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Notable Structural Property of 2,4,6-Tri-*tert*-butylanilide Enolates: Interconversion between the Rotamers and Their Reactivity

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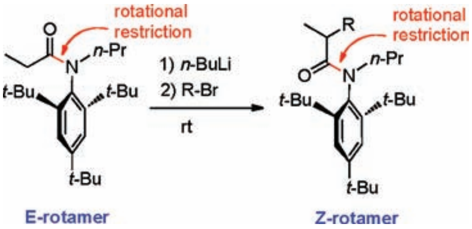
ABSTRACT



Interconversion between the separable 2,4,6-tri-*tert*-butylanilide rotamers was found to easily occur through formation of the lithium enolate. Protonation of the anilide enolate gave the anilide rotamer mixture of *E*-major. On the other hand, reactions of lithium enolate prepared from 2,4,6-tri-*tert*-butylpropionanilide with alkyl bromides preferentially afforded a *Z*-rotamer of alkylated products.

Amide C(O)−N bonds have a higher rotational barrier than a C−N bond of simple amines because of the double bond character. Rotational isomerism based on such amide bonds plays an important role in the chemical reactivity of substrates having an amide tether[1] and the regulation of actions of biologically active peptides.[2] On the other hand, amide rotamers are generally difficult to isolate because their interconversion occurs easily at rt.

2,6-Di-*tert*-butyl anilide derivatives, which were reported by Chupp et al. in 1967, are a rare example of separable amide rotamers (Figure 1).[3,4] However, a systematic study using anilide substrates other than α-haloacetanilides and stereoselective synthesis of anilide rotamers has not been described. In addition, the structural properties between the rotamers have not been investigated in detail.

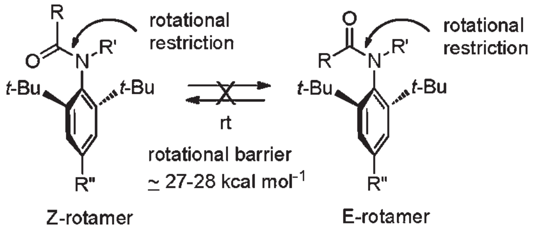


Figure 1. Separable 2,6-di-*tert*-butylanilide rotamers.

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[1] (a) Gshwend, H. W.; Lee, A. O. *J. Org. Chem.* **1978**, *38*, 2169–2175. (b) Sniekus, V.; Cueva, J. C.; Solan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896–898. (c) Ishikawa, T.; Senzaki, M.; Kadoya, R.; Miyake, N.; Izawa, M.; Saito, S. *J. Am. Chem. Soc.* **2001**, *123*, 4607–4608. (d) Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem.—Eur. J.* **2002**, *8*, 1279–1289. (e) Li, X.; Curran, D. P. *Org. Lett.* **2010**, *12*, 612–614.

[2] (a) Tanatani, A.; Azumaya, I.; Kagechika, H. *Yuki Gosei Kagaku Kyokaishi* **2000**, *58*, 556–567. (b) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4011. (d) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6398–6401.

[3] (a) Chupp, J. P.; Olin, J. F. *J. Org. Chem.* **1967**, *32*, 2297–2303. (b) Molin, W. T.; Porter, C. A.; Chupp, J. P.; Naylor, K. *Pest. Biochem. Phys.* **1990**, *36*, 277–280.

[4] Examples of separable amide rotamers: (a) Mannschreck, A. *Tetrahedron Lett.* **1965**, 1341–1347. (b) Toldy, L.; Radics, L. *Tetrahedron Lett.* **1966**, 4753–4757. (c) Staab, H. A.; Lauer, D. *Tetrahedron Lett.* **1966**, 4593–4598. (d) Staab, H. A.; Lauer, D. *Chem. Ber.* **1968**, *101*, 864–878. (e) Schlecker, R.; Seebach, D.; Lubosch, W. *Helv. Chim. Acta* **1978**, *61*, 512–516. (f) Seebach, D.; Wykypiel, W.; Lubosch, W.; Kalinowski, H. O. *Helv. Chim. Acta* **1978**, *61*, 3100–3102. (g) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592–601. (h) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145–8153. (i) Tan, L. T.; Williamson, R. T.; Gerwick, W. H. *J. Org. Chem.* **2000**, *65*, 419–425.

