ORGANIC LETTERS

2006
Vol. 8, No. 20
4509−4511

Asymmetric Multicomponent Reactions: Diastereoselective Synthesis of Substituted Pyrrolidines and Prolines

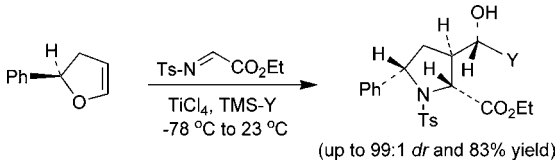
Arun K. Ghosh,* Sarang Kulkarni, Chun-Xiao Xu, and Phillip E. Fanwick

Departments of Chemistry and Medicinal Chemistry, Purdue University, West Lafayette, Indiana 47907

akghosh@purdue.edu

Received July 7, 2006

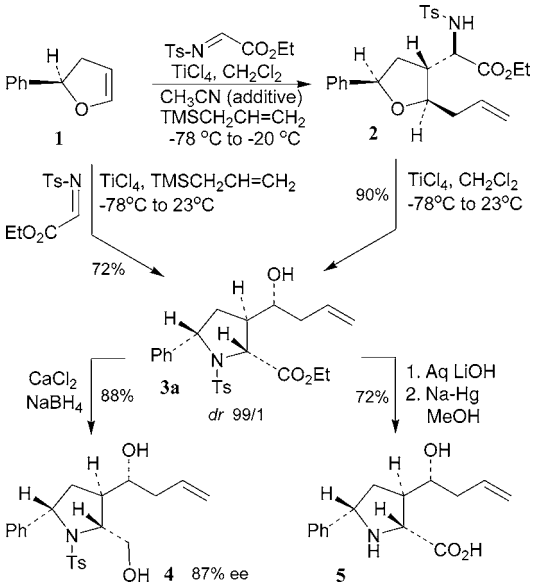
ABSTRACT



A novel diastereoselective synthesis of substituted pyrrolidines has been developed. Asymmetric multicomponent reactions of optically active phenyldihydrofuran, *N*-tosyl imino ester, and silane reagents in a one-pot operation afforded highly substituted pyrrolidine derivatives diastereoselectively. The reaction is quite efficient and constructed up to three stereogenic centers in a single operation.

Multicomponent reactions (MCRs) that provide functionalized heterocyclic scaffolds in a single operation and in a stereodefined manner are of enormous importance in synthetic organic and medicinal chemistry. Despite the significance and potential of MCRs, there exist only a few versatile multicomponent reactions that truly generate diverse molecules with multiple stereocenters.[1] Our development of multicomponent reactions led to syntheses of a variety of substituted tetrahydrofurans and tetrahydropyrans containing multiple stereocenters.[2] Recently, we described multicomponent reactions with *N*-tosylimino ester that provided rapid access to a range of functionalized novel α-amino acids containing cyclic ether templates.[3] As depicted in Scheme 1, multicomponent reactions of *N*-tosylimino ester with optically active phenyldihydrofuran (**1**) at −78 to −20 °C in the presence of allyltrimethylsilane as the nucleophile and CH_3CN as the additive provided a single diastereomer **2** in very good yield. Interestingly, in the absence of CH_3CN

Scheme 1. Asymmetric Multicomponent Reaction



(1) (1) For recent reviews of multicomponent reactions, see: (a) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (b) Strubing, D.; Neumann, H.; Hubner, S.; Klaus, S.; Beller, M. *Tetrahedron Lett.* **2005**, *61*, 11345; (c) Nair, V.; Sreekumar, V.; Bindu, S.; Suresh, E. *Org. Lett.* **2005**, *7*, 2297.

(2) (a) Ghosh, A. K.; Kawahama, R.; Wink, D. *Tetrahedron Lett.* **2000**, *41*, 8425. (b) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 1083. (c) Ghosh, A. K.; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 4751. (d) Ghosh, A. K.; Kawahama, R. *J. Org. Chem.* **2000**, *65*, 5433.

(3) Ghosh, A. K.; Xu, C.-X.; Kulkarni, S. S.; Wink, D. *Org. Lett.* **2005**, *7*, 7.

