Pergamon

Tetrahedron Letters 43 (2002) 6657–6660

TETRAHEDRON LETTERS

Regio- and stereochemistry of inter- and intramolecular titanium-mediated coupling of imides and mono-substituted olefins

Se-Ho Kim, Yongyoub Park, Hyunah Choo and Jin Kun Cha*

Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487, USA

Received 13 June 2002; accepted 3 July 2002

Abstract—The intramolecular titanium-mediated coupling reaction of α-substituted succinimides and mono-substituted olefins took place with complete regiocontrol, but without diastereoselectivity. The corresponding intermolecular coupling exhibited lack of regio- and diastereocontrol. Also included were stereochemical studies of catalytic hydrogenation and $NaBH_3CN$ reduction of the cyclization products.

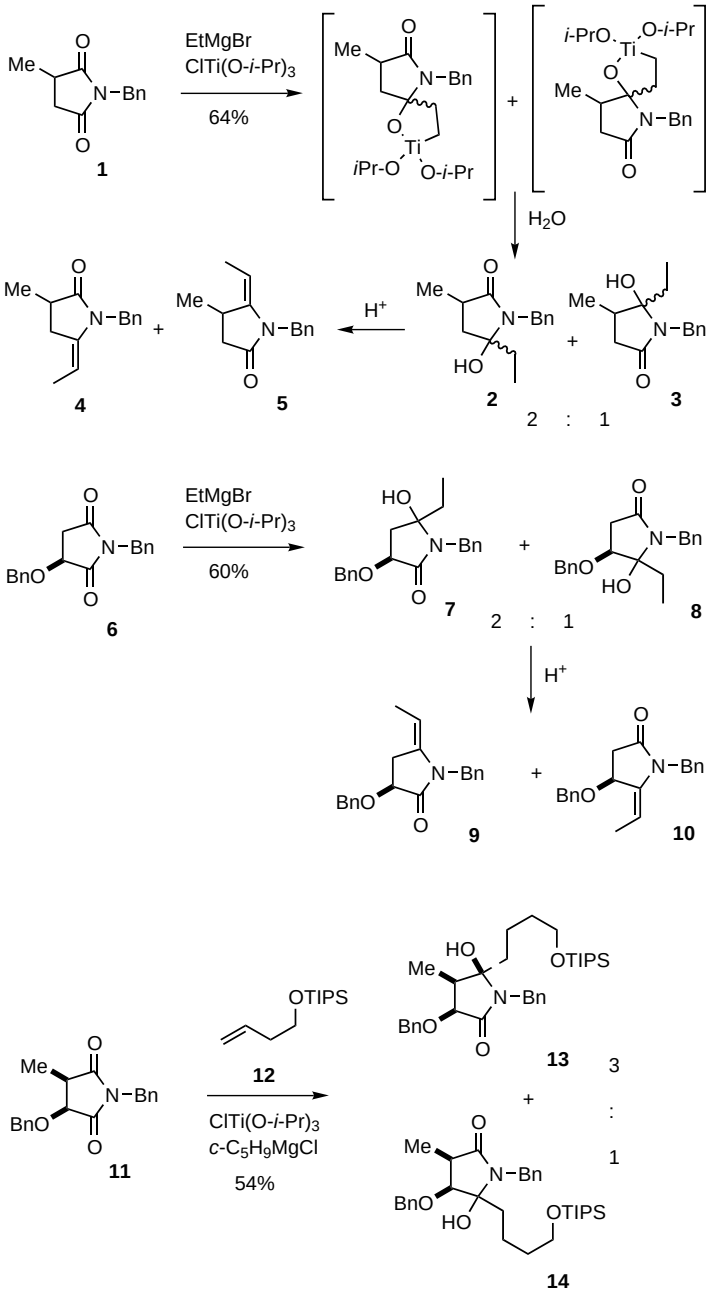
Recently we developed a new, general method for preparing nitrogen heterocycles by means of titanium-mediated cyclization of ω-vinyl imides,[1] which in turn evolved from the Kulinkovich cyclopropanation.[2] This annulation approach was successfully implemented toward the stereocontrolled syntheses of pyrrolizidine, indolizidine, and other alkaloids by our laboratory and others.[3,4] To broaden the utility of the titanium-mediated cyclization for the syntheses of nitrogen heterocycles, we have examined the regio- and stereochemistry of the intermolecular and intramolecular titanium-mediated coupling reactions of unsymmetrically substituted succinimides bearing α-substituents. As enantiomerically pure starting materials are readily available by standard methods, this strategy could lend itself to an enantioselective synthesis of a diverse group of nitrogen-containing heterocycles.

