Tetrahedron Letters 53 (2012) 4332–4336

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Studies on rotational barriers of N–C axially chiral compounds: increase in the rotational barrier by aromatization

Naomi Suzumura [a], Masato Kageyama [a], Daichi Kamimura [a], Takahiro Inagaki [a], Yasuo Dobashi [b], Hiroshi Hasegawa [b], Haruhiko Fukaya [b], Osamu Kitagawa [a,*]

[a] Department of Applied Chemistry, Shibaura Institute of Technology, 3-7-5 Toyosu, Kohto-ku, Tokyo 135-8548, Japan
[b] School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

ARTICLE INFO

Article history:
Received 7 May 2012
Revised 31 May 2012
Accepted 4 June 2012
Available online 12 June 2012

Keywords:
Axially chiral
Aromatization
Quinolinone
Quinazolinone
Rotational barrier

ABSTRACT

The rotational barriers in axially chiral quinolin-2-one and quinazolin-2-one possessing *N*-(*ortho*-*tert*-butyl)phenyl group were found to significantly increase in comparison with those of corresponding dihydroquinolin-2-one and dihydroquinazolin-2-one. Analysis of transition state structure during N–Ar bond rotation based on DFT calculation indicates that the increase in the rotational barrier is due to considerable distortion of the nitrogen-containing heterocyclic part.

Recently, atropisomeric compounds with an N–C chiral axis have received much attention as novel chiral molecules. Various N–C axially chiral compounds such as **I**–**VI** owing to rotational restriction around an N–Ar bond have been reported to date (Fig. 1).[1–8] Almost all the N–C axially chiral compounds have *ortho*-substituted aniline skeletons as a common structure, and it is well known that their stabilities (rotational barrier around a chiral axis) strongly depend on the bulkiness of the *ortho*-substituent. For example, although *ortho*-*tert*-butylanilides **IA** and *N*-(2-*tert*-butylphenyl)imides **IIA** are stable atropisomeric compounds having high rotational barriers ($\Delta G^{\neq}$ = 28–30 kcal/mol),[2] in their *ortho*-methyl derivatives **IB** and **IIB**, the rotation around the N–Ar bond easily occurs at RT ($\Delta G^{\neq}$ = 19–20 kcal/mol).[1g,m,2b,f] On the other hand, a considerable number of stable atropisomeric compounds having an *ortho*-methyl group such as **III**–**VI**[1b-d,11] have been also known ($\Delta G^{\neq} \simeq$ 30 kcal/mol).[3] However, there has been no report on the origin of the remarkable difference of the rotational barrier between **IB**–**IIB** and **III**–**VI**. In general, the relationship between the structure and the atropisomerism in N–C axially chiral compounds has not been investigated in detail to date.[4]

The elucidation of the factor, which influences the rotational barrier around an N–C chiral axis, is important from the viewpoint of not only atropisomeric chemistry but also medicinal chemistry, because aromatic heterocycles possessing an *N*-(*ortho*-substituted)phenyl group such as **III** (methaqulone: a sedative-hypnotic

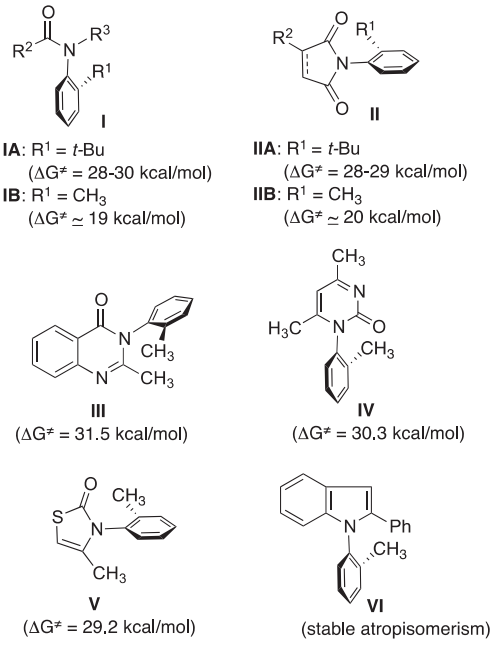


Figure 1. Various N–C axially chiral compounds.

