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**Authors:** Ryu Yamasaki, Kento Morita, Hiromi Iizumi, Ai Ito, Kazuo Fukuda, and Iwao Okamoto



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# *N*-Ethynylation of Anilides Decreases Double-Bond Character of Amide Bond while Retaining Trans Conformation and Planarity

Ryu Yamasaki*[a], Kento Morita[a], Hiromi Iizumi[a], Ai Ito[a], Kazuo Fukuda[a] and Iwao Okamoto*[a]

**Abstract:** In recent, activated amide bonds had been attracted intense attention, however, most of them had twisted amide character. To add a new strategy to activate amide bonds with maintaining its planarity, we envisioned to introduce alkynyl group on amide nitrogen to disrupt amide resonance by $n_N \rightarrow C_{sp}$ conjugation. In this context, the conformations and properties of *N*-ethynyl-substituted aromatic amides were investigated by DFT calculation, crystallography and NMR. In contrast to the cis conformational preference of *N*-ethyl- and vinyl-substituted acetanilides, *N*-ethynyl-substituted acetanilide favors trans conformation in the crystal and in solution. It also has a decreased double bond character of the C(O)–N bond, without twisting of the amide. *N*-Ethynyl-substituted acetanilides undergo selective C(O)–N bond or N–C(sp) bond cleavage reactions and may have potential applications as activated amides for coupling reactions or easily cleavable tethers.

## Introduction

Amide bonds are ubiquitous in proteins and peptides, and are also found in many biologically relevant small molecules. Their key features, such as planarity, stability to nucleophiles, short C–N bond length, and high rotational barrier, are a consequence of their resonance structure.[1] On the other hand, the challenge of breaking the amide bond under mild conditions has also attracted intense interest, and many studies have demonstrated the increased lability of twisted amides.[2] However, in many cases, the necessary modifications, such as the introduction of bridging structure or a sulfonyl group, are quite major.

From a structural perspective, the partial double bond character of the amide bond permits the existence of two distinct conformations, cis and trans,[3] and a secondary amide bond, such as that in acetanilide (**1**), is normally more stable in trans form (Figure 1). However, the introduction of an *N*-alkyl group on the nitrogen atom of aromatic amide, as in **2**, causes a conformational alteration from trans to cis,[4] and this may cause loss of biological activity.[5,6] A key factor in the cis preference is considered to be the occurrence of steric and electronic repulsion between the carbonyl group and the phenyl moiety in the trans conformer.[7] The effect of such electrostatic repulsion has been verified and applied to molecular conformational switching systems.[8]

[a] Dr. Ryu Yamasaki, Kento Morita, Hiromi Iizumi, Dr. Ai Ito, Dr. Kazuo Fukuda, Prof. Dr. Iwao Okamoto
Showa Pharmaceutical University
3-3165 Higashi-Tamagawagakuen, Machida, Tokyo, Japan 194-8543
E-mail: yamaryu@ac.shoyaku.ac.jp, iokamoto@ac.shoyaku.ac.jp

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In this context, we hypothesized that substitution of an alkynyl group with an sp carbon in place of $sp^3$ carbon of alkyl groups would be a useful strategy to activate the amide bond; introduction of an unsaturated bond would extend the resonance structure, and weaken the amide bond without disruption of planarity. To our knowledge, there has been no study so far on acyclic *N*-ethynyl anilide, although structural studies of *N*-vinyl anilides have been reported.[9] Considering the unique synthetic utility of *N*-ethynyl amides (also known as ynamides),[10] we anticipated that the decreased double bond character of *N*-ethynyl amide might prove useful for further amide bond transformations.[11] Here, we report the structural properties of *N*-ethyl (**3**), vinyl (**4**), and ethynyl (**5**)-substituted acetanilides and related aromatic amide derivatives in solution and in the crystal state (Figure 1). We also describe selective hydrolysis and cleavage reactions of these compounds.

