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Efficient and Practical Deacylation Reaction System in a Continuous Packed-Bed Reactor

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Supporting Information

ABSTRACT: The ester deacylation reaction is widely applied in organic synthesis for preparing desired hydroxy compounds, as the acyl group is often used for protecting the hydroxyl group. This reaction is usually performed by acid, base, or enzyme catalysts, which have to be removed by complicated workups such as extraction or filtration in batch mode. Therefore, a simple deacylation process is desirable to improve productivity, especially at the industrial scale. In this work, we established an efficient and practical packed-bed reactor system for undertaking the deacylation reaction using an anion-exchange resin that provides a simple process compared with batch processing. We also demonstrated that this technique is applicable to the preparation of a wide variety of desired pharmaceutical intermediates containing hydroxy groups in good to excellent yields.

KEYWORDS: *packed-bed reactor, deacylation, anion-exchange resin, pharmaceutical intermediate, hydroxy compounds*

INTRODUCTION

Hydroxy compounds are found in many chemical products, such as pharmaceuticals, agrochemicals, and other fine chemicals. In general, the hydroxyl group, which has high reactivity, is protected to avoid undesired reactions during multistep synthesis. Since acyl groups are often utilized as the protecting group for hydroxyl groups,[1−3] the development of a deacylation process that enables a simple reaction and workup is highly desirable. It has been reported that deacylation reactions of esters can be achieved by hydrolysis or alcoholysis with acid, base, or enzyme catalysts in liquid−liquid and liquid−solid systems.[4−9] However, deacylation in batch mode requires complicated processes including extraction and filtration to remove the catalyst prior to the next step.[4−9] Furthermore, it is predicted that product loss might be observed at the liquid−liquid separation step in the case of highly water-soluble hydroxy compounds.[10] Process improvement and development of the deacylation reaction in batch mode, especially large-scale production, is desirable in terms of productivity.

We realized a simple system for the deacylation process by using a continuous packed-bed flow reactor. Desired hydroxy compounds can be readily obtained by feeding acyl compounds into a column loaded with the catalyst, thus avoiding the need for extraction and filtration. Furthermore, this system enables acceleration of the reaction because of higher exposure of the catalyst while achieving excellent heat and mass transfer. This provides easy scale-up compared with a conventional batch system. Several research groups that have harnessed packed-bed flow reactor systems have reported their studies and outlined the many advantages stemming from the use of these systems.[11−18] For example, Sibasaki-Kitagawa and co-workers[19−21] and Hirano and co-workers[22] successfully performed transesterification using packed-bed and fixed-bed reactor systems with ion-exchange resins for the production of biodiesel whose composition included a desired fatty acid ester. In these cases, hydroxy compounds were absorbed on the ion-exchange resin, and solvent flushing was required after the main reaction to obtain them with high purity. We believe that packed-bed flow reactor systems employing an ion-exchange resin as a catalyst will provide an efficient and practical deacylation process.

In this study, we established a continuous flow system for the deacylation reaction using an inexpensive and commercially available anion-exchange resin, as depicted in Figure 1. The anion-exchange resin in the column is activated by the displacement of chloride into methoxide form prior to the main reaction. The substrate **1** in methanol is pumped into the column at a controlled reaction temperature, producing a continuous stream of the desired alcohol **2** without the necessity for extraction and catalyst filtration. Additionally, when the methyl ester byproduct **3** has a low boiling point (i.e., R^2 = Me, ^{t}Bu), both **3** and methanol can be easily removed by evaporation. Thus, it is expected that the productivity of the deacylation process can be dramatically improved by using the flow process compared with the conventional batch mode.

