Diastereoselective Synthesis of 1-Allyl and 1,2-bis(Allyl)-1,2- diols: Versatile Synthons For Substituted Tetrahydrofuran Derivatives

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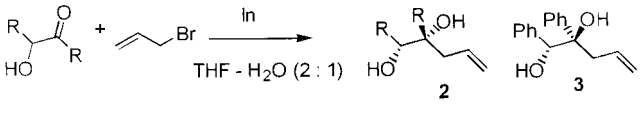
Abstract: 2-Hydroxyketones and 2-ketoaldehydes undergo indium mediated highly diastereoselective mono and bis- allylation reactions to give respective 1-allyl **2a-c** and 1,2-bis (allyl)- **7a-c** 1,2 diols. **2a** undergoes I_2 / $NaHCO_3$ and *m*-CPBA mediated diastereoselective intramolecular cyclizations to provide respective (*2S*, 3R*, 5S**)-2,3-diphenyl-4-hydroxy-5-iodo methyltetrahydrofuran **4a** and (*2S*, 3R*, 5R**)-2,3-diphenyl-4-hydroxy-5-hydroxymethyl tetrahydrofuran **5b** as major product.

Key words: diastereoselective, allylation, cyclisation, hydroxyketones, ketoaldehydes

The stereoselective 1,2-additions especially allylation to carbonyl compounds continue to have central position in asymmetric organic synthesis[1]. The stereoselectivity stems from the chelated intermediates and is considerably affected by the choice of the solvents, different additives and pH of the reaction medium along with the nature of the substituent present on the carbonyl and allyl substrate. In recent years, the indium[2] mediated allylations have shown that the presence of water does not inhibit the operation of chelation control and often exceeds than that attainable with corresponding magnesium, cerium or chromium reagents in anhydrous media[3]. α-Hydroxy/ alkoxy/ amino moiety in carboxaldehydes[4] and cyclohexanone[5] lead to considerable π-facial discrimination but thioethers lead to poor stereoselectivity. However, the acyclic hydroxy ketones[6] have been less studied and generally show poor stereoselectivity. Further, indium mediated allylations of 1,2-dioxo compounds give mono allylated hydroxy ketones[7] or diallylated products[8] with poor diastereoselectivity. Here, we unravel both these limitations and report that acyclic 2-hydroxyketones undergo diastereoselective monoallylation and 2-ketoaldehydes undergo diastereoselective diallylation to provide respective 1-allyl (**2a-c**) and 1,2-bisallyl- (**7a-c**) 1,2-diols. **2a** undergoes diastereoselective cyclisations to tetrahydrofuran derivatives **4** and **5**.

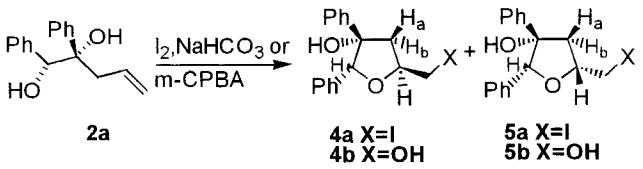
The solution of **1a**, allyl bromide and indium metal (suspension) (1: 1.5: 1) in THF-H_2O (2: 1) on stirring at 30±1 °C for 6-8 h, after HCl hydrolysis, CH_2Cl_2 extraction and chromatography provides **2a** (92%)[9], mp 95 °C (Lit.[10] m.p. 96-97 °C). On performing the reaction under Grignard conditions at reflux temperature, the second diastereomer **3** is also formed but again formation of **2a** through a chelate intermediate is preferred (**2a : 3**:: 9: 1). The stereochemistry of **2a** has been defined on the basis of COSY and NOE experiments on its cyclised products **4** and **5**. This procedure offers a convenient alternative to similar allylations performed through tetraallyltin[10]. Similarly, α-hydroxyketone **1b** undergoes highly diastereoselective allylation to provide **2b,** M^+ m/z 234 but in case of **2c,** M^+ m/z 196, de is lowered to 95% (Scheme 1). The stereochemistries for **2b** and **2c** have been defined in analogy with **2a**.



Scheme 1

The solution of **2a** in dry CH_3CN containing suspended $NaHCO_3$ (3 equiv) was stirred at 30 °C for 5 min followed by addition of iodine (3 equiv) and stirring for 72 hours. The reaction mixture after workup and chromatography gave two isomeric products (4:1 ratio) with M^+ m/z 380 (Scheme 2). In case of fast moving component[11] (minor), the irradiation of singlet at δ 5.29 (2-H) shows positive NOE signals at δ 4.6 (5-H), 2.78(4-H_a) and 7.04, 7.38 (ArH) and irradiation of AB quartet at δ 2.78 shows positive signals at δ 2.48(4-H_b), 4.61(5-H), 5.29 (2-H) and 7.38 (ArH). These observations show that two aryl rings are on the opposite side of furan ring and 2-H and 5-H are on the same side of tetrahydrofuran ring and has been assigned the structure **5a**. In case of slow moving (major) component, irradiation of singlet at δ 5.53 (2-H) does not show NOE for H-5 (δ 4.55 - 4.60) and has been assigned the structure (*2S*, 3R*, 5S**)-2,3-diphenyl-4-hydroxy-5-iodo methyltetrahydrofuran **4a**. The lowering of reaction temperature increases the overall yield of products but does not affect the diastereoselectivity which is only marginally affected by use of CH_2Cl_2 or toluene as solvents.