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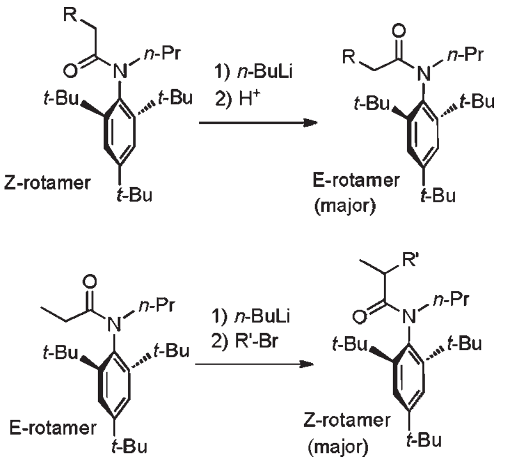
Recently, we succeeded in the highly selective stereodivergent synthesis of *E*- and *Z*-rotamers of various N-allylated 2,4,6-tri-*tert*-butylanilide derivatives using Pd chemistry.[5] Furthermore, the thermodynamic stabilities of anilide rotamers were also clarified. In this paper, we report on the novel structural property of 2,4,6-tri*tert*-butylanilide derivatives, namely, interconversion between the anilide rotamers through the formation of the lithium enolate and notable reactivity of the anilide enolate toward several electrophiles (Scheme 1). In some cases, this process occurs with almost complete inversion of the rotational isomerism. The detailed mechanisms on the interconversion and the reaction are also described.

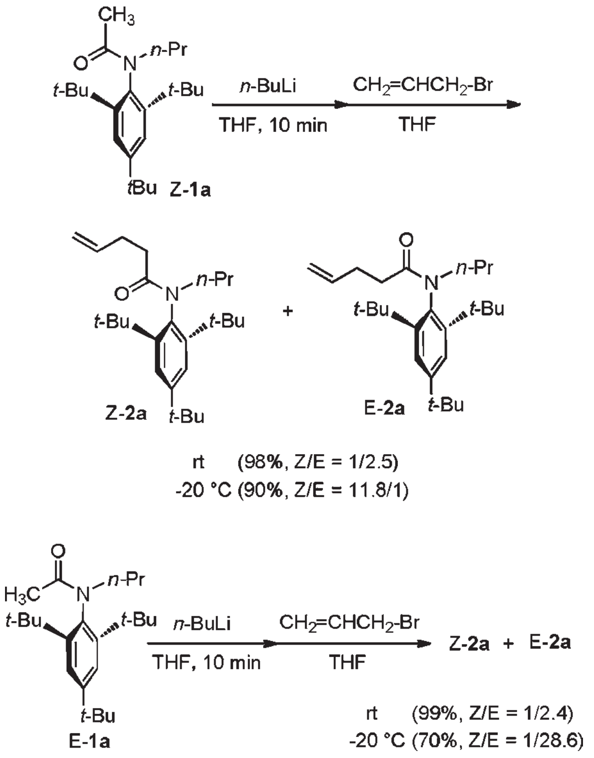
Scheme 1. Interconversion between Anilide Rotamers through the Formation of Lithium Enolates and the Reaction with an Electrophile



In the course of our investigation of the allylation with lithium enolate prepared from N-propyl 2,4,6-tri-*tert*-butylacetanilide **1a**, we unexpectedly found that the rotational isomerism of the allylated product was remarkably changed by the reaction temperature. That is, when the *Z*-rotamer *Z*-**1a** was treated with *n*-BuLi for 10 min at rt and subsequently reacted with an allyl bromide, the *E*-rotamer of allylated product **2a** was obtained as a major isomer (*Z*-**2a**/*E*-**2a** = 1/2.5, Scheme 2). In contrast, the enolate formation from *Z*-**1a** at −20 °C and the subsequent allylation gave *Z*-**2a** as a major rotamer (*Z*-**2a**/*E*-**2a** = 11.8/1, Scheme 2). In both reactions, allylated product **2a** was obtained in an excellent yield (98% and 90%).