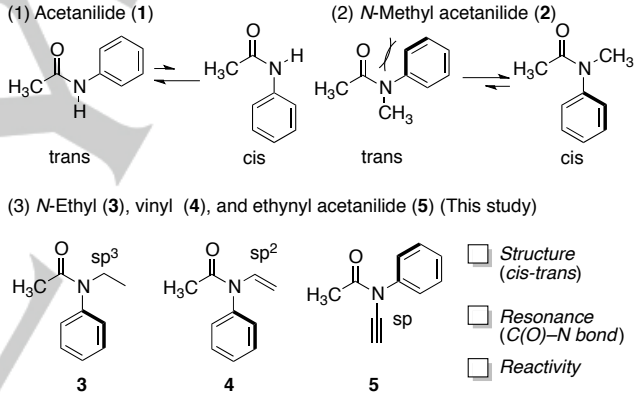



***Figure 1.*** *N*-Substituted anilide derivatives and definitions of conformers.

## Results and Discussion

We commenced our project by performing density functional theory (DFT) calculations (B97D/6-311G(d,p)) provided in Table 1 and in the SI. The calculated stable amide conformer of **5** was trans, while those of **3** and **4** were cis (Table 1). The dihedral angles between the amide plane and phenyl plane in all conformers of **3**–**5** were 40–90º, implying that all substituent groups, including unsaturated hydrocarbon groups (**4** and **5**) on the amide nitrogen atom induce distortion of the phenyl group from the amide plane (Table S1). In contrast, no significant twisting of the amide plane itself was observed in the stable conformers of compounds **3**–**5** (Table S1, $\chi_N$ and $\tau$). *N*-Vinyl acetanilide derivative (**4**) was more stable in *s*-trans form in terms of the N–C($sp^2$) bond (see SI).

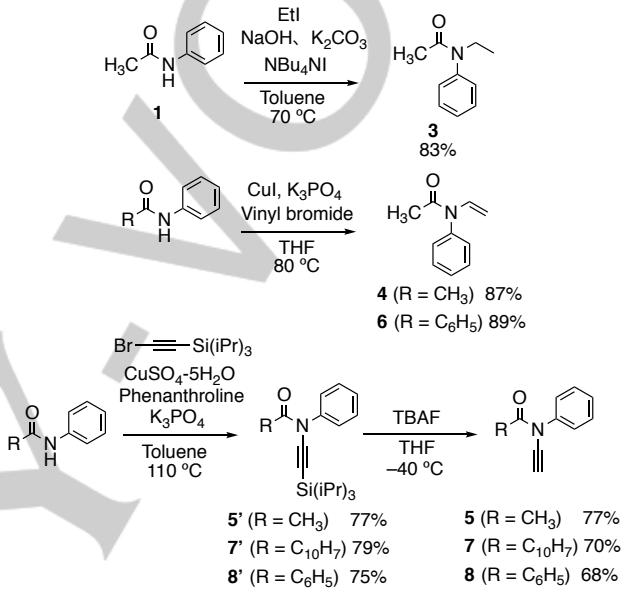
***Table 1:*** Structural characters of compounds **3**–**5**.

| | **3** | **4** | **5** |
|---|---|---|---|
| Calcd stable str.[a] | cis | cis | trans |
| $\Delta G$ (kcal/mol) [b] | 3.6 | 2.5 | 1.5 |
| Crystal Str. | cis | cis | trans |
| C(O)–N (Å) | 1.355, 1.364[c] | 1.33, 1.420[d] | 1.391 |
| C=O (Å) | 1.238, 1.229[c] | 1.29, 1.176[d] | 1.215 |
| N–C($sp^x$) (Å) | 1.476, 1.475[c] | 1.35, 1.43[d] | 1.364 |
| N–C(Ph) (Å) | 1.436, 1.440[c] | 1.417, 1.460[d] | 1.454 |
| $\chi_N$[e] (°) | 10.0, 7.3[c] | 0, 0[d] | 5.1 |
| $\tau$[f] (°) | 8.4, 2.6 [c] | 0, 0[d] | 3.5 |
| $\Sigma_{(\tau+\chi N)}$ (°) | 18.4, 9.9[c] | 0, 0[d] | 8.6 |
| NMR stable str. | cis | cis | trans |
| $\Delta G_{213\,K}$ (kcal/mol) | 1.4 | 1.5 | 0.9 |
| $\Delta G_{Tc}^{\ddagger}$ (kcal/mol) | 14.1 | 13.0 | 12.1 |
| IR C=O ($cm^{-1}$) | 1655 | 1680 | 1689 |

[a] Calculated at the B97D/6-311G(d,p) level. [b] At 213 K. [c] Two molecules exist in an unsymmetric unit. [d] The structure shows disorder, which generated two kinds of molecules. [e] Pyramidalization angle around the nitrogen atom. [f] Twist angle of the nitrogen atom.

