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Highly diastereoselective allylation of lactols and their ethers using molecular iodine

J. S. Yadav *, B. V. Subba Reddy, A. Srinivas Reddy, Ch. Suresh Reddy, S. Satyanarayana Raju

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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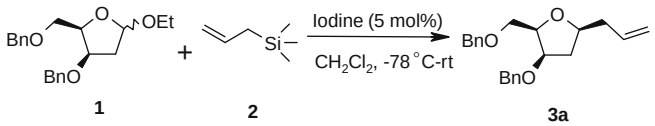
ABSTRACT

Lactols and their ethers undergo smooth allylation with allyltrimethylsilane in the presence of 5 mol % iodine in dichloromethane at −78 °C to afford *C*-allylfuranosides in good yields and with high diastereoselectivity. The use of iodine makes this method simple, convenient and practical. This is the first report on the allylation of lactols with allyltrimethylsilane using molecular iodine as a catalyst. Enhanced diastereoselectivity is the key feature of this protocol.

The stereoselective addition of allylsilanes to aldehydes, referred to as the Sakurai–Hosomi reaction has been recognized as an efficient method for carbon–carbon bond formation and has been applied extensively in organic synthesis, especially in natural products synthesis.[1,2] In particular, the addition of carbon nucleophiles to oxocarbenium ions has proven to be a useful method for the functionalization of tetrahydrofuran rings.[3–5] Lewis acids such as $SnBr_4$ and $BF_3{\cdot}OEt_2$ have been utilized to accomplish the allylation of five-membered ring acetals.[6,7] Five-membered ring iminium ions have also been known to undergo nucleophilic attack by transition structures similar to those for oxocarbenium ions.[8] However, many of these Lewis acids are highly corrosive, moisture sensitive and require stoichiometric amounts and also provide the products with low diastereoselectivity. Recently, elemental iodine has received considerable attention in organic synthesis because of its high tolerance to air and moisture, low-cost, nontoxic nature and ready availability, affording the corresponding products with high selectivity in excellent yields. The mild Lewis acidity associated with iodine has led to its use in organic synthesis using catalytic to stoichiometric amounts.[9]

In continuation of our interest on the use of molecular iodine for various transformations,[10] we herein report for the first time, a direct and metal-free substitution of acetals with allyltrimethylsilane using molecular iodine as a novel catalyst. As a preliminary study, the cyclic acetal (**1**) was treated with allyltrimethylsilane (**2**) in the presence of 5 mol % of molecular iodine. The reaction proceeded smoothly at −78 °C-rt and the desired *C*-allylated product **3a** was obtained in 85% yield with 9:1 diastereoselectivity (Scheme 1, Table 1).

In this allylation, the major product **3a** was found to be 1,3-*syn* isomer. The stereochemistry of **3a** was assigned on the basis of coupling constants and also by comparison with authentic sample.[11] The remarkable catalytic activity of iodine provided the incentive for further study of reactions with various cyclic acetals. Interestingly, various cyclic acetals especially 2-deoxy acetals participated well in this reaction. Low selectivity was observed with methylallyltrimethylsilane (Table 1, entries b, f, j and l). The 1,3-*syn* selectivities observed for acetals (Table 1, entries a–f) are reversed when the 3-alkoxy group is replaced with a methyl group (Table 1, entries g–n). Nucleophilic substitution reactions with *trans*- and *cis*-disubstituted acetals revealed that a methyl group at C-3 biases nucleophiles to attack with high 1,3-*anti*-stereoselectivity (Table 1, entries g–n).[11] The allylation of lactol afforded the required product in 92% yield in a ratio of 96:4 (Table 1, entry h). It is worth mentioning here that the presence of 1.2 equiv of iodine led to allylation with concomitant debenzylation (Table 1, entry i). In addition, cyclic acetals derived from 2-deoxyribose gave higher yields compared to the acetals prepared from 2-deoxyxylose. The scope and generality of this process are illustrated with respect



1 2 3a

Scheme 1. Preparation of product **3a**.

* Corresponding author. Tel.: +91 40 27193535; fax: +91 40 27160512.
E-mail address: yadavpub@iict.res.in (J.S. Yadav).

