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TiCl₄-Promoted Tandem Carbonyl or Imine Addition and Friedel-Crafts Cyclization: Synthesis of Benzo-fused Oxabicyclooctanes and Nonanes

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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 TiCl₄-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 TiCl₄-mediated multicomponent reactions of vinyl ethers, carbonyl, or imine electrophiles with various nucleophiles (TMS-Nu, or 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 TiCl₄ activated electrophile followed by addition of an external nucleophile to the generated oxocarbenium ion (2). Towards 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 trapping the oxocarbenium 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-

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

oxabicyclo[4.2.1]nonane ring systems with α -hydroxyl, and α -amino esters in good to excellent yields and high diastereoselectivity.

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 amide¹¹ using carbonyldiimidazole (CDI) and NH(OMe)Me·HCl in near quantitative yield. Treatment of the resulting amide with allylmagnesium bromide at $-78\text{ }^{\circ}\text{C}$ furnished the allyl ketone which was subjected to borane reduction and hydroboration to provide racemic diol **7a** in 54% yield over 3 steps. Oxidation of diol **7a** with TPAP in the presence of NMO and 4 Å M.S at $23\text{ }^{\circ}\text{C}$ 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 steps.¹² Starting with appropriately substituted phenylalkanoic acid, racemic dihydrofurans **1b–d** 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 $-78\text{ }^{\circ}\text{C}$ was treated with a 1 M TiCl_4 solution in CH_2Cl_2 . The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min and then warmed to $-20\text{ }^{\circ}\text{C}$ over 1 h. The reaction was quenched with a saturated solution of K_2CO_3 and the mixture was warmed to $23\text{ }^{\circ}\text{C}$. 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 and ^{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 non-bonding interactions are less than for **9a**. This reaction incorporated three new chiral centers. The core structure and relative stereochemistry of **5b** was determined by X-ray crystallographic analysis, as shown in Figure 2.^{14,15} The stereochemical outcome of both chiral centers are consistent with our previous report of the 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 Table 1, we have also explored the formation of benzo-fused 9-oxabicyclo[4.3.1]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[5.3.1]decane 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 $\text{BF}_3\cdot\text{OEt}_2$ afforded a single deoxygenated product **5e** in 62% yield over two steps (entry 5). The inherent difficulty in forming 9-member ring systems may have limited the intramolecular Friedel-Crafts annulation process. Our attempts to facilitate cyclization of the lactol mixture with $\text{BF}_3\cdot\text{OEt}_2$ at $-78\text{ }^{\circ}\text{C}$ to $23\text{ }^{\circ}\text{C}$ 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 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 esters, 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 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[4.3.1]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-fused 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 benzyl dihydrofuran 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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

Figure 1.
Current and previous studies of multicomponent reactions

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

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

Scheme 2.
Synthesis of oxabicyclooctanes

Table 1Reactions of dihydrofurans with *N*-tosyliminoacetate

entry	dihydrofurans	major product	yield (dr)
1.	1a	5a	80 (99:1)
2.	1b	5b	71 (99:1)
3.	1c	5c	69 (99:1)
4.	1d	5d	62 (99:1)
5.	1e	5e	62 (99:1)
6.	1f	5f	32 (2:1)

Table 2

Reactions of dihydrofurans with ethyl pyruvate and ethyl glyoxalate

entry	dihydrofuran	major product	yield (dr)
1.	1a	10a	50 (4:1)
2.	1a	10b	52 (1:1)
3.	1b	10c	44 (99:1)
4.	1c	10d	54 (99:1)
5.	1d	10e	54 (99:1)