ORGANIC LETTERS

2011
Vol. 13, No. 7
1646–1649

Enabling the Synthesis of Perfluoroalkyl Bicyclobutanes *via* 1,3 γ-Silyl Elimination

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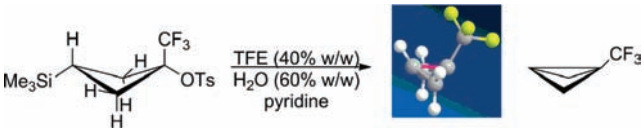
Received January 14, 2011

ABSTRACT



Two new bicyclobutanes were prepared from cyclobutyl systems by a novel, solvolytic, carbocation-based methodology. An electron-withdrawing perfluoroalkyl group at the incipient cationic center enhances neighboring-group participation of the γ-silyl group, inducing facile, remarkably selective 1,3-elimination yielding only bicyclobutanes. The method unlocks potential access to a host of EWG-substituted strained rings and a potential new method for the synthesis of trifluoromethylcyclopropanes.

The preparation of [1.1.0]bicyclobutane, **3**, by Wiberg,[1] represented a milestone in the syntheses of strained organic systems. Since then, traditional Wurtz coupling or other anionic-type ring-closure methods have been used in the preparation of **3** and its derivatives.[2] To date, however, the trifluoromethyl derivative of **3** has not been prepared by these or any other methods, likely due to the tendency of the CF_3 moiety to eliminate fluoride under anionic conditions.[3] Herein we report the first synthesis of 1-(trifluoromethyl)bicyclo[1.1.0]butane, **9a**, *via* novel cationic bridgehead bond formation methodology utilizing electron-withdrawing-group (EWG) enhanced γ-silyl elimination. Despite the expected large strain energy[4] of **9a**, the reaction gives bridgehead bond formation free of side products.

Under solvolytic conditions, γ-silyl substrates are known to form cyclopropanes *via* 1,3 γ-silyl elimination as a consequence of strong neighboring-group participation by the back lobe of the C−Si bond to the γ-silyl substituent (otherwise known as "percaudal" participation).[5] While the W conformation (Figure 1) maximizes the propensity for ring closure, even under ideal circumstances cyclopropanes are formed in very low yield and are not the major products.[6] In contrast, our new methodology combines the destabilizing effect of an α-CF_3 group with the electron-releasing effects of a γ-silyl substituent in order to induce selective 1,3 γ-silyl elimination under mild conditions. With

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10.1021/ol200121f
Published on Web 03/02/2011

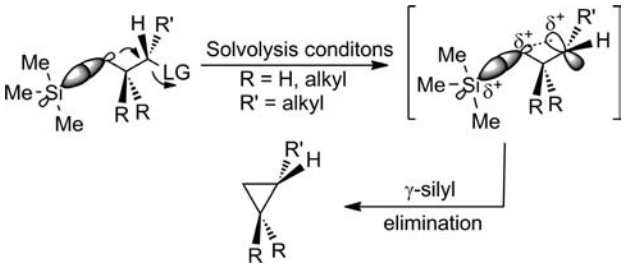


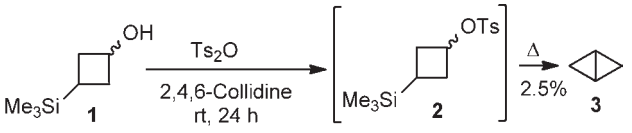
Figure 1. Silyl-promoted percaudal participation to yield 1,3 C−C bond formation.

the relative ease of incorporation of silicon into organic compounds,[7] exploration of EWG-directed γ-silyl elimination as a viable synthetic tool has the potential to provide avenues to desirable trifluoromethylcyclopropyl groups which have been described as important motifs for enhancing lipophilicity in pharmaceutical targets.[8] Current methods of preparation of these cyclic moieties are quite limited.[9]

