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A Safe and Efficient Synthetic Route to a 2,5-Dimethyl-1-aryl-1*H*-imidazole Intermediate

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Supporting Information

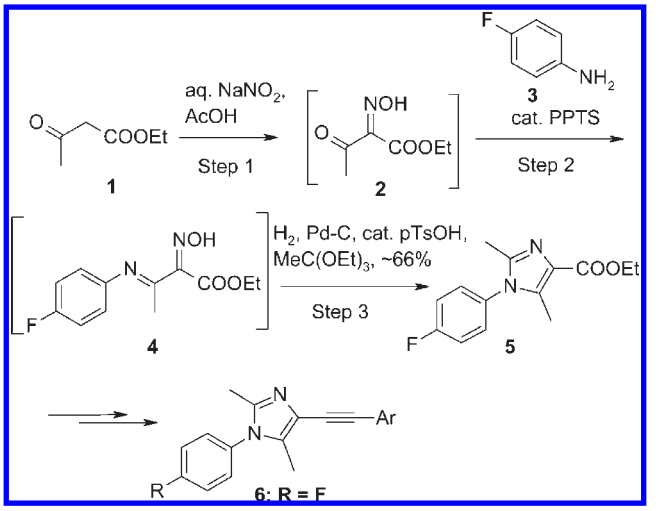
ABSTRACT: An optimized route to an iodo-imidazole intermediate in the synthesis of 4-ethynyl-2,5-dimethyl-1-aryl-1*H*-imidazoles (**6**) was devised. Important data for the optimization work was obtained by carrying out a DOE study to gain understanding of the parameters that affect the key intramolecular cyclization to build the imidazole ring. Additional information on the reaction mechanism of this step was obtained by carrying out a flow NMR experiment. In order to complete the proof of concept, the iodo-imidazole intermediate was converted to two ethynyl imidazoles (**6a**, **b**) using metal-catalyzed reactions.

1. INTRODUCTION

1-(4-Fluorophenyl)-2,5-dimethyl-1*H*-imidazole-4-carboxylic acid ethyl ester (**5**) is a key intermediate in the synthesis of 1-(4-fluorophenyl)-2,5-dimethyl-4-arylethynyl-1*H*-imidazoles (**6**), which have been shown to play an important role in the treatment of metabotropic glutamate receptor-mediated disorders, such as anxiety and chronic or acute pain.[1] The current synthesis of intermediate **5** (Scheme 1)[2] relies on the reaction of 3-oxo-butyric acid ethyl ester (**1**) with sodium nitrite to form its hydroxyimino derivative **2**. Subsequent treatment of **2** with 4-fluoroaniline (**3**) and catalytic amounts of pyridinium *p*-toluenesulphonate (PPTS) furnishes the desired 4-fluorophenylimino intermediate **4**. Formation of the imidazole ring (**5**) is then achieved via a one-pot metal-catalyzed reduction and cyclization step using triethylorthoacetate, hydrogen, and Pd(C).[3]

Although intermediate **5** can be obtained in good yield and purity through this route, the scalability of the process is affected by potential safety hazards. Studies have shown that the addition of sodium nitrite in the formation of **2** is highly exothermic, exhibiting an adiabatic temperature rise of 96 °C. In addition, accelerating rate calorimetry studies (ARC) performed on concentrated samples of intermediates **2** and **4** showed accelerating self-heat and gas generation rates with increasing temperature and rapid runaway. This type of behavior could be of particular concern when residual amounts of **2** and **4** accumulate around the vessel walls during the reaction.[4] The potential safety hazards associated with the route described above prompted us to re-evaluate an alternate approach to the synthesis of 4-arylethynyl-1*H*-imidazoles (**6**) where the ethynyl functionality is introduced via metal catalyzed coupling reactions.[1a,1b] This route is

Scheme 1. Existing route to ester 5



exemplified in Scheme 2 with the synthesis of ethynyl imidazole **10** from precursor **9**.[1b] One of the main concerns of this route is the low yields associated with the formation of diiodo-imidazole **8** and iodo-imidazole **9**.[1b] In addition, low selectivity in the introduction of the methyl group at C5 in compounds such as **8** can lead to reduced yields in the synthesis of 5-methyl-iodo-imidazole intermediates. In order to circumvent these problems a different approach to the synthesis of this type of iodo-imidazole was sought, which could in turn facilitate the overall synthesis of ethynyl imidazoles.

