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Direct Synthesis of Pyrroles via Heterogeneous Catalytic Condensation of Anilines with Bioderived Furans

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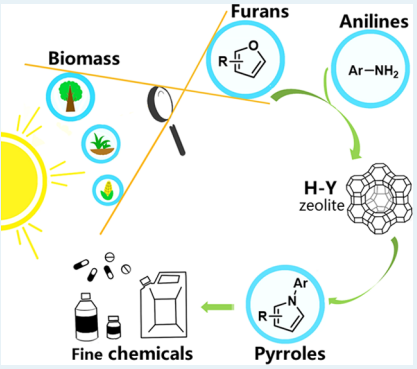
Supporting Information

ABSTRACT: Given the wide applications of pyrroles in agriculture, pharmaceuticals, and supramolecular and materials chemistry, a mild and eco-friendly route to produce functionalized pyrroles from bioderived feedstocks is highly desirable. Described herein is a mild and convenient synthesis of pyrroles via direct condensation of an equimolar amount of structurally diverse anilines with biobased furans catalyzed by a simple and efficient solid acid H form zeolite Y catalyst. The protocol tolerates a large variety of functional groups and offers a general and versatile method for scale-up synthesis of a variety of N-substituted pyrrole compounds. Most importantly, the bioactive pyrrole-derived drug pyrvinium, which has lately been confirmed as highly effective in curing colon cancer, can be obtained by this method.



KEYWORDS: *bioderived furans, condensation, pyrrole synthesis, solid-acid catalysis, zeolite Y*

1. INTRODUCTION

Over the past decades, the world has become increasingly dependent on oil as a primary source of chemicals and energy. This growth in demand, in combination with dwindling reserves, has resulted in a call for converting feedstocks derived from renewable sources. Lignocellulosic materials offer an attractive alternative,[1] as they are the only carbon sources that are widely available apart from oil and coal and can be readily transformed into several important platform compounds possessing many useful chemical linkages, e.g., furanic and phenyl rings,[2] which provide an excellent entry point for downstream processing. While significant recent efforts have been directed toward formulating new catalytic routes and processes to convert platform compounds to various high-density biosynthetic fuels,[3] the development of novel transformations that are orthogonal or complementary to the existing methods for green and sustainable chemical synthesis is still a very important topic of huge industrial interest.[4]

Nitrogen heterocycles,[5] in particular functionalized pyrroles,[6] are important structural motifs of a vast array of naturally occurring and pharmacologically active molecules (Figure 1). The limitations of traditional heterocycle synthetic methodologies[7] have stimulated considerable interest in developing new, efficient catalytic methods for the synthesis of pyrrole compounds.[8] An approach pioneered by Kempe and co-workers,[8c,e] involving a homogeneous or heterogeneous iridium-catalyzed dehydrogenative coupling of biogenic secondary alcohols with amino alcohols, has emerged as an attractive alternative for construction of pyrrole skeletons. Despite its usefulness, the separation and recovery of the costly and potentially toxic iridium species remains a pressing issue in establishing a greener, more sustainable synthesis. Moreover, some other problems associated with this system, including the necessity of copious amounts of strong base and the lack of N-substituted pyrrole preparation, deserve rectification.

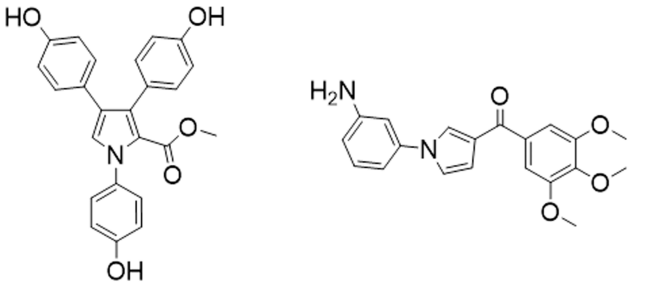


Figure 1. Bioactive N-substituted pyrrole compounds.

