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Microwave-assisted solid phase diazotation: A method for the environmentally benign synthesis of benzotriazoles

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A novel environmentally benign approach based on microwave-assisted solid phase diazotation to convert *o*-phenylenediamines to substituted benzotriazoles is described. Excellent yields were obtained for a broad range of phenylenediamines proving the efficacy of the method. The reaction was carried out in solid phase under microwave irradiation taking advantage of the strong microwave absorption capability of K-10 montmorillonite that acted as a catalyst and medium in one. The catalyst is recyclable, the reaction occurs with high efficiency and does not produce any harmful waste.

Introduction

Primary amines are easily converted to diazonium salts by a diazotation.¹ Diazonium salts are important intermediates for the production of halides² or azo compounds³ and they can undergo multiple elimination or substitution processes.^{4,5} The conventional method of diazotation uses sodium nitrite and requires a strong acid such as hydrochloric acid,¹ sulfuric acid⁶ or *p*-toluenesulfonic acid⁷ to in situ generate the nitrous acid. Although the traditional diazotation is performed in water, the use of mineral acid solution, the need for the low temperature handling of the diazonium salt and the significant amount of waste due to often low selectivities open opportunities for decreasing the environmental impact of this reaction.

One commonly applied approach to diminish the negative impact of liquid mineral acid catalysis is the application of solid acid catalyzed heterogeneous catalytic methods.^{8,9} The broad variety of available solid acids, from acidic ion-exchange resins to metal oxides, zeolites or clays resulted in a major shift from traditional mineral acid catalysis toward heterogeneous catalytic solid acid catalyzed transformations that became a mainstream approach in environmentally benign organic synthesis.¹⁰⁻¹² Montmorillonite-based clays have become the catalyst of choice in a number of organic reactions due to their low price, their ease of use, recyclability and the varied acidity they possess.¹³⁻¹⁶ In addition,

clays are strong microwave absorbers, thus their use can be effectively combined with microwave-assisted organic synthesis that is another contributor to sustainable synthesis.^{17,18}

Continuing our efforts in developing environmentally benign synthetic methods¹⁹, in the present work we extend the applications of microwave-assisted K-10 montmorillonite catalyzed methods to solid phase diazotations and the synthesis of benzotriazoles. Benzotriazoles belong to an important class of substrates that are versatile in organic synthesis and are also of great interest in medicinal chemistry. They are easily alkylated to obtain N-alkylated azoles²⁰; they can also undergo allylation by metal catalysis to form allylbenzotriazoles.²¹ A few asymmetrical allylation were reported, highlighting the chiral character that benzotriazoles can provide as precursors in the asymmetrical allylic amination.²¹ The various products obtained from benzotriazoles offer multiple applications such as a backbone for dyes production.^{22,23} The use of substituted benzotriazoles in drug design has attracted attention due to their antiproliferative activity.²⁴ Some studies have shown that benzotriazole derivatives inhibit the growth of many human cancer cells and/or induce apoptosis of unhealthy cells.^{25,26} Different synthesis routes are available for the preparation of substituted benzotriazoles. These methods include, the two steps synthesis from benzo-1,2,3,4-tetrazine 1,3-dioxides with sodium dithionite or tin chloride via the intermediate 1-nitrosobenzotriazoles.²⁷ Most methods, however, rely on the use of NaN₃ as a reagent using various synthetic strategies.²⁸⁻³²

Herein, we report a novel microwave-assisted solid acid catalyzed method for the synthesis of substituted benzotriazoles via an in situ solid phase diazotation and subsequent intramolecular cyclization of *o*-phenylenediamines. The approach offers a simple experimental setup, short reaction times, high yield and exclusive selectivities, the use of a recyclable solid acid catalyst and a filtration only work-up.

Results and discussion

In the present method, the solid phase diazotation of *o*-phenylenediamines has been effectively carried out on the surface

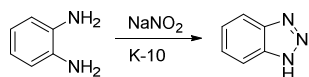
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of a solid acid, K-10 montmorillonite activated by microwave irradiation. This catalyst is a commercially available, environmentally benign solid acid, which is prepared from natural montmorillonite. Its Hammett acidity constant ($H_0 \approx -8$)³³ suggests a significant acid strength similar to that of *cc* HNO₃. In addition, K-10 has a high surface area, about 250–300 m²/g, is stable under high temperature conditions and is an excellent microwave absorber making it an ideal catalyst and medium for solvent-free microwave-assisted reactions.^{18,34} In order to achieve an efficient chemical process, a broad range of reaction conditions were examined using *o*-phenylenediamine as a model substrate (Table 1).

