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Specific reactivity of 2,4,6-tri-*tert*-butylanilide anions and its application to benzylation reagent

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ABSTRACT

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The reaction of methyl iodide with an anilide anion prepared from 2,4,6-tri-tert-butylanilide and

NaH in CH₃CN gave N-methyl anilide (N-alkylation product) as a major product, while in the

reaction of benzyl bromide with the anilide anion in DMF, O-benzyl imidate (O-alkylation product) was obtained with almost complete selectivity. The treatment of O-benzyl imidate with

alcohols and carboxylic acids in the presence of trifluoromethane sulfonic acid gave benzyl

In 1967, Chupp *et al.* reported that an amide bond of 2,6di-*tert*-butylanilides has a high rotational barrier (27-28 kcal mol⁻¹), and Z- and E-rotamers based on the amide bond can be isolated at an ambient temperature.¹ This study is noteworthy as a rare example of a separable amide rotamer,² while a systematic study using anilide substrates other than α haloacetanilides, stereoselective syntheses of anilide rotamers, and the structural property have not been investigated in detail.

We succeeded in a highly selective stereodivergent synthesis of Z- and E-rotamers of various N-allylated 2,4,6-tri*tert*-butylanilide derivatives via Pd(0) and Pd(II)-catalyzed Nallylations (Scheme 1).^{3,4} These reactions proceed through the formation of O-allyl imidate **II** followed by Pd(0)-catalyzed intermolecular O,N-allylic rearrangement [N-allylation via π allyl-Pd complex] or Pd(II)-catalyzed intramolecular O,Nallylic rearrangement [Pd(II)-catalyzed aza-Claisen rearrangement] to give Z- or E-rotamer with high stereoselectivity, respectively.^{3a,b}

The selective formation of *O*-allyl imidate **II** (*O*-allylation product) observed in the reaction of an allylic electrophile with 2,4,6-tri-*tert*-butylanilide anions should be noteworthy because the reaction of allyl bromide with ordinary anilide anions prepared from acetanilide and 2-*tert*-butylacetanilide gave *N*-allyl anilides (*N*-allylation products) with almost complete selectivity.^{5,6}



Scheme 1. Highly stereoselective synthesis of anilide Z- and E-rotamers via O-allyl imidate II.

On the other hand, since the reaction with alkyl halides other than allyl bromide was not investigated, the generality on the unique *O*-alkylation of 2,4,6-tri-*tert*-butylanilide anions was not necessarily clear. In this Letter, we report the specific reactivity of 2,4,6-tri-*tert*-butylanilide anions toward several alkyl halides. Furthermore, the application of the obtained *O*-

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benzylation products (O-benzyl imidates) to a benzylation reagent is described.

First, we investigated the alkylation with 2,4,6-tri-tertbutylacetanilide 1a as a substrate. The results on the reaction of several alkyl halides with the anilide anion prepared from 1a and NaH in DMF (or CH₃CN) at rt are shown in Table 1. The N- vs O-alkylation selectivity was significantly influenced by the bulkiness of alkyl halides. That is, similar to allyl bromide (Scheme 1 and entry 1 in Table 1), the reaction with benzyl bromide in DMF afforded O-benzyl imidate 4a in 83% yield without the formation of N-benzylation product 5a (entry 2). In the reaction with ethyl iodide, although O-ethyl imidate 6a was obtained in a good yield (91%), the formation of a small amount of N-ethyl anilide 7a was observed (7%, entry 3). Meanwhile, the reaction with methyl iodide proceeded with slight N-alkylation selectivity to give N-methyl anilide 9a and O-methyl imidate 8a in 51% and 39% yields, respectively (entry 4). Thus, the N-alkylation selectivity showed an increasing tendency with a decrease in the bulkiness of alkyl halide.

The *N*- vs *O*-alkylation selectivity in the reaction with ethyl and methyl iodides also strongly depended on the solvent. The reaction in CH₃CN led to an increase in the *N*-alkylation selectivity to give *N*-ethylation and *N*-methylation products **7a** and **9a** in better yields than those in DMF (entries 7 and 8), while in the reactions with allyl bromide and benzyl bromide, such a solvent effect was not observed (entries 5 and 6).

Table 1. *N*- vs *O*-alkylation selectivity in the reaction of 2,4,6-tri-*tert*-butylacetanilide anion with several alkyl halides.^a



 a **1a** (0.5 mmol), NaH (0.75 or 1.15 mmol), R-X (0.75 mmol), solvent (5 mL), at rt. ^bIsolated yield. ^cThe ratio was determined by 400 MHz ¹H-NMR.

