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Iodine as a versatile reagent for the Prins-cyclization: an expeditious synthesis of 4-iodotetrahydropyran derivatives

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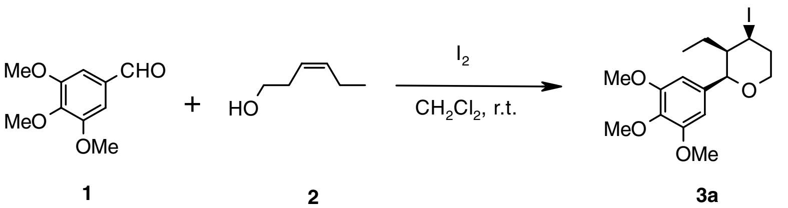
Abstract—Iodine is found to be an efficient reagent for the coupling of homoallylic alcohols with aldehydes under mild conditions to produce 4-iodotetrahydropyran derivatives in excellent yields in a short reaction time with high selectivity. The use of iodine makes this procedure simple, convenient and cost-effective.

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] Recently, indium halides and TMSI have been found to be useful for this transformation.[4,5] However, many of the classical methods often involve the use of expensive reagents, extended reaction times and also generate a mixture of products.[3] Therefore, the development of a simple and efficient protocol using inexpensive and readily available reagents would extend the scope of the 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 iodotetrahydropyran. 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 the Prins-cyclization is anticipated, in addition to experimental simplicity, to preclude the use of external metal catalysts and harsh acidic conditions.

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 Prins-cyclization for the rapid synthesis of highly substituted tetrahydropyrans from homoallylic alcohols and aldehydes using molecular iodine under neutral conditions. Accordingly, treatment of *cis*-hex-3-en-1-ol with



Scheme 1. .

Keywords: Prins-cyclization; Molecular iodine; Homoallylic alcohol; 4-Iodopyrans.

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Table 1. Iodine-promoted preparation of 4-iodotetrahydropyran derivatives

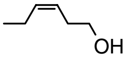
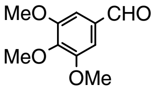
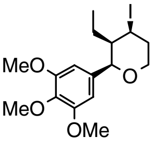
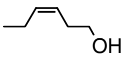
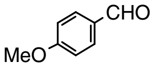
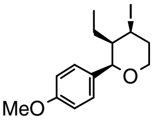
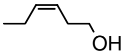
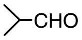
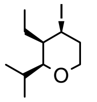
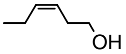
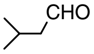
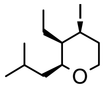
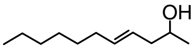
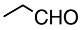
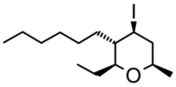
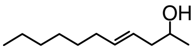
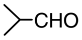
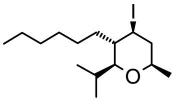
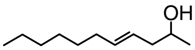
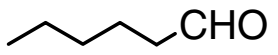
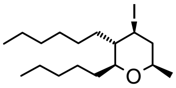
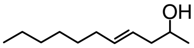
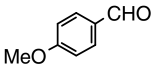
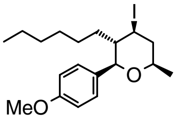
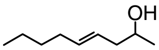
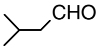
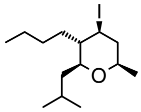
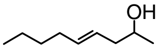
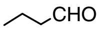
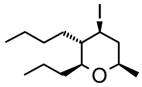
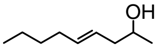
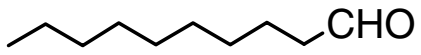
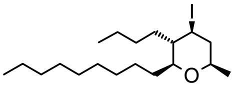
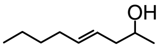
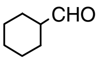
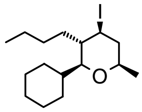
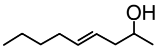
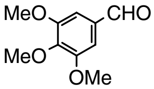
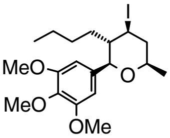
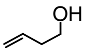
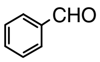
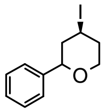
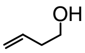
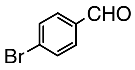
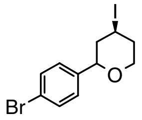
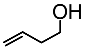
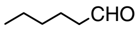
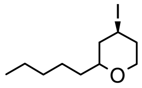
Entry	Homoallyl alcohol	Aldehyde	Iodopyran[a]	Time (min)	Yield[b] (%)
a				35	92
b				40	88
c				60	90
d				65	91
e				70	90
f				80	93
g				85	90
h				45	85
i				75	88
j				75	90
k				80	91
l				70	92
m				55	85