Table 1. Optimization of reaction conditions in the K-10 catalyzed solid phase diazotization-cyclization of *o*-phenylenediamine to benzotriazole.^a



Entry	Solvent	T (°C)	Time (h)	Yield (%)
1	-	110 ^{MW}	1	14
2	200 μL H ₂ O	110 ^{MW}	1	30
3	200 μL MeOH	110 ^{MW}	1	15
4	H ₂ O	110 ^{MW}	1	48
5	MeOH ^b	110 ^{MW}	1	60
6	EtOH ^b	110 ^{MW}	1	17
7	H ₂ O ^b	110 ^{MW}	1	99
8	H ₂ O ^{b,d}	110 ^{MW}	1	80
9	H ₂ O ^{b,c}	110 ^{MW}	1	99
10	H ₂ O ^b	90 ^{MW}	1	72
11	H ₂ O ^b	110 ^{MW}	0.5	94
12	H ₂ O ^b	130 ^{MW}	1	98
13	H ₂ O ^b	110 ^{CH}	5	79
14	H ₂ O ^b	110 ^{CH}	10	90

^a 500mg of K-10, 0.5mmol of NaNO₂, 0.5mmol of substrate. ^b 3mL of solvent, removed before reaction; ^c 1.5mL of H₂O, removed before reaction; ^d 250mg of K-10; ^{MW} microwave irradiation; ^{CH} conventional heating.

The effect of the sample preparation was first investigated. The completely solvent-free reaction, when K-10 and the reactants were simply mixed in a dry form, afforded only 14% of benzotriazole (Table 1, entry 1). Adding a small amount of solvent to the reaction mixture increased the yield to 30% using water but had no effect when methanol was used (Table 1, entries, 2,3). Performing the reaction with more water (3mL) was not decisive (Table 1, entry 4), thus it was concluded that the presence of the solvent during the reaction was not the optimum. It was found that using water for mixing the catalyst and reactants and subsequently evaporating the solvent under vacuum before carrying out the reaction was a highly effective method. The yield of the desired product increased when alcohols were replaced with water. In this case, the benzotriazole formation was nearly quantitative (Table 1, entry 7). Based on our earlier experience with K-10 catalyst,^{18,19} the addition of water ensured the dissolution of sodium nitrite and its uniform distribution on the surface of the clay. Carrying out the reaction in water, however, had negative effects: (i) water significantly

decreased the acidity of K-10 and (ii) also kept the NaNO₂ in the solution thus it could not react efficiently on the surface. In addition, in that system likely, water served as the major microwave absorber and thus the energy transfer was not effective. After evaporation of the solvent, however, the reactants were all adsorbed on the surface of the catalyst uniformly and the direct absorption of the microwaves by K-10 readily provided the necessary activation energy.

Next, the diazotation of *o*-phenylenediamine was carried out for screening the reaction temperature. The temperature set to 110 °C was shown to afford the highest yield of product (Table 1, entry 9). Decreasing the temperature to 90 °C reduced the yield by more than 20% (Table 1, entry 10) and small amount of byproduct (phenazine) was detected when the temperature was raised to 130 °C (Table 1, entry 12). A reaction time of 1h was needed to reach completion of the reaction even though after 30min the yield was already excellent (Table 1, entries 7, 11). When the amount of K-10 was reduced by 50%, the yield of benzotriazole was found to decrease to 80% (Table 1, entry 8). However, reducing water by half (later evaporated), also afforded the same yield as when the reaction performed with 3mL H₂O (Table 1, entry 9), thus it was concluded that the reaction can be carried out effectively in different scales as long as enough water is applied to distribute the NaNO₂ on the surface of the catalyst.

While the microwave-assisted reactions appeared to provide excellent yields in short times it was decided to carry out reactions under conventional heating to observe whether the use of the microwave irradiation is justified or necessary. When carried out in an oil bath at the same temperature the reaction was sluggish and required 5 h to obtain 79% and 10 h to reach 90% yield (Table 1, entries 13,14). Allowing longer times did not improve the yield, as significant amount of byproducts were generated. As another factor in the microwave vs. conventional heating comparison, the energy efficiency of the reactions has to be determined, as the shorter reaction times do not automatically qualify for an energy efficient, i.e. greener reaction.³⁵ Reactions, activated by both microwave irradiation and conventional heating, respectively, have been carried out under otherwise same conditions and the energy consumption of the reactions were measured as described previously.³⁵ The data are summarized in Scheme 1.

