The Preparation of 6-Bromo-3,4-dihydro-2*H*-pyrans from Tetrahydropyran-2-ones via a Ni(0)-catalysed Coupling Reaction and their Halogen-metal Exchange to 6-Lithio-3,4-dihydro-2*H*-pyrans.

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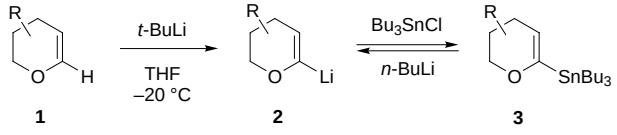
Abstract: The enol triflate derivatives prepared from readily accessible tetrahydropyran-2-ones undergo Ni(0)-catalysed substitution with LiBr to give the corresponding 6-bromo-3,4-dihydro-2*H*-pyrans under mild conditions. The 6-bromo-3,4-dihydro-2*H*-pyrans undergo halogen-metal exchange with *tert*-butyllithium to give the corresponding 6-lithio-3,4-dihydro-2*H*-pyrans.

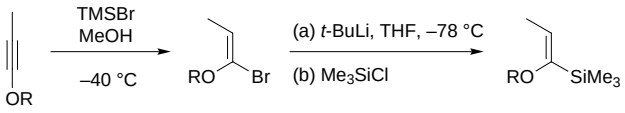
Key words: 6-bromo-3,4-dihydro-2*H*-pyrans, lactones, Ni(0), coupling, halogen-metal exchange

6-Lithio-3,4-dihydro-2*H*-pyrans **2** are synthetically useful acyl anion equivalents.[1,2] Boeckman and Bruza reported the first practical and direct synthesis of **2** by metallation of the dihydropyran **1** (Scheme 1) with *t*-BuLi (1.0 equiv) in THF at -20 °C to 0 °C.[3] The metallation reaction is sensitive to substitution. Quantitative conversion is often only achieved with a large excess of *t*-BuLi in which case heteroatom substituents - or the THF - may undergo competing metallation.[4] Even simple alkyl-substituted dihydropyrans may require ≥4 equivalents of *t*-BuLi for satisfactory conversion.[5] In order to avoid the complications associated with the presence of excess *t*-BuLi, the 6-lithio-3,4-dihydro-2*H*-pyran **2** can be converted to its stable and isolable 6-tributylstannyl-3,4-dihydro-2*H*-pyran **3** by reaction with Bu_3SnCl and the lithium derivative regenerated by the transmetallation of the stannane **3** with *n*-BuLi in THF at –78 °C.[6] The ease, generality and efficiency of the tin-lithium transmetallation reaction stimulated the development of several alternative syntheses of the stannanes **3** from lactone[7–12] sulfone[13,14] or alkynol precursors.[15–18]



Scheme 1

Recently Yu and Jin[19] described the synthesis and subsequent lithium-halogen exchange of α-bromo vinyl ethers as shown in Scheme 2. Their method for the first time provided a route to α-lithiated enol ethers with β-alkyl substituents. Unfortunately the Yu-Jin procedure cannot be easily adapted to the cyclic series owing to the method used to synthesise the α-bromo vinyl ethers.



Scheme 2

We now report a synthesis of 6-bromo-3,4-dihydro-2*H*-pyrans from tetrahydropyran-2-ones **4a**–**d** based on the Ni(0)-catalysed coupling of enol triflates **5a**–**d** with LiBr (Scheme 3) and their halogen-metal exchange with *t*-BuLi to the corresponding 6-lithio-3,4-dihydro-2*H*-pyrans **7a**–**d**. In a typical procedure a mixture of *N*-phenyltrifluoromethanesulfonimide (1.2 equiv) and tetrahydropyran-2-one **4a** (1 equiv) in THF was added dropwise to a solution of KHMDS (1.4 equiv) in THF at –78 °C. Without aqueous workup, the reaction mixture was concentrated in vacuo and the residue filtered through an alumina plug using hexanes-ether to yield the enol triflate **5a**. Care must be taken to avoid the removal of all traces of solvent from the enol triflate, otherwise decomposition takes place. The crude enol triflate **5a** was then immediately treated with LiBr (12 equiv) and $[Ph_3P]_2Ni(0)$ (10 mol%) prepared by reaction of DIBALH with $Ni(acac)_2$ according to the procedure of Mori and co-workers.[20] After 12 h at room temperature, the labile 6-bromo-3,4-dihydro-2*H*-pyran **6a** was isolated by a standard aqueous workup and purified by column chromatography. The NMR spectra of **6a**–**d** revealed the presence of triphenylphosphine and other minor contaminants (up to 10%) but attempts to remove them by further chromatography or distillation resulted in products of worse quality with poor mass recovery. Therefore, the labile α-bromo dihydropyrans were used immediately in the next step.

