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Synthesis of Functionalised Bicyclo[4.4.0] and Spiro [5.4] Compounds by Tin-Mediated Radical Cyclization†

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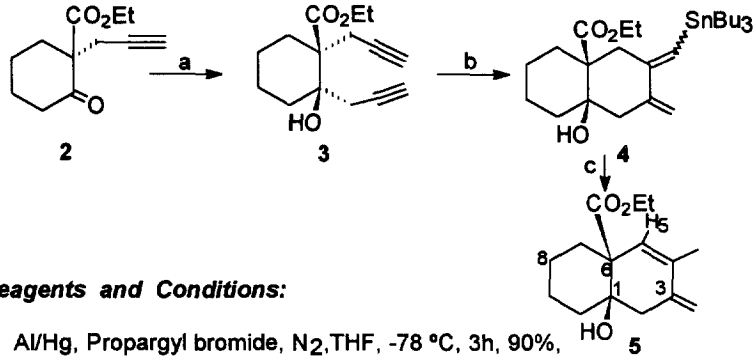
Abstract: **Functionalised bicyclo[4.4.0] system 5, and spiro [5.4] system 10 were synthesised from the bispropargyl compound 3 and the mono-propargyl compound 6 by tin- mediated radical cyclization.**

Many naturally occurring compounds posses carbon frameworks, comprising of bicyclic, spirocyclic ring systems and hence have gained considerable interest from a synthetic point of view.[1] The synthesis of several functionalised molecules with well-defined stereochemistry have become feasible *via* radical reactions, particularly those involving tin-mediated intramolecular cyclization.[2] As part of our ongoing research programme,[3] we became interested in employing a tin-mediated radical cyclization reaction for the construction of functionalised bicyclic and spirocyclic systems.

In this paper, we report the synthesis and tri-*n*- butyltin-mediated radical cyclization reaction of the bispropargyl compound **3** and the monopropargyl compound **6**. The synthesis of the bispropargyl compound **3** and its radical cyclization reaction is outlined in scheme **1**. 2-Carbethoxy cyclohexanone **1**[4] was propargylated[5] at the 2-position with propargyl bromide in presence of potassium-*t*-butoxide in *t*-butanol to yield 2-carbethoxy-2-propargyl cyclohexanone **2** in 70% yield. The IR spectrum of **2** showed a peak at 3300 cm^{-1} (-C≡C-H) and its ^1H NMR showed a peak at δ 2.5; this triplet for acetylenic proton confirms the presence of the propargyl unit in compound **2**. Addition of propargyl aluminium sesquibromide solution to compound **2** at -78 °C under inert condition yields bispropargyl compound **3** as a solid (m.p: 110-112 °C) after silica gel column purification. Compound **3** showed IR absorptions at 3650 (OH), 3300(-C≡C-*H*), 1725-1730 (ester carbonyl) cm^{-1}. Its ^1H NMR showed peaks at δ 3.1, a singlet for the -OH proton and two triplets at δ 2.0 and δ 1.9 for the two acetylenic protons and its ^{13}C



Reagents and Conditions:

a) Al/Hg, Propargyl bromide, N_2,THF, -78 °C, 3h, 90%,
b) 2.2 equiv. *n*-Bu_3SnH, AIBN, N_2, 80-85 °C, 5-10 min.80%
c) 4 equiv. PPTS, CH_2Cl_2, rt, 48h, 100%

