ORGANIC LETTERS

2010
Vol. 12, No. 2
244−247

Polarity-Reversible Conjugate Addition Tuned by Remote Electronic Effects

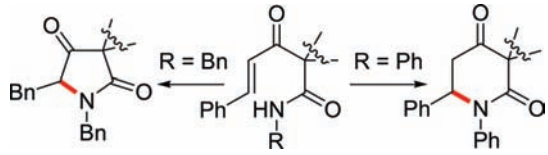
Yifei Li, Xianxiu Xu,* Jing Tan, Peiqiu Liao, Jingping Zhang, and Qun Liu*

Department of Chemistry, Northeast Normal University, Changchun 130024, China

xuxx677@nenu.edu.cn; liuqun@nenu.edu.cn

Received November 3, 2009

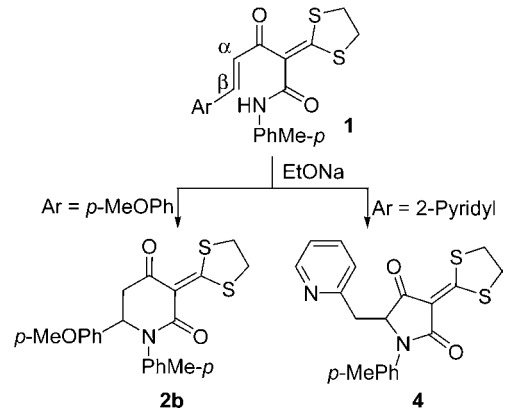
ABSTRACT



A new concept, polarity-reversible conjugate addition, has been described, based on the findings that the polarity of a classical Michael acceptor can be reversed through remote electronic effects. In addition, the remote electronic effects are tunable, and both five- and six-membered nitrogen rings can be constructed starting from acyclic precursors having the same enone structure unit simply by varying a remote substituent in the molecules.

The conjugate addition (or Michael addition) of nucleophilic species to alkenes substituted with electron-withdrawing groups (such as carbonyl, nitro, or sulfonyl) to give 1,4-addition products is one of the most fundamental reactions in organic chemistry.[1,2] Through our research in this area[3] we found that biologically active tetramic acid derivatives **4** can be synthesized via an unusual intramolecular aza-anti-Michael addition of *N*-aryl-cinnamoylacetamides **1** bearing a β-electron-deficient aromatic/heteroaromatic group under basic conditions (addition of amide anion to the enone α-C-atom, Scheme 1, **1** to **4**).[4] However, in one case where the enone moiety of *N*-aryl-cinnamoylacetamide **1** has a β-electron-rich 4-methoxyphenyl group, the intramolecular aza-Michael adduct **2b** was produced in 20% yield (Scheme 1).[4] The significant difference in the orientation of the conjugate addition reactions, which has not been defined in the literature,[1,2,4−6] prompted us to initiate studies on the structural dependence of the cyclization process. In this communication we describe a new concept, polarity-revers-

Scheme 1. Regiodivergent Reactions of **1**



(1) (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Pergamon: Oxford, 1992. (b) Jung, M. E. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 4, pp 1−67.

(2) For recent reviews, see: (a) Enders, D.; Saint-Dizier, A.; Lannou, M.-I.; Lenzen, A. *Eur. J. Org. Chem.* **2006**, 29–49 (phospha-Michael addition). (b) Nising, C. F.; Brase, S. *Chem. Soc. Rev.* **2008**, *37*, 1218–1228 (oxa-Michael addition). (c) Sun, X.-L.; Tang, Y. *Acc. Chem. Res.* **2008**, *41*, 937–948 (ylide-initiated Michael addition−cyclization reactions). (d) Enders, D.; Luttgen, K.; Narine, A. A. *Synthesis* **2007**, 959–980 (asymmetric sulfa-Michael addition).

(3) For selected examples, see: (a) Tan, J.; Xu, X.; Zhang, L.; Li, Y.; Liu, Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 2868–2872. (b) Dong, D.; Bi, X.; Liu, Q.; Cong, F. *Chem. Commun.* **2005**, 3580–3582. (c) Bi, X.; Dong, D.; Liu, Q.; Pan, W.; Zhao, L.; Li, B. *J. Am. Chem. Soc.* **2005**, *127*, 4578–4579.

