

Hydrothermal water enabling one-pot transformation of amines to alcohols

Lanxin Wu^a, Jiong Cheng^a, Xiaoguang Wang^{a*} and Yang Yang^{a,*}

^a*School of Environmental Science and Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China*

*Corresponding author:

xg.w826@sjtu.edu.cn (Xiaoguang Wang); yangyang0120@sjtu.edu.cn (Yang Yang)

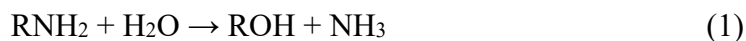
ABSTRACT

While the amination of primary alcohols to amines is quite normal, the reverse reaction, deamination of amines to alcohols is rare. Recent advances achieve the transformation by catalytic multistep processes. We report a one-pot method that enables water nucleophilic attack of amines through the unique catalytic role of hydrothermal water. By achieving dehydrogenation of amines or building targeting group, we fulfilled amines transformation by subsequent reduction or direct deamination, which could further link to the utilization of naturally abundant glutamic acid. The method avoids oxidants, catalysts or multistep, thus achieves simple, green and selective transformation of primary amines.

Keywords: amines utilization; C–N functionalization; alcohols; Hydrothermal

Introduction

Primary amines, as cheap and naturally occurring substances, have been widely utilized as building blocks because the amino functionality is present vastly in biomolecules, pharmaceuticals, and manufacture of dyes and polymers [1]. Traditionally, the utilization of amines have focused on N–H functionalization, such as reductive aminations or cross-couplings [2, 3], however, harnessing the C–N bond as a functional group for deamination transformations remains quite limited. Numerous methods for the preparation of primary amines by amination of alcohols, aldehydes, or halogenated hydrocarbons have been introduced [4-6], while the reverse reaction, a substitution of the amino group with a different nucleophile, such as direct conversion of amines to alcohols, is still challenging [7]. To achieve this, organic solvents and complex homogeneous catalysts are generally required for C–N functionalization [8]. Until recently, the simple, direct conversion of amines to alcohols, using water as the only reagent (eqn (1)) is still quite rare [9].



The difficulties include: if the reaction takes place through S_N2-type displacement, it would be unfavourable, as NH₃ is a poor leaving group, while H₂O is a convenient leaving group [8, 10]. On the other hand, if the reaction proceeds through an S_N1 displacement, strongly acidic conditions are generally required, while the yield and selectivity is commonly poor [10]. It has been reported that deamination could be accomplished by the oxidation of amines with HNO₂, which could lead to the formation of diazonium salts, followed by reaction with various nucleophiles [11, 12]. However, diazonium salts are commonly unstable, and the formation of carbocation intermediate is inevitable, which causes low selectivity of such reaction strategy [11, 13].

Featured with “green” and environmentally benign benefit, hydrothermal

chemistry has drawn growing research attention in recent decades. Using nearcritical or supercritical water instead of organic solvents in chemical processes, hydrothermal reactions offer not only environmental advantages, but also merits in enhancing chemical transformation through the unique and functional characteristics of hydrothermal water (HW) [14, 15]. For instance, water near its critical point possesses much lower dielectric constant and consequently, HW behaves like many organic solvents in that organic compounds enjoy high solubilities in HW. Moreover, the ion product, or dissociation constant (K_w) for HW is much higher than it is for ambient liquid water [16-18]. Accordingly, HW can boast a higher H^+ and OH^- ion concentration. As such, HW is an effective medium for acid/base catalyzed reactions of organic compounds, such as elimination, hydrolysis and rearrangements reactions [19, 20].

By taking advantage of the natural merits of hydrothermal reactions, we assume two strategies regarding the nucleophile substitution of the amino group with water (Fig. 1): (1) achieve the dehydrogenation of amines by the assistance of HW, leading to the formation of imines, and then grow -OH group on the formed imines by the nucleophilic attack of water, which was rather convenient because of the formed C=C bond; (2) build targeting carboxyl group, then liberate deamination by turning $-NH_2$ to NH_3^+ through the intramolecular ring, which can be more convenient to leave with the assistance of HW.