10.1021/ol061672i CCC: $33.50
Published on Web 08/29/2006

additive, this multicomponent reaction typically afforded tetrahydrofuran derivative **2** along with varying amounts (15−30%) of pyrrolidine derivative **3a** as the byproduct. Presumably, a Lewis acid catalyzed intramolecular rearrangement led to the formation of pyrrolidine derivative **3**. The presence of CH_3CN additive completely prevented the formation of pyrrolidine derivative **3**. Pyrrolidine rings are inherent to numerous bioactive natural products and medicinal agents.[4] The biological significance of functionalized pyrrolidines and prolines continues to stimulate interest in their design and synthesis. In this context, a number of practical synthetic methodologies have been developed recently.[5] In our continuing interest in probing enzyme-active sites with designed ligands containing heterocyclic templates,[6] we sought to optimize the above multicomponent reaction conditions so as to synthesize functionalized pyrrolidine heterocycles in a stereopredictable manner. Herein we report asymmetric multicomponent reactions of optically active phenyldihydrofuran, *N*-tosylimino ester, and silane reagents in a one-pot operation to afford functionalized pyrrolidine and proline derivatives diastereoselectively.

As mentioned above, the multicomponent reaction of *N*-tosylimino ester,[7] 5-phenyldihydrofuran (**1**),[8,9] and allyltrimethylsilane in the absence of CH_3CN additive provided phenyltetrahydrofuran **2** along with pyrrolidine derivative **3a** as the byproduct. We anticipated that the formation of pyrrolidine byproduct **3a** evolved from phenyltetrahydrofuran **2** by a $TiCl_4$-promoted formation of benzylic carbocation followed by intramolecular ring closure with the sulfonamide. To examine this presumption, phenyltetrahydrofuran **2** was treated with 1.2 equiv of $TiCl_4$ in CH_2Cl_2 at −78 °C, and the resulting mixture was warmed to 23 °C for 2 h. Indeed, phenyltetrahydrofuran **2** smoothly converted to pyrrolidine derivative **3a** as a single diastereomer in 90% yield. We then optimized the multicomponent reaction conditions to provide pyrrolidine derivative **3a**. Thus, asymmetric multicomponent reactions leading to effective synthesis of various functionalized pyrrolidines were carried out as follows. Optically active phenyldihydrofuran (**1**, 1.2 equiv) and *N*-tosylimino ester (1 equiv) in CH_2Cl_2 were treated with $TiCl_4$ (1 M solution in CH_2Cl_2, 1.2 equiv) at −78 °C for 1 h. Allyltrimethylsilane (3 equiv) was added, and the resulting mixture was allowed to warm to 23 °C and stirred for 1 h. After this period, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. Standard workup and flash chromatography over silica provided pyrrolidine derivative **3a** in 72% yield as a single diastereomer (by ^1H and ^{13}C NMR analysis). Reduction of **3a** with $NaBH_4$ in the presence of $CaCl_2$ in a mixture of EtOH and THF afforded diol **4** in 88% yield. The assignment of stereochemistry of the three new chiral centers of **3a** was made on the basis of the X-ray structure of **4** in Figure 1 as well as extensive NOESY experiments.[10]

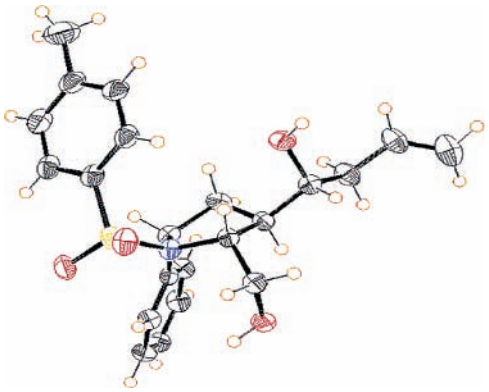


Figure 1. ORTEP drawing of X-ray structure of **4**.

The optical purity of compound **4** was determined by its conversion to the corresponding Mosher ester.[11] The ^{19}F NMR analysis of the Mosher esters established that the optical purity was 87% ee. Compound **3a** was also converted to proline derivative **5** by saponification using aqueous LiOH followed by exposure of the resulting acid to Na−Hg in methanol at reflux.[12] Proline derivative **5** was obtained in 72% yield in a two-step sequence.

