Iodine-promoted Prins-cyclization of ketones — A facile synthesis of spirocyclic-4-iodo-tetrahydropyrans and 5,6-dihydro-2*H*-pyrans

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Abstract: Homoallylic and homopropargylic alcohols undergo smooth coupling with ketones in the presence of molecular iodine at ambient temperature to produce spirocyclic-4-iodotetrahydropyrans and 5,6-dihydro-2*H*-pyrans, respectively, in high yields in a short reaction time with high selectivity. The use of molecular iodine makes this procedure quite simple, more convenient, and cost-effective.

Key words: Prins-cyclization, iodine, homopropargylic alcohol, spirocyclic-4-iodopyrans.

Résumé : Sous l'influence d'iode moléculaire, à la température ambiante, les alcools homoallyliques et homopropargyliques conduisent à un couplage en douceur avec les cétones pour conduire respectivement à la formation, avec des rendements élevés et une sélectivité élevée, de 4-iodotétrahydropyranes et de 5,6-dihydro-2*H*-pyranes spirocycliques après de temps de réactions courts. L'utilisation de l'iode moléculaire rend cette méthode très simple, plus commode et plus efficace au point de vue des coûts.

Mots-clés : cyclisation de Prins, iode, alcool homopropargylique, 4-iodopyranes spirocycliques.

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Introduction

The tetrahydropyran ring system is a core unit in a number of natural products such as avermectins, aplysiatoxins, oscillatoxins, latrunculins, talaromycins, and acutiphycins (1). In particular, spirocyclic-tetrahydropyran derivatives are found in various biologically active molecules. Generally, tetrahydropyran derivatives are prepared via Prins-cyclization using acid catalysis (2–4). Although a large number of methods are available for the Prins-cyclization of aldehydes, only a few procedures are reported for ketones (5–7). Therefore, the development of a simple and convenient method involving inexpensive and readily available reagents would extend the scope of the Prins-cyclization in natural product synthesis (8). Recently, molecular iodine has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformations, affording the corresponding products with high selectivity in excellent yields (9). The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to perform several organic transformations using stoichiometric levels to catalytic amounts. Owing to advantages associated with this ecofriendly catalyst, molecular iodine has been explored as a powerful reagent for various organic transformations (10).

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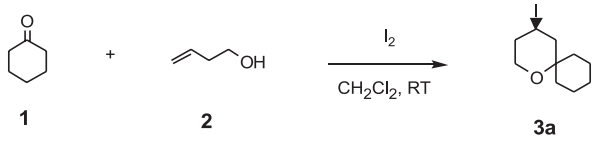
Scheme 1.



Results and discussion

In this article, we report an efficient and metal catalyst free Prins-cyclization for the rapid synthesis of spirocyclic-tetrahydropyrans from homoallylic alcohols and ketones using molecular iodine under neutral conditions. Accordingly, treatment of 3-buten-1-ol with cyclohexanone in the presence of molecular iodine at ambient temperature for 30 min gave the corresponding 4-iodotetrahydropyran in 96% yield (Scheme 1).

Similarly, various ketones such as cyclopentanone, cyclododecanone, acetone, 2-butanone, 3-pentanone, 2-hexanone, and 2-adamantanone underwent smooth coupling with 3-buten-1-ol to give the respective spirocyclic-4-iodotetrahydropyrans in excellent yields (Table 1, entries **b**–**h**). Encouraged by the results obtained with 3-buten-1-ol, we turned our attention to various substituted homoallylic alcohols. Interestingly, 1-phenyl-3-buten-1-ol reacted efficiently with cyclohexanone and cyclododecanone to produce 2,4,6-trisubstituted pyran derivatives (Table 1, entries **i** and **j**). Likewise, the coupling of 2-butanone with 1-nonen-4-ol

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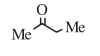
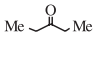
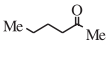
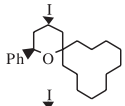
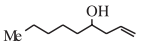
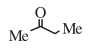
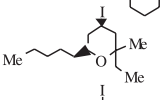
Table 1. Iodine-catalyzed preparation of spirocyclic-4-iodotetrahydropyran derivatives.

Entry	Alcohol	Ketones	Pyrans[a]	Time (min)	Yield (%)[b]
a				30	96
b				35	94
c				50	88
d				40	90
e				45	89[c]
f				50	92
g				60	91[c]
h				70	85
i				50	94
j				50	86
k				45	90[c]
l				60	90
m				60	88
n				65	92
o				65	85
p				65	84

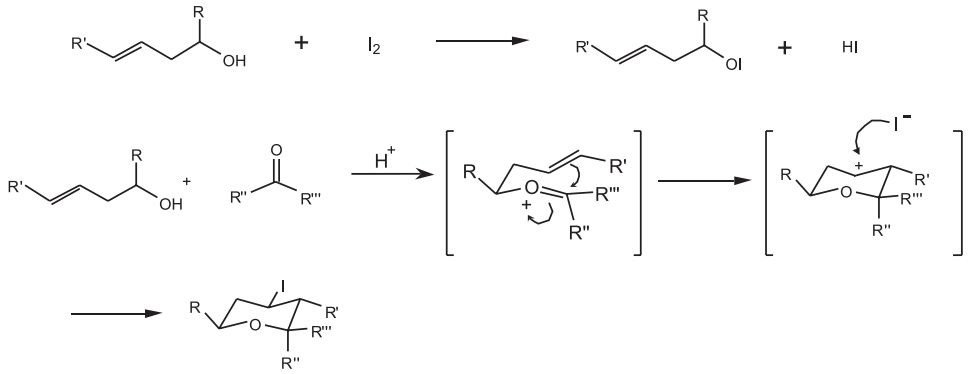
[a]All products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectroscopy.
[b]Isolated and upoptimized yields.
[c]cis–trans ratio 2:1

gave the corresponding trisubstituted pyran in 90% yield (Table 1, entry **k**). Furthermore, simple homopropargylic alcohol underwent smooth coupling with cyclohexanone to produce spirocyclic dihydropyran derivative **3l** (Scheme 2).

