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Synthesis of (±)-Pregabalin by Utilizing a Three-step Sequential-Flow System with Heterogeneous Catalysts

Haruro Ishitani,[b] Kan Kanai,[a] Yuki Saito,[a] Tetsu Tsubogo,[b] and Shū Kobayashi*[a,b]

Abstract: (±)-Pregabalin has been synthesized by utilizing flow methods. Three-step sequential-flow reactions starting from commercial isovaleraldehyde and methyl malonate proceeded smoothly with heterogeneous catalysts to afford the desired compound. The total yield was 75%–quant, and a space-time yield (STY) of 52.2 g/L·d was reached. In addition, a heterogeneous catalyst for the Knoevenagel reaction of aldehydes with malonates, which is the first step of the synthesis, has been developed.

Introduction

Flow synthesis of fine chemicals is superior to batch synthesis in terms of environmental compatibility, efficiency, and safety. In addition, it has the advantage of on-demand manufacturing of required amounts of products.[1] Toward a sustainable society, flow synthesis is attracting much attention as a new method of synthesis to replace batch synthesis, which is currently a mainstream process.[2] Generally, in the manufacturing process of fine chemicals, multistep chemical conversion is necessary; however, a large amount of waste is generated in the work-up of a reaction at each stage. However, in flow synthesis, it is possible to exclude the work-up process by connecting multiple flow reactions (sequential flow method). In particular, when flow reactions with heterogeneous catalysts are used, separation of products from catalysts can be easily carried out in addition to achieving increased efficiency of the catalytic reactions, and it is expected that more efficient production can be realized.[3]

Pregabalin (**1**, trade name: Lyrica) is a γ-amino acid derivative that is widely used as a therapeutic agent for nervous system disorders such as epilepsy, anxiety disorder, and neuropathic pain. In a reported production process,[4] routes are known in which the basic skeleton is synthesized by Knoevenagel condensation, 1,4-addition reaction of cyanide, hydrolysis, decarboxylation, reduction of the CN group, and finally optical resolution.[4c] Here toxic CN sources and a large amount of Raney nickel in the reduction step are required. As another method, asymmetric synthesis utilizing enzymes and organic bases, synthesis using D-mannitol as a starting material,[4b] and, more recently, synthesis utilizing a flow reaction[4f] have also been reported. In this paper, we report pregabalin synthesis by using a sequential-flow method utilizing heterogeneous catalysts as a next generation synthetic method.

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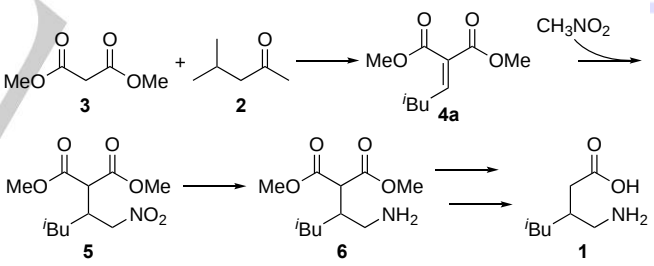
Results and Discussion

Scheme 1 shows a synthetic route to pregabalin by using a sequential-flow method employing heterogeneous catalysts. Alkylidene malonate **4a** could be obtained by Knoevenagel condensation of commercially available isovaleric aldehyde (**2**) and malonic acid ester **3**. Subsequently, nitromethane could add to **4a** through 1,4-addtion, then the nitro group could be reduced to an amino group. Finally, ester hydrolysis and decarboxylation could be carried out to obtain pregabalin **1**. Effective heterogeneous catalysts could be used at each stage. According to this synthetic route, the by-products are only H_2O, produced by Knoevenagel condensation and the reduction, MeOH, by hydrolysis of the ester, and CO_2, by decarboxylation of the carboxylic acid, which could be easily removed or added to subsequent flow reactions. The scheme is expected to be a synthetic route that is suitable for sequential-flow synthesis.

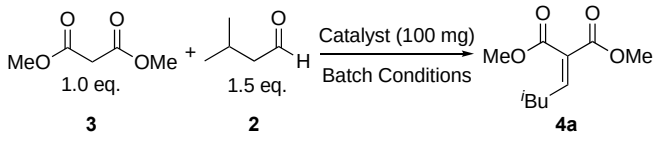


Scheme 1. Synthetic route to Pregabalin under sequential-flow conditions.

