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Continuous Catalytic Hydrogenation of a Key Intermediate of Riluzole Using a Micropacked-bed Reactor

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A continuous selective catalysis of 4-(Trifluoromethoxy)aniline, a key intermediate in the preparation of riluzole, was studied using a micropacked-bed reactor (μPBR) packed with Pt/BAC catalysts. The effects of technological parameters such as solvent types, gas flow rates and liquid flow rates were investigated. It was indicated that the continuous hydrogenation process exhibited higher efficiency, selectivity and safety with less energy consumption compared to the traditional batch reduction process. The newly developed reactor system demonstrated a sustained and stable catalytic performance after 20 h running.

Keywords: Micropacked-bed reactor | Continuous-flow catalytic hydrogenation | Riluzole

Riluzole (2-Amino-6-(trifluoromethoxy)benzothiazole), developed by Sanofi, is a derivative of benzothiazoles, which is the only drug available for the treatment of motor neuron diseases. It is also the first drug approved by the FDA and EMEA for the treatment of amyotrophic lateral sclerosis (ALS).[1,2] At present, the most commonly used process for the preparation of riluzole is shown in Figure 1.[3]

A critical step in the above process is the conversion of substituted nitrobenzene (4-(trifluoromethoxy)nitrobenzene, 4-TFMNB) to corresponding aniline (4-(trifluoromethoxy)-aniline, 4-TFMA) via catalytic hydrogenation. Typically, the nitration product 4-TFMNB obtained in industry inevitably contains a certain number of 2-TFMNB isomers. With the concern of feasibility and safety issues, the nitro compounds are generally separated through distillation after hydrogenation in industry. Because of the presence of isomers in the raw materials, the catalytic hydrogenation could be evaluated by comparing the conversion and selectivity of nitro in the raw materials. In the batch process, the problem focuses on the low selectivity and long reaction time when conducting the hydrogenation reaction. Additionally, long reaction time is unfavored because of the incidence of side effects.

In the past decade, continuous flow chemistry has attracted great interests in the field of catalytic hydrogenation because of its advantages of greenness and safety in process intensification.[4–7] Consequently, a series of new reactors and devices have been developed, such as micropacked-bed reactors (μPBR),[8–11] catalytic static mixers[12–14] and wall-coated microreactors.[15] Compared with traditional batch processes, the μPBR has advantages of excellent gas–liquid–solid mass transfer and heat transfer, so one can accurately control the reaction parameters such as temperature, pressure and gas and liquid flow rates to modulate the conversion rate and selectivity.[16,17] Chen and co-workers improved the selectivity of anilines prepared by

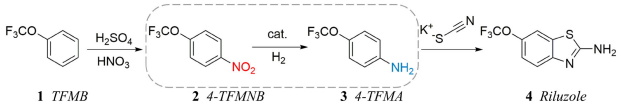

Figure 1. The process for the preparation of riluzole.

nitroarene hydrogenation, and were able to maintain a high reaction activity via a μPBR fitted with a TPP/Raney Ni catalyst.[18] Rahman and co-workers demonstrated that μPBR could be operated under continuous flow conditions for synthesizing aromatic nitrobenzoic acids in water, and 100% selectivity of 4-aminobenzoic acid was achieved at a liquid flow rate of 0.5 mL/min.[19] Uozumi and coworkers reported polystyrene–poly(ethylene glycol) resin bound Pt catalyzed continuous-flow hydrogenation of nitrobenzenes. The flow hydrogenation of nitrobenzenes efficiently proceeded within 31 s to give the corresponding anilines, respectively, in excellent yields with good efficiency and chemoselectivity. Moreover, the long-term continuous-flow hydrogenation of nitrobenzenes was realized, and without significant loss of catalytic activity.[20]

In this study, a continuous flow system of μPBR was developed for fast and efficient selective hydrogenation of 4-TFMNB to prepare 4-TFMA using hydrogen gas as a reductant. The solvents suitable for the reaction were screened, and the effects of gas flow rates, liquid flow rates and their concentrations were investigated. The objective was to establish a trusted method of continuous production of 4-TFMA with high efficiency.