Similarly, 3-pentyn-1-ol also reacted well with several ketones such as cyclopentanone, cyclohexanone, cyclododecanone, and 3-pentanone to generate 2,3,4-trisubstituted pyran derivatives in high yields under similar conditions (Table 1, entries **m**–**p**). However, no reaction was observed in

Scheme 2.

Scheme 3.



the absence of a catalyst even after a long reaction time (12 h). As solvent, dichloromethane appeared to give the best result. In all cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and the products were obtained in excellent yields with high diastereoselectivity. Only a single isomer was obtained in each reaction, the structure of which was confirmed by ^{1}H NMR and also by comparison with authentic samples (6). The formation of the products may be further explained by hemi-acetal formation and subsequent Prins-type cyclization (Scheme 3).

Other iodide sources such as LiI, *t*-Bu_4NI, and NaI failed to produce the desired product. Cyclic ketones gave slightly higher yields when compared with acyclic ketones. As depicted in Table 1, a variety of ketones participated in Prins-cyclization under these reaction conditions. The scope and generality of this process is illustrated with respect to various ketones and homoallylic and homopropargylic alcohols, and the results are presented in Table 1.

In summary, we describe a rapid and efficient Prins-cyclization of ketones to produce spirocyclic-4-iodo-tetrahydropyrans in high yields with high selectivity. The use of inexpensive and readily available molecular iodine has made this procedure simple, convenient, and practical. In addition to its simplicity, efficiency, and milder reaction conditions, this method provides a rapid access for spirocyclic-4-iodo tetrahydropyran derivatives with diverse chemical structures.

Experimental

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a PerkinElmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H, ^{13}C NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. TLC was monitored on 0.25 mm precoated silica gel plates (60F-254).

General procedure

A mixture of homoallylic alcohol (2 mmol), ketone (1 mmol), and iodine (1 mmol) in dichloromethane (5 mL) was stirred at 23 °C for a specified time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with water and extracted with ether (2 × 10 mL). The combined organic layers were washed with aqueous sodium thiosulfate and brine and dried over anhydr. Na_2SO_4. The removal of solvent, followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate – hexane, 0.5:9.5), gave pure 4-iodotetrahydropyran. The products thus obtained were characterized by IR and NMR spectroscopy. The characterization data was found to be consistent with the authentic samples (6).

4-Iodo-1-oxaspiro[5.5]undecane (a)

Liquid. IR (KBr, cm^{-1}) ν: 2924, 2853, 1630, 1457, 1075. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.19–1.66 (m, 10H), 1.99 (d, *J* = 12.8 Hz, 2H), 2.19–2.24 (m, 2H), 3.51–3.60 (m, 2H), 4.37–4.38 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.0, 21.2, 26.0, 29.2, 39.8, 39.8, 40.3, 49.6, 61.9, 74.6. LCMS: 279 (M – 1). Anal. calcd for $C_{10}H_{17}OI$: C 42.87, H 6.12; found: C 42.92, H 6.08.

4-Iodo-2-phenyl-1-oxaspiro[5.5]undecane (i)

Liquid. IR (KBr, cm^{-1}) ν: 3063, 3028, 2926, 2853, 1637, 1492, 1448, 1059, 757, 698. ^{1}H NMR (200 MHz, $CDCl_3$) δ: d 1.25–1.75 (m, 10H), 2.08–2.16 (m, 2H), 2.33 (dd, *J* = 4.5, 12.8 Hz, 1H), 2.56 (d, *J* = 12.8 Hz, 1H), 4.52–4.62 (m, 2H), 7.23–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.5, 26.2, 26.2, 30.1, 30.1, 40.0, 47.4, 49.2, 72.3, 75.5, 125.6, 125.6 125.6, 125.6, 128.5, 128.5. LCMS: 355 (M – 1). Anal. calcd for $C_{16}H_{21}OI$: C 53.94, H 5.94; found: C 53.99, H 5.89.

4-Iodo-1-oxaspiro[5.5]undec-4-ene (l)

Liquid. IR (KBr, cm^{-1}) ν: 2927, 2854, 1633, 1452, 1333, 1268, 1208, 1084, 759. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.25–1.72 (m, 10H), 2.51 (td, *J* = 2.2, 5.2 Hz, 2H), 3.76 (t, *J* = 5.2 Hz, 1H), 6.26 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.4, 21.4, 25.5, 35.2, 39.4, 39.4, 60.2, 60.2, 91.1, 144.2. LCMS: 277 (M – 1). Anal. calcd for $C_{10}H_{15}OI$: C 43.18, H 5.44; found: C 43.24, H 5.39.

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