* Corresponding author. Tel.: +81 3 5859 8161; fax: +81 3 5859 8101.
E-mail address: kitagawa@shibaura-it.ac.jp (O. Kitagawa).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.06.007

drug) frequently have strong pharmacological activity, and the activities differ significantly between enantiomers due to an axial chirality.[1c,k,5] In connection with our previous study on N–C axially chiral chemistry,[2c,6,7] we had an interest in elucidating the unknown factor which brings about an increase in the rotational barrier.

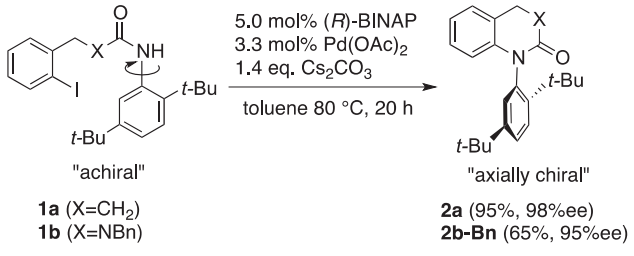
In this Letter, we report on the notable relationship between the aromatic structure and the rotational barrier in N–C axially chiral compounds. Namely, we found that the rotational barrier around an N–C chiral axis significantly increases by the aromatization (the conversion to the corresponding aromatic compounds). The origin of increase in the rotational barrier based on DFT calculation is also described.

After a detailed survey of the literature on N–C axially chiral compounds, we noticed that most of the stable atropisomeric compounds possessing a small substituent at the *ortho*-position are nitrogen-containing aromatic heterocycles.[3] That is, in stable atropisomeric compounds **III**–**VI**, the nitrogen atom of the chiral axis is contained in the aromatic skeleton such as quinazolinone, pyrimidinone, thiazolone, and indole (the lone pair on nitrogen of **III**–**VI** contributes to aromaticity), while the nitrogen of the achiral **IB** and **IIB** exists in the non-aromatic part. These may indicate that aromatic structure plays an important role on the atropisomerism in N–C axially chiral compounds.

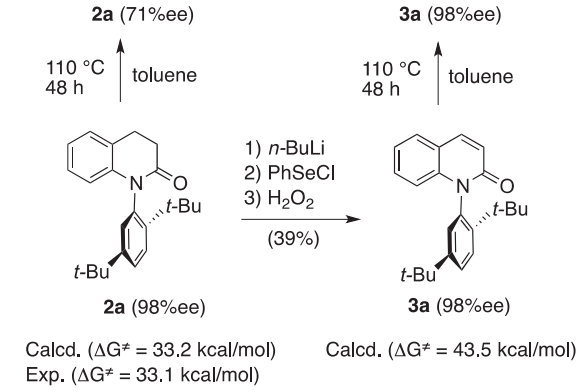
Meanwhile, since the steric circumstances between **IB**–**IIB** and **III**–**VI** are remarkably different, it would not be possible to deny the contribution of the steric factor on the rotational barrier (steric repulsion during N–Ar bond rotation). To clarify the contribution of aromatic skeleton, a comparison of the rotational barriers of aromatic and non-aromatic compounds having similar steric circumstances is required.

We previously reported on the highly enantioselective synthesis of atropisomeric 1-(2,5-di-*tert*-buthyphenyl)dihydroquinolin-2-one **2a** (98%ee) and 1-(2,5-di-*tert*-buthyphenyl)-3-benzyl-dihydroquinazolin-2-one **2b-Bn** (95%ee) through (R)-BINAP-$Pd(OAc)_2$ catalyzed intramolecular Buchwald-Hartwig amination (Scheme 1).[7] Firstly, we investigated the conversion of **2a** and **2b-Bn** to the aromatic versions **3a** and **3b**. Quinolin-2-one **3a** (98%ee) and quinazolin-2-one **3b** (95%ee) were prepared without racemization through the conversion shown in Schemes 2 and 3, respectively. It was expected that the contribution of aromatic structure on the rotational barrier should be clarified by the comparison of the rotational barriers between **2a** and **3a** (**2b** and **3b**) because the steric circumstances of **3a** (**3b**) are very similar to that of **2a** (**2b**).

