Enantioselective Synthesis of 4-Hydroxy-3-(3-Oxo-1-Phenyl Butyl)-2H-1-Benzopyran-2-One (Warfarin)

Ayhan S. DEMİR, Cihangir TANYELİ, Volkan GÜLBEYAZ
Middle East Technical University, Department of Chemistry,
06531 Ankara-TURKEY
Hülya AKGÜN
Hacettepe University, Faculty of Pharmacy,
Department of Pharmaceutical Chemistry,
06100 Ankara-TURKEY

Oral anticoagulant Warfarin (4-hydroxy-3-(3-oxo-1-phenyl butyl)-2H-1- benzopyran-2-one) is synthesized in optically active form starting from 4- hydroxycoumarin via formation of optically active enamines followed by Michael addition reaction with benzyliden acetone at low temperature. Different amines gave 17-68% ee and the chemical yield was 22-71%, depending on the reaction conditions and the structure of chiral amines.

Introduction

Warfarin (4-hydroxy-3-(3-oxo-1-phenyl butyl)-2H-1-benzopyran-2-on) **1** is a vitamin K1 antagonist widely employed as a rodenticide and as a therapeutic drug for the treatment of such coagulation disorders as thrombophlebitis, pulmonary embolism, and myocardial infraction, [1,2] and more recently has been used as a probe to investigate the multiplicity and catalytic activity of microsomal and purified cytochrome P-450 preparations[3]. The clinical and environmental importance of warfarin has promoted a number of invetigations to determine its pharmacological and biological fate. The R and S enantiomers of warfarine have a different activity. (S)-Warfarin is five to eight times more potent an anticoagulant than (R)-Warfarin. In man (S)-warfarin is metabolized faster than the R isomer. Because of its clinical and pharmacological importance, considerable effort has been devoted for the synthesis of both enantiomers of warfarin[4-9].

Although successful routes to warfarin and its derivatives are documented in the literature, the reported yieds are poor to moderate at best. Warfarin has been synthesized by the Michael addition of 4-hydroxycoumarin to benzalacetone under a number of acid- or base-catalyzed conditions[10-12]. Traditionally, the reaction has most often been run in water containing a catalytic amount of triethylamine (5 mole %). Hermodson et al.[13] used essentially the same conditions. Fasco et al.[14] followed a similar route, to obtain a homogeneous system. Substituted dioxane has been used as the solvent and piperidine as the catalyst.

A further refinement was reported by Cook et al[15] who, in their synthesis of 3'-bromowarfarin, heated a solution of **m**-bromobenzal acetone and 4-hydroxycoumarin in pyridine at reflux. However, rarely was the overall yield of warfarine as high as 65%. Trager et al[16]. synthesized warfarin in 93% yield by refluxing 4-hydroxycoumarine with benzalacetone in methanol. The R and S enantiomers of warfarine were obtained by the separation of the quinidine salt of racemic warfarin. In this work we tried to synthesize optically active warfarin *via* enantioselective Michael addition reactions. The chiral information was introduced using chiral amines and amino acid derivatives.

Experimetal Section

All reagents were of commercial quality, and reagent quality solvents were used without further purification. IR spectra were determined on a Philips model PU9700 spectrometer. ^{1}H NMR spectra were determined on a Bruker AC 80 MHz FT, AC 200 MHz and Varian 400 MHz FT spectrometers. GC analyses were deteremined on a HP 5890 gas chromatography. Mass spectra were obtained on VGTrio2 spectrometer at an ionization energy of 70 eV. Optical rotation values were measured with a Perkin Elmer P241 polarimeter. Elemental analyses were performed at the Middle East Technical University analysis Center.

Synthesis of Benzopyrane Enamines

A mixture of equimolar amounts (40 mmol) of amine and 4-hydroxycoumarine with catalytic amount of toluenesulfonic acid was refluxed in benzen under a Dean stark trap. The reaction was monitored by PTLC (EtOAc: hexane 3:1) (2-3 h). At the end of the reaction benzene was evaported and the residue was dissolved in 60 ml of EtOAc, washed with water and brine, and dried over ($MgSO_4$). Evaporation of solvent gave a yellow solid, which was prufied by washing with pentane.