(4) Bi, X.; Zhang, J.; Liu, Q.; Tan, J.; Li, B. *Adv. Synth. Catal.* **2007**, *349*, 2301–2306.

(5) For a review of anti-Michael addition, see: Lewandowska, E. *Tetrahedron* **2007**, *63*, 2107–2122.

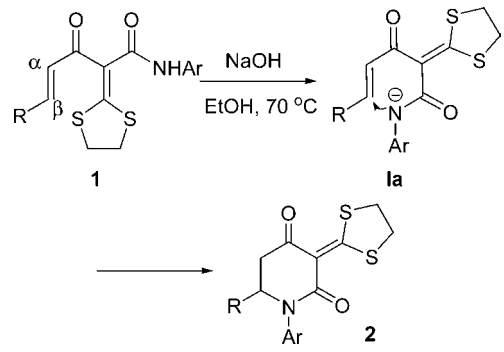
10.1021/ol902551m
Published on Web 12/17/2009

ible conjugate addition, based on the fact that the polarity of a classical Michael acceptor can be reversed and either intramolecular aza-Michael-adducts **2** (six-membered nitrogen rings) or intramolecular aza-anti-Michael adducts **4** (five-membered nitrogen rings) can be constructed, preferentially, through remote electronic effects.

To understand the reason why the cyclization reactions have different regioselectivity (Scheme 1), the present study aimed first to examine the β-substituent dependence of the reactions of *N*-aryl-alkenoylacetamides **1**. After optimization of the reaction conditions, the intramolecular aza-Michael adduct, piperidine-2,4-dione **2a**, was obtained in 61% yield by treatment of *N*-(4-methylphenyl)-cinnamoylacetamide **1a** (1.0 mmol) with NaOH (1.0 equiv) in EtOH (5.0 mL) at 70 °C for 1.0 h (Table 1, entry 1).[7] Under identical conditions, a series of selected experiments was performed, and the results are summarized in Table 1. It was proven that *N*-(4-methylphenyl)-alkenoylacetamides **1a**−**1h** with phenyl (entry 1), an electron-rich aromatic (entries 2−4) and hetero aromatic group (entries 5 and 6), alkyl (entry 7), or less electron-deficient aromatic group (entry 8) at the β-position of the enone moiety can afford the corresponding intramolecular aza-Michael adducts **2a**−**2h** in good to high yields, respectively. In addition, intramolecular aza-Michael adducts **2i**−**2k** were also obtained from the corresponding arylamides **1i**−**1k** bearing an electron-deficient *N*-(*p*-chlorophenyl) group (entries 9 and 10) or *N*-phenyl (entry 11).

The above results suggest that *N*-aryl-alkenoylacetamides **1** bearing alkyl, phenyl, electron-rich, or less electron-deficient aryl groups at the β-position of the enone moiety favor intramolecular aza-Michael addition (Table 1). In contrast, as demonstrated by previous experiments,[4] substrates **1** bearing a more electron-deficient aromatic substituent at the β-position of the enone moiety prefer intramolecular aza-anti-Michael addition (also see Scheme 1). Clearly, these results, which show changes in the orientation of conjugate addition reactions, cannot be compared with the

Table 1. Intramolecular aza-Michael Addition of *N*-Aryl-alkenoyl-acetamides **1**[a]



entry	1	R	Ar	time (h)	2	yield[b] (%)
1	**1a**	Ph	4-MePh	1.0	**2a**	61
2	**1b**	4-MeOPh	4-MePh	1.0	**2b**	71
3	**1c**	3,4-O_2CH_2Ph	4-MePh	1.5	**2c**	74
4	**1d**	4-MePh	4-MePh	1.0	**2d**	65
5	**1e**	2-thienyl	4-MePh	2.0	**2e**	82
6	**1f**	2-furyl	4-MePh	1.5	**2f**	96
7	**1g**	*t*-Bu	4-MePh	0.5	**2g**	80
8	**1h**	4-BrPh	4-MePh	3.8	**2h**	71
9	**1i**	4-ClPh	4-ClPh	1.5	**2i**	60
10	**1j**	2-furyl	4-ClPh	2.5	**2j**	75
11	**1k**	Ph	Ph	1.0	**2k**	72
12	**1l**	4-ClPh	2,6-Me_2Ph	1.5	**2l**	83

[a] Conditions: **1** (1.0 mmol), NaOH (1.0 equiv), in EtOH (5 mL), 70 °C. [b] Yield of isolated products.

