ORGANIC LETTERS

2012
Vol. 14, No. 8
2002–2005

$TiCl_4$-Promoted Tandem Carbonyl or Imine Addition and Friedel–Crafts Cyclization: Synthesis of Benzo-Fused Oxabicyclooctanes and Nonanes

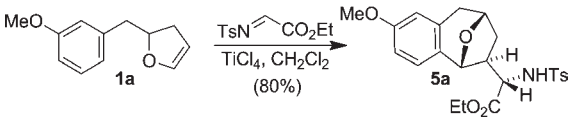
Arun K. Ghosh,* Cuthbert D. Martyr, and Chun-Xiao Xu

Department of Chemistry and Department of Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, Indiana 47907, United States

akghosh@purdue.edu

Received February 27, 2012

ABSTRACT



A new and convenient synthesis of benzo-fused 8-oxabicyclo[3.2.1]octane and 9-oxabicyclo[4.2.1]nonane derivatives are described. The reaction involved a $TiCl_4$-mediated tandem carbonyl or imine addition followed by a Friedel–Crafts cyclization to provide these functionalized derivatives in good to excellent yields and high diastereoselectivity.

Functionalized benzo-fused oxabicyclooctanes and nonanes are unique heterocyclic frameworks, and their use in molecular design is rather limited. In connection with our work in probing the enzyme active site using designed ligands, we have been particularly interested in stereochemically defined oxabicyclic heterocyclic scaffolds.[1] The benzannulated 8-oxabicyclo-[3.2.1]octane ring system is also inherent to bioactive natural products, bruguierol A–C.[2,3] Several syntheses of benzo-fused 8-oxabicyclo[3.2.1]octanes have been previously described.[4] The structural novelty and antibacterial activity of bruguierol C also led to several recent reports of the synthesis of the 8-oxabicyclo[3.2.1]octane core in the literature.[5]

We have previously developed $TiCl_4$-mediated multicomponent reactions of vinyl ethers, carbonyl, or imine electrophiles with various nucleophiles (TMS-Nu, alcohols, or amines).[6] These reactions provided rapid access to a range of functionalized tetrahydrofuran and tetrahydropyran derivatives with multiple chiral centers.[7] The effectiveness of these multicomponent reactions was demonstrated in the synthesis of natural products.[8] Also, a number of functionalized cyclic ether derivatives have shown intriguing activity against HIV-1 protease.[9] As outlined in Figure 1, the reaction proceeded by addition of vinyl ether (**1**) to a $TiCl_4$ activated electrophile followed by addition of an

