JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Atropisomerization in *N*-aryl-2(1*H*)-pyrimidin-(thi)ones: A Ring-Opening/Rotation/Ring-Closure Process in Place of a Classical Rotation around the Pivot Bond

Ennaji Najahi,[‡,§] Nicolas Vanthuyne,[†] Françoise Nepveu,[‡,§] Marion Jean,[†] Ibon Alkorta,[∥] José Elguero,[∥] and Christian Roussel*[,†]

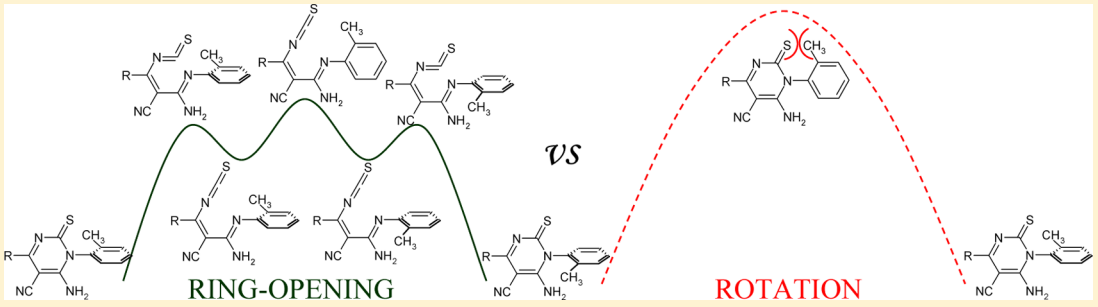
[†]Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, 13397, Marseille, France

[‡]Université de Toulouse, UPS, PHARMA-DEV, UMR 152, 118 Route de Narbonne, 31062 Toulouse cedex 9, France

[§]IRD, UMR 152, 31062 Toulouse cedex 9, France

[∥]Instituto de Quimica Medica (IQM-CSIC), Juan de la Cierva, 3, 28006 Madrid, Spain

Supporting Information



ABSTRACT: Uncatalyzed racemization processes in atropisomeric diphenyl-like frameworks are classically described as the result of the rotation around the pivotal single bond linking two planar frameworks. Severe constraints leading to more or less distorted transition states account for the experimental barrier to atropenantiomerization. In 1988, one of us hypothesized that, in *N*-aryl-2(1*H*)-pyrimidin-(thi)ones, a ring-opening/ring-closure process was contributing to the observed racemization process accounting for the lower barriers in the sulfur analogues than in oxygen analogues. Now, a series of six novel 6-amino-5-cyano-1,4-disubstituted-2(1*H*)-pyrimidinones **5a**−**5f** and two 6-amino-5-cyano-4-*p*-tolyl-1-substituted-2(1*H*)-pyrimidinethiones **6a** and **6b** were synthesized and characterized through spectroscopic and X-ray diffraction studies. Semipreparative HPLC chiral separation was achieved, and enantiomerization barriers were obtained by thermal racemization. The rotational barriers of 6-amino-5-cyano-1-*o*-tolyl-4-*p*-tolyl-2(1*H*)-pyrimidinone (**5b**) and 6-amino-5-cyano-1-(naphthalen-1-yl)-4-*p*-tolyl-2(1*H*)-pyrimidinone (**5e**) were found to be 120.4 and 125.1 kJ·mol^{-1} (*n*-BuOH, 117 °C), respectively, and those of the corresponding thiones were 116.8 and 109.6 kJ·mol^{-1} (EtOH, 78 °C), respectively. DFT calculations of the rotational barriers clearly ruled out the classical rotation around the pivotal bond with distorted transition states in the case of the sulfur derivatives. Instead, the ranking of the experimental barriers (sulfur versus oxygen, and *o*-tolyl versus 1-naphthyl in both series) was nicely reproduced by calculations when the rotation occurred via a ring-opened form in *N*-aryl-2(1*H*)-pyrimidinethiones.

INTRODUCTION

Atropisomerism in *N*-aryl heterocyclic frameworks attracts a lot of interest in the design of new chiral ligands, in a drug's activity, in symmetry breaking, and in the stereochemical outcome of natural products.[1] Since the pioneering work of Bock and Adams, the barriers to rotation in many *N*-aryl axially chiral five- or six-membered heterocycles have been measured,[1−4] and they match with a classical model of rotation around the pivotal bond, which takes into account the steric substitution pattern along the axis to rotation like in substituted biphenyl.[5] Few papers concerning restricted rotation about the carbon−nitrogen single bond in 1-aryl-2(1*H*)-pyrimidin-(thi)-ones have been reported.[6−10] Kashima et al. were the first to isolate enantiomers resulting from atropisomerism in 1-aryl-4,6-dimethyl-2(1*H*)-pyrimidinones. 2′-Methyl derivative **1** was resolved using D-camphor sulfonic acid, and the barrier to rotation was 125.8 kJ·mol^{-1} in MeOH,[6] and 126.1 kJ·mol^{-1} (solvent not specified) (Figure 1).[7] The barriers for 1-aryl-4,6-dimethylpyrimidin-2(1*H*)-ones were compared to those obtained for the 2(1*H*)-thione analogues.[7] The authors stated that "the rotational barrier was expected to increase when sulphur replaced oxygen"; however, the barrier was found to be smaller for the sulfur analogue (**2**: 115.8 kJ·mol^{-1}) and a "pronounced single bond character of the thiocarbonyl group" was advocated to account for these unexpected results. Roussel

Received: October 8, 2013
Published: December 4, 2013

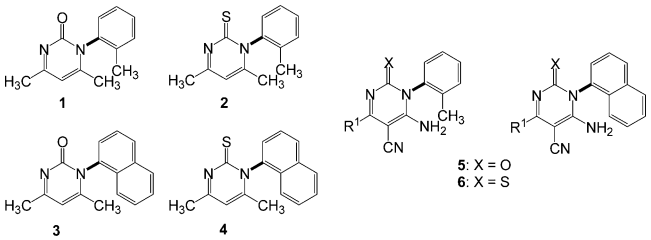


Figure 1. Structure of *N*-aryl-2(1*H*)-pyrimidin-(thi)ones **1**–**6**.

et al. revisited the barriers to atropisomerization for 1-(2-methylphenyl)-4,6-dimethylpyrimidin-2(1*H*)-one **1** and the corresponding thione **2** in diglyme, after separation of the enantiomers on microcrystalline cellulose triacetate (MCTA).[8] The experimental values of the barriers were 118.2 and 107.7 kJ·mol^{-1}, for **1** and **2**, respectively, confirming a lower barrier for the sulfur derivative. These values are lower than those reported by Kashima et al. for the same compounds, and they are consistent with the solvent effect reported more recently by Sakamoto et al.[9]

To account for the lower barrier in the sulfur derivative and the weak sensitivity to the buttressing effect, Roussel et al. hypothesized a ring-opening and a ring closure that would be easier in the thio derivative **2** than in the oxygen analogue **1**.[8] The experimental barriers would thus refer to the energy of the electrocyclic ring-opening process and not to the classical rotation around the pivotal bond.

