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Intramolecular Bicyclization of Hydroxypentynyliodonium Triflate Derivatives to Furnish Cyclopentannelated Tetrahydrofurans: The First Examples of Cyclopentene Formation Following Alkoxide Addition to Alkynyliodonium Salts.

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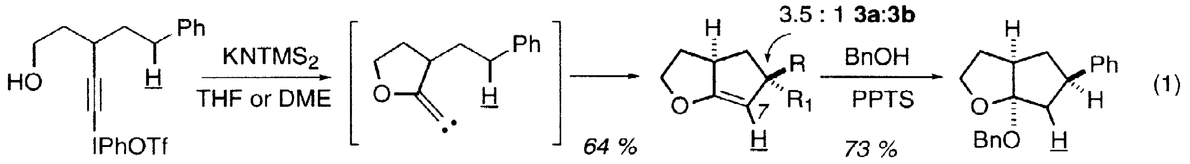
Abstract: Several hydroxyalkynyliodonium triflates can be bicyclized with $KNTMS_2$ to provide cyclopentannelated tetrahydrofuran derivatives in modest to good yields. The diastereoselectivity of C-H insertion by the intermediate carbene is better than that observed with the corresponding NTs analogs. Product lability and an electronic mismatch between hydroxide nucleophile and iodonium electrophile likely contribute to the modest yields. © 1998 Elsevier Science Ltd. All rights reserved.

The combination of certain nucleophiles with alkynyliodonium salts provides a versatile and efficient synthesis of cyclopentene rings.[1] The "softness", or polarizability, of the nucleophile is critical for effective addition to the selective iodonium salt electrophile. Prior studies have shown that acceptable carbon nucleophiles include a range of β-dicarbonyl derivatives, while oxygen and nitrogen nucleophiles are more limited and encompass only carboxylate (and related species)[2a] or phenoxide[2b-d] and azide,[2e,f] respectively. However, more recent developments have revealed that amine derivatives, in particular sulfonamides, fall within the permissible range of nucleophilicity for productive addition to alkynyliodonium salts. Both dihydropyrroles and cyclopentenannelated pyrrolidine derivatives can be formed from inter- and intramolecular versions of this process, respectively.[3] Attempts to extend the intermolecular heterocyclization reaction to alkoxide nucleophiles were frustrated by an inability to tune the nucleophilicity of the RO^- moiety. However, the facility of intramolecular bicyclizations of pentynyliodonium tosylamides suggested that similar proximity effects might be exploited to override the unfavorable electronics for addition of alkoxide to alkynyliodonium salt. The successful realization of this goal is described herein.



1

2

3a R = Ph, R_1 = H
3b R = H, R_1 = Ph

4

These studies commenced with the 2-phenethyl-substituted hydroxypentynyliodonium triflate **1**, eq. (1). This substrate bears an activating phenyl ring to facilitate C-H insertion by the putative alkylidene carbene intermediate **2**. A thorough survey of reaction parameters, including solvent (THF, Et_2O, DME, dioxane), base ($KNTMS_2$, $LiNTMS_2$, $NaNTMS_2$, n-BuLi, NaH), rate and sequence of base addition, and concentration (0.01