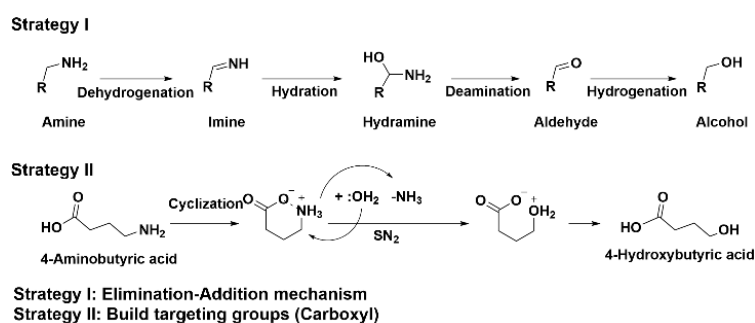


Figure 1. Proposed strategies for the deamination of amines and further transformation to alcohols.

Furthermore, if the built carboxyl group was on the γ position to amino group, it could link to a natural amino acid, glutamic acid (as shown in Fig. S1, ESI†). As the most widespread amino acid composition of plant biomass, the conversion of glutamic acid into chemicals has drawn growing research attention in recent years [21, 22]. Through decarboxylation, glutamic acid can offer great chemical structure for the nucleophile substitution of the amino group with the naturally possessed γ - carboxyl group. Indeed, hydrothermal reaction has been proven as efficient reaction media for decarboxylation, which is typically applied for fatty acids conversion to biodiesel [23]. Thus, the direct conversion of glutamic acid to γ -hydroxybutyric acid (GHB) might be accomplished with simple hydrothermal reactions. Considering that GHB is a well-known hypnotic agent [24], this direct transformation of glutamic acid to GHB through one-pot reaction can be one valuable example in the field of medicine production through bio-based stocks.

Overall, the system described herein effectively exploits the function of HW for selective transformation from amines to alcohols. It uses water as the only reagent, without complex catalysts or oxidants, thus establishing a green method of direct deamination of aliphatic amines in water.

Results and Discussion

We explored the feasibility of the first strategy by using Zn as the source of H_2 for the hydrogenation of aldehyde, as in-situ H_2 generation from Zn splitting HW has shown high efficiency in hydrogenation according to our previous research [25, 26]. Pd/C (5 wt.%) was prepared as the catalyst due to its high efficiency in hydrogenation and stability under hydrothermal conditions (the synthesis procedure, and XRD, SEM, TEM, XPS analysis of Pd/C catalyst can be found in ESI†), and hexylamine was used as the representative of aliphatic amine. The preliminary experiments were performed

under 300 °C, which was the common temperature for the oxidation of Zn [26]. As shown in Fig. S3 (ESI†) hexylamine could be converted to hexanol, pentanol, and hexanamide under the reaction conditions, along with a little hexanenitrile and hexanoic acid, and further quantification study with GC-FID indicated that the yield of hexanol was 48.4%. TOC analysis was then performed to study the product selectivity of hexanol, and it was found that hexanol constituted 92.3% of the total products.

Then, a sequence of reaction parameters was varied to enhance the transformation from hexylamine to hexanol. Fig. 2a shows the influence of reaction temperature. At 150 and 175 °C, the yield of hexanol was quite moderate, while raising the temperature to 225 °C increased the yield abundantly. This was probably because the reaction was endothermic (the molar enthalpy of the reaction is listed in Table S1, ESI†). However, too high temperatures (>225 °C) thoroughly decreased the hexanol yield, and pentanol and hexanamide were observed to increase (Fig. S4, ESI†). Thus, it is probable that higher temperatures were favourable for the production of pentanol and hexanamide, and their formation might consume hexanol as the reactant. Fig. 2b shows the yield of the product as functions of reaction time in the transformation of hexylamine. Hexanol was rapidly formed in the first 2 h, whereas the yield decreased abruptly when the reaction time was longer. As enhanced formation of pentanol and hexanamide was also observed (Fig. S5, ESI†), these results suggested that with time prolonging, the product hexanol might turn to pentanol or hexanamide through consecutive reactions. As a result, the optimal hexanol yield as 84.8% was obtained at 225 °C for 2 h.