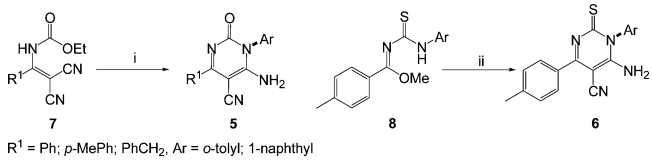
Sakamoto et al. have recently reported the barrier to racemization for the 1-(2-methylphenyl)-4,6-dimethylpyrimidin-2(1*H*)-one **1**[9] and for the 1-(1-naphthyl) analogue **3** in different solvents after separation of the enantiomers on "Chiralcel OD".[10] The barriers (vide infra) were strongly solvent-dependent, but noteworthy in the same solvent, the barriers were almost identical for the 2-methylphenyl and 1-naphthyl analogues. These new data bring additional evidence that the racemization barrier is surprisingly insensitive to the steric contribution of the *ortho* substituent in the methyl and 1-naphthyl series. Such a behavior is hardly accounted for on the basis of a racemization process involving a simple rotation around the pivot bond. The barriers for 1-(1-naphthyl)-4,6-dimethylpyrimidin-2(1*H*)-one **3** and the corresponding thione **4** have been reported in 2010 after separation of the enantiomers on "Chiralcel OD".[10] Here again, the barrier was lower in the thione analogue in three different solvents. Referring to AM1 calculations on the barrier of *N*-aryl-pyridone analogue,[11] Sakamoto et al. concluded that "a mechanism involving non-planar conformation may contribute to the racemization of **3** and **4**, because the alcohol adduct from the open form could not be obtained. However, a mechanism involving open form could not be perfectly excluded".[10]

Clearly, further experimental data and appropriate calculations were mandatory in this domain. In the course of our studies on a series of *N*-aryl-2(1*H*)-pyrimidin-(thi)ones,[12] we report herein the barriers of racemization in 6-amino-5-cyano-1,4-disubstituted-pyrimidinones **5a**–**5f** and the 6-amino-5-cyano-4-*p*-tolyl-1-substituted-pyrimidinethiones **6a** and **6b**. If one considers the substitution pattern around the pivotal *N*-aryl bond, compounds **5a**–**5f** to **6a**–**6b** differ from the previous studies in the field of atropisomeric 2(1*H*)-pyrimidin-(thi)ones by the introduction of a NH_2 substituent at the place of a Me group in compounds **1**–**4**. The effective steric requirements derived from rotational barriers are very similar for a methyl and an amino group in the 6-aryl-1,1,5-trimethylindane model,[13a] whereas an amino group is found slightly larger than a methyl group in the more recent 1-aryl-3-isopropyldimethylsilylbenzene model.[13b,c] The experimental barriers will be compared to the calculated ones for a classical rotation around the pivotal bond or for a ring-opening process.

RESULTS AND DISCUSSION

The 2(1*H*)-pyrimidinones **5a**–**5f** were synthesized in good yields by the condensation of ethyl 2,2-dicyanovinylcarbamate derivatives **7** with primary aromatic amines (*o*-tolylamine or naphthalen-1-ylamine).[12] Starting from the methyl *N*-(aminothiocarbonyl)imidates **8**[14] and malononitrile, the 2(1*H*)-pyrimidinethiones **6a** and **6b** were obtained in acceptable yield (Scheme 1).

Scheme 1. Synthesis of *N*-aryl-2(1*H*)-pyrimidin-(thi)ones 5 and 6[a]



[a]Reagents and conditions: (i) primary aromatic amines, chlorobenzene, 110 °C, (2–4) h (80–96% yields); (ii): malononitrile, Na/MeOH, reflux, 4 h (63–66% yields).

X-ray crystallographic analyses of *N*-(1-naphthyl)-2(1*H*)-pyrimidinone **5d** revealed that the pyrimidinone crystallized in the monoclinic and centrosymmetric space group *P*21/*c*.[12] Each single crystal of pyrimidinone **5d** is composed of both enantiomers (Figure 2). The two arene planes are almost perpendicular to each other (inter-ring dihedral C11–N2–C12–C21: 73.22°) in each molecule.

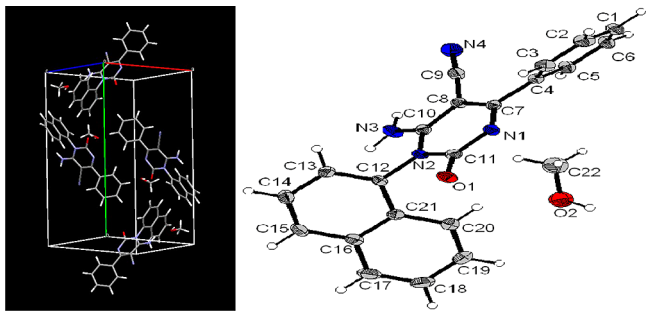
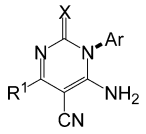


Figure 2. Packing diagram of **5d** in the *P*21/*c* crystal system.

Each compound **5** and **6** exists as a pair of enantiomers that were nicely separated on several chiral stationary phases. The enantiomers were obtained in high optical purity by semi-preparative chromatography without noticeable racemization during the collection and evaporation of the solvent. The details of chromatographic data are given in the Supporting Information. Having in hand pure enantiomers, they were submitted to thermal racemization in an alcoholic medium. The solvents, butan-1-ol or ethanol, were chosen according to the barrier range of the individual samples, butan-1-ol for the compounds **5a**–**5f** and ethanol for compounds **6a** and **6b**. The rotation barriers (enantiomerization barriers) are reported in

dx.doi.org/10.1021/jo402149f | J. Org. Chem. 2013, 78, 12577–12584

Table 1. Barriers to Rotation of the C−N Bond in 6-Amino-5-cyano-1,4-disubstituted-2(1*H*)-pyrimidin-(thi)ones



compd	X	R^1	Ar	solvent	T (°C)	$10^5\ k\ (s^{-1})^a$	$\Delta G^{\ddagger b}$ (kJ·mol^{-1})
5a	O	phenyl	*o*-tolyl	butan-1-ol	117	59.4	120.5
5b	O	*p*-tolyl	*o*-tolyl	butan-1-ol	117	62.0	120.4
5c	O	benzyl	*o*-tolyl	butan-1-ol	117	25.2	123.3
5d[12]	O	phenyl	1-naphthyl	butan-1-ol	117	12.6	125.6
5e[12]	O	*p*-tolyl	1-naphthyl	butan-1-ol	117	14.5	125.1
5f[12]	O	benzyl	1-naphthyl	butan-1-ol	117	16.9	124.6
6a	S	*p*-tolyl	*o*-tolyl	ethanol	78	3.1	116.8
6b	S	*p*-tolyl	1-naphthyl	ethanol	78	36.4	109.6

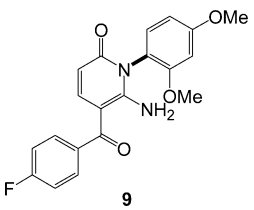
[a]Rate constant of enantiomerization. [b]Enantiomerization barrier.