The α-bromo dihydropyrans **6a**–**d** underwent halogen-metal exchange on treatment with *t*-BuLi (2 equiv) at –78 °C in Et_2O to give the α-lithiated dihydropyrans **7a**–**d**. Quenching with D_2O, gave the 6-deuterio derivatives **8a**–**d** in 49–61% overall yield from the lactones **4a**–**d**. By the same protocol, the deuterated 4,5-dihydrobenzo[*b*]oxepine **10** was prepared in 62% overall yield from the corresponding lactone **9**. The sequence fails with

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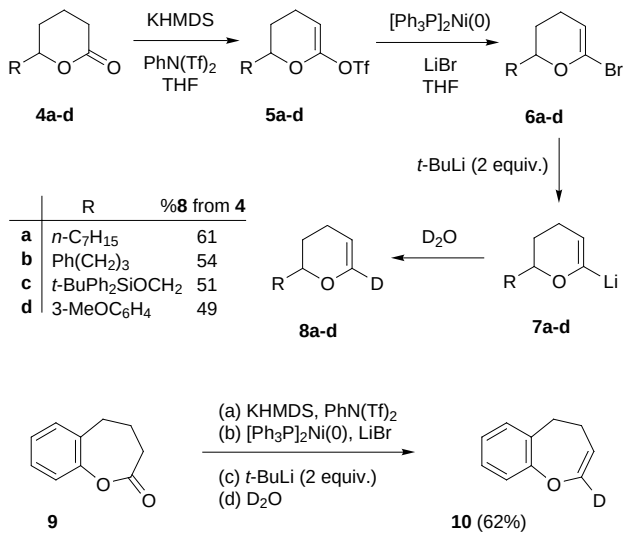
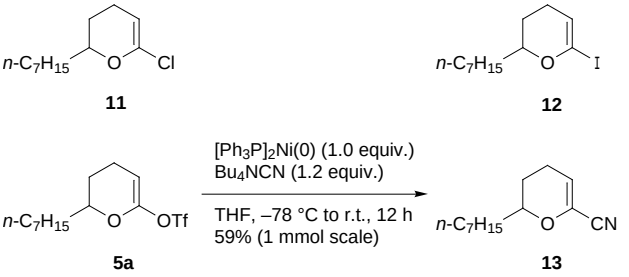


Scheme 3

5-membered ring lactones because the requisite enol triflates cannot be formed.

The lactone **4a** was converted to the corresponding chloro- and iodo-analogues **11** and **12** using LiCl and LiI respectively. The chloro derivative **11** was more stable than bromo derivative **6** but halogen metal exchange required 6 equivalents of *t*-BuLi and 12 equivalents of THF at room temperature for complete conversion to the lithium species. The iodo analogue **12** could only be handled in dilute solution and was too unstable to be practical. Finally, in order to demonstrate that nucleophiles other than halogen participate in the Ni(0)-catalysed coupling, we prepared the nitrile **13** in 59% yield as shown in Scheme 4.



Scheme 4

In conclusion, we have devised a 3-step synthesis of cyclic α-lithiated enol ethers from readily available lactone precursors based on the Ni(0)-catalysed coupling of halide ions with enol triflates. The prime advantages are the use of Ni(0) rather than Pd(0) in the crucial coupling step and the avoidance of toxic and expensive tin intermediates. However, the instability of the enol triflate and α-bromo dihydropyran intermediates limits the scale of the sequence.

General Procedure for the Preparation of Enol Triflates 5a–d

To a solution of KHMDS (0.41 M in toluene, 1.4 equiv) in THF (1.7 mL) at –78 ºC was added a mixture of *N*-phenyltrifluoromethanesulfonimide (1.2 equiv) and the lactone **4a**–**d** (1 equiv) in THF (3 mL) over a period of 1 h. The reaction mixture was allowed to stir for 15 min at –78 °C and then concentrated in vacuo to about one quarter of its original volume and the residue was flushed through an alumina plug (deactivated with 5% water) using hexanes–Et_2O (0.5% Et_3N) to yield the enol triflate. The eluent was concentrated in vacuo to a volume of 2 mL and used immediately in the next step. If all of the solvent is removed, the enol triflates decompose rapidly. For the purposes of calculating quantities of reagents in the next step, we assumed a yield of 100%.