Next, compounds **3**–**5** were synthesized by means of *N*-alkylation with EtI for **3** and Cu-catalyzed N–C coupling reactions for **4**[13] and **5**[14] (Scheme 1). It is noteworthy that TIPS protected *N*-alkynyl compounds (**5'**, **7'** and **8'**) were relatively stable and could be stored for several months, however terminal alkyne compounds (**5**, **7** and **8**) decomposed within an hour in $CD_2Cl_2$ solution at 40 ºC and should be stored in refrigerator.

The structures of those compounds were determined by X-ray single crystallography (Figure 2).[15] All compounds existed in the conformer calculated to be more stable, i.e., **3** and **4** took cis conformation in terms of the C–N bond, and **5** took trans conformation. The vinyl double bond of 4 showed disorder that made precise structural analysis difficult. Therefore, *N*-vinyl benzanilide derivative **6** was prepared similarly and analyzed crystallographically. It was found to be in cis form without any disorder. In the crystal state, the vinyl moiety of **4** and **6** existed in *s*-trans conformation as regards the N–C($sp^2$) bond. In addition, naphthalene *N*-ethynyl derivative **7** existed as the trans conformer in the crystal state. Structural analysis based on the crystal structures of acetanilide derivatives (Table 1) and benzoyl derivatives (Table 2) was shown, including *N*-methylbenzanilide reported previously as a reference.[16] As a whole, amide nitrogen atoms of **3**–**7** kept relatively planar (Table 1 and S4, $\chi_N$, $\tau$ and $\Sigma_{(\tau+\chi N)}$),[17] and acetanilide derivatives, **3**–**5**, had more planar amide nitrogen character and smaller $\Sigma_{(\tau+\chi N)}$ values than those of benzoyl derivatives, **6**, **7** and *N*-methylbenzanilide. In addition, phenyl group were also tilted from amide plane in the crystal state, in accordance with the calculations (Figure 2 and Table S4).




**Scheme 1.** Synthesis of *N*-substituted anilides.

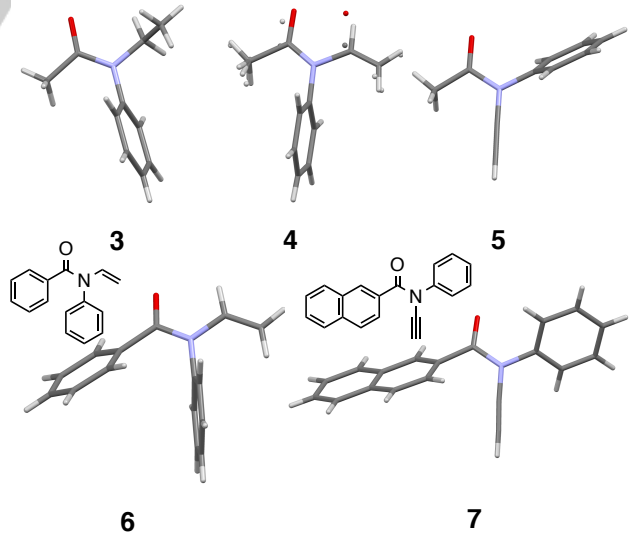



***Figure 2***. Crystal structures of **3**–**7**.

***Table 2:*** Structural analysis of compounds **6**, **7**, and *N*-methylbenzanilide.

| | **6** | **7** | N-methylbenzanilide[a] |
|---|---|---|---|
| Crystal Str. | cis | trans | cis |
| C(O)–N (Å) | 1.382 | 1.394 | 1.355 |
| C=O (Å) | 1.228 | 1.224 | 1.232 |
| N–C($sp^x$) (Å) | 1.416] | 1.367 | 1.469 |
| N–C(Ph) (Å) | 1.445 | 1.449 | 1.437 |
| $\chi_N$[b] (°) | 9.9 | 12.6 | 18.1 |
| $\tau$[c] (°) | 8.7 | 9.7 | 6.6 |
| $\Sigma_{(\tau+\chi N)}$ (°) | 18.6 | 22.3 | 24.7 |

[a] Adopted from CCDC 1183593. [b] Pyramidalization angle around the nitrogen atom. [c] Twist angle of the nitrogen atom.

