Stereomutations of Conformational Atropisomers of Hindered 1,2-Diaryltetrahydropyrimidines[‡]

M. Beatriz Garcia,[a][‡‡] Stefano Grilli,[a] Lodovico Lunazzi,[a] Andrea Mazzanti,*[a] and Liliana R. Orelli*[a][‡‡]

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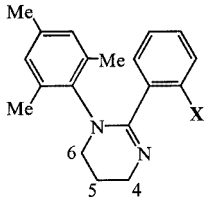
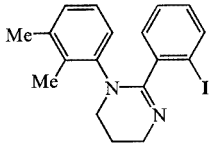
The barriers required to interconvert the conformational enantiomers (atropisomers) of three 2-(*o*-halophenyl)-1-mesityl-1,4,5,6-tetrahydropyrimidines (the *ortho*-halogen substituents being I, Br, Cl) have been measured by low-temperature ^{1}H NMR spectroscopy. In addition, the barrier for the inversion of the heterocyclic six-membered ring has been determined by monitoring the ^{13}C NMR spectra at even lower temperatures. When the mesityl substituent is replaced by a 2,3-dimethylphenyl group, two stereogenic axes are created, generating two diastereomeric conformers. These were identified by low-temperature NMR as existing in a 10:1 population ratio, with a 11.5 kcal·mol^{-1} interconversion barrier.

Introduction

Recently we reported[2] that conformational enantiomers (atropisomers) generated in *N*-aryltetrahydropyrimidines by restricted aryl−N bond rotation can be detected by variable-temperature NMR spectroscopy. Tetrahydropyrimidines with *ortho* substituents (such as the halogen atoms in compounds **1**−**3**) on the C-2 phenyl group should similarly display conformational atropisomers, due in this case to the restricted aryl−C bond rotation.



X = I (**1**), Br (**2**), Cl (**3**)



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Furthermore, if the aryl−N and the aryl−C bond rotation rates were sufficiently slow, a pair of unequally populated conformational diastereoisomers would be detectable, provided that neither of the two aryl substituents possessed a local twofold symmetry axis, as occurs, for instance, in the case of derivative **4**. Compounds **1**−**3** were synthesized in order to investigate, in particular, the aryl−C-2 bond rotation process, and compound **4** (in which a second stereogenic axis is available) in order to study the interconversion of these conformational diastereoisomers.

Results and Discussion

The presence of a bulky halogen atom in the *ortho* position of the C-phenyl group in derivatives **1**−**3** significantly twists the plane of the corresponding ring with respect to the average dynamic plane of the heterocyclic six-membered ring. In the case of **1** (X = I), for instance, MM calculations[3] suggest that the plane of the *o*-iodophenyl ring should be nearly orthogonal to the plane defined by the N−C=N moiety [the N1−C2−C−C(I) dihedral angle is computed as −108°]. Such a situation entails the existence of two enantiomers (atropisomers) when the rotation rate about the heterocyclic and *o*-iodophenyl moieties is negligible. The MM-computed ground-state structures for the atropisomers of **1** are shown in Scheme 1a, and identified as enantiomers (*M*) and (*P*).[4]

When the rotation process described is rendered sufficiently slow at an appropriately low temperature, the molecule does not exhibit any element of symmetry (C_1 point group), so the methylene hydrogen atoms of the tetrahydropyrimidine ring become diastereotopic, yielding anisochronous NMR signals as a consequence. Figure 1 shows the NMR spectral region for the methylene hydrogen atoms in positions 4 and 6[5] of derivative **1** as a function of temperature (in order to simplify the traces, the spectra were