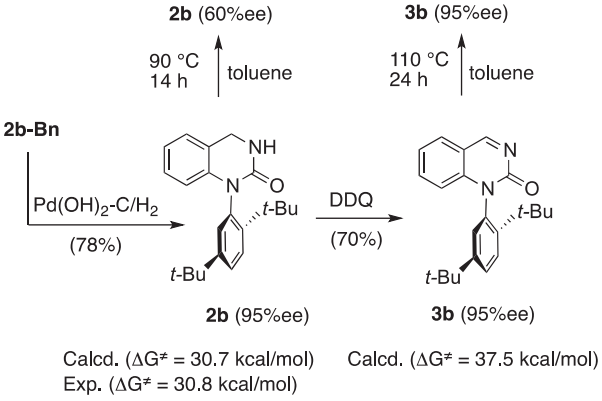
Thermal isomerization with **2a** (98%ee) having a non-aromatic lactam part and aromatic quinolin-2-one **3a** (98%ee) was performed under toluene reflux conditions (Scheme 2). After 48 h, the ee of **2a** was reduced by 71%ee, and the rotational barrier of **2a** was estimated to be 33.1 kcal/mol (at 110 °C) by Eyring plot ($t_{1/2}$ = 98 h at 110 °C).[9] Under the same conditions, with **3a**, a detectable change of the ee was not observed. Since the rotational barrier of **3a** was difficult to estimate by a thermal isomerization



Scheme 1. Highly enantioselective synthesis of atropisomeric compounds **2a** and **2b-Bn**.



Scheme 2. The conversion to **3a** and rotational barriers of **2a** and **3a**.



Scheme 3. The conversion to **3b** and rotational barriers of **2b** and **3b**.

experiment (further heating resulted in the decomposition of **3a**), the estimation based on DFT calculation was investigated.[10] The $\Delta G^{\neq}$ values of **2a** and **3a**, which were calculated at the B3LYP/6-31G(d) level, were 33.2 and 43.5 kcal/mol (at 110 °C), respectively. The calculated $\Delta G^{\neq}$ value (33.2 kcal/mol) of **2a** was almost the same as the experimental $\Delta G^{\neq}$ value (33.1 kcal/mol), and this indicates the high reliability of the present DFT method. In addition, it should be noted that the $\Delta G^{\neq}$ value of **3a** dramatically increases in comparison with that of **2a** (more than 10 kcal/mol).

Similar results were also obtained in the case of dihydroquinazolin-2-one **2b** and quinazolin-2-one **3b**. That is, after heating for 14 h at 90 °C in toluene, the ee of **2b** was reduced by 60% from 95%, while the ee of **3b** was not changed even after 24 h under toluene reflux conditions (Scheme 3). The $\Delta G^{\neq}$ value of **2a** based on Eyring plot was 30.7 kcal/mol (at 110 °C, $t_{1/2}$ = 4.3 h at 110 °C).[11] The DFT calculations of **2b** and **3b** were subsequently performed, and these $\Delta G^{\neq}$ values were calculated to be 30.8 and 37.5 kcal/mol (at 110 °C), respectively.[10] Similar to the case of **2a** and **3a**, the $\Delta G^{\neq}$ value of **3b** remarkably increased in comparison with that of **2b** (6.8 kcal/mol).

Thus, it was found that the rotational barrier of N–C axially chiral compounds significantly increased by the conversion to the corresponding aromatic compounds. To elucidate the origin of the increase in the rotational barrier by the aromatization, X-ray crystallography of dihydroquinolinone **2a** and quinolinone **3a** was investigated. Unfortunately, since a good single crystal of **2a** was not obtained, the crystal structure of the α-methylated derivative **2a-Me**,[12] which has a similar rotational barrier to **2a**, was compared with that of **3a** (Fig. 2).[13]

In both compounds **3a** and **2a-Me**, the 2,5-di-*tert*-butylphenyl group is perpendicular toward the quinolinone ring (<C2-N1-C1′-C2′ = −95.8° and −95.9°), and understandably, each amide part