First, the Knoevenagel reaction, which is the first step of this synthesis, was examined. The Knoevenagel reaction is a carbon–carbon bond-formation reaction that is catalyzed by bases, and amines such as piperidine have been used as homogeneous catalysts. Although it has been reported that some heterogeneous base catalysts are effective,[5, 6] only one example of a combination of an aliphatic aldehyde and a malonic acid ester,[5p] such as required here, is known. Moreover, the heterogeneous base catalyst used therein does not necessarily have sufficient activity. Therefore, we first studied heterogeneous base catalysts for the Knoevenagel reaction using an aliphatic aldehyde and a malonic acid ester. The results of screening a range of solid base catalysts using batch reactions are shown in Table 1. Although good results were not obtained when general solid strong bases such as CaO and

KF/alumina, and Amberlite IRA 900, which is a strong basic resin, were used, the desired adduct **4a** was obtained in 81% yield when primary amine-modified silica (Chromatorex NH) was used. On the other hand, when amino group-modified silica containing both primary and secondary amines (Chromatorex DNH) was used, the yield was only 57%.

Table 1. Heterogeneous base catalyst screening for the Knoevenagel condensation.

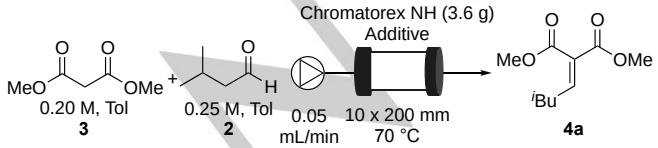


Entry	Catalyst	Conditions	Yield [%] [a]
1	CaO	Tol, 70 °C, 14 h	36
2	KF/alumina	Tol, RT, 14 h	Trace
3	Amberlite IRA900	Tol, RT, 14 h	Trace
4	Chromatorex NH	Tol, 70 °C, 14 h	81
5	Chromatorex DNH	Tol, 70 °C, 14 h	57

[a] Determined by GC analysis.

Based on the above results, flow reactions were performed using Chromatorex NH (Table 2). First, a column with an inner diameter of 10 mm and a length of 100 mm was packed with catalyst, and a 0.2 M toluene solution of malonate and a 0.25 M toluene solution of isovaleraldehyde (**2**) were fed at 70 °C at a flow rate of 0.05 mL/min. As a result, the yield after 24 h from the start of the solution feeding was 52% (entry 1). To improve the yield, the reaction was carried out by diluting the catalyst with various additives. When the catalyst was diluted with silica gel or Celite, the yield was not improved; however, it was found that molecular sieves were effective. In particular, when MS 4A was used, the yield after 24 h was 92%, and a yield of >95% could be maintained for >50 h. It was found that high yields could be maintained for >100 h (90–100%, 110 h), when a column reactor having an inner diameter of 10 mm and a length of 300 mm was used.

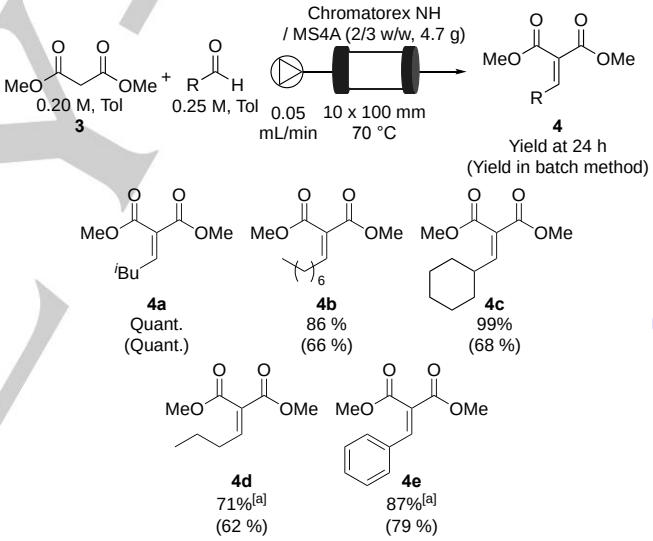
Table 2. Effect of additives on the flow system with a column packed with amino-silica catalyst.



Entry	Additive	Yield at 24 h [%] [a]
1	None (100 mm column)	52
2	MS 4A	92
3	MS 3A	81
4	Silica gel [b]	43
5	Celite	44

[a] Determined by GC analysis. [b] CARiACT Q-10 was used.