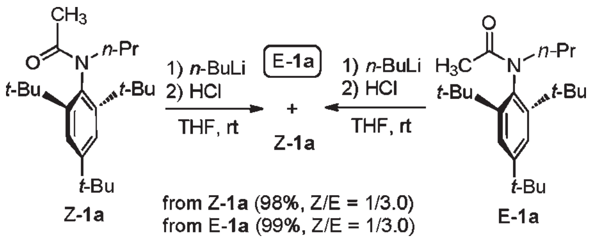
The allylation with *E*-rotamer *E*-**1a** was also examined. Allylation of *E*-**1a** at −20 °C proceeded with almost complete retention of the rotational isomerism to give *E*-**2a** with a high rotamer ratio (*Z*-**2a**/*E*-**2a** = 1/28.6, Scheme 2). On the other hand, in the allylation of *E*-**1a** at rt, the rotamer mixture was obtained in a ratio of *Z*-**2a**/*E*-**2a** = 1/2.4. This *Z*/*E* ratio (1/2.4) is very similar to that (1/2.5) in the allylation of *Z*-**1a** at rt.

Scheme 2. Allylation with Lithium Enolate Prepared from *Z*-**1a** and *E*-**1a**



A similar isomerization was also observed in the protonation of the anilide enolate. The treatment of *Z*-**1a** with *n*-BuLi for 10 min at rt and subsequent protonation by HCl aq gave a rotamer mixture of *E*-major in a ratio of *Z*-**1a**/*E*-**1a** = 1/3.0 (Scheme 3). Under the same conditions, the reaction with *E*-**1a** also gave a rotamer mixture in the same *Z*/*E* ratio (*Z*-**1a**/*E*-**1a** = 1/3.0). Such isomerization was hardly observed through the treatment with *n*-BuLi for 10 min at −20 °C and subsequent protonation.

Scheme 3. Protonation with Lithium Enolate Prepared from *Z*-**1a** and *E*-**1a**



These results indicate that the interconversion of the anilide enolate **1A** occurs quickly at rt (but slowly at −20 °C) to afford the equilibrium mixture of *E*-**1A** and *Z*-**1A** within 10 min (Figure 2). *E*-**1A** may be somewhat

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(5) (a) Ototake, N.; Nakamura, M.; Dobashi, Y.; Fukaya, H.; Kitagawa, O. *Chem.—Eur. J.* **2009**, *15*, 5090–5095. (b) Nakamura, M.; Takahashi, I.; Yamada, S.; Dobashi, Y.; Kitagawa, O. *Tetrahedron Lett.* **2011**, *52*, 53–55.

more stable than *Z*-**1A** and exist as a major isomer.[6] The preferential generation of the *E*-rotamer observed in the protonation and allylation of **1A** at rt may be due to this equilibrium ratio.

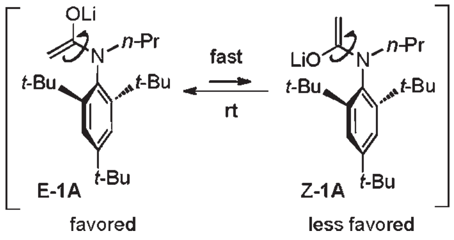
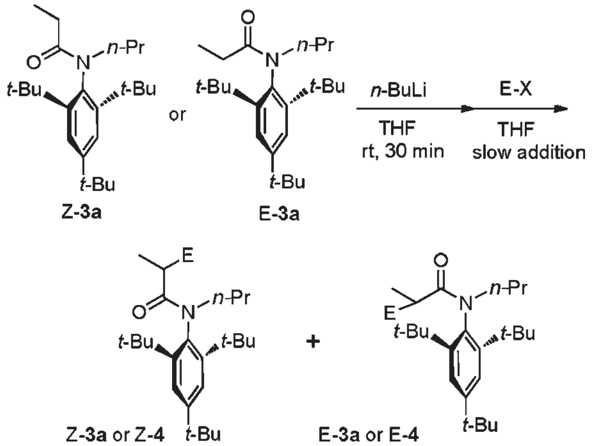


Figure 2. Interconversion between lithium enolates *E*-**1A** and *Z*-**1A**.