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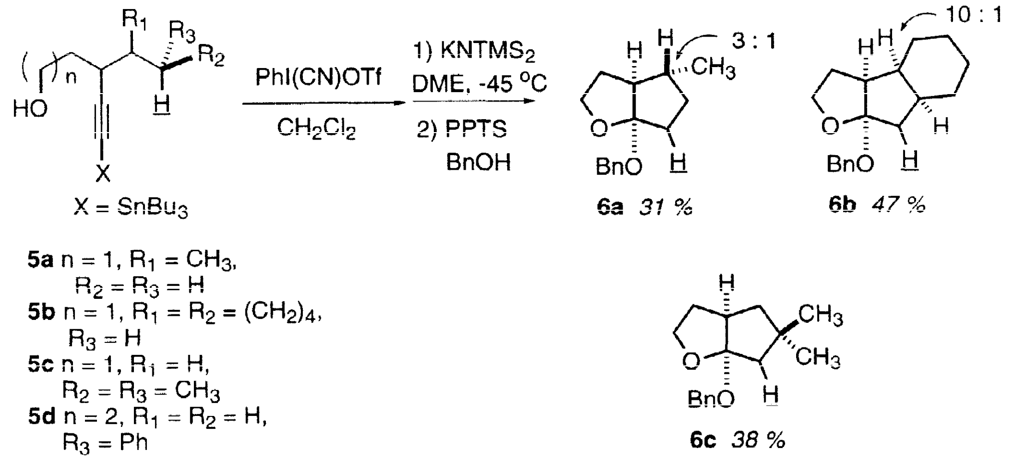
M → 0.025 M) led to the following optimized conditions for formation of the bicyclic product **3**[4]: Solid $KNTMS_2$ in one portion was added to a 0.01 M solution of the alkynyliodonium salt **1** in DME at -45 °C. The solution was warmed to rt and worked up with Et_2O/ice cold brine. Under this protocol, consistent yields of the cyclopentenannelated tetrahydrofuran **3** could be obtained following flash column chromatography[5] on silica gel using 1.5% Et_2O/1% Et_3N/hexane as eluent. Base in the eluent was necessitated by the extreme acid sensitivity of the strained enol ether product. In situ derivatization of this labile moiety as its monobenzyl ketal **4**[4] proved to be a convenient alternative to isolation of **3**. The C-H connectivity of **4** was established by an ^1H-^{13}C HMQC experiment while the stereochemical assignment rested upon analysis of ^1H NMR coupling and DNOE data.

Attempts to extend this bicyclization to several related substrates exposed the limited range of structural variation that is tolerated in this transformation, eq. (2). In these cases, even greater acid sensitivity of the first-formed enol ether compared with **3**, coupled with a similar lability of the derived ketal, tended to depress yields in this three-step sequence. Nevertheless, initial cyclization of alkoxide nucleophile and iodonium salt electrophile under the optimized conditions did proceed for the iodonium salts prepared from **5a**-**5c**, and the derived carbene successfully inserted into pendant primary (**6a**), secondary (**6b**), and tertiary (**6c**) C-H bonds en route to bicyclic products. As with **4**, a combination of NMR techniques supported the assignments of structure and stereochemistry. Extending the tether between nucleophile and electrophile by one methylene (**5d**) did not afford a substrate which bicyclized. For every substrate examined, substantial amounts of deiodinated alkynylalcohol **5** (X = H) could be identified in the crude reaction mixture. These reduced but otherwise uncyclized products plausibly could arise from direct alkoxide attack at iodine[6] followed by ejection of alkynyl anion and eventual reduction of the nascent RO–IPh bond by unidentified processes.[7] The failure of the six-membered ring cyclization (**5d**) along with the inefficient bicyclizations of the other substrates are indicative of just how precariously balanced the favorable steric and unfavorable electronic factors are in this transformation.



(2)

The stereochemistry of C-H insertion by the intermediate carbene is notable when compared to the similar NTs substrates. Thus, the bicyclization of a substrate analogous to **1** with NHTs instead of OH (cf. **i**)[3] affords a bicyclic product related to **3** (cf. **ii**)[3] as a 1.4:1 mixture of *syn*-to-*anti* diastereomers (compare **3a**:**3b** = 3.5:1). Similarly, the NHTs substrate related to **5b** proceeds to a **6b** analog (NTs instead of O) with only a 3.5:1 preference for the isomer shown. The improved diastereoselectivity of alkylidene carbene C-H insertion in the oxygen series compared to the NTs series may be traced to a difference in electrophilicity for the intermediate carbenes. C(7) in enol ether **3a** resonates at δ 92.7 while the equivalent carbon in the NTs series is significantly further downfield at δ 104.6. If the relatively greater electon density at C(7) in **3a** implied by these values is even partially represented in the precursor alkylidene carbene's terminus, then the carbene preceding oxacycle **3a** is likely to be less electrophilic and hence less reactive to C-H insertion than the NTs-substituted version. This less reactive oxygen-substituted carbene should operate through later, more product-like diastereomeric transition states where the attendant steric interactions are more pronounced (and presumably more discriminating) than in the NTs series. Further studies of the scope of this novel reaction and assessment of the applicability of this transformation in natural product synthesis are ongoing.