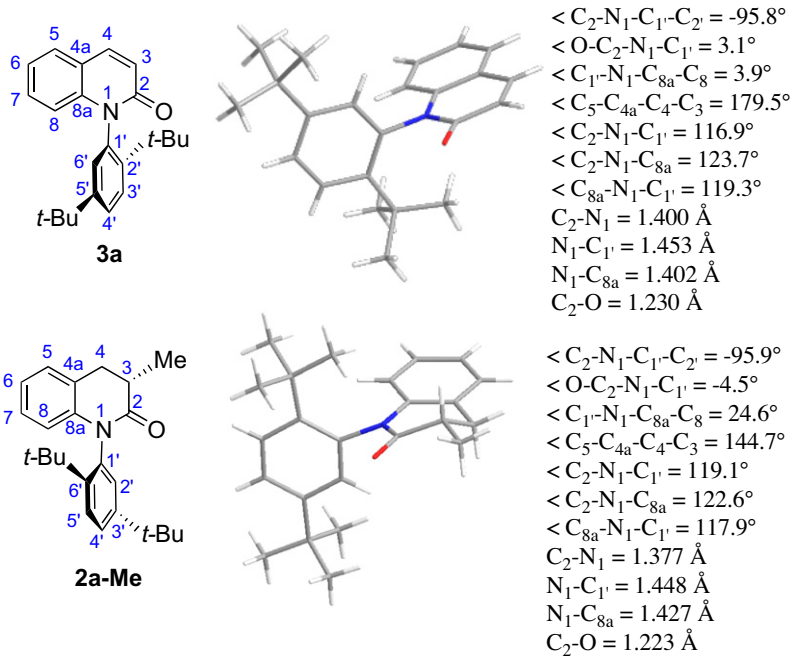


Figure 2. X-ray crystal structures of **3a** and **2a-Me**.

has almost a planar structure (<O-C2-N1-C1′ = 3.1° and −4.5°). On the bond lengths of the carbonyl group (C–O) and the chiral axis (N-C1′), the sp^2 character of the nitrogen atom, and the three bond angles around the nitrogen atom (<C8a-N1-C1′, <C2-N1-C1′, <C2-N1-C8a), significant difference between **3a** and **2a-Me** was not observed. Although it was found that the amide C–N bond (C2-N1) of **3a** is slightly longer (0.023 Å) than that of **2a-Me** and the N1-C8a bond distance of **3a** is shorter (0.025 Å) in comparison with that of **2a-Me**, the high rotational barrier of **3a** cannot be rationalized on the basis of the differences of these bond lengths.

On the other hand, in the crystal structure of **2a-Me**, a slight distortion of the amide part from the benzene plane was found (<C1′-N1-C8a-C8 = 24.6°), while in aromatic **3a**, the benzene and lactam rings are almost on the co-planar (<C1′-N1-C8a-C8 = 3.9°). The distorted structure of **2a-Me** may alleviate the steric repulsion between *ortho*-substituent (C2′-H or *ortho*-*t*Bu group) and C8-hydrogen during the N–Ar bond rotation to lead to a decrease in the rotational barrier in comparison with planar compounds **3a**.

However, it is still unclear that such a slight distortion in the ground state is the primary factor for the remarkable difference of the rotational barrier between **2a** and **3a**. Therefore, we considered the structure of the transition state during the N–Ar bond rotation by DFT method.[10] The structures of the ground state and transition state of **2a**, which was estimated by DFT, are shown in Figure 3. The calculated ground state structure is similar to the crystal structure of **2a-Me**.

As the transition state structures during the N–Ar bond rotation in **2a**, **TS-2a** or **TS-2A** through the rotation of the *ortho*-*tert*-butyl group toward the carbonyl group or benzene C8 sides, should be possible. DFT calculation indicates that the rotation proceeds via **TS-2a** but not **TS-2A** because **TS-2A** has an extremely high activation energy in comparison with **TS-2a** (the steric repulsion between the C8-hydrogen and the *ortho*-*tert*-butyl group in **TS-2A** may be stronger than that between the carbonyl oxygen and the *ortho*-*tert*-butyl group in **TS-2a**).

In **TS-2a** having almost a parallel 2,5-di-*tert*-butylphenyl group toward the dihydroquinolinone ring (<C2-N1-C1′-C2′ = −1.3°), considerable changes on bond distances and angles around the nitrogen atom were found. Namely, the C2-N1 and the N1-C8a bonds are elongated (0.034 Å and 0.027 Å), and the <C2-N1-C1′ increase by 14.6° while <C2-N1-C8a decrease by 15.2° from the ground state conformer [the bond length of chiral axis (N1-C1′) and <C8a-N1-C1′ hardly change]. In addition, it should be noteworthy that remarkable distortion from planarity of amide part was found (<O-C2-N1-C1′ = −41.9°, sp^2 character of amide nitrogen is maintained in the transition state).[14] These structural changes may lead to alleviation of the steric repulsion between the carbonyl oxygen and the bulky *ortho*-*tert*-butyl group.