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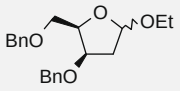
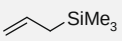
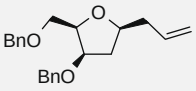
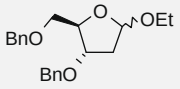
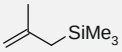
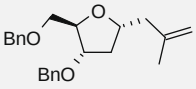
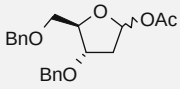
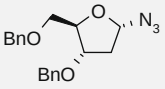
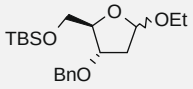
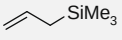
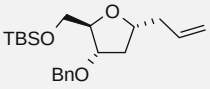
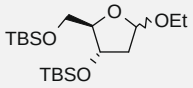
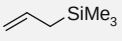
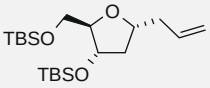
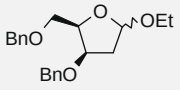
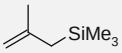
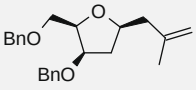
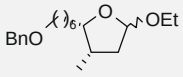
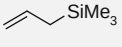
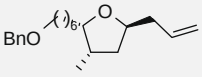
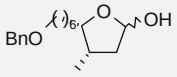
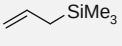
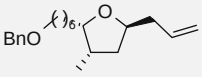
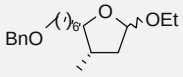
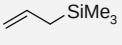
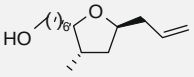
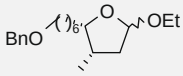
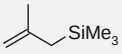
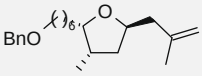
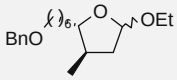
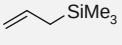
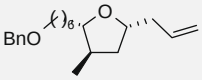
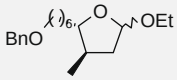
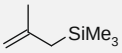
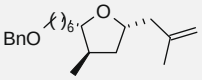
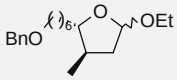
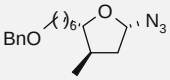
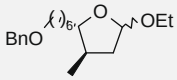
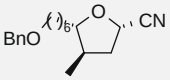
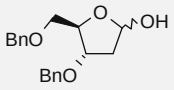
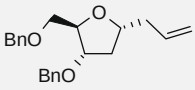
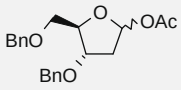
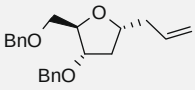
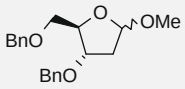
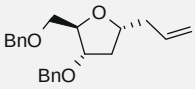
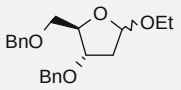
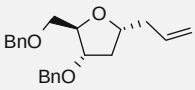
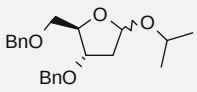
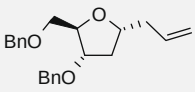
Table 1
Diastereoselective allylation of five-membered ring oxocarbenium ions using iodine

Entry	Substrate (**1**)		Product[a] (**2**)	Time (h)	Yield[b] (%)	Ratio[c] (%)
a				24	85	90:10
b				16	90	86:14
c		$TMSN_3$		13	80	70:30
d				15	85	98:2
e				16	87	90:10
f				20	80	88:12
g				2.0	90	>99
h				3.0	92	96:4
i				4.0	90	>99
j				2.0	95	89:11
k				2.0	97	83:17
l				2.0	95	90:10
m		$TMSN_3$		0.5	93	55:45
n		TMSCN		0.5	90	60:40

[a] All products were characterized by ^1H, ^{13}C NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after purification.
[c] Ratio was determined by HPLC of the crude product.

Table 2
Effect of leaving group on rate of reaction and diastereoselectivity

Entry	Substrate (**1**)	Product[a] (**2**)	Time (h)	Yield[b] (%)	Ratio[c] (%)
a			24	80	82:18
b			19	83	88:12
c			22	85	97:3
d			15	92	99:1
e			10	95	99:1

[a] All products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after chromatography.
[c] Ratio was determined by HPLC.

to various cyclic acetals and trialkylsilyl nucleophiles (Table 1).[12] The reactions were sluggish with cyclic acetals derived from either xylose or ribose. The reactions were clean and high yielding merely with 2-deoxycyclic acetals. In case of 3-alkoxy acatals, the nucleophile adds to the same face as the alkoxy substituent at C-3. These results led us to hypothesize that the alkoxy group at C-3 controls the approach of the nucleophile onto the same face of the oxocarbenium ion.[11] This method is compatible with acid labile protective groups such as TBS ethers (Table 1, entries d and e). This method was also effective for the azidation and cyanation of acetals with trimethylsilyl azide and trimethylsilyl cyanide, respectively, under identical conditions (Table 1, entries c, m and n). Eventually, we have studied the leaving ability of various functionalities such as OH, ethers and esters and the results are presented in Table 2. Of these, isopropyl acetal was found be more effective in terms of conversion and reaction rate (Table 2, entry e).

In conclusion, we have described a novel protocol for the substitution of five-membered cyclic acetals with allyltrimethylsilane using 5 mol % of molecular iodine as a catalyst. Enhanced diastereoselectivity, high conversions, mild reaction conditions and operational simplicity are the noteworthy features of this methodology.