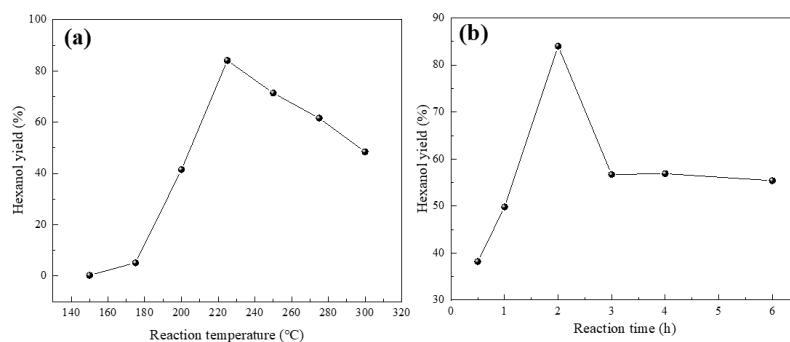


Figure 2. The effects of reaction temperature (a) and reaction time (b) on hexylamine hydrothermal conversion to hexanol (Reaction conditions: (a) 0.1 mol·L⁻¹ hexylamine, 0.1 g 5% Pd/C, 0.1 g Zn, 50% water filling, 2 h; (b) 0.1 mol·L⁻¹ hexylamine, 0.1 g 5% Pd/C, 0.1 g Zn, 50% water filling, 225 °C).

Thus, an investigation on the products variations was performed by tracking the reaction intermediates. As shown in Fig. S5 (ESI[†]), with the start of reaction, hexanol was produced quickly, along with a little formation of pentanol and hexanamide. With time prolonged, hexanol continued to accumulate, in accompany with the increased formation of pentanol and hexanamide. Furthermore, hexanenitrile and hexanoic acid were observed. Considering that hexanenitrile can be easily converted to hexanamide through hydration, and pentanol could be produced from hexanoic acid through decarbonylation, a common process for carboxylic acid under reducing hydrothermal conditions, especially in the presence of Pd as the catalyst [27, 28], it is assumed that pentanol and hexanamide were the products of hexanoic acid and hexanenitrile, respectively. Indeed, corresponding acid is commonly formed through dehydrogenation of alcohols under anaerobic conditions [8], especially with the base catalytic effect of HW. Furthermore, nitriles can be produced by the consecutive dehydrogenation of imines. Thus, we assume the hexanoic acid and hexanenitrile were generated by hexanol and imine through dehydrogenation, respectively, which lead to pentanol and

hexanamide as the products. A brief diagram of the above reaction pathways are illustrated in Fig. 3. It can be seen that the generation of hexanoic acid consumed product hexanol and then lead to the formation of pentanol, thus, with the increase of pentanol, product hexanol decreased correspondingly, which agreed with the previous results in that prolonged reaction time facilitated pentanol production and decreased the concentration of hexanol.

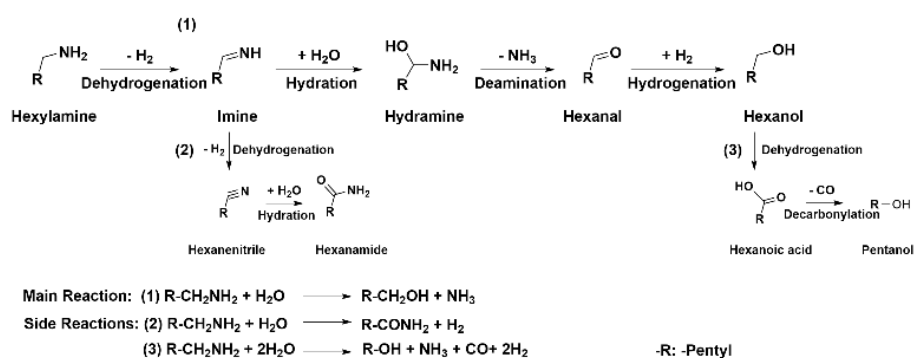


Figure 3. Proposed reaction pathways of hexylamine under hydrothermal conditions.

The second strategy for amines transformation into alcohols was studied with γ -aminobutyric acid as the representative. The reaction was performed without any agent or catalyst while simply under hydrothermal conditions. As shown in Fig. S6 (ESI[†]), only γ -hydroxybutyric acid (GHB) and 2-pyrrolidinone were produced, and the quantitative study with GC-FID indicated that the yields of the two products were 23.8% and 76.0%, respectively. The production of 2-pyrrolidinone was simply accomplished by the dehydration of γ -aminobutyric acid.