To obtain insight into the dominant conformation in solution, we performed variable-temperature $^1$H-NMR (VT-NMR). The preferred conformations of **3**–**5** were determined based on NOE, and the cis/trans ratios were measured by integration of the acetyl $CH_3$ peak at 213 K in $CD_2Cl_2$ or $CDCl_3$ (Figure 3 and SI). The major conformer of **3**–**5** in solution was the same as that identified by crystallography. The free energy differences ($\Delta G_{213\ K}$) between cis and trans were also calculated from the cis/trans ratios and the tendency was in good accord with the calculated trend; **3** and **4** were predominantly in cis form (1.4 and 1.5 kcal/mol, respectively), and **5** showed moderate preference for the trans conformer (0.9 kcal/mol) (Table 1). It is noteworthy that the chemical shift of the major ortho proton peak of the phenyl group of **5** was remarkably different from that of **3** or **4**, probably due to an anisotropic effect of the carbonyl group (Figure 3).

Since *N*-ethynyl-substituted acetanilide derivative (**5**) favoured trans conformation, we next probed the generality of this phenomenon. The solution structures of benzanilide derivatives bearing an *N*-ethynyl group (**8**) and **7** were examined by $^1$H-NMR. In both cases, trans conformation was more favorable by 0.5 and 0.4 kcal/mol, respectively, in $CD_2Cl_2$ at 178 K (see SI). Thus, trans conformational preference of *N*-ethynylated anilides seemed to be a quite general phenomenon.

At this stage, we believed that electronic repulsion between the triple bond and carbonyl group encountered in the cis conformer of **5** would be the major origin of the trans conformer preference (Figure 4).[18] In the case of *N*-vinyl derivative (**4**), the vinyl moiety can avoid this repulsion in the *s*-trans conformer, which is not possible in **5**. In **7** and **8**, repulsion between Ar and alkyne moieties could make the trans conformation less stable than **5**.

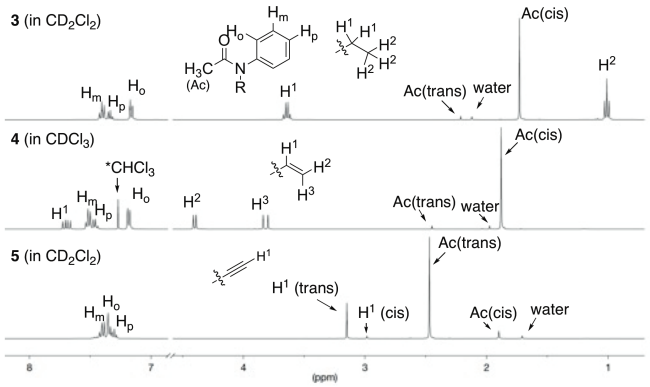



***Figure 3***. $^1$H-NMR spectra (400 MHz, 213 K, in $CD_2Cl_2$ for **3** and **5**, in $CDCl_3$ for **4**) of **3**–**5**.