Table 1; in all cases, first-order kinetic data were obtained (see the Supporting Information).

The barriers to rotation in compounds **5** and **6** are particularly unexpected and deserve a careful analysis. In the series of the pyrimidinones (X = O, **5a**,**5b**/**5d**,**5e**), the barriers are significantly higher (ca. 5 kJ·mol^{-1}) for the 1-naphthyl substituent than for the *o*-tolyl analogues. This is what is expected from the steric requirement of a 1-naphthyl group compared to that of an *o*-tolyl group. In the 1-naphthyl group, the C_8-H mimics the steric requirement of a locked methyl group as it was shown in comparing the kinetics of *N*-methylation of quinoline and 2-methylpyridine.[15] Sakamoto et al. reported the barriers to rotation about the *N*-aryl axis in pyrimidinones **1** and **3** in propan-1-ol, xylene, and DMF. The barriers were quite sensitive to the solvent. The barriers in propan-1-ol were 126.2 and 127.5 kJ·mol^{-1} for **1**[9] and **3**,[10] respectively; thus, the barrier was slightly higher for the 1-naphthyl derivative than for the *o*-tolyl group without the marked difference we observed in comparing **5a** with **5d** and **5b** with **5e**. It is worth mentioning that the barrier in **5a** or **5b** is smaller than the barrier in **1** (ca. 6 kJ·mol^{-1}) in alcohols while the ranking of the sizes of an amino and a methyl group is $NH_2 \geq CH_3$ in biaryls depending on the model.[13a−c]

Shirok et al. reported the synthesis of a series of 6-amino-1-aryl-2-pyridones.[11a] Three compounds bearing a methyl, isopropyl, or methoxy group in the *ortho*-position were particularly relevant for our study since they provide a similar environment around the pivotal bond than the one that consists of an amino group and a carbonyl in compounds **5**. Unfortunately, the experimental rotation barrier was not reported for the methyl analogue but for the sole methoxy one. The experimental barrier in compound **9** (139 kJ·mol^{-1} in boiling water) is ca. 20 kJ·mol^{-1} higher than that in **5a**,**5b** (Scheme 2).[11b]

Scheme 2. Structure of Compound 9



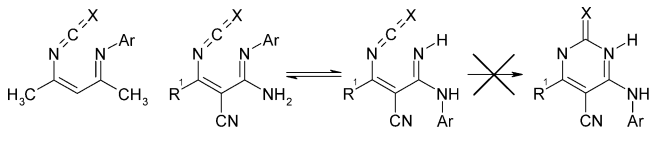
9

Going from pyrimidinones (X = O) **5a**,**5b** to pyrimidinethione (X = S) **6a**, the barriers are significantly smaller in the latter case. As mentioned before, such a behavior is already exemplified in the literature for this type of frameworks.[7−10] Quite unexpectingly, the barrier was found to be smaller in the pyrimidinethione **6b** than in pyrimidinethione **6a**, the difference being 7.5 kJ·mol^{-1}. In these pyrimidinethiones, the 1-naphthyl group has thus an apparent smaller steric requirement than the *o*-tolyl group during the rotation process, whereas the opposite holds true in the pyrimidinone series!

One of us proposed many years ago that the lower barrier in the case of pyrimidinethiones was an indication of the contribution of a ring-opening process leading to an isothiocyanate intermediate **10** in which the rotation of the *N*-aryl group will be quite fast and insensitive to the buttressing effect. In other words, the experimental barrier would result from the ring-opening process and the higher stability of the isothiocyanate than that of the isocyanate would account for the lower barrier to rotation in the pyrimidinethione.

Compounds **5** and **6** were particularly attractive since we expected that intermediate **11** might tautomerize into intermediate **12**, which, after rotation and cyclization, would lead to pyrimidinethione **13** (Scheme 3). The rearranged

Scheme 3. Structures of Isothiocyanate Generated from 2(1*H*)-Pyrimidin-(thi)ones



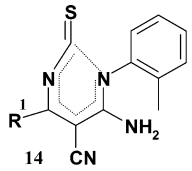
10 **11** **12** **13**

pyrimidinethiones **13** were not detected during the racemization process, probably pointing out a large preference for the tautomer **11** in which conjugation with the aryl group is favorable. Another explanation would be that the easy rotation of the *N*-aryl group occurred on the reaction pathway leading to the formation of intermediate **11** during a considerably elongated N···C state before a complete dissociation is attained, such as in **14** (Scheme 4).

Such an elongated state that maintains a weak bonding character between the nitrogen atom and the sp carbon atom being formed would as well prevent the formation of the rearranged product. It would also prevent a possible

dx.doi.org/10.1021/jo402149f | J. Org. Chem. 2013, 78, 12577−12584

Scheme 4



intermolecular reaction of the formed isothiocyanate with the alcoholic solvent. Sakamoto et al. pointed out that the formation of carbamate was not observed when the racemization of compound **4** was performed in alcoholic solvent.[10] The formation of (thio)carbamates was also not observed during our racemization studies in butan-1-ol or ethanol.

DFT CALCULATIONS

The geometry of the systems has been optimized at the B3LYP/6-31G(d) computational method. Frequency calculation has been carried out at the same computational level to confirm that the obtained structures correspond to energetic minima or true transition states (number of imaginary frequencies zero and one, respectively).[16] In addition, in some selected cases, the effect of the solvent has been considered using the polarizable continuum model (PCM) with the parameters of the butan-1-ol and ethanol.[17] The calculations were performed on compounds **5a**, **5d**, **6′a**, and **6′b**. Compounds **6′a** and **6′b** are the analogues of **6a** and **6b** in which the R^1 *p*-tolyl group was replaced by a phenyl group. The similarity of the experimental barriers in the couples **5a**−**5b**, and **5d**−**5e**, respectively, justifies this simplification for the calculations.

In a first series of calculations, the racemizations were calculated through a pure classical rotational process for the pyrimidone and for the pyrimidinethione series according to the two possible transition states (Table 2).