Such changes were also observed in the case of quinolinone **3a** (Fig. 4). The transition state structure **TS-3a** estimated by DFT method indicates the considerable distortion of the amide part, increase in the bond lengths (C2-N1, N1-C8a) and bond angle (<C2-N1-C1′), and decrease in <C2-N1-C8a in comparison with the ground state structure. Furthermore, in **TS-3a**, the benzene and lactam rings were found to be not on the co-planar (<C5-C4a-C4-C3 = 159.3°).

We especially focused on the remarkable distortion of the unsaturated lactam part in **TS-3a** (the twisting of the amide bond and the distortion of the lactam ring from the benzene). Such distortion in rigid aromatic lactam **3a** would bring about the larger strain energy in comparison with that in flexible non-aromatic lactam **2a** as well as the decrease in the aromatic stabilization energy. Hence, the rotational barrier of **3a** may significantly increase more than that of **2a**.

The transition state structures **TS-2b** and **TS-3b** during N–Ar bond rotation of dihydroquinazolin-2-one **2b** and quinazolin-2-one **3b** by DFT method are shown in Figure 5. Similar to **TS-2a** and **TS-3a**, in **TS-2b** and **TS-3b**, a remarkable distortion of the amide part is caused (<O-C2-N1-C1′: **TS-2b**; 50.9°, **TS-3b**; −50.7°). Furthermore, in **TS-3b**, the distortion of the pyrimidinone ring from the benzene plane was also found (<C5-C4a-C4-N3 = 159.2°). Since **TS-3b** may bring about more significant destabilization than **TS-2b** by an increase in the strain energy and a decrease in the aromatic stabilization energy, the rotational barrier of **3b** considerably increases in comparison with that of **2b**.

In conclusion, we found that aromatic structure brings about a remarkable increase in the rotational barrier of N–C axially chiral compounds. Furthermore, through the analysis of the transition

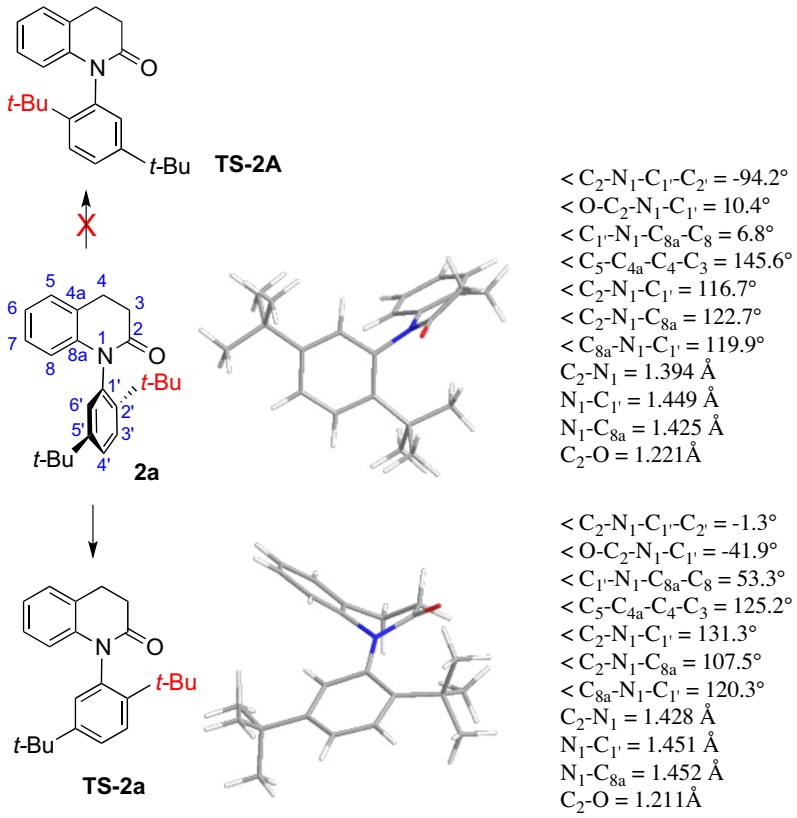


Figure 3. The ground state and transition state structures during N–Ar bond rotation of **2a** on the basis of DFT calculation.