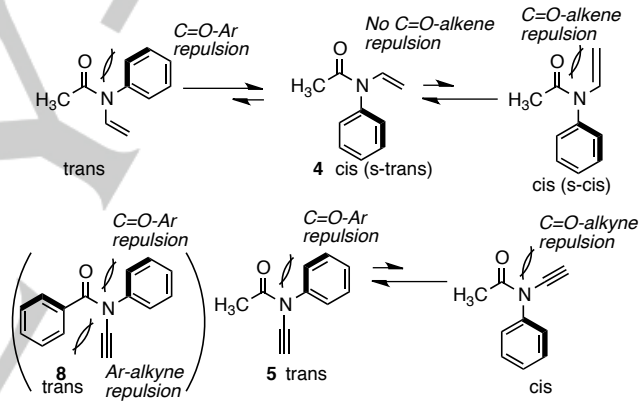
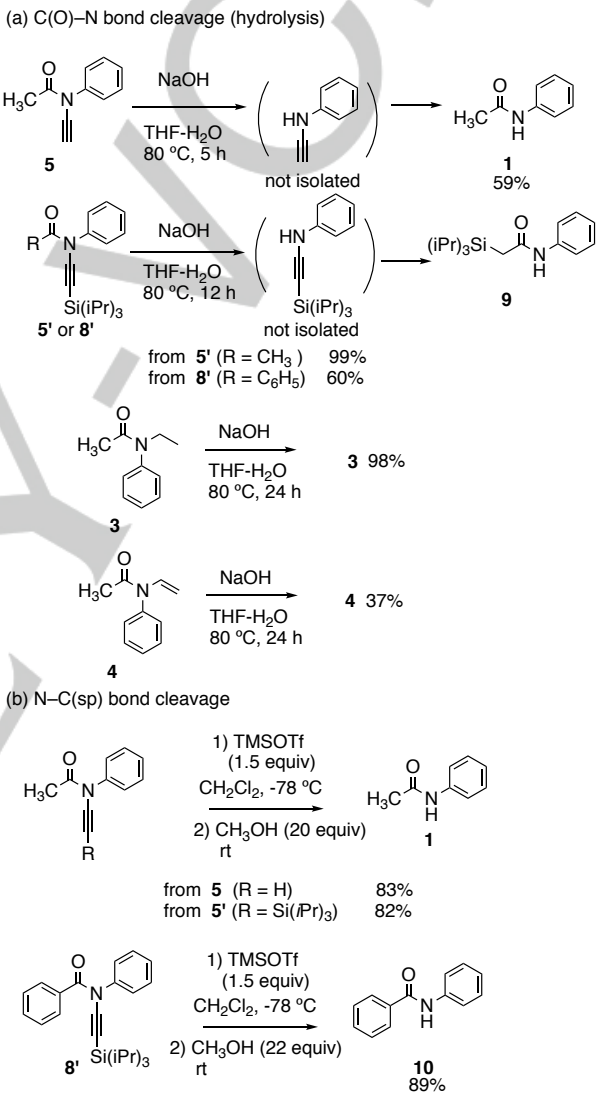



***Figure 4***. Possible explanations of conformational preference of **4** and **5**.

Next, the effects of the *N*-ethynyl group on the C(O)–N double bond character and rotational barrier were investigated. *N*-Vinyl acetanilides are reported to have a lower rotation barrier of the C–N bond compared to corresponding secondary amides,[19] albeit few *N*-ethynyl acetanilides have been examined. Taking the C(O)–N bond lengths in the crystal structure as a measure of the double bond character, we found that the C(O)–N bond was lengthened (**5** > **3**, **7**>**6**>*N*-methylbenzanilide) in the opposite order to the C=O bond length (**3** > **5**, *N*-methylbenzanilide > **6** > **7**) (Table 1 and 2). A similar trend was also observed in the results of DFT calculation (Table S1). This reflects the reduced amide bond resonance of **5**, probably due to the $n_N \rightarrow C_{sp}$ conjugation, which disrupts amide resonance.[20] In fact, the N–C ($sp^x$) bond lengths were 1.476 (or 1.475) Å for **3**, 1.416 Å for **6**(**4**) and 1.364 Å for **5** in the crystal state, which implies that the nitrogen lone-pair strongly delocalized to the N–C(sp) bond (Table 1). The reduced C(O)–N bond character was also reflected in the rotational barriers calculated based on the results of VT-NMR (Table 1 and S5).[21] The rotational barriers were estimated by the coalescence method,[22] and the results are shown in Table 1 and SI. The rotational barrier of **3** was roughly estimated to be 14.1 kcal/mol, which is close to that of *N*-methyl acetanilide (**2**),[8a] while those of **4** and **5** were decreased to 13.0 and 12.1 kcal/mol, respectively. It is noteworthy that the rotational barrier of **5** was comparable to that of *N*-acyl pyrroles[20b] and showed a possibility of *N*-alkynyl substituted anilides as a new type of ground-state-destabilized amides.[23] In addition, the peak position of C=O stretching vibration in the IR spectra (KBr) indicated decreased amide resonance of **4** and **5**; the peak of **3** was at 1655 $cm^{-1}$, while those of **4** and **5** were at 1680 and 1689 $cm^{-1}$, respectively. This shift of wavenumber is consistent with disfavored amide resonance in **4** and **5**.[24]

