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The silylalkyne-Prins cyclization: a novel synthesis of 4-iododihydropyrans

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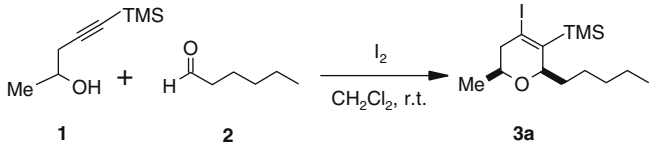
ABSTRACT

The silylated secondary homopropargylic alcohols undergo smooth coupling with aldehydes in the presence of molecular iodine under mild reaction conditions to produce 4-iododihydropyrans in good yields. This method is highly stereoselective, affording *cis*-dihydropyrans exclusively.

The Prins-cyclization is a powerful synthetic tool for the construction of six-membered tetrahydropyran derivatives.[1] The tetrahydropyran ring system is a core unit in a number of natural products such as avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins, and acutiphycins.[2] Tetrahydropyran derivatives are usually prepared via Prins-cyclization using acid catalysis.[3] The Prins-type cyclization between homopropargylic alcohols and aldehydes has been reported using inexpensive and environmentally friendly iron(III) halides to produce 2-alkyl-4-halo-5,6-dihydro-2*H*-pyrans.[4] In addition, silyl modified-Prins cyclization has been reported to furnish tri-, tetra-, and penta-substituted dihydropyrans.[5] However, many of the classical methods often require strong Lewis acids, extended reaction times and also produce a mixture of products.[3] Furthermore, there have been no reports on the synthesis of iodosubstituted dihydropyrans though iodo group is labile for further manipulation. Therefore, the use of simple, convenient, cost-effective, and readily available reagents would extend the scope of silyl-modified Prins-cyclization in natural product synthesis.[6] In recent years, molecular iodine-catalyzed or mediated reactions have gained importance in organic synthesis. The mild Lewis acidic nature of iodine has been exploited in several transformations.[7] Thus, we envisaged that molecular iodine could play a dual role as a catalyst that initially promotes hemi-acetal formation and as a nucleophile that subsequently attacks the carbocation to afford an iododihydropyran. One advantage of such a method would be that the equimolar amount of HI generated in situ during the reaction may participate in the hemi-acetal formation and subsequent cyclization. Thus, such a protocol for Prins-cyclization is anticipated, in addition to experimental simplicity, to preclude the use of external metal catalysts and harsh acidic conditions was obtained.

In continuation of our interest on the use of molecular iodine for various transformations,[8] we herein report the first direct and metal catalyst-free silylalkyne-Prins cyclization for the rapid synthesis of highly substituted dihydropyrans from silylated secondary homopropargylic alcohols and aldehydes using molecular iodine under neutral conditions. Initially, we have attempted the coupling of TMS-alkynol (**1**) with *n*-hexanal in the presence of molecular iodine at room temperature. The reaction was complete in 2h and the desired (4-iodo-6-methyl-2-pentyl-5,6-dihydro-2*H*-pyran-3-yl)trimethylsilane **3a** was obtained in 80% yield with all *cis*-selectivity (Scheme 1).

To test the scope of this reaction, we have performed the reaction between secondary trimethylsilyl propargylic alcohols and several aldehydes using molecular iodine as promoters. The results are summarized in Table 1.[9] Similarly, butyraldehyde, isovaleraldehyde, cyclohexanecarboxaldehyde, and propanal underwent smooth coupling with silylalkynols to give the respective 4-iododihydropyrans in good yields (Table 1, entries a–i). Interestingly, acid-sensitive phenyl acetaldehyde also participated well



Scheme 1. Prins cyclization of 5-(trimethylsilyl)pent-4-yn-1-ol with *n*-hexanal.