Then, we systematically investigated the influence of reaction parameters such as reaction temperature (Fig. 4a), time (Fig. 4b) and water filling (Fig. 4c) on the conversion of γ -aminobutyric acid to GHB. The major findings from these experiments include: (1) the GHB yield was enhanced by increasing the reaction temperature. On the other hand, accompanying the formation of GHB, the yield of 2-pyrrolidinone

decreased. This opposite variation pattern indicated a competing state for the formation of GHB and 2-pyrrolidinone, moreover, the formation of 2-pyrrolidinone was more easily accomplished under relative low reaction temperature, whereas GHB was inclined to be formed at higher temperatures with higher energy input; (2) The production of GHB could also be enhanced by prolonging the reaction time, however, the yield reached a plateau when the reaction time was longer than 3 h. Similar influence was also observed for the formation of 2-pyrrolidinone, while the optimal yield of 2-pyrrolidinone was reached sooner. Such results further agree with the influence of reaction temperature in that the formation of 2-pyrrolidinone was more dynamic favoured, while the synthesis of GHB had to overcome a higher reaction barrier; (3) Varying the water filling had little influence on the formation of GHB, while the formation of 2-pyrrolidinone could be enhanced with higher water filling. Based on the above result, the optimal yield of GHB was 26.4% when γ -aminobutyric acid reacted at 300 °C for 3 h. In addition, the curve of reaction temperature indicated that continuous increasing the temperature could lift GHB yield. However, considering the energy budget and safety issues, the experiments with higher reaction temperatures were not performed. Nevertheless, these results indicated that hydrothermal reactions were able to facilitate the transformation of γ -aminobutyric acid to GHB, while efficient catalysts are needed to gain better yield under the current reaction conditions.

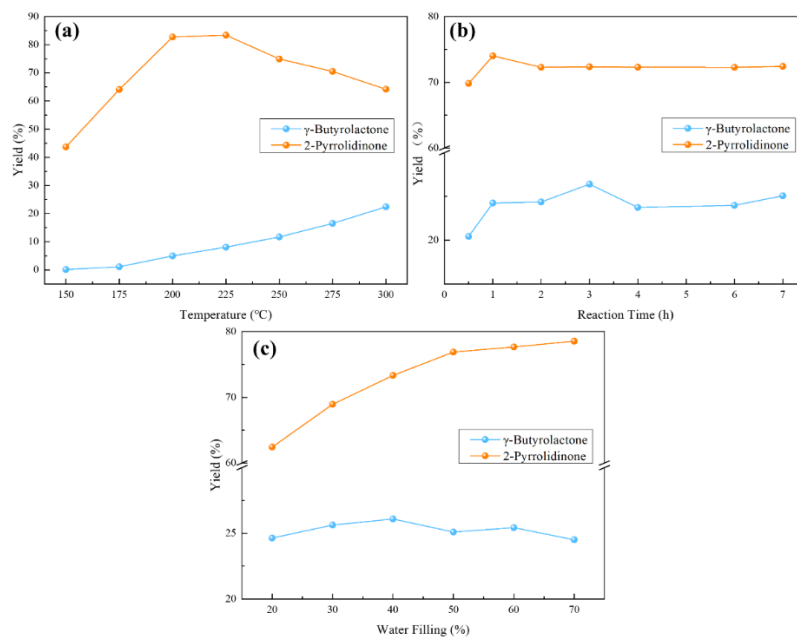


Figure 4. The effects of reaction temperature (a), reaction time (b) and water filling (c) on γ -aminobutyric acid hydrothermal conversion to GHB (Reaction conditions: (a) $0.1 \text{ mol}\cdot\text{L}^{-1}$ γ -aminobutyric acid, 50% water filling, 1 h; (b) $0.1 \text{ mol}\cdot\text{L}^{-1}$ γ -aminobutyric acid, 50% water filling, $300 \text{ }^\circ\text{C}$; (c) $0.1 \text{ mol}\cdot\text{L}^{-1}$ γ -aminobutyric acid, $300 \text{ }^\circ\text{C}$, 3 h).

With optimized conditions in hand, we then examined the reaction scope of glutamic acid, the most widespread amino acid composition of plant biomass, which has only one more carboxyl group compared to γ -aminobutyric acid (Fig. S1, ESI†). As shown in Fig. 5, the yield of GHB was 2.3% when glutamic acid reacted for 3 h under $300 \text{ }^\circ\text{C}$, and GC-MS analysis indicated that apart from GHB, 2-pyrrolidinone dominated the products (Fig. S7, ESI†), which was probably produced by decarboxylation and dehydration of glutamic acid. While the reaction can be performed in water alone, the conversions are typically low. Thus, we attempted to enhance the product yield by prolonging the reaction time. However, only a little increase to 3.6% was obtained when the reaction time was 4 h, and further prolonging the reaction time decreased the yield slightly (Fig. S8, ESI†), which was probably caused by the further

conversion of GHB to propanoic acid or propanamide (Fig. S9, ESI†). As shown in Fig. S10 (ESI†), GHB might form propanoic acid through dehydrogenation and decarbonylation, which could transform to propanamide by amidation. In the meantime, the yield of 2-pyrrolidinone was observed to increase with the reaction time, which reached plateau when the reaction time was prolonged to 12 h.