General Procedure for the Preparation of α-Bromo Dihydropyrans 6a–d

A solution of DIBALH (1.5 M in toluene, 0.2 mmol) was added dropwise to a mixture of $Ni(acac)_2$ (0.1 mmol) and PPh_3 (0.2 mmol) in THF (25 mL), at 0 °C. The dark red-brown mixture was stirred at r.t. for 15 min, then cooled to –78 °C. To the mixture was added LiBr (12 mmol) and THF (9.2 mL) and enol triflate (1 mmol) in THF (3 mL/1 mmol) at –78 °C. The dark red-brown mixture was allowed to warm gradually to r.t. overnight. Saturated aqueous $NaHCO_3$ (20 mL) was added and the mixture filtered through celite and the layers separated. The aqueous layer extracted with Et_2O (3 × 100 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was rapidly flushed through an alumina plug (deactivated with 5% water) using hexanes–Et_2O (0.5% of Et_3N). The polarity of the eluent was adjusted according to the polarity of the product. NMR spectroscopic analysis of the crude product revealed up to 10% contamination by triphenylphosphine and other minor impurities. Attempts to remove the impurities by chromatography resulted in substantial loss of material and product degradation; therefore, the crude α-bromo dihydropyrans were used immediately in the next step. For the purposes of calculating quantities of reagents in the next step, we assumed a yield of 100%.

A sample of 6-bromo-2-heptyl-3,4-dihydro-2*H*-pyran (**6a**) (ca 95% pure) gave the following spectroscopic data: IR (film): 1647 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ = 4.97 (1 H, br dd, *J* = 4.6, 2.9 Hz, C=CH), 3.78 (1 H, m, OCH), 1.80–1.27 (16 H, m), 1.02 (3 H, t, *J* = 8 Hz, CH_3); ^{13}C NMR (100 MHz, C_6D_6): δ = 132.8 (C), 101.9 (CH), 81.0 (CH), 35.4 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 27.4 (CH_2), 25.8 (CH_2), 23.4 (CH_2), 23.0 (CH_2), 14.7 (CH_3); LRMS (EI + mode): *m/z* (%) = 260, 262 (M^+, 20), 181 (20), 163 (25), 135 (17), 111 (20), 83 (62), 69 (60), 55 (100), 41 (50); HRMS (EI + mode): Found, ^{79}Br, 260.0776. $C_{12}H_{21}BrO$ requires M, 260.0775.

General Procedure for Halogen-metal Exchange Reactions

To a solution of the α-bromo dihydropyrans **6a**–**d** in anhydrous diethyl ether was added *t*-BuLi (1.5 M solution in pentane, 2 equiv) at –78 °C. The reaction mixture was stirred for about 30 min at –78 °C whereupon the intermediate 6-lithio-3,4-dihydro-2*H*-pyrans **7a**–**d** were quenched with D_2O. Standard aqueous workup returned the α-deuterated dihydropyrans **8a**–**d** after column chromatography or Kugelrohr distillation.

2-Heptyl-3,4-dihydro-2*H*-pyran-6-*d* (8a): IR (film): 1632 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ = 4.71 (1 H, m, CD=C*H*), 3.78 (1 H, apparent tt, *J* = 7.8, 4.5 Hz, OCH), 1.90–1.15 (16 H, m), 1.01 (3 H, t, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75 MHz, C_6D_6): δ = 144.9 (CD), 100.2 (CH), 75.6 (CH), 36.2 (CH_2), 32.6 (CH_2), 30.4 (CH_2), 30.1 (CH_2), 28.7 (CH_2), 26.1 (CH_2), 23.5 (CH_2), 20.7 (CH_2), 14.7 (CH_3).

2-(3-Phenylpropyl)-3,4-dihydro-2*H*-pyran-6-*d* (8b): IR (film): 1630 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ = 7.12–6.94 (5 H, m, Ph), 4.68 (1 H, ddd, *J* = 4.6, 2.3, 0.8 Hz, CD=C*H*), 3.71 (1 H, apparent tt, *J* = 8.2, 4.8 Hz, OCH), 2.38 (2 H, apparent t, *J* = 7.4 Hz, CH_2Ph), 1.90–1.20 (8 H, m); ^{13}C NMR (75 MHz, C_6D_6): δ = 144.9 (CD),

143.1 (C), 129.1 (2 CH), 129.0 (2 CH), 126.5 (CH), 100.2 (CH), 75.6 (CH), 36.5 (CH_2), 35.6 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 20.6 (CH_2).