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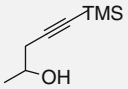
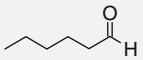
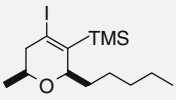
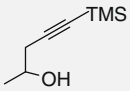
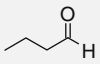
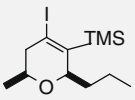
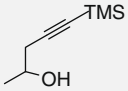
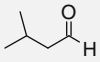
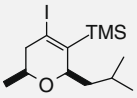
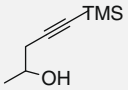
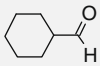
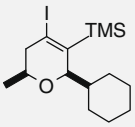
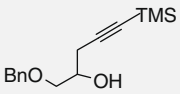
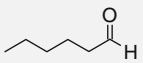
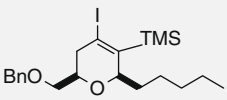
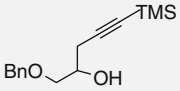
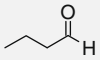
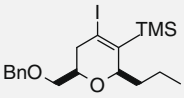
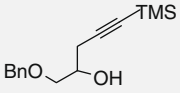
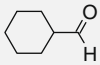
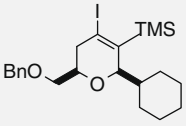
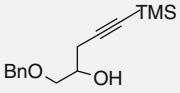
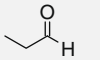
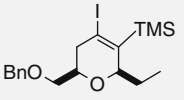
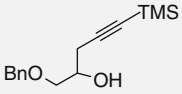
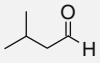
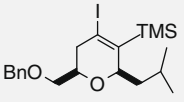
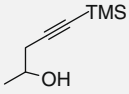
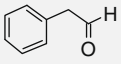
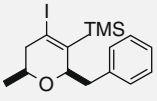
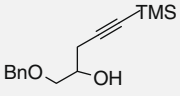
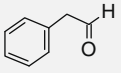
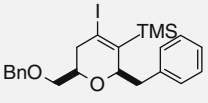
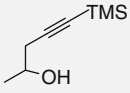
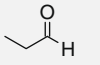
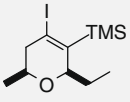
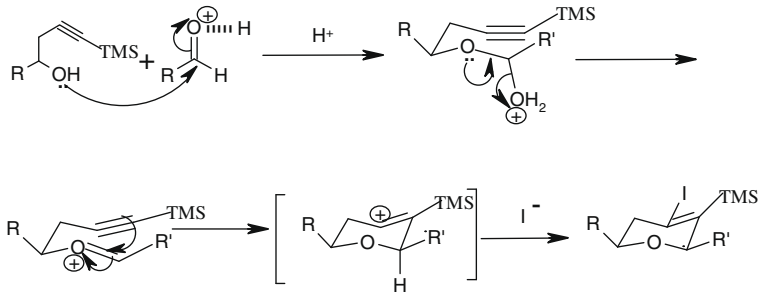
Table 1
Iodine-promoted Prins type cyclization of TMS-alkynols with aldehydes

Entry	Alcohol	Aldehyde	Product[a]	Time (h)	Yield[b] (%)
a				2.0	80
b				2.0	80
c				1.5	85
d				1.0	90
e				2.0	80
f				2.0	80
g				1.0	90
h				2.0	80
i				1.5	85
j				3.0	72
k				3.0	72
l				2.0	80

[a] The products were characterized by IR, NMR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

in this reaction (Table 1, entries j and k). The desired six-membered dihydropyrans were exclusively formed in good yields. No traces of the products resulting from the oxonia rearrangement were observed. The reaction works well with a wide range of aldehydes except aromatic aldehydes. In the absence of silyl group, the reaction failed to give the desired products. Therefore, the presence of the silyl group at the alkyne is crucial for the reaction to takes place. In the absence of catalyst, the reaction did not go even after long reaction time (12 h) under reflux conditions. The alkyne silyl-Prins reaction proceeds at room temperature with complete diastereocontrol, affording the *cis*-2,6-dihydropyran exclusively.[4,5f] As a solvent, dichloromethane appeared to give the best results. The reactions were clean and the products were obtained in excellent yields and with high diastereoselectivity as determined from the NMR spectrum of the crude product. Only a single diastereoisomer was obtained from each reaction, the structure of which was confirmed by ^{1}H NMR and also by comparison with authentic samples.[5f] Mechanistically, the reaction may initiate via an acetal formation from secondary silyl-homopropargylic alcohol and an aldehyde. Thus initially formed acetal may undergo dehydration to generate the oxocarbenium ion. This highly reactive intermediate may undergo Prins-cyclization to give the β-carbocation which may be subsequently trapped by iodide ion to give the desired product (Scheme 2).[10]

The rationale for the cis-selectivity involves the formation of an (*E*)-oxocarbenium ion via a chair-like transition state, which has



Scheme 2. A plausible reaction mechanism.

increased stability relative to the open oxocarbenium ion due to delocalization. The optimal geometry for this delocalization places the hydrogen atom at C4 in a pseudo-axial position, which favors equatorial attack of the nucleophile.[11]

In summary, we have developed a simple, convenient, and efficient method for the coupling of silylated secondary homopropargylic alcohols with aldehydes under neutral conditions to produce 2,6-dialkyl-4-iodo-5,6-dihydro-*2H*-pyran-3-yl)-trimethyl-silane in good yields. The method is mild, selective, and convenient and the reaction conditions are amenable to scale-up.