The present catalyst was applicable to the Knoevenagel reaction of a malonate with various aldehydes (Scheme 2). In the flow reactions, the desired adducts **4** were obtained from various aliphatic aldehydes in high yields by using a column reactor with an inner diameter of 10 mm and a length of 100 mm When an aromatic aldehyde was used, the reactivity was somewhat decreased; however, **4e** was obtained in 87% yield by increasing the size of the column reactor. It is interesting that equal or higher yields were obtained for all substrates under flow conditions compared with those under batch conditions. [7]

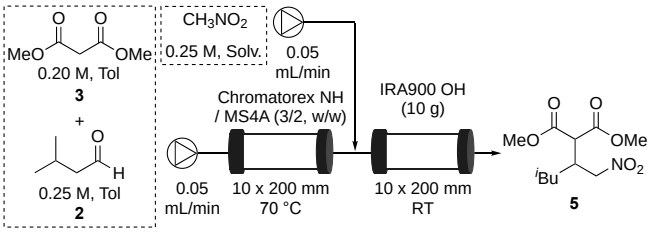


Scheme 2. Substrate scope of the reaction with respect to aldehyde. [a] 10 x 200 mm column reactor was used.

Next, the Michael addition reaction of nitromethane, as the second stage of pregabalin synthesis, was investigated. As a catalyst for the 1,4-addition reaction of nitromethane to *alkylidenemalonate*, organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,1,3,3-tetramethylguanidine (TMG) have been reported, and in many cases, an excess of nitromethane is used.[8] To our knowledge, no examples using a heterogeneous catalyst have been reported to date. Therefore, we searched for solid, strong bases that were suitable for a flow reaction, and it was found that Amberlite IRA 900 OH, which is a strong basic resin, was effective. The resin was packed in a column reactor and a two-step sequential-flow reaction was conducted (Table 3). When a toluene solution of nitromethane was mixed with a stream from

the first flow (Knoevenagel reaction), the desired adduct (**5**) was obtained in good yield after 22 h, but a problem of persistence was found (entry 1). We revealed that alcohols were effective keeping high yields for a longer time. When methanol was mixed with the solvent system of nitromethane, the yield after 52 h was improved (entry 2), and further improvement in yield was observed when 1-propanol was used (entry 3). By using this as the optimum condition, we moved to the third stage of the flow reaction.

Table 3. Two-step flow synthesis of **5**.

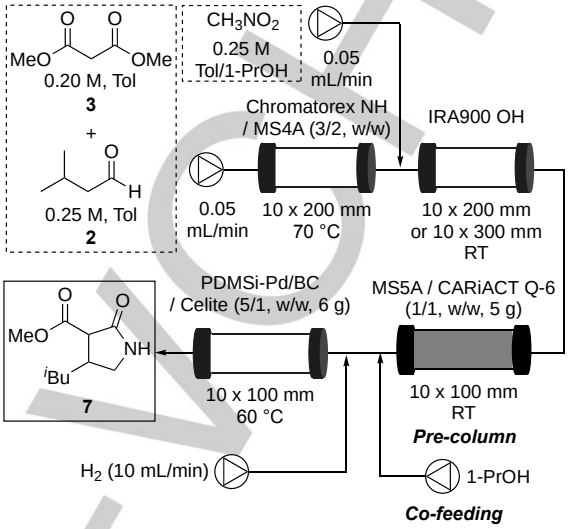


Entry	Solv. of Nitromethane	Yield at 22 h [%] [a]	Yield at 52 h [%] [a]
1	Toluene	98	45
2	Toluene/MeOH = 1/1	95	81
3	Toluene/1-PrOH = 1/1	Quant.	91

[a] Determined by GC analysis.

For the reduction of the nitro group at the third step, polysilane-supported bone charcoal palladium catalyst, which was developed in our laboratory, was used.[9] In this step, intramolecular cyclization would be expected to proceed smoothly after reduction of the nitro group to afford γ-lactam **7**. First, a column reactor packed with a Pd catalyst and Celite, connected to a two-step flow, and a three-step sequential-flow system consisting of three column reactors was assembled and reacted (Table 4, entry 1). The reaction proceeded smoothly, and the desired compound **7** was obtained in 59–78% yield (34 h). However, compared with the yield of intermediate **5**, the yield of **7** had scope for improvement, and further investigations were conducted. It was already known from studies on the batch reaction that this reduction gave good results when a polar solvent was used. Therefore, 1-propanol was used as a co-solvent before the third step, and, at the same time, a pre-column filled with MS 5A and silica gel was connected (entry 2). In this case, the reaction proceeded quantitatively from 20 to 40 h from the start of the third step. On the other hand, when the flow rate of the co-solvent was increased, the yield remained around 80% (entry 3). Given that the lifetime of the entire flow system depended on the catalyst lifetime of the ion exchange resin used in the second step reaction, investigations were continued using a 30 cm column reactor at the second step (entry 4). As expected, improvement was observed in the lifetime, and 75–100% yields of the desired compound **7** could be maintained for about 45 h. The space-time yield (STY) was reached to 52.2 g/L·d. On the other hand, when the precolumn was omitted, the yield remained about 75% (entry 5).