Scheme 1

NMR showed peaks at δ 73.0 for the 4°- carbon with the -OH, and δ 53.4 for the 4° -carbon attached to the ester unit while peaks at δ 71.6 and δ 70.8 showed the presence of two acetylenic terminal carbons. Mass spectrum of compound **3** showed a molecular ion peak at *m/z* 248 (M^+). Radical cyclization of compound **3** (scheme 1) under inert conditions with 1.2 equivalent of tri- *n*- butyltin hydride (TBTH)[9] and cat. amount of azobisisobutyronitrile (AIBN) at 80-85 °C afforded a number of inseparable products. Radical cyclization of **3** with 2.2 equivalents of tin hydride was exothermic and went to completion within 5- 10 min. (TLC showed the complete disappearance of starting material and formation of a less polar product and its IR spectrum showed the disappearance of -C≡C-H absorptions at 3300cm^{-1}). The crude vinyl stannane[6t] **4** thus obtained was subjected to protiodestannylation without further purification with pyridinium-*p*-toluenesulfonate (PPTS) in dichloromethane to afford compound **5**, which was purified by column chromatography (silica gel). The IR spectrum of compound **5** showed absorptions at 3520(OH), 1630 (exomethylene), 1730 (ester carbonyl)cm^{-1}. The ^1H NMR of **5** showed a broad multiplet at δ 5.8 for the H_5 proton, and at δ 4.9-5.0 a multiplet for the exomethylene protons and its mass spectrum showed a molecular ion peak at *m/z* 250 (M^+). It also showed satisfactory elemental analysis. The formation of **5** from **4** can be explained by the isomerization of one of the exocyclic double bonds in **4** during the protiodestannylation step. The relative stereochemistry of compound **5** was assigned based on literature analogy.[3]

The formation of **4** from **3** by the addition of the tin hydride to **3** can be explained by figure **1**. Addition of tri-*n*-butyltin radical to one of the propargyl units of compound **3** would give a radical, which upon 6-*exo* cyclization give another radical

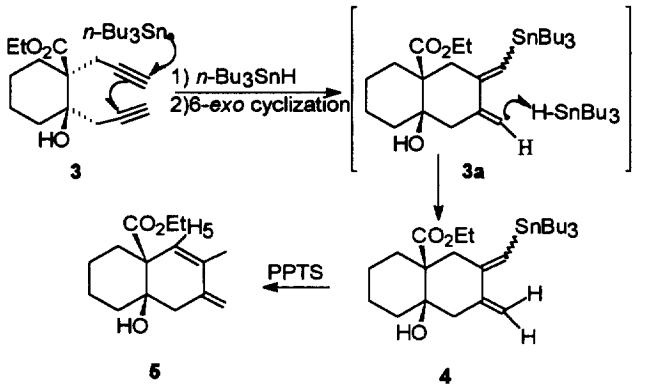
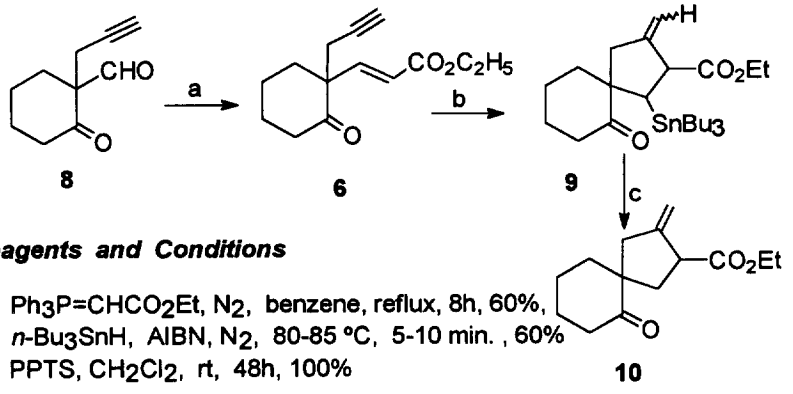


Figure 1

intermediate **3a** which on quenching by a second molecule of tin hydride leads to compound **4**. It is possible to extend this methodology to other similarly functionalised cyclic alkanes to give alternative bicyclic compounds with an exocyclic double bond and, in turn, to the synthesis of larger polycycles.

The synthesis of monopropargyl compound **6** and its radical cyclization reaction is schematically represented in scheme **2**. 2-Formyl cyclohexanone **7**[7] was propargylated[5] at 2-position as described for compound **1** to yield **8** in 75% yield after purification by vacuum distillation. Compound **8** showed IR absorption peak at 3300 cm^{-1} for the presence of a -C≡C-H group. Its ^1H NMR showed peaks at δ 2.6 for the -C≡C-H proton and at δ 9.5, singlet for the formyl proton. Wittig reaction of compound **8** with (carbethoxymethylene) triphenylphosphorane in refluxing benzene afforded compound **6**.