Table 2. Calculated Barriers for Racemization through Pure Rotational Processes

compds	X	R^1	*N*-aryl	*G* (Hartree)	$\Delta G^{\ddagger}$ (kJ·mol^{-1})
5a	O	Ph	*o*-tolyl	−988.353051	
5a-ts1[a]				−988.310552	**111.6**
5a-ts2				−988.301026	136.6
5d	O	Ph	1-naphthyl	−1102.65948	
5d-ts1				−1102.61341	**120.9**
5d-ts2				−1102.60503	142.9
6′a	S	Ph	*o*-tolyl	−1311.30680	
6′a-ts1	S			−1311.25799	**128.1**
6′a-ts2	S			−1311.25297	141.3
6′b	S	Ph	1-naphthyl	−1425.61262	
6′b-ts1	S			−1425.56184	**133.3**
6′b-ts2	S			−1425.55765	144.3

[a]ts1 and ts2 are the two possible transition states for the pure rotation processes.

If we consider the lower of the two possible transition states (in bold in Table 2), the barriers in the gas phase are following the expected order of steric requirements: in the series pyrimidone and pyrimidinethione, the barriers are higher for the 1-naphthyl group than for the *o*-tolyl group, and for the same substituent on the nitrogen, the barriers are higher for the pyrimidinethiones.

The racemization of the oxo derivatives is possible through rotation of the aromatic ring. The most favorable TSs for the racemization correspond to those cases where the more bulky group of the aromatic ring is in *syn* to the oxo group (Figure 3). This process reproduces the experimental data showing a higher steric demand for the rotation of the naphthyl group in comparison to the *o*-tolyl group.

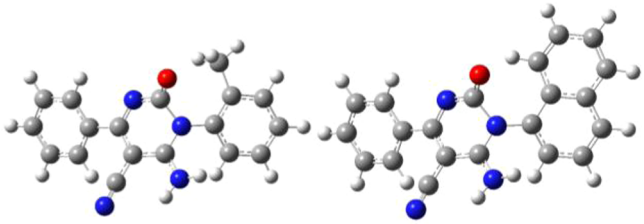


Figure 3. The most favorable transition states for the rotation of *o*-tolyl and 1-naphthyl groups in compounds **5a** and **5d**.

In a second step, the barriers were calculated through a ring-opening + rotation process. All the attempts to obtain the open structure with X = O have been unsuccessful. In all cases, the system reverts toward the original pyrimidinone. For the pyrimidinethiones, a very easy ring-opening occurs through TS with 69.8 and 66.8 kJ·mol^{-1} for **6′a** and **6′b**, respectively (Table 3). The ring-opening energy + the low rotation energy of the aryl groups in the open form is the determining step for the racemization: 91.1 and 83.3 kJ·mol $^{-1}$ for **6′a** and **6′b**, respectively, for the low-energy TSs. Interestingly, the increased conjugation of the naphthyl group accounts for the lower barrier in **6′b** in comparison to **6′a**. The results for the opening reaction and the racemization process through rotation are gathered in Table 3. The gas-phase calculations reproduce the ranking of the experimental barriers.

The racemization of the thioxo derivatives may proceed through an opening of the pyrimidine, followed by the rotation of the aromatic ring and ring-closure back to the pyrimidinethione. The ranking of the barriers in **6′a** and **6′b** results from the difference in conjugation of the *o*-tolyl group and naphthyl group in the rotation TS. The stability of the open structure for the C═NH tautomer (**12**, R^1 = phenyl) as well as the cyclization process has been calculated. Both the open structure and the TS for the cyclization are less favorable by ca. 18 kJ·mol^{-1} than in tautomer **11** (R^1 = phenyl).

In addition to the calculation in vacuum, the effect of the solvent (butan-1-ol for X = O and ethanol for X = S) has been considered using the polarizable continuum model (PCM) with the parameters of the butan-1-ol and ethanol for the structures corresponding to minima and the most favorable TSs. The PCM model that does not localize hydrogen bonds is for sure a rough estimation in the present case. Nevertheless, the resulting barriers are worth mentioning (Table 4) and shall be handled with high care. We shall limit our discussion in saying that the inclusion of solvent provides values astonishingly close to those obtained experimentally. In a more realistic way, the trends revealed by the experimental data are correctly reproduced by the calculations when a pure rotation process is operating in the pyrimidinone series, and a ring-opening−rotation−ring-closure process is operating in the pyrimidinethione series.

dx.doi.org/10.1021/jo402149f | J. Org. Chem. 2013, 78, 12577−12584

Table 3. Calculated Enantiomerization Barriers* for a Stepwise Ring-Opening + Rotation Process in Pyrimidinethiones 6′a (*o*-Tolyl) and 6′b (1-Naphthyl)

compds	*G* (Hartree)	ΔG‡ (kJ·mol^{-1})
6′a (ground state)	−1311.30680	
6′a (TS for the open form)	−1311.28019	69.8
6′a (open form **11** like)	−1311.28268	63.3
6′a (TS1 for *o*-tolyl rotation in open form)	−1311.25923	124.9
6′a (TS2 for *o*-tolyl rotation in open form)	−1311.27208	**91.1***
6′b (ground state)	−1425.61262	
6′b (TS for the open form)	−1425.58716	66.8
6′b (open form **11** like)	−1425.59072	57.5
6′b (TS1 for 1-naphthyl rotation in open form)	−1425.58089	**83.3***
6′b (TS2 for 1-naphthyl rotation in open form)	−1425.56328	129.5

Table 4. Summary of the Experimental and Calculated Barriers with and without PCM Model

X	R^1	*N*-aryl	solvent	ΔG‡ exptl (kJ·mol^{-1})	ΔG‡ vac calcd (kJ·mol^{-1})	ΔG‡ PCM calcd (kJ·mol^{-1})
O	phenyl	*o*-tolyl	butan-1-ol	120.5	111.6	121.9
O	phenyl	1-naphthyl	butan-1-ol	125.6	120.9	129.6
S	phenyl	*o*-tolyl	ethanol	116.8[a]	91.1[b]	114.6[b]
S	phenyl	1-naphthyl	ethanol	109.6[a]	83.3[b]	105.5[b]

[a]Experimental data for **6a** and **6b**. [b]Calculated data for **6′a** and **6′b**.

The comparison of the pure rotation process and the ring-opening−rotation process is cartooned in Figure 4. This figure

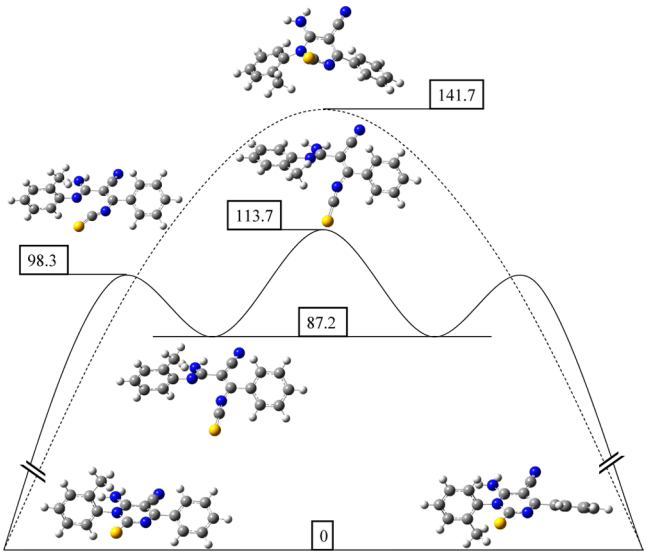


Figure 4. Comparison of a pure rotation versus a ring-opening−rotation process for **6′a**. All the reported calculated values (in kJ·mol^{-1}) are those obtained using the PCM model for butan-1-ol.

is, of course, providing quite a rigid and stepwise description of what might be occurring. The rotation around the *N*-aryl axis may occur at any point during the ring-opening process without the requirement to reach a full open form in which the rotation is quite easy. The rotation may occur in **14**.