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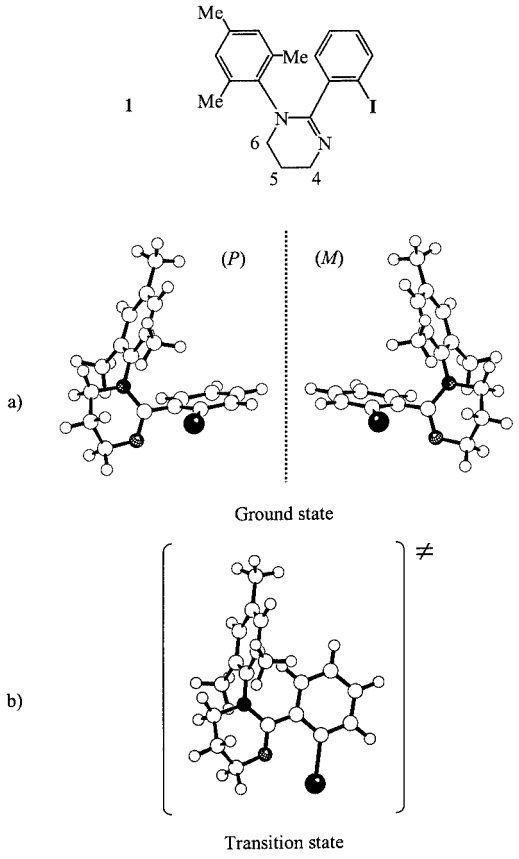
[a] Department of Organic Chemistry "A. Mangini", University of Bologna,
Viale Risorgimento 4, 40136 Bologna, Italy
Fax: (internat.) + 39-051/209-3654
E-mail: mazzand@ms.fci.unibo.it
[‡‡] On leave of absence from the Departamento de Quimica Organica, Facultad de Farmacia y Bioquimica, Universidad de Buenos Aires, Junin 956, Buenos Aires, 1113 Argentina,
E-mail: lorelli@ffyb.uba.ar



Scheme 1. a) MM-computed[3] structures of the (*P*) and (*M*) atropisomers of **1**; b) transition state for the (*P*)/(*M*) interconversion

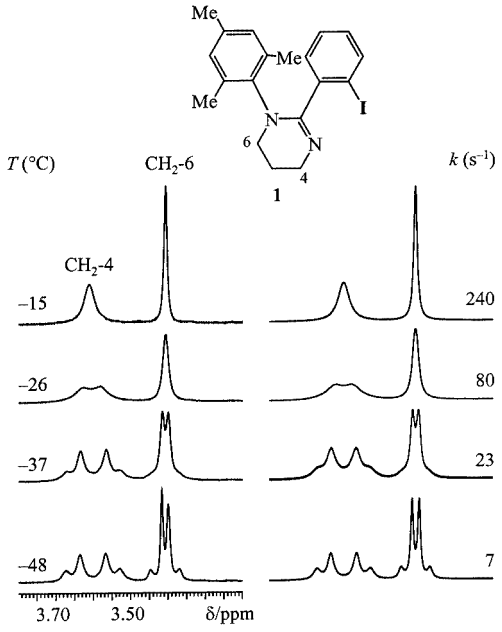


Figure 1. Left: temperature dependence of the ^{1}H NMR signals (400 MHz in CD_2Cl_2) of the CH_2 hydrogen atoms in position 4 (downfield) and 6 (upfield) obtained with decoupling of the methylene signal in position 5 of derivative **1**; right: line shape simulations obtained with the rate constants reported

recorded with simultaneous decoupling of the methylene signal in position 5).

The single sharp lines observed at ambient temperature broaden and eventually decoalesce on cooling: at −48 °C both the downfield and upfield signals appear as an AB-type system (the geminal *J* coupling constants being −15 and −12 Hz, respectively). Computer line-shape analysis yields the rate constants, and hence the free energy of activation ($\Delta G^{\neq}$ as in Table 1), for the observed dynamic process.[6]

Analogous spectral features were observed for compounds **2** (X = Br) and **3** (X = Cl); the corresponding enantiomerisation barriers arising from the aryl−C-2 bond rotation are also listed in Table 1. The $\Delta G^{\neq}$ values for the latter compounds are almost equal to that of **1**, despite the different bulkiness of iodine, bromine and chlorine. This suggests that the rotation transition state is the one in which the halogen atom crosses over the nitrogen atom in position 3, as shown for the case of **1** in Scheme 1b. The energy of this transition state does not depend on the dimensions of the halogen atoms, essentially being determined by the steric interaction between the mesityl (2,4,6-trimethylphenyl) moiety and the *ortho*-hydrogen of the halophenyl ring. Such interaction would be expected to be nearly the same in **1**, **2** and **3**, making the energy differences between the transition and the ground states extremely close to one another.

Table 1. Measured barriers ($\Delta G^{\neq}$ in kcal·mol^{-1}) for the dynamic processes of compounds **1**−**4**

Compound	**1**[a] X = I	**2**[a] X = Br	**3**[a] X = Cl	**4**[a]
Aryl−C2 rotation	12.2	12.7	12.5	11.5
Aryl−N1 rotation	> 22	> 22	> 22	19.8
Ring inversion	8.9	10.1	8.4	9.1

[a] The experimental uncertainty is ±0.2 kcal·mol^{-1}.