2. RESULTS AND DISCUSSION

As we searched for a suitable way to build the imidazole ring we were intrigued by a report from Eloy et al. on the synthesis of imidazoles from acetamidic esters and propargylamine.[5] In order to assess the feasibility of constructing the desired imidazole ring in this fashion, 4-fluoroaniline (**3**) was reacted with triethylorthoacetate to provide acetamidic ester **11** and its reaction with propargylamine (**12**) was investigated (Scheme 3). Formation of intermediate **14** was expected to proceed via an intramolecular cyclization of intermediate **13**. Subsequent iodination of imidazole **14** could then lead to iodo-imidazole **15** (Scheme 3). However, numerous efforts to form the desired imidazole **14** in

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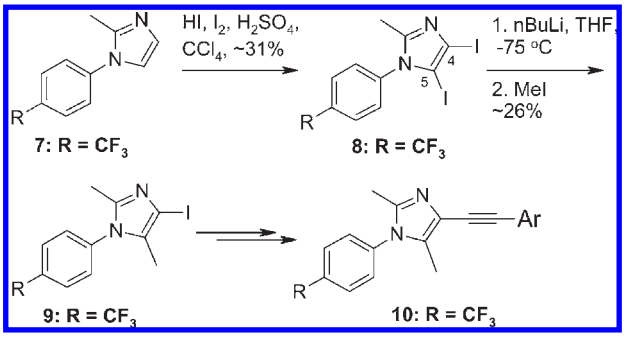
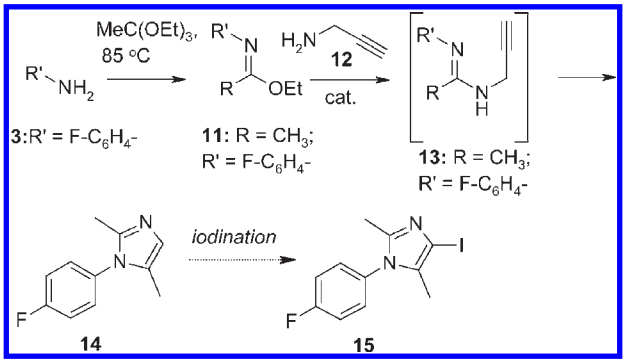
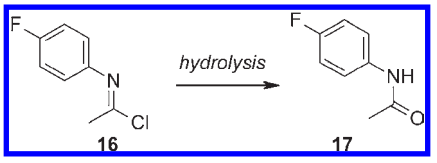
Scheme 2. Synthesis of 4-arylethynyl-1*H*-imidazoles from iodoimidazole 9



Scheme 3. Synthesis of imidazoles from acetamidic esters



Scheme 4. Hydrolysis product of compound 16

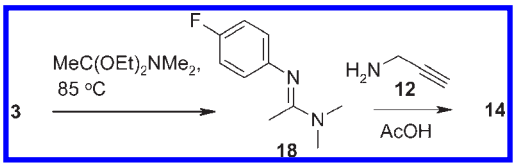


toluene and MeTHF from **11** were unsuccessful. The use of catalysts such as TsOH, $ZnCl_2$, and $Pd(OAc)_2$ did not result in increased formation of 1-(4-fluorophenyl)-2,5-dimethyl-1*H*-imidazole **14**. Attempts to detect intermediate **13** by standard analytical tools were unsuccessful, presumably due to its instability.

Failure to produce compound **14** led us to believe that the harsh reaction conditions needed to react precursor **11** with propargylamine (**12**) were resulting in the decomposition of precursor **11**. In an attempt to favor formation of intermediate **13**, the reactivity of precursor **11** was modified. Initial attempts focused on replacing acetamidic ester **11** with the more reactive *N*-(4-fluorophenyl)acetimidoyl chloride (**16**).[6] Compound **16**, however, was found to be unstable and hydrolyzed readily to *N*-(4-fluorophenyl)acetamide (**17**) during its reaction with **12** (Scheme 4). Careful drying did not improve the result.

