CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201300201

Unique Structural Properties of 2,4,6-Tri-*tert*-butylanilide: Isomerization and Switching between Separable Amide Rotamers through the Reaction of Anilide Enolates

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Abstract: Herein, we report a unique structural property of 2,4,6-tri-*tert*-butylanilide, which can be separated into its amide rotamers at room temperature. Interconversion between the rotamers of anilide enolates occurs readily at room temperature and their reaction with electrophiles gives mixtures of the rotamers in a ratio that depends on the reactivity of the corresponding electrophile. That is, the reaction of the 2,4,6-tri-*tert*-butylacetanilide enolate with reactive electrophiles, such as allyl bromide or protic acids, gives mixtures of the anilide rotamers in which the *E* rotamer is the major component, whereas less-reactive electrophiles, such as 1-bromopropane and 2-iodopropane, yield mixtures of the rotamers in which the *Z* rotamer is the major component. The rotameric ratio of the product is also strongly dependent on the reactivity of the anilide enolate. Switching between the anilide rotamers can be achieved through protonation of a less-reactive enolate by a less-reactive protic acid and thermal isomerization of the anilide.

Keywords: amides · electrophilic addition · enolates · isomerization · rotamers

Introduction

Rotational isomers, owing to the double-bond character of the amide C(O)–N bond, play a key role in regulating the activity of biologically active peptides and functional molecules that contain amide skeletons.[1] Moreover, these isomers are known to significantly influence the chemical reactivity of substrates that contain an amide tether.[2] Although the existence of such amide rotamers is often confirmed by means of NMR spectroscopy, they generally cannot be isolated because interconversion between the two rotamers occurs easily at room temperature.

In 1967, Chupp and Olin reported that the amide bond in 2,6-di-*tert*-butylanilides had a high rotational barrier (27–28 kcal mol^{-1}) and that the individual rotamers could be isolated at room temperature (Figure 1).[3] This report is noteworthy as a rare example of a separable amide rotamer,[4] but no systematic study with anilide substrates, other than α-haloacetanilides ($R^1 = XCH_2$; X = Cl, Br, I), or the stereoselective syntheses of anilide rotamers have been reported. In addition, the structural properties of these anilides have not been investigated in detail.

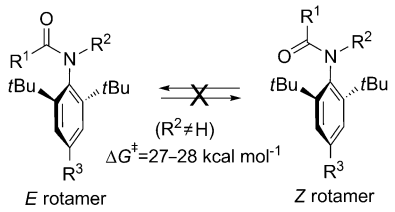

Figure 1. Separable rotamers of 2,6-di-*tert*-butylanilides.

Recently, we reported the highly selective stereodivergent synthesis of the *E* and *Z* rotamers of various *N*-allylated 2,4,6-tri-*tert*-butylanilide derivatives through Pd-catalyzed N-allylation and aza-Claisen-rearrangement reactions.[5] Moreover, the relative thermodynamic stabilities of the obtained anilide rotamers was also clarified.[5]

Herein, we report a unique structural property of 2,4,6-tri-*tert*-butylanilide derivatives.[6] Interconversion between the rotamers of anilide enolates proceeds readily at room temperature and their reaction with some electrophiles gives mixtures of rotamers in a ratio that depends on the reactivities of both the enolate and the electrophile (Scheme 1). Switching between anilide rotamers through protonation of the anilide enolates and thermal isomerization is also described.

Results and Discussion

Isomerization through the formation of acetanilide enolates: During the course of our investigation of the reactivity of a

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201300201.

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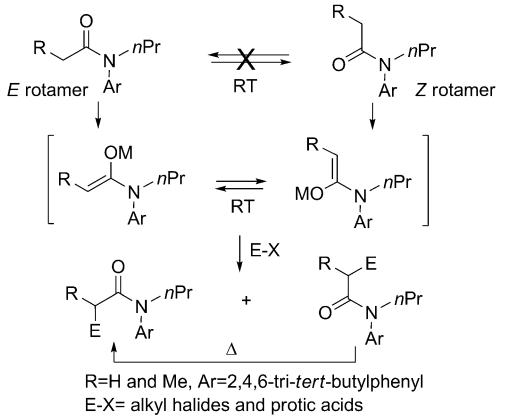
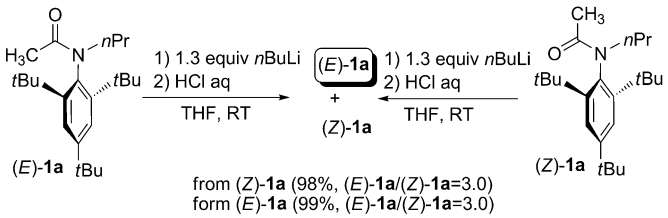