CONCLUSION

The atropisomerization of *N*-aryl pyrimidinones mostly proceeds by a classical rotation process around the pivotal bond. The ranking of the barriers for *o*-tolyl and 1-naphthyl fits this model, and the trend is supported by DFT calculations.

The atropisomerization of *N*-aryl pyrimidinethiones mostly proceeds through a ring-opening process, followed by the rotation of the aryl group in an open or nearly open form. The calculations were performed for a stepwise process; a smoother process that combines ring-opening and concomitant rotation of the aryl groups is probably quite realistic. It accounts for the low barrier in pyrimidinethiones in comparison to pyrimidinones. A better conjugation of the naphthyl group with the imino group in the TS accounts for the lower barrier in the 1-naphthyl than in the *o*-tolyl derivative. The open form is not populated enough to react significantly with the alcoholic solvent to yield thiocarbamate during racemization experiments. Because the tautomeric form **12** is less stable than **11** by ca. 18 kJ·mol^{-1}, the rearranged product **13** is not formed during the racemization experiment time scale.

The traditional picture of atropisomerization about a pivotal *N*-aryl axis shall take into account ring-opening when it is possible.[18]

EXPERIMENTAL SECTION

Chemicals. Commercial reagent grade chemicals were used as received without additional purification. All reactions were followed by TLC (Kieselgel 60 F-254). Column chromatography was performed on silica gel (60−200 mesh). Solvents used for enantioselective chromatography and determination of the rotation barrier were HPLC grade.

General. ^{1}H, ^{13}C, and ^{1}H−^{1}H COSY NMR spectra were recorded at 300, 400, or 600 MHz (^{1}H), 75 or 125 MHz (^{13}C), and 300 MHz (^{1}H−^{1}H COSY) using $(CD_3)_2SO$ as solvent with $(CD_3)_2SO$ (δ_H 2.5) or $(CD_3)_2SO$ (δ_C 39.5). Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (0 ppm) as the internal reference, and the following multiplicity abbreviations were used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; *J* in hertz. The mass spectra were recorded on an ion trap mass spectrometer using electrospray as an ionization source. Melting points are uncorrected. For chromatography on chiral stationary phases, the analytical analyses were monitored by a DAD-detector and a circular dichroism detector.

Synthesis. Preparation of 6-amino-5-cyano-1-*o*-tolyl-4-substituted-2(1*H*)-pyrimidinones (**5a−5c**). The 2(1*H*)-pyrimidinones **5a−5c** were prepared according to the reported procedure.[12] The 2(1*H*)-pyrimidinones **5d−5f** have been already described.[12]

dx.doi.org/10.1021/jo402149f | J. Org. Chem. 2013, 78, 12577−12584

6-Amino-5-cyano-4-phenyl-1-o-tolyl-2(1H)-pyrimidinone (**5a**). Yield: 82% (248 mg). White solid, mp 227−229 °C. IR (KBr, cm^{-1}): 3514, 3462, 2217, 1666, 1599, 1581, 1555. ^1H NMR: (DMSO-d_6, 300 MHz): δ 2.08 (s, 3H, CH_3), 7.30−7.45 (m, 6H), 7.52−7.62 (m, 3H), 7.85 (dd, J = 9 Hz, J = 3 Hz, 2H), the NH_2 are located under the aromatic area according to the total integration. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.1 (CH_3), 72.7 (*C*-CN), 117.0 (CN); 9*C*-H_{arom}:128.4, 128.7, 128.76 (×2), 128.83 (×2), 130.2, 131.5, 132.0; 5C_q: 133.8, 136.1, 137.3, 153.4, 160.1; 172.2 (*C*═O). MS-(+)ESI, m/z (%): 303 ([M + H]$^+$, 100), 325 ([M + Na]$^+$, 4), 627 ([2 M + Na]$^+$, 38). HRMS-ESI (m/z): cald for $C_{18}H_{15}N_4O$ [M + H]$^+$ 303.1246, found 303.1257.

6-Amino-5-cyano-1-o-tolyl-4-p-tolyl-2(1H)-pyrimidinone (**5b**). Yield: 96% (303 mg). White solid, mp 221−223 °C. IR (KBr, cm^{-1}): 3510, 3462, 2210, 1671, 1645, 1609, 1578, 1548. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.07 (s, 3H, *o*-CH_3), 2.40 (s, 3H, *p*-CH_3), 7.29−7.44 (m, 6H), 7.77 (d, J = 9 Hz, 2H), the NH_2 are located under the aromatic area according to the total integration. ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.2 (*o*-CH_3), 21.5 (*p*-CH_3), 72.4 (*C*-CN), 117.1 (CN); 8*C*-H_{arom}:128.3, 128.8, 128.9 (×2), 129.3 (×2), 130.2, 132.0; 6C_q: 133.9, 134.5, 136.1, 141.6, 153.4, 160.1; 171.9 (*C*═O). MS-(+)ESI, m/z (%): 317 ([M + H]$^+$, 100), 339 ([M + Na]$^+$, 3), 655 ([2 M + Na]$^+$, 38). HRMS-ESI (m/z): cald for $C_{19}H_{17}N_4O$ [M + H]$^+$ 317.1402, found 317.1416.

6-Amino-4-benzyl-5-cyano-1-o-tolyl-2(1H)-pyrimidinone (**5c**). Yield: 92% (290 mg). White solid, mp 256−258 °C. IR (KBr, cm^{-1}): 3517, 3464, 2212, 1682, 1611, 1567, 1529. ^1H NMR (DMSO-d_6, 300 MHz): ^1H NMR (DMSO-d_6, 300 MHz): δ 2.00 (s, 3H, CH_3), 3.89 (d, J = 15 Hz, 1H, CH_2), 3.95 (d, J = 15 Hz, 1H, CH_2), 7.22−7.41 (m, 9H), 7.80 (br, 2H−NH_2). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.1(*o*-CH_3), 43.4 (CH_2), 73.6 (*C*-CN), 116.4 (CN); 9*C*-H_{arom}: 127.3, 128.3, 128.8, 129.0 (×2), 129.5 (×2), 130.2, 131.9; 5C_q: 133.8, 136.0, 137.0, 153.5, 159.3; 175.7 (C═O). MS-(+)ESI, m/z (%): 317 ([M + H]$^+$, 100), 339 ([M + Na]$^+$, 4), 655 ([2 M + Na]$^+$, 29). HRMS-ESI (m/z): cald for $C_{19}H_{17}N_4O$ [M + H]$^+$ 317.1402, found 317.1416.