A recent report by Díaz et al. describes the synthesis of amidines through an amine-exchange reaction under mild conditions.[7] In order to test this approach, the synthesis of compound **14** from *N*′-(4-fluorophenyl)-*N*,*N*-dimethylacetamidine (**18**) was attempted next. Intermediate **18** was produced quantitatively from 4-fluoroaniline (**3**) and dimethylacetamide

Scheme 5. Synthesis of imidazole 14 from amidine 18



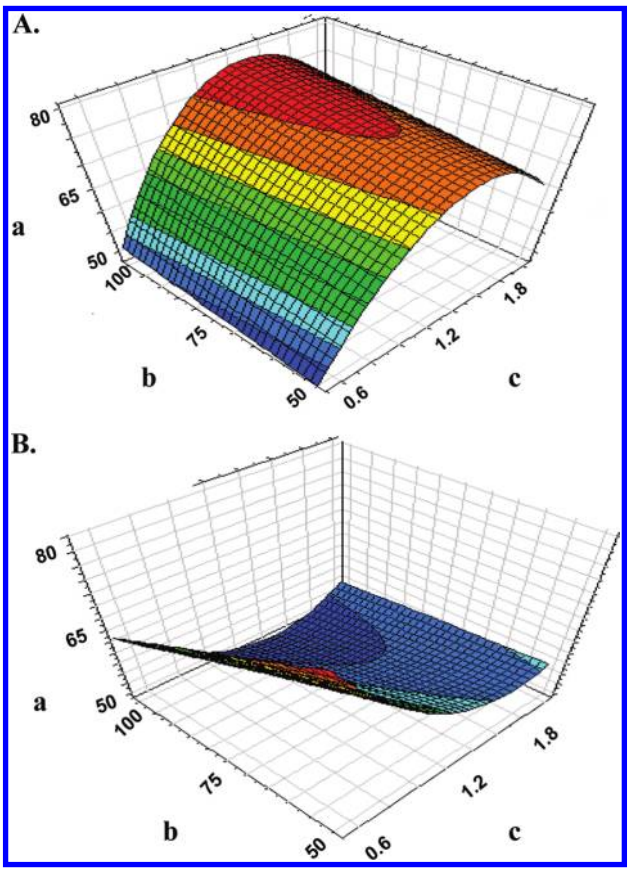


Figure 1. Surface plots. (A) Percentage of product **14** (a) as a function of temperature (b) and equivalents of **12** (c). (B) Percentage of starting material **18** (a) as a function of temperature (b) and equivalents of **12** (c). Compounds **14** and **18** were measured by GC analysis. Temperatures were measured in °C.

dimethylacetal (Scheme 5). Reaction of **18** with propargylamine (**12**) in acetic acid led to the successful formation of imidazole **14** (Scheme 5).

With these results in hand, a DOE study using a fractional factorial design was carried out to gain more understanding on the impact of variables such as reaction temperature, reaction time, and equivalents of propargylamine (**12**) on the formation of product **14**. The effects of these variables were monitored by measuring the percentages of imidazole **14**, 4-fluoroaniline (**3**), and starting material (**18**) by GC analysis. The study consisted of 11 runs with 3 center points.

Surface plots were generated to view the levels of product (**14**) (Figure 1A) and starting material (**18**) (Figure 1B) as a function of temperature and equivalents of propargylamine (**12**). Of particular interest was the curvature observed in the levels of product **14** as the equivalents of propargylamine (**12**) were increased. As shown in Figure 1A, the percentage of product increased as expected when the amount of propargyalmine (**12**)

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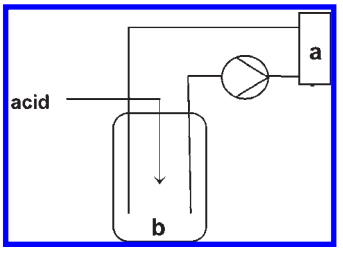