Scheme 1. Isomerization and switching between 2,4,6-tri-*tert*-butylanilide rotamers through the formation of anilide enolates.

lithium enolate that was prepared from *N*-(*n*-propyl)-2,4,6-tri-*tert*-butylacetanilide (**1a**), we unexpectedly found that the reaction of an anilide enolate with an electrophile gave mixtures of anilide rotamers. That is, when *Z* rotamer (*Z*)-**1a** was treated with *n*BuLi (1.3 equiv) for 10 min at RT, followed by HCl (aq), rotamer mixtures in which the *E* rotamer was the major component were obtained in the ratio of (*E*)-**1a**/(*Z*)-**1a** = 3.0:1 (Scheme 2). Under the same conditions, the reaction of *E* rotamer (*E*)-**1a** also gave rotamer mixtures with the same *E/Z* ratio (3.0:1, Scheme 2).

These results indicate that the interconversion between the rotamers of anilide enolate **1A** occurs quickly at RT to afford equilibrium mixtures of (*E*)-**1A** and (*Z*)-**1A** within 10 min (Figure 2). Enolate (*E*)-**1A** may be somewhat more stable than (*Z*)-**1A** and exist as the predominant rotamer.[5,7] The preferential formation of anilide (*E*)-**1a** in the protonation of enolate **1A** may be due to the equilibrium ratio of **1A**.



Scheme 2. Protonation with the lithium enolate that was prepared from rotamers (*E*)-**1a** and (*Z*)-**1a**.

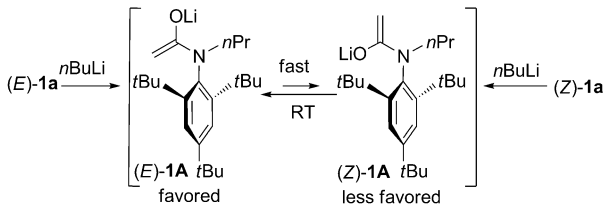


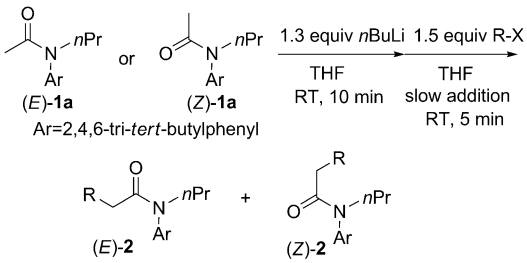
Figure 2. Interconversion between lithium enolates (*E*)-**1A** and (*Z*)-**1A**.

Rotation around the N–C bond of enolate **1A** should occur more easily in comparison with that of anilide **1a** because of the decrease in double-bond character. In asymmetric α-alkylation reactions with chiral amide enolates, it has been pointed out that such a N–C bond rotation may bring about a decrease in stereoselectivity.[8] However, because ordinary amide rotamers cannot be isolated at RT, N–C bond rotation in the amide enolate has so far been difficult to confirm. Scheme 2 should provide the first evidence for N–C bond rotation in an amide enolate.

The reactions of acetanilide enolate **1A** with various alkyl halides were further examined under the conditions given in Scheme 2 (Table 1). In these alkylation reactions, an interesting tendency of the isomerization step was observed.

The reaction of enolate **1A** with allyl bromide gave a similar result to the protonation shown in Scheme 2. That is, the allylation of enolate **1A**, which was prepared from rotamers (*E*)-**1a** and (*Z*)-**1a**, proceeded smoothly to afford rotamer mixtures of allylation product **2b** in ratios of (*E*)-**2b**/(*Z*)-**2b** = 2.4:1 and 2.5:1, respectively (Table 1, entries 1 and 2). In the reaction with benzyl bromide, preferential formation of *E* rotamer (*E*)-**2c** was also observed, although the *E/Z* ratios decreased slightly ((*E*)-**2c**/(*Z*)-**2c** = 1.8:1 and 1.7:1; Table 1, entries 3 and 4). In contrast to Table 1, entries 1–4, with 3-bromocyclohexene, *Z* rotamer (*Z*)-**2d** was obtained as the major isomer ((*E*)-**2d**/(*Z*)-**2d** = 1:2.6 and 1:2.3; Table 1, entries 5 and 6). The preference for the *Z* rotamer increased with decreasing reactivity of the alkyl halide. The reaction with 1-bromopropane gave the product (**2e**) in the ratio (*E*)-**2e**/(*Z*)-**2e** = 1:6.2 (Table 1, entries 7 and 8). In the reaction with less-reactive 2-iodopropane, a further increase in the preference for the *Z* rotamer was observed ((*E*)-**2f**/(*Z*)-**2f** = 1:15.4 and 1:18.9; Table 1, entries 9 and 10). Thus, the rotamer ratios of the alkylated products (**2**) were found

Table 1. Reaction of 2,4,6-tri-*tert*-butylacetanilide enolates with various alkyl halides.