	Yields (%)	Energy Use (kWh)	Energy Efficiency (kWh/%)
MW _{0.33h}	89	0.08	8.99 · 10 ⁻⁴
CH _{7h}	89	0.17	19.10 · 10 ⁻⁴

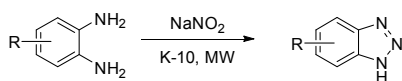
$E_{CH} / E_{MW} = 2.12$

Scheme 1. Comparison of the energy efficiency of the microwave-assisted (MW) and conventionally heated diazotation/intermolecular cyclization reaction of *o*-phenylenediamine.

It was observed that after both reactions reached around 90% yield the reaction rates slowed as expected. While irradiating the reaction for 0.75h with microwaves yielded 97% yield, the energy consumption doubled (0.15 kWh). Similar observation was made for the conventionally heated reaction, a mere 1% increase in yield required about 10h and 1.4 times more energy (0.24 kWh). All in all, based on the calculated data in Scheme 1, the microwave activation clearly appears to be superior to the conventional heating; it is shorter, more energy efficient and yields the product with exclusive selectivity.

After optimization, in order to extend the scope of the method to other substrates, the diazotation of various substituted phenylenediamines was studied under the above optimized conditions (Table 2).

Table 2. Synthesis of benzotriazoles via the diazotation of *o*-phenylenediamines by K-10 montmorillonite catalyst in solid phase.



Entry	Substrate	Product	Temperature	Yield
1	<i>o</i> -phenylenediamine		110	99
2	4,5-dichloro- <i>o</i> -phenylenediamine		150	98
3	4-methyl- <i>o</i> -phenylenediamine		110	98
4	3,4-dimethyl- <i>o</i> -phenylenediamine		110	92
5	3-bromo-5-trifluoromethyl- <i>o</i> -phenylenediamine		110	97
6	4- <i>tert</i> -butyl- <i>o</i> -phenylenediamine		130	94
7	4-chloro- <i>o</i> -phenylenediamine		110	99
8	4,5-dimethyl- <i>o</i> -phenylenediamine		120	95
9	4-chloro-5-fluoro- <i>o</i> -phenylenediamine		110	98

Reaction conditions: 1h under microwave irradiation, 500mg of K-10, 1.5 mL of water (removed before the reaction); 0.5mmol of NaNO₂ and 0.5mmol of substrate.

Excellent yields were obtained for every substrate, which possessed either electron-withdrawing or electron-donating substituents. The reaction showed only negligible substituent effect; the reaction of 4,5-dichloro-*o*-phenylenediamine (Table 2,

entry 2) required higher temperature to achieve a close to quantitative yield.

After the scope of the reaction has been established the catalyst has been subjected to several successive experiments in order to assess its recyclability in the process. For simplicity, the reaction of the unsubstituted *o*-phenylenediamine was selected as a test reaction. Based on several recycling experiments the catalyst was washed with a small amount of ethyl acetate containing a small amount of formic acid to remove impurities from the surface and reactivate the catalyst. The air-dried catalyst was then reused in the next reaction. The data of the recycling experiments are shown in Fig. 1. The yields appear to remain steady indicating that the catalyst is recyclable in the transformation.

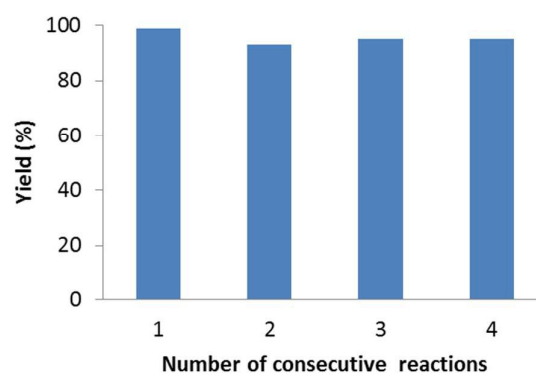
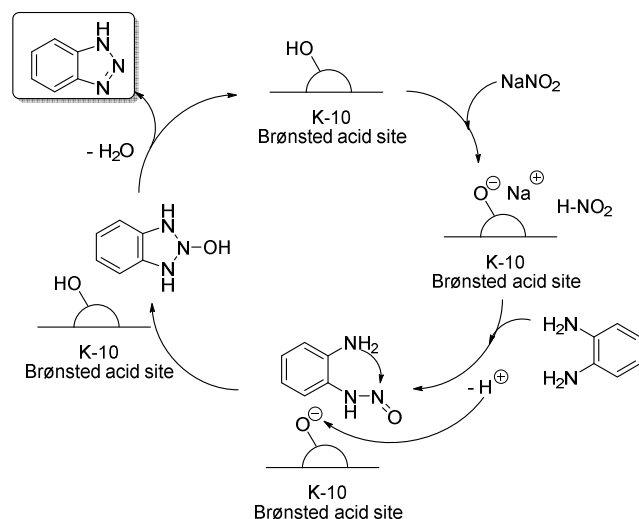


Figure 1. Yield of the benzotriazole formation in the microwave-assisted K-10 montmorillonite-catalyzed diazotation-cyclization reaction of *o*-phenylenediamine with NaNO₂ using the same recycled catalyst sample in four successive reactions.