Figure 2. Setup for the study of the reaction of derivative **18** to generate imidazole **14** using flow NMR. A mixture of compound **18** and compound **12** were stirred in a vessel (b), and acetic acid was dosed over time. The mixture was cycled through the flow cell (a) as the reaction progressed and ^{1}H NMR spectra were acquired.

was elevated to 1.25 equiv. However, additional amounts of propargylamine (**12**) led to lower levels of imidazole **14**. Interestingly, the starting material (**18**) was consumed under these latter conditions (Figure 1B). This nonlinear relationship between product (**14**) levels and amounts of propargylamine (**12**) suggested that the desired reaction path can become less favored when increasing amounts of propargylamine (**12**) are used in the system. The consumption of the starting material (**18**) indicated the existence of a side reaction.

Additional details on the nature of the side reaction could not be derived from the data, because the effect of the variables was measured directly by the formation of product **14** without the detection of intermediate **13**. For this reason, we began to consider other analytical approaches for the detection of this intermediate during the reaction. In recent years flow NMR has become a useful tool for reaction monitoring.[8] This inline monitoring technique relies on cycling the reaction mixture through a flow probe as the reaction takes place. ^{1}H NMR spectra are acquired periodically over time to collect information as the reaction progresses, thus circumventing the need of sample collection and preparation. Figure 2 shows a simplified diagram of the flow NMR setup used to study the reaction of **18** to imidazole **14**.

For the flow NMR experiment, compound **18** and propargylamine (**12**) were mixed at 0−4 °C in a vessel. Acetonitrile was used as a solvent to thin the mixture and facilitate the pumping of the solution through the flow probe. ^{1}H NMR spectra were acquired periodically, and acetic acid was added. The data collected showed that the formation of *N*-(4-fluorophenyl)-*N*′-prop-2-ynyl acetamidine **13** occurred rapidly and cleanly. This was evident by the sudden disappearance of the *N*,*N*-dimethyl peak (Figure 3) as the reaction intermediate (**13**) formed.

The reaction mixture was subsequently heated to 80 °C and maintained at this temperature. Analysis of the spectra showed that cyclization of **13** to the desired imidazole **14** was accompanied by the formation of a byproduct, which was identified as 2,5-dimethyl-1-prop-2-ynyl-1*H*-imidazole (**20**).[7] A snapshot of the reaction progress is shown in Figure 4.

The proposed mechanism for the formation of byproduct **20** is shown in Scheme 6. It is believed that, as the temperature is increased, propargylamine (**12**) reacts with intermediate **13**, forming **19** and displacing 4-fluoroaniline (**3**). Subsequent intramolecular cyclization of intermediate **19** leads to the formation of imidazole **20**.

Since both reactions (the desired and side reaction) are acid catalyzed, a study was initiated to investigate the effect of the acid in the transformation of **18** to **14**. As shown in Table 1, the use of TFA (entry c) did not provide detectable levels of imidazoles **14**