	1a	R–X	2	Yield [%][a]	*E/Z*[b]
1	(*E*)-**1a**	allyl–Br	**2b**	99	2.4:1
2	(*Z*)-**1a**	allyl–Br	**2b**	98	2.5:1
3	(*E*)-**1a**	$PhCH_2$–Br	**2c**	70	1.8:1
4	(*Z*)-**1a**	$PhCH_2$–Br	**2c**	74	1.7:1
5	(*E*)-**1a**	3-bromocyclohexene	**2d**	57	1:2.6
6	(*Z*)-**1a**	3-bromocyclohexene	**2d**	53	1:2.3
7	(*E*)-**1a**	nC_3H_7–Br	**2e**	84	1:6.2
8	(*Z*)-**1a**	nC_3H_7–Br	**2e**	80	1:6.2
9	(*E*)-**1a**	iC_3H_7–I	**2f**	71	1:15.4
10	(*Z*)-**1a**	iC_3H_7–I	**2f**	62	1:18.9

[a] Yield of isolated product. [b] Ratio estimated by ^{1}H NMR (400 MHz) spectroscopy.

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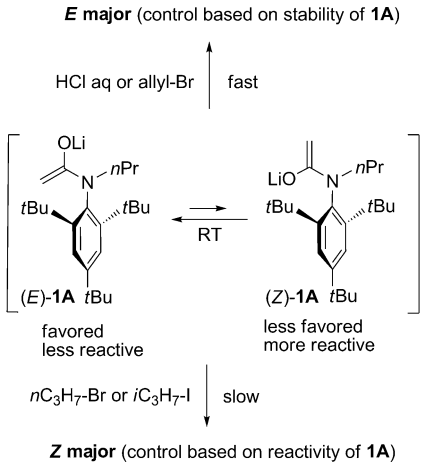


Figure 3. Origin of the selectivity for the *E* or *Z* rotamers in the reaction of acetanilide enolate **1A** with different electrophiles.

to significantly depend on the reactivity of the alkylated reagents.

These results may be rationalized as follows (Figure 3): In the reaction with a reactive alkyl halide, such as allyl bromide, the α-alkylation might proceed at a faster rate than interconversion between enolates (*E*)-**1A** and (*Z*)-**1A**. Hence, similar to the protonation shown in Scheme 2, the rotameric ratio of allylation product **2b** is mainly determined by the equilibrium ratio of enolate **1A** to give compound (*E*)-**1a** as the major product. On the other hand, with a less-reactive alkyl halide, because alkylation occurs slowly in comparison with the interconversion of the enolate, the rotameric ratio is influenced by the relative reactivity of enolate rotamers (*E*)-**1A** and (*Z*)-**1A** rather than by the thermodynamic stability of enolate **1A**. Rotamer (*E*)-**1A** should be less reactive than (*Z*)-**1A**, because the α-carbon atom of rotamer (*E*)-**1A** is shielded by two *ortho-tert*-butyl groups. Accordingly, compound (*Z*)-**2** is preferentially obtained through the selective alkylation of reactive enolate (*Z*)-**1A**. The contribution of the reactivity of the enolate to controlling the outcome should increase with decreasing the reactivity of the alkyl halides, thereby leading to an increase in the preference for the *Z* rotamer (Figure 4).

The isomerization shown in Scheme 2 and Table 1 was barely noticeable at −20 °C. When rotamer (*Z*)-**1a** was treated with *n*BuLi for 10 min at −20 °C and subsequently reacted with HCl (aq) or allyl bromide, only a small amount of the *E* rotamer was formed (Scheme 3). These results indicate that rotation around the N−C bond of enolate **1A** occurs very slowly at −20 °C.