At the temperatures at which anisochronous methylene signals were observed, compounds **1**−**3** exhibit two lines for the two *ortho*-methyl groups of the mesityl substituent. Line-shape analysis of these lines yielded the same $\Delta G^{\neq}$ values as determined by monitoring of the corresponding methylene signals. This implies that the same process is responsible for both effects, and also that the rotation barrier for the mesityl moiety must be higher than that for the *o*-halophenyl ring. This is because the mesityl group, like the *o*-halophenyl ring, is nearly orthogonal to the average dynamic plane of the tetrahydropyrimidine (see Scheme 1a) so that, when the rotation of the *o*-halophenyl group becomes slow, two anisochronous methyl signals (one for the methyl *anti*, the other for the methyl *syn* to the halogen atom) can only be observed if the mesityl ring rotation is already "frozen". Had the latter motion been the faster one, the *ortho*-methyl groups would have displayed a single line. As a consequence, it is impossible to observe two anisochronous *ortho*-methyl lines in the presence of a fast rotation

of the *o*-halophenyl group in **1**−**3** and the mesityl rotation barrier therefore cannot be determined.

If this barrier is sufficiently high, however, a chiral environment would render these methyl groups, which are enantiotopic in an achiral medium, diastereotopic at ambient temperature: the corresponding signals would thus appear anisochronous even in the presence of a fast rotation process of the *o*-halophenyl ring.

The single line of the *ortho*-methyl groups of **1** (X = I) splits at ambient temperature in the presence of an appropriate excess (molar ratio 15:1) of enantiopure Pirkle's alcohol.[7] The two lines do not display the broadening features typical of an exchange process even when the temperature is raised to +120 °C (Figure 2), indicating that the rotation barrier of the mesityl ring must be higher than 22 kcal·mol^{-1}.[8]

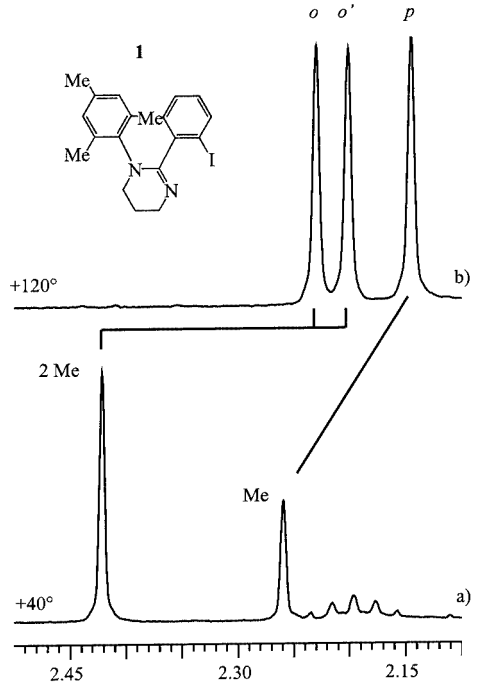
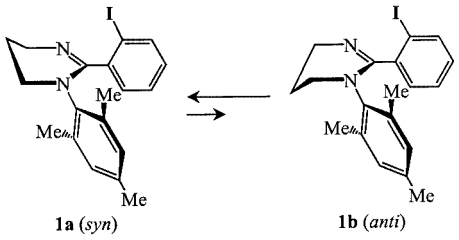


Figure 2. a) ^{1}H methyl signals (300 MHz in tetrachloroethylene) of **1**, showing a single line for two *ortho*-methyl substituents at +40 °C; b) in a chiral environment (see text) the two *ortho*-methyl groups exhibit two lines over the whole temperature range examined (+40 to +120 °C), the spectrum obtained at the highest accessible temperature (+120 °C) is displayed

MM calculations[3] predict that, in addition to the structure reported for **1** in Scheme 1a, derivatives **1**−**3** should exhibit a second energy minimum, reachable by inversion of the tetrahydropyrimidine ring. As shown in Scheme 2, this second conformer (which in the case of **1b** is computed to have an energy 0.14 kcal·mol^{-1} higher[9] than **1a**) has the CH_2 moiety of position 5 in an *anti*, rather than in a *syn*, relationship with respect to the halogen atom. The presence of this minor conformer should be amenable to experimental verification, because ring-inversion processes in six-membered heterocycles possessing endocyclic double bonds display barriers in a range (7−11 kcal·mol^{-1} [10]) accessible to NMR detection.