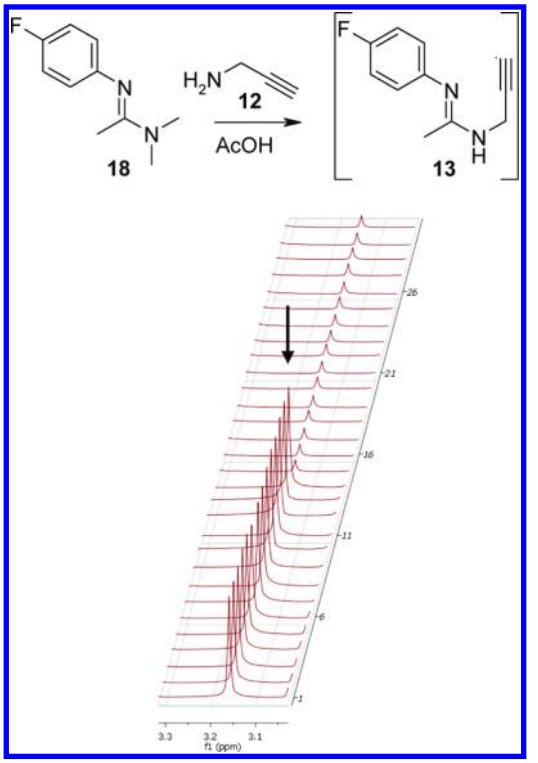

Figure 3. ^{1}H NMR spectra acquired with a flow probe for the reaction of **18** with compound **12** to give intermediate **13**. A reaction mixture consisting of compound **18**, propargylamine (**12**) and acetonitrile is cycled through the probe. The addition of acetic acid leads to the formation of intermediate **13**. This is evident by the disappearance of the *N*,*N*-dimethyl peak as intermediate **13** is formed.

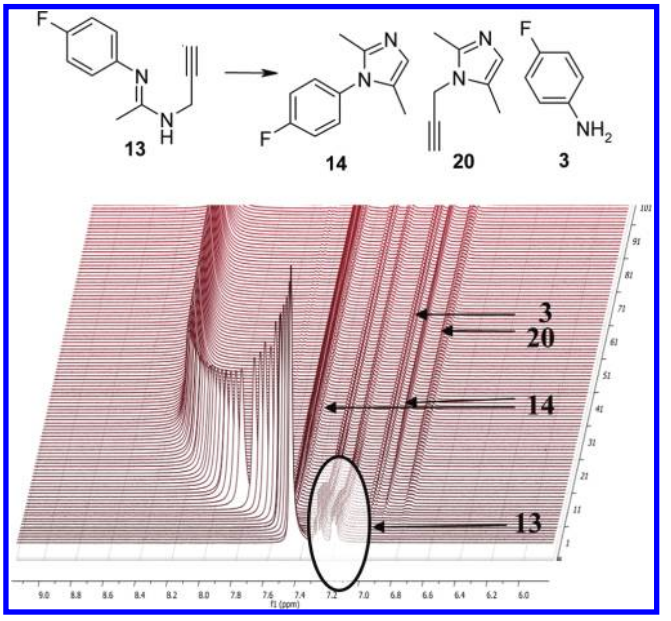

Figure 4. Snapshot of the reaction from **13** to imidazole **14**. Key chemical shifts are indicated for compounds **13**, **14**, and **3**. Analysis of the ^{1}H NMR spectra shows the formation of imidazole **20** as a byproduct.

or **20**, while the use of formic acid (entry b) produced only 18% of imidazole **14**. Surprisingly, reaction of **18** with propargylamine (**12**) in hydrochloric acid (entry d) gave high levels of imidazole **14** as the sole imidazole product. In order to explain the selective

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Scheme 6. Proposed mechanism for the formation of imidazoles 14 and 20

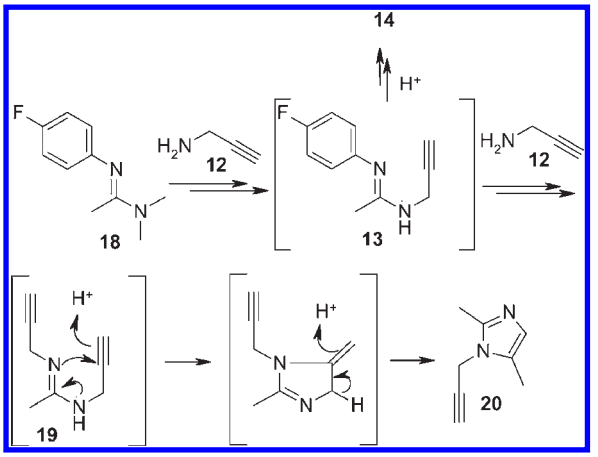


Table 1. Effect of acid on the formation of imidazoles 14 and 20[a]