(1) Ghosh, A. K.; Anderson, D. D.; Weber, I. T.; Mitsuya, H. *Angew. Chem., Int. Ed.* **2012**, *51*, 2–27.
(2) Han, L.; Huang, X.; Sattler, I.; Moellmann, U.; Lin, W.; Grabley, S. *Planta Med.* **2005**, *17*, 160–164.
(3) Lefort, A.; Baptista, M.; Fantin, B.; Depardieu, F.; Arthur, M.; Carbon, C.; Courvalin, P. *Antimicrob. Agents Chemother.* **1999**, *43*, 476–482.
(4) (a) Sammes, P. G.; Whitby, R. J. *J. Chem. Soc., Chem. Commun.* **1984**, 702–703. (b) Marson, C. M.; Campbell, J.; Hursthouse, M. B.; Abdul Malic, K. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1122–1124. (c) Oda, K.; Nakagami, R.; Nishizono, N.; Machida, M. *Chem. Lett.* **2000**, *29*, 1386–1387. (d) Wu, Y.; Li, Y.; Wu, Y.-L. *Helv. Chim. Acta* **2001**, *84*, 163–171.
(5) (a) Solorio, D. M.; Jennings, M. P. *J. Org. Chem.* **2007**, *72*, 6621–6623. (b) Ramana, C. V.; Salian, S. R.; Gonnade, R. G. *Eur. J. Org. Chem.* **2007**, 5483–5486. (c) Fananas, F. J.; Fernandez, A.; Cevic, D.; Rodriguez, F. *J. Org. Chem.* **2009**, *74*, 932–934. (d) Sarkar, D.; Venkateswaran, R. V. *Tetrahedron Lett.* **2011**, *52*, 3232–3233. (e) Hu, B.; Xing, X.; Ren, J.; Wang, Z. *Tetrahedron* **2010**, *66*, 5671–5674.
(6) (a) Ghosh, A. K; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 1083–1086. (b) Ghosh, A. K; Kawahama, R. *Tetrahedron Lett.* **1999**, *40*, 4751–4754.
(7) (a) Ghosh, A. K; Kawahama, R; Wink, D. *Tetrahedron Lett.* **2000**, *41*, 8425–8429. (b) Ghosh, A. K; Xu, C.-X; Kulkarni, S. S; Wink, D. *Org. Lett.* **2005**, *7*, 7–10. (c) Ghosh, A. K; Kulkarni, S; Xu, C-X; Fanwick, P. E. *Org. Lett.* **2006**, *8*, 4509–4511. (d) Ghosh, A. K; Kass, J. *Chem. Commun.* **2010**, *46*, 1218–1220.
(8) (a) Ghosh, A. K.; Kawahama, R. *J. Org. Chem.* **2000**, *65*, 5433–5435. (b) Ghosh, A. K.; Kass, J. *Org. Lett.* **2012**, *14*, 510–512.
(9) Ghosh, A. K. PCT Int. appl. 2009, WO 2009091941 A1 20090723.

10.1021/ol300494q
Published on Web 04/04/2012

external nucleophile to the generated oxocarbenium ion (**2**). Toward the synthesis of benzannulated 8-oxabicyclo-[3.2.1]octane rings, we set out to investigate the viability of carbonyl addition or Povarov-type imine addition followed by traping the oxocarbenium ion intermediate with an internal nucleophile, particularly with electron-rich aromatic systems.[10] Herein, we report a convenient synthesis of substituted benzo-fused 8-oxabicyclo[3.2.1]octane and 9-oxabicyclo[4.2.1]nonane ring systems with α-hydroxyl, and α-amino esters in good to excellent yields and high diastereoselectivity.

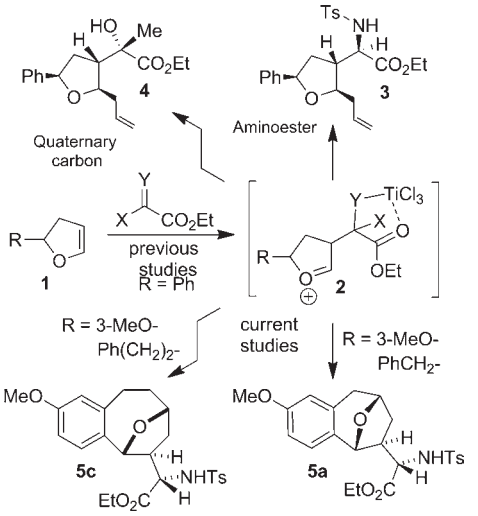
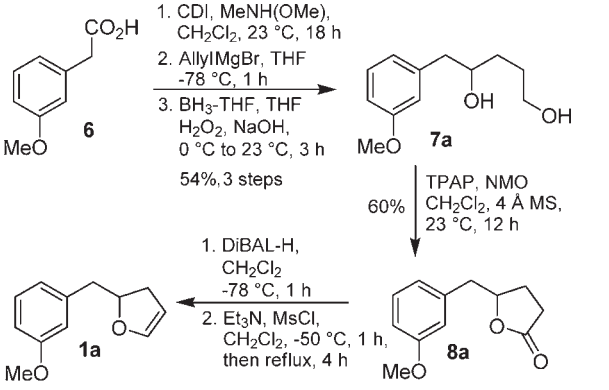


Figure 1. Current and previous studies of multicomponent reactions.