Scheme 2. Representation of the conformers of **1** generated by the six-membered ring-inversion process; according to calculations, **1a** is more stable than **1b** (see text)

Figure 3 displays the ^{13}C NMR lines of the methylene carbon atoms of **1** in positions 4 and 6[11] as a function of temperature. Whereas the downfield line remains sharp, the upfield line broadens below −30 °C and sharpens again on further cooling to −110 °C. This behaviour is typical of an exchange process between two conformers in which the amount of the minor species is too low to be observed.[12,13] In the current case, the signal of a conformer with a 10−15% percent population would be too small to be detected above the noise, due to poor solubility at low temperature.

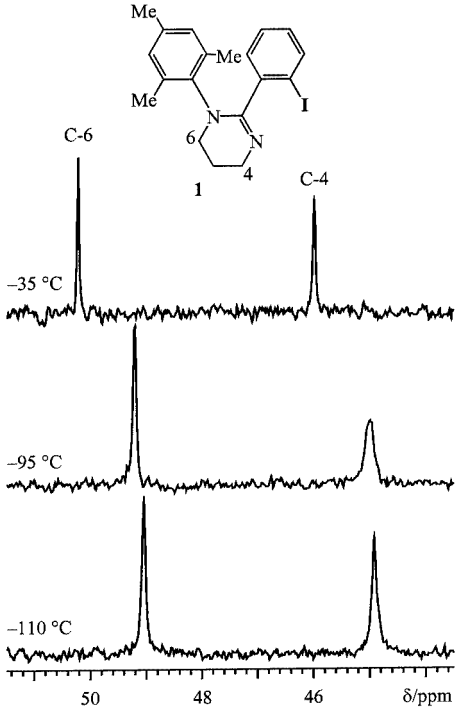


Figure 3. Temperature dependence of the ^{13}C NMR signals (75.5 MHz in CHF_2Cl/CD_2Cl_2) of the methylene group in positions 4 (upfield) and 6 (downfield) of derivative **1**; the former line exhibits its maximum broadening at −95 °C

The barrier for the observed dynamic process of **1** can nonetheless be determined, since the maximum incremental line-width ($\Delta\omega$) is related to the rate constant by the equation $k = 2\pi\Delta\omega$.[12] The upfield line reached its maximum

width (13 Hz, whereas the intrinsic line-width for non-exchanging signals under the conditions used was 5 Hz) at −95 °C, so a rate constant of 50 s^{-1}, corresponding to $\Delta G^{\neq}$ = 8.9 kcal·mol^{-1}, is derived. Analogous ^{13}C NMR spectral features were observed for **2** (X = Br) and **3** (X = Cl), the corresponding barriers being reported in Table 1.

It should be mentioned that, in principle, the observed dynamic process might be attributable to exchange between conformers created by nitrogen inversion rather than by ring inversion. Since the effects of these motions on the NMR spectra would be the same in both cases, it is impossible to make a choice solely on experimental grounds. Calculations, however, suggest that the structure of the formally sp^3-hybridized nitrogen atom of **1** is essentially planar, since the three C−N−C angles are very close to 120° [the degree of pyramidalisation, defined as 360° − Σ(R−N−R),[14] is only 1°]. This agrees with results previously obtained for the crystal structure of another 1,2-diaryltetrahydropyrimidine.[2] Accordingly, the energy difference with respect to the planar transition state would be expected to be negligible and the nitrogen inversion barrier presumably much too low[2] for NMR detection. To produce nitrogen inversion barriers as large as the observed value of 8.8 kcal·mol^{-1} a much higher degree of pyramidalisation would be required. Even trialkylamines such as trimethylamine, dimethylpentylamine, ethyldimethylamine, and diethylmethylamine, which exhibit degrees of pyramidalisation as large as 27°,[14] have nitrogen inversion barriers lower than 8.8 kcal·mol^{-1}, their values being 8.3,[15] 8.2,[16] 8.6,[17] and 7.9[18] kcal·mol^{-1}, respectively. Further support for this interpretation is offered by the barrier (10.1 kcal·mol^{-1}) measured for **2** (X = Br), since this value is much too high to be attributable to nitrogen inversion.