Conversion of bioderived furans in the presence of amines or related derivatives is an alternative way to make pyrrole compounds (Figure 2). Due to the high potential of furans as intermediates in a variety of synthetic transformations, there is a continuing interest in the development of novel methods for their conversion to other heterocyclic systems.[9] In early research on the interaction of a primary amine with furan compounds over Al_2O_3 at 400 °C,[10] the conversion of furan

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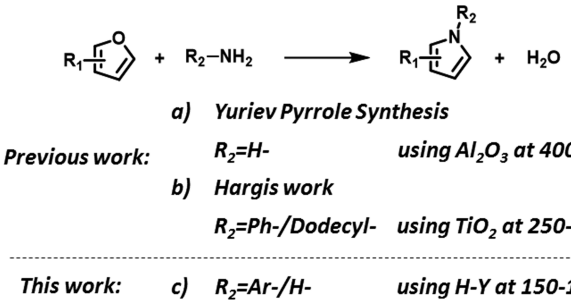


Figure 2. Synthesis of pyrroles via catalytic condensation of furans with amines or anilines.[10,12]

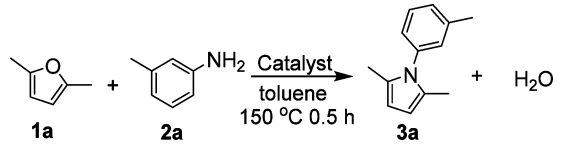
and tetrahydrofuran into pyrroles and pyrrolidines in 20−60% yields was achievable. A subsequent follow-up study in the 1970s showed that the conversion of furan with ammonia to pyrrole can take place selectively at 320 °C by employing synthetic zeolites as the catalyst.[11] A titania catalyst was later reported to deliver somewhat higher activity for this type of reaction over a temperature range of 250−300 °C.[12] However, this system is still not adequately effective and requires the presence of excessive amines relative to furans to yield the corresponding pyrrole derivatives in the range of 30−55%.

Herein we describe a potent and highly selective route for heterogeneous catalytic condensation of an eqimolar amount of structurally diverse anilines with various bioderived furans. Applying a simple and efficient solid acid H form zeolite Y catalyst, this atom-efficient transformation proceeds under additive-free mild conditions and provides straightforward access to a variety of N-substituted pyrrole derivatives in good to excellent yields (Figure 2), often with high selectivities.[6c,13] Of particular significance is that the process is workable on a large scale under neat conditions. To the best of our knowledge, the procedure reported in the present work represents the most efficient, simple, and clean catalytic system for the selective construction of N-substituted pyrroles to date.

2. RESULTS AND DISCUSSION

At the outset of our studies we chose 2,5-dimethylfuran as the model furan-based compound. 2,5-Dimethylfuran, an important derivative of 5-hydroxymethylfurfural,[14] has gained tremendous recent attention due to its benefits as a promising next-generation biofuel. Of special interest is the fact that direct cycloaddition of 2,5-dimethylfuran and ethylene represents an innovative pathway to selectively producing *p*-xylene (PX),[15] a key commodity product that is currently obtained commercially from petroleum sources.[16] We initiated our study by examining the equimolar condensation of 2,5-dimethylfuran (**1a**) with *m*-methylaniline (**2a**) in the presence of a range of inorganic metal oxide materials using toluene as solvent under 150 °C. The preparation procedure for these inorganic metal oxides and relevant characterization data are provided in the Supporting Information. It was revealed that the reaction barely occurred over acidic oxide (Nb_2O_5) (Table 1, entry 1) and amphoteric oxide (ZrO_2) (Table 1, entry 2), affording only a very limited amount of *N*-(*m*-tolyl)-2,5-dimethylpyrrole (**3a**), while basic oxides (CeO_2 and MgO) did not catalyze the reaction at all (Table 1, entries 3 and 4). Interestingly, on application of an amorphous SiO_2−Al_2O_3 mixed oxide, which has been widely studied and proven highly effective for a variety of acid-catalyzed organic transformations,[17] appreciable levels of