We first planned to investigate the feasibility of Povarov-type imine addition followed by intramolecular Friedel–Crafts annulation with electron-rich aromatic systems such as 2-(3-methoxybenzyl)-2,3-dihydrofuran **1a** or dihydrofuranylmethylbenzo[1,3]dioxole derivative **1b** and tosyliminoacetate. Synthesis of dihydrofuran **1a** is shown in Scheme 1. Commercially available 3-methoxy phenylacetic acid **6** was converted to the corresponding Weinreb amide[11] using carbonyldiimidazole (CDI) and NH(OMe)-Me·HCl in near-quantiative yield. Treatment of the resulting amide with allylmagnesium bromide at −78 °C furnished the allyl ketone which was subjected to borane reduction and hydroboration to provide racemic diol **7a** in 54% yield over three steps. Oxidation of diol **7a** with TPAP in the presence of NMO and 4 Å MS at 23 °C afforded lactone **8a** in 60% yield. DIBAL-H reduction of the lactone and subsequent mesylation and elimination gave the desired racemic dihydrofuran **1a** in 73% yield over two

Scheme 1. Synthesis of Methoxybenzyl-2,3-dihydrofuran



steps.[12] Starting with appropriately substituted phenylalkanoic acid, racemic dihydrofurans **1b**–**f** were prepared conveniently.[13]

We examined the reaction of dihydrofuran **1a** and *N*-tosyliminoacetate as shown in Scheme 2. Thus, a mixture of **1a** and *N*-tosyliminoacetate in CH_2Cl_2 at −78 °C was treated with a 1 M $TiCl_4$ solution in CH_2Cl_2. The mixture was stirred at −78 °C for 15 min and then warmed to −20 °C over 1 h. The reaction was quenched with a saturated solution of K_2CO_3, and the mixture was warmed to 23 °C. Standard workup and flash chromatography furnished benzo-fused 8-oxabicyclo[3.2.1]octane derivative **5a** in 80% yield as a single diastereomer (by ^1H, ^{13}C NMR and HPLC analysis). Encouraged by this result, we then investigated dihydrofuran **1b**. As shown in Table 1, the reaction with **1b** and *N*-tosyliminoacetate also provided 8-oxabicyclo[3.2.1]octane derivative **5b** in 71% yield and with excellent diastereoselectivity (entry 2). The outcome of the methoxy regiochemistry can be rationalized based upon transition-state models **9a** and **9b**. Presumably, model **9b** is preferred as the developing nonbonding interactions are less than those for **9a**. This reaction incorporated three new chiral centers. The core structure and relative stereochemistry of **5b** were determined by X-ray crystallographic analysis, as shown in Figure 2.[14,15] The stereochemical outcomes of both chiral centers are consistent with our previous report of related amino acid structures.[7c]

Our attempts to generate benzo-fused 7-oxa-bicyclo-[2.2.1]heptane with 3-substituted phenyl dihydrofuran were unsuccessful. Furthermore, reaction with benzyl dihydrofuran did not provide the desired 8-oxabicyclo[3.2.1]octane derivative under the indicated conditions. As depicted in

(10) (a) Povarov, L. S.; Mikhailov, B. M. *Izv. Akad. Nauk SSR, Ser. Khim.* **1963**, 953–956. (b) Kouznetsov, V. V. *Tetrahedron*. **2009**, *65*, 2721–2750.

(11) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815–3819.

(12) Walker, J.; Chen, J.; Wise, D. S; Townsend, L. B. *J. Org. Chem.* **1996**, *61*, 2219–2221.

(13) See Supporting Information for the synthesis of other dihydrofurans **1b**–**f**.

(14) Single-crystal X-ray analysis was performed in-house; Dr. Phil Fanwick, X-ray Crystallography laboratory, Department of Chemistry, Purdue University, West Lafayette, IN 47907.