Substitution of the mesityl group of **1** by a 2,3-dimethylphenyl group (as in **4**) renders the molecule asymmetric (C_1 point group) if the Ar−N bond rotation (Ar = 2,3-dimethylphenyl) is sufficiently slow. In such a compound the methylene hydrogen atoms in positions 4 and 6 are diastereotopic (and their ^1H NMR signals consequently anisochronous) even at ambient temperature. At higher temperatures these signals broaden and coalesce, so that line-shape simulations provide a number of rate constants (Figure 4), from which a barrier of 19.8 kcal mol^{-1} for the Ar−N bond rotation is obtained. This value is lower than that for the rotation of the mesityl substituent in **1** (vide supra), since in **4** there is only one methyl group, rather than two, in the *ortho* positions of the rotating *N*-aryl substituent.

When the rotation rate of the *o*-iodophenyl group (Ar′) also becomes negligible, a pair of conformational diastereoisomers is generated, owing to the fact that derivative **4** exhibits two stereogenic axes (Ar−N and Ar′−C) under these conditions.

According to MM calculations,[3] the conformer with the two methyl groups in an *anti* relationship to the iodine atom (**4a**) has an energy 0.45 kcal·mol^{-1} lower than that in the *syn* relationship (**4b**); each of them, of course, exists as pair of enantiomers, but for convenience only the enantiomer (*P*) is shown in Scheme 3. It should also be noted that the

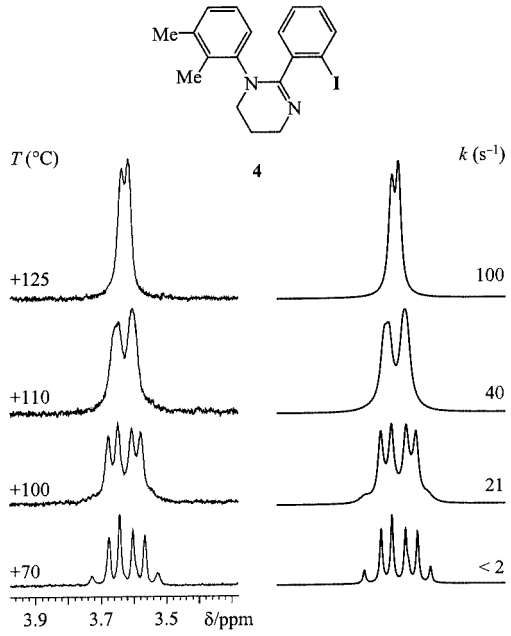
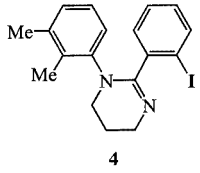
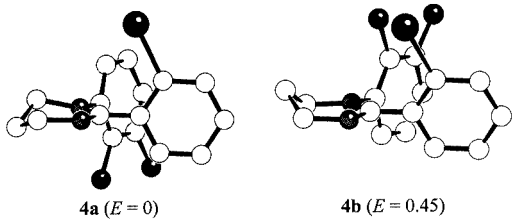


Figure 4. Left: temperature dependence of the ^1H NMR signals (300 MHz in DMSO) of the CH_2 hydrogen atoms of **4** in position 4 and 6 obtained with decoupling of the methylene signal in position 5; at +70 °C these methylene groups still display two overlapped AB-type spectra, whereas at +125 °C they yield two single lines, owing to the rapid rotation of the 2,3-dimethylphenyl ring; right: line-shape simulations obtained with the rate constants reported

six-membered ring in the more stable conformer **4a** would be predicted to adopt a different conformation than in the case of **4b**. Evidently the change in the relative disposition of the iodine atom in **4a** with respect to **4b** also requires a modification of the ring shape in order to minimize the energy of the ground state.





Scheme 3. MM-computed[3] conformational diastereoisomers generated by restricted rotation about the aryl−N-1 and aryl−C-2 stereogenic axes of **4**; only the (*P*) enantiomers of **4a** and **4b** are shown for simplicity; the calculated relative energies (*E*) are in kcal·mol^{-1}

The ^1H NMR spectrum of **4** shows how each methyl group signal broadens on cooling and splits below −80 °C into a pair of lines with a 10:1 intensity ratio (Figure 5). Line-shape simulation provides the appropriate rate con-

stants, and hence the barrier ($\Delta G^{\neq}$ = 11.5 kcal·mol^{-1}), for the interconversion of the major (**4a**) into the minor (**4b**) conformer.