RESULTS AND DISCUSSION

Feasibility Study. As a preliminary study, we chose some commercially available substrates (**4**−**6**) with simple structures and performed the deacylation reaction in the packed-bed system, as depicted in Table 1. An anion-exchange resin (DIAION PA 308, produced by Mitsubishi Chemical Co., Ltd.) was filled into the column as the catalyst. The reaction temperature was controlled by an HPLC column oven. Prior to the main reaction, sodium methoxide in methanol or aqueous sodium hydroxide was fed into the column using a transfer

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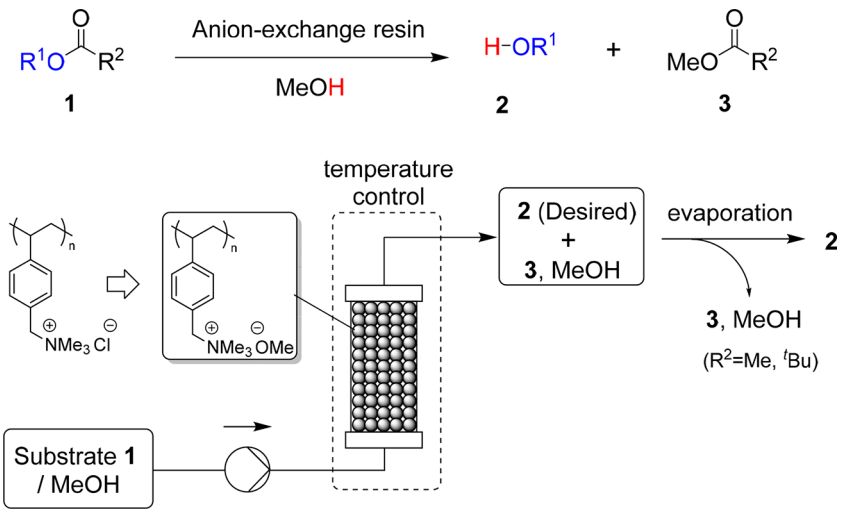
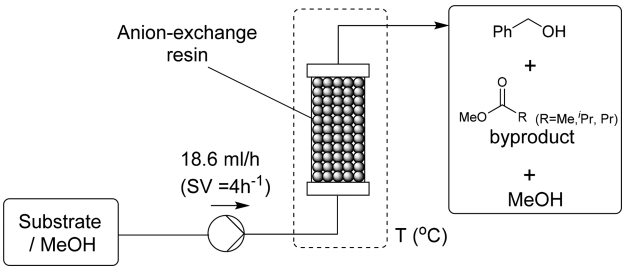
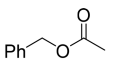
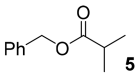
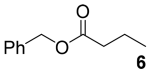


Figure 1. Illustration of the packed-bed flow reactor system used for the deacylation process.

Table 1. Deacylation Reaction with an Anion-Exchange Resin in a Packed-Bed Reactor[a]



Run	Substrate	Pretreatment for resin [b]	Residence time (min)	T (°C)	Conversion (%) [c]	Yield (%) [c]
1	 4	Method-A	< 15 [d]	25	98 [e]	98
2		Method-B	< 15 [d]	25	97 [e]	97
3 [f]		Method-A	120 [g]	25	98 (65) [h]	98
4	 5	Method-A	< 15 [d]	25	76 [e]	75
5		Method-A	< 15 [d]	50	88 [e]	90
6	 6	Method-A	< 15 [d]	50	95 [e]	93

[a]4.7 mL of resin was filled into an Omnifit column, and 3 g of substrate was used. [b]In method A, NaOMe was used. In method B, NaOH was used. [c]Determined by HPLC analysis. [d]The residence time was determined as the resin volume in the column (in mL) divided by the flow rate (in mL/h). [e]Reaction conversion was examined after stabilization in flow. The stabilization time was more than 30 min. [f]The result of batch conditions using 4.7 mL of resin and 3 g of **4**. [g]Reaction time in batch. [h]The result for a reaction time of 15 min is indicated in parentheses.

pump, causing the chloride to exchange to methoxide. This was performed to activate the catalyst before its use in the main reaction. The methanol solution of the substrate was supplied to the column packed with the catalyst at a space velocity (SV) of 4 h^{-1}. The solution emerging from the reaction site was then collected in the flask.