These results can be rationally explained on the basis of a steric factor and the hard and soft acids and bases (HSAB) theory (Figure 1). The reactions of ordinary anilide anions with alkyl halides (soft electrophile) preferentially occur on soft nitrogen atom but not on hard oxygen atom to afford an *N*-alkylation product with almost complete selectivity (HSAB)

control). In contrast, in 2,4,6-tri-*tert*-butylanilide anion, the *N*-alkylation is prevented by the steric hindrance due to two *ortho-tert*-butyl groups and an alkylation product on less hindered oxygen atom is selectively obtained (steric control). When small methyl iodide is used as an alkylation reagent, the selectivity may be controlled by not only a steric factor but also an HSAB factor to give the mixtures of *N*- and *O*-methylation products. Since the polarity of CH₃CN is slightly lower in comparison with that of DMF, the polarization of methyl iodide in CH₃CN may be smaller than that in DMF (methyl iodide in CH₃CN may be more soft electrophile than that in DMF).⁷ Therefore, the reaction with methyl iodide in CH₃CN may bring about an increase in the methylation on soft nitrogen atom.



The amide rotamers in *N*-ethyl anilide **7a** and *N*-methyl anilide **9a** could be separated by MPLC, while the *Z*- and *E*-rotamers selectivity in the *N*-alkylation was poor (entries 3, 4, 7, 8).⁸

 Table 2. Reaction of several 2,4,6-tri-tert-butylanilide anions with Me-I.^a

	l <i>_∖t</i> -Bu 3u	1) NaH 2) CH ₃ -I solvent, rt		-Bu +	R 0 N t-Bu Z-9 t-	∠CH ₃ <i>t-</i> Βι] ⊡Bu	R + t-Bu + E- S	CH ₃ N ⁻ CH ₃
entry	1	R	solvent	8	8	9	9	9
					(%) ^b		(%) ^b	(Z/E) ^c
1	1a	CH ₃	DMF	8a	39	9a	51	1/1.2
2	1b	C_2H_5	DMF	8b	43	9b	55	2
3	1c	CO_2Me	DMF	8c	19	9c	68	>30
4	1a	CH_3	CH ₃ CN	8a	8	9a	84	1/1.3
5	1b	C_2H_5	CH ₃ CN	8b	trace	9b	82	5
6	1c	CO ₂ Me	CH ₃ CN	8c	5	9c	62	>30

^a**1** (0.5 mmol), NaH (0.75 mmol), R-X (0.75 mmol), solvent (5 mL), at rt. ^bIsolated yield. ^cThe ratio was determined by 400 MHz ¹H-NMR.

Under the conditions shown in Table 1, the effect of acyl substituents in the reaction with methyl iodide was further explored (Table 2). Similar to acetanilide **1a**, the reaction with propionanilide **1b** and ester anilide **1c** in DMF also proceeded with low *N*-methylation selectivity (*O*-methyl **8**/*N*-methyl **9** = 43/55 and 19/68, entries 2 and 3). When CH₃CN was used instead of DMF, a remarkable increase in the *N*-methylation selectivity was observed (entries 5 and 6).

The Z- and E-rotamers selectivity in the N-methylation was significantly influenced by the bulkiness of the acyl substituent.^{3a,b} The N-methylation of acetanilide **1a** proceeded in a poor E-selectivity (Z/E = 1/1.2-1/1.3, entries 1 and 4), while in **1b** bearing slightly larger substituent (Et) than that (Me) of **1a**, low or moderate Z-selectivity was observed (Z/E = 2 and 5, entries 2 and 5).⁸ In contrast, the reaction of **1c** bearing relatively large substituent (CO₂Me) proceeded with almost complete Z-selectivity (entries 3 and 6).^{3a,b}

These results can be explained as shown in Figure 2.^{3a,b} In substrates **1c** bearing a relatively large ester group, since the transition state **TS-E9**, which gives *E*-rotamer *E*-**9**, should be disfavored because of the steric repulsion between the *ortho-tert*-butyl groups and the R substituent, *Z*-**9** is obtained with complete selectivity via **TS-Z9**. Meanwhile, with substrates bearing a small acyl group, the reaction proceeds not only via **TS-Z9** but also via **TS-E9** to afford the mixtures of *Z*-**9** and *E*-**9**.



Figure 2. Possible transition state model for Z-rotamer selectivity.