(15) CCDC 867872 contains the supplementary crystallographic data for compound **5b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Scheme 2. Synthesis of Oxabicylooctanes

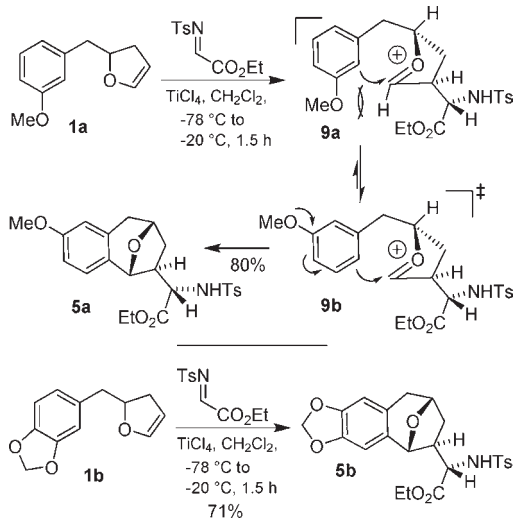


Table 1. Reactions of Dihydrofurans with *N*-Tosyliminoacetate

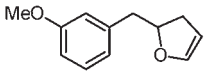
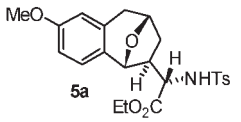
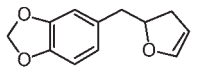
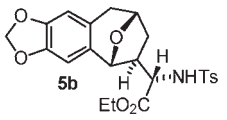
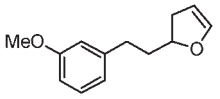
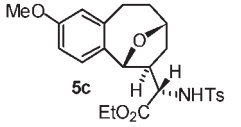
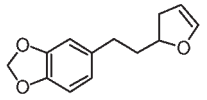
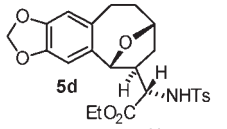
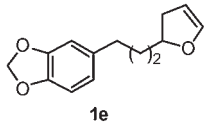
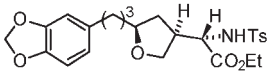
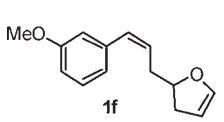
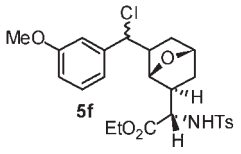
entry	dihydrofurans	major product	yield (dr)
1.			80 (99:1)
2.			71 (99:1)
3.			69 (99:1)
4.			62 (99:1)
5.			62 (99:1)
6.			32 (2:1)

Table 1, we have also explored the formation of benzo-fused 9-oxabicyclo[4.2.1]nonanes with dihydrofurans **1c** and **1d**. As can be seen, the corresponding cyclizations proceeded well, and the corresponding oxabicyclononanes were obtained in good yield and as a single diastereomer (entries 3 and 4). Our subsequent attempts to form 10-oxabicyclo[5.2.1]decane

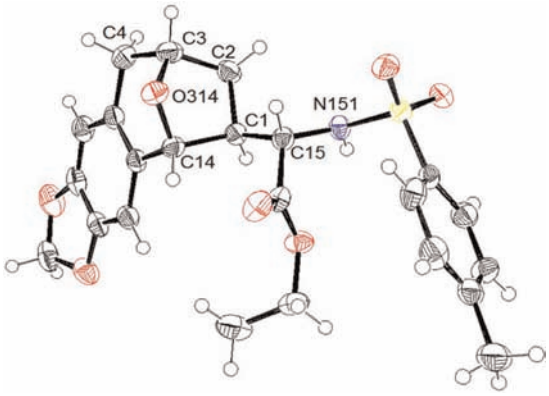
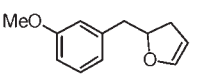
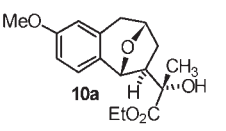
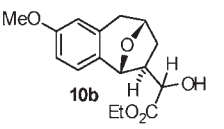
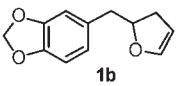
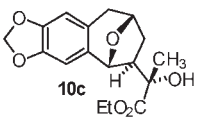
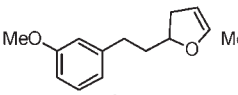
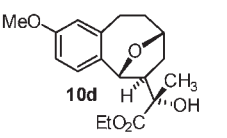
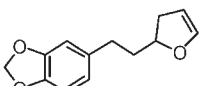
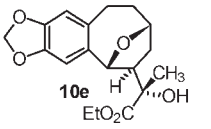