Table 1. Catalytic Condensation of 2,5-Dimethylfuran with *m*-Methylaniline over Different Catalysts[a,b]



entry	catalyst	conversion (%)	yield (%)
1	Nb_2O_5	3	3
2	ZrO_2	trace	trace
3	CeO_2	n.r.[d]	n.r.
4	MgO	n.r.	n.r.
5	SiO_2−Al_2O_3	42	42
6	H-ZSM-5 (18)	34	34
7	H-BEA (12.5)	63	63
8	H-MOR (12.5)	9	9
9	H-Y (2.6)	96	96
10	H-Y (3.2)	91	91
11	H-Y (5)	85	85
12[c]	H-Y (2.6)	99	99

[a]Reaction conditions unless specified otherwise: 1 mmol of 2,5-dimethylfuran, 1 mmol of *m*-methylaniline, 2 mL of toluene, 150 mg of catalyst, 150 °C, 5 bar of N_2, 0.5 h, naphthalene as internal standard. [b]Conversion and yield were determined by GC. [c]0.7 h. [d]No reaction.

condensation activity were observed, thus furnishing the desired **3a** in a yield of approximately 42% (Table 1, entry 5).

Inspired by this promising result, we then sought to explore the potentiality of several crystalline aluminosilicate zeolites to be used for this direct condensation reaction. A series of medium- and large-pore zeolites with different Si/Al ratios (see the corresponding X-ray diffraction patterns in Figure S1 in the Supporting Information) were evaluated. The H-Y zeolite experiment with a silicon to aluminum ratio of 2.6, that is, H-Y (2.6), was found to yield a significant amount of **3a**, 96% (Table 1, entry 9). Note that H-Y zeolites with Si/Al ratios of 3.2 and 5 gave 91% and 85% yields of **3a**, respectively (Table 1, entries 10 and 11). Additionally, further improvements can be achieved by performing the reaction over H-Y (2.6) over a longer time, which permits access to **3a** in 99% yield in a very short time of 0.7 h (Table 1, entry 12). This result is remarkable and becomes more relevant as the catalyst can be reused, at least five times, without obvious loss of activity (Figure S2 in the Supporting Information). The high efficiency of H-Y for the direct condensation relative to other common zeolite catalysts is shown clearly (Table 1). For instance, significantly lower yields (<65%) of **3a** were observed in the reactions with BEA-, MOR-, and ZSM-5-type zeolites (entries 6−8). These preliminary results underscore the importance of the pore structure[18] in enabling the desired transformation.

To understand the role of acid sites, all of the zeolites were subjected to NH_3-TPD analysis and the results are compiled in Table S1 and Figure S3 in the Supporting Information as the strength of weak (type 1, around 200 °C) and medium/strong (type 2, around 300−400 °C) acid sites. It can be inferred that H-MOR (12.5) and H-ZSM-5 (18), which have type 2 acid sites with a desorption temperature of over 400 °C, gave relatively lower yields of **3a**. On the other hand, the H-BEA (12.5) and all H-Y zeolite samples, possessing type 2 acid sites with a desorption temperature of below 320 °C, gave significantly higher yields of **3a** in comparison to H-MOR (12.5) and H-ZSM-5 (18). From these results it can be

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deduced that an optimized yield of **3a** could be obtained with zeolite-based catalysts with moderate acid strengths. In this context, the inferior performance of H-MOR (12.5) and H-ZSM-5 (18) may be explained by their strongly acidic nature, which would inhibit the desired condensation, presumably due to a stronger binding interaction between the N-containing intermediates and the active sites.