As an application of the present reaction, we next attempted the development of a new benzylation reagent using *O*-benzyl imidate products 4.⁹ That is, the reaction of 2,4,6-tri-*tert*butylacetanilide anion with benzyl bromide gave *O*-benzyl imidate **4a** in a good yield without the formation of *N*-benzyl anilide **5a** (entries 2 and 6 in Table 1). If such complete *O*benzylation selectivity is also observed in other 2,4,6-tri-*tert*butylanilide substrates, it should provide a facile synthetic method of various *O*-benzyl imidate derivatives **4** and some of them may work as an effective benzylation reagent.

As per our expectation, the benzylation with anions from anilides **1c** and **1d** gave *O*-benzyl imidates **4c** and **4d** with complete selectivity (Scheme 2), while in the reaction with trifluoroacetanilide **1d**, a decrease was observed in the chemical yield due to the instability of imidate **4d**.



Scheme 2. Selective synthesis of O-benzyl imidates 4.

The benzylation with *O*-benzyl imidate products **4a**, **4c**, **4d** was explored subsequently. Although *O*-benzyl trichloroacetimidate and trifluoroacetimidate (commercially available) have been known as a benzylation reagent, which can be used under the acidic conditions, these reagents are liquid materials and difficult to store for a long time as they are moisture sensitive.^{10,11} On the other hand, our imidates **4a** and **4c**

were solid (easily handleable) and can be purified without any decomposition through extraction and column chromatography (In trifluoroacetimidate **4d**, the decomposition to **1d** via hydrolysis was observed during extraction and chromatographic purification).¹²

Initially, the benzylation of 2-phenylethanol 10a with Obenzyl acetimidate 4a as a reagent was investigated (Table 3). After the survey of acids, solvents, and the amount of imidate reagent 4a, it was found that the reaction with 1.3 equiv of 4a in the presence of trifluoromethane sulfonic acid (2.0 equiv) in 1,4dioxane solvent provides the best result. In this case, benzyl ether **11a** was obtained at a high yield (88%, entry 6). Under the same conditions, the benzylation with ester imidate 4c and trifluoroacetimidate 4d completed in a shorter reaction time (5 h and 3 h) to afford 11a in 94% and 99%, respectively (entries 7 and 8). Thus, the imidate reagent bearing an electronwithdrawing group led to an increase in the reactivity. In the present reaction, 2.0 equiv of CF₃SO₃H was required to obtain a maximum yield, while the reaction in the presence of 1.0 or 1.5 equiv of CF₃SO₃H resulted in a decrease in the chemical yield. When 2.0 equiv of CH₃SO₃H was used as an acid, no the product 11a was obtained. In the reactions in Table 3, dibenzyl ether was formed as a side product (In entries 6-8, dibenzyl ether side products were obtained in 10%, 5% and 4% yields, respectively).

 Table 3. Optimization of the reaction conditions in benzylation of

 10a with imidate 4.^a

Ph	+ R N Ar	$\frac{\text{CF}_3\text{SO}_3\text{H}}{\text{solvent, rt}}$	Ph OBn
10a	4a (R = Me)	11a
	4c (R = CC	₀₂Me)	
	4d (R = CF	3)	
	Ar = 2,4,6-tri-	tert-butylpher	nyl

entry	4 (equiv)	solvent	time (h)	yield (%) ^b
1	4a (1.0)	1,4-dioxane	18	79
2	4a (1.0)	CH_2Cl_2	18	12
3	4a (1.0)	DMF	18	trace
4	4a (1.0)	CH ₃ CN	18	trace
5	4a (1.0)	THF	18	0
6	4a (1.3)	1,4-dioxane	18	88
7	4c (1.3)	1,4-dioxane	5	94
8	4d (1.3)	1,4-dioxane	3	99

^a**10a** (0.5 mmol), **4** (0.5 or 0.65 mmol), CF₃SO₃H (1.0 mmol) solvent (5 mL), at rt. ^bThe yield was determined by ¹H-NMR analysis of the mixture of **11a** and dibenzyl ether (side product).