Stirring of **2a** with *m*-CPBA in $CHCl_3$ at 30 °C for 24 hours gave a mixture of two diastereomers[12] **4b** and **5b** (16: 84). However, on lowering reaction temperature to 0 °C, the yield of minor component **4b** is increased (Scheme 2) and use of CH_3CN as solvent leads to complex mixure. Therefore, both I_2 / $NaHCO_3$ and *m*-CPBA medi-

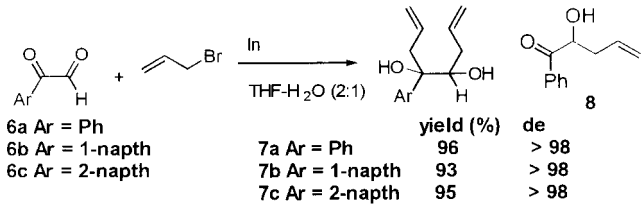


Solvent	Temp. °C	X	4:5	yield %
CH_3CN	30	I	80:20	40
CH_3CN	0	I	86:14	90
CH_2Cl_2	0	I	75:25	87
Toluene	0	I	80:20	75
$CHCl_3$	30	OH	16:84	60
$CHCl_3$	0	OH	37:63	83
CH_3CN	0	m-CPBA	Complex mixture	

ated cyclizations on lowering of temperature result in higher ratio of **4** over **5**.

Scheme 2

The allylation of phenylglyoxal (**6a**) with allyl bromide and indium metal (1: 3: 2) under above conditions gave diallylated product **7a**, (96%), M^+ m/z 218. ^1H NMR of the crude reaction mixture or the pure compound show presence of only one diastereomer and formation of second diastereomer could not be observed. On performing the reaction by using one equivalent of indium metal, only diallylated product **7a** is formed and part of phenylglyoxal remains unreacted. The formation of monoallylated product **8** is not observed. The earlier attempts on allylation of **6a** have lead to formation of **8** or its mixture with **7a** in 5:12 ratio in overall 17% yield[13]. In order to assess the generality of the process, the reaction has been studied with **6b** and **6c** (Scheme 3). These reactions constitute first examples, where keto aldehydes undergo diastereoselective bis allylation.



Scheme 3

Therefore, 2-hydroxyketones and 2-ketoaldehydes undergo indium mediated highly diastereoselective mono- and bis(allylation) reactions to give 1-allyl-(**2a-c**) and 1,2-bis(allyl)- (**7a-c**) 1,2-diols, respectively. **2a** undergoes I_2 / $NaHCO_3$ and *m*-CPBA mediated diastereoselective intramolecular cyclizations to give diastereomerically two different tetrahydrofurans (**4**/**5**) as major products. The effect of various substituents in the reactants - ketones and allyl halides on diastereoselectvity is under investigation.

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(9) *General Procedure*: The carbonyl compound **1** (0.5 mmol), allyl bromide (0.75 mmol), indium metal (0.5 mmol) were taken in THF - H_2O (2:1) mixture (20 mL) and the reaction mixture was stirred at 30±1 °C till the indium metal dissolved. The turbid reaction mixture was treated with dil. HCl and was extracted with $CHCl_3$. The solvent was distilled off and the residue was column chromatographed (silica gel, 60-120 mesh) to isolate allyl addition product.
2a: (80%), mp 94-5 °C; M^+ m/z 237 (M^+ -OH); ^1H NMR ($CDCl_3$): δ 2.37 (s, 1H, OH, exchanges with D_2O), 2.48(s, 1H, exchanges with D_2O, OH),, 2.73 (dd, J_1 = 14.1Hz, J_2 = 8.6Hz, 1H, 1/2CH_2), 2.93(dd, J_1 = 14.1Hz, J_2 = 5.4 Hz, 1H, 1/2 CH_2), 4.77(s, 1H, CH), 5.05-5.19 (m, 2H, =CH_2), 5.45 - 5.61 (m, 1H, =CH), 6.95 - 7.24 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): δ 42.47 (-ve, CH_2), 78.25(ab, C), 80.36(+ve, CH), 119.57 (-ve, CH_2), 126.49(+ve, CH), 126.78(+ve, CH), 127.33(+ve, CH), 127.49(+ve, CH), 127.76 (+ve, CH), 133.31(+ve, CH), 139.35 (ab, C), 141.55(ab, C).
3a: (10%), mp 90 °C, M^+ m/z 254 (M^+); ^1H NMR ($CDCl_3$): δ 1.58 (b, 1H, OH), 2.93(dd, J_1 = 13.8Hz, J_2 = 7.4Hz, 1H), 3.13(dd, J_1 = 13.8Hz, J_2 = 7.4 Hz, 1H), 4.05 (1H, OH), 4.98 (s, 1H, CH), 5.06 - 5.15 (m, 2H, =CH_2), 5.63 - 5.75 (m, 1H, =CH), 7.14 -7.74 (m, 10H, ArH).
2b (90%), liquid, M^+ m/z 234(M^+); ^1H NMR ($CDCl_3$): δ 1.25 (s, 1H, OH, exchanges with D_2O), 1.48 (s,1H, OH, exchanges with D_2O), 2.70(dd, J_1 = 14Hz, J_2 = 8.1Hz, 1/2 CH_2), 2.84 (dd, J_1 = 14Hz, J_2 = 6.2 Hz, 1/2 CH_2), 4.83 (s, 1H, CH), 5.11 - 5.20 (m, 2H, =CH_2), 5.59 - 5.72 (m, 1H, =CH), 6.03 (d, J = 2.8Hz, 1H, =CH), 6.11(d, J_1 = 2.8 Hz, 1H, =CH), 6.24(t, J = 2.8Hz, 1H, =CH), 6.25 (t, J = 2.8Hz, 1H, =CH), 7.28 (d, J = 2.8Hz, 1H, =CH), 7.29 (d, J = 2.8Hz, 1H, =CH); ^{13}C NMR ($CDCl_3$):

