Tetrahedron: *Asymmetry* 25 (2014) 813–820

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Asymmetric synthesis of warfarin and its analogues on water

Maria Rogozińska-Szymczak[a], Jacek Mlynarski[a,b,*]

[a] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland
[b] Faculty of Chemistry, Jagiellonian University, Ingardena 3, 30-060 Krakow, Poland

ARTICLE INFO

Article history:
Received 25 February 2014
Accepted 16 April 2014
Available online 28 May 2014

ABSTRACT

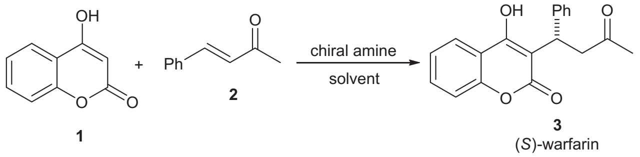
The asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketones on water without organic co-solvents is reported to be catalysed by organic primary amines. The application of enantiomerically pure (*S*,*S*)-diphenylethylenediamine affords a series of important pharmaceutically active compounds in good to excellent yields (73–98%) and with good enantioselectivities (up to 76% *ee*) via reactions accelerated by ultrasound. In particular, our developments led to an efficient protocol for the 'solids on water' formation of the anticoagulant warfarin in both enantiomeric forms. The presented scalable and environmentally friendly organocatalytic approach affords the target drug in enantiomerically pure form.

1. Introduction

The conjugate addition of enolates to α,β-unsaturated acceptors (Michael reaction) is one of the most important carbon–carbon bond-forming reactions in organic synthesis.[1] This reaction can be controlled by chiral catalysts resulting in a formation of enantiomerically pure Michael adducts. For this reason there is a continuing need for the development of enantioselective catalytic protocols leading to the asymmetric synthesis of drugs and bioactive compounds by means of conjugate Michael additions.[2]

Since the beginning of this century, asymmetric organocatalysis[3] has emerged as a parallel and more environmentally acceptable methodology[4] for the production of enantiomerically pure compounds and is also a way to introduce chirality into Michael reactions.[5] The application of purely organic catalysts is now presented to be an enabling technology for the efficient synthesis of the drug and several biologically relevant molecules.[6] Recent achievements in chemical efficiency have also focused on the economic and ecological aspects of organocatalysis.[7] From a green chemistry perspective, the use of water instead of even a small additive of organic solvent is preferred to decrease environmental contamination. Thus additional efforts have also been made to develop efficient organocatalysts for asymmetric reactions in pure water.[8]

The use of asymmetric Michael reactions to generate biologically relevant molecules has been actively investigated over the last few decades. Recently some organocatalytic procedures for the synthesis of drug-like scaffolds have been recorded. One successful and instructive example is the straightforward production of chiral warfarin via the well-established Michael addition of 4-hydroxycoumarin to benzylideneacetone (Scheme 1).



Scheme 1. Asymmetric synthesis of warfarin by the Michael addition of 4-hydroxycoumarin to benzylideneacetone.

As one of the most effective anticoagulants, warfarin has been introduced for clinical use (warfarin®, jantoven®, uniwarfin®, coumadin®, marevan®) as a racemate. However, the activity and metabolism of both enantiomeric forms are dissimilar. The (*S*)-form was proved to be more active to its mirror image.[9] Taking into account this feature, the asymmetric synthesis of anticoagulant drugs seems to be not only rational but indispensable.

In 2003, Jørgensen reported the first one-step synthesis of enantiomerically enriched warfarin from simple materials catalysed by secondary amine catalysts.[10] Primary[11] and secondary[12] amino-acid based amines have also been shown to be efficient in this asymmetric procedure. Usually 20 mol % catalyst loading was needed for the long reaction carried out in organic solvents.

---

* Corresponding author. Tel./fax: +48 12 663 2035.
E-mail address: jacek.mlynarski@gmail.com (J. Mlynarski).
URL: http://www.jacekmlynarski.pl (J. Mlynarski).

http://dx.doi.org/10.1016/j.tetasy.2014.04.008
0957-4166/

However, some catalysts seemed to be superior to others resulting in the formation of the adduct in good to excellent enantioselectivities,[11b,12b] even with small catalyst loading (5 mol %).[13]

Applied catalysts have been derived from amino acids or *cinchona* alkaloids and their preparation required further efforts. In 2006, Chin demonstrated that the application of 10 mol % of (*R*,*R*)-diphenylethylenediamine in THF resulted in the selective formation of (*R*)-warfarin in 94% yield after 48 h (ca. 80% *ee*).[14] Recently, the efficiency of this catalyst was further improved upon by tosylation (Ts-DPEN catalyst) and metal salt additive.[15] The reaction in THF gave warfarin in 64% yield after 24 h with 5 mol % of amine and metal salt combination. In all cases, harmful organic solvents were used as reaction media. The application of small amounts of low molecular organocatalysts in aqueous solvents has so far been unsuccessful.[16]