The nature and relative distribution of the acidic sites in different zeolites were investigated by pyridine-adsorbed FT-IR spectra. As illustrated in Figure S4 in the Supporting Information, the characteristic pyridine-adsorbed IR bands attributed to both Lewis acid (1446−1452 cm^{-1}) and Brønsted acid sites (1540−1544 cm^{-1}) were observed in all samples. A higher fraction of Brønsted to Lewis acid sites is shown to be beneficial to increasing the overall **3a** yield (Table S2 in the Supporting Information). This is indeed the case for H-Y (2.6). That low activity was shown by H-ZSM-5 and H-MOR, despite a relatively high B/L ratio of these two samples, was probably due to their distinctly lower weak acid site concentrations, as inferred from the NH_3-TPD tests (Figure S3 in the Supporting Information). To further validate the role of a Brønsted acid in facilitating this reaction, a separate control experiment involving the condensation of **1a** and **2a** over H-Y (2.6) in the presence of 2,6-lutidine or pyridine under otherwise identical reaction conditions was carried out. It is known that pyridine can interact with both Brønsted and Lewis acid sites via protonation and coordination, while 2,6-lutidine can interact selectively with the Brønsted acid sites due to steric hindrance.[19] As shown in Scheme S1 in the Supporting Information, a significant decrease in the yield of **3a** was registered in both cases, thus confirming the indispensable role of Brønsted acid sites in promoting the direct condensation.

From a practical perspective, reactions that can be performed without the use of solvents would be particularly desirable. Upon subjecting the H-Y (2.6) material to neat equimolar mixtures of **1a** and **2a** (100 mmol), the yield of **3a** can reach over 97%, although an elevated temperature (180 °C) and a longer reaction time of ca. 18 h were required (Scheme S2 in the Supporting Information). During the course of the reaction, we identified the formation of a tiny amount of 2,5-hexanedione. This result suggested that 2,5-hexanedione could be an intermediate on the pathway to produce **3a**. This is not surprising, in view of the fact that the reaction of 2,5-hexanedione with a variety of amines, also known as the Paal−Knorr reaction, is one of the simplest and most economical methods for the synthesis of biologically important and pharmacologically useful pyrrole derivatives.[20] In agreement with this assumption, it was revealed that, in the absence of **2a**, 2,5-hexanedione was obtained as the sole product (ca. 26% in yield) under otherwise identical reaction conditions. Interestingly, the reaction profiles with respect to time under standard condensation conditions, shown in Figure S5 in the Supporting Information, depict that, even during the initial stage of the catalytic reaction, there is no formation of the 2,5-hexanedione intermediate. This seemingly "abnormal" phenomenon can however be explained by the fact that the formation of **3a** directly from 2,5-hexanedione occurs at a much higher rate than that from **1a**.[20b]

To gain further mechanistic insight and validate the positive role of H-Y (2.6) in promoting the desired direct condensation, we evaluated the rate-determining step, namely 2,5-hexanedione formation from **1a**, over different zeolites. The fact that the 2,5-hexanedione yields correlated well with the **3a** yields under the standard reaction conditions strongly indicated that the constant formation of 2,5-hexanedione during the reaction process was a key factor for achieving high yields of **3a** (Figure 3). At this juncture, it should be mentioned that the conversion

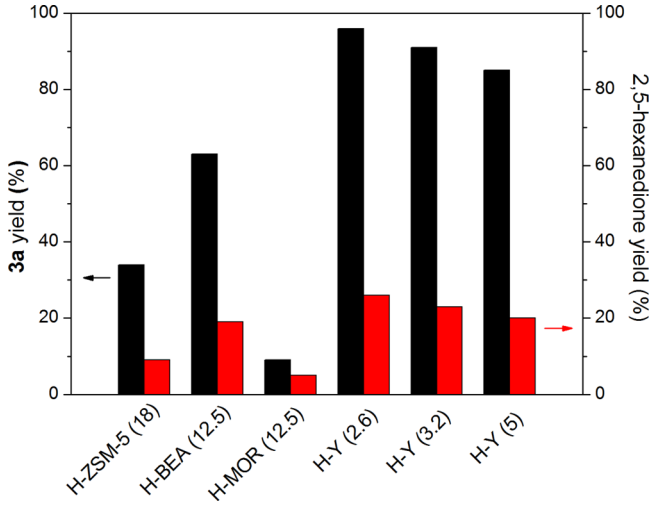

Figure 3. Relation between 2,5-hexanedione formation from 2,5-dimethylfuran and the standard reaction over various zeolite samples. Reaction conditions: (black) 1 mmol of 2,5-dimethylfuran, 1 mmol of *m*-methylaniline, 2 mL of toluene, 150 mg of catalyst, 150 °C, 5 bar of N_2, 0.5 h; (red) 1 mmol of 2,5-dimethylfuran, 2 mL of toluene, 150 mg of catalyst, 150 °C, 5 bar of N_2, 1 h.