The mechanism of the reaction follows a plausible pathway, as depicted in Scheme 2. While the chemical events during the reaction likely follow the established mechanistic pathway³⁶ the role of the catalyst appears interesting. As mentioned above, K-10 montmorillonite is a sufficiently strong solid acid catalyst that possesses both Lewis and Brønsted acid centers.³⁷ The Brønsted centers of K-10 appear to be able to replace the Na-cation in the reagent and effectively produce HNO₂ that initiates the reaction. Once the nitroso intermediate formed and a proton is lost the intermediate cyclizes. In the last step, a water elimination, aided by the strong acidity of K-10, occurs to form the triazole. Based on the recycling experiments, it appears that the donated protons return to a large extent to reform the acidic surface OH centers of the catalyst, thus effectively regenerating the acidity. In addition to serving as the reaction initiator acid, K-10 is well-known about its strong microwave absorbing property that ensures the rapid and uniform heating of the reaction mixture. This property is the most likely reason for the higher energy efficiency of the microwave-assisted reactions.³⁴



Scheme 2. Proposed reaction mechanism of the formation of 1,2,3-benzotriazoles via a microwave-assisted K-10 montmorillonite catalyzed solid phase diazotation and subsequent cyclization reaction of *o*-phenylenediamine.

Conclusions

In conclusion, an environmentally benign solid phase diazotation protocol has been established and its use has been demonstrated in the subsequent cyclization of *o*-phenylenediamines to substituted 1,2,3-benzotriazoles. The major advantages of the approach are as follows: (i) the reaction itself occurs on the surface of the catalyst that also serves as a medium, thus minimal amount of solvent was used to prepare the reaction mixture (H₂O), and isolate the product; (ii) there is no need for the separate preparation of the diazonium salt as the reaction occurs in a domino fashion; (iii) the yields are nearly quantitative, and the selectivity is exclusive thus the product does not require purification; (iv) no harmful byproducts are generated; (v) the product isolation entails a simple filtration/evaporation; (vi) the catalyst is recyclable; (vii) the combination of microwave irradiation with a strong microwave absorber catalyst/medium ensures short reaction times and high energy efficiency; and finally (viii) the approach uses commercially available inexpensive materials, including the substrates, reagent and catalyst. Based on these major advantages the process can be considered as an environmentally benign alternative to available processes for the preparation of substituted benzotriazoles and in general, could serve as a broadly applicable green diazotation method that could open new possibilities in the future synthetic application of diazonium salts.

Experimental section

All phenylenediamines, solvents and the K-10 montmorillonite were purchased from Thermo Fisher Scientific and Sigma Aldrich

and used without further purification. Water used as solvent was deionized water.

The mass spectrometric identification of the products has been carried out by an Agilent 6850 gas chromatograph-5973 mass spectrometer system (70 eV electron impact ionization) using a 30 m long DB-5 type column (J&W Scientific). The ¹H and ¹³C spectra were recorded on a 400 MHz Agilent MR400DD2 spectrometer in CDCl₃, C₆D₆ and DMSO-*d*₆, respectively, using tetramethylsilane or the residual solvent signal for reference.

General procedure K-10 montmorillonite (500 mg), *o*-phenylenediamine (0.5 mmol) and NaNO₂ (0.5 mmol) were suspended in 1.5 mL of water and stirred for 5 min. The solvent was then evaporated *in vacuo* until the reaction mixture was completely dry. The dry mixture was transferred into a microwave reaction vessel and the reaction was heated to 110 °C by microwave irradiation using a CEM Discover microwave reactor. After completion of the reaction, two portions of 2 mL of EtOAc were used to extract the product. A centrifugation was applied to separate the catalyst and the EtOAc solution of the product. Finally, EtOAc was removed *in vacuo* to obtain the solid product. The benzotriazoles were isolated as pure products and did not require further purification. The spectral characteristics of the products are listed below. The spectral data are in agreement with the structures.

Catalyst recycling The portion of K-10 that was used in the previous cycle was stirred in 5 mL ethyl acetate and 200 μL of formic acid for 4 h. The clay was then filtered and rinsed using two portions of 15 mL of ethyl acetate. Before reusing the catalyst for another reaction, it was dried overnight at 90 °C.