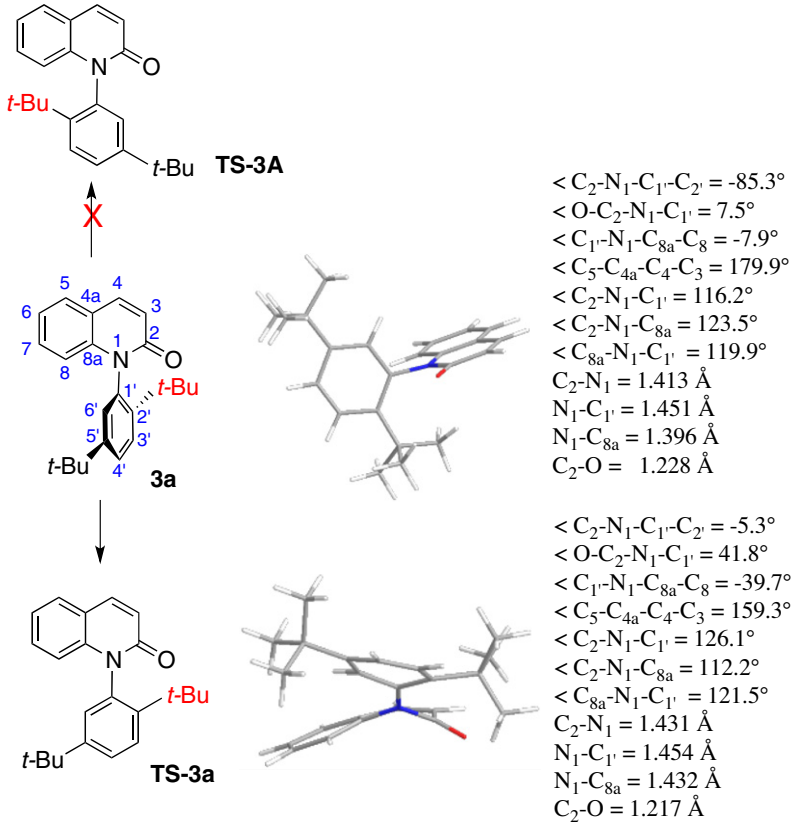


Figure 4. The ground state and transition state structures during the N–Ar bond rotation of **3a** on the basis of DFT calculation.

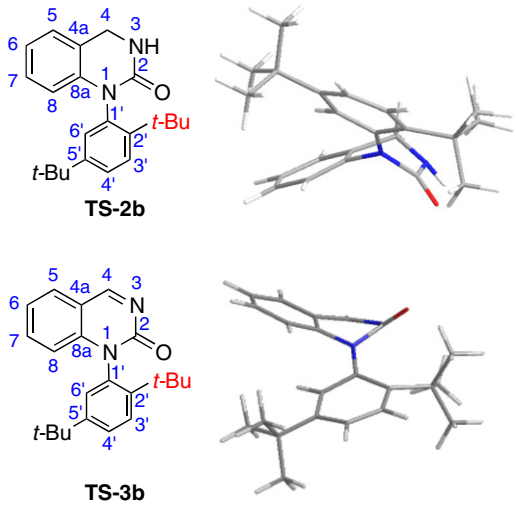


Figure 5. The transition state structures **TS-2b** and **TS-3b** during N–Ar bond rotation of **2b** and **3b** on the basis of DFT calculation.

state structure during the N–Ar bond rotation based on DFT calculation, the origin of increase in the rotational barrier of aromatic compounds was strongly suggested to be due to the significant twisting of the nitrogen-containing heterocyclic part. This result indicates that in aromatic heterocycles possessing an *ortho*-substituted phenyl group on the nitrogen atom, there is a high possibility of having stable axial chirality. In addition, this knowledge is important from the viewpoint of not only N–C axially chiral chemistry but also medicinal chemistry, because aromatic heterocycles possessing an N-(*ortho*-substituted)phenyl group frequently have strong pharmacological activity.