level for 2,5-dimethylfuran to 2,5-hexanedione transformation was rather low, although with an extended reaction time, implying an equilibrium nature of 2,5-dimethylfuran to 2,5-hexanedione interconversion. Taken together, these results suggest that the coupling with anilines significantly accelerated the conversion of **1a** because of the thermodynamic driving force. Relevant mechanistic information was further obtained upon studying a concentration-dependent reaction of **1a** with **2a** over H-Y (2.6), which indicates first and zero order for **1a** and **2a**, respectively (Figure S6 in the Supporting Information). Note that a negative order (ca. −1.3) was observed for **1a** in a high-concentration range of **1a**. This change in sign of the substrate order at higher **1a** concentration may be explained by the formation of a strongly bound H-Y-2,5-dimethylfuran complex leading to substrate inhibition in this case.[21]

Building upon these results, we proceeded to examine the substrate scope for this zeolite-mediated direct pyrrole formation. As depicted in Scheme 1, various structurally diverse anilines, including meta- and para-substituted and heterocyclic anilines, could be transformed into the corresponding pyrroles in excellent yields without any side products being detected. More significantly, a wide variety of synthetically useful functional groups, both electron-withdrawing and electron-donating, were not affected in the catalytic condensation. For example, both nitro- and methoxy-substituted anilines were selectively transformed into the corresponding nitro- or methoxypyrroles (**3f**,**g**). Methyl- or amino-substituted anilines, whether in a meta or para position, could react smoothly, providing the corresponding pyrroles in high yields (**3a**,**c**−**e**). A halo-substituted aniline, such as chloroaniline, was also tolerated (**3h**). Moreover, this catalytic condensation process is not limited to phenylpyrrole production, and pyridyl- or naphthylpyrrole could also be obtained readily and efficiently

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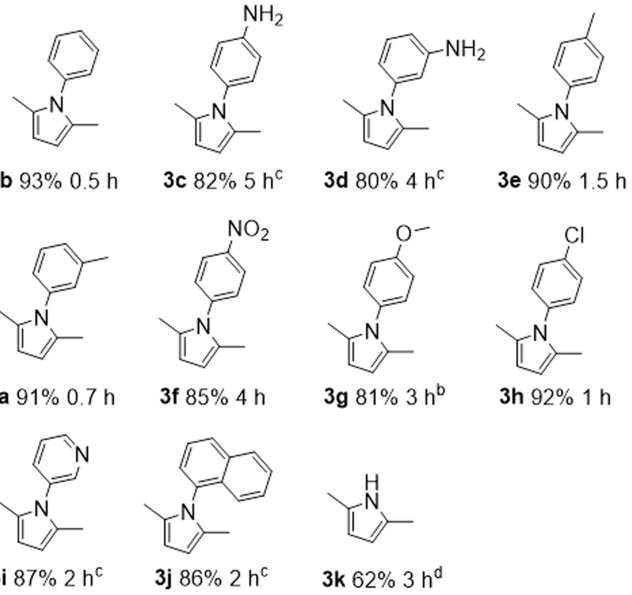
Scheme 1. Catalytic Condensation of 2,5-Dimethylfuran with Structurally Diverse Anilines[a,b]

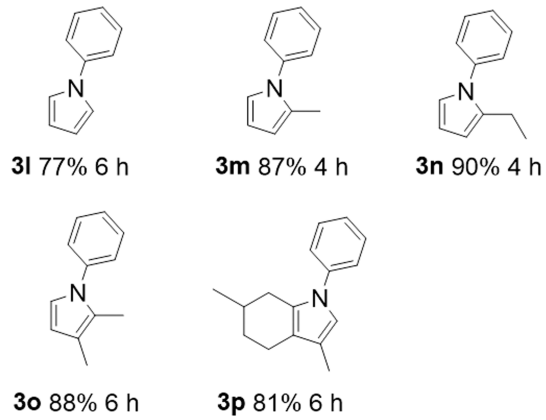


[a]Reaction conditions unless specified otherwise: 1 mmol of 2,5-dimethylfuran, 1 mmol of anilines, 2 mL of toluene, 150 mg of H-Y (2.6), 5 bar of N_2, 150 °C, naphthalene as internal standard. [b]Yield was based on isolated products. [c]200 mg of H-Y (2.6). [d]2 MPa of NH_3, 2 mL of *n*-heptane.