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9. *Typical procedure*: A mixture of homopropargylic alcohol (0.156 g, 1 mmol), aldehyde (0.2 g, 2 mmol), and iodine (0.127 g, 1 mmol) in dichloromethane (5 mL) was stirred at 23 °C for the specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction was quenched with water and the reaction mixture was extracted with ether (2×10 mL). The combined organic layers were washed with aqueous sodium thiosulfate, brine, and dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5/9.5) gave the pure 4-iododihydropyran. The products thus obtained were characterized by IR, NMR and mass spectrometry. The spectral data were found to be consistent with authentic samples.[5]
(4-Iodo-2-isobutyl-6-methyl-tetrahydro-2H-pyran-3-yl) trimethylsilane (**3c**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.48–4.41 (m, 1H), 3.65–3.53 (m, 1H), 2.66 (dt, J = 3.0, 5.6, 11.5 Hz, 1H), 2.56 (ddd, J = 3.2, 4.7, 6.0 Hz, 1H), 1.46–1.23 (m, 3H), 1.12 (d, 3H, J = 6.0 Hz), 0.92 (d, 3H, J = 1.7 Hz), 0.90 (d, 3H, J = 1.8 Hz), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.5, 105.2, 78.9, 70.2, 52.4, 45.1, 24.4, 24.0, 21.2, 20.5, 0.47; IR (neat): ν 2955, 2865, 1582, 1462, 1415 cm^{-1}; FAB-MS: m/z 354 [M]$^+$.
(2-Cyclohexyl-4-iodo-6-methyl-tetrahydro-2H-pyran-3-yl)trimethylsilane (**3d**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.27–4.18 (m, 1H), 3.64–3.52 (m, 1H), 2.59 (dt, J = 2.2, 4.5 Hz, 1H), 2.43 (ddd, J = 3.0, 4.3, 6.6 Hz,1H), 1.84–1.35 (m, 7H), 1.29–1.08 (m, 7H), 0.27 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.0, 104.8, 84.2, 69.9, 52.6, 43.1, 30.3, 27.2, 26.6, 24.8, 20.7, 0.33; IR (neat): ν 2929, 2852, 1671, 1584, 1448 cm^{-1}; FAB-MS: m/z 380 [M]$^+$.
2-Benzyl-4-iodo-6-methyl-tetrahydro-2H-pyran-3-yl)trimethylsilane (**3j**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.27–7.08 (m, 5H) 4.63–4.53 (m, 1H), 3.57–3.43 (m, 1H), 2.95 (d, 1H, J = 13.7 Hz) 2.52 (dt, J = 8.1, 8.4, 14.1 Hz, 1H). 2.31 (ddd, J = 2.8, 4.3, 6.9 Hz, 1H), 2.38–2.25 (m, 1H), 1.0 (d, 3H, J = 6.0 Hz), 0.31 (s, 9H); ^{13}C NMR (75 Mz, $CDCl_3$): δ 145.2, 129.6, 127.8, 126.1, 106.6, 80.7, 70.1, 52.2, 42.3, 20.5, 0.36; IR (neat): ν 3061, 3029, 2968, 2926, 2896, 2854, 1942, 1669, 1582 cm^{-1}; FAB-MS: m/z 388 [M]$^+$.
(2-Ethyl-4-iodo-6-methyl-tetrahydro-2H-pyran-3-yl)trimethylsilane (**3l**): ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.40–4.34 (m, 1H), 3.67–3.56 (m, 1H), 2.63 (dt, J = 2.6, 11.8 Hz, 1H), 2.54 (ddd, J = 3.2, 4.5, 6.2 Hz, 1H),1.77–1.63 (m, 1H), 1.52–1.37 (m, 1H), 1.14 (d, 3H, J = 6.0 Hz), 0.90 (t, 3H, J = 7.3, 14.7 Hz), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.6, 105.4, 81.2, 70.2, 52.5, 20.7, 9.2, 0.43; IR (neat): ν 2969, 2926, 2854, 1645, 1585 cm^{-1}; FAB-MS: m/z 326 [M]$^+$.
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