First, benzyl acetate (**4**) was used as the starting material, and the cleavage of acetyl groups was conducted in the flow process at 25 °C. As the result, an excellent yield (98%) of the desired product, benzyl alcohol, was obtained (run 1). To examine the effect of the pretreatment procedure, the activated methoxide type resin was prepared with sodium hydroxide (method B in the Experimental Section) instead of sodium methoxide (method A in the Experimental Section) before the flow reaction process. In method B, hydroxide of the resin was transformed into methoxide by methanol after sodium hydroxide treatment. It was found that a comparable reaction yield (97%) was obtained in spite of the difference in the pretreatment method (run 2). Additionally, the comparative batch reaction was performed using the same concentration and ratio of **4** and active resin. The desired product was obtained in comparable reaction conversion and yield to flow mode (run 3). However, a prolonged reaction time was necessary to achieve excellent reaction conversion because of the insufficient exposure of the catalyst in the batch reaction. Furthermore, poor filterability of the resin was observed in the purification process. It was confirmed that the deacylation efficiency was highly improved by the use of the packed-bed

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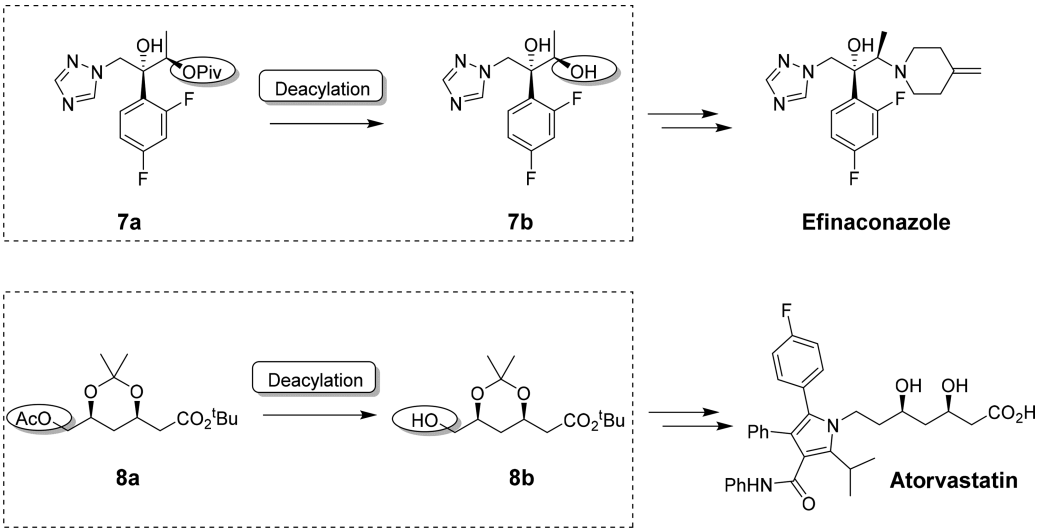
Scheme 1. Synthesis of Pharmaceutical Intermediates by Deacylation Reactions



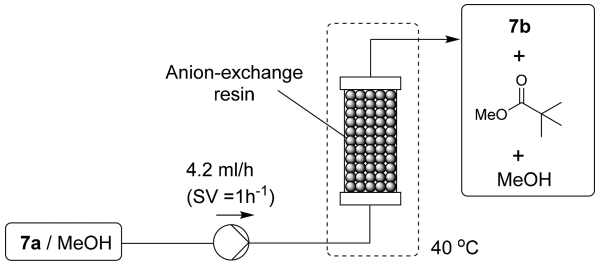
reactor system and that this system gives good operability over the conventional batch conditions.

Next, the flow reaction was carried out under the same conditions as in run 1 using benzyl isobutyrate (**5**), which has a more bulky structure. As a result, a decrease in the reaction yield was observed (75%; run 4). An improvement in the reaction yield was observed when the reaction temperature was increased from 25 to 50 °C (90%; run 5). Additionally, good results were also obtained in the case of benzyl butyrate (**6**) at higher reaction temperature (93%; run 6). Moreover, it was confirmed that byproducts such as methyl acetate, isopropyl acetate, and propyl acetate were completely removed by evaporation in all of the experiments. These studies revealed that a packed-bed reactor system employing an anion-exchange resin is applicable to several deacylation reactions to produce the desired hydroxy compounds while eliminating byproducts without the need for a complicated purification step.

