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Iodotrimethylsilane induced diastereoselective synthesis of tetrahydropyranones by a tandem Knoevenagel–Michael reaction☆

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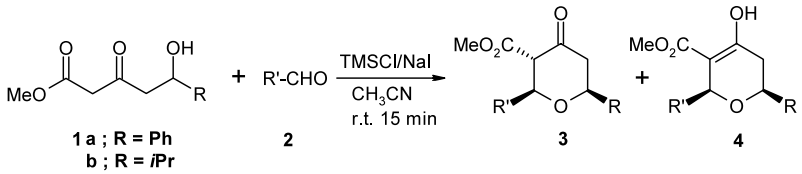
Abstract—The synthesis of multifunctionalized tetrahydropyranones has been achieved at room temperature with iodotrimethylsilane by a tandem Knoevenagel condensation of aldehydes with aldol adducts prepared from β-keto esters and aldehydes, followed by a Michael reaction. The reactions are highly diastereoselective affording a single isomer in high yields.

Tetrahydropyran ring systems are part of the backbone of various carbohydrates and are important building blocks of many biologically active natural products such as marine toxins and polyether antibiotics.[1,2] This then prompted extensive studies in forming these pyran structural derivatives, and therefore, a number of methods have been developed for the construction of pyran rings. Among these, manipulation of carbohydrates,[3] Prins reactions,[4] hetero-Diels–Alder cyclizations,[5] intramolecular epoxide opening and Michael reactions[6] are widely used methods. Despite the success of these methods, the search for a novel strategy for the efficient assembly of multifunctionalized tetrahydropyrans continues to be a significant goal in organic synthesis. Iodotrimethylsilane (TMSI),[7] with its remarkable reactivity has a wide spectrum of synthetic applications. In continuation of our interest on the applications of TMSI[8] and also prompted by the recent report[9] on the diastereoselective synthesis of THPs based on the Maitland–Japp reaction,[10] we herein present our results on an iodotrimethylsilane-mediated highly efficient synthesis of 2,3,6-trisubstituted tetrahydro-4-pyranones at room temperature by a novel Knoevenagel/Michael reaction sequence of aldol products with aldehydes (Scheme 1). The required aldol products **1a**–**c** were prepared by a reported procedure from methyl acetoacetate by generating a dianion and reacting it further with aldehydes.

Treatment of aldol product **1a** with cyclohexane carboxaldehyde **2b** in the presence of iodotrimethylsilane generated in situ from chlorotrimethyl silane (TMSCl) and NaI in acetonitrile, resulted in the formation of tetrahydropyranones **3** and **4** in 86% yield as a 90:10 mixture of keto and enol tautomers. The ratio of the products was deduced from the ^{1}H NMR spectrum of



Scheme 1.

Keywords: aldol products; iodotrimethylsilane; Knoevenagel; Michael reaction; THPs.
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the crude reaction mixture. The reaction was spontaneous and complete within 15 min at room temperature and involved a Knoevenagel condensation of the aldehyde **2** with the aldol adduct **1**, followed by a Michael addition giving the THP products. The reaction was found to be highly diastereoselective affording only a single diastereomer. The keto-tautomer **3** was isolated in its pure form by careful flash column chromatography[11] and the structure of the product was confirmed by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. The structure was further studied by NOE experiments. From ^{1}H NMR studies large values of vicinal couplings J_{Ha-Hb} and J_{Hc-Hd} of about 11 Hz suggested their diaxial disposition in a chair conformation for the six-membered ring.

Furthermore, NOEs between H_a and H_d and H_b and H_c confirmed the $^{c}C_a$ chair conformation for the six-membered ring. This is in agreement with the energy minimized structure as shown in Figure 1. The C2 and C6 substituents are *cis*, the C5 and C6 substituents are *trans* and in this conformation all three bulky substituents occupy the energetically favorable equatorial positions in the six-membered ring. Therefore it can be concluded that the reaction is under thermodynamic control.

To investigate the scope and generality of the present procedure, different aldol products **1b** and **1c** were prepared from isobutanal and cyclohexanone respectively and reacted with a range of aromatic, as well as aliphatic, aldehydes and the results are presented in Table 1.

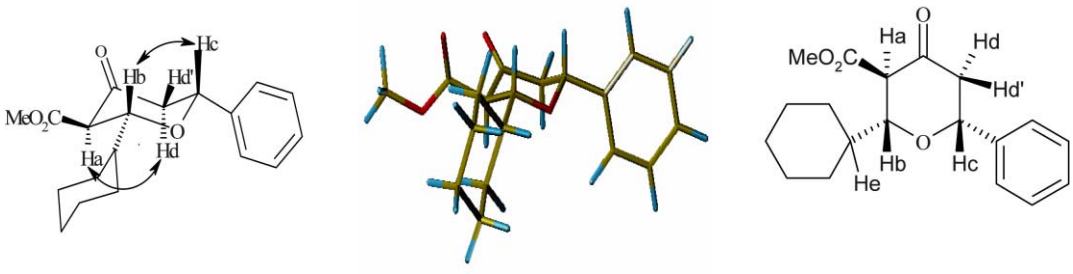
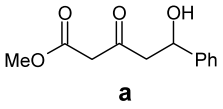
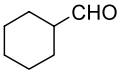
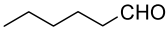
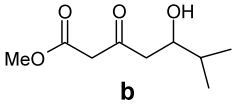
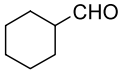
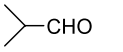
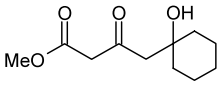
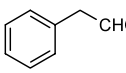
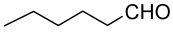
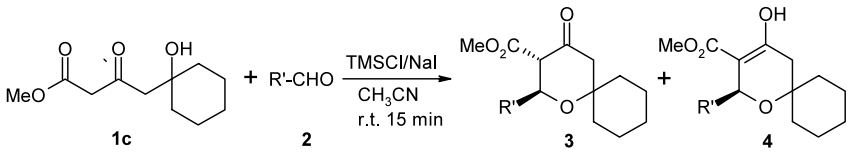