Despite the significant advances in this field, the synthesis of optically active warfarin and its analogues represent a considerable synthetic challenge. Moreover, it is still desirable to develop environmentally and economically acceptable protocols for this important transformation. Herein we report our studies on the asymmetric organocatalytic preparation of anticoagulant warfarin and its analogues by using green chemistry type Michael reactions controlled by a readily available commercial chiral primary amine (diphenylethylenediamine) 'on water'.[17]

2. Results and discussion

To select promising catalysts, we first examined the reaction of 4-hydroxycoumarin **1** to α,β-unsaturated ketone **2** leading to warfarin **3**. This model Michael addition reaction was investigated using a series of primary amine organocatalysts **4**–**14** (Scheme 2). By using readily available primary amines **4**–**11** as catalysts and also the natural starting point for more sterically hindered examples, we prepared a series of hydrophobic amines equipped with an alkyl chain **12**–**14**[18] for test reactions in an aqueous environment.

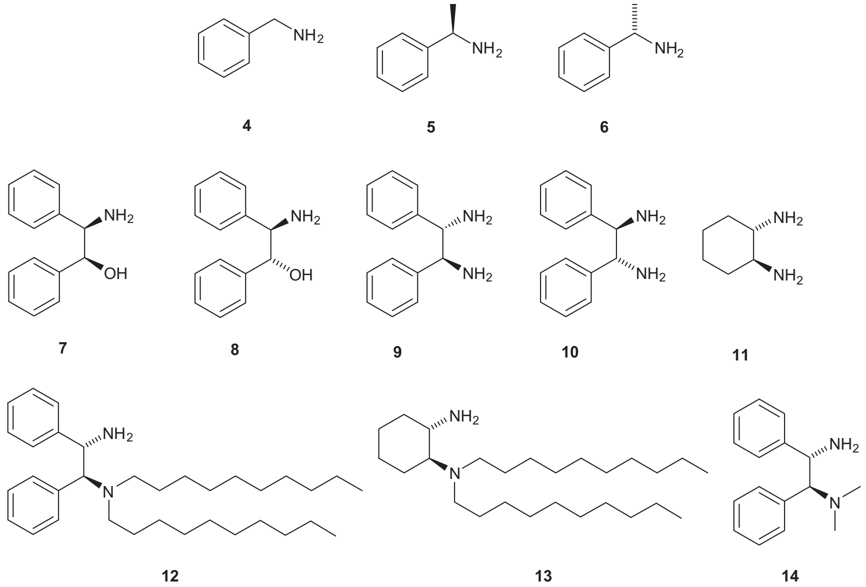
In order to assess the efficiency of Michael reactions promoted by selected catalysts, initial screening was conducted in wet THF (10 vol % water) at room temperature in the presence of 10 mol % of amines. The results are summarised in Table 1. The application of all of the tested chiral catalysts resulted in the stereoselective formation of warfarin in various yields ranging from 22% to almost the quantitative formation of the adduct (98%). The most promising catalyst in terms of *ee* and yield was the commercially available (*S*,*S*)-diphenylethylenediamine (Table 1, entry 6). This catalyst can be obtained in both enantiomeric forms by using a reliable protocol on a multigram scale.[19] Thus, the application of the (*S*,*S*)-configured amine gave (*S*)-warfarin while enantiomeric catalyst **10** resulted in the preferential formation of (*R*)-enantiomer (Table 1, entry 7). This simple and promising catalyst surpassed the application of other tested amines in terms of efficiency and stereoselectivity. Another promising catalyst was diaminocyclohexane **11** but the observed yield was worse when compared to the best catalyst **9**. The reaction catalysed by structurally modified amines **12**–**14** gave poor to moderate enantioselectivities only (Table 1, entries 10–12).

Table 1
Initial catalyst screening[a]

Entry	Catalyst	Yield (%)[b]	*ee* (%)[c]
1	**4**	55	rac.
2	**5**	30	24 (*S*)
3	**6**	34	20 (*R*)
4	**7**	22	18
5	**8**	22	20 (*R*)
6	**9** (*S*,*S*)	98	55 (*S*)
7	**10** (*R*,*R*)	91	53 (*R*)
9	**11**	56	44
10	**12**	31	31
11	**13**	44	13
12	**14**	40	30

[a] The reaction was performed by employing **1** (0.50 mmol), **2** (0.60 mmol), catalyst (0.05 mmol, 10 mol %) and mixture THF/H_2O (9:1) as a solvent (1 mL) at rt for 20 h.
[b] Isolated yield after silica gel chromatography.
[c] *Ee*'s were determined by HPLC analysis on a chiral phase (Daicel AD-H column).

After (*S*,*S*)-catalyst **9** was identified as being the most effective, we then evaluated the solvent effect and possible diminishing of catalyst loading. Dry THF and its solution with water provided warfarin in similar yields and stereoselectivities (Table 2, entries 1 and 2). Increasing the amount of water led to no change in reaction efficiency (Table 1, entry 4). However, the good enantioselectivity observed for the reaction when carried out in pure water at rt



Scheme 2. Chiral primary amines tested in Michael reaction.