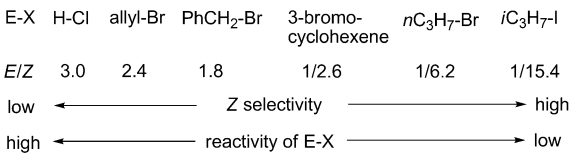
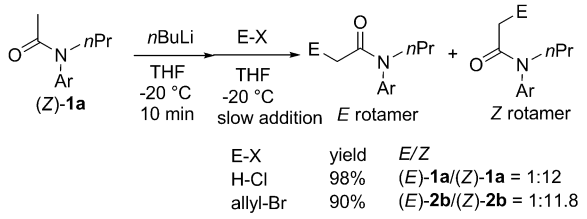


Figure 4. Relationship between the selectivity for the *Z* rotamer and the reactivity of the electrophile.

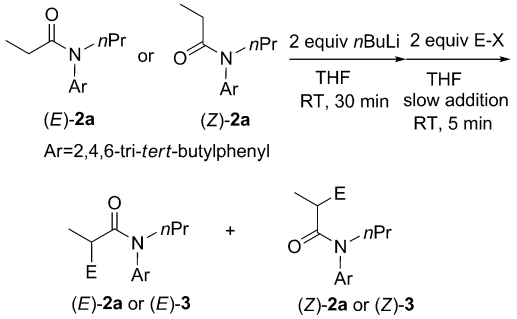


Scheme 3. Reaction of compound (*Z*)-**1a** with electrophiles at −20 °C.

Isomerization through the formation of propionanilide enolate: Next, the reaction of propionanilide enolate with various electrophiles was examined further (Table 2). After treating compound (*E*)-**2a** or (*Z*)-**2a** with *n*BuLi (2 equiv) for 30 min at RT in THF,[10] the resulting anilide enolate was reacted with various electrophiles. Protonation of the anilide enolate that was prepared from compounds (*E*)-**2a** and (*Z*)-**2a** afforded (*E*)-**2a** as the major rotamer in the ratio *E*/*Z* = 2.1:1 (Table 2, entries 1 and 2). Although the *E*-selectivity was lower, these results were similar to those with acetanilide **1a** (Scheme 2). Moreover, the reaction with allyl bromide preferentially gave *Z* rotamer (*Z*)-**3b** in *E*/*Z* ratios = 1:6.8 and 1:7.3 (Table 2, entries 3 and 4). With benzyl bromide, similar preference for the *Z* rotamer was also observed ((*E*)-**3c**/(*Z*)-**3c** = 1:8.6 and 1:9.1; Table 2, entries 5 and 6).

These *Z*-selectivities are notably in contrast with the observed *E*-selectivity in the allylation and benzylation of acetanilide **1a**. This contrast can be explained by the reactivity of the enolate. Because the reactivity of propionanilide enolate **2A** is lower than that of acetanilide enolate **1A**, the reaction with reactive allyl bromide and benzyl bromide may proceed at a slower rate than the interconversion between

Table 2. Reaction of 2,4,6-tri-*tert*-butylpropionanilide enolates with various alkyl halides.



	2a	E−X	2a or 3	Yield [%][a]	*E*/*Z*[b]
1	(*E*)-**2a**	H−Cl (aq)	**2a**	95	2.1:1
2	(*Z*)-**2a**	H−Cl (aq)	**2a**	93	2.1:1
3	(*E*)-**2a**	allyl−Br	**3b**	98	1:6.8
4	(*Z*)-**2a**	allyl−Br	**3b**	95	1:7.3
5	(*E*)-**2a**	$PhCH_2$−Br	**3c**	93	1:8.6
6	(*Z*)-**2a**	$PhCH_2$−Br	**3c**	86	1:9.1
7	(*E*)-**2a**	nC_3H_7−Br	**3e**	73	1:46
8	(*Z*)-**2a**	nC_3H_7−Br	**3e**	75	1:46

[a] Yield of the isolated product. [b] Ratio estimated by ^1H NMR (400 MHz) spectroscopy.

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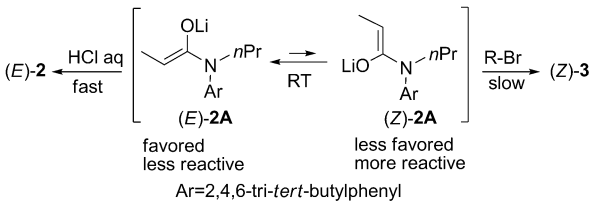


Figure 5. Origin of the selectivity for the *E* or *Z* rotamers in the reaction of propionanilide enolate **2A** with different electrophiles.

enolates (*E*)-**2A** and (*Z*)-**2A** (Figure 5). Accordingly, the rotameric ratios are controlled by the relative reactivity of enolate **2A**, rather than by the stability of compound **2A**, which preferentially generates alklylation product (*Z*)-**3** from reactive enolate (*Z*)-**2A**. Thus, rotamer selectivity was found to be influenced not only by the reactivity of the electrophile but also by the reactivity of the enolate.