Preparation of Pharmaceutical Intermediates by Deacylation Reaction in a Flow Reactor. It has been reported that the chiral compounds **7b** and **8b** described in Scheme 1 are key intermediates of efinaconazole and atorvastatin.[23−26] As the next step, we addressed the preparation of these hydroxy compounds from the corresponding precursors **7a** and **8a** containing pivaloyl and acetyl groups, respectively, in a packed-bed reactor system to expand the range of applications.

First, the optimal anion-exchange resin for this reaction was investigated by using **7a** as the starting material in continuous flow mode (Table 2). Several basic resins with different physical properties (Table 2) were chosen for this study. The resin was displaced from chloride to methoxide ion. The methanol solution of **7a** was subsequently supplied to the packed-bed reactor with SV = 1 h^{-1} at 40 °C. The results revealed that resins with lower cross-linking density tended to give better reaction yields, with the DOWEX 1X2 (100−200 mesh) affording the best result (92% yield; run 1). Presumably, the low cross-linking density of the resin might provide wide reaction sites with substrates and methoxide ion, resulting in higher reactivity. However, it was found that the unit cost of this resin is very high compared with other tested resins, thus making it not ideal for scaled processing. Therefore, we chose DIAION PA 306s as the optimal anion-exchange resin for this study in terms of the economics and availability for bulk scale, despite the fact that the reaction yield was slightly lower compared with that using DOWEX 1X2.

Table 2. Screening of Anion-Exchange Resins for the Deacylation Reaction[a]



	anion-exchange resin				
run	name	type	ion-exchange capacity (equiv/L)	cross-linking density (%)	yield (%)[b]
1	DOWEX 1X2 (100−200 mesh)	gel	0.6	2	92
2	DIAION PA306s	porous	≥0.8	3	87
3	DIAION PA308	porous	≥1.0	4	74
4	DIAION HPA25L	highly porous	≥0.5	25	49
5	AMBERLITE IRA900J	MR	≥1.0	no data	58

[a]4.2 mL of resin was filled in an Omnifit column, and 2 g of **7a** was used. [b]Determined by HPLC analysis.

To achieve an excellent reaction yield, we examined the optimal reaction conditions required for the preparation of **7b** using DIAION PA 306s in continuous flow mode, and the results are shown in Table 3. Initially, the methanol solution of **7a** was fed into the column with SV = 5 h^{-1} at 25 °C. The results indicated that the deacylation reaction hardly proceeded (8% yield; run 1). To improve the reaction yield, the SV and temperature were examined. The results showed that decreasing the SV, which enables prolonged residence time, and increasing the reaction temperature led to an excellent yield (98% yield; run 4). Similarly, the synthesis of **8b** in continuous flow mode was investigated to show the broad applicability of our system. An excellent yield was obtained

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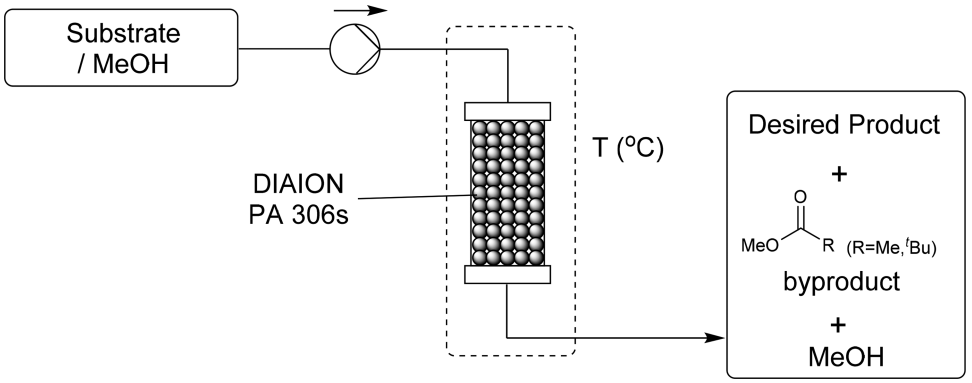
Table 3. Preparation of Pharmaceutical Intermediates Using a Packed-Bed Reactor System with DIAION PA 306s Resin[a]