Acknowledgments

This work was partly supported by a Grant-in-Aid (C22590015) for Scientific Research and the Ministry of Education, Science, Sports, and Culture of Japan.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.007.

References and notes

1. Typical examples of atropisomeric compounds having an N–C chiral axis: (a) Bock, L. H.; Adams, R. *J. Am. Chem. Soc.* **1931**, *53*, 374; (b) Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1599; (c) Mannschreck, A.; Koller, H.; Stühler, G.; Davis, M. A.; Traber, J. *Eur. J. Med. Chem. Chim. Ther.* **1984**, *19*, 381; (d) Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076; (e) Kawamoto, T.; Tomishima, M.; Yoneda, F.; Hayami, J. *Tetrahedron Lett.* **1992**, *33*, 3169; (f) Dai, X.; Wong, A.; Virgil, S. C. *J. Org. Chem.* **1998**, *63*, 2597; (g) Curran, D. P.; Liu, W.; Chen, C. H. *J. Am. Chem. Soc.* **1999**, *121*, 11012; (h) Hata, T.; Koide, H.; Taniguchi, N.; Uemura, M. *Org. Lett.* **2000**, *2*, 1907; (i) Shimizu, K. D.; Freyer, H. O.; Adams, R. D. *Tetrahedron Lett.* **2000**, *41*, 5431; (j) Tetrahedron Symposium-in-print on Axially Chiral Amides (Atropisomerism), J. Clayden, (Ed.), *Tetrahedron*, **2004**, *60*, 4325–4558.; (k) Tokitoh, T.; Kobayashi, T.; Nakada, E.; Inoue, T.; Yokoshima, S.; Takahashi, H.; Natsugari, H. *Heterocycles* **2006**, *70*, 93; (l) Kamikawa, K.; Kinoshita, S.; Furusyo, M.; Takemoto, S.; Matsuzaka, H.; Uemura, M. *J. Org. Chem.* **2007**, *72*, 3394; (m) Yilmaz, E. M.; Dogan, I. *Tetrahedron Asymmetry* **2008**, *19*, 2184.
2. Typical papers on atropisomeric *ortho-tert*-butylanilides: (a) Curran, D. P.; Qi, H.; Geib, S. J.; DeMello, N. C. *J. Am. Chem. Soc.* **1994**, *116*, 3131; (b) Kishikawa, K.; Tsuru, I.; Kohomoto, S.; Yamamoto, M.; Yamada, K. *Chem. Lett.* **1994**, 1605; (c) Kitagawa, O.; Izawa, H.; Sato, K.; Dobashi, A.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **1998**, *63*, 2634; (d) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295; (e) Bach, T.; Schröder, J.; Harms, K. *Tetrahedron Lett.* **1999**, *40*, 9003; (f) Curran, D. P.; Geib, S.; Demello, N. *Tetrahedron* **1999**, *55*, 5681; (g) Kondo, K.; Iida, T.; Fujita, H.; Suzuki, T.; Yamaguchi, K.; Murakami, Y. *Tetrahedron* **2000**, *56*, 8883; (h) Dantale, S.; Reboul, V.; Metzner, P.; Philouze, C. *Chem. Eur. J.* **2002**, *8*, 632; (i) Bennett, D. J.; Blake, A. J.; Cooke, P. A.; Godfrey, R. A.; Pickering, P. L.; Simpkins, N. S.; Walker, M. D.; Wilson, C. *Tetrahedron* **2004**, *60*, 4491.
3. In addition to **III**–**VI**, other stable N–C axially chiral aromatic heterocycles (quinolin-2-one and pyridin-2-one) having an *N*-(*ortho*-methyl)phenyl group have also been reported. (a) Mintas, M.; Mihaljevic, V.; Koller, H.; Schuster, D.; Mannschreck, A. *J. Chem. Perkin Trans. 2* **1990**, 619; (b) Sakamoto, M.; Utsumi, N.; Ando, M.; Seki, M.; Mino, T.; Fujita, T.; Katoh, A.; Nishino, T.; Kashima, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4360; (c) Tanaka, K.; Takahashi, Y.; Suda, T.; Hirano, M. *Synlett* **2008**, 1724. See also Ref. 1l..
4. In the course of study on atropisomeric lactams, we previously reported that the ring size of lactam considerably influences the stability of the atropisomerism. That is, a six-membered ring lactam possessing larger bond angle (<CO-N-C = 124.1°) was found to have a higher rotational barrier than a five-membered ring lactam possessing a smaller bond angle (<CO-N-C = 112.1°). However, a remarkable difference of the rotational barrier between imide **IIB** [1m,2b,f] and thiazol-2-one **V**[1d] having a five-membered ring structure cannot be rationalized on the basis of such bond angle. Kitagawa, O.; Fujita, M.; Kohriyama, M.; Hasegawa, H.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 8539.