Reagents and Conditions

a) $Ph_3P=CHCO_2Et$, N_2, benzene, reflux, 8h, 60%,
b) *n*-Bu_3SnH, AIBN, N_2, 80-85 °C, 5-10 min., 60%
c) PPTS, CH_2Cl_2, rt, 48h, 100%

Scheme 2

Radical cyclization of compound **6** under inert conditions with 1.2 equivalent of

TBTH and cat. amount of AIBN at 80-85 °C afforded **9**. The crude vinyl stannane[6t] **9** thus obtained was subjected to protiodestannylation as described for compound **4** to afford compound **10**, which was purified by column chromatography. The IR spectrum of the compound **10** showed peaks at 1730 (ester carbonyl), 1690 (carbonyl) and 1620 (double bond) cm^{-1}. The ^1H NMR of compound **10** showed a peak at δ 4.8-5.0 as a multiplet for the exomethylene protons. Its mass spectrum showed a molecular ion peak at *m/z* 236 (M^+) and also showed satisfactory elemental analysis. The formation of **9** from **6** by the addition of the tin hydride in a 5-*exo-trig* fashion to **6** can be explained by figure **2**. Addition of the tri-*n*-butyltin radical to the alkene unit of compound **6** would give a radical intermediate **6a**, which upon intramolecular 5-*exo* cyclization gives compound **9**.

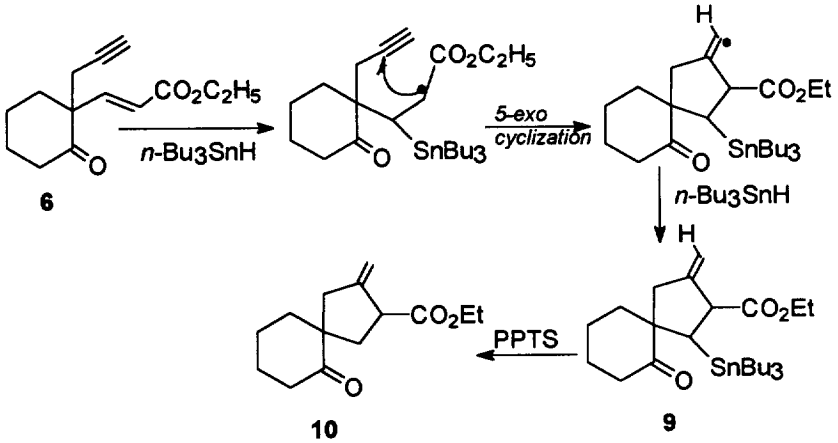


Figure 2

It is possible to extend this methodology to other similarly functionalised cyclic alkanes to give spirocyclic compounds with an exocyclic double bond and, in turn, to the synthesis of functionalised spirocycles. In conclusion, a general method of synthesis of functionalised bicyclic and spirocyclic systems from cycloalkanone propargyl derivatives by tin-mediated radical cyclization has been achieved. Further studies in this direction are underway.

EXPERIMENTAL

General Considerations

All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 598 spectrophotometer. ^1H NMR spectra were recorded either at 90 MHz on a Varian EM-390 or at 400 MHz on a JEOL GSX 400 spectrophotometer or at 200 MHz on a BRUKER DPX 200 and ^{13}C NMR spectra were recorded at 22.5 MHz on a JEOL FX 90Q

spectrophotometer or at 50.3 MHz on a BRUKER DPX 200 as indicated. Chemical shifts are reported in ppm(δ) with TMS as standard and coupling constants are expressed in Hertz. Mass spectra were recorded on a JEOL JMS-DX 303 HF mass spectrometer. Elemental analysis was performed using a Perkin-Elmer 240B elemental analyser. Thin layer chromatograms (TLC) were developed on glass plates coated with silica gel-G (ACME) of 0.25mm thickness and visualised with iodine. Column chromatography was carried out with SiO_2 (ACME, 100-200 mesh) using hexane-ethyl acetate mixture as eluent. For dry experiments glasswares used were thoroughly dried in an air oven, cooled and assembled under a stream of nitrogen. The organic extracts of crude products were dried over anhydrous $MgSO_4$. Solvents were reagent grade and were purified according to literature procedure[8]. Unless otherwise stated all reported compounds were homogeneous liquids. Tri-*n*-butyltin hydride[9] (TBTH) was prepared according to the literature procedure.