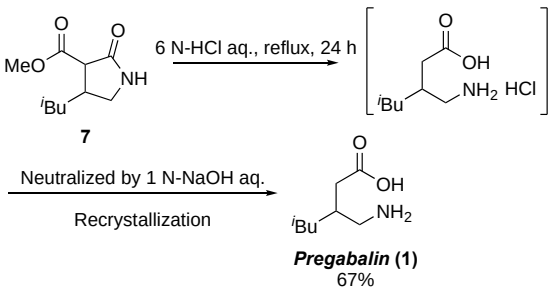
Table 4. Three-step sequential-flow synthesis of **7**.



Entry	Pre-column, Co-feeding [mL/min]	Yield [%] [b] ~12 h	~24 h	~36 h	~ 48 h
1	w/o, w/o	78 (9 h)	75 (24 h)	59 (34 h)	ND (48 h)
2	w/, 0.05	79 (12 h)	96 (23 h)	96 (32 h)	63 (47 h)
3	w/, 0.10	71 (12 h)	83 (24 h)	65 (32 h)	No Anal.
4[a]	w/, 0.05	76 (8 h)	>99 (21 h)	88 (34 h)	>99 (45 h)
5[a]	w/o, 0.05	70 (8 h)	72 (23 h)	58 (31 h)	63 (43 h)

[a] In the second step, 10 x 300 mm column reactor was employed. [b] Determined by GC analysis.

After the solvents of the reaction solution obtained by the three-step sequential-flow reaction were distilled off, **7** was obtained as a white solid by recrystallization. Compound **7** was converted into pregabalin (**1**) by heating in hydrochloric acid and then neutralization. [10] The desired compound was obtained in 67% yield based on methyl malonate (**3**) (Scheme 2).



Scheme 3. Conversion of **7** into Pregabalin (**1**)

Conclusions

In summary, we have completed the synthesis of (±)-Pregabalin by using a three-step sequential-flow system with heterogeneous catalysts. Knoevenagel reaction of commercial isovaleraldehyde with methyl malonate, 1,4-addition of nitromethane, and reduction of a nitro group proceeded smoothly under the sequential-flow conditions. Heterogeneous catalysts worked well in each step. We are currently investigating an asymmetric synthesis of (*S*)-Pregabalin.

Experimental Section

Experimental procedure of 3-step flow reaction for the synthesis of γ-lactam (7): For the Knoevenagel reaction, Chromatorex NH and MS4A (2/3, w/w, 14 g) were mixed and packed in a SUS column (10 x 300 mm) with column ends equipped with a filter. Toluene was flowed into the column by a plunger pump (for HPLC, 0.50 mL/min) to prepare the catalyst slurry. The solution of dimethyl malonate (**3**, 80 mmol), isovaleraldehyde (**a**, 100 mmol), 1,3,5-trimethylbenzene (40 mmol, internal standard) and toluene (400 mL) was mixed in a volumetric flask and then flowed into the column which was heated at 70 °C. For the 1.4-addition reaction, an anion exchanged resin catalyst (IRA900 OH) was washed with a 1M NaOH aqueous solution and then methanol. After that, by using methanol, an anion exchanged resin catalyst (10 g, MeOH wet.) was packed in a glass column (10 x 200 mm) with column ends equipped with a filter. Toluene and *n*-propanol (1/1, v/v) were flowed into the column by a plunger pump (for HPLC, 0.50 mL/min) to prepare the catalyst slurry. After stabilization of the Knoevenagel flow, the solution of nitromethane (75 mmol) in toluene and *n*-propanol (1/1, v/v, 300 mL) was mixed with the Knoevenagel product solution via a connector. The mixture was then flowed into the 1,4-addition column. For the reduction, PDMSi-Pd/BC (Pd: 0.30 mmol/g (dry)) and Celite (5/1, w/w, 6 g) were mixed and packed in a SUS column (10 x 100 mm), and MS 5A and silica gel (CARiACT Q-6) (1/1, w/w, 5 g) were mixed and packed in a glass column (10 x 100 mm) as the pre-column. *n*-Propnaol was flowed into the column by a intelligent pump (0.50 mL/min) to prepare the catalyst slurry. After stabilization of the 2-step flow, the stream was flowed into the pre-column. The stream after the pre-column was mixed with *n*-propanol (flow rate: 0.05 mL/min), and the resulting diluted solution was flowed into the reduction column reactor with hydrogen gas generated from water using a hydrogen generator (RHG-200, Round science) at 10 mL/min of flow rate. A reduction column oven was set at 60 °C. At the end of the stream, a reaction solution was collected and directly analyzed by GC in appropriate time.