1H-benzo[d][1,2,3]triazole: ¹H NMR: (CDCl₃, 400 MHz): δ(ppm) = 7.48 (d, 2H), 7.94 (d, 2H). ¹³C NMR: (CDCl₃, 100 MHz): δ(ppm) = 114.73, 126.57, 138.07. MS: C₆H₅N₃: 119(M⁺, 100%); 91(67%); 64(48%).

5-(tert-butyl)-1H-benzo[d][1,2,3]triazole: ¹H NMR: (C₆D₆, 400 MHz): δ(ppm) = 1.14 (s, 9H), 7.15-7.61 (m, 3H). ¹³C NMR: (C₆D₆, 100 MHz): δ(ppm) = 31.01, 34.70, 109.76, 115.05, 123.95, 149.02. MS: C₉H₁₃N₃: 175(M⁺, 32%); 132(100%).

4,5-dimethyl-1H-benzo[d][1,2,3]triazole: ¹H NMR (CDCl₃, 400 MHz): δ(ppm) = 2.40 (s, 3H), 2.61 (s, 3H), 7.21-7.55 (m, 2H). ¹³C NMR ((CD₃)₂SO, 100 MHz): δ(ppm) = 14.22, 18.94, 112.43, 121.99, 128.38, 132.77, 138.75, 139.32. MS: C₈H₉N₃: 147(M⁺, 100%); 118(93%).

5,6-dimethyl-1H-benzo[d][1,2,3]triazole: ¹H NMR (CDCl₃, 400 MHz): δ(ppm) = 2.32 (s, 6H), 7.58 (s, 2H). ¹³C NMR (CDCl₃, 100 MHz): δ(ppm) = 20.64, 114.06, 136.13, 138.07. MS: C₈H₉N₃: 147(M⁺, 100%); 118(91%); 91(50%).

5-methyl-1H-benzo[d][1,2,3]triazole: ¹H NMR (CDCl₃, 400 MHz): δ(ppm) = 2.48 (s, 3H), 7.24-7.25 (d, 1H), 7.60 (s, 1H), 7.80-7.83 (d, 1H). ¹³C NMR (CDCl₃, 100 MHz): δ(ppm) = 21.59, 113.07, 115.47, 122.84, 136.81, 137.97, 138.93. MS: C₇H₇N₃: 133(M⁺, 100%); 104(99%); 77(30%).

5-chloro-1H-benzo[d][1,2,3]triazole: ¹H NMR ((CD₃)₂SO, 400 MHz): δ(ppm) = 7.41, 7.48 (d, 1H), 7.92-8.02 (m, 2H). ¹³C NMR ((CD₃)₂SO, 100 MHz): δ(ppm) = 114.72, 117.27, 126.30, 130.52, 138.41, 139.64. MS: C₆H₄ClN₃: 153 (M⁺, 100%); 125(60%); 63(48%).

5,6-dichloro-1H-benzo[d][1,2,3]triazole: ^1H NMR ($(\text{CD}_3)_2\text{SO}$, 400 MHz): $\delta(\text{ppm}) = 8.26$ (s, 2H). ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$, 100 MHz): $\delta(\text{ppm}) = 116.99, 128.59, 138.68$. MS: $\text{C}_6\text{H}_3\text{Cl}_2\text{N}_3$: 187(M^+ , 100%); 189(64%); 159(73%).

4-bromo-6-(trifluoromethyl)-1H-benzo[d][1,2,3]triazole: ^1H NMR ($(\text{CD}_3)_2\text{SO}$, 400 MHz): $\delta(\text{ppm}) = 8.28$ (s, 1H), 7.77 (s, 1H). ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$, 100 MHz): $\delta(\text{ppm}) = 109.60, 113.88, 122.62, 125.49, 125.81, 140.95, 142.61$. MS: $\text{C}_7\text{H}_3\text{BrF}_3\text{N}_3$: 245(M^+ , 100%); 118(91%), 91(50%).

5-chloro-6-fluoro-1H-benzo[d][1,2,3]triazole: ^1H NMR ($(\text{CD}_3)_2\text{SO}$, 400 MHz): $\delta(\text{ppm}) = 8.27$ (s, 1H), 7.98 (s, 1H). ^{13}C NMR ($(\text{CD}_3)_2\text{SO}$, 100 MHz): $\delta(\text{ppm}) = 109.60, 113.84, 122.65, 125.59, 125.91, 140.84, 142.57$. MS: $\text{C}_6\text{H}_3\text{ClFN}_3$: 171(M^+ , 100%); 143(60%).

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