Asian Journal of Chemistry; Vol. 26, No. 12 (2014), 3659-3660

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.16782

NOTE

Development of Two Scalable Industrial Process for Cinchona Alkaloid Catalyst Recovery: Application to the Large-Scale Production of (+)-Biotin

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Received: 29 November 2013; *Accepted*: 20 February 2014; *Published online*: 5 June 2014; AJC-15314

Two scalable chemical processes for the cinchona alkaloid catalyst recovery were demonstrated. In the first approach, the organocatalyst quinine was removed first as the neutral tartrate from alcohol, one recrystallization giving pure salt. Quinine was then recovered in 95 % yield by basification of its aqueous tartrate salt and could be reused without any further purification. In the second approach, the pure quinine catalyst could be easily obtained in almost quantitative yield and with 99 % chemical purity after a single recrystallization from toluene and its spectral data (^{1}H NMR and the value of specific rotation) were in agreement with those of the literature previously reported. The methods are versatile and applicable for industrial-scale synthesis of biologically relevant substance (+)-biotin.

Keywords: Recovery, Cinchona alkaloid, Quinine, Catalyst, (+)-Biotin, Vitamin H.

The total synthesis of (+)-biotin is an old but still attractive research area in both industry and academia[1-3]. The continued chemical synthetic activity in this field stems from the fact that it is an important water-soluble B-complex group of vitamins. For example, it plays an essential nutritional role in human and animal health[4-6]. Although various synthetic protocols[1-3] are available for the total chemical synthesis of (+)-biotin, literature reports in industrially applicable syntheses remain scarce. It's well known that the major challenges in designing industrially attractive processes for fine chemicals include the development of low-cost, atom-efficient and recyclable processes that are easily scalable, nonhazardous and at the same time highly selective[7].

Recently, we reported series of highly enantioselective desymmetrization of *meso*-cyclic anhydride using quinine (Fig. 1. a) and its derivatives (Fig. 1. b-e) as organocatalyst to construct the key chiral building block of (+)-biotin[8-12]. Despite the indisputable advances that have been made, cinchona alkaloid derivative catalysts (Fig. 1. b-e) suffer from difficulties with organocatalyst preparation. Therefore, quinine catalyst (Fig. 1. a) is favourable for industrial application in terms of commercially available. In continuation of our interest in the development of industrial-scale synthesis of (+)-biotin, investigation of the quinine recovery came into our specific attention.

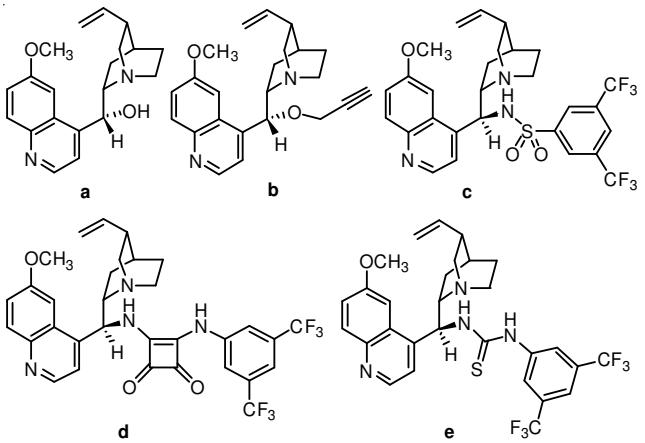


Fig. 1. Structure of cinchona alkaloid and its derivatives catalysts

Reports are available in the literature[8] related to the recovery method for the quinine catalyst and successfully applied on the preparation of the key chiral intermediate of (+)-biotin in laboratory small-scale. Although the ^{1}H NMR and HPLC analysis of the directly recovered quinine without any further purification is the same with the original sample, the utility of this recovered organocatalyst in the large scale recycle were disappointing because of the value of specific rotation of

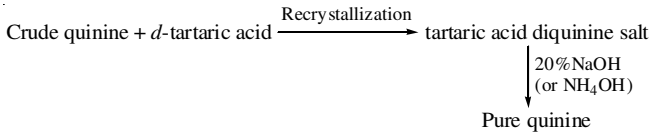
recovered quinine were not in agreement with those of the literature previously reported[13]. Our efforts therefore focused on the purification of the recovered quinine catalyst, with the goal to rapidly come up with a practical solution for an improved and scalable process.