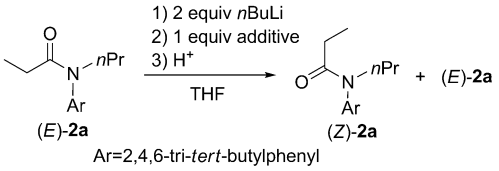
The reaction with less-reactive 1-bromopropane proceeded in an almost-completely *Z*-selective manner to give propylated product (*Z*)-**3e** (*E*/*Z* = 1:46; Table 2, entries 7 and 8). It should be noted that the propylation of (*E*)-**2a** occurred with almost-complete inversion of the rotational isomerism (Table 2, entry 7).

In these reactions, a solution of the alkyl bromide in THF was slowly added to the enolate in THF (about 5 min), whereas quick addition of alkyl bromide resulted in a considerable decrease in the *Z*-selectivity.

Switching between the anilide rotamers: Next, as an application of isomerization through the formation of the enolate, reversible interconversion between the anilide rotamers was investigated.[9] We previously reported that, in N-allylated 2,4,6-tri-*tert*-butyl anilides, the *E* rotamers were thermodynamically more stable than the *Z* rotamers and that thermal isomerization of the anilides gave rotameric mixtures in which the *E* rotamer was the major component.[5] Accordingly, if the *Z* rotamers could be preferentially formed through the protonation of the anilide enolate, switching between the anilide rotamers should be achievable. However, the protonation of enolates **1A** and **2A** with HCl (aq), by exerting control that was based on the thermodynamic stability of the enolates, gave rotameric mixtures in which the *E* rotamer was the major component (Scheme 2, Table 2, entries 1 and 2; Table 3, entry 1). Moreover, we expected that the reaction of a less-reactive anilide enolate with a less-reactive proton source might lead to control based on the reactivity of the enolate to preferentially form the *Z* rotamer.

Although lithium enolate **2A**, which was prepared from propionanilide (*E*)-**2a**, was protonated by using the bulky 2,6-di-*tert*-butylphenol (DTB-phenol), no change in selectivity was observed ((*E*)-**2a**/(*Z*)-**2a** = 2.2:1; Table 3, entries 1 and 2). To decrease the reactivity of the enolate, the addition of several metal salts was examined. When a solution of enolate **2A** was treated with CuI (1 equiv), followed by HCl (aq), compound **2a** was obtained with slight *Z*-selectivity ((*E*)-**2a**/(*Z*)-**2a** = 1:1.2; Table 3, entry 3). After the addition

Table 3. Protonation of 2,4,6-tri-*tert*-butylpropionanilide enolates.



	Additive	H^+	*E*/*Z*[a]
1	none	HCl (aq)	2.1:1
2	none	DTB-phenol[b]	2.2:1
3	CuI	HCl (aq)	1:1.2
4	CuI	DTB-phenol[b]	1:4.6
5	CuI[c]	DTB-phenol[b]	1:2.7
6	$ZnCl_2$	DTB-phenol[b]	1.5:1
7	$NiBr_2$	DTB-phenol[b]	3.5:1
8	Cp_2ZrCl_2	DTB-phenol[b]	5.4:1

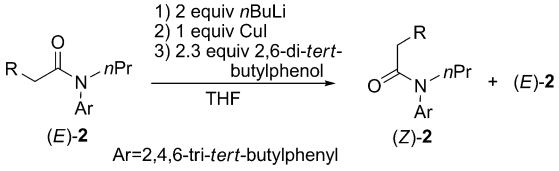
[a] Ratio estimated by ^{1}H NMR (400 MHz) spectroscopy. [b] DTB-phenol = 2,6-di-*tert*-butylphenol. [c] CuI (2 equiv).

of CuI, protonation by 2,6-di-*tert*-butylphenol led to an increase in *Z*-selectivity and, in this case, compound (*Z*)-**2a** was preferentially obtained in the ratio *E*/*Z* = 1:4.6 (Table 3, entry 4). The additive effect of CuI is specific; such *Z*-selectivity was not observed with other metal salts (Table 3, entries 6–8).

This *Z*-selective protonation with copper enolate can be applied to various anilides (**2c**–**2g**, Table 4). Under the same conditions, the *E* rotamers of anilides **2c**–**2g** were converted into rotameric mixtures with *E*/*Z* ratios of 1:2.2 to 1:6.1 (Table 4, entries 2–6). In these reactions, the slow addition (about 15 min) of 2,6-di-*tert*-butylphenol (in THF) to the copper enolate was required. Quick addition of 2,6-di-*tert*-butylphenol resulted in lower *Z*-selectivity.