Synthesis of Imidate (8). To a solution of iminoester (10 mmol), prepared according to the method described by Pinner,[19] in methanol and 4-methylbenzonitrile (15/15 mL) was bubbled with dry HCl. Then, the iminoester was free of its salt, in 50 mL of ether, by a solution of sodium carbonate. (*o*-Tolyl or 1-naphthyl)isothiocyanate (10 mmol) was added dropwise at 0 °C in the iminoester solution. The mixture was stirred for 2 h, and the ether was evaporated. The imidate was recrystallized from petroleum ether.

(Z/E)-1-(Methoxy-p-tolyl-methylene)-3-o-tolyl-thiourea (**8a**). Yield: 78% (2.32 g). White solid, mp 139−141 °C. IR (KBr, cm^{-1}): 3138, 2943, 1659, 1524, 1436, 1289, 1242, 1208, 1183, 1151, 1099. MS-(+)ESI, m/z (%): 299 ([M + H]$^+$, 100), 321 ([M + Na]$^+$, 9). HRMS-ESI (m/z): cald for $C_{17}H_{19}N_2OS$ [M + H]$^+$ 299.1218, found 299.1208. *Z-isomer*: ^1H NMR (DMSO-d_6, 300 MHz): δ 2.06 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 7.07−7.24 (m, 4H), 7.27 (d, J = 9 Hz, 2H), 7.57 (d, J = 9 Hz, 2H), 10.82 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.7, 21.5, 55.0, 126.5, 127.1, 127.3, 127.5, 128.7, 129.5, 130.8, 134.1, 137.4, 142.5, 154.9, 189.3. *E*-isomer: ^1H NMR (DMSO-d_6, 300 MHz): δ 2.07 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 7.07−7.24 (m, 4H), 7.32 (d, J = 9 Hz, 2H), 7.79 (d, J = 9 Hz, 2H), 10.67 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 17.9, 21.5, 55.1, 126.5, 127.4, 127.9, 128.1, 128.8, 129.4, 130.8, 134.8, 137.9, 142.0, 156.9, 190.6.

(Z/E)-1-(Methoxy-p-tolyl-methylene)-3-naphthalen-1-yl-thiourea (**8b**). Yield 86% (2.87 g). White solid, mp 134−136 °C. IR (KBr, cm^{-1}): 3134, 2946, 1675, 1515, 1497, 1280, 1241, 1210, 1158, 1099. MS-(+)ESI, m/z (%): 335 ([M + H]$^+$, 100). HRMS-ESI (m/z): cald for $C_{40}H_{36}N_4NaO_2S_2$ [2M + Na]$^+$ 691.2177, found 691.2177. *Z-isomer*: ^1H NMR (DMSO-d_6, 300 MHz): δ 2.31 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 7.26 (d, J = 9 Hz, 2H), 7.35−7.55 (m, 7H), 7.95 (d, J = 9 Hz, 2H), 11.40 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.5, 54.8, 123.6, 124.6, 125.7, 126.0, 126.7, 127.0, 127.8, 128.4, 128.7, 129.0, 129.4, 134.0, 134.7, 142.5, 154.9, 190.0. *E-isomer*: ^1H NMR (DMSO-d_6, 300 MHz): δ 2.40 (s, 3H, CH_3), 3.96 (s, 3H, CH_3), 7.19 (d, J = 9 Hz, 2H), 7.35−7.55 (m, 7H), 7.87 (d, J = 9 Hz, 2H), 11.12 (br, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.5, 55.3, 123.1, 124.4, 125.7, 126.0, 126.6, 127.6, 128.1, 128.5, 128.8, 129.5, 129.8, 134.2, 135.2, 142.1, 157.0, 191.7.

General Procedure for Preparation of 2(1*H*)-pyrimidinethiones (6a and 6b). To a solution of Na (0.14 g, 6 mmol) in dry MeOH (15 mL) were added malononitrile (0.33 g, 5 mmol) and the imidate **8** (5 mmol). The solution was stirred under reflux for 4 h and cooled to room temperature. Glacial HOAc (0.4 g, 7 mmol) and water (50 mL) were added. The precipitate was collected by filtration and recrystallized from MeOH to yield the 2(1*H*)-pyrimidinethione **6**.

6-Amino-5-cyano-1-o-tolyl-4-p-tolyl-2(1H)-pyrimidinethione (**6a**). Yield: 63% (1.04 g). Yellow solid, mp 251−253 °C. IR (KBr, cm^{-1}): 3533, 3429, 2214, 1699, 1610, 1545, 1516, 1318, 1243, 1172, 1149, 1007. ^1H NMR (CD_3OD, 600 MHz): δ 2.19 (s, 3H, *o*-CH_3), 2.44 (s, 3H, *p*-CH_3), 7.24 (d, J = 7.2 Hz, 1H), 7.36 (dd, J = 0.6 Hz, J = 8.4 Hz, 2H), 7.43−7.50 (m, 3H), 7.88 (d, J = 8.4 Hz, 2H). (DMSO-d_6, 400 MHz): δ 2.08 (s, 3H, *o*-CH_3), 2.41 (s, 3H, *p*-CH_3), 7.26 (dd, J = 6.4 Hz, J = 2 Hz, 1H), 7.37−7.42 (m, 5H), 7.82 (d, J = 8 Hz, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 16.7 (*o*-CH_3), 21.0 (*p*-CH_3), 77.5 (*C*-CN), 116.0 (CN); 8*C*-H_{arom}: 127.84, 128.27, 128.68 (×2), 128.91 (×2), 129.77, 131.84; 6C_q: 132.98, 134.97, 136.5, 141.56, 157.78, 164.03; 180.73 (*C*═S). MS-(+)ESI, m/z (%): 333 ([M + H]$^+$, 100), 355 ([M + Na]$^+$, 12). HRMS-ESI (m/z): cald for $C_{19}H_{17}N_4S$ [M + H]$^+$ 333.1174, found 333.1181.