The rotation around a N–C bond of the enolate **1A** should easily occur in comparison with that of anilide **1a** because of the decrease in the double bond character. In asymmetric α-alkylation using chiral amide enolates, it has been pointed out that such a N–C bond rotation brings about a decrease in stereoselectivity.[7] However, since the amide rotamers of the α-alkylated products cannot be isolated at rt, the N–C bond rotation in the amide enolate has so far been difficult to confirm. Scheme 2 should provide the first direct evidence for N–C bond rotation in an amide enolate.

The reaction with the lithium enolate from N-propyl 2,4,6-tri*tert*-butylpropionanilide **3a** was further investigated (Table 1).[8] The protonation of enolate **3A**, which was prepared from *Z*-**3a** and *E*-**3a** by treating with *n*-BuLi (30 min at rt), gave the mixture of the anilide rotamer in the same ratio (*Z*-**3a**/*E*-**3a** = 1/2.1), respectively (entries 1,2). These slight *E*-rotamer selectivities are similar to those of protonation and allylation using acetanilide enolate **1A**.

Table 1. Reaction of Propionanilide **3a** with Several Electrophiles



entry	3	E–X	3 or 4	yield (%)[a]	Z/E[b]
1	*Z*-**3a**	H–Cl aq	**3a**	93	1/2.1
2	*E*-**3a**	H–Cl aq	**3a**	95	1/2.1
3	*Z*-**3a**	allyl–Br	**4a**	95	7.3/1
4	*E*-**3a**	allyl–Br	**4a**	98	6.8/1
5	*Z*-**3a**	$PhCH_2$–Br	**4b**	86	9.1/1
6	*E*-**3a**	$PhCH_2$–Br	**4b**	93	8.6/1
7	*Z*-**3a**	*n*-C_3H_7–Br	**4c**	75	46/1
8	*E*-**3a**	*n*-C_3H_7–Br	**4c**	73	46/1

[a] Isolated yield. [b] The ratio was determined by 400 MHz ^1H NMR.

Contrarily, the reaction of enolate **3A** from *Z*-**3a** and *E*-**3a** with allyl bromide led to the preferential formation of *Z*-rotamer *Z*-**4a** (entries 3, 4). In these cases, the mixture of the allylated products *Z*-**4a** and *E*-**4a** was obtained in ratios of *Z*/*E* = 7.3/1 and 6.8/1, respectively. In these reactions, the THF solution of the allyl bromide was slowly added to enolate **3A** in THF (2–3 min), while the quick addition of allyl bromide resulted in a considerable decrease in *Z*-selectivity (*Z*/*E* = 1.1–3.1/1).[9] The reaction with benzyl bromide also proceeded with similar *Z*-selectivity to give benzylated product **4b** in ratios of *Z*/*E* = 9.1/1 (from *Z*-**3a**) and 8.6/1 (from *E*-**3a**), respectively (entries 5, 6). With *n*-propyl bromide, the *Z*-isomer of propylated product *Z*-**4c** was obtained in almost complete selectivity (*Z*/*E* = 46/1, entries 7, 8). In particular, it should be noteworthy that propylation of *E*-**3a** occurred with almost complete inversion of the rotational isomerism to selectively afford the *Z*-rotamer of the propylated product *Z*-**4c** (entry 8 and Scheme 4).

The considerable change of selectivity by the electrophile may be rationalized as follows (Figure 3). The protonation

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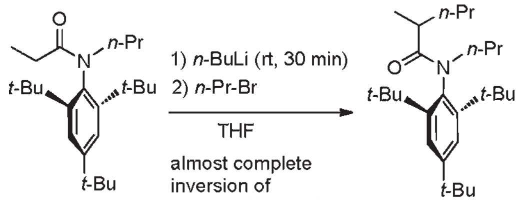
[6] In N-substituted anilide derivatives, it is well-known that *E*-rotamers are generally more stable than *Z*-rotamers. We also previously reported that the isomerization of N-allyl 2,4,6-tri-*tert*-butyl-acetanilide and -propionanilide under thermal conditions gives the equilibrium mixture of *E*-major in *E*/*Z* ratios of 10.1 and 6.0, respectively (see ref 5a). The thermal instabilities of *Z*-rotamers have been rationalized on the basis of n-π repulsion between the lone pairs on the carbonyl oxygen and aromatic ring and steric repulsion with the substituent on nitrogen atom. In anilide enolates **1A** and **3A**, *E*-rotamers may be also thermodynamically favored more than *Z*-rotamers. Typical papers on the *E*-rotamer preference of N-alkylated anilide derivatives: (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1956**, 2995–3001. (b) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177–6180. (c) Azumaya, I.; Yamaguchi, K.; Okamoto, I.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1995**, *117*, 9083–9084. (d) Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715–4720.