Michael Reaction (Entry 1)

10 mmol of enamine and 10 mmol of benzalacetone were dissolved in 40 ml of methanol. To this mixture was added a catalytic amount of p-toluene sulfonic acid and stirred at RT for 14 h (the reaction was monitored by TLC). After removal of the solvent the residue was stirred in 40 ml of methylene chloride and 20 ml of 2N HCl solution for 1h. The organic layer was separated and aqueous layer was extracted again with 50 ml of methylene chloride. The combined extracts were washed with aq. $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated. Purification was carried out using flash column chromatography (Hexane: EtOAc 1:5) and warfarine was isolated as a ligh yellow solid. The spectroscopic data are in agreement with literature values m.p. 169-171 $^\circ$C (crytallization in acetone- water), lit. 170-171°C[10-12].

Michael Reaction (Entry 2)

An LDA solution was prepared from diisopropylamine (1.20 ml, 8.4 mmol) in THF (15 ml) and n-BuLi (1.55 M in hexane, 5.44 ml, 8.4 mmol at-78° C for 30 min. A solution of aminobenzopyrane (8 mmol) in THF (15 ml) was added to this, and the resulting solution was stirred for 40 minutes. This solution was added to a solution of benzalacetone (10 mmol) and TMSCl (20 mmol) in THF (15 ml) at-78°C and stirred for 3h. The reaction was quenched by 10% HCl (50 ml) and the mixture was stirred vigorously at RT for 1h and was then extracted with EtOAc (3X50 ml). The combined extracts were washed with aq. $NaHCO_3$ and brine,

dried $(MgSO_4)$, and concentrated. Column chromatography (hexane: EtOAc 1:5) provided warfarine as a light yellow solid.

4-(2-Methoxycarbonylpyrrolidino)-2H-1-benzopyran-2-one(3a)

Yellow solid, m.p. 83-85 °C.

IR(KBr):3050-2800, 1740, 1700, 1590 cm^{-1}

^{1}H-NMR (CDCl$_3$): δ 1.70-2.38 (m, 4H, 2β-NH$_2$), 3.12-3.34 (m, 2H, NH$_2$), 3.42 (s, 3H, OCH$_3$), 4.05 (m, 1H, NCH), 5.43 (s, 1H, olef H), 7.15-7.45 and 7.61-7.88 (m, 4H, Ar-H).

Anal. calcd for $C_{15}H_{15}NO_4$ (273.10) C:65.91, H:5.54, N:5.13 found: C:66.13, H:5.71, N:5.26.

4-(2-Methoxycarbonylpyrrolidino)-2H-1-benzopyran-2-one(3b)

Yellow solid, m.p. 57-58 °C.

IR(KBr):3060-2800, 1710, 1600, 1590 cm^{-1}

^{1}H-NMR (CDCl$_3$): δ 1.72-2.45 (m, 4H, 2β-NH$_2$), 3.18-3.90 (m, 4H, NCH$_2$, OCH$_2$), 3.27 (s, 3H, OCH$_3$), 4.09 (m, 1H, NCH), 5.40 (s, 1H, olef H), 7.11-7.50 and 7.62-7.90 (m, 4H, ArH).

^{13}C-NMR (CDCl$_3$): δ 25.14 (C-10), 29.79 (C-9), 54.41 (C-8), 59.29 (C-13), 59-62 (C-11), 72.27 (C-12), 89.27 (C-12), 89.36 (C-2), 116.91 (C-3a), 117.91 (C-7), 122.93 (C-4), 125.84 (C-5), 131.28 (C-6), 154.33 (C-7a), 156.33 (C-3), 162.90 (C-1).