Optical rotations were obtained on a *JASCO* P1020 digital polarimeter. Melting points were measured with a WRS-1B digital melting point apparatus and are uncorrected. Chemical reagents were obtained from commercial sources and used as received.

Resolution approach: The crude quinine (100 g, 0.3 mol) was dissolved in hot 95 % ethanol (160 mL) and treated with a hot solution of *d*-tartaric acid (23.2 g, 0.15 mol). Colorless needles of quinine tartrate crystallized overnight and were filtered, washed with a little cold 95 % ethanol and air dried. Quinine was recovered in 95 % yield by basification of its aqueous tartrate salt with 20 % aqueous NaOH to pH = 14 and extracted with ethyl acetate (3 × 200 mL). The organic phases were combined and dried over Na_2SO_4. Evaporation of the solvent gave the pure quinine as a white crystalline powder, yield: 95.3 g (95 %); m.p.: 172.3-172.7 °C; $[\alpha]_D^{26.4}$: -154.3° (*c* 1, CH_3CH_2OH). {Lit.[13] m.p.: 172-175 °C; $[\alpha]_D^{26}$: -154.1° (c 1, CH_3CH_2OH)}, spectrally indistinguishable from natural quinine.

Recrystallization approach: The crude quinine (100 g, 0.3 mol) was purified by crystallization from toluene. After cooled to room temperature, the precipitated colourless crystals was filtered and dried at 80 °C *in vacuo* for 3 h to afford pure quinine as a white crystalline powder, yield: 99.4 g (99 %); m.p.: 174.6-175.4 °C; $[\alpha]_D^{26.7}$: -154.0° (*c* 1, CH_3CH_2OH). {Lit. [13] m.p.: 172-175 °C; $[\alpha]_D^{26}$: -154.1° (*c* 1, CH_3CH_2OH)}, spectrally indistinguishable from natural quinine.

This purification method is shown in **Scheme-1**, which is based on the resolution processes to purify the recovered quinine organocatalyst. Initially the crude quinine was dissolved in hot 95 % ethanol and treated with a hot solution of *d*-tartaric acid. Then through one recrystallization from hot 95 % ethanol to give the colourless needles of quinine tartrate salt. Finally, quinine was recovered in 95 % yield by basification of its aqueous tartrate salt, with spectral properties (^{1}H NMR and the value of specific rotation) matching those of an authentic sample.



Scheme-I: Resolution approach process

In order to simplify the chemical purification processes, we next investigate the recrystallizaiton method. The optimization of the recrystallizaiton solvent was then undertaken and the results are illustrated in Table-1. It was found that amongst five different solvents examined, the optimum recrystallization solvent in terms of recovery ratio was toluene (Table-1, entry 2). The quinine catalyst could be easily obtained in almost quantitative yield and with 99 % chemical purity after a single recrystallization from toluene, its ^{1}H NMR and the value of specific rotation were in agreement with those of the literature previously reported.

TABLE-1
OPTIMIZATION OF THE RECRYSTALLIZATION SOLVENT

Entry	Solvent	Recovery ratio* (%)
1	Et_2O	0
2	Toluene	99
3	CH_2Cl_2	0
4	AcOEt	0
5	Acetone	0

* The isolated yield of pure quinine

Conclusion

We have developed two efficient industrial-scale methods for the recovery of cinchona alkaloid organocatalyst quinine. The first method, which is based on the chemical resolution approach, gave the recovered quinine in two steps and 95 % yield. The second method stemming from recrystallizaton approach obtained the recovered quinine in single step and 99 % recovery ratio. These two chemical processes were readily scaled up with the target catalyst quinine being isolated in high yield and high chemical purity.

ACKNOWLEDGEMENTS

The authors gratefully acknowledged the financial support from Shanghai Municipal Education Commission.

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