2-[(*tert*-Butyldiphenylsilyloxy)methyl]-3,4-dihydro-2*H*-pyran-6-*d* (8c): IR (film): 1651 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ = 7.93–7.87 (4 H, m, ArH), 7.35–7.31 (6 H, m, ArH), 4.64 (1 H, dd, *J* = 4.4, 2.6 Hz, CD=C*H*), 4.01–3.80 (3 H, m, OCH and CH_2OSi), 1.85-1.71 (4 H, m), 1.28 (9 H, s, *t*-Bu); ^{13}C NMR (75 MHz, C_6D_6): δ = 142.9 (CD), 134.7 (4 CH), 132.9 (2 C), 128.6 (4 CH), 124.4 (2 CH), 98.6 (CH), 74.3 (CH), 65.2 (CH_2), 25.7 (3 CH_3), 23.2 (CH_2), 18.2 (C), 18.2 (CH_2).

2-(3-Methoxyphenyl)-3,4-dihydro-2*H*-pyran-6-*d* (8d): IR (film): 1650, 782 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ = 7.22 (1 H, apparent t, *J* = 7.9 Hz), 7.16 (1 H, br s with fine splitting), 7.02 (1 H, d, *J* = 7.7 Hz), 6.85 (1 H, apparent ddd, *J* = 8.2, 2.6, 0.8 Hz), 4.81 (1 H, dd, *J* = 7.2, 5.1 Hz, C2H), 4.70–4.76 (1 H, m), 3.47 (3 H, s, OCH_3), 2.11–1.77 (4 H, m); ^{13}C NMR (75 MHz, C_6D_6): δ = 160.7 (C), 144.9 (CD), 144.7 (C), 129.9, 118.7, 113.6, 112.2, 100.7, 77.4 (all CH), 55.0 (CH_3), 31.2 (CH_2), 20.8 (CH_2).

4,5-Dihydrobenzo[*b*]oxepine-2-*d* (10): IR (film): 1640 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ = 7.18 (1 H, d, *J* = 7.9 Hz, ArH), 7.08–7.00 (1 H, m, ArH), 6.95 (2 H, m), 4.61 (1 H, t, *J* = 3.97 Hz, CH=CD), 2.87 (2 H, t, *J* = 5.8 Hz, $ArCH_2$), 2.11 (2 H, dt, *J* = 7.2, 4.6 Hz, CD=CHCH_2); ^{13}C NMR (75 MHz, C_6D_6): δ = 159.3 (CO), 144.0 (CD), 134.1 (C), 130.5, 127.8, 124.4, 121.0, 108.4 (all CH), 33.2 (CH_2), 28.0 (CH_2).

6-Heptyl-5,6-dihydro-4*H*-pyran-2-carbonitrile (13): A solution of DIBALH (1.3 mL, 2 mmol, 1.5 M in toluene, 200 mol%) was added dropwise to a mixture of $Ni(acac)_2$ (0.257 g, 1 mmol, 100 mol%) and PPh_3 (0.524 g, 2 mmol, 200 mol%) in toluene (2.3 mL), at 0 °C. The dark red-brown mixture was stirred at r.t. for 15 min., then cooled to –78 °C. To the reaction mixture was added THF (4 mL) followed by a solution of tetrabutylammonium cyanide (0.331 g, 1.2 mmol, 1.2 equiv) and enol triflate **5a** (approximately 1 mmol) in THF (5 mL) over a period of 1.5 h at –78 °C. The dark red-brown mixture was allowed to warm gradually to r.t. overnight. The reaction mixture was hydrolysed with saturated aqueous $NaHCO_3$ (20 mL) and extracted with Et_2O (3 × 100 mL). Filtration through Celite was necessary to separate the layers. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography on alumina deactivated with 5% water, eluting with hexanes containing 0.5% of Et_3N, to give the nitrile **13** (0.122 g, 59% over 2 steps): IR (film): 2231, 1643 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ = 5.11 (1 H, ddd, *J* = 4.8, 3.5, 1.0 Hz, C=CH), 3.42–3.34 (1 H, m, OCH), 1.54–1.05 (16 H, m), 1.03 (3 H, t, *J* = 7 Hz, CH_3); ^{13}C NMR (100 MHz, C_6D_6): δ = 130.5 (C), 116.0 (CH), 115.7 (CN), 77.4 (CH), 35.3 (CH_2), 32.5 (CH_2), 30.2 (CH_2), 29.9 (CH_2), 26.6 (CH_2), 25.6 (CH_2), 23.4 (CH_2), 21.1 (CH_2), 14.7 (CH_3).

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