Some time ago, we speculated[10] that the W conformation of the *cis*-cyclobutyl system might be sufficiently favorable to lead to the formation of **3** from 1,3 γ-silyl elimination under solvolysis conditions. Siehl et al. found conformationally dependent γ-silyl stabilization of the cyclobutyl system during rearrangement of the 1-(*tert*-butyldimethylsilyl)bicyclobutonium ion to the 3-*endo*-(*tert*-butyldimethsilyl)dimethylsilylbicyclobutonium ion at −115 °C.[11] More recently, during the course of our investigations, Creary et al. reported evidence of percaudal participation during solvolyses of *cis*-3-(trimethylsilyl)cyclobutyl systems (unsubstituted, α-methyl, α-phenyl). However, Creary did not observe the formation of **3**.[12]

We had also examined the products of solvolytic studies[10a,b] of various unsubstituted *cis*-3-(trimethylsilyl)cyclobutyl substrates and obtained only substitution with retention or β-silyl elimination, in agreement with Creary's findings.[12] However, we subsequently found (Scheme 1) that *in situ* pyrolysis[13] of the tosylate, **2**, did yield **3**, albeit in very low yield (2.5% by ^{1}H NMR).

Scheme 1. Bicyclobutane *via* 1,3 γ-Silyl Elimination



Subsequent to the apparent lack of facile 1,3-elimination in the solvolysis of unsubstituted silylcyclobutyl systems, we postulated that the installation of an EWG at the α-carbon could increase percaudal participation and favor bicyclobutane formation.

Indeed, Gassman[14] has suggested that enhancement of neighboring-group participation in carbocations can be accomplished by the installation of an α-CF_3 or other EWG such as CN. Additionally, during our own mechanistic studies on acyclic α-CF_3 substituted γ-trimethylsilyl systems, we observed enhanced γ-silyl participation in electron-deficient cations.[15] With these encouraging precedents, we embarked on the synthesis of **9a** (Scheme 2).

A [2 + 2]-cyclization of vinyltrimethylsilane, **4**, with dichloroketene, generated *in situ* from trichloroacetyl chloride, and subsequent dehalogenation of the dichlorocyclobutyl ketone **5** gave cyclobutanone **6** in yields comparable to the literature.[16,17] Trifluoromethylation of **6** by the Prakash method[18] produced **7a**. By analogy to hydride reductions and other 1,2-additions to cyclobutanones,[2b,12] we expected the major isomer of trifluoromethylation to be the 1*s*, 3*s* "*cis*" (with respect to the Me_3Si and the OH) isomer as opposed to the 1*r*, 3*r* "*trans*" (with respect to the Me_3Si and the OH) isomer. Indeed, using $^{19}F\{^1H\}$ HOESY[9] (Figure 2) and $^1H\{^1H\}$ NOESY NMR (see Supporting Information) the identity of the major isomer in the product was confirmed to be 1*s*, 3*s*, with a 94:6 1*s*, 3*s*:1*r*, 3*r* ratio as determined by ^{1}H NMR (and GC-MS). The tosylate **8a** was prepared from **7a** by deprotonation with KH and subsequent reaction with *p*-toluenesulfonic anhydride.

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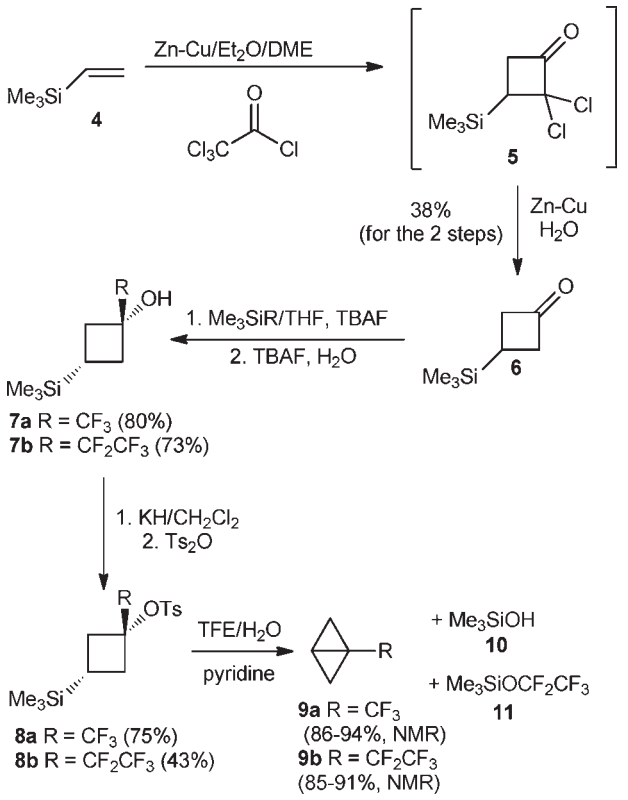
Scheme 2. Preparation and Solvolysis of **8a** and **8b**



