diluted with NMP (8.0 mL, 4 L/kg). The resultant slurry was heated to 110 °C and solid sodium azide (1.55 g, 23.8 mmol, 2.0 equiv) was added in a single portion. After 18 h at 110 °C, the dark brown reaction mixture was cooled to 20 °C and diluted with additional NMP (8 mL, 4 L/kg). The diluted reaction stream was washed with 25 wt% aqueous NaOH (2 x 20 mL), then diluted with water (16 mL). The resultant aqueous NMP solution was washed with MTBE (24 mL), then heated to 70 °C and acidified by dropwise addition of 25 wt% citric acid (20 mL) *[Note: From results obtained after this experiment (see Table 2), there was probably still a substantial amount of NaN_3 in this stream upon acidification; do not attempt to replicate this procedure]*. The resultant slurry was cooled slowly to 20 °C over the course of 1 h, aged at 20 °C for 1 h more, then filtered. The filter cake was washed with water (3 x 5 mL) and dried under vacuum (150 torr) at 60 °C with a slow nitrogen purge for 68 h to afford **2** (2.07 g, 82% yield, 99.5% purity by HPLC) as an off-white crystalline solid. mp 223 – 226 °C (dec). ^{1}H NMR (DMSO-D6, 500 MHz): δ 8.04 (d, 1H, J = 2.5 Hz), 7.60 (dd, 1H, J = 9.0, 2.5 Hz), 7.28 (d, 1H, J = 9.0 Hz), 3.96 (s, 3H). ^{13}C NMR (DMSO-D6, 125 MHz): δ 155.3, 150.2, 132.4, 128.4, 124.7, 114.2, 113.9, 56.3.

Benzylamine Hydrazoic Acid Salt (3). A freshly prepared solution of sodium azide (2.26 g, 34.8 mmol, 1.00 equiv) in water (25 mL) was added dropwise over the course of 5 min to a solution of benzylamine hydrochloride (5.00 g, 34.8 mmol, 1.00 equiv) in water (25 mL) at 20 °C. The resultant homogeneous solution was stirred gently for 15 min, then decanted into a glass crystallization dish. Evaporation from the dish (no stirring) at 20 °C over the course of 16 h reduced the overall volume to approximately 25 mL and afforded a number of large colorless needles, which were collected, rinsed with water (3 mL), and dried under vacuum (150 torr) at 35 °C with a slow nitrogen purge for 22 h to afford **3** (1.21g, 23% yield) as a colorless crystalline solid. ^{1}H NMR (DMSO-D6, 500 MHz): δ 8.10 (br s, 3H), 7.48 – 7.33 (m, 5H), 3.99 (s, 2H). ^{13}C NMR (DMSO-D6, 125 MHz): δ 134.4, 128.9 (2C), 128.7 (2C), 128.4, 42.4. Elemental analysis: theoretical C: 55.98%, H: 6.71%, N: 37.31%, Cl: 0.00%, Na: 0.00%; observed C: 55.74%, H: 6.87%, N: 36.90%, Cl: 0.61%, Na: 0.24%; residual water (Karl Fischer method): 0.13 wt%.

4-chloro-2-(2*H*-tetrazol-5-yl)phenol (4). (Reaction vessel: 20 L glass jacketed reactor equipped with a sprayball inlet, an overhead stirrer, a glass thermometer measuring headspace temperature, a nitrogen inlet [flow rate 500 mL/min], and a condenser cooled to –8 °C connected via plastic tubing to a hydrazoic acid trap consisting of 1.5 liters of 2.5 wt% aqueous NaOH; entire setup enclosed in a walk-in hood). With the jacket temperature at 20 °C, tetrahydrofuran (2.5 L, 4.0 L/kg), 5-chloro-2-hydroxy-benzonitrile (**5**, 622 g, 4.05 mol, 1.00 equiv) and benzylamine hydrochloride (668 g, 4.65 mol, 1.15 equiv) were charged into the reactor. Benzylamine (217 g, 2.02 mol, 0.50 equiv) was added [Note: exotherm of 11 °C], followed by sodium azide (290 g, 4.46 mol, 1.10 equiv). The sodium azide charge was rinsed into the reactor with water (0.5 L, 0.8 L/kg) [Note: endotherm of 8 °C]. The reactor jacket was heated to 85 °C and the reactor contents were refluxed at an internal temperature of ~64 °C for 22 h. At the conclusion of the reaction, the reactor contents were cooled to 45 °C and washed with 30 wt% aqueous NaOH (4 x 2.5 L, 4 x 4 L/kg) at 45 °C. The washed organic layer was diluted with water (6.2 L, 10 L/kg) and cooled to 20 °C. Concentrated aqueous HCl (1.86 L, 3 L/kg, ~5.5 equiv) was added dropwise to the homogeneous solution over the course of 80 min [Note: highly exothermic; temperature is kept <30 °C by slow addition]. The resultant slurry was aged for 1 h more at 20 °C, then drained and filtered. The filter cake was washed with water (3 x 2.5 L), then transferred to trays and dried in a vacuum oven (40 h at 150 torr, 60 °C, slow N_2 purge) to afford **4** (687 g, 86.3% yield) as an off-white crystalline solid. mp 228 – 231 °C (dec). ^{1}H NMR (DMSO-D6, 500 MHz): δ 7.95 (d, 1H, J = 2.5 Hz), 7.43 (dd, 1H, J = 9.0, 2.5 Hz,), 7.08 (d, 1H, J = 9.0 Hz), 3.56 (br s, 1H). ^{13}C NMR (DMSO-D6, 125 MHz): δ 154.3, 150.8, 132.3, 128.2, 123.2, 118.3, 112.3.

Substrate Scope Evaluation (Table 3). Procedure A: Aryl nitrile (9.00 mmol), benzylamine (0.49 mL, 4.50 mmol, 0.50 equiv), and benzylamine hydrochloride (1.49 g, 10.35 mmol, 1.15 equiv) were suspended in a mixture of THF (5.0 mL) and water (1.0 mL). Solid sodium azide (644 mg, 9.90 mmol, 1.10 equiv) was added and the resultant mixture was heated to 65 °C with stirring. Aliquots (5 uL) were removed after 8 h, 24 h, and 48 h and diluted into 1.0 mL aqueous acetonitrile for HPLC analysis. Procedure B: Aryl nitrile (9.00 mmol), benzylamine (0.49 mL, 4.50 mmol, 0.50 equiv), and benzylamine hydrochloride (1.49 g, 10.35 mmol, 1.15 equiv) were suspended in a mixture of NMP (5.0 mL) and water (1.0 mL). Solid sodium azide (644 mg, 9.90 mmol, 1.10 equiv) was added and the resultant mixture was heated to 90 °C with stirring. Aliquots (5 uL) were removed after 1.5 h, 4 h, 8 h, 24 h, and 48 h and diluted into 1.0 mL aqueous acetonitrile for HPLC analysis.

SUPPORTING INFORMATION

^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, and **4**.

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