Considering decarboxylation was involved in the conversion of glutamic acid to GHB, our further effort to enhance GHB yield was paid by adding Pd based catalysts. Expectedly, simple Pd/C lead to obvious increase in the product yield (Fig. 5), which indicated that catalysts were indispensable in the reaction. Thus, Pd based catalysts with different supports were prepared and applied for the reaction. Pd/SiO₂ intriguingly enhanced the reaction with lifting the yield of GHB to 11.6%, and Pd/Al₂O₃ and Pd/ZrO₂ showed moderate catalytic role in the reaction. To explore the reason for Pd/SiO₂ superior catalytic performance, we first examined GHB yield under different pH. As shown in Fig. S11 (ESI†), while the addition of a strong acid or a base has only adverse effects in the conversion of glutamic acid, pH around 4 increased the yield to GHB abundantly when starting from glutamic acid. We consequently measured pH values of different supports, and the pH of SiO₂ lies properly around 4 (Table S2). Thus, we assume the moderate acidity of SiO₂ lead to its superior catalytic effect in the reaction. We next turned our attention to further lift the yield of GHB from glutamic acid. After optimizing the reaction time, we got the highest yield as 15.6% for GHB and 56% for 2-pyrrolidinone, which was obtained when glutamic acid reacted for 4 h under 300 °C with Pd/SiO₂.

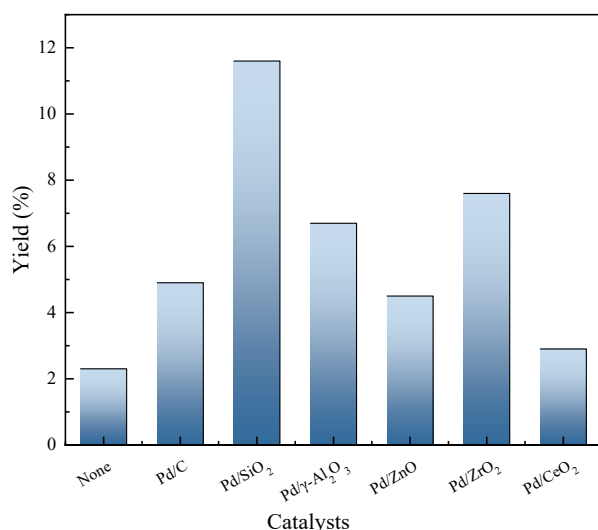


Figure 5. GHB yields without and over different Pd-based catalysts (Reaction conditions: $0.1 \text{ mol}\cdot\text{L}^{-1}$ glutamic acid, 50% water filling, 3 h, $300 \text{ }^{\circ}\text{C}$, 0.1 g catalyst).

Conclusion

In summary, direct conversion of primary amines to primary alcohols was achieved using water under hydrothermal conditions, which could further link to the utilization of amino acid for the production of bio-based drugs. While the traditional conversion of amines to alcohols is a multistep process involving several complex catalysts and requiring the presence of oxidants equivalents, a one-pot deamination to alcohols in water by taking advantage of the unique properties of hydrothermal water (HW) is interesting. The reactivity of HW for the deamination of amines is due to its ability to achieve dehydrogenation of amines and alcohols as well as hydrogenation of imines and aldehydes within the same system, and also the ability to achieve deamination through the inductive effect of targeting group. The major drawbacks in this system are the consecutive conversion of product and the high energy barrier to form the targeting product. While the former can be surpassed by optimizing the reaction conditions, the latter may need further investigation in active catalysts. We hope that if optimized for each application, the reaction described herein could find use in the synthesis of primary

alcohols, the preparation of value-added chemicals, and the treatment of waste water containing nitrogen contaminant.