Solvolysis of **8a** was performed in deuterated aqueous trifluoroethanol (TFE) ranging from 40% to 100% by weight (40T−100T) using various proton scavengers including pyridine, pyridine-d_6, 2,6- lutidine, or 2,4,6-collidine. ^{1}H NMR analysis of the solvolysis products showed, after approximately 12 h, complete and sole conversion of 1*s*, 3*s* **8a** to **9a** and the expected byproducts of the 1, 3-elimination: trimethylsilanol,[19] **10**, and 2,2,2-trifluoroethoxytrimethylsilane, **11**.[20] Peaks of **9a** in the spectra were similar to those of **3**,[21] with the expected slight downfield shifts. Yields as determined by ^{1}H NMR ranged from 86 to 94%.

Despite complete conversion, yields were somewhat less than quantitative, likely resulting from a combination of the unreactivity of the 1*r*, 3*r* isomer as well as the volatility of the product **9a** (see Supporting Information). We also prepared and solvolyzed the pentafluoroethyl analog **8b**, with similar results. By ^{1}H NMR, **9b** was formed exclusively, in 85−91% yield.

For further characterization, we conducted a large-scale solvolysis of **8a** in aqueous TFE. While **9a** formed just as readily in the small scale studies, isolation was complicated by losses due to the volatility (bp 28 °C) of **9a** and by difficulty in separation of the TMS ether byproduct, **11**,

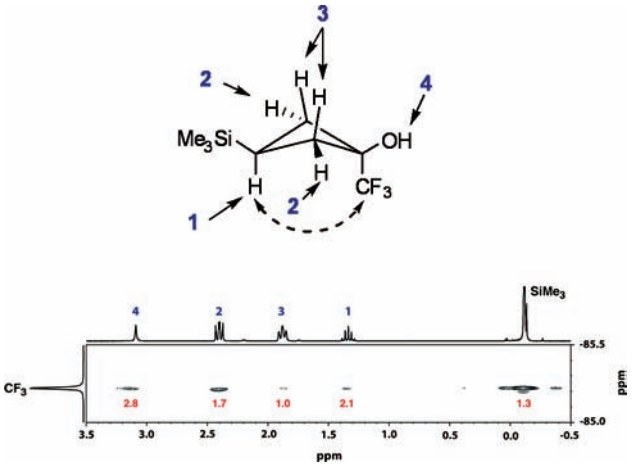


Figure 2. ^{19}F{^{1}H}HOESY of cyclobutanol **7a**. The red numbers correspond to the intensity of the cross peak per proton normalized to the weakest signal.

which apparently forms a low-boiling azeotrope with the TFE and/or **9a**. Conducting the reaction in 40T changed the major byproduct to the higher boiling silanol, **10**. Careful fractionation using a salt-water ice-cooled condenser and receiving flask left only small amounts of **10** and TFE in the crude product. Dissolving the crude distillate in 1,1,2-trichloroethane, washing with water, and redistillation afforded pure **9a** (97 mol % by ^{1}H NMR) as a volatile, colorless liquid in 40% yield.