The scope and limitation in the present benzylation were further examined under optimized conditions (Table 4). Although trifluoroacetimidate **4d** is the most reactive benzylation reagent, ester imidate **4c** was used in the reaction provided in Table 4 because **4d** could not be prepared in a good yield (Scheme 2). The reaction of 2-(2-chloroethoxy)ethanol **10b** also gave benzyl ether **11b** in a good yield (86%, entry 2). The present method can also be applied to the benzylation of secondary alcohols **10c,d**, while the yields slightly lowered in comparison with those of primary alcohols **10a,b** (entries 3, 4). In the reaction of optically active ethyl lactate **10d**, the

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racemization was scarcely observed. In contrast to primary and secondary alcohols **10a-d**, the reaction with tertiary alcohol **10e** gave the complex mixtures involving dehydration (alkenes) side products and the desired benzyl ether **11e** was not obtained (entry 5). The present benzylation method requires a somewhat larger amount of CF_3SO_3H (2.0 equiv) in comparison with the methods using trichloroacetimidate and trifluoroacetimidate reagents because a chemically more stable imidate **4c** is used as a reagent. Accordingly, the tertiary carbocation from alcohol **10e** as well as the benzyl cation from **4c** may be formed to result in the complex mixtures. This is the limitation of the present benzylation.

The present method was also applied to the benzylation of carboxylic acids. The reaction of benzoic acid **10f** and 3-(2-bromophenyl)propanoic acid **10g** gave benzyl esters **11f** and **11g** in 76% and 87% yields, respectively, while in these cases, 2.0 equiv of imidate **4c** and the addition of MS 5A were required (entries 6 and 7). Thus, N-(2,4,6-tri-*tert*-butyl)phenyl *O*-benzyl imidate **4c** was found to work as a benzylation reagent for alcohols and carboxylic acids.

Table 4. Benzylation of various alcohols and carboxylic acids with imidate 4c.^a

R−ОН 10		1.3 equiv imidate 4c 2.0 equiv CF ₃ SO ₃ H 1,4-dioxane, rt	R-OBr 11	1
entry	10	R-OH	11	yield (%)
1	10a	Ph(CH ₂) ₂ OH	11a	94 ^b
2	10b	Cl(CH ₂) ₂ O(CH ₂) ₂ OH	11b	86 ^c
3	10c	cyclohexanol	11c	71 ^b
4^{f}	10d	(S)-MeCH(OH)CO ₂ Et	11d ^d	64 ^c
5	10e	Ph(CH ₂) ₂ C(OH)Me ₂	11e	0 ^e
$6^{\mathrm{f},\mathrm{g}}$	10f	PhCO ₂ H	11f	76 ^b
$7^{\mathrm{f},\mathrm{g}}$	10g	$2\text{-}BrC_6H_4(CH_2)_2CO_2H$	11g	87 ^c

^a**10** (0.5 mmol), **4c** (0.65 mmol), **1**,4-dioxane (5 mL), at rt. ^bThe yield was evaluated by ¹H-NMR analysis of the mixtures of **11** and dibenzyl ether (side product). ^cIsolated yield. ^dThe ee of **11d** was 98%. ^eThe complex mixtures involving alkenes were obtained. ^f2.0 Equiv of **4c** was used. ^gMS 5A was added.

In conclusion, we disclosed the specific reactivity of 2,4,6tri-*tert*-butylanilide anions with alkyl halides. The reactions with allyl and benzyl bromides proceeded with complete *O*-alkylation selectivity to give *O*-alkylated imidates in good yields. In the reaction with less bulky methyl iodide, the *N*-methylation products were obtained as a major product. The *N*- vs *O*methylation selectivity strongly depended on a solvent. Furthermore, *O*-benzyl imidate products were found to be used as a reagent for the benzylation of alcohols and carboxylic acids.

Supplementary Materials

Experimental procedures and characterization data for all new compounds (1d, 4a, 4c, 4d, 6a-9a, 8b-c, 9b-c), and copies of ¹H-NMR and ¹³C-NMR spectra of new compounds, benzyl ethers and esters 11a-g. Supplementary data associated with this article can be found in the online version.

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- 8. The stereochemistries of Z- and E-rotamers were determined on the basis of the chemical shift of α -hydrogens (**7a**, **9a**, **9b**) or ester methyl hydrogens (**9c**). That is, these hydrogens of E-**7**,**9** appear in higher field side than those of Z-**7**,**9** because of anisotropy effect by twisted 2,4,6-tri-*tert*-butylphenyl group. See ref. 3.
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(Highlights)

Reaction of *tert*-butylanilide anions with benzyl bromide gives O-benzyl imidates.

Reaction of *tert*-butylanilide anions with methyl iodide gives *N*-methyl anilides.

O-Benzyl imidates are used as a benzylation reagent of alcohols and carboxylic acids.

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