We investigated the feasibility of this reaction protocol with a number of nucleophiles, and the results are summarized in Table 1. Multicomponent reactions with allyltributylstannane in the presence of 1.2 equiv of $TiCl_4$ proceeded with excellent diastereoselectivity (dr = 99/1, Table 1, entry 2) and good yield. When triethylsilane was used as a nucleophile, pyrrolidine derivatives were obtained

(4) (a) Trost, B. M.; Pinkerton, A. B.; Kremzow, D. *J. Am. Chem. Soc.* **2000**, *122*, 12007. (b) Leclercq, S.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Moore, R. E., Eds.; Springer-Verlag: New York, 2000; Vol. 79, p 115. (c) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, *67*, 5445. (d) Hanessian, S.; Bayrakdariyan, M.; Luo, X. *J. Am. Chem. Soc.* **2002**, *124*, 4716.

(5) For recent syntheses of pyrrolidines: (a) David, F. A.; Xu, H.; Wu, Y.; Zhang, J. *Org. Lett.* **2006**, *8*, 2273. (b) Cabrera, S.; Arrayas, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394. (c) Hanessian, S.; Yun, H.; Hou, Y.; Tintelnot-Blomely, M. *J. Org. Chem.* **2005**, *70*, 6746. (d) Liu, Z.; Rainier, J. D. *Org. Lett.*, **2005**, *7*, 131. (e) Garner, P.; Kaniskan, H. U. *J. Org. Chem.* **2005**, *70*, 10868. (f) Kumareswaran, R.; Shin, S.; Gallou, I.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 7157.

(6) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan, K.; Hussain, K. A.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 687.

(7) (a) Tschaen, D. M.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058. (b) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131.

(8) Phenyldihydrofuran was prepared using asymmetric Heck reactions in optically enriched form, see: (a) Ozawa, F.; Kubo, A.; Hayashi, T. *Tetrahedron Lett.* **1992**, *33*, 1485. (b) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.

(9) Optical purity of 5-phenyl dihydrofuran was 88% ee.

(10) Crystal data for **4**: $C_{22}H_{27}NO_4S$; MW = 401.53; colorless crystal; crystal system, block; space group, *P*21; cell parameters, a = 13.99719-(11) Å, b = 10.4573(4) Å, c = 14.4138(11) Å, α =96.230(3)°, V = 2097.3-(2) Å^3, Z = 4; Mo Kα radiation (λ = 0.71073 Å, T = 150 K), R1 = 0.045, wR2 = 0.076 ($I > 2\sigma(I)$); R1 = 0.081, wR2 = 0.089 (all data). Crystallographic data has been deposited with the Cambridge Crystallographic Data Center (deposition no. 611303). These data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif, by email to data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, U.K.

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) (a) Birkinshaw, T. N.; Holmes, A. B. *Tetrahedron Lett.* **1987**, *28*, 813; (b) Chavez, F.; Sherry, A. D. *J. Org. Chem.* **1989**, *54*, 2990.

Table 1. Structures and Diastereoselectivities of Pyrrolidine Derivatives[a]

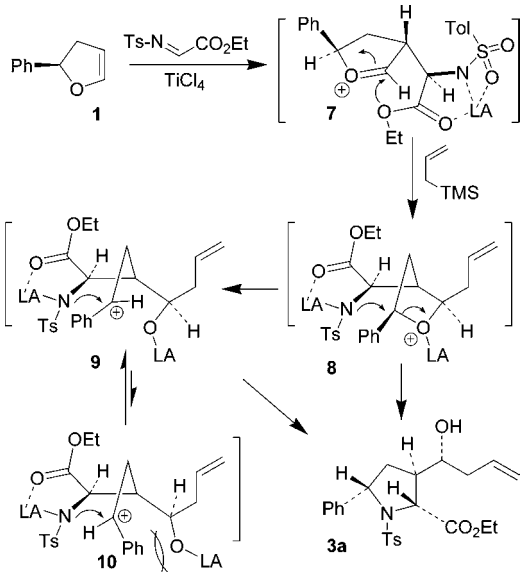
entry	nucleophile	equiv of $TiCl_4$	major Product(s)	yield (%)[b]	dr[c]
1	Me_3Si	1.2	**3a**	72	99/1
2	*n*-Bu_3Sn	1.2	**3a**	68	99/1
3	Et_3SiH	1.2	**3b**	69	90/10
4	*n*-Bu_3SnH	1.2	**3b**	53	85/15
5	Ph, OTBS **6a**	4.2	**3c**	63	99/1
6	TBSO, *t*-Bu **6b**	4.2	**3d**	83	99/1
7	TBSO, OPh **6c**	4.2	**3e**	76	99/1
8	OMe, OTMS **6d**	4.2	**3f**	61	99/1

