

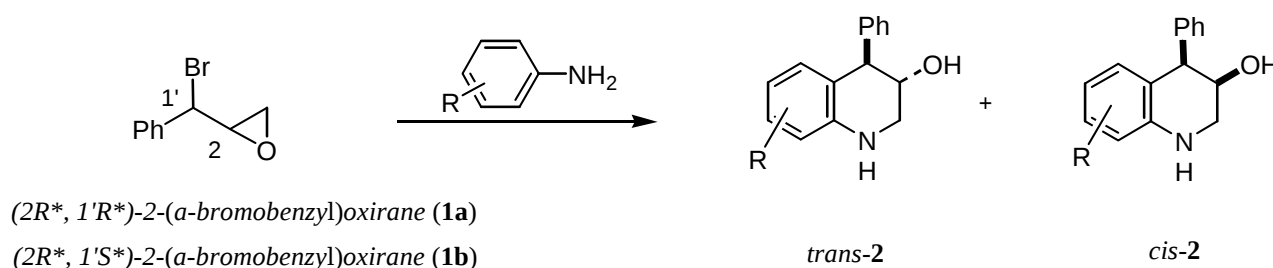
A NEW SYNTHESIS OF 4-PHENYLQUINOLINES BY REACTION OF 2-(α -BROMOBENZYL)OXIRANES WITH ANILINE DERIVATIVES

Michinori Karikomi, Hiroshi Tsukada, and Takashi Toda,*

Department of Applied Chemistry, Faculty of Engineering,
Utsunomiya University, Yoto7-1-2, Utsunomiya 321-8585, Japan

Abstract- Several 4-phenylquinoline derivatives were synthesized by reaction of (2*R**,1'*R**)-2-(α -bromobenzyl)oxiranes (**1a**) with aniline derivatives, and the following treatment of the formed 3-hydroxy-4-phenyl-1,2,3,4-tetrahydroquinolines (**2**) with the Rydon reagent, and potassium *t*-butoxide and air oxidation.

Quinolines are interesting as biologically active compounds;¹ especially in connection with the synthesis of marine-derived alkaloids,² there is increasing interest in methods for synthesis of pyridoacridines and pyridoacridones. 4-Arylquinolines and 4-aryl-1,2,3,4-tetrahydroquinolines are a good starting material for synthesis of these marine-derived alkaloids.³ Therefore, if we could find a simple synthetic method of 4-arylquinolines, synthesis of this alkaloid family should be achieved successfully. In this communication, we report a novel stereoselective synthesis of 1,2,3,4-tetrahydroquinolines (**2**) and their aromatization sequence to 4-phenylquinolines.



In one of our previous studies, the reaction of (2*R**,1'*R**)-2-(α -bromobenzyl)oxirane (**1a**) with aliphatic primary amines afforded *trans*-2-phenyl-3-hydroxyazetidines in good to excellent yields.⁴

In the course of this study, we found that the reaction of **1a** with aromatic amines gave *trans*-3-hydroxy-4-phenyl-1,2,3,4-tetrahydroquinolines (**2**). On the other hand, (2*R**,1'*S**)-2-(α -bromobenzyl)oxirane (**1b**), which is diastereomer of **1a**, gave the corresponding *cis*-2, selectively.⁵ The stereochemical outcome suggested that the ring closure proceeds with inversion at the benzyl carbon.

Generally, Friedel-Crafts type alkylation has long been pointed out to proceed with almost complete racemization when an optically active alkylating reagent was used.⁶ To our knowledge, few studies of stereospecific electrophilic substitution reaction on arenes with no catalytic procedure have been reported.^{7, 8}

When (2*R**,1'*R**)-2-(α -bromobenzyl)oxirane (**1a**) was treated with 2.0 equiv of aniline derivatives in methanol, *trans*-3-hydroxy-4-phenyl-1,2,3,4-tetrahydroquinoline derivatives (**2a**) were obtained (Method A). However, the results of method A are not satisfactory, because the reaction takes longer and gives low yields.

Recently, rare earth triflates have been used as activating reagents of oxiranes.⁹ Addition of 0.1 equiv of Yb(OTf)₃ to the above reaction system in methylene chloride solution (Method B)¹⁰ greatly improved the results: increasing yields of **2a** and saving reaction time. The results are shown in the Table 1.

Table 1. Synthesis of *trans*-4-Phenyl-1,2,3,4-tetrahydroquinolines (**2a**, **2c-2l**) by reactions of (2*R**, 1'*R**)-2-(α -bromobenzyl)oxirane (**1a**) with various aniline derivatives.

Entry	Amine	Method ^a	Solvent	Temp/°C	Time/h	Product (Yield/% ^b)
1	aniline	A	MeOH	rt	33	2a (40)
2	aniline	B	CH ₂ Cl ₂	rt	0.5	2a (43)
3	<i>o</i> -anisidine	A	MeOH	50	33	2c (8-MeO) (60)
4	<i>o</i> -anisidine	B	CH ₂ Cl ₂	rt	12	2c (8-MeO) (61)
5	<i>m</i> -anisidine	A	MeOH	rt	46	2d (7-MeO) (29 ^c)
6	<i>m</i> -anisidine	B	CH ₂ Cl ₂	rt	1	2d (7-MeO)(15), 2e (5-MeO) (48)
7	<i>p</i> -anisidine	A	MeOH	rt	48	2f (6-MeO) (29)
8	<i>p</i> -anisidine	B	CH ₂ Cl ₂	rt	1.5	2f (6-MeO) (42)
9	<i>o</i> -toluidine	A	MeOH	rt	1	2g (8-Me) (51)
10	<i>o</i> -toluidine	B	CH ₂ Cl ₂	rt	1	2g (8-Me) (51)
11	<i>m</i> -toluidine	B	CH ₂ Cl ₂	rt	1	2h (7-Me)(14), 2i (5-Me) (29)
12	<i>p</i> -toluidine	B	CH ₂ Cl ₂	rt	1	2j (6-Me) (56)
13	2-MeO-5-Me-aniline	B	CH ₂ Cl ₂	rt	1	2k (8-MeO-5-Me) (47)
14	2-MeO-5-Cl-aniline	B	CH ₂ Cl ₂	rt	1	2l (8-MeO-5-Cl) (49)

^aSee text. ^bYield was determined by ¹H NMR. Isolation procedure, see note 10. ^cYield of 7-substituted **2**.