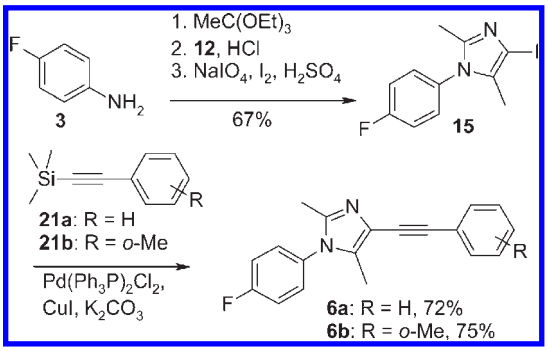
entry	acid	20 (%)[b]	14 (%)[b]
a	acetic acid	9.4	77.9
b	formic acid	ND[c]	18.2
c	trifluoroacetic acid	ND	ND
d	hydrochloric acid	ND	93.1

[a] Representative reaction conditions: amidine **18** was cooled to 0−4 °C, acid and propargylamine (**12**) were added. The mixture was heated to 85 °C and held at this temperature for ~5 h. A sample was collected and treated with Na_2CO_3 (aq); the products were extracted with MTBE. [b] Values measured by GC analysis in area %. [c] ND = not detected.

formation of imidazole **14**, the effect of the acid on the amine exchange step to generate **13**, as well as on the subsequent cyclization step, needs to be considered. It has been reported that amine exchanges using strong acids are less effective, presumably due to the strong acid−base interaction between the acid and nucleophile.[7] Nevertheless, it could be suggested that strongly acidic conditions lead to an increase in the rate of cyclization of **13** to **14**. As a result, the aminolysis of **13** to **19** is minimized, and the formation of imidazole **20** is avoided.

The final workup involved the dilution of the reaction mixture with methyl *tert*-butyl ether (MTBE) and extraction with aqueous sodium carbonate and water, followed by concentration of the organic phase. No agitation issues were observed during the concentration of the solution, and the concentrate remained as a stirable liquid upon cooling. Attempts to crystallize compound **14** in situ from aqueous and organic media were unsuccessful. However, the reaction of **14** to **15** was easily telescoped by diluting the concentrate (**14**) with methanol and sulfuric acid (Scheme 7) and treating the solution with sodium periodate and iodine.[9,10] Interestingly, addition of iodine upfront followed by heating of the reaction mixture to reflux gave an incomplete reaction with starting material levels as high as 50%. In this case, use of excess iodine and other solvents such as THF did not result in an increase in product formation.[11] This problem was circumvented by dosing a solution of iodine in methanol to the mixture while the reaction mixture stirred at 60 °C. This type of addition allowed the starting material (**14**) to be consumed over time. Once cooled, the reaction was quenched with sodium

Scheme 7. Optimized synthesis to ethynyl imidazoles 6



bisulfite, and the desired product **15** was precipitated by addition of aqueous sodium hydroxide. To complete the proof of concept, iodo-imidazole **15** was reacted with two alkynes (**21**) using Sonogashira coupling conditions. As seen in Scheme 6, the desired 1-(4-fluorophenyl)-2,5-dimethyl-4-arylethynyl-1*H*-imidazoles **6a**, **b** were isolated in good yields.[1a,1b]

To assess the safety of the synthesis of **14** from **18** we looked at the reaction enthalpy and associated adiabatic temperature rise for the formation of **13** and its subsequent intramolecular cyclization to **14**. The reaction enthalpy was measured in a Super CRC reaction microcalorimeter. The adiabatic temperature rise was calculated to be 71.7 °C. This suggests that an accidental loss of cooling would raise the batch temperature to ~72 °C, which lies within the specified reaction conditions. Additionally, ARC studies were completed to determine the thermal stability of the mixture. In contrast to the original route, the exotherm observed did not show acceleration of self-heat rates or generation of pressure at temperatures below 218 °C.[12]