[a] All reactions were carried out as described in the text. [b] Yields refer to the isolated product. [c] Diastereomeric ratio determined by ^1H NMR and ^{13}C NMR.

as a mixture of diastereomers (*dr* = 90/10, Table 1, entry 3). The corresponding reactions with tributyltin hydride also provided pyrrolidine derivative **3b**. However, diastereoselectivity and yield were further reduced (Table 1, entry 4). We then examined a number of enolsilanes and ketene acetals as the nucleophiles. These reactions were considerably sluggish in the presence of 1.2 equiv of $TiCl_4$. Multicomponent reactions with enolsilane **6a** in the presence of 1.2 equiv of $TiCl_4$ at −78 to +23 °C provided a mixture (∼1:1) of tetrahydrofuran and pyrrolidine derivatives. The use of 4.2 equiv of $TiCl_4$, however, afforded only pyrrolidine derivative **3c** as a single diastereomer in 63% yield (Table 1, entry 5). The corresponding reaction with *tert*-butyl enol ether **6b** also gave a single diastereomer **3d** in excellent yield (Table 1, entry 6). These reactions with ketene acetals **6c** and **6d** also proceeded with excellent diastereoselectivity.

Lewis acid catalyzed formation of pyrrolidines as well as a high degree of diastereoselectivity associated with these reactions can be rationalized on the basis of the proposed models in Scheme 2. As described previously,[3] we presume that reaction of phenyldihydrofuran and *N*-tosylimino ester in the presence of $TiCl_4$ at −78 °C would furnish oxocarbenium ion **7** which minimizes nonbonding interactions in the transition state. Reaction of **7** with allytrimethylsilane at −78 to −20 °C in the presence of CH_3CN would provide tetrahydrofuran **2** as described previously.[3] However in the absence of CH_3CN, Lewis acid activation of tetrahydrofuran would result in a new oxonium ion **8**. The S_N2 nucleophilic attack of sulfonamide nucleophile (*N*Ts) to the LA-activated oxonium ion **8** may account for the observed complete inversion for **3a** and **3c**−**f** (Table 1, entries 1, 2, and 5−8). Alternatively, oxonium ion **8** may subsequently lead to a benzylic carbonium ion **9**. Further rotation of the carbon−carbon bond around the benzylic carbonium ion could provide an alternate carbonium ion **10**. An intramolecular S_N1 attack by the *N*Ts is likely to proceed through **9** over **10** to provide **3a** predominantly because of the absence of developing nonbonding interactions between the phenyl ring and the bulky metal alkoxide. The proposed models account for the observed diastereoselectivity with triethylsilane and tributyltinhydride (Table 1, entries 3 and 4) where steric bulk of metal alkoxide is considerably reduced.

Scheme 2. Stereochemical Models



In summary, we have developed highly diastereoselective $TiCl_4$-catalyzed multicomponent coupling reactions to provide functionalized pyrrolidines with multiple stereocenters. The overall process is quite efficient and the protocol has constructed up to three contiguous asymmetric centers in a single operation. Further studies are under investigation in our laboratory.

Acknowledgment. Financial support by the National Institutes of Health (GM 53386) is gratefully acknowledged.

Supporting Information Available: Experimental procedures, spectral data for compounds **3**−**5**, and ^1H NMR and ^{13}C NMR spectra for compounds **3**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061672I