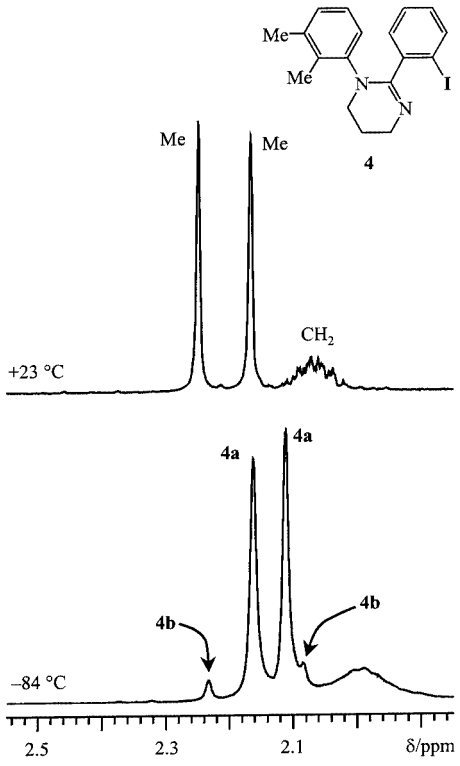


Figure 5. Top: ^{1}H NMR methyl signals (300 MHz in CD_2Cl_2) of **4** at ambient temperature; bottom: each methyl line splits into two, due to the presence of a pair of conformational diastereoisomers **4a** and **4b** (see Scheme 3) in a 10:1 ratio

This barrier is lower than that observed in **1** ($\Delta G^{\neq}$ = 12.2 kcal·mol^{-1}) because the rotating ring experiences smaller steric hindrance in the presence of the 2,3-dimethylphenyl system than in that of the bulkier mesityl moiety.

At even lower temperatures, some of the ^{13}C NMR signals of the major diastereoisomer **4a** display spectral features analogous to those seen in Figure 3. Again, this was interpreted as due to a slow ring-inversion process between two conformers, one present in a proportion too small to be observed. As in the previous cases, determination of the maximum line broadening[12] allowed the ring-inversion barrier to be measured ($\Delta G^{\neq}$ = 9.1 kcal·mol^{-1}); this value is equal to that of **1** within the experimental uncertainty of ±0.2 kcal·mol^{-1}. This indicates that, in contrast to the case of the two rotation processes (see Table 1), the ring inversion is almost unaffected by the different bulkiness of the *N*-phenyl substituent of **1** with respect to **4**.

Experimental Section

NMR Measurements: The spectra were obtained either at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C or at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C (Varian Gemini 300 or Mercury 400, respectively). The samples for determination at very low temperatures were prepared by connecting the NMR tubes containing the desired compound (and some CD_2Cl_2 for locking purposes) to a vacuum line. The gaseous solvent (CHF_2Cl) was subsequently condensed therein by means of liquid nitrogen cooling. The tubes were then sealed under vacuum and introduced into the precooled probes of the spectrometers. The temperature was calibrated by means of an Ni/Cu thermocouple inserted into the NMR probe before the measurements. Computer simulation of line shapes was performed with a PC version of the computer program based on DNMR6 routines,[19] and the best fit was visually judged by superimposition of the plotted and the experimental traces.

Material: 1,2-Diaryl-1,4,5,6-tetrahydropyrimidines **1**−**4** were synthesized by ring closure of the corresponding *N*-acyl-*N*′-aryl-1,3-propanediamines.[20,21] Yields and physical data of new compounds are as follows.

2-(2-Chlorophenyl)-1-(2,4,6-trimethylphenyl)-1,4,5,6-tetrahydropyrimidine (3): This compound was obtained in 71% yield (0.443 g). M.p. 107−109 °C (benzene/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.14 (m, 2 H), 2.15 (s, 3 H), 2.30 (br. s, 6 H), 3.47 (t, *J* = 5.80 Hz, 2 H), 3.73 (t, *J* = 5.50 Hz, 2 H), 6.72 (br. s, 2 H), 6.78 (dt, *J* = 7.6, 1.8 Hz, 1 H), 6.84 (dd, *J* = 7.8, 1.7 Hz, 1 H), 6.93 (dt, *J* = 7.4, 1.2 Hz, 1 H), 7.76 (dd, *J* = 7.9, 1.2 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C, TMS): δ = 19.19 (CH_3), 20.92 (CH_3), 22.20 (CH_2), 44.65 (CH_2), 48.65 (CH_2), 126.80 (CH), 128.21 (CH), 129.27 (3 CH), 133.64 (C), 136.83 (C), 139.72 (C), 140.14 (CH), 159.01 (C) ppm. MS (E.I.): *m*/*z* = 312 and 314 [M$^{+\cdot}$]. $C_{19}H_{21}ClN_2$ (312.84): calcd. C 72.95, H 6.77, N 8.95; found C 73.00, H 6.71, N 8.91.