Although the protonation of acetanilide enolate was also investigated under the same conditions, in this case, compound (*E*)-**1a** was obtained as the major rotamer ((*E*)-**1a**/(*Z*)-**1a** = 2.5:1). This result indicates that the reaction of acetanilide copper enolate with 2,6-di-*tert*-butylphenol still occurs at a faster rate than the interconversion between enolate rotamers.

Table 4. Protonation of various 2,4,6-tri-*tert*-butylanilide enolates.



	(*E*)-**2**	R	Yield [%][a]	*E*/*Z*[b]
1	(*E*)-**2a**	CH_3	81	1:4.6
2	(*E*)-**2c**	$PhCH_2$	88	1:4.1
3	(*E*)-**2d**	cyclohexene-3-yl	84	1:2.2
4	(*E*)-**2e**	nC_3H_7	88	1:4.6
5	(*E*)-**2f**	iC_3H_7	93	1:3.7
6	(*E*)-**2g**	cyclohexyl	78	1:6.1

[a] Yield of the isolated product. [b] Ratio estimated by ^{1}H NMR (400 MHz) spectroscopy.

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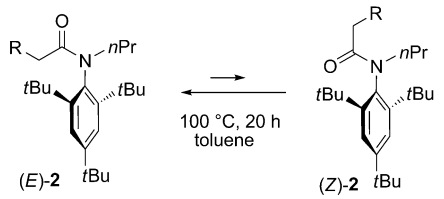
Table 5. Thermal isomerization between the anilide rotamers.



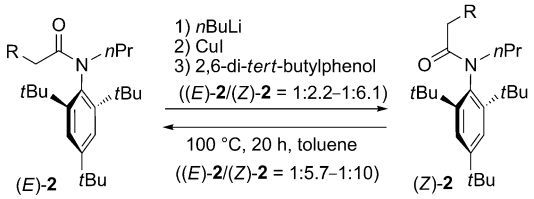
	2	R	E/Z[a,b]	E/Z[b,c]
1	**2a**	CH_3	*Z* only	10:1
2	**2c**	$PhCH_2$	1:3.5	8.4:1
3	**2d**	cyclohexene-3-yl	*Z* only	6.2:1
4	**2e**	nC_3H_7	1:4.7	8.3:1
5	**2f**	iC_3H_7	1:3.8	5.7:1
6	**2g**	cyclohexyl	*Z* only	6.2:1

[a] Ratio before heating. [b] Ratio estimated by ^{1}H NMR (400 MHz) spectroscopy. [c] Ratio after heating (equilibrium ratio).

The results of the thermal isomerization of anilides **2a**–**2g** are shown in Table 5. When anilides **2a**–**2g**, in which the *Z* rotamers were the major components, were heated for 20 h at 100 °C in toluene, in all cases, equilibrium mixtures were obtained in which the *E* rotamers were the major components, with (*E*)-**2**/(*Z*)-**2** ratios of 5.7:1 to 10:1. The *E*/*Z* ratios of hindered anilides **2d**, **2f**, and **2g** (*E*/*Z* = 5.7:1 to 6.2:1; Table 5, entries 3, 5, and 6) were slightly lower than those of less-hindered anilides **2a**, **2c**, and **2e** (*E*/*Z* = 8.3:1 to 10:1; Table 5, entries 1,2,4). As mentioned in our previous paper, these *E*-selectivities can be explained by the destabilization of the *Z* rotamer, owing to 1) the n–π repulsion between the lone pair on the carbonyl oxygen atom and the π-electron on the *tert*-butylphenyl group and 2) steric repulsion between the *n*-propyl group and the acyl substituent.[5,7]

Thus, reversible interconversion (switching) between anilide rotamers was achieved through the protonation of anilide enolates and the thermal isomerization of anilides (Scheme 4).

The stereochemistry of the anilide rotamers was determined based on the chemical shifts in their ^{1}H NMR spectra. In general, the α-hydrogen atoms in compounds (*E*)-**2** and (*E*)-**3** appeared at higher field (δ = 0.2–0.4 ppm) than those of compounds (*Z*)-**2** and (*Z*)-**3**, owing to the anisotropy that was caused by the large twist angle in the *tert*-butylphenyl group. These stereochemical assignments were also confirmed by NOESY experiments. For examples, in the *Z* rotamers of compounds **2f** and **3e**, a strong NOE correlation between the N-CH_2 hydrogen atoms and the α-hydrogen atoms was observed, whereas, in the *E* rotamers, no NOE between these hydrogen atoms was detected.