Treatment of succinimide **1**[5] with ethylmagnesium bromide in the presence of chlorotitanium triisopropoxide in THF gave a ~2:1 mixture of both regioisomers **2** and **3** in 64% yield (Scheme 1), and each regioisomer existed as a diastereomeric mixture, complicating analysis of ^{1}H NMR spectra. In order to simplify structural elucidation, the initial adducts **2** and **3** were converted by an acid catalyst (HCl, $CHCl_3$) to the corresponding enamides **4** and **5**, respectively. Coupling of α-benzyloxysuccinimide **6**[5d] and ethylmagnesium bromide exhibited the identical sense and a similar level (~2:1) of regioselectivity to furnish **7** and **8** in 60% yield.[6] In a competition experiment to gauge relative directing effects of the alkyl versus alkoxy groups, the olefin exchange-mediated coupling of **11** and **12** was investigated to afford a 3:1 mixture of **13** and **14** in 54% yield. The low levels of regiocontrol in these coupling reactions were disappointing, yet informative, especially in the context of the known preferential attack by nucleophiles at the more hindered carbonyl group of succinimides, that was rationalized on the basis of the nucleophilic trajectories.[7] For example, addition of a Grignard reagent to **6** was known to take place at the more substituted carbonyl group.[5d,7a] The present examples, taken together, are in accord with the mechanistic premise that the titanium-mediated coupling reactions of imides do not involve simple nucleophilic attack at the carbonyl group by the presumed dialkoxytitanacyclopropane intermediate, but require its initial complexation to the π-electrons of the carbonyl group. The complexation of the titanium metal to the carbonyl group is anticipated to occur more readily at the less hindered carbonyl moiety. Moreover, comparable selectivities exhibited by the methyl and the benzyloxy groups suggest that the complexation process is largely influenced by steric effects, rather than inductive effects. On the other hand, the 3:1 regioselectivity for coupling of **11** in favor of **13** over **14**, albeit moderate, might be attributed to inductive effects by the electronegative benzyloxy substituent. When there are substituents α to both carbonyl groups, the observed diastereoselectivity could be rationalized by preferential addition of the titanacyclopropane intermediate at the more electron-rich carbonyl group.

Keywords: pyrrolizidine alkaloids; *N*-acylhemiaminals; titanium; succinimides.

* Corresponding author. Tel.: 205-348-8550; fax: 205-348-9104; e-mail: jcha@bama.ua.edu

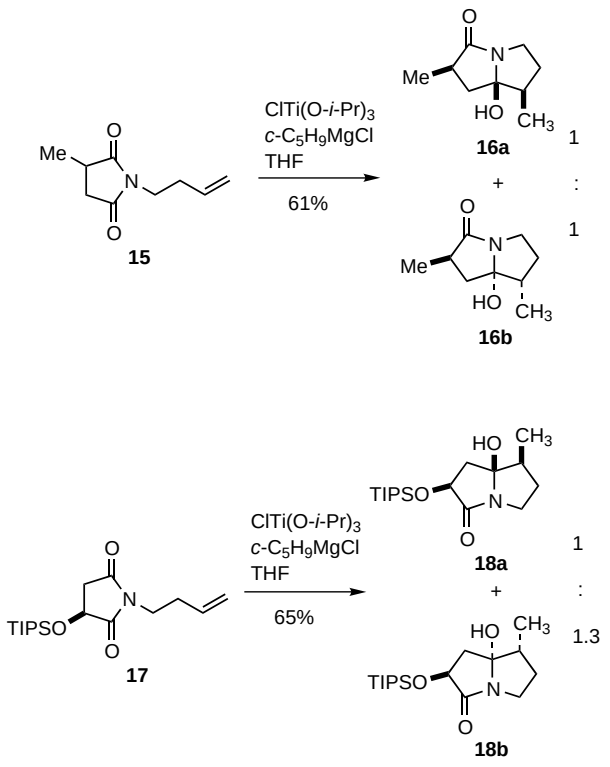
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01442-9



Scheme 1.