MS (m/z) [% bp]=259 (M$^+$, 3), 214 (100, b.p., M$^+$-CH$_2$ OCH$_3$), 145(47), 101(8), 89(14), 70(25), 63(8), 45(8), 41(11), 39(8).

Anal. calcd for $C_{15}H_{17}NO_3$ (259.30) C:69.48 H:6.61 N:5.40 found: C:69.04 H:6.66 N:5.22

$[\alpha]_D^{20}$ =-42.0 [c=1.2; CHCl3] for (S)-Enantiomer.

$[\alpha]_D^{20}$ =+42.0 [c=1.2; CHCl3] for (R)-Enantiomer.

4-(1-phenylethylamino)-2H-1-benzopyran-2-one (3c)

Yellow solid, m.p. 70-72 °C.

IR(KBr):3410, 3050-2850, 1700, 1610, 1560 cm^{-1}

^{1}H-NMR (CDCl$_3$): δ 1.32 (d,J=7Hz, 3H, CH$_3$), 3.98-4.3 (m, 1H, CH), 5.42 (s, 1H, CH), 7.12-7.45 and 7.61-7.89 (m, 9H, ArH).

Anal. calcd for $C_{17}H_{15}NO_2$ (265.31) C:76.96 H:5.70 N:5.28 found: C:76.73 H:5.61 N:5.11

$[\alpha]_D^{20}$ =-23.21 [c=1.2; CHCl3] for (S)-Enantiomer.

$[\alpha]_D^{20}$ =+24.4 [c=1.2; CHCl3] for (R)-Enantiomer.

4-(-methoxy-3.3-dimethyl-2-butylamino)-2H-1-benzopyran-2-one (3d)

Colorless solid, m.p. 86-88 °C.

IR(KBr): 3420, 3000-2850, 1700, 1610, 1590 cm^{-1}.

^{1}H-NMR (CDCl$_3$): δ 0.98 (s, 6H, 3CH$_3$), 2.48-2.61 (m, H, NCH), 3.15-3.58 (m, 2H, CH$_2$), 3.41 (s, 3H, CH$_3$), 5.42, (s, 1H, CH), 7.12-7.51 and 7.62-7.80 (m, 4H, ArH).

Anal. calcd.for $C_{16}H_{21}NO_3$ (275.35) C:69.79 H:7.69 N:5.09 found C:69.53 H:7.74 N:4.96.

4-(1-*t*-Butoxycarbonyl-3-methyl-2-butylamino)-2H-1-benzopyran- 2-one (3e)

Yellow solid, m.p. 111-113 °C.

IR(KBr): 3420, 3010-2840, 1750, 1710, 1610, 1590 cm^{-1}.

^{1}H-NMR (CDCl$_3$): δ 0.92 (d, J=7Hz, 6H, 2CH$_3$), 1.41 (s, 9H, 3CH$_3$), 1.48-1.61 (m, 1H, CH), 2.43-2.77 (m, H, NCH), 3.17-3.77 (m, 2H, CH$_2$), 3.38 (s, 3H, CH$_3$), 5.36 (s, 1H, CH), 7.12-7.45 and 7.61-7.82 (m, 4H, ArH).