Scheme 4. Switching between anilide rotamers (*E*)-**2** and (*Z*)-**2**.

Conclusion

We have reported a unique isomerization between the separable rotamers of 2,4,6-tri-*tert*-butylanilide derivatives through the formation of the anilide enolate; that is, in anilide enolates, interconversion between the rotamers readily occurs at room temperature and their reaction with electrophiles gives rotameric mixtures of the products in a ratio that depends on the reactivity of the electrophiles. The reaction of the 2,4,6-tri-*tert*-butylacetanilide enolate with reactive electrophiles predominantly gives the *E* rotamer, whereas, in the reaction with less-reactive electrophiles, the *Z*-rotamer products predominate. The rotamer ratio in the products is also strongly dependent on the reactivity of the anilide enolate. Furthermore, as an application of this isomerization reaction, switching between the anilide rotamers was achieved. These results show a new structural property of 2,4,6-tri-*tert*-butylanilide derivatives.

Experimental Section

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are expressed in δ (ppm) downfield of $CHCl_3$ (δ = 7.26 ppm) and $CDCl_3$ (δ = 77.0 ppm), respectively. Mass spectra were recorded by using electron impact or chemical ionization. Column chromatography was performed on silica gel (75–150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a pre-packed silica-gel column (10 μm, 25 × 4 cm i.d.) with a UV detector.

General procedure for the α-alkylation of acetanilide 1a: Under a N_2 atmosphere, *n*BuLi (0.24 mL, 1.6 M in *n*-hexane) was added to a solution of compound (*E*)-**1a** (104 mg, 0.3 mmol) in THF (4.0 mL). After stirring for 10 min at RT, a solution of 1-bromopropane (55 mg, 0.45 mmol) in THF (1.0 mL) was slowly added (over 5 min) and the reaction mixture was stirred for a further 30 min at RT. Then, the mixture was poured into a 2% HCl solution and extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc, 20:1) gave a mixture of compounds (*Z*)-**2e** and (*E*)-**2e** (98 mg, 84% yield) in a 6.2:1 ratio. Compounds (*Z*)-**2e** (less polar) and (*E*)-**2e** (more polar) were separated by MPLC (*n*-hexane/EtOAc, 20:1).

(*Z*)- and (*E*)-*N*-(*n*-Propyl)-*N*-(2,4,6-tri-*tert*-butylphenyl)pentamide ((*Z*)-2e and (*E*)-2e)

(*Z*)-**2e**: M.p. 97–98 °C; ^{1}H NMR ($CDCl_3$): δ = 7.36 (s, 2H), 3.37–3.42 (m, 2H), 2.24 (t, *J* = 7.3 Hz, 2H), 1.65 (quint, *J* = 7.5 Hz, 2H), 1.39 (sext, *J* = 7.5 Hz, 2H), 1.33 (s, 18H), 1.28 (s, 9H), 1.02–1.14 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.85 ppm (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 174.7, 148.0, 146.7, 132.0, 125.0, 53.2, 37.3, 34.8, 34.6, 33.1, 31.3, 26.3, 22.7, 20.3, 14.0, 11.6 ppm; IR (KBr): $\tilde{\nu}$ = 1645 cm^{-1}; MS: *m*/*z*: 388 $[M+H]^+$; HRMS: *m*/*z* calcd for $C_{26}H_{46}NO$: 388.3579 $[M+H]^+$; found: 388.3582.

(*E*)-**2e**: M.p. 98–99 °C; ^{1}H NMR ($CDCl_3$): δ = 7.39 (s, 2H), 3.40–3.47 (m, 2H), 1.96 (t, *J* = 7.3 Hz, 2H), 1.59 (quint, *J* = 7.8 Hz, 2H), 1.32 (s, 18H), 1.31 (s, 9H), 1.24 (sext, *J* = 7.8 Hz, 2H), 0.97–1.10 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.83 ppm (t, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 174.0, 149.0, 146.8, 131.8, 125.9, 51.8, 37.6, 35.9, 34.7, 33.5, 31.3, 26.6, 22.6, 19.5, 14.0, 11.6 ppm; IR (KBr): $\tilde{\nu}$ = 1647 cm^{-1}; MS: *m*/*z*: 388 $[M+H]^+$; HRMS: *m*/*z* calcd for $C_{26}H_{46}NO$: 388.3579 $[M+H]^+$; found: 388.3584.