2-(2-Bromophenyl)-1-(2,4,6-trimethylphenyl)-1,4,5,6-tetrahydropyrimidine (2): This compound was obtained in 74% yield (0.528 g). M.p. 111−112 °C (benzene/cyclohexane). ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C, TMS): δ = 2.09 (m, 2 H), 2.12(s, 3 H), 2.27 (br. s, 6 H), 3.42 (m, 2 H), 3.76 (m, 2 H), 6.71 (br. s, 2 H), 6.95 (m, 3 H), 7.43 (m, 1 H) ppm. ^{13}C NMR (75.45 MHz, CD_2Cl_2, 25 °C, TMS): δ = 19.19 (CH_3), 21.44 (CH_3), 23.03 (CH_2), 45.60 (CH_2), 49.84 (CH_2), 127.74 (CH), 130.55 (CH), 130.70 (CH), 130.99 (CH), 134.98 (CH) ppm. MS (E.I.): *m*/*z* = 356 and 358 [M$^{+\cdot}$]. $C_{19}H_{21}BrN_2$ (357.29): calcd. C 63.87, H 5.92, N 7.84; found C 63.93, H 5.87, N 7.81.

2-(2-Iodophenyl)-1-(2,4,6-trimethylphenyl)-1,4,5,6-tetrahydropyrimidine (1): This compound was obtained in 72% yield (0.290 g). M.p. 150−152 °C (cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.10 (m, 2 H), 2.12 (s, 3 H), 2.26 (br. s, 6 H), 3.45 (m, 2 H,), 3.62 (m, 2 H), 6.71 (br. s, 2 H), 6.94 (dt, *J* = 7.6, 1.1 Hz, 1 H), 7.00 (dd, *J* = 7.9, 1.8 Hz, 1 H), 7.07 (m, 1 H), 7.24 (dd, *J* = 8.0, 1.1 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_2Cl_2, 25 °C, TMS): δ = 17.99 (CH_3), 20.35 (CH_3), 21.52 (CH_2), 43.83 (CH_2), 48.75 (CH_2), 126.25 (CH), 129.59 (CH), 129.73 (CH), 130.18 (CH), 130.59 (CH) ppm. MS (E.I.): *m*/*z* = 404 [M$^{+\cdot}$]. $C_{19}H_{21}IN_2$ (404.29): calcd. C 56.45, H 5.24, N 6.93; found C 56.51, H 5.20, N 6.88.

1-(2,3-Dimethylphenyl)-2-(2-iodophenyl)-1,4,5,6-tetrahydropyrimidine (4): This compound was obtained in 74% yield (0.577 g). M.p. 105−107 °C (cyclohexane). ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C, TMS): δ = 2.07 (m, 2 H), 2.17 (s, 3 H), 2.25 (s, 3 H), 3.42−3.73 (m, 4 H), 6.74−6.91 (m, 3 H), 7.06 (d, *J* = 4.6 Hz, 1 H), 7.12 (m, 2 H), 7.07 (m, 1 H), 7.66 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (75.5 MHz, CD_2Cl_2 25 °C, TMS): δ = 15.49 (CH_3), 20.77 (CH_3), 22.26 (CH_2), 45.33 (CH_2), 50.31 (CH_2), 126.24 (CH), 126.86 (CH); 127.85 (CH), 128.88 (CH), 129.69 (CH), 134.76 (C), 138.92 (C), 139.79 (CH), 142.76 (C), 144.75 (C), 157.66 (C) ppm. MS (E.I.): *m*/*z* = 390 [M$^{+\cdot}$]. $C_{18}H_{19}IN_2$ (390.26): calcd. C 55.40, H 4.91, N 7.18; found C 55.47, H 4.87, N 7.13.

N-Acyl-*N*′-aryl-1,3-propanediamine intermediates were synthesized by aminolysis of the corresponding *N*-(3-bromopropyl)benzamides.[21] Yields and physical data are as follows.