The formation of 5-substituted **2** was negligible.

The stereochemistry of *trans*- and *cis*-isomers of **2a** and **2b** was confirmed by comparison of their ¹H NMR spectral data: mainly coupling constants of the protons at the 2, 3, and 4 positions, and nOe relations with the *ortho* protons of the 4-phenyl group and the above protons. Therefore, this reaction provides a

stereoselective synthesis of 3-hydroxy-4-phenyl-1,2,3,4-tetrahydroquinolines (**2**).

Aromatisation of the tetrahydro moiety of **2** was achieved by treatment of **2** with the Rydon reagents (PPh_3 in CCl_4), and following dehydrochlorination with air oxidation of the formed 3-chloro-4-phenyl-1,2,3,4-tetrahydroquinolines in the presence of $t\text{-BuOK}$ in $t\text{-BuOH}$. The yields of 4-phenylquinoline derivatives are excellent. The results are shown in the Table 2.

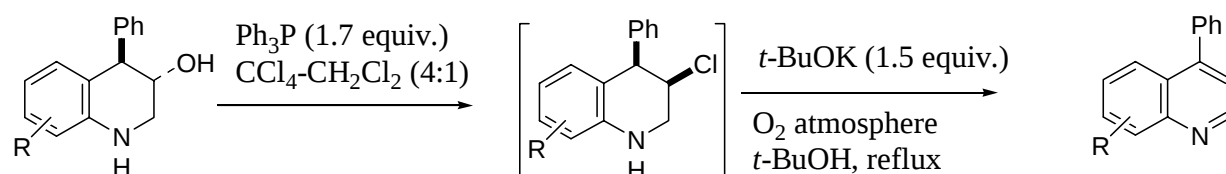


Table 2. Synthesis of 4-Phenylquinolines

Entry	Substrate/R	Time / h	mp / °C	Yield (%) ^b
1	2a (H)	6	227-230 ^a	86 ¹¹
2	2j (6-Me)	4	219-222 ^a	82 ¹¹
3	2h (7-Me)	6	227-231 ^a	83
4	2d (7-MeO)	6	250-253 ^a	88 ¹²
5	2c (8-MeO)	4	114-115	81
6	2k (8-MeO-5-Me)	18	152-153	77
7	2l (8-MeO-5-Cl)	4	131-134	73

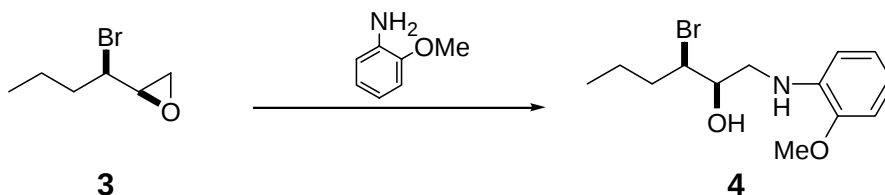
^a Isolated as the picrate. ^b Yields were based on the 1,2,3,4-tetrahydroquinolines.

The starting (2*R**,1'*R**)-2-(α -bromobenzyl)oxirane (**1a**) is readily available by a two-step reaction of *trans*-cinnamyl alcohol in good yield.¹³ Thus, our method is a most simple synthesis of 4-phenyl-1,2,3,4-tetrahydroquinolines and 4-phenylquinolines under mild conditions.

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5. The reaction of **1b** with *p*-anisidine gave a mixture of *cis*- and *trans*-isomers of **2** in 29% yield (*cis* : *trans* = 85 : 15).

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8. The unique feature of this reaction is the ring closure process between the aromatic carbon and benzyl bromide carbon. When (2*R**,1'*R*'*)-2-(α -bromobutyl)oxirane (**3**) was treated with *o*-anisidine under Method B conditions, only 1-(*o*-methoxyphenyl)amino-3-bromo-2-hydroxyheptane (**4**) was obtained. Accordingly, the formation of tetrahydroquinolines (**2**) could be recognized as an intramolecular S_N2 type ring closure reaction that took place between the activated aromatic moiety and the benzyl bromide carbon.



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10. General procedure (Method B): An aniline derivative (2.0 mmol) was added to a solution of 2-(α -bromobenzyl)oxirane (**1a**) (213 mg, 1.0 mmol) and Yb(OTf)₃ (62 mg, 0.1 mmol) in dichloromethane. The mixture was stirred at rt for the indicated period (see Table 1), then poured into aqueous 1*N*-NaOH (2 mL). The solution was filtrated onto celite. The aqueous solution was extracted three times with dichloromethane (50 mL), and the combined organic extracts were dried (Na₂SO₄). After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by silica gel column chromatography eluting with hexane/AcOEt (4:1) and recrystallisation from acetone to give **2**. The crude product was also used for the determination of the yield. The integration of 5-H of **2** at ¹H NMR can estimate the formation of **2** by using coumarin as an internal standard.
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