Acknowledgements

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Keywords: Continuous-flow reaction • Heterogeneous catalysis • Pregabalin • Knoevenagel • 1,4-Addition • Hydrogenation

[1] Selected reviews of continuous-flow synthesis: a) J. C. Pastre, D. L. Browne, S. V. Ley, *Chem. Soc. Rev.* **2013**, *42*, 8849−8869; b) R. Porta, M. Benaglia, A. Puglisi, *Org. Process Res.Dev.* **2016**, *20*, 2−25; c) S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425−436; d) J. Britton, C. L. Raston, *Chem. Soc. Rev.* **2017**, *46*, 1250−1271.

[2] a) J. Woodcock, the 25th annual AAPS meeting, October 2011 (http://www.fiercepharma.com/story/fdas-woodcock-what-expect-next-25-years-medicine/2011-10-23; b) S. Chatterjee, FDA Perspective on Continuous Manufacturing, IFPAC Annual Meeting, January 2012 (http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM341197.pdf).

[3] T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329-332

[4] Pregabalin synthesis: a) M. S. Hoekstra, D. M. Sobieray, M. A. Schwindt, T. A. Mulhern, T. M. Grote, B. K. Huckabee, V. S. Hendrickson, L. C. Franklin, E. J. Granger, G. L. Karrick, *Org. Process Res. Dev.* **1997**, *1*, 26−38; b) S. Izquierdo, J. Aguilera, H. H. Buschmann, M. García, A. Torrens, R. M. Ortuño, *Tetrahedron: Asymmetry* **2008**, *19*, 651−653; c) C. A. Martinez, S. Hu, Y. Dumond, J. Tao, P. Kelleher, L. Tully, *Org. Process Res. Dev.* **2008**, *12*, 392−398; d) O. Bassas, J. Huuskonen, K. Rissanen, A. M. P. Koskinen, *Eur. J. Org. Chem.* **2009**, 1340−1351; e) L. Chu, C. Ohta, Z. Zuo, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 10886−10889; f) D. Ghislieri, D. K. Gilmore, P. H. Seeberger, *Angew. Chem. Int. Ed.*, **2015**, *54*, 678−682; g) M. Moccia, M. Cortigiani, C. Monasterolo, F. Torri, C. D. Fiandra, G. Fuller, B. Kelly, M. F. A. Adamo, *Org. Process Res. Dev.* **2015**, *19*, 1274−1281.