Bead-shaped activated carbon (BAC) is a highly spherical activated carbon made from petroleum pitch. Its excellent adsorption capacity, strength and flowability enables wide-ranging uses, especially in catalyst support.[21,22] In μPBR, BAC would produce a low pressure drop that would make the reactor operation feasible.[22] A commercial BAC produced by Kureha Co., Ltd., was used as the support in this study. The range of BAC diameter was 0.60–0.84 mm (0.70 mm in average). Pt/BAC catalyst was prepared using an impregnation method. The catalysts used for μPBR were firstly characterized. A TEM image of the Pt/BAC catalyst is shown in Figure 2. It was observed that metal particles with relatively uniform particle size evenly dispersed at the surface of Pt/BAC catalyst. From the size distribution of Pt nanoparticles, the average particle size of Pt nanoparticles was determined to be about 5.3 nm. CO chemisorption and N_2 physisorption were conducted to further characterize the catalyst. A summary of detailed physical properties of Pt/BAC catalyst is listed in Table 1.

The μPBR (H-Flow-S05) equipment was provided by Oushisheng (Beijing) Technology Co., Ltd, and a schematic

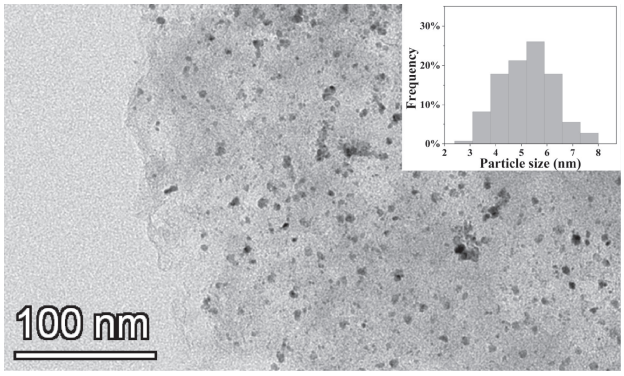

Figure 2. TEM image of the Pt/BAC sample.

Table 1. Physical property of Pt/BAC catalyst.

Property	Value	Units	Technique
Surface area	1233	$m^2 \cdot g^{-1}$	BET
Pore volume	0.41	$mL \cdot g^{-1}$	BJH model
Pore diameter	3.6	nm	BJH model
Pt loading	0.50	wt %	ICP-OES
Pt nanoparticle diameter	5.30	nm	TEM
Pt surface area	2.0	$m^2 \cdot g^{-1}$	CO Chemisorption

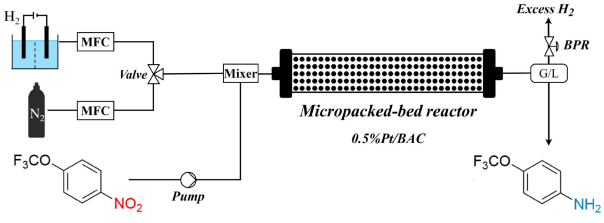

Figure 3. Schematic overview of the continuous flow system for hydrogenation. MFC, mass flow controller; BPR, back-pressure regulator; G/L, gas-liquid separator.

overview of the continuous flow system is shown in Figure 3. The μPBR was comprised of two sections: a stainless steel pipe and the catalyst. Stainless steel tubes were inert to solvent and catalyst components. In addition, they can work well over a wide range of temperature and pressure. Pictures and detailed parameters of the μPBR are provided in Figure S2, Table S2 and Table S3.

Solvents have great influence on the hydrogenation, which would affect the solubility of hydrogen and interactions between the reactant and catalyst.[23] Effect of some common organic solvents on the conversion and selectivity obtained from GC analysis is listed in Table 2. The concentration of substrate was specified at 0.118 M, and the substrate can dissolve completely in all of the tested solvents. Under the same experimental conditions, the substrate was residual while the solvents were ethanol and tetrahydrofuran. Except for the above two solvents, the conversion of substrate in the other three solvents were >99.9%. Considering the selectivity and environmental protection, methanol was selected as the solvent, which was consistent with the industrial production.

The gas-liquid flow rate has a profound importance as it may affect the flow regime and the mixing efficiency in the

Table 2. Influence of solvent for the hydrogenation using micropacked-bed reactor.