Anal. calcd. for $C_{17}H_{23}NO_4$ (305.37) C:66.86 H:7.59 N:4.59 found C:66.81 H:7.41 N:4.32.
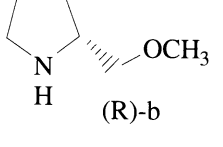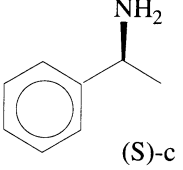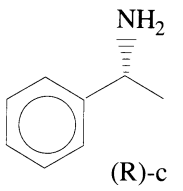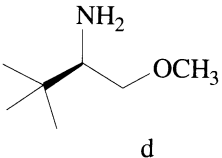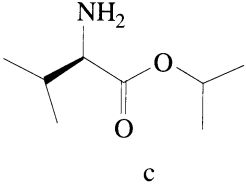
Results and Discussions
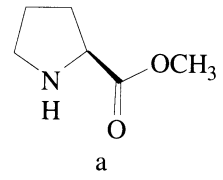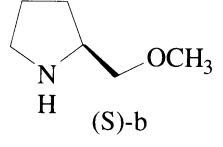
For the asymmetric synthesis of warfarine, 4-hydroxycoumarine was converted into its enamine derivatives using different chiral amines and amino acids. As shown in Scheme 1, the reaction of 4-hydroxycoumarin (**2**) with amine derivatives **3** gave under reflux in benzene the enamine derivatives **4** as a solid in good yield. Some of the enamines are synthesized using both enantiomers of chiral auxiliary. The products are identified using ^{1}H NMR, and IR spectroscopy.
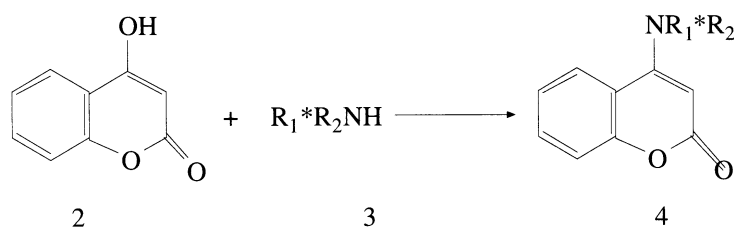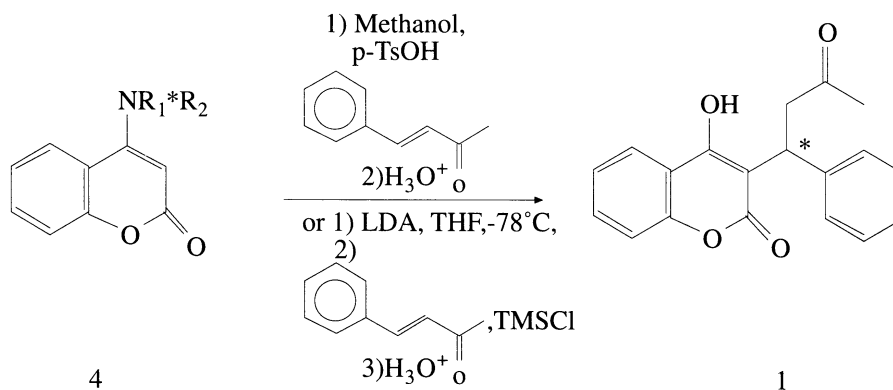

Scheme 1.

For the Michael addition reaction of enamine with benzalacetone two different reactions are carried out. The enamine with primary amine group was deprotonated using LDA at- 78°C in THF. Benzalacetone and Lewis acid (TMSCl) was then added at the same temperature. After stirring at 30°C for 4h the mixture was warmed to RT and hydrolyzed with HCl solution. After purification of the crude product the desired product **1** was obtained in 58-71 % yield (Table 1). The use of Lewis acid other than TMSCl (ZnCl$_2$, MgCl$_2$, LiCl) gave lover ee by the test reaction with **3e** as shown in table 2. The reaction gave very low yields without Lewis acids (14%). The best optical yield was obtained using valine and *t*-leucine derivatives. Steric bulkiness should be responsible for this result. In the other procedure, the enamines **4a,b** were stirred with benzalacetone at RT in toluene for 48 hrs and the reaction was monitored by TLC. No reaction was observed. The use of different solvents such as benzene, cyclohexane and methylene chloride was also tried but did not result in any product formation. The reaction was carried out in methanol with a catalytic amount of *p*- toluenesulfonic acid at RT, whence warfarine was obtained in 22-31 % yield after acid hydrolysis of enamine and purification (by column chromatography followed by crystallization) of the crude product (Scheme 2).