[5] Recent reports using heterogeneous catalyst: a) S. M. Ribeiro, A. C. Serra, A. M. d'A. R. Gonsalves, *Appl. Catal. A: Gen.* **2011**, *399*, 126−133; b) Mst. N. Parvin, H. Jin M. B. Ansari,S.-M. Oh, S.-E. Park, *Appl. Catal. A: Gen.* **2012**, *413−414*, 205−212; c) H. Mahmoudi, R. Malakooti, *Reac. Kinet. Mech. Cat.* **2014**, *113*, 241−255; d) Y.-L. Zhang S. Liu, S. Liu, F. Liu, H. Zhang, Y. He, F.-S Xiao, *Catal. Commun.* **2011**, *12*, 1212−1217; e) Y. Wang, L. Wang, C. Liu, R. Wang, *ChemCatChem* **2015**, *7*, 1559−1565; f) K. Mangala, K. SreeKumar, *J. Appl. Polym. Sci.* **2015**, 41593−41599; g) R. Jin, Z. Bian, J. Li, M. Ding, L. Gao, *J. Chem. Soc., Dalton Trans*. **2013**, *42*, 3936−3940; h) Y. Yang, H.-F. Yao, F.-G Xi, E.-Q. Gao, *J. Mol. Catal. A: Chem.* **2014**, *390*, 198−205; i) Y. Luan, Y. Qi, H. Gao, R. S. Andriamitantsoa, N. Zheng, G. Wang, *J. Mater. Chem. A.* **2015**, *3*, 17320−17331; j) A. Taher, D.-J Lee, B.-K. Lee, I.-M. Lee, *Synlett* **2016**, *27*, 1433−1437; k) G. B. B. Varadwaj, S. Rana, K. M. Parida, *J. Chem. Soc., Dalton Trans.* **2013**, *42*, 5122−5129; l) Y. Sun, C Cao, P. Huang, S. Yang, W. Song, *RSC Adv.* **2015**, *5*, 86082−86087; m) S. M. Islam, A. S. Roy, R. C. Dey, S. Paul, *J. Mol. Catal. A: Chem.* **2014**, *394*, 66−73; n) J. Xu, K. Shen, B. Xue, Y.-X. Li, *J. Mol. Catal. A: Chem.* **2013**, *372*, 105−113; o) M. Zhang, P. Zhao, Y. Leng, G. Chen, J. Wang, J. Huang, *Chem. Eur. J.* **2012**, *18*, 12773−12782; p) M. Bouhrara, C. Ranga, A. Fihri, R. R. Shaikh, P. Sarawade, A.-H. Emwas, M. N. Hedhili, V. Polshettiwar, *ACS Sus. Chem. Eng*. **2013**, *1*, 1192−1199.

[6] Knoevenagel reaction under flow conditions: a) D. Xu, S. Shi, Y. Wang, *RSC Adv.* **2013**, *3*, 23075−23079; b) E. Angeletti, C. Canepa, G. Martinetti, P. Venturello, *J. Chem. Soc., Perkin. Trans. 1* **1989**, 105−107: c) A. R. Bogdan, B. P. Mason, K. T. Sylvester, D. T. McQuade, *Angew. Chem. Int. Ed.* **2007**, *46*, 1698−1701. d) P. Watts, C. Wiles, *Chem. Eng. Technol.*, **2007** *30*, 329−333. e) V. Pandarus, G. Gingras, F. Beland, R. Ciriminna, M. Pagliaro, *Catal. Sci. Technol.* **2011** *1*, 1600−1604.

[7] The reaction under batch conditions was conducted at 70 °C for 14 h using dimethyl malonate (1.0 mmol), aldehyde (1.25 mmol), catalyst (100 mg) and MS 4A (150 mg).

[8] 1,4-Addition of nitromethane: a) T. Lambertus, PCT Int. Appl. WO 2009149928(A1), 2009; b) J. Shi, A. Taveras, R. Van De Water, R. Lamer, K. Hong, M. Biamonte, J. Chao, PCT Int. Appl. WO 2010117425(A1), 2010; c) M. Albelt, F. Zepeck, A. Berger, W. Riethorst, H. Schwab, D. Luschnig, P. Remler, J. Salchenegger, D. Osl, D. A. De Souza, PCT Int. Appl. WO 2009141362(A2), 2009.

[9] Y. Saito, H. Ishitani, S. Kobayashi, *Asian J. Org. Chem*. **2016**, *5*, 1124−1127.

[10] H. Y. Bae, C. E. Song, *ACS Catal*. **2015**, *5*, 3613−3619.

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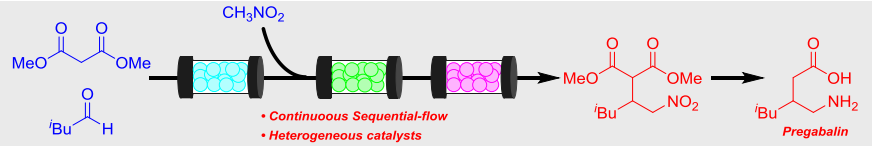

Pregabalin can be synthesized by utilizing flow methods. In this synthesis, there-step sequential-flow reaction with heterogeneous catalysts was employed to give the precursor of pregabalin in 75%–quant. yield, and a space-time yield (STY) of 52.2 g/L·d was reached.

Continuous-flow synthesis

*Haruro Ishitani, Kan Kanai, Yuki Saito, Tetsu Tsubogo, and Shū Kobayashi**

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