Run	Substrate	Desired Product	Column Diameter (mm)	Resin (ml)	T (°C)	SV (h^{-1})	Yield[d] (%)
1			0.9	3.9	25	5	8
2			0.9	3.9	40	4	76
3[b]			0.9	4.2	40	1	87
4			0.9	3.9	50	1	98
5[c]	**7a**	**7b**	2.2	198	50	1	99
6			0.9	4.7	25	25	78
7	**8a**	**8b**	0.9	4.7	25	5	98

[a]Resin was filled into an Omnifit column; 2 g of **7a** and 3 g of **8a** were used. [b]The result of run 2 in Table 2. [c]Resin was filled into a large column, and 42 g of **7a** was used. [d]Determined by HPLC analysis.

when the same conditions as in Run 1 were used (98% yield; run 7). It was noteworthy that the acetyl group was selectively deacylated in this system, while cleavage of the *tert*-butyl ester was avoided. In addition, in run 5 a large-scale experiment was performed using a wide inner diameter (22 mm, ca. 2.4 times that of run 4) and high throughput (198 mL/h throughput of **7b**: 72 mmol/hr, ca. 51 times that of run 4) to showcase the scalability of this process. A large-sized glass column with a jacket was prepared, and 198 mL of resin (ca. 51 times that of run 4) was filled into the column. After catalyst activation, **7a** dissolved in methanol was transferred into the large column using a diaphragm pump with SV = 1 h^{-1} at 50 °C. A total of 32 g of the desired product **7b** was successfully obtained in a yield comparable to that in the small-scale experiment without a high-pressure drop. Thus, we demonstrated that our packed-bed reactor system with an anion-exchange resin for deacylation reactions is applicable to the synthesis of high-value pharmaceutical intermediates as well as being compatible with large-scale processes.

Finally, we studied the durability of the basic resin used as the catalyst during continuous flow operation for several days. The reaction conversion was examined following the supply of a methanol solution of **7a** to a DIAION PA 306s column with SV = 1 h^{-1} at 50 °C for 7 days. As shown in Figure 2 (blue line), it was found that high catalytic performance was maintained for 94 h, after which a decrease in the reaction

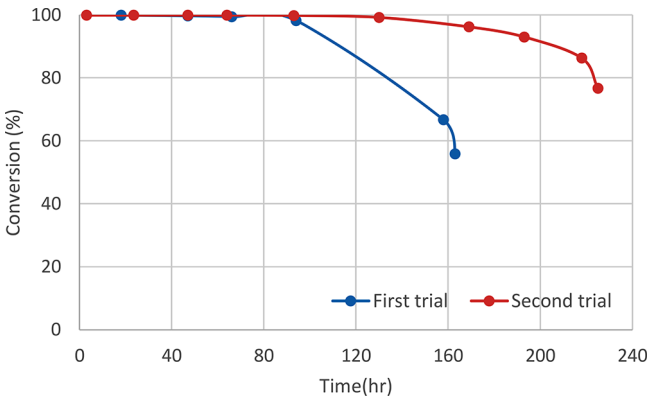


Figure 2. Durability study of the base catalyst in continuous flow mode.

conversion due to deactivation of the resin was observed. Presumably, the deactivation of the catalyst occurred over an extended reaction period because the methoxide ion, which is an active species, was replaced by an inactive pivalate ion stemming from the pivaloyl group in **7a**.

We tried to regenerate the deactivated catalyst using the following procedures. A sodium hydroxide solution was supplied to the column packed with deactivated resin to exchange the pivalate ions into hydroxide ions on the resin,

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followed by water flushing to remove the residual sodium hydroxide in the reaction site. Finally, methanol was used to flush and replace the hydroxide with methoxide and to remove the water. The methanol solution of **7a** was fed into the column, and the reaction conversion was examined again. It was found that the reaction conversion increased to 99.9%. The methanol solution of **7a** was pumped into a column filled with regenerated resin with SV = 1 h^{-1} at 50 °C for 10 days, after which the reaction conversion was examined again. As shown in Figure 2 (red line), it was confirmed that the catalyst was efficiently recycled and that catalytic performance increased compared with that of the first trial. According to these results, we concluded that catalyst activation from chloride to methoxide ions under the current pretreatment procedure was insufficient. Thus, the optimal methodology for activation to achieve high catalytic performance will be investigated in the near future.