under slightly modified conditions (**3i**,**j**). The catalytic system was also adaptable to the condensation of ammonia to prepare an N-unsubstituted pyrrole (**3k**).

The generality of this methodology has been extended to fabricate a variety of polysubstituted pyrrole derivatives from other bioderived furans (Scheme 2). For example, when 2-methylfuran and 2-ethylfuran were exposed to these zeolite-mediated condensation conditions, the resulting *N*-phenyl-2-methylpyrrole and *N*-phenyl-2-ethylpyrrole could be obtained in high to excellent yields, respectively (**3m**,**n**). Furthermore, menthofuran, a major side product in the manufacture of mint oils from peppermint,[22] could also be readily converted into the

Scheme 2. Catalytic Condensation of Bioderived Furans with Aniline[a,b]



[a]Reaction conditions: 1 mmol of furan, 1 mmol of aniline, 2 mL of toluene, 150 mg of H-Y (2.6), 5 bar of N_2, 180 °C, naphthalene as internal standard. [b]Yield was based on isolated products.

4,5,6,7-tetrahydroindole derivative, which is an important precursor to a variety of important therapeutic agents (**3p**).[23] It must be noted here that, in contrast to the case as depicted in Scheme 1, harsher reaction conditions such as higher temperatures (180 °C) and longer reaction times (4−6 h) are required to achieve full conversion of these bioderived furans. This behavior could be explained by assuming that the intermediate formation of reactive 1,4-diketone species from these furans was much more difficult in comparison with the formation of 2,5-hexanedione from **1a**.[15b]

To highlight this atom-efficient zeolite-catalyzed pyrrole synthesis, we focused our attention on the synthesis of a target compound of critical practical importance. Pyrrole-vinylquinoline (C) is the requisite precursor readily quarternized into pyrvinium, which is well-known for its anthelmintic functions against pinworms.[24] Very lately, pyrvinium has also been confirmed to be highly effective in curing colon cancer by blocking a signaling pathway implicated in tumor cells.[25] A key step for the construction of C involves the synthesis of A, which is commonly achieved by the condensation of aniline with fossil-based 2,5-hexanedione (Scheme S3 in the Supporting Information). We have now found that, by employing entirely biorenewable 2,5-dimethylfuran as the alternative starting material, the desired A can be yielded in an efficient and highly selective fashion (Figure 4), which enables the fabrication of C via intermediate B, according to the procedure in ref 26.

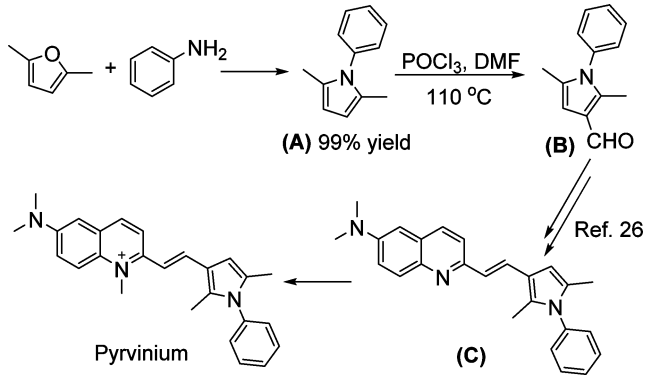


Figure 4. Novel synthetic route for pyrvinium.