3. CONCLUSIONS

An optimized approach to the synthesis of 1-(4-fluorophenyl)-2,5-dimethyl-4-arylethynyl-1*H*-imidazoles (**6**) from iodo-imidazole **15** was devised starting from 4-fluoroaniline (**3**). The route relies on the reaction of *N*′-(4-fluorophenyl)-*N*,*N*-dimethylacetamidine **18** with propargylamine (**12**) to produce acetamidine **13**, which upon intramolecular cyclization furnished the desired imidazole core (**14**). This route avoids the thermal hazards associated with the synthesis of compounds **2** and **4** as shown by thermal analysis data. Key parameters which affect the formation of imidazole **14** were identified in a DOE study, while flow NMR data provided mechanistic information for the formation of **14**. These studies helped to elucidate a side reaction, which can be avoided by choosing the appropriate acid for the reaction. Final synthesis of the key intermediate 1-(4-fluorophenyl)-4-iodo-2,5-dimethyl-1*H*-imidazole (**15**) was achieved by reaction of 1-(4-fluorophenyl)-2,5-dimethyl-1*H*-imidazole (**14**) with iodine and sodium periodate. To complete the proof of concept two ethynyl imidazoles (**6a**, **b**) were synthesized from **15** using Sonogashira coupling conditions.

4. EXPERIMENTAL SECTION

General Methods. Statistical analysis of the DOE was carried out using Modde 7 by Umetric Inc.

GC Analysis. GC analysis was performed on an Agilent 6890 gas chromatograph equipped with FID and an Optima 5-Amin (Macherey-Nagel) column (30 m × 0.25 mm, 0.5 μm film

thickness). Carrier gas/flow: helium/2.0 mL/min. Inlet temperature: 200 °C; split ratio 20:1. Detector temperature: 300 °C; H_2 flow = 30 mL/min; air flow = 300 mL/min; makeup gas = helium (30 mL/min). Injection volume: 2 μL. Gradient: 100−300 at 10 °C/min.

Flow NMR. Spectra were acquired on a Varian VNMRS 400 MHz spectrometer operating at a ^{1}H frequency of 399.75 MHz. The probe was a Varian inverse detect 3 mm/60 μL triple resonance (HCN) probe equipped with single-axis pulsed field gradients. Solvent suppression was achieved using the WET pulse sequence, and all data were acquired with no deuterium lock. The reaction mixture was transferred from the reaction flask to the flow probe and back in a single loop via a Hewlett-Packard series 1050 HPLC pump operating at a flow rate of 1.0 mL/min. An acquisition time of 2.318 s with a relaxation delay of 0.682 s was used, and eight scans were acquired for each spectrum.

***N′*-(4-Fluorophenyl)-*N*,*N*-dimethylacetamidine (18).** 4-Fluoroaniline (24.12 g, 0.217 mmol) and (46.33 g, 347 mmol) of *N*,*N*-dimethylacetamide dimethylacetal were heated to 85 °C while stirring and were kept at this temperature overnight. The mixture was cooled to room temperature to give the desired product in 99% purity (a/a GC). MS *m*/*z* 180 $[M]^+$. The mixture was used as is.

Flow NMR Experiment. *N′*-(4-Fluorophenyl)-*N*,*N*-dimethylacetamidine (**18**) (1.0 g, 5.2 mmol) and propargylamine (**12**) (0.409 g, 7.4 mmol) were added to acetonitrile (30 mL) at 0 °C. Glacial acetic acid (1.0 g, 16.6 mmol) was then added to the mixture over 2 min. After 10 min, the reaction was heated to 80 °C and stirred for 3 h. Note: these solvents were not deuterated.

1-(4-Fluorophenyl)-2,5-dimethyl-1*H*-imidazole (14). *N′*-(4-Fluorophenyl)-*N*,*N*-dimethylacetamidine (**18**) (101 g, 560 mmol) was cooled to 0 °C and 36.5−38% hydrochloric acid (61.3 g, 1.68 mol) was added over 40 min. Propargylamine (**12**) (37.0 g, 673 mmol) was added to the mixture and the mixture was stirred for 15 min. The reaction temperature was increased to 85 °C and kept at this temperature for 5 h. The mixture was cooled to 25 °C and MTBE (404 mL) and an aqueous solution of saturated sodium bicarbonate (202 mL) were charged while stirring. The phases were separated, and the aqueous phase was washed with MTBE (404 mL). The combined organic phases were washed with water (202 mL). The organic phase was separated, and the solvent was distilled off to give **14** as an oil in 94% purity (a/a GC). MS *m*/*z* 190 $[M]^+$. ^{1}H NMR (400 MHz, DMSOd_6) δ 7.58−7.26 (m, 4H), 6.65 (s, 1H), 2.10 (s, 3H), 1.96 (s, 3H). The product was used as is in the next step.