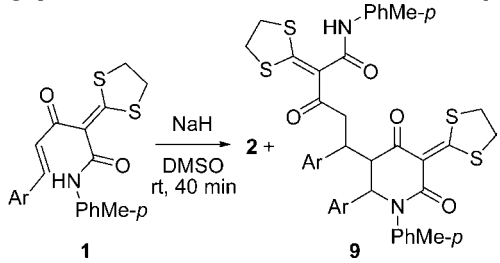
results in the literature,[1,2,5] regardless of Michael[1,2] or anti-Michael addition.[5]

To gain a better insight into the difference in the regioselectivity, the intramolecular conjugate addition reactions of cinnamoylacetamides **3** having an *N*-alkyl instead of an *N*-aryl group on the amide nitrogen were performed to examine the electronic effects beyond the enone moiety. To our surprise, instead of the intramolecular aza-Michael adduct like **2a** (Table 1, entry 1), the intramolecular aza-anti-Michael adduct, tetramic acid derivative **4a**, was obtained in 78% yield by treatment of *N*-benzyl amide **3a** (1.0 mmol) with NaH (1.0 equiv) in DMSO (5.0 mL) at room temperature for 0.5 h (Table 2, entry 1)! Further experiments showed that not only alkylamides **3b** and **3c** bearing β-electron-deficient aromatic group (Table 2, entries 2 and 3) but also the alkylamides **3d** and **3e** (Table 2, entries 4 and 5) bearing β-electron-rich aromatic group can react very smoothly to give the corresponding anti-Michael adducts **4b**−**4e** in high yields.[8]

For comparison, under the same conditions as in Table 2, the alkylamides **5a** and **5b** led to the formation of intramo-

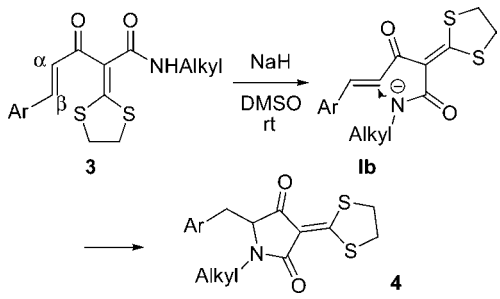
(6) (a) Li, Y.; Liang, F.; Bi, X.; Liu, Q. *J. Org. Chem.* **2006**, *71*, 8006–8010. (b) Bi, X.; Liu, Q.; Sun, S.; Liu, J.; Pan, W.; Zhao, L.; Dong, D. *Synlett* **2005**, 49–54. (c) Cheng, X.; Liang, F.; Shi, F.; Zhang, L.; Liu, Q. *Org. Lett.* **2009**, *11*, 93–96. (d) Liu, J.; Wang, M.; Han, F.; Liu, Y.; Liu, Q. *J. Org. Chem.* **2009**, *74*, 5090–5092.

(7) The reaction of *N*-aryl amide **1a** (Ar = Ph, 1.0 mmol) with NaH (1.0 equiv) in DMSO (5.0 mL) at room temperature for 40 min gave a mixture of **2a** and **9a** in 38% and 35% yields, respectively. It was found that **9a** was formed in a diastereospecific manner on the basis of its ^{1}H and ^{13}C NMR spectra. Similarly, a mixture of **2d** and **9d** was obtained in 30% and 22% yields, respectively, from **1d** (Ar = *p*-MePh) under identical conditions for 40 min. The configurations of **9a** and **9d** were further confirmed on the basis of the X-ray diffraction analysis of **9d** (CCDC 751596). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