References

- [1] M.A. Ashley, T. Rovis. *J. Am. Chem. Soc.* 142 (2020) 18310-18316.
- [2] P. Ruiz-Castillo, S.L. Buchwald. *Chem. Rev.* 116 (2016) 12564-12649.
- [3] O.I. Afanasyev, E. Kuchuk, D.L. Usanov, D. Chusov. *Chem. Rev.* 119 (2019) 11857-11911.
- [4] P.A. Dub, T. Ikariya. *ACS Catal.* 2 (2012) 1718-1741.
- [5] K. Das, R. Shibuya, Y. Nakahara, N. Germain, T. Ohshima, K. Mashima. *Angew. Chem. Int. Ed.* 51 (2012) 150-154.
- [6] S. Bahn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller. *Chem, Eur. J.* 17 (2011) 4705-4708.
- [7] S.M.A. Rahman, H. Ohno, N. Maezaki, C. Iwata, T. Tanaka. *Org. Lett.* 2 (2000) 2893-2895.
- [8] J.R. Khusnutdinova, Y. Ben-David, D. Milstein. *Angew. Chem. Int. Ed.* 52 (2013) 6269-6272.
- [9] S.M.A. Rahman, H. Ohno, T. Murata, H. Yoshino, N. Satoh, K. Murakami, D. Patra, C. Iwata, N. Maezaki, T. Tanaka. *J. Org. Chem.* 66 (2001) 4831-4840.
- [10] R.J. Baumgarten. *J. Chem. Educ.* 43 (1966) 398.
- [11] T. Cupido, J. Spengler, K. Burger, F. Albericio. *Tetrahedron Lett.* 46 (2005) 6733-6735.
- [12] S. Deechongkit, S.-L. You, J.W. Kelly. *Org. Lett.* 6 (2004) 497-500.
- [13] I. Shin, M.-r. Lee, J. Lee, M. Jung, W. Lee, J. Yoon. *J. Org. Chem.* 65 (2000) 7667-7675.
- [14] X. Wang, Y. Yang, H. Zhong, T. Wang, J. Cheng, F. Jin. *Green Chem.* 23 (2021) 430-439.
- [15] X. Wang, Y. Yang, T. Wang, H. Zhong, J. Cheng, F. Jin. *ACS Sustain. Chem. Eng.* 9 (2021) 1203-1212.
- [16] F. Jin, Y. Gao, Y. Jin, Y. Zhang, J. Cao, Z. Wei, R.L. Smith Jr. *Energy Environ. Sci.* 4 (2011) 881.
- [17] L. Lyu, X. Zeng, J. Yun, F. Wei, F. Jin. *Environ. Sci. Technol.* 48 (2014) 6003-6009.
- [18] R. He, B. Hu, H. Zhong, F. Jin, J. Fan, Y.H. Hu, Z. Jing. *ChemComm* 55 (2019) 1056-1059.
- [19] F. Jin, H. Enomoto. *Energy Environ. Sci.* 4 (2011) 382-397.
- [20] Y. Yang, H. Zhong, R.T. He, X.G. Wang, J. Cheng, G.D. Yao, F.M. Jin. *Green Chem.* 21 (2019) 1247-1252.
- [21] T.M. Lammens, M.C.R. Franssen, E.L. Scott, J.P.M. Sanders. *Biomass Bioenergy* 44 (2012) 168-181.
- [22] L. Claes, R. Mattheessen, I. Rombouts, I. Stassen, T. De Baerdemaeker, D. Depla, J.A. Delcour, B. Lagrain, D.E. De Vos. *ChemSusChem* 8 (2015) 345-52.
- [23] H. Zhong, C. Jiang, X. Zhong, J. Wang, B. Jin, G. Yao, L. Luo, F. Jin. *J. Clean. Prod.* 209 (2019) 1228-1234.
- [24] O.C. Snead, K.M. Gibson. *N. Engl. J. Med.* 352 (2005) 2721-2732.
- [25] H. Zhong, L. Wang, Y. Yang, R. He, Z. Jing, F. Jin. *ACS Appl. Mater. Inter.* 11 (2019) 42149-42155.
- [26] H. Zhong, G. Yao, X. Cui, P. Yan, X. Wang, F. Jin. *Chem. Eng. J.* 357 (2019) 421-427.
- [27] J. Mitra, X.Y. Zhou, T. Rauchfuss. *Green Chem.* 17 (2015) 307-313.
- [28] C. Sarkar, S.C. Shit, D.Q. Dao, J. Lee, N.H. Tran, R. Singuru, K. An, D.N. Nguyen, Q.V. Le, P.N. Amaniampong, A. Drif, F. Jerome, P.T. Huyen, T.T.N. Phan, D.V.N. Vo, N.T. Binh, Q.T. Trinh, M.P. Sherburne, J. Mondal. *Green Chem.* 22 (2020) 2049-2068.