d 40.78 (-ve, CH_2), 72.86 (ab, C), 76.07 (+ve, CH), 107.14 (+ve, CH), 107.68 (+ve, CH), 110.20 (+ve, CH), 119.52 (-ve, CH_2), 132.66 (+ve, CH), 141.68 (+ve, CH), 141.82 (+ve, CH), 152.8 (ab, C), 155.18 (ab, C).

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(11) The assignement of signals is based on ^{1}H-^{1}H COSY and HMQC studies. **4a:** *Lower R_f component:* (80%); liquid; M^+ m/z 380(M^+); ^{1}H NMR($CDCl_3$): δ 1.79 (bs, 1H, OH), 2.45 (dd, J_1 = 8.8Hz, J_2 = 6.4Hz, 4-H_a), 2.62 (dd, J_1 = 8.8Hz, J_2 = 3.8 Hz, H-4$_b$), 3.51 (dd, J_1 = 7Hz, J_2 = 2.6Hz, 1H of 5-CH_2I), 3.61 (dd, J_1 = 7Hz, J_2 = 4Hz, 1H of 5-CH_2I), 4.55 - 4.60 (m, 1H, H-5), 5.53 (s, 1H, H-2), 6.98 - 7.45 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): δ 12.41(-ve, CH_2), 49.20(-ve, CH_2), 76.79(+ve, CH), 83.18(ab, C), 89.52(+ve, CH), 124.43(+ve, CH), 126.31(+ve, CH), 126.57(+ve, CH), 128.05(+ve, CH), 128.62(+ve, CH), 135.15(ab, C), 144.46(ab, C).
5a: *Higher R_f Component :* (20%); M^+ m/z 380; ^{1}H NMR($CDCl_3$): δ 2.48(dd, J_1 = 9.2 Hz, J_2 = 2.6 Hz, 4-H_b), 2.78 (dd, J_1 = 9.2 HZ, J_2 = 6 Hz, 4-H_a), 3.63 (d, J = 4.4 Hz, 2H, 5-CH_2I), 4.57 - 4.72 (m, 1H, 5-H), 5.29 (s, 1H, 2-H), 7.01 - 7.39 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): δ 10.25(-ve, CH_2), 48.40(-ve, CH_2), 78.34(+ve, CH), 82.33(ab, C), 91.02(+ve, CH), 125.41(+ve, CH), 126.68(+ve, CH), 127.31(+ve, CH), 128.38(+ve, CH), 128.40(+ve, CH), 134.97(ab, C), 142.38(ab, C).

(12) **5b:** (60%); m.p. 160 °C (CH_2Cl_2); M^+ m/z 270(M^+); ^{1}H NMR($CDCl_3$): δ 2.45 (dd, J_1 = 9.4Hz, J_2 = 2.2 Hz, 1H, 4-H_b), 2.84 (dd, J_1 = 9.4Hz, J_2 = 6.8 Hz, 1H, 4-H_a), 3.79 (dd, J_1 = 7.6 Hz, J_2 = 2.2 Hz, 1H, 5-CH_2OH), 4.08 (dd, J_1 = 7.6Hz, J_2 = 1.6 Hz, 1H, 5−CH_2OH), 4.49 - 4.73 (m, 1H, H-5), 5.19 (s, 1H, H-2), 7.03 - 7.45 (m, 10H, ArH); ^{13}C NMR ($CDCl_3$): δ 45.03(-ve, CH_2), 63.28(-ve, CH_2), 77.89(+ve, CH), 80.56(ab, C), 89.96(+ve, CH), 125.55(+ve, CH), 126.42(+ve, CH), 126.97(+ve, CH), 127.8(+ve, CH), 136.28(ab,C), 141.43(ab, C).

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