Entry	Solvent	Conv. [%]	Selec. [%]	TOF $[mol \cdot g^{-1} \cdot h^{-1}]$	STY $[g \cdot L^{-1} \cdot h^{-1}]$
1	Methanol	>99.9	98.2	0.751	296
2	Ethanol	98.9	90.2	0.744	269
3	Ethyl acetate	>99.9	97.4	0.751	293
4	Tetrahydrofuran	98.8	89.9	0.743	261
5	Toluene	>99.9	96.1	0.751	289

Experiment conditions: Concentration = 0.118 M; Reaction temperature = 60 °C; Reaction pressure = 2 MPa; V_G = 60 sccm; V_L = 1.0 mL/min; Reactor volume = 6.6 mL; V_L is the liquid flow rate; V_G is the hydrogen flow rate. Conv. is conversion, $Conversion = \frac{C_0 - C_a}{C_0}$, C_0 is the original concentration of 4-TFMNB and 2-TFMNB in the reactant, Ca is the concentration of 4-TFMNB and 2-TFMNB in the product. Selec. is selectivity, $Selectivity = \frac{A_{4-TFMA} + A_{2-TFMA}}{A_i}$, $A_{4\text{-TFMA}}$ and $A_{2\text{-TFMA}}$ are the peak area of 4-TFMA and 2-TFMA in GC, A_i is the total peak area of all products in GC. flow $rate_{Subs}$ $(mol\,h^{-1}) = (V_L/1000) \times$ Concentration $\times$ 60 $min\,h^{-1}$; flow $rate_{Prod}$ $(mol\,h^{-1})$ = flow $rate_{Subs} \times$ (Conversion/100 $\times$ Selectivity/100); TOF $(mol_{prod}\,g_{pt}^{-1}\,h^{-1})$ = flow $rate_{Subs} \times$ (Conversion/100)/m_{Pt}; STY $(g\,L^{-1}\,h^{-1})$ = flow $rate_{Prod} \times$ MW_{Prod}/reactor volume.

Table 3. Influence of gas-liquid flow rate for the hydrogenation using micropacked-bed reactor

Entry	V_G [sccm]	V_L [mL/min]	t [min]	Conv. [%]	Selec. [%]	TOF $[mol \cdot g^{-1} \cdot h^{-1}]$	STY $[g \cdot L^{-1} \cdot h^{-1}]$
1	20	1	4.98	>99.9	98.0	0.751	295
2	20	1.5	3.97	>99.9	97.8	1.127	442
3	20	2	3.40	99.6	95.5	1.498	574
4	20	2.5	3.22	99.3	94.2	1.867	705
5	40	1	4.81	>99.9	98.0	0.751	295
6	40	1.5	3.55	>99.9	97.8	1.127	442
7	40	2	3.22	>99.9	96.8	1.502	583
8	40	2.5	2.84	>99.9	95.6	1.878	720
9	60	1	4.63	>99.9	98.2	0.751	296
10	60	1.5	3.41	>99.9	98.0	1.127	443
11	60	2	3.05	>99.9	97.3	1.502	586
12	60	2.5	2.63	>99.9	96.7	1.878	729

Experiment conditions: Reaction temperature = 60 °C; Reaction pressure = 2 MPa; Concentration = 0.118 M; Solvent is methanol; t is residence time.

system.[8] A major objective of the research was to identify the gas-liquid flow rate. Therefore, experiments were carried out under different gas flow rates and liquid flow rates. As can be seen from Table 3, when hydrogen flow rate was 20 sccm, >99.9 conversion of substrate and high selectivity of product can be obtained at relatively lower liquid flow rates. The hydrogen flow rate was increased subsequently, and >99.9% conversions was obtained at all of the tested liquid flow rates. To explain the phenomenon, a test on residence time distribution (RTD) experiment was conducted. The mean residence time in the

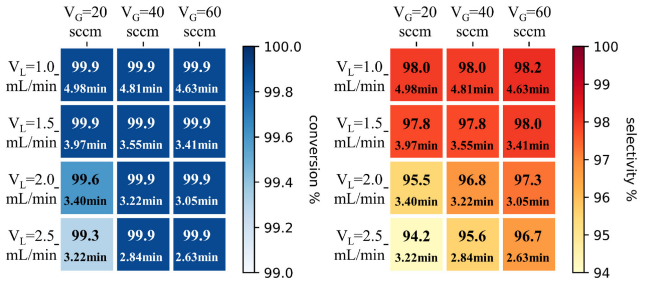

Figure 4. Effect of gas-liquid flow rate and mean residence times.