General procedure for propargylation[5] of ketones 1 and 7 : *Synthesis of* 2 *and* 8

To a solution of potassium-*t*- butoxide (6.5g, 1equiv., 0.0580 mol) in *t*-butanol (100mL) the cycloalkanones (10g, 1 equiv., 0.0580 mol) in *t*- butanol (25mL) were added over a period of 15 min. at room temperature under nitrogen atmosphere. Stirring was continued for an additional 15 min. and freshly distilled propargyl bromide (1 equiv.) was added. After refuxing for 6h, the precipitated KBr was filtered off. Concentration of the filtrate under reduced pressure gave colourless viscous liquids which upon vacuum distillation afforded the pure propargylated products.

***Data for compound* 2**

8.5g,; Yield : 70%; b.p: 110-112 °C / 5mm; IR(CCl_4, ν_{max}) cm^{-1}: 3300(-C≡C-H), 2100(-C≡C-), 1725-1730 (ester carbonyl), 1705(cyclic carbonyl); ^1H NMR (90MHz, $CDCl_3$ / TMS): δ 4.2(q, *J*=7.33, 2H, $CO_2CH_2CH_3$), 2.5(t, *J*= 2.44, 1H, C≡C-H), 1.4-1.8(m, 10 H, *methylenes*), 1.3(t, 3H, *J*=7.33, $CO_2CH_2CH_3$); Mass Spectrum *m/z* : 208 (M^+).

***Data for compound* 8**

7.8g; Yield :60%; b.p: 75-80 °C / 0.5mm; IR(CCl_4, ν_{max}) cm^{-1}: 3300(-C≡C-H), 2100(-C≡C-), 1710(carbonyl), 1705(formyl); ^1H NMR (90MHz, $CDCl_3$/TMS) : δ 9.5 (s, 1H, CHO), 2.6(t, *J*=2.43, 1H, C≡C-H), 1.4-1.8(m, 10H, *methylenes*); Mass Spectrum *m/z* : 164 (M^+).

Wittig olefination reaction of 8 : *Synthesis of* 6

To a solution of **8** (10.16g, 1 equiv., 0.062 mol) in dry benzene (50 mL) was added (carbethoxymethylene) triphenylphosphorane (21.28g, 1 equiv., 0.062 mol). The solution was

refluxed for 8h under nitrogen atmosphere. The solution was cooled and the solvent was removed under reduced pressure to give a thick brown mass. Digestion of the mass with petroleum ether (10x25 mL) and concentration of the extract under reduced pressure afforded the olefinated compound. The olefinated compound **6** was purified by passing through a silica gel column using hexane-ethyl acetate (95:5) as eluent.

***Data for compound* 6**

8.75g; Yield : 60% ; IR(CCl_4, ν_{max}) cm^{-1} : 3300(-C≡C-H), 2100(-C≡C-), 1725-1730(ester carbonyl), 1700(carbonyl), 1630(enone double bond); ^1H NMR(400MHz, $CDCl_3$/TMS): δ 7.01(d, *J*=15.8, 1H, H_7), 5.82(d, *J*=15.8, 1H, H_8), 4.2(q, *J*=7.33, $CO_2CH_2CH_3$, 2H), 2.55(t, 2H, H_{12}), 2.3-2.5(m, 4H, *methylenes*), 2.03(dd, 1H, -C≡C-H), 1.6-1.8 (m, 4H, *methylenes*), 1.3(t, *J*=7.33, $CO_2CH_2CH_3$, 3H); ^{13}C NMR (100. 6 MHz, $CDCl_3$/TMS): δ 206.8, 165.2, 148.0, 122.6, 79.4, 71.1, 62.4, 53.4, 39.7, 35.7, 26.6, 26.2, 21.0, 13.7 ; Mass Spectrum *m/z* : 235 (M^+); Elemental Analysis: Calcd for $C_{14}H_{19}O_3$: C, 71.45 , H, 8.14 %, Found C, 71. 50, H, 8.22 % .