1-(4-Fluorophenyl)-4-iodo-2,5-dimethyl-1*H*-imidazole (15). Sodium periodate (3.67 g, 17.1 mmol), 1-(4-fluorophenyl)-2,5-dimethyl-1*H*-imidazole (**14**) (9.99 g, 52.6 mmol), 2.4 M sulfuric acid (17.5 mL, 42.1 mmol) and methanol (l00 mL) were heated to 60 °C. A solution of iodine (9.43 g, 37.2 mmol) in methanol (100 mL) was added over 1 h. The mixture was stirred for 4 h at this temperature. The mixture was cooled to 20 °C, and a solution of sodium bisulfite (0.175 g, 1.68 mmol) in water (50 mL) was added. The pH of the mixture was adjusted to pH = 14 with 42% sodium hydroxide. The solids were filtered and washed with water (20 mL). The solids were dried under vacuum at 60 °C overnight to give 1-(4-fluorophenyl)-4-iodo-2,5-dimethyl-1*H*-imidazole (**15**) (11.1 g, 67%) as a brown solid. MS *m*/*z* 316 $[M]^+$. ^{1}H NMR (400 MHz, DMSOd_6) δ 7.54−7.30 (m, 4H), 2.06 (s, 3H), 1.91 (s, 3H).

1-(4-Fluorophenyl)-2,5-dimethyl-4-phenylethynyl-1*H*-imidazole (6a). 1-(4-Fluorophenyl)-4-iodo-2,5-dimethyl-1*H*-imidazole (**15**) (350 mg, 1.11 mmol), trimethyl(phenylethynyl)silane (338 mg, 1.94 mmol), triphenylphosphine (58.1 mg, 0.221 mmol), copper(I) iodide (5.16 mg, 0.058 mmol), potassium carbonate (765 mg, 5.54 mmol), bis(triphenylphosphine)palladium-(II) chloride (40.4 mg, 0.058 mmol), NMP (1.0 mL) and methanol (0.75 mL) were heated to 77 °C. The mixture was stirred overnight at this temperature. The mixture was cooled to room temperature, passed through a Celite bed, and added to ice. The solids were filtered, and the desired product was recrystallized from 10% ethyl acetate and 90% hexanes. The solids were filtered and dried under vacuum at 60 °C overnight to give 1-(4-fluorophenyl)-2,5-dimethyl-4-phenylethynyl-1*H*-imidazole (**6a**) as a tan solid (230 mg, 72%). MS *m*/*z* 291 $[M]^+$. ^{1}H NMR (500 MHz, DMSOd_6) δ 7.54−7.37 (m, 9H), 2.12 (s, 3H), 2.09 (s, 3H).

1-(4-Fluorophenyl)-2,5-dimethyl-4-*o*-tolylethynyl-1*H*-imidazole (6b). Compound **6b** was synthesized using the procedure described above for **6a**. 1-(4-Fluorophenyl)-2,5-dimethyl-4-*o*-tolylethynyl-1*H*-imidazole (**6b**) was isolated as a tan solid (141 mg, 75%). MS *m*/*z* 305 $[M]^+$. ^{1}H NMR (500 MHz, DMSOd_6) δ 7.56−7.38 (m, 5H), 7.25 (dddd *J* = 26.8, 15.3, 7.3 Hz, 3H), 2.43 (s, 3H), 2.11 (3H), 2.09 (s, 3H).

■ ASSOCIATED CONTENT

Supporting Information. Data obtained from the DOE study. ARC data for compounds **2**, **4** ,and **14** as well as ^{1}H NMR and IR spectra, GC and MS analyses for key intermediates **18**, **14**, **15**, **6a**, **6b**. This material is available free of charge via the Internet at http://pubs.acs.org

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