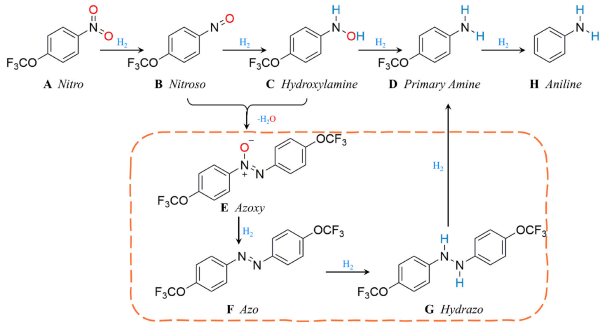

Figure 5. Mechanism of catalytic 4-(trifluoromethoxy)nitrobenzene reduction.

active catalyst bed of the μPBR was then determined. The results on mean residence time are shown in Table 3 and Figure 4. Detailed experimental methods and further explanations are provided in the Support Information. It was demonstrated that both liquid flow rate and gas flow rate had a certain degree of effect on the residence time, and liquid flow rate was considered as the dominant factor. Under the condition of constant gas flow rate, the increase of liquid flow rate led to a decrease in residence time and relative inadequate hydrogen gas resulting in the incompleteness of reaction. With constant liquid flow rate, selectivity increased with the increase of gas flow rate, which might due to the addition of hydrogen despite the decrease in the residence time of gas flow rate. At the same ratio of gas to liquid rate, selectivity decreased with the increase of liquid flow rate, which was due to the decrease in the residence time.

The types and chemical structures of intermediates in the product were identified by GC-MS. The GC-MS spectra are provided in the Support Information. Azoxy and azo compounds were clearly identified in the GC-MS spectra, but no significant nitroso or hydroxylamine compounds were observed. It was indicated that the intermediates of this reaction were mainly azoxy and azo compounds. In addition, a small amount of aniline was observed. A mechanism of the reaction is proposed in Figure 5. Starting from the aromatic nitro compound, reduction reactions were required to get the corresponding aniline, which could be achieved via two routes: the direct route or the condensation route.[8,19,24] In the direct route, two steps of sequential fast hydrogenations of the nitro compounds to the nitroso and hydroxylamine compounds would occur before undergoing the slow eventual reduction to the primary amine. In the condensation route, nitroso and hydroxylamine could be condensed into an azoxy compound which can be deoxygenated

Table 4. Influence of solvent and concentration for the hydrogenation using micropacked-bed reactor

Entry	Concentration [M]	Con. [%]	Selec. [%]	TOF [mol·g^{-1}·h^{-1}]	STY [g·L^{-1}·h^{-1}]
1	0.118	>99.9	98.2	0.751	296
2	0.375	98.9	97.8	1.499	588
3	1.13	81.4	74.7	3.679	1103
4	1.5	29.1	47.5	1.740	331

Experiment conditions: Reaction temperature = 60 °C; Reaction pressure = 2 MPa; VG = 60 sccm; VL = 1.0 mL/min; Solvent is methanol.

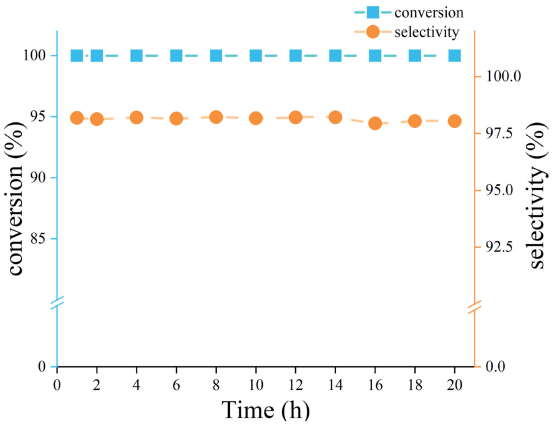

Figure 6. Stability study of μPBR.

and reduced under the action of hydrogen before undergoing a final split to form two monomeric primary amines. Therefore, it was considered that the condensation route was the main route of the reaction, in which azoxy hydrogenation was the rate-controlling step. Furthermore, the primary amine may continue to convert to aniline by overreaction.