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General procedure for the α-alkylation of propionanilide 2a: Under a N_2 atmosphere, *n*BuLi (0.37 mL, 1.6 M in *n*-hexane) was added to a solution of compound (*E*)-**2a** (107 mg, 0.3 mmol) in THF (4.0 mL). After stirring for 30 min at RT, a solution of allyl bromide (73 mg, 0.6 mmol) in THF (1.0 mL) was slowly added (over 5 min) and the reaction mixture was stirred for a further 30 min at RT. Then, the mixture was poured into a 2% HCl solution and extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc, 25:1) gave a mixture of compounds (*Z*)-**3b** and (*E*)-**3b** (118 mg, 98% yield) in a 6.8 ratio. Compounds (*Z*)-**3b** (less polar) and (*E*)-**3b** (more polar) were separated by MPLC (*n*-hexane/EtOAc, 20:1).

(*Z*)- and (*E*)-*N*-(*n*-Propyl)-*N*-(2,4,6-tri-*tert*-butylphenyl)-2-methyl-4-pentenamide ((*Z*)-3b and (*E*)-3b)

(*Z*)-**3b**: M.p. 101–103 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.38$ (s, 2H), 5.83 (dddd, $J = 6.4$, 8.2, 10.1, 16.9 Hz, 1H), 5.09 (d, $J = 16.9$ Hz, 1H), 5.06 (d, $J = 10.1$ Hz, 1H), 3.46–3.57 (m, 2H), 2.68 (m, 1H), 2.48 (m, 1H), 2.21 (td, $J = 8.7$, 14.2 Hz, 1H), 1.36 (s, 9H), 1.35 (s, 9H), 1.29 (s, 9H), 1.16 (d, $J = 6.9$ Hz, 3H), 1.03–1.14 (m, 2H), 0.84 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 176.9$, 147.9, 146.8, 146.7, 136.5, 132.7, 125.2, 125.0, 116.9, 53.1, 37.6, 37.5, 37.1, 36.9, 34.6, 33.4, 31.3, 20.4, 15.5, 11.6 ppm; IR (KBr): $\tilde{\nu} = 1639\ cm^{-1}$; MS: *m/z*: 400 $[M+H]^+$; elemental analysis calcd (%) $C_{27}H_{45}NO$: C 81.14, H 11.35, N 3.50; found: C 80.68, H 11.22, N 3.50.

(*E*)-**3b**: M.p. 92–94 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.41$ (s, 2H), 5.54 (dddd, $J = 6.4$, 8.2, 10.5, 17.0 Hz, 1H), 4.92 (d, $J = 10.5$ Hz, 1H), 4.89 (d, $J = 17.0$ Hz, 1H), 3.42–3.48 (m, 2H), 2.37 (m, 1H), 2.08–2.25 (m, 2H), 1.36 (s, 9H), 1.35 (s, 9H), 1.31 (s, 9H), 1.04–1.17 (m, 2H), 1.02 (d, $J = 6.4$ Hz, 3H), 0.90 ppm (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 176.8$, 148.9, 147.3, 147.1, 136.0, 130.7, 126.4, 116.8, 52.8, 37.72, 37.70, 37.6, 36.6, 34.6, 33.8, 33.7, 31.2, 19.5, 16.5, 11.6 ppm; IR (KBr): $\tilde{\nu} = 1641\ cm^{-1}$; MS: *m/z*: 400 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{45}NO$: C 81.14, H 11.35, N 3.50; found: C 80.76, H 11.34, N 3.54.

General procedure for protonation of the copper enolate: Under a N_2 atmosphere, *n*BuLi (0.30 mL, 1.6 M in *n*-hexane) was added to a solution of compound (*E*)-**2e** (97 mg, 0.25 mmol) in THF (3.0 mL). After stirring for 30 min at RT, CuI (48 mg, 0.25 mmol) was added and the reaction mixture was stirred for a further 20 min at RT. Then, a solution of 2,6-di-*tert*-butylphenol (119 mg, 0.58 mmol) in THF (4.0 mL) was slowly added to the mixture (over 15 min) and the mixture was stirred for a further 30 min at RT. The mixture was poured into an aqueous solution of NH_4Cl and extracted with EtOAc. The EtOAc extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography on silica gel (*n*-hexane/EtOAc, 20:1) gave a mixture of compounds (*E*)-**2e** and (*Z*)-**2e** (85 mg, 88% yield) in a 4.6:1 ratio.

Acknowledgements

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

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[10] The use of *n*BuLi (1 equiv) resulted in a decrease in the chemical yield, owing to the incomplete formation of the enolate.

Received: January 19, 2013
Published online: March 27, 2013

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