We next examined the titanium-mediated cyclization of ω-vinyl imides **15** and **17** (Scheme 2).[8] In both cases, complete regiocontrol, but with no apparent diastereoselectivity, was observed to afford a ca. 1:1 mixture of **16a** and **16b** and a 1:1.3 mixture of **18a** and **18b**, in 61 and 65% yield, respectively. Steric effects were amplified in the intramolecular coupling reactions to the full extent that a tethered dialkoxytitanacyclopropane was added exclusively to the less encumbered carbonyl group. The structures (including the stereochemistry) of **16a**,**b** and **18a**,**b** were determined by COSY and difference NOE measurements, and the structure of **18b** was unequivocally established by X-ray analysis.[9]

As demonstrated in our previous work,[3a] reduction of the *N*-acylhemiaminal functionality of the cyclization products furnished a new entry to the pyrrolizidine and indolizidine alkaloids. Toward this end, each of **16a**,**b** and **18a**,**b** was separately subjected to catalytic hydrogenation and $NaBH_3CN$ reduction (Scheme 3). Catalytic hydrogenation of **16a**,**b** and **18a**,**b** with PtO_2 (in EtOAc containing a small amount of chloroform as the source of HCl[10]) afforded exclusively **19** and **22**, respectively, in 78–94% yield. This observation that hydrogenation of the two diastereomers (e.g. **16a** and **16b**; **18a** and **18b**) gave the same *cis*[11] lactams as single isomers validated the intermediacy of the corresponding enamides (structures not shown),[3a] where hydrogena-

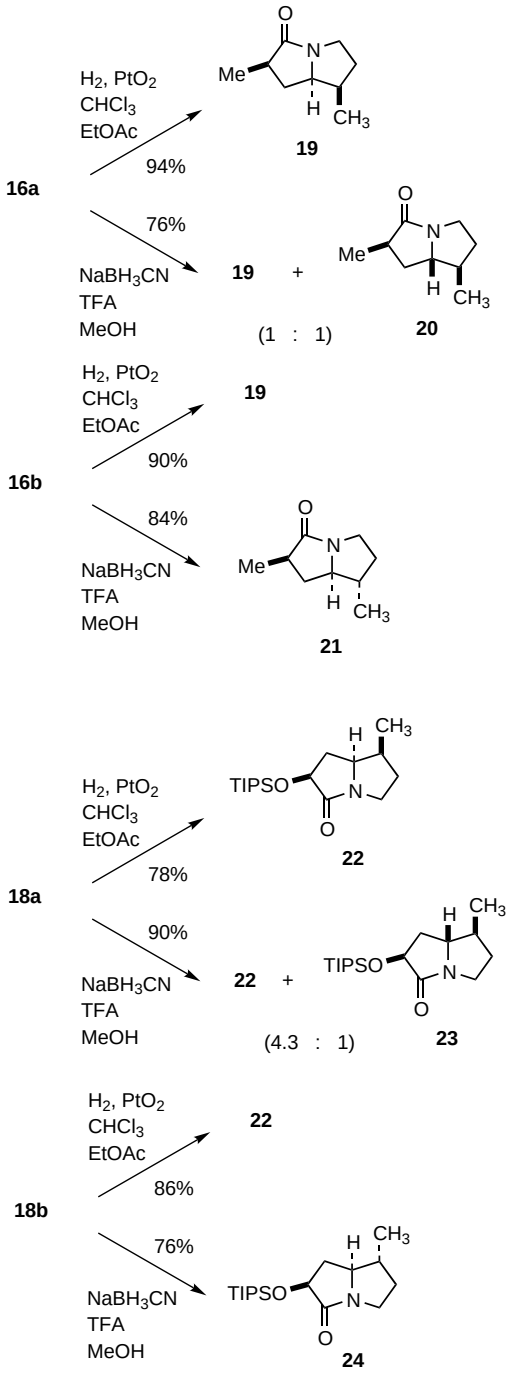


Scheme 2.

tion occurred from the less hindered face away from the α-substituent (i.e. Me or OTIPS).