6-Amino-5-cyano-1-(naphthalen-1-yl)-4-p-tolyl-2(1H)-pyrimidinethione (**6b**). Yield: 65% (1.2 g). Yellow solid, mp 263−265 °C. IR (KBr, cm^{-1}): 3527, 3386, 2215, 1698, 1610, 1551, 1518, 1445, 1330, 1242, 1173, 1007. ^1H NMR: (DMSO-d_6, 300 MHz): δ 2.44 (s, 3H, *p*-CH_3), 7.41 (d, J = 9 Hz, 2H), 7.54−7.69 (m, 6H), 7.88 (d, J = 9 Hz, 2H), 8.08−8.10 (m, 2H). (CD_3OD, 600 MHz): δ 2.47 (s, 3H, *p*-CH_3), 7.39 (d, J = 8.1 Hz, 2H), 7.56−7.62 (m, 4H), 7.68 (t, J = 7.8 Hz, 1H), 7.93 (d, J = 8.1 Hz, 2H), 8.05 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.6 (*p*-CH_3), 77.7 (*C*-CN), 116.2 (CN); 11*C*-H_{arom}:121.5, 126.3, 126.6, 127.17(×2?), 128.55, 128.66 (×2), 128.84 (×2), 129.93; 7C_q: 128.24, 133.2, 134.0, 134.7, 141.4, 158.48, 164.24; 182.3 (*C*═S). MS-(+)ESI, m/z (%): 369 ([M + H]$^+$, 100), 391 ([M + Na]$^+$, 10). HRMS-ESI (m/z): cald for $C_{22}H_{17}N_4S$ [M + H]$^+$ 369.1174, found 369.1165.

Chromatographic Screening. The resolution of the enantiomers of compounds **5a**−**5f** and **6a** and **6b** was performed on several chiral stationary phases using various eluents to select the best conditions for future semipreparative separation. Immobilized Daicel columns Chiralpak IA, IB, IC, and ID were used in all cases, and (*S*,*S*)-Ulmo was also screened in some cases. The temperature was regulated at 25 °C, and the flow rate was set at 1 mL/min. For each compound, excellent separations with α > 1.65 were achieved on one or several columns. For all the samples, Chiralpak IB gave very poor or no separation, whereas IA, IC, or ID columns produced baseline separation. For solubility reasons, the racemates were dissolved in a mixture of ethanol and chloroform, which prevented the use of coated polysaccharide phases. The separations were monitored using a DAD detector and a circular dichroism detector set at 254 nm. All the chromatographic data including mobile phase composition, retention times and retention factors, enantioseparation and resolution obtained from screening experiments are reported for each compound in the Supporting Information. When the sensitivity was sufficient, the CD signs at 254 nm in the mobile phase of the first and second eluted enantiomers are also given.

Enantiomer Enrichment and Isolation. **5a.** Chiralpak IA (10 × 250 mm; mobile phase: hexane/ethanol/chloroform 70/10/20; flow: 5 mL/min; UV at 290 nm. Sample preparation: 98 mg in 20 mL of chloroform and 20 mL of the mobile phase. 100 injections (400 μL). Recovery: 40 mg of each enantiomer was obtained (98% ee). α_D^{25} = +98 (*c* 0.24, $CHCl_3$) for the first eluted enantiomer.

5b. (*S*,*S*)-Ulmo (10 × 250 mm); mobile phase: hexane/ethanol/chloroform 60/20/20; flow: 5 mL/min; UV at 300 nm. Sample preparation: 142 mg in 10 mL of chloroform, 10 mL of ethanol and 5 mL of hexane. 36 injections (700 μL). Recovery: 65 mg of each enantiomer (99% ee). α_D^{25} = −87 (*c* 0.26, $CHCl_3$) for the first eluted enantiomer.

5c. Chiralpak IC (10 × 250 mm); mobile phase: hexane/ethanol/chloroform 50/30/20; flow: 5 mL/min; UV at 300 nm. Sample preparation: 150 mg in 30 mL of chloroform, 30 mL of ethanol and 15 mL of hexane. 75 injections (1000 μL). Recovery: 72 mg of each enantiomer (99% ee). α_D^{25} = +94 (*c* 0.36, $CHCl_3$) for the first eluted enantiomer.

5d. Chiralpak IA (10 × 250 mm); mobile phase: hexane/ethanol/chloroform 70/10/20; flow: 5 mL/min; UV at 300 nm. Sample preparation: 95 mg in 15 mL of chloroform, 15 mL of ethanol and 5 mL of hexane. 70 injections (500 μL). Recovery: 39 mg of each enantiomer (98% ee). α_D^{25} = +67 (*c* 0.29, $CHCl_3$) for the first eluted enantiomer.

5e. Chiralpak IA (10 × 250 mm); mobile phase: hexane/ethanol/chloroform 70/10/20; flow: 5 mL/min; UV at 330 nm. Sample preparation: 75 mg in 15 mL of chloroform, 15 mL of ethanol and 20 mL of hexane. 100 injections (450 μL). Recovery: 32 mg of each enantiomer (97% ee). α_D^{25} = +68 (*c* 0.26, $CHCl_3$) for the first eluted enantiomer.

5f. Chiralpak IA (10 × 250 mm); mobile phase: hexane/ethanol/chloroform 70/10/20; flow: 5 mL/min; UV at 260 nm. Sample preparation: 63 mg in 30 mL of chloroform, 30 mL of ethanol and 10 mL of hexane due to the poor solubility of the sample. 140 injections (500 μL). Recovery: 29 mg of each enantiomer (98% ee). α_D^{25} = +62 (*c* 0.036, $CHCl_3$) for the first eluted enantiomer.

6a. Chiralpak IA (10 × 250 mm); mobile phase: hexane/ethanol/chloroform 70/10/20; flow: 5 mL/min; UV at 400 nm. Sample preparation: 97 mg in 6 mL of chloroform/ethanol (8:2). 45 injections (130 μL). Recovery: 36 mg of each enantiomer (98% ee). α_D^{25} = +150 (*c* 0.11, $CHCl_3$) for the first eluted enantiomer.

6b. Chiralpak IA (10 × 250 mm); mobile phase: hexane/ethanol 70/30; flow: 5 mL/min; UV at 400 nm. Sample preparation: 55 mg in 10 mL of chloroform/ethanol (1:1). 50 injections (200 μL). Recovery: 5 mg of each enantiomer (97% ee). α_D^{25} = +157 (*c* 0.059, $CHCl_3$) for the first eluted enantiomer.

Kinetic Experiments. The kinetics of racemization were performed off-line in butan-1-ol or ethanol at 117 or 78 °C, respectively. The progress of the racemization was monitored by enantioselective chromatography. The barriers reported in Table 1 are enantiomerization barriers in the solvent and at the given temperature. Experimental data and treatments of the first-order graphs are reported in the Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

Chromatographic analysis; kinetics of enantiomerization; crystallographic data (CIFs); ^1H NMR, ^{13}C NMR, and $^1H-^1H$ COSY NMR spectra for compounds **5a**−**5f**, **6a**, **6b**, **8a**, and **8b**; analysis LC-DAD-LIF-MS for **5a**-**5f**; and tables of atom coordinates and absolute energies from theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: christian.roussel@univ-amu.fr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank Dr. Carine Duhayon for providing the X-ray crystal analysis and Pierre Perio, Roseline Rosas, and Dr. Daniel Farran for their help in the physicochemical characterization of our compounds.