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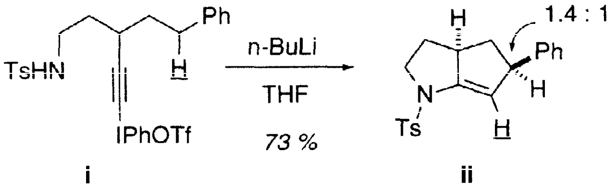
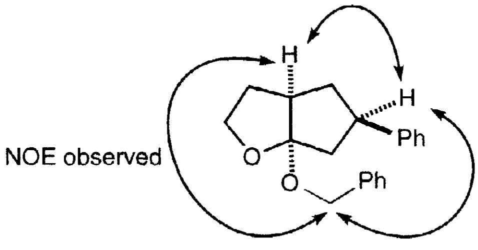


4. Representative spectral data: **3a**: IR (thin film) 1676 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.34-7.15 (m, 5H), 4.64-4.58 (m, 2H), 4.49-4.39 (m, 1H), 4.24-4.19 (m, 1H), 3.33-3.12 (m, 1H), 2.53-2.45 (m, 1H), 2.18-1.99 (m, 1H), 1.69 (m, 1H), 1.40 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 166.8, 146.7, 128.3 127.1, 126.2, 92.7, 77.7, 54.2, 46.5, 42.0, 31.3; CIMS *m/z* (relative intensity) 187 (MH$^+$, 100), 159 (38), 109 (62); HRMS Calcd for C$_{13}$H$_{14}$O: 186.1038, Found 186.1045.

4: ^{1}H NMR (500 MHz, benzene-d$_6$) δ 7.40-7.38 (m, 2H), 7.23-7.06 (m, 8H), 4.72 (d, *J* = 11.9 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 3.95-3.88 (m, 2H), 3.27-3.20 (m, 1H), 2.57 (dddd, *J* = 11.3, 8.1, 7.6, 3.8 Hz, 1H), 2.52-2.48 (m, 1H), 2.07-1.98 (m, 2H), 1.94-1.82 (m, 1H), 1.37-1.26 (m, 2H); ^{13}C

NMR (50 MHz, acetone-d_6) δ 144.9 (*C*), 140.5 (*C*), 129.1 (*C*H), 128.9 (*C*H), 128.3 (*C*H), 127.8 (*C*H), 127.7 (*C*H), 126.9 (*C*H), 120.2 (*C*), 69.4 (CH_2), 65.2 (CH_2), 49.8 (*C*H), 46.3 (*C*H), 43.4 (*C*H), 41.1 (CH_2), 31.8 (CH_2); CIMS *m/z* (relative intensity) 295 (MH^+, 3.7), 187 (61, -OCH_2Ph), 91 (100); Anal. calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53; Found: C, 81.58; H, 7.47.



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6. a) See ref. 1a, p 1154. b) For examples of 2-lithiofuran displacing an alkyne anion from alkynyl(aryl)iodonium tosylates, see Margida, A. J.; Koser, G. F. *J. Org. Chem.* **1984**, *49*, 4703.
7. It is possible that intermediate RO-IPh^+ species are reduced to alcohol with concomitant oxidation of solvent. Thus, treament of alkoxide **i** with alkynyliodonium salt **2** in THF gave no intermolecular addition products, but did provide a 33 % yield of the known THF adduct **iii**. Presumably, oxidation of THF to the electrophilic carbenium ion **ii** is followed by trapping with **i**.