Reduction of **16b** with $NaBH_3CN$ (TFA, MeOH) furnished the *trans*[11] isomer **21** as a single isomer in 84% yield, whereas that of **16a** gave a 1:1 mixture of **19** and **20** in 76% yield. An analogous divergence in the diastereoselectivity for $NaBH_3CN$ reduction was also found for **18a** and **18b**: exceptionally high stereoselectivity was found for reduction of **18b** to afford **24** in 76% yield. In contrast, the corresponding reduction of **18a** gave a 4.3:1 mixture of **22** and **23**. The hydride reduction of the pyrrolizidine and indolizidine immonium ions was shown to proceed with a high degree of *syn* stereoselectivity with respect to an adjacent substituent, most likely due to a stereoelectronically preferred pseudoaxial attack of hydride ion on the immonium ions having the adjacent substituent (i.e. methyl group) at the pseudoequatorial position.[3a,12] These results on the $NaBH_3CN$ reduction were in accord with a consequence of double stereodifferentiation: the highly diastereoselective reductions of **16b** and **18b** were considered to be 'matched', since α-delivery of hydride ion was reinforced by the inherent diastereofacial preferences of the two substituents. On the other hand, 'mismatched' reductions of **16a** and **18a** took place with poor stereoselectivity, since the two directing groups opposed each other in their diastereofacial biases.

In summary, the regioselectivity of the intermolecular and intramolecular titanium-mediated coupling reactions of unsymmetrically substituted succinimides and terminal olefins has been investigated so as to broaden



Scheme 3.

the utility of the titanium-mediated cyclization in the syntheses of nitrogen heterocycles: although the intermolecular coupling reactions exhibited lack of regio- and diastereocontrol, the intramolecular processes were found to take place with complete regiocontrol, but without diastereoselectivity. Also included were the stereochemical outcomes of catalytic hydrogenation and $NaBH_3CN$ reduction of the resulting *N*-acylhemiaminals. Studies are currently under way to enhance diastereoselectivity by a judicious juxtaposition of a preexisting stereocenter in a ω-vinyl tether.

Acknowledgements

We thank the National Institutes of Health (GM35956) for generous financial support.

References

1. Lee, J.; Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1997**, *119*, 8127.
2. For excellent reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789; (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835.
3. (a) Kim, S.-H.; Kim, S.-I.; Lai, S.; Cha, J. K. *J. Org. Chem.* **1999**, *64*, 6771; (b) Sung, M. J.; Lee, C.-W.; Cha, J. K. *Synlett* **1999**, 561; (c) Kim, S.-H.; Cha, J. K. *Synthesis* **2000**, 2113.
4. (a) Ollero, L.; Mentink, G.; Rutjes, F. P. J. T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **1999**, *1*, 1331; (b) Cao, B.; Xiao, D.; Joullié, M. M. *Org. Lett.* **1999**, *1*, 1799.
5. (a) **1**: prepared in two steps from methylsuccinic anhydride: 1. $BnNH_2$; 2. AcCl. See also (b) Watanabe, T.; Hamaguchi, F.; Ohki, S. *Yakugaku Zasshi* **1973**, *93*, 845 (*Chem. Abstr.* *79*: 78328); (c) Puertas, S.; Rebolledo, F.; Gotor, V. *Tetrahedron* **1995**, *51*, 1495; (d) **6**: Huang, P. Q.; Wang, S. L.; Ye, J. L.; Ruan, Y. P.; Huang, Y. Q.; Zheng, H.; Gao, J. X. *Tetrahedron* **1998**, *54*, 12547.
6. Application of the olefin exchange-mediated procedures[1,3] to coupling of imides **1** and **6** with olefin **12** also provided comparable results as the above-mentioned reactions employing ethylmagnesium bromide by direct adaptation of the original Kulinkovich procedure.
7. (a) Wijberg, J. B. P. A.; Schoemaker, H. E.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 179; (b) Kayser, M. M.; Morand, P. *Tetrahedron Lett.* **1979**, *20*, 695; (c) Kayser, M. M.; Salvador, J.; Morand, P. *Can. J. Chem.* **1983**, *61*, 439. Cf: (d) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734; (e) Baldwin, J. E. *Further Perspectives in Organic Chemistry*; Ciba Foundation Symposium 53; Elsevier: Amsterdam, 1979; pp. 85–99.
8. (a) Prepared by the Mitsunobu reaction of the respective imides and 3-butenol in excellent yields. See also: (b) Lee, Y. S.; Lee, J. Y.; Kim, D. W.; Park, H. *Tetrahedron* **1999**, *55*, 4631.
9. We thank Professor Robin Rogers for a single-crystal X-ray analysis of **18b**.
10. Cf. Secrist, J. A., III; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335.
11. The *cis*/*trans* nomenclature refers to the relative stereochemistry of the two respective methine hydrogens.
12. For stereoselective $NaBH_3CN$ reduction of iminium compounds, see: Ohnuma, T.; Tabe, M.; Shiiya, K.; Ban, Y. *Tetrahedron Lett.* **1983**, *24*, 4249.