[7] (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 84. (b) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1984**, *25*, 857–860. (c) Katsuki, T.; Yamaguchi, M. *Yuki Gosei Kagaku Kyokaishi* **1986**, *44*, 532–544. (d) Hughes, A. D.; Price, D. A.; Simpkins, N. S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1295–1304. (e) Kolonk, K. J.; Guzei, I. A.; Reich, H. J. *J. Org. Chem.* **2010**, *75*, 6163–6172.

[8] The stereochemistries of the alkylated products **2** and **4** were determined based on chemical shifts in NMR spectra. α-Hydrogen atoms of the *E*-rotamer appeared at higher fields than those of the *Z*-rotamer because of the anisotropy effect caused by the *tert*-butylphenyl group having a large twist angle (see ref 5a). These stereochemical assignments were also confirmed by an NOE experiment. For example, in the *Z*-isomer of propylation product **4c**, the strong NOE between the α-hydrogen atom and hydrogen atoms of N-CH_2 was observed, while, in the *E*-isomer, no NOE between these hydrogen atoms was detected.

[9] In the allylation with the enolate from acetanilide *E*-**1a**, the *Z*/*E* ratio of the allylated product **2a** was hardly changed by the addition rate of the allyl bromide.

Scheme 4. Propylation with Lithium Enolate from *E*-**3a**



E-3a

Z-4c

of enolate **3A** proceeds at a faster rate than the interconversion between *Z*-**3A** and *E*-**3A** to give the rotamer mixture **3a** of *E*-major in a near-equilibrium ratio of enolate **3A** (similar to acetanilide enolate **1A**, *E*-**3A** may be slightly more stable than *Z*-**3A**[6]). On the other hand, since the reaction of **3A** with an alkyl bromide occurs at a slow rate in comparison with the equilibrium rate between *Z*-**3A** and *E*-**3A**, the rotamer ratio of the alkylated product may depend on the relative reactivity of *Z*-**3A** and *E*-**3A** rather than the equilibrium ratio. *E*-**3A** should be less reactive than *Z*-**3A**, because the α-carbon of *E*-**3A** is shielded by two *ortho*-*tert*-butyl groups. Accordingly, the *Z*-products *Z*-**4a**–**c** should be preferentially obtained through the selective alkylation of reactive enolate *Z*-**3A**. In particular, with less reactive *n*-propyl bromide, alkylation from the reactive *Z*-**3A** should occur with almost complete selectivity.

In conclusion, we found interconversion between 2,4,6-tri-*tert*-butylanilide rotamers through the formation of an anilide enolate and notable reactivity of the enolate toward several electrophiles. This is a novel structural property of these anilide derivatives. Furthermore, the reaction mechanism on the basis of equilibrium and reactivity between the rotamers of the anilide enolate intermediate was also clarified.

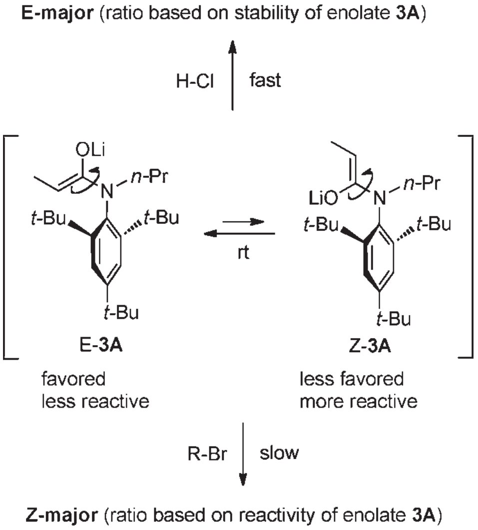


Figure 3. Interconversion and reactivity of lithium enolate from anilide **3a**.

Supporting Information Available. Experimental procedures and characterization data for all new compounds, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.