Table 1. Enamines of 4-hydroxycoumarine and their Michael reactions

Amine 3	Enamine 4	Warfarin 1	
	Yield (%)	(Yield(%)	ee(%)
a	86	22	17(R)
(S)-b	91	31	20(R)
(R)-b	88	29	21(S)
(S)-c	93	63	51(R)
(R)-c	91	66	47(S)
d	87	71	63(R)
c	83	58	68(R)

All spectroscopic data of the product ([1] H NMR, IR) were identical with the literature values. Comparison of optical rotation values gave the optical yield 17-68 % ee. The use of L-amino acid derivatives gave R enantiomer). The Michael addition reaction of (R-) metoxymethylpyrrolidin with benzalacetone gave S configurated warfarine in 29 % chemical and 21 % optical yield. The same result was obtained using phenylethylamine enantiomers. The absolute configuration of product depends on the absolute configuration of the adduct. In both cases, by using S configured chiral auxiliary, $Si - Si$ attack occurs and the attack happens from the less hindered side of enamine derivatives to give the R product. Lewis acids are playing their roles as an activator for benzalacetone. The following figure shows the favored transition state for the Michael addition reaction.
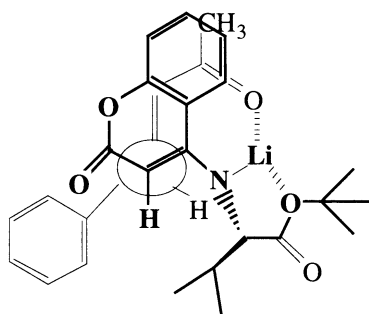
Scheme 2.

Table 2. Michael reaction of **3e** with benzalacetone in the presence of different Lewis acids

Lewis Acid	Product 1	
	Yield (%)	ee(%)
-	23	14
$ZnCl_2$	56	64
$MgCl_2$	53	51
LiCl	57	53
TMSCl	58	68

Acknowledgments

References

1. R. A. O'Reilly, P. M. Aggeler, **Pharmacol. Rev., 13**, 35 (1970).

2. W. B. Jackson, P. J. Spear, C. G. Wright, **Pest control 39**, 13 (1971).

3. W. R. Porter, C. Wheeler, W. F. Trger, **Biochem. Pharmacol., 30**, 3099, (1981).

4. B. D. West, S. Preis, C. H. Schroeder, K. P. Link., **J. Am. chem. Soc., 83**, 2676, (1961).

5. G. Blaschke, Angew. Chem., **92**, 14, (1980).

6. G. L. Jeyaraj, W. R. Porter., **J. Heterocyclic. Chem., 22**, 535, (1985).

7. M. J. Fasco, P. P. Dymerski, J. D. Wass, L. S. Kaminsky, **J. Med. Chem., 21**, 1054-59, (1978).

8. C. R. Wheeler, W. F. Trager., **J. Med. Chem., 22,** 1122-1124, (1979).

9. D. S. Hewich, J. Mc. Feven., **J. Phar. Pharmacol., 25,** 458, (1973).

10. P. Bravo, C. Ticozzi., **Synthesis.,** 894, (1985).

11. M. A. Stahmann, L. H. Graf, C. F. Huebner, S. Rosemaan, K. P. Link, **J. Am. chem. Soc., 66,** 900, (1944).

12. M. Ikawa, M. Stahmann, K. P. Link., **J. Am. Chem. Soc., 66,** 902- 906, (1944).

13. M. A. Hermudson, W. M. Baker, L. P. Link, **J. Med. Chem., 14,** 167, (1971).

14. M. J. Fasco, L. J. Piper, L. S. Kaminsky, **J. Chromatogr., 131,** 365, (1977).

15. C. E. Cook, R. Tallent, N. H. Ballentine, G. F. Taylor, J. A. Kepler, **J. Label. Comp. Radiopharm., 16,** 623, (1979).

16. E. Bush, W. F. Trager, **J. Pharm. Sci., 72,** 389, (1983).