■ REFERENCES

(1) Alkorta, I.; Elguero, J.; Roussel, C.; Vanthuyne, N.; Piras, P. *Adv. Heterocycl. Chem.* **2012**, *105*, 1.

(2) (a) Bock, L. H.; Adams, R. J. *J. Am. Chem. Soc.* **1931**, *53*, 374. (b) Dai, X.; Wong, A.; Virgil, S. C. *J. Org. Chem.* **1998**, *63*, 2597. (c) Tokitoh, T.; Kobayashi, T.; Nakada, E.; Inoue, T.; Yokoshima, S.; Takahashi, H.; Natsugari, H. *Heterocycles* **2006**, *70*, 93. (d) Mintas, M.; Mihaljevic, V.; Koller, H.; Schuster, D.; Mannschreck, A. *J. Chem., Perkin Trans. 2* **1990**, *4*, 619. (e) Suzumura, N.; Kageyama, M.; Kamimura, D.; Inagaki, T.; Dobashi, Y.; Hasegawa, H.; Fukaya, H.; Kitagawa, O. *Tetrahedron Lett.* **2012**, *53*, 4332. (f) Ototake, N.; Morimoto, Y.; Mokuya, A.; Fukaya, H.; Shida, Y.; Kitagawa, O. *Chem.—Eur. J.* **2010**, *16*, 6752. (g) Ambrogi, M.; Ciogli, A.; Mancinelli, M.; Ranieri, S.; Mazzanti, A. *J. Org. Chem.* **2013**, *78*, 3709.

(3) (a) Erol, S.; Dogan, I. *Chirality* **2012**, *24*, 493. (b) Yilmaz, E. M.; Dogan, I. *Tetrahedron: Asymmetry* **2008**, *19*, 2184. (c) Erol, S.; Dogan, I. *J. Org. Chem.* **2007**, *72*, 2494. (d) Demir-Ordu, O.; Yilmaz, E. M.; Dogan, I. *Tetrahedron: Asymmetry* **2005**, *16*, 3752. (e) Oguz, S. F.; Dogan, I. *Tetrahedron: Asymmetry* **2003**, *14*, 1857. (f) Oguz, F. S.; Berg, U.; Dogan, I. *Enantiomer* **2000**, *5*, 405.

(4) (a) Chappaz-Gillot, C.; Canard, G.; Andreoli, F.; Vanthuyne, N.; Giorgi, M.; Naubron, J.-V.; Monnier, V.; Rosas, R.; Roussel, C.; Balaban, T. S. *Eur. J. Org. Chem.* **2012**, 6526. (b) Roussel, C.; Vanthuyne, N.; Bouchekara, M.; Djafri, A.; Elguero, J.; Alkorta, I. *J. Org. Chem.* **2008**, *73*, 403. (c) Vanthuyne, N.; Andreoli, F.; Fernandez, S.; Roman, M.; Roussel, C. *Lett. Org. Chem.* **2005**, *2*, 433.

(5) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*; Royal Society of Chemistry: Cambridge, U.K., 2008.

(6) Kashima, C.; Katoh, A.; Omote, Y.; Nakata, Y. *Heterocycles* **1978**, *9*, 469.

(7) Kashima, C.; Katoh, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1599−1602.

(8) Roussel, C.; Adjimi, M.; Chemlal, A.; Djafri, A. *J. Org. Chem.* **1988**, *53*, 5076.

(9) 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.

(10) Sakamoto, M.; Yagishita, F.; Ando, M.; Sasahara, Y.; Kamataki, N.; Ohta, M.; Mino, T.; Kasashima, Y.; Fujita, T. *Org. Biomol. Chem.* **2010**, *8*, 5418.

(11) (a) Schirok, H.; Alonso-Alija, C.; Benet-Buchholz, J.; Göller, A. H.; Grosser, R.; Michels, M.; Paulsen, H. *J. Org. Chem.* **2005**, *70*, 9463. (b) A methoxy group has a smaller effective van der Waals radii than a methyl group, and thus, a lower barrier in **9** than in **5a** was expected. However, during the rotation process and whatever the rotation pathway, the oxygen of the methoxy group passes in front of a flanking substituent bearing a lone pair of electrons (C═O or NH_2) that might increase the barrier through lone pair−lone pair repulsion. Comparison between the barriers in **9** and **5a** that were obtained in different solvents is thus difficult. The authors performed AM1 calculations of the barrier, and they found a considerable deformation of the pyridone cycle and a considerable out-of-plane bending of the rotating group. AM1 calculations might not be well designed for such barrier calculation, and a ring-opening involving the transient formation of a ketene and amine was not considered.

(12) (a) Najahi, E.; Sudor, J.; Chabchoub, F.; Nepveu, F.; Zribi, F.; Duval, R. *Molecules* **2010**, *15*, 8841. (b) Najahi, E.; Sudor, J.; Nepveu, F.; Zribi, F.; Duval, R.; Chabchoub, F. *Heterocyclic Lett.* **2011**, *1*, 9.

(13) (a) Bott, G.; Field, L.-D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618. (b) Ruzziconi, R.; Spizzichino, S.; Lunazzi, L.; Mazzanti, A.; Schlosser, M. *Chem.—Eur. J.* **2009**, *15*, 2645. (c) Lunazzi, L.; Mancinelli, M.; Mazzanti, A.; Lepri, S.; Ruzziconi, R.; Schlosser, M. *Org. Biomol. Chem.* **2012**, *10*, 1847.

(14) (a) Krechl, J.; Perez, M. A.; Cuadrado, F. J.; Soto, J. L. *Synthesis* **1988**, *2*, 122. (b) Zarguil, A.; Boukhris, S.; El Efrit, M. L.; Souizi, A.; Essassi, E. M. *Tetrahedron Lett.* **2008**, *49*, 5883.

(15) Roussel, C.; Balaban, A. T.; Berg, U.; Chanon, M.; Gallo, R.; Klatte, G.; Memiaghe, J. A.; Metzger, J.; Oniciu, D.; Pierrot-Sanders, J. *Tetrahedron* **1983**, *39*, 4209.

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009.

(17) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(18) A ring−chain−ring tautomerization was recently advocated to account for the thermal atropisomerization of axially chiral *N*-(*o*-aryl)-4-hydroxy-2-oxazolidinone derivatives. (a) Demir-Ordu, O.; Dogan, I. *Chirality* **2010**, *22*, 641. (b) Yildirim, A.; Konuklar, F. A. S.; Saron, C.; Van Speybroeck, V.; Waroquier, M.; Dogan, I.; Aviyente, V. *Chem.—Eur. J.* **2012**, *18*, 12725.

(19) Pinner, A. *Chem. Ber.* **1894**, *27*, 2861−2870.