Through these studies, we demonstrated that the DIAION PA 306s has high durability for the deacylation reaction of **7a** and that regeneration of the catalysts is readily achievable.

CONCLUSIONS

We have established an efficient and practical packed-bed reactor system with an anion-exchange resin as a catalyst for deacylation reactions. This simple system produces the desired hydroxy compounds, including pharmaceutical intermediates, without time-consuming purification steps such as extraction and filtration. Moreover, we have demonstrated that this system can be easily scaled-up and provides excellent yields across a number of reactions. It was confirmed that the catalyst is highly durable and readily regenerable. To establish a manufacturing process, more efforts are currently being investigated in our laboratory to optimize the method for large-scale production.

EXPERIMENTAL SECTION

HPLC Methods. HPLC analysis was performed on a Shimazu LC20 chromatograph. The method was altered according to the substrate used.

Analysis of Benzyl Alcohol. A Shiseido Capcell Pak C_{18} type MG (250 mm × 4.6 mm) analytical column was used at 30 °C. The UV detector was set at 220 nm. Mobile phases A (0.1% phosphoric acid) and B (acetonitrile) were utilized at a flow rate of 1.0 mL/min. Mobile phase B was increased linearly from 25% to 95% over 25 min and maintained at 95% for 3 min, providing a retention time of 8.5 min for benzyl alcohol.

*Analysis of **7b**.* A Shiseido Capcell Pak C_{18} type MG (250 mm × 4.6 mm) analytical column was used at 30 °C. The UV detector was set at 210 nm. Mobile phases A (0.1% phosphoric acid) and B (acetonitrile) were utilized at a flow rate of 1.0 mL/min. Mobile phase B was maintained at 30% for 15 min, increased linearly from 30% to 60% over 10 min, maintained at 60% for 20 min, increased linearly from 60% to 90% over 5 min, and maintained at 90% for 10 min, providing a retention time of 5 min for **7b**.

*Analysis of **8b**.* YMC-Pack ODS-A A-303 (250 mm × 4.6 mm) analytical column was used at 30 °C. The UV detector was set at 210 nm. An acetonitrile/water mixture (40:60 v/v) was utilized as the mobile phase at a flow rate of 1.0 mL/min, providing a retention time of 22 min for **8b**.

General Preparation of Methoxide-Type Resins. *Method A.* The glass column (Omnifit column, 10 mm i.d.) containing an anion-exchange resin (Cl type) was filled with methanol, and the inner temperature was maintained at 25 °C by the column oven. Sodium methoxide dissolved in methanol (1 M, 2.5 volumes/resin volume) was fed into the column using a transfer pump with SV = 4 h^{-1}. Finally, methanol (3.0 volumes/resin volume) was fed into the column at the same flow rate to remove the sodium methoxide.

Method B. A glass column (Omnifit column, 10 mm i.d.) containing an anion-exchange resin (Cl type) was filled with water, and the inner temperature was maintained at 25 °C by the column oven. Sodium hydroxide (1 M, 2.5 volumes/resin volume) was fed into the column using a transfer pump with SV = 4 h^{-1}. Next, water (4.5 volumes/resin volume) was fed into the column at the same flow rate to remove the sodium hydroxide. Finally, methanol (4.5 volumes/resin volume) was fed into the column with SV = 10 h^{-1}.

General Procedure for the Deacylaion Reaction in the Packed-Bed Reactor (Preparation of 7b). The substrate solution in methanol (ca. 0.4 M) was prepared in a bottle. The solution was then transferred into the column filled with the methoxide-type resin using a diaphragm pump (SIMDOS 10, KNF Japan Co., Ltd.) at a temperature of 50 °C (SV = 1 h^{-1}). Once the bottle was empty, the residual reaction mixture in the column was flushed with methanol at the same flow rate, and the collected solution was concentrated in vacuo. Finally, the reaction yield was calculated from the concentration of the desired product in the concentrate using HPLC analysis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00393.

General Information and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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