3. CONCLUSIONS

In summary, we have successfully developed a heterogeneous zeolite-catalyzed procedure for the direct and straightforward synthesis of N-substituted pyrroles starting from bioderived furans and anilines. Such a transformation is atom and step economical for constructing structurally diverse N-substituted pyrroles from bioderived furans in the absence of any supplementary additives under mild and convenient conditions. This method is a privileged alternative to construct an N-substituted pyrrole-based scaffold, thus complementing traditional catalytic methods that typically use 1,4-diketone derivatives and Paal−Knorr reactions.

4. EXPERIMENTAL SECTION

4.1. General Procedure for Direct Condensation of Furans with Anilines. A mixture of furans (1 mmol), anilines (1 mmol), zeolite catalysts (designated amount), toluene (2 mL), and naphthalene (1 mmol, as the internal standard) were

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charged into a 50 mL Hastelloy-C high-pressure Parr reactor. The resulting mixture was vigorously stirred (800 rpm) under an N_2 atmosphere (5 atm) at the designed temperature for the given reaction time. After completion of the reaction, the reaction mixture was filtered and the catalyst was washed thoroughly with ethanol. Then the filtrate was concentrated and dried under reduced pressure using a rotary evaporator. The crude product was purified by column chromatography (silica gel (200−300 mesh); petroleum ether (60−90 °C)/ethyl acetate mixture) to afford the product. All of the products were identified by ^{1}H NMR and ^{13}C NMR, and the spectra obtained were compared with the standard spectra. The conversion and yields were determined with an Agilent 7820A gas chromatograph equipped with a HP-INNOWax column (30 m × 0.32 mm × 0.25 μm) and a flame ionization detector (FID).

4.2. Procedure for Large-Scale Condensation of 2,5-Dimethylfuran with *m*-Methylaniline under Neat Conditions. A mixture of 2,5-dimethylfuran (100 mmol), *m*-methylaniline (100 mmol), and H-Y (2.6) (150 mg) were charged into a 50 mL Hastelloy-C high-pressure Parr reactor. The resulting mixture was vigorously stirred (800 rpm) under an N_2 atmosphere (5 atm) at 180 °C for 18 h. After completion of the reaction, the reaction mixture was filtered and the catalyst was washed thoroughly with ethanol. Then the filtrate was concentrated and dried under reduced pressure using a rotary evaporator. The crude product was purified by column chromatography (silica gel (200−300 mesh); petroleum ether (60−90 °C)/ethyl acetate mixture) to afford the product. All of the products were identified by ^{1}H NMR and ^{13}C NMR, and the spectra obtained were compared with the standard spectra. The conversion and yields were determined with an Agilent 7820A gas chromatograph equipped with a HP-INNOWax column (30 m × 0.32 mm × 0.25 μm) and a flame ionization detector (FID) after proper dilution and addition of a certain amount of naphthalene as the internal standard.

4.3. Recovery and Reuse of Catalysts. The catalyst was collected after filtration and washed with ethanol three times and then with distilled water several times. The catalyst was then dried at 100 °C for 12 h and calcined at 550 °C for 6 h before being used for the next reaction.

4.4. Characterization. The crystal structures were characterized with X-ray diffraction (XRD) on a Bruker D8 Advance X-ray diffractometer using an Ni-filtered Cu Kα radiation source at 40 kV and 40 mA. NH_3-TPD profiles were obtained using a Micromeritics ChemiSorb 2750 instrument. Typically, the zeolite samples (100 mg) were pretreated at 550 °C under He flow (25 mL min^{-1}) for 0.5 h and then cooled to 100 °C to adsorb NH_3. The TPD profiles were recorded from 100 to 600 °C at a heating rate of 10 °C min^{-1}. FT-IR studies were carried out on an EQUINOX 55 (Bruker) FT-IR spectrometer. The sample was degassed at 300 °C for 1 h under He in order to remove adsorbed water and then cooled to 30 °C. After that, small aliquots of pyridine were subsequently exposed to the sample at 30 °C for 15 min. Prior to the measurement the weakly physically adsorbed pyridine was removed by flowing He at 30 °C for 1 h, and the spectra were then collected at 200 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b02953.

Additional data and explanations as described in the text (PDF)

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Notes

The authors declare no competing financial interest.

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