To investigate the feasibility of industrial applications, the condition of substrate concentration was further studied. When the concentration was 0.375 M (Table 4, Entry 2), the conversion can reach >99.9% with the space time yield (STY) of 588 g·L^{-1}·h^{-1}, but the selectivity slightly declined. When the concentration increased (Table 4, Entries 3–4), the substrate presented in the GC spectra of the product, and the conversion and selectivity decreased significantly. STY was proportional to the concentration, so the STY value was able to be maintained at a higher value at 1.13 M than that at 0.375 M in spite of the fact that the conversion became lower.

In the above experiments, high catalytic activity and conversion were obtained in most cases. To further investigate the stability of the catalyst and the continuous flow system for long-time operation, continuous operation was performed under the conditions of 1 mL/min flow rate, 0.375 M 4-TFMNB, 60 sccm hydrogen flow rate, hydrogen pressure of 2 MPa and reaction temperature of 60 °C. From Figure 6, the catalysts exhibited high and stable catalytic activity with no substrate identified in product solution under a 20-h continuous operation. The flow hydrogenation conducted for 20 h provided 1200 mL of the solution of product (0.375 M, 77.6 g).

Table 5. Comparison of performance of conventional batch and continuous flow[a]

	Batch	μPBR
Reaction time	200 min	4.6 min
Reaction volume	100 mL	6.6 mL
Selectivity	96.9%	98.2%
STY [$g \cdot L^{-1} \cdot h^{-1}$]	9.6	296

[a]Experimental conditions: concentration of TFMNB in methanol: 0.375 M; Reaction temperature = 60 °C; Reaction pressure = 2 MPa; Batch: the amount of the Pt/BAC catalyst (0.5 wt %): 1.0 g; raw material volume was 50 mL; stirring speed was 700 rpm/min; μPBR: VG = 60 sccm; VL = 1.0 mL/min.

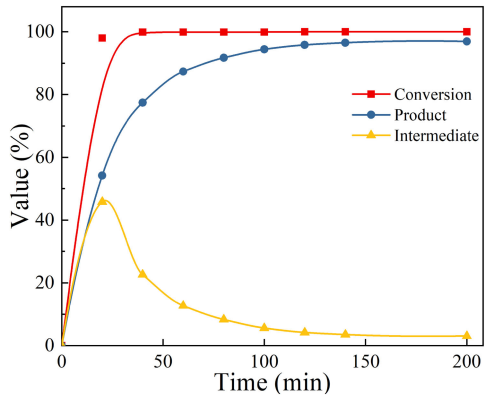

Figure 7. Conversion and selectivity of different reaction times under batch conditions.

The performance of a traditional batch reactor was subsequently compared with the micropacked-bed reactor (Table 5). The conversion and selectivity for different reaction time under batch conditions were investigated, and the results were shown in Figure 7. Experimental devices and details are provided in the Supporting Information. From Figure 7, it was observed that the conversion was higher than 90% at 20 min, but azoxy and azo intermediate content was also high at this time point. It was further proved that the condensation route was the main route of the reaction, which matches our previous conjecture. With the increase of reaction time, the intermediate gradually transformed, and the content of intermediate remained constant after 120 minutes. The advantages of μPBR over the traditional batch process were apparently demonstrated in Table 5.

In this study, a micropacked-bed reactor (μPBR) filled with Pt/BAC catalyst was successfully applied for an efficient approach of continuous flow hydrogenation of 4-TFMNB for the preparation of the key intermediate 4-TFMA of riluzole. Under the optimized operational conditions, the use of micropacked beds provided excellent reactivity and selectivity without post-processing steps of catalyst removal or recovery. It was also proposed that the capital chemistry progress remained at the production of primary amine through the formation of azoxy compound and a series of subsequent reduction steps. Additionally, no inactivation was observed after 20 h running of continuous flow.

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Supporting Information is available on https://doi.org/10.1246/cl.210716.

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