(8) The configurations of **4a**−**4e** were further confirmed on the basis of the X-ray diffraction analysis of **4b**. CCDC 739101 (**4b**) and CCDC 739100 (**6b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Intramolecular aza-anti-Michael Addition of *N*-Alkyl-cinnamoylacetamides **3**[a]

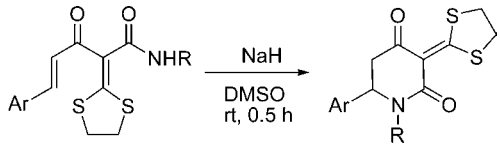


entry	3	Ar	alkyl	time (h)	4	yield[b] (%)
1	**3a**	Ph	Bn	0.5	**4a**	78
2	**3b**	4-BrPh	Bn	0.5	**4b**	76
3	**3c**	2-ClPh	Bn	0.5	**4c**	73
4	**3d**	2-furyl	Bn	0.5	**4d**	86
5	**3e**	2-furyl	*n*-Pr	0.5	**4e**	89
6	**3f**	4-ClPh	*t*-Bu	1.0	**4f**	60

[a] Conditions: **3** (1.0 mmol), NaH (1.0 equiv), in DMSO (5 mL), room temperature. [b] Yield of isolated products.

lecular aza-Michael adducts **6a** and **6b** in 67% and 70% yields, respectively (Scheme 2), whereas in the presence of

Scheme 2. Intramolecular aza-Michael Addition of *N*-Alkyl-cinnamoylacetamides **5a** and **5b**



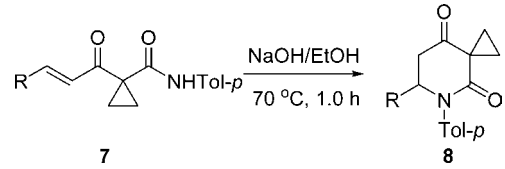
5a, **6a**: Ar = 4-MeOPh, R = Bn (67%);
5b, **6b**: Ar = 4-MeOPh, R = Me (70%)

relatively weak base, for example, under the reaction conditions as described in Table 1, no reaction product was detected and the starting materials were recovered unchanged, presumably as a result of the decreased acidity of the amino group in alkylamides **5** compared with that of the amino group in arylamides **1**. The structure of **6a** and **6b** was further confirmed by the X-ray diffraction analysis of **6b**.[8] These results, similar to that obtained with arylamides **1b** (Table 1, entry 2), show the role of the strong electron-donating β-methoxyphenyl group in the regioselectivity of the reactions (see also Scheme 1).

To understand the source of the unusual divergence in the regioselectivity of the above processes, several selected experiments were conducted to evaluate the influence of steric, kinetic, and thermodynamic effects on the reaction.

First, the reaction of selected *N*-(4-methylphenyl)-cinnamoylacetamides **7a**−**7c** bearing a tetra-substituted carbon atom between two carbonyl groups were examined with the aim of evaluating proximity effects.[9] Under the conditions as described in Table 1, the intramolecular aza-Michael adducts **8a**−**8c** were obtained in good yields, respectively (Scheme 3), which indicates the reactions of **7a**−**7c** subjected

Scheme 3. Intramolecular aza-Michael Addition of *N*-(4-Methylphenyl)-cinnamoylacetamides **7a**−**7c**



7a, **8a**: R = *p*-ClPh (71%);
7b, **8b**: R = *p*-MePh (61%);
7c, **8c**: R = 2-Furyl (54%)

to the same mechanism as **1a**−**1l**. Therefore, it is impossible to predict a substantial impact of the proximity effect on the intramolecular conjugate addition reactions because both five- (Scheme 1)[4] and six-membered rings (Table 1 and Scheme 3) can be formed preferentially depending on the nature of the β-substituent on the enone moiety.