***N*′-(2-Chlorobenzoyl)-*N*-(2,4,6-trimethylphenyl)-1,3-propanediamine:** This compound was obtained as an oil (73% yield, 0.963 g). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.60−7.63 (m, 1 H, aromatics), 7.29−7.38 (m, 3 H, aromatics), 6.82 (s, 2 H, aromatics), 6.70 (br. s, 1 H, NHCO), 3.66 (q, 2 H, NCH_2), 3.04 (t, 2 H, NCH_2), 2.25 (s, 6 H, CH_3 *ortho*), 2.22 (s, 3 H, CH_3 *para*), 1.90 (quint, 2 H, $CH_2CH_2CH_2$) ppm. MS: *m*/*z* = 330 [$M^{+\cdot}$].

***N*′-(2-Bromobenzoyl)-*N*-(2,4,6-trimethylphenyl)-1,3-propanediamine:** This compound was obtained as an oil (64% yield, 0.957 g). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.56 (dd, 1 H, aromatics), 7.48 (dd, 1 H, aromatics), 7.33 (dt, 1 H, aromatics), 7.22−7.25 (m, 1 H, aromatics), 6.82 (s, 2 H, aromatics), 6.67 (br. s, 1 H, NHCO), 3.64 (q, 2 H, CH_2N), 3.05 (t, 2 H, CH_2N), 2.25 (s, 6 H, CH_3 *ortho*), 2.21 (s, 3 H, CH_3 *para*), 1.90 (quint, 2 H, $CH_2CH_2CH_2$) ppm. MS: *m*/*z* = 374 [$M^{+\cdot}$].

***N*′-(2-Iodobenzoyl)-*N*-(2,4,6-trimethylphenyl)-1,3-propanediamine:** This compound was obtained as an oil (51% yield, 1.076 g). ^{1}H NMR: δ = 7.96 (d, 1 H, aromatics), 7.47−7.49 (m, 2 H, aromatics), 7.11−7.14 (m, 1 H, aromatics), 6.94 (s, 2 H, aromatics), 6.67 (br. s, 1 H, NHCO), 3.76 (q, 2 H, CH_2N), 3.19 (t, 2 H, CH_2N), 2.39 (s, 6 H, CH_3 *ortho*), 2.34 (s, 3 H, CH_3 *para*), 2.05 (quint, 2 H, $CH_2CH_2CH_2$) ppm. MS: *m*/*z* = 422 [$M^{+\cdot}$].

***N*-(2,3-Dimethylphenyl)-*N*′-(2-iodobenzoyl)-1,3-propanediamine:** This compound was obtained in 75% yield (1.224 g). M.p. 90−92 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.84−7.87 (m, 1 H, aromatics), 7.35−7.37 (m, 2 H, aromatics), 7.08−7.11 (m, 1 H, aromatics), 6.99−7.04 (m, 1 H, aromatics), 6.59 (d, 1 H, aromatics), 6.55 (d, 1 H, aromatics), 6.04 (br. s, 1 H, NHCO), 4.04 (br. s, 1 H, NHAr), 3.60 (q, 2 H, CH_2N), 3.37 (t, 2 H, CH_2N), 2.27 (s, 3 H, CH_3Ar), 2.06 (s, 3 H, CH_3Ar), 1.97 (quint, 2 H, $CH_2CH_2CH_2$) ppm. MS: *m*/*z* = 408 [$M^{+\cdot}$].

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[6] Within experimental error, the $\Delta G^{\neq}$ values determined by NMR were found to be independent of temperature, indicating a negligible value for $\Delta S^{\neq}$. This feature has often been observed in conformational processes; see for instance: S. Hoogosian, C. H. Bushweller, W. G. Anderson, G. Kigsley, *J. Phys. Chem.* **1976**, *80*, 643. L. Lunazzi, G. Cerioni, K. U. Ingold, *J. Am. Chem. Soc.* **1976**, *98*, 7484. F. Bernardi, L. Lunazzi, P. Zanirato, G. Cerioni, *Tetrahedron* **1977**, *33*, 1337. L. Lunazzi, C. Magagnoli, M. Guerra, D. Macciantelli, *Tetrahedron Lett.* **1979**, 3031. L. Lunazzi, D. Macciantelli, L. Grossi, *Tetrahedron* **1983**, *39*, 305. J. E. Anderson, D. A. Tocher, D. Casarini, L. Lunazzi, *J. Org. Chem.* **1991**, *56*, 1731. M. A. Cremonini, L. Lunazzi, G. Placucci, R. Okazaki, G. Yamamoto, *J. Am. Chem. Soc.* **1992**, *114*, 6521. R. Borghi, L. Lunazzi, G. Placucci, G. Cerioni, E. Foresti, A. Plumitallo, *J. Org. Chem.* **1997**, *62*, 4924.

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