The remarkably decreased amide resonance of *N*-ethynyl anilides could promote C(O)–N bond scission reactions (Scheme 2(a)). To test this idea, *N*-ethynyl acetanilide **5** was subjected to basic hydrolysis at 80 ºC, to afford acetanilide (**1**) by cleavage of amide bond followed by hydration of the resultant ynamine by water.[25] The yield of the hydrolysis was improved by using TIPS-protected derivatives, **5'**, and the TIPS terminated amide compound **9** was obtained as sole product in excellent yield.[26] The structure of **9**, the formal transacylation product, was unambiguously confirmed by X-ray crystallography (see SI).[27] This hydrolysis of the amide bond was also applicable to benzanilide derivatives **8'** and the corresponding **9** was obtained in 60% yield. These results support the reaction proceeded through the hydrolysis of C(O)–N bond and successive hydration of resultant ynamine, since the imide produced by hydration of alkyne of ynamide would leads to a mixture of two products, **9** and **1** (or **10**). To check the reactivity of amides, we exposed **3** and **4** to the same condition (at 80 ºC); this resulted in the recovery of most of the reactants in the case of **3**, and partial recovery in the case of **4**. Notably, selective cleavage of the N–C(sp) bond was also possible (Scheme 2(b)). Iwasawa and coworkers reported that TMSBr reacted with tosyl ynamide to afford β-bromo alkene compounds,[28] and observed dealkynylation by using methanol as a nucleophile. Similarly, non-nucleophilic TMSOTf activated the triple bond of *N*-alkynyl anilide derivatives, probably through the coordination to carbonyl group, furnished anilides with N–C(sp) bond cleaved after a treatment with methanol. When **5** or **5'** was reacted with TMSOTf followed by dry methanol, **1** was obtained in high yield. Benzanilide derivative **8'** similarly afforded benzanilide in good yield. This result confirmed that the reaction proceeded via N–C(sp) bond cleavage.




**Scheme 2.** Selective C(O)–N and N–C(sp) bond cleavage reactions.

## Conclusions

In conclusion, we have found that aromatic tertiary amides bearing an *N*-ethynyl group favor trans conformation, while *N*-ethyl and vinyl aromatic amides take cis conformation. The C(O)–N bond of *N*-ethynyl substituted amides has decreased double-bond character and is more easily hydrolyzed than *N*-ethyl-substituted amides, affording formally transacylated

secondary amides by hydrolysis of the ynamine. Interestingly, these substituted anilides, including *N*-ethynyl-substituted compounds, do not have a pyramidalized nitrogen atom, even though they are susceptible to hydrolysis. In addition, the N–C(sp) bond can be selectively cleaved by TMSOTf and MeOH. Given the decreased double bond character of *N*-ethynyl-substituted amides, these compounds might be useful as activated amide substrates for coupling reactions. The results presented here should also be useful in the design and structure-activity relationship studies of conformationally controlled biologically active compounds, as well as cleavable tether groups for drug-delivery systems.

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**Keywords:** Amides • Alkynes • Conformation analysis • Ynamides • Transacylation

[1] A. Greenberg, C. M. Breneman, J. F. Liebman, *The amide linkage: Structural significance in chemistry, biochemistry, and materials science*, John Wiley & Sons, New York, **1999**.

[2] For recent reviews of twisted amides, see; a) M. Szostak, J. Aube, *Chem Rev*. **2013**, *113*, 5701–5765; b) C. Liu, M. Szostak, *Chem. Eur. J*. **2017**, *23*, 7157–7173; c) S. Adachi, N. Kumagai, M. Shibasaki, *Chem. Sci*. **2017**, *8*, 85–90.

[3] In this paper, cis and trans, defined as shown in Figure 1, are used instead of *E* and *Z* nomenclature to avoid confusion, since the priority of the phenyl group would be different between **3** and **5**.