Table 1 (*continued*)

Entry	Homoallyl alcohol	Aldehyde	Iodopyran[a]	Time (min)	Yield[b] (%)
n				60	89
o				70	87
p				40	90

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.

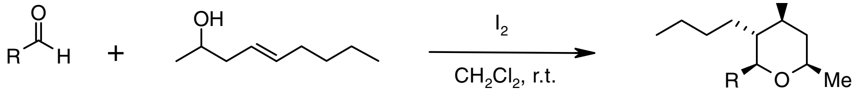
[b] Isolated and unoptimized yield.

3,4,5-trimethoxybenzaldehyde in the presence of molecular iodine at ambient temperature for 35 min gave the corresponding 4-iodotetrahydropyran in 92% yield with all cis-selectivity (Scheme 1).

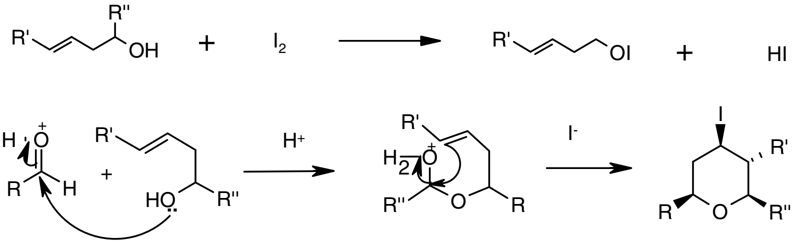
Similarly, *p*-anisaldehyde, isobutyraldehyde and isovaleraldehyde underwent smooth coupling with *cis*-hex-3-en-1-ol to give the respective 4-iodotetrahydropyrans in excellent yields (Table 1, entries b–d). The use of *cis*-homoallylic alcohols afforded 2,3,4-trisubstituted tetrahydropyrans with the all cis-configuration while *trans*-homoallylic alcohols gave 2,3,4-trisubstituted tetrahydropyrans with the trans–trans-configuration. Interestingly, *trans*-undec-4-en-2-ol reacted efficiently with a variety of aldehydes such as *n*-propanal, isobutyraldehyde, *n*-hexanal and *p*-anisaldehyde to produce 2,3,4,6-tetrasubstituted pyran derivatives (Table 1, entries e–h). Likewise, *trans*-non-4-en-2-ol gave the corresponding 2,3,4,6-tetrasubstituted pyrans with the trans–trans-configuration (Table 1, entries i–m, Scheme 2).

In addition, the unsubstituted homoallylic alcohol, but-3-en-1-ol also produced 2,4-disubstituted tetrahydropyrans in high yields (Table 1, entries n–p) under similar conditions. However, no reaction was observed in the absence of iodine even after a long reaction time (12 h). As solvent, dichloromethane appeared to give the best results. 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 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.[5] The formation of the products may be explained by hemi-acetal formation and subsequent Prins-type cyclization (Scheme 3).

Other reagents such as LiI, KI and NaI failed to produce the desired product. The nature of the substituents on the aromatic ring shows some effect on this conversion. It should be noted that aliphatic, simple aromatic and moderately activated aldehydes such as chloro- or bromo-substituted benzaldehyde gave higher yields of products compared to strongly activated or deactivated aldehydes. The scope and generality of this process is



Scheme 2.