Furthermore, the steric effects of the remote *N*-aryl/alkyl groups were considered. Under the conditions as described in Table 1, the cyclization of arylamide **1l** having a sterically hindered *N*-aryl group (2,6-dimethylphenyl) led to the corresponding aza-Michael adduct **2l** in 83% yield (Table 1, entry 12). In a comparison, the anti-Michael adduct **4f** was obtained in 60% yield (Table 2, entry 6) when the reaction of alkylamide **3f** bearing a bulky *N*-*tert*-butyl group was carried out under the conditions as described in Table 2. These results suggest that the remote steric effect from either the *N*-alkyl or *N*-aryl group is less significant. Therefore, the nature of the substituent on the remote amide nitrogen atom seems to play a key role in determining the regioselective induction observed.

Finally, the influence of kinetic and thermodynamic factors on the reaction was investigated by performing the reaction at different temperatures. Treatment of *N*-aryl-cinnamoylacetamide **1b** under the same conditions as in Table 1 but at room temperature for 24 h led to the recovery of **1b** in 93% yield. No product **2b** could be detected. On the other hand, performing the reaction of *N*-alkyl-cinnamoylacetamide **3a** under the same conditions as in Table 2 but at 70 °C for 1.0 h led to the anti-Michael adduct **4a** in 53% yield. The corresponding intramolecular Michael adduct was not detected. In addition, compound **4a** was recovered in 89% yield under the conditions of Table 2 after reaction at 70 °C for 24 h. As a result, all of the results (including the results in Scheme 1 and ref 7) do not give any information concerning

(9) For a general discussion of the importance of the proximity effects in intramolecular reactions, see: (a) Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128–134. (b) Menger, F. M. *Acc. Chem. Res.* **1993**, *26*, 206–212. (c) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766.

kinetic and thermodynamic control on reaction products of the tunable conjugate addition.[10]

Taken together, the previous[4] and present results, including the impact of the nature of β-substituents of the enone moiety, a carbon atom between two carbonyl groups, the electronic and steric effects of the *N*-aryl/alkyl groups, and kinetic and thermodynamic factors as well, suggest that the polarity-reversible intramolecular conjugate addition of *N*-aryl/alkyl-alkenoylacetamides can be tuned by a remote substituent and can be viewed as remote electronic effects in nature.[4,11] Therefore, it is understandable that the ability to reverse the polarity of the classical conjugate addition of the enone unit mainly depends on the electron-donating nature of the remote amide anion, as indicated by the calculation results.[4]

Collectively, our findings allow us to conclude that (1) the regioselectivity of an intramolecular Michael addition reaction can be tuned by the remote electronic effects, and (2) the degree of the polarity reversal of a Michael acceptor depends on the electron-donating ability of the remote substituent. As expected, the more electron-donating (higher electron density) alkylamide anion **Ib** (Table 2) has a stronger ability to tune the polarity-reversal of the enone moiety than the less electron-donating arylamide anion **Ia** (Table 1). As a result, the tiny change in a remote substituent can even lead to a pronounced polarity return, for example, the formation of five-membered nitrogen rings **4a**, **4b**, **4d**, **4f** versus six-membered nitrogen rings **2a**, **2h**, **2f**, **2i**. Moreover, this research is helpful in understanding the nature of the electronic effects in similar systems[6a,b] and provides a basis for more detailed investigation.

In summary, we have described a new concept, polarity-reversible conjugate addition and showed how the regioselectivity of a conjugate addition can be reversed with a simple and subtle change in a remote substituent. This concept provides new insights into the conjugate addition chemistry. Further studies and applications of this concept are in progress.

Acknowledgment. Financial support of this research provided by the NNSFC (20872015), the Science Foundation for Young Teachers of NENU (20090404), and the Young Scientific Research Foundation of Jilin Province (20090149) is gratefully acknowledged.

Supporting Information Available: Experimental details and spectra data for all new compounds and crystal structure data for **4b**, **6b** and **9d** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902551M

(10) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476–482.

(11) For selected examples of catalyst-controlled regiodivergent synthesis of cyclic compounds, see: (a) Xiao, Y.; Zhang, J. *Chem. Commun.* **2009**, 3594–3596. (b) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500–10051. (c) Alcaide, B.; Almendros, P.; del Campo, T. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 6684–6687. (d) Xiong, T.; Zhang, Q.; Zhang, Z.; Liu, Q. *J. Org. Chem.* **2007**, *72*, 8005–8009.