[4] a) W. E. Stewart, T. H. Sidwell, *Chem. Rev*. **1970**, *70*, 517–551; b) S. Kasino, K. Ito, M. Haisa, *Bull. Chem. Soc. Jpn*, **1979**, *52*, 365–369; c) A. Itai, Y. Toriumi, N. Tomioka, H. Kagechika, I. Azumaya, K. Shudo, *Tetrahedron Lett*. **1989**, *30*, 6177–6180; d) A. Itai, Y. Toriumi, S. Saito, H. Kagechika, K. Shudo, *J. Am. Chem. Soc*. **1992**, *114*, 10649–10650.

[5] For a review, see; Y. Zheng, C. M. Tice, S. B. Singh, *Bioorg. Med. Chem. Lett*. **2017**, *27*, 2825–2837.

[6] For typical examples, see; a) H. Kagechika, E. Kawachi, Y. Hashimoto, T. Himi, K. Shudo, *J. Med. Chem*. **1988**, *31*, 2182–2192; b) C. S. J. Walpole, R. Wigglesworth, S. Bevan, E. A. Campbell, A. Dray, I. F. James, K. J. Masdin, M. N. Perkins, J. Winter, *J. Med. Chem*. **1993**, *36*, 2373–2380.

[7] S. Saito, Y. Toriumi, N. Tomioka, A. Itai, *J. Org. Chem*. **1995**, *60*, 4715–4720.

[8] a) R. Yamasaki, A. Tanatani, I. Azumaya, S. Saito, K. Yamaguchi, H. Kagechika, *Org. Lett*. **2003**, *5*, 1265–1267; b) I. Okamoto, R. Yamasaki, M. Sawamura, T. Kato, N. Nagayama, T. Takeya, O. Tamura, H. Masu, I. Azumaya, K. Yamaguchi, H. Kagechika, A. Tanatani, *Org. Lett*. **2007**, *9*, 5545–5547; c) I. Ai, M. Sato, R. Yamasaki, I. Okamoto, *Tetrahedron Lett*. **2016**, *57*, 438–441.

[9] A. V. Afonin, B. A. Trofimov, S. F. Malysheva, A. V. Vashchenko, *Zhurnal Organicheskoi Khimii*, **1992**, *28*, 225–236.

[10] For recent reviews, see; a) K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Hsung, *Chem. Rev*. **2010**, *110*, 5064–5106; b) G. Evano, N. Blanchard, G. Compain, A. Coste, C. S. Demmer, W. Gati, C. Guissart, J. Heimburger, N. Henry, K. Jouvin, G. Karthikeyan, A. Laouiti, M. Lecomte, A. Martin-Mingot, B. Métayer, B. Michelet, A. Nitelet, C. Theunissen, S. Thibaudeau, J. Wang, M. Zarca, C. Zhang, *Chem. Lett*. **2016**, *45*, 574–585.

[11] For recent reviews of activation of amides, see; a) M. Szostak, G. Meng, S. Shi, *Synlett* **2016**, *27*, 2530–2540; b) J. E. Dander, N. K. Garg, *ACS Catal*. **2017**, *7*, 1413–1423; c) C. Meng, M. Szostak, *Eur. J. Org. Chem*. **2018**, 2352–2365; d) S. Shi, S. P. Nolan, M. Szostak, *Acc. Chem. Res*. **2018**, *51*, 2589–2599; e) M. B. Chaudhari, B. Gnanaprakasam, *Chem. Asian J*. **2019**, *14*, 76–93.

[12] M. J. Frisch, et al. *Gaussian 09*, Revision Ds.01; Gaussian, Inc.: Wallingford, CT, **2013**. (See SI for full citation.)

[13] L. Jiang, G. E. Job, A. Klapars, S. L. Buchwald, *Org. Lett*. **2003**, *5*, 3667–3669.

[14] a) M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc*. **2003**, *125*, 2368–2369; b) J. R. Dunetz, R. L. Danheiser, *Org. Lett*. **2003**, *5*, 4011–4014; c) X. Zhang, Y. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. Shen, M. R. Tracey, *J. Org. Chem*. **2006**, *71*, 4170–4177; d) T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc*. **2008**, *130*, 833–835.