Scheme 3.

illustrated with respect to various aldehydes and homoallylic alcohols (Table 1).[9]

In summary, molecular iodine is proved to be a useful and novel reagent for Prins-cyclization to produce highly substituted tetrahydropyrans in excellent yields in short reaction times. The experimental procedure is simple, convenient and the reaction conditions are amenable to scale-up. This method provides an easy access to 4-iodotetrahydropyrans with diverse chemical structures.

Acknowledgement

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9. *General procedure*: A mixture of homoallylic alcohol (2 mmol), aldehyde (1 mmol) and iodine (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 mixture was quenched with water and 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-iodotetrahydropyran. The products thus obtained were characterized by IR, NMR and mass spectroscopy. The spectral data were found to be consistent with authentic samples.[5] (**3b**) *3-Ethyl-4-iodo-2-(4-methoxyphenyl)tetrahydro-2H-pyran*: Liquid, IR (KBr): ν 2968, 2855, 1452, 1090, 1043, 922, 872, 769 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 0.34 (t, $J = 7.0$ Hz, 3H), 1.38–1.51 (m, 1H), 1.55–1.67 (m, 1H), 1.92–2.01 (m, 2H), 2.31 (dq, $J = 5.0$ Hz, 12.6 Hz, 1H), 3.56 (dt, $J = 2.2$, 11.8 Hz, 1H), 3.77 (s, 3H), 3.96 (dd, $J = 4.7$, 11.3 Hz, 1H), 4.54 (s, 1H), 4.72 (td, $J = 3.9$, 12.8 Hz, 1H), 6.79 (d, $J = 8.6$ Hz, 2H), 7.14 (d, $J = 8.6$ Hz, 2H). EIMS: *m/z* (%): 346 (20), 219 (30), 188 (50), 127 (30), 69 (70), 55 (100). (**3i**) *3-Butyl-4-iodo-2-isopropyl-6-methyltetrahydro-2H-pyran*: Liquid, IR (KBr): ν 2925, 2854, 1460, 1373, 1150, 1087, 759 cm^{-1}.^1H NMR (200 MHz, $CDCl_3$): δ 0.85 (d, $J = 6.7$ Hz, 3H), 0.92 (t, $J = 7.3$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H), 1.12 (d, $J = 6.0$ Hz, 3H), 1.13–1.36 (m, 4H), 1.46–1.76 (m, 3H), 1.87 (dq, $J = 2.0$, 6.7 Hz, 1H), 2.05 (q, $J = 10.9$ Hz, 1H), 2.42 (dd, $J = 4.3$, 12.8 Hz, 1H), 2.02 (dd, $J = 1.8$, 7.9 Hz, 1H), 3.31 (dt, $J = 1.8$, 6.2 Hz, 1H), 4.22 (dt, $J = 4.3$, 11.3 Hz, 1H). EIMS: *m/z* (%): 324 (10), 197 (20), 154 (50), 136 (50), 107 (40), 95 (50), 81 (50), 69 (80), 55 (100). (**3p**) *4-Iodo-2-pentyltetrahydro-2H-pyran*: Liquid, IR (KBr): ν 2915, 2861, 1440, 1370, 1145, 1087, 761 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): 0.89 (t, $J = 7.3$ Hz, 3H), 1.27–1.48 (m, 8H), 1.92 (q, $J = 12.4$ Hz, 1H), 2.22 (dt, $J = 3.6$, 8.0 Hz, 2H), 2.30 (td, $J = 2.1$, 13.1 Hz, 1H), 3.17–3.22 (m, 1H), 3.32–3.39 (m, 1H), 3.81 (td, $J = 3.6$, 10.9 Hz, 1H), 4.21 (tt, $J = 3.6$, 4.3 Hz, 1H). EIMS: *m/z* (%): 282 (10), 155 (80), 127 (35), 69 (70), 55 (100).