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12. *General procedure*: A solution of lactol ether (100 mg, 0.31 mmol) and allyltrimethylsilane (0.15 mL, 0.94 mmol) in 2 mL CH_2Cl_2 was cooled to −78 °C. Then a freshly prepared 1.0 M solution of I_2 (5 mol %) in CH_2Cl_2 was added dropwise (0.015 mL, 0.015 mmol), and the solution was allowed to stir at −78 °C for 1 h and slowly brought to room temperature. After complete conversion as indicated by TLC, the reaction was quenched with water (10 mL) and the reaction mixture was extracted with dichloromethane (3 × 10 mL). The combined extracts were washed with a 15% solution of aqueous sodium thiosulfate, dried over anhydrous Na_2SO_4 concentrated in vacuo. The resulting crude residue was purified by column chromatography to afford allyl derivative as a colourless liquid with >99% stereoselectivity, which was characterized by LC–MS: using Eclipse XDB C18 column. Column size: 150 × 4.6 mm with 5 μm particle size. Eluent: CH_3CN/H_2O (65/35) with flow rate 1.0 mL/min at 25 °C (λ_{max} = 210 nm). Spectral data for the selected products: Compound **3j** (Table 1): Viscous liquid, $[\alpha]_D^{20}$ −5.0 (*c* 1.5, $CHCl_3$); IR (KBr): *ν* 2930, 2856, 1454, 1104, 887, 735, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.19–7.32 (m, 5H), 4.73 (s, 1H), 4.68 (s, 1H), 4.46 (s, 2H), 4.16 (q, 1H, *J* = 6.8 Hz), 3.76–3.84 (m, 1H), 3.42 (t, 2H, *J* = 6.8 Hz), 2.00–2.32 (m, 3H), 1.74 (s, 3H), 1.67–1.72 (m, 2H), 1.54–1.66 (m, 2H), 1.23–1.48 (m, 8H), 0.89 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 143.2, 138.6, 128.2, 127.5, 127.4, 111.9, 81.0, 75.1, 72.8, 70.4, 44.9, 39.8, 35.7, 30.3, 29.6, 26.5, 26.1, 22.9, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{34}O_2$ $[M+Na]^+$ 353.2456, found: 353.2444. Compound **3k** (Table 1): Viscous liquid, $[\alpha]_D^{20}$ −19 (*c* 1.5, $CHCl_3$); IR (KBr): *ν* 2930, 2854, 1450, 1360, 1100, 993, 910, 730, 690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.23–7.32 (m, 5H), 5.65–5.88 (m, 1H), 4.96–5.10 (m, 2H), 4.46 (s, 2H), 3.83–3.98 (m, 1H), 3.43 (t, 2H, *J* = 6.6 Hz), 3.19–3.31 (m, 1H), 2.03–2.40 (m, 3H), 1.22–1.84 (m,

12H), 0.98 (d, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 134.8, 127.9, 127.2, 127.1, 116.3, 86.0, 76.6, 72.5, 70.2, 40.5, 38.9, 37.8, 34.3, 29.4, 29.40, 25.9, 25.8, 17.4. HRMS (ESI) m/z calcd for $C_{21}H_{32}O_2$ $[M+H]^+$ 317.2480, found: 317.2478. Compound **3b** (Table 1): Viscous liquid, $[\alpha]_D^{20}$ +39.5 (c 1.5, $CHCl_3$). IR (KBr): ν 2929, 2860, 1647, 1453, 1362, 1101, 739, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24–7.40 (m, 10H), 4.79 (s, 1H), 4.75 (s, 1H), 4.44–4.60 (m, 4H), 4.07–4.32 (m, 3H), 3.52 (dd, 2H, J = 1.4, 4.8 Hz), 2.44–2.53 (m, 1H), 2.21–2.32 (m, 2H), 1.77–1.82 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 138.1, 128.1, 127.3, 112.1, 82.0, 80.5, 76.9, 73.1, 71.2, 70.6, 44.0, 37.3, 22.6; HRMS (ESI) m/z calcd for $C_{23}H_{28}O_3$ $[M+Na]^+$ 375.1936, found: 375.1950. Compound **3d** (Table 1): Viscous liquid, $[\alpha]_D^{20}$ +24 (c 1.5, $CHCl_3$); IR (KBr): ν 2928, 2790, 1620, 1480, 1370, 1130, 740, 679 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.36 (m, 5H), 5.74–5.89 (m, 1H), 5.02–5.14 (m, 2H), 4.52 (s, 2H), 4.05–4.18 (m, 3H), 3.54–3.70 (m, 2H), 2.42–2.53 (m, 1H), 2.21–2.38 (m 2H), 1.75–1.84 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 135.0, 128.3, 127.4, 116.8, 83.9, 80.8, 78.5, 71.4, 63.8, 40.4, 37.3, 25.8, 18.2, −5.3, −5.4; HRMS (ESI) m/z calculated for $C_{21}H_{34}O_3Si$ $[M+Na]^+$ 385.2175, found: 385.2182.