Figure 2. ORTEP diagram displaying the relative stereochemistry of the bridged oxabicylic derivative **5b**.

with dihydrofuran **1e** were unsuccessful. In this case, the corresponding lactols were obtained as a mixture of diastereomers. Subsequent reduction of the lactol mixture with triethylsilane in the presence of $BF_3{\bullet}OEt_2$ afforded a single deoxygenated product **5e** in 62% yield over two steps (entry 5). The inherent difficulty in forming nine-member ring systems may have limited the intramolecular Friedel–Crafts annulation process. Our attempts to facilitate cyclization of the lactol mixture with $BF_3{\bullet}OEt_2$ at −78 to 23 °C were also unsuccessful. We have also examined cyclization using a *cis*-olefin derivative **1f** in order to bring the aromatic nucleophile in close proximity to the oxocarbenium ion intermediate. The expected

Table 2. Reactions of Dihydrofurans with Ethyl Pyruvate and Ethyl Glyoxalate

entry	dihydrofuran	major product	yield (dr)
1.			50 (4:1)
2.	1a		52 (1:1)
3.			44 (99:1)
4.			54 (99:1)
5.			54 (99:1)

product was not observed; instead a kinetically favored bicyclic[2.2.1]heptane **5f** was obtained as a 2:1 mixture in 32% yield.

To further expand the scope of this intramolecular Friedel–Crafts annulation, we evaluated reactions with commercially available ethyl glyoxalate and ethyl pyruvate to generate α-hydroxyl and α-hydroxy-α-methyl ester functionalities. The results are shown in Table 2. Reaction of dihydrofuran **1a** with ethyl pyruvate provided 8-oxabicyclo[3.2.1]octane **10a** as a 4:1 mixture of diastereomers in 50% yield (entry 1). The corresponding reaction with ethyl glyoxalate as an electrophile afforded a 1:1 mixture of diastereomers (entry 2). Reaction of dihydrofuran **1b** with ethyl pyruvate furnished 8-oxabicyclo-[3.2.1]octane **10c** with excellent diastereoselectivity and in 44% yield (entry 3). The corresponding reactions with dihydrofurans **1c** and **1d** afforded benzo-fused 9-oxabicyclo-[4.2.1]nonanes **10d** and **10e** with excellent diastereoselectivity (entries 4 and 5).

In summary, we have developed a convenient method for generating substituted benzo-fused 8-oxabicyclo[3.2.1]-octanes and benzo-fuzed 9-oxabicyclo[4.2.1]nonanes using substituted electron-rich benzyldihydrofurans and phenethyldihydrofurans. The reactions of *N*-tosyliminoacetate and ethyl pyruvate proceeded with excellent diastereoselectivity. The reaction of 3-substituted phenyldihydrofuran and benzyldihydrofuran did not provide Friedel–Crafts annulation products. Also, this annulation reaction is limited to the formation of benzo-fused 8-oxabicyclo[3.2.1]octanes and benzo-fused 9-oxabicyclo-[4.2.1]nonanes. The corresponding reactions for 9- and 10-membered rings or larger were unsuccessful. The design of molecular probes utilizing these substituted oxabicyclo derivatives is currently underway in our laboratory.

Acknowledgment. Financial support by the National Institutes of Health is gratefully acknowledged. We would like to thank Dr. K.V. Rao (Purdue University) for helpful discussions. We also thank Dr. Phil Fanwick (Purdue University) for X-ray structure determination.

Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.