HETEROCYCLES, Vol. 55, No. 7, 2001, pp. 1249 - 1252, Received, 26th April, 2001

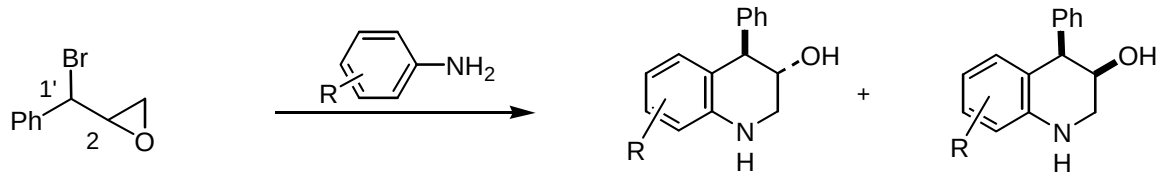
A NEW SYNTHESIS OF 4-PHENYLQUINOLINES BY REACTION OF 2-(α-BROMOBENZYL)OXIRANES WITH ANILINE DERIVATIVES

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-tetrahydro-quinolines (**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-tarahydroquinolines 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.



(2R, 1'R*)-2-*(*a-bromobenzyl*)*oxirane* (**1a**)
(2R, 1'S*)-2-*(*a-bromobenzyl*)*oxirane* (**1b**)

trans-**2**

cis-**2**

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 proceeded 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_2Cl_2	rt	0.5	**2a** (43)
3	*o*-anisidine	A	MeOH	50	33	**2c** (8-MeO) (60)
4	*o*-anisidine	B	CH_2Cl_2	rt	12	**2c** (8-MeO) (61)
5	*m*-anisidine	A	MeOH	rt	46	**2d** (7-MeO) (29 [c])
6	*m*-anisidine	B	CH_2Cl_2	rt	1	**2d**(7-MeO)(15), **2e**(5-MeO) (48)
7	*p*-anisidine	A	MeOH	rt	48	**2f** (6-MeO) (29)
8	*p*-anisidine	B	CH_2Cl_2	rt	1.5	**2f** (6-MeO) (42)
9	*o*-toluidine	A	MeOH	rt	1	**2g** (8-Me) (51)
10	*o*-toluidine	B	CH_2Cl_2	rt	1	**2g** (8-Me) (51)
11	*m*-toluidine	B	CH_2Cl_2	rt	1	**2h**(7-Me)(14), **2i** (5-Me) (29)
12	*p*-toluidine	B	CH_2Cl_2	rt	1	**2j** (6-Me) (56)
13	2-MeO-5-Me-aniline	B	CH_2Cl_2	rt	1	**2k** (8-MeO-5-Me) (47)
14	2-MeO-5-Cl-aniline	B	CH_2Cl_2	rt	1	**2l** (8-MeO-5-Cl) (49)

[a] See text. [b] Yield was determined by ^{1}H NMR. Isolation procedure, see note 10. [c] Yield 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 ^{1}H 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*-BuOK in *t*-BuOH. The yields of 4-phenylquinoline derivatives are excellent. The results are shown in the Table 2.

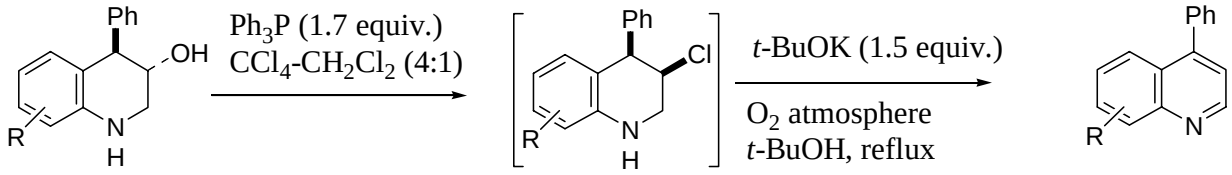


Table 2. Synthesis of 4-Phenylquinolines

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

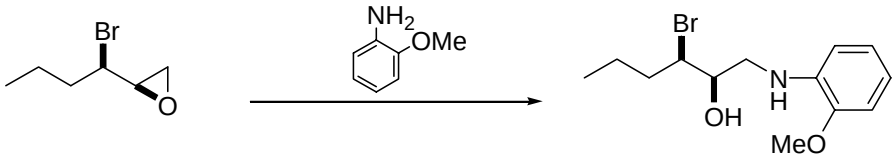
[a] Isolated as the picrate. [b] Yields were based on the 1,2,3,4-tetrahydroquinolines.

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.

REFERENCES

1. J. A. Joule, K. Mills, and G. F. Smith, *'Heterocyclic Chemistry 3rd ed.'*, Chapman & Hall, 1995, pp. 120-121; A. R. Katritzky, S. Rachwal, and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031.
2. T. F. Molinski, *Chem. Rev*., 1993, **93**, 1825.
3. A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc*., 1988, **110**, 4051.
4. T. Toda, M. Karikomi, M. Oshima, and M. Yoshida, *Heterocycles*, 1992, **33**, 511.
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).

6. O. Piccolo, F. Spreafico, G. Visentin, and E. Valoti, *J. Org. Chem*., 1985, **50**, 3945 and references cited therein.
7. O. Piccolo, U. Azzena, G. Melloni, G. Delogu, and E. Valoti, *J. Org. Chem*., 1991, **56**, 183; F. Effenberger and T. Weber, *Angew. Chem., Int. Ed. Engl*., 1987, **26**, 142.
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 intramoleculer S_N2 type ring closure reaction that took place between the activated aromatic moiety and the benzyl bromide carbon.



3 **4**

9. M. Chini, P. Crotti, L. Favero, and M. Pireschi, *Tetrahedron Lett*., 1994, **35**, 433.
10. General procedure (Method B): An aniline derivative (2.0 mmol) was added to a solution of 2-(α-bomobenzyl)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 1N-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 (Na_2SO_4). 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 ^{1}H NMR can estimate the formation of **2** by using coumarin as an internal standard.
11. B. I. Ardashev and B. A. Tertov, *Zh. Obshch. Khim*., 26, 218; *J. Gen. Chem. U.S.S.R*., 1956, **26**, 233. (Engl. transl.)(*Chem. Abstr*., 1956, **50**, 13926i).
12. B. D. Tileak, T. Ravindoranathan, and K. N. Subbaswami, *Indian J. Chem*., 1968, **6**, 422 (*Chem. Abstr*., 1969, **70**, 37630b).
13. M. Yoshida, T. Hide, M. Oshima, and T. Toda, *Heterocycles*, 1992, **33**, 507.