Figure 1. Characteristic NOEs, minimum energy structure and chemical structure for compound **3** (R′ = cyclohexyl, R = phenyl).

Table 1. Iodotrimethylsilane-mediated synthesis of tetrahydropyranones[a]

Entry	Aldol adduct **1**	Aldehyde **2**	Product **3**	Yield[b] (%)	Ratio[c] **3/4**
1		Ph CHO	**a**	90	100:0
2	 **a**		**b**	86	90:10
3			**c**	85	93:7
4		*p*-Br-C_6H_4 CHO	**d**	80	88:12
5		Ph CHO	**e**	90	92:8
6	 **b**		**f**	85	100:0
7			**g**	82	100:0
8		*p*-CH_3-C_6H_4 CHO	**h**	87	95:5
9		Ph CHO	**i**	89	90:10
10	 **c**	*p*-Cl-C_6H_4 CHO	**j**	85	95:5
11			**k**	80	93:7
12			**l**	82	100:0

a) All products were characterized by ^{1}H, ^{13}C NMR, IR and Mass spectroscopy.
b) Isolated yields after purifcation.
c) Ratio has been calculated from the ^{1}H NMR spectrum of the crude reaction mixture.



Scheme 2.

The aldol product **1c** prepared from cyclohexanone when reacted with aldehydes gave spiro fused products (Scheme 2). All the reactions were completed within 15 min and were highly diastereoselective giving only a single diastereomer exclusively in good yields. This strategy has the advantage of being very flexible; by judicious choice of the appropriate aldehyde, a range of side chains can be installed at the C-2 position and by use of different aldehydes in the preparation of the aldol products, a side chain can be installed at the C-6 position.

In conclusion, a flexible and efficient approach to the synthesis of methyl 2,6-disubstituted-4-oxo-tetrahydropyran-5-carboxylates has been described which involves iodotrimethylsilane mediated reaction of aldol products with a range of aldehydes. This method offers several advantages including enhanced reaction rates, the ready availability of the reagents at low cost, simplicity of operation and selectivity which make it a useful and attractive strategy for the synthesis of tetrahydropyran-4-one derivatives of medicinally and chemically important compounds.

Acknowledgements

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11. **Typical procedure**: Trimethylsilyl chloride (0.9 mmol, 0.1 mL) was added to a stirred mixture of aldol adduct **1a** (0.9 mmol, 0.200 g) and cyclohexane carboxaldehyde **2b** (0.9 mmol, 0.101 g), sodium iodide (0.9 mmol, 0.134 g), in acetonitrile (6 mL) at room temperature. The reaction immediately turned yellowish and was complete within 15 min as indicated by TLC. The solvent was removed under reduced pressure, then ethyl acetate was added, which was washed with an aqueous sodium bisulfate solution and followed by brine. The organic phase was separated, dried over Na_2SO_4 and concentrated to give a crude product which was purified by flash column chromatography using silica gel (60–120 mesh) eluting with EtOAc:*n*-hexane (1:9) to afford methyl 6-cyclohexyl-4-oxo-2-phenyl-tetrahydropyran-5-carboxylate **3b** as a white solid. Mp 105–107°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.12–1.48 (m, 5H), 1.66 (m, 2H), 1.75–1.83, (m, 4H), 2.50 (ddd, 1H, $J_{c-d}=11.6$ Hz, $J_{d-d'}=14.4$ Hz, $J_{a-d}=1.0$ Hz, H-d), 2.73 (dd, 1H, $J_{d,d'}=14.4$ Hz, $J_{c-d'}=2.7$ Hz, H-d′), 3.55 (dd, 1H, $J_{a-b}=10.8$ Hz, $J_{a-d}=1.0$ Hz, H-a), 3.80 (s, 3H, OMe), 3.96 (dd, 1H, $J_{a-b}=10.8$ Hz, $J_{b-e}=2.1$ Hz, H–b), 4.70 (dd, 1H, $J_{c-d}=11.6$ Hz, $J_{c-d'}=2.7$Hz, H-c), 7.29–7.39 (m, 5H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): 25.9, 26.3, 26.4, 30.0, 41.5, 48.9, 52.1, 60.0, 78.0, 82.3, 125.3, 127.9, 128.6, 140.6, 168.7, 202.6. FABMS (*m*/*z*): 315 (M−1), 283, 233, 205, 154, 137, 111.