The ease of formation of **9a** and **9b** demonstrates the utility of EWGs to enhance 1,3 C−C bond formation *via* the γ-silyl effect as well as to stabilize highly strained systems by the so-called "perfluoroalkyl effect,"[22] which protects the product by preventing electrophilic degradation and raising activation energies of isomerization.[22a] The Baeyer strain of **9a** is calculated to be more than 8 kcal/mol lower than **3** and 2.6 kcal/mol lower than bicyclobutane-1-carbonitrile.[4] Indeed, we have found that **9a** can be stored indefinitely in a sealed vial in the freezer without decomposition. The cyano analog has been reported to polymerize spontaneously at room temperature.[23] Interestingly, we have also noted in the ^{1}H NMR that there is a significant downfield shift on the bridgehead H from **9a** to **9b**, while the *exo*-H shifts upfield, and the *endo*-H remains virtually unchanged (see Supporting Information). Thus, there must be a large influence of the electron-withdrawing substituent on the electron density of the bridgehead bond.

Moreover, the results of our study are in sharp contrast to previous solvolytic studies of other tertiary γ-silyl systems in which participation of the silyl substituent was

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either nearly nonexistent[24] or insufficient to effect bridgehead bond formation by silyl elimination.[12] We propose that the exclusivity of **9a** as the only solvolysis product results from a combination of factors, as shown in our proposed mechanism (Figure 3).

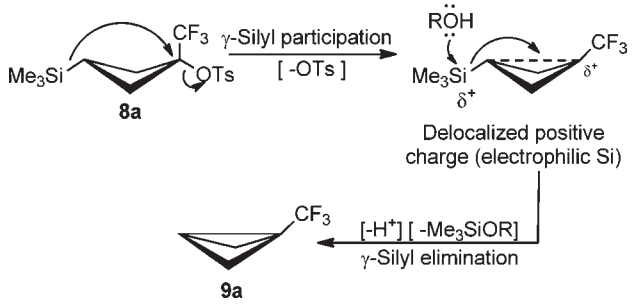

Figure 3. Proposed reaction mechanism for formation of **9a**.

Increased electron demand at the cationic center due to the α-EWG causes increased participation of the silyl group. The greater degree of bonding character between the α- and γ-carbons as well as the amplified positive charge character (and therefore increased electrophilicity) of the silicon allow for more facile abstraction of the silyl group by nucleophilic solvent molecules. The reduction of positive charge and the increase in steric bulk at the α-carbon precludes pathways for rearrangement or substitution.

As expected, the reaction appears to be highly conformationally dependent. The 1*s*, 3*s* isomers of **8a** and **8b** which possess the proper W conformation reacted completely, while the *endo*-sickle-like 1*r*, 3*r* isomers failed to react during the reaction time. Indeed, the peaks for the minor isomer, which were partially obscured in the ^{1}H NMR spectra of the initial reaction mixtures, became unmasked as the reaction proceeded and the major isomer was consumed, giving further support to a conformationally dependent mechanism and partially explaining the nonquantitative yields seen in the solvolyses.

We present the first documented case of using enhanced γ-silyl interactions *via* an "electron-deficient" cation to synthesize novel bicyclobutanes. This method represents a potential new way to prepare a variety of highly strained, high-energy, bridgehead polycyclic hydrocarbons containing electron-withdrawing groups as well as a potential new way to prepare trifluoromethylcyclopropanes. We are currently investigating the effectiveness of this methodology for cyclopropanation in acyclic systems, as well as the scope of the reaction in terms of other EWGs.

Acknowledgment. This work was supported by Stonehill College and by the Office of Naval Research (Award Number N0014-08-1-1160). We thank Dr. Chris Canlas of the University of California, Berkeley for his assistance with the ^{19}F{^{1}H} HOESY spectroscopy and Barbara Anzivino, Dr. Louis Liotta, and Dr. Pamela Lombardi of Stonehill College, and the Stonehill College Chemistry Department for helpful discussions.

Supporting Information Available. Experimental procedures, characterization data, and spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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