5. Reviews on medicinal drugs having atropisomeric structure (a) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398; (b) LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005.
6. (a) Kitagawa, O.; Hirotaka, H.; Dobashi, A.; Taguchi, T.; Shiro, M. *Tetrahedron Lett.* **1997**, *38*, 4447; (b) Kitagawa, O.; Taguchi, T. *Yuki Gosei Kagaku Kyokaishi* **2001**, *59*, 680; (c) Takahashi, M.; Kitagawa, O. *Yuki Gosei Kagaku Kyokaishi* **2011**, *69*, 985; (d) Ototake, N.; Morimoto, Y.; Mokuya, A.; Fukaya, H.; Shida, Y.; Kitagawa, O. *Chem. Eur. J.* **2010**, *16*, 6752. and references cited therein.
7. (a) Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676; (b) Kitagawa, O.; Yoshikawa, M.; Tanabe, H.; Morita, T.; Takahashi, M.; Dobashi, Y.; Taguchi, T. *J. Am. Chem. Soc.* **2006**, *128*, 12923.
8. Catalytic enantioselective synthesis of N-C axially chiral compounds by other groups (a) Brandes, S.; Bella, M.; Kjoersgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147; (b) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586; (c) Duan, W.; Imazaki, Y.; Shintani, R.; Hayashi, T. *Tetrahedron* **2007**, *63*, 8529; (d) Oppenheimer, J.; Hsung, R. P.; Figueroa, R.; Johnson, W. L. *Org. Lett.* **2007**, *9*, 3969; (e) Clayden, J.; Turner, H. *Tetrahedron Lett.* **2009**, *50*, 3216; (f) Onodera, G.; Suto, M.; Takeuchi, R. *J. Org. Chem.* **2012**, *77*, 908; (g) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916.
9. The rate constants for the racemization of **2a** were measured at three different temperatures (96.0 °C, 103.1 °C, and 109.5 °C) in toluene. These data were subjected to an Eyring plot to determine the rotational barrier (see Supplementary data).
10. DFT calculations at the level of B3LYP1/6-31G(d) were performed by Firefly (PC GAMESS) quantum chemical package (version 7.1.G, Alex A. Granovsky, Firefly version 7.1.G, www http://classic.chem.msu.su/gran/firefly/index.html). All structures were fully optimized and then subjected to the frequency analysis. For the ground state, the absence of the imaginary frequency was confirmed in every case. Transition states relevant to the rotational barrier were identified by the following two criteria: (1) The frequency analysis gave only one imaginary frequency. (2) The exhaustive IRC calculations provided one pair of enantiomeric atropisomers. Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A.; *J. Comput. Chem.* **1993**, *14*, 1347.
11. The rate constants for the racemization of **2b** were measured at four different temperatures (74.4 °C, 82.2 °C, 88.8 °C, and 98.5 °C) in toluene. These data were subjected to an Eyring plot to determine the rotational barrier (see Supplementary data).
12. The crystal structure of **2a-Me**; see Supplementary data in Ref. 7a.
13. CCDC-866228 (**3a**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.com.ac.uk/data_request/cif.
14. Ab initio studies of axially chiral quinazolin-4-one derivatives such as **III** (Fig. 1) have been reported by Sapse and co-workers. The transition state structures during the N–Ar bond rotation estimated by an ab initio calculation with a HF/6-31G* basis set are similar to those shown in Figures 3–5. That is, the considerable distortion of the amide part and an increase in the bond length (C2-N1, N1-C8a) and bond angle (<C2-N1-C1′) were found. However, there has been no previous mention of the relationship between the aromatic structure and the rotational barrier. Azanli, E.; Rothchild, R.; Sapse, A-M. *Spectrosc. Lett.* **2002**, *35*, 257.