[15] The data of crystals (CCDC 1895329 for **3**, CCDC 1895328 for **4**, CCDC 1895326 for **5**, CCDC 1895327 for **6** and CCDC 1895330 for **7**) can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

[16] A. Itai, Y. Toriumi, N. Tomioka, H. Kagechika, I. Azumaya, K. Shudo, *T Tetrahedron Lett*. **1989**, *30*, 6177–6180.

[17] a) R. Szostak, J. Aube, M. Szostak, *Chem. Commun*. **2015**, *51*, 6395–6398; b) R. Szostak, J. Aube, M. Szostak, *J. Org. Chem*. **2015**, *80*, 7905–7927.

[18] An example of a similar situation, which repulsion of carbonyl oxygen and alkyne determines the preferred conformation, see; M. Pilkington, S. Tayyip, J. D. Wallis, *J. Chem. Soc. Perkin Trans. 2* **1994,** 2481–2484.

[19] a) D. G. Gehring, W. A. Mosher, G. S. Reddy, *J. Org. Chem*. **1966**, *31*, 3436-3437; b) R. R. Fraser, J.-L. A. Roustan, J. R. Mahajan,. *Can. J. Chem*. **1979**, *57*, 2239-2244.

[20] For a example of $n_N \rightarrow \pi_{Ar}$ conjugation for amide activation, see; a) G. Meng, R. Lalancette, R. Szostak, M. Szostak, *Org. Lett*. **2017**, *19*, 4656–4659; b) G. Meng, R. Szostak, M. Szostak, *Org. Lett*. **2017**, *19*, 3596–3599.

[21] a) J. I. Mujika, J. M. Matxain, L. A. Eriksson, X. Lopez, *Chem. Eur. J*. **2006**, *12*, 7215–7224; b) C. R. Kemnitz, M. J. Loewen, *J. Am. Chem. Soc*. **2007**, *129*, 2521–2528.

[22] M. Oki, *Applications of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH Publishers, New York, **1985**.

[23] V. Pace, W. Holzer, G. Meng, S. Shi, R. Lalancette, R. Szostak, M. Szostak, *Chem. Eur. J*. **2016**, *22*, 14494–14498.

[24] A. J. Bennet, V. Somayaji, R. S. Brown, B. D. Santarsiero, *J. Am. Chem. Soc*. **1991**, *113*, 7563–7571.

[25] a) S. Xu, J. Liu, D. Hu, D. X. Bi, *Green Chem*. **2015**, *17*, 184–187; b) H. Huang, L. Tang, Y. Xi, G. He, H. Zhu, *Tetrahedron Lett*. **2016**, *57*, 1873–1876.

[26] In the coupling reaction for the synthesis of **5**, a small amount of **9** was observed, probably due to hydrolysis of **5'** by contaminating $H_2O$.

[27] The data of crystals (CCDC 1895325 for **9**) can be obtained free of charge from The Cambridge Crystallographic Data Center via http://www.ccdc.cam.ac.uk/data_request/cif.

[28] K. Ohashi, S. Mihara, A. H. Sato, M. Ide, T. Iwasawa, *Tetrahedron Lett*. **2014**, *55*, 632–635.

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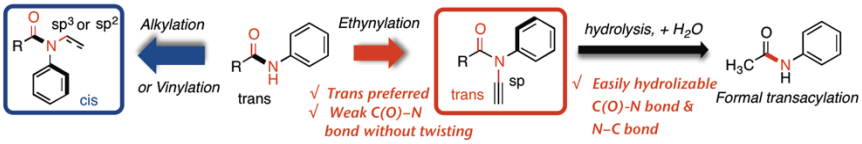


*Dr. Ryu Yamasaki*, Kento Morita, Hiromi Iizumi, Dr. Ai Ito, Dr. Kazuo Fukuda and Prof. Dr. Iwao Okamoto**

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*N-Ethynylation of Anilides Decreases Double-Bond Character of Amide Bond while Retaining Trans Conformation and Planarity*

*N*-Ethynylation of anilides keep trans conformation of secondary amide, while N-alkylation and vinylation do not. In addition, *N*-ethnylated anilide has weakened C(O)–N bond character without twisting of amide nitrogen, and easily hydrolyzed to afford transacylated amide.