Propargylation of 2: *Synthesis of* 3

Aluminium amalgam was prepared from aluminium foil (0.972g, 0.036 mol, 3 equiv.) and mercuric chloride (10 mg, cat. amount) in THF (15 mL) by vigorously stirring the mixture at room temperature for 1h under nitrogen atmosphere. A solution of propargyl bromide (4.284g, 0.036, 3equiv.) in dry THF (25 mL) was slowly added to a stirred suspension at such rate so as to maintain a temperature of 30-40 °C, and after the addition stirring at 40 °C was continued until a dark grey solution was obtained (*Ca.* 1h). The propargylaluminium sesquibromide solution thus obtained was added to a solution of the ketone **2** (2.469g, 0.012mol) in dry ether (100mL) at -78 °C and the reaction mixture was stirred at that temperature for 3h, then poured into ice water and extracted with ether (4x25mL). The combined ether extract was washed with brine, dried and concentrated. The residual liquid thus obtained was subjected to column chromatography over silica gel to afford pure propargylated compound **3** .

***Data for compound* 3**

2.52g; Yield : 90% : m.p : 110-112 °C ; IR (CCl_4, ν_{max}) cm^{-1} : 3650(OH), 3300 (-C≡C-H), 2100(-C≡C-), 1725-1730(ester carbonyl); ^1H NMR (400MHz, $CDCl_3$/TMS): δ 4.2(q, *J*=7.33, $CO_2CH_2CH_3$, 2H), 3.1(s, OH, 1H), 2.9(d, H_A , 1H), 2.7(d, $H_{A'}$, 1H), 2.5(d, H_B , 1H), 2.3(d, $H_{B'}$, 1H), 2.0(t, H_C , 1H), 1.9(t, $H_{C'}$, 1H), 1.3-1.8(m, *methylenes*, 6H), 1.2(t, *J*=7.33, $CO_2CH_2CH_3$, 3H); ^{13}C NMR (100. 6 MHz, $CDCl_3$/TMS): δ 174.7, 80.6, 76.3, 73.0, 71.6, 70.8, 61.2, 53.4, 31.6, 30.1, 27.8, 21.8, 21.1, 20.5, 14.0; Mass Spectrum *m/z* : 248 (M^+). Elemental Analysis: Calcd for

$C_{15}H_{20}O$: C, 72.54 , H, 8.12 %, Found C, 72.46, H, 8.07 %.

General procedure for radical cyclization of 3 and 6 : *Synthesis of* 5 *and* 10

A flame dried 100 mL round bottomed flask equipped with a magnetic stirring bar was flushed with analar nitrogen and the propargylated alcohol (0.0021 mol, 1 equiv.), tributyltin hydride (TBTH, 0.0030 mol, 1.2 equiv.) and azobisisobutyronitrile (AIBN, 0.001mol) were added. The entire assembly was lowered into an oil bath maintained at a temperature between 75-85 °C, and the mixture was stirred. After an induction period of less than 5 min. an exothermic reaction occurred which produced a small amount of gas and the reaction mixture was allowed to stir for an additional 10 min, at which point TLC showed the reaction to be essentially complete (also by IR). The unpurified vinylstannane thus obtained was subjected as such to protiodestannylation.

To the crude vinylstannane in methylene chloride (20 mL) was added pyridinium *p*-toluene sulphonate (PPTS, 4 equiv.) and the reaction mixture was stirred at room temperature for 48h at which time TLC analysis showed complete disappearance of the starting material and the formation of a more polar compound. The solvent was removed under reduced pressure, and the residue was extracted with hexane-ethyl acetate (2:3, 10x25 mL). The combined extracts were concentrated under reduced pressure, and the crude product was chromatographed over silica gel to give destannylated product.

***Data for compound* 5**

Yield : 80% ; IR(CCl_4) cm^{-1}: 3520 (OH), 1730(ester carbonyl), 1630 and 1620(double bonds) ; ^1H NMR(200.1 MHz,): δ 5.8(m, 1H, H_5), 4.9-5.0(m, 2H, *exomethylene*), 4.2(q, 2H, *J*=7.33, $CO_2CH_2CH_3$), 4.0(brs, 1H, OH), 2.2(m, 3H, CH_3), 1.2-1.8(m, 10H, *methylenes*), 1.1(t, 3H, *J*=7.33, $CO_2CH_2CH_3$); ^{13}C NMR(50.3 MHz): δ 13.8, 20.6, 21.6, 27.5, 30.8, 32.1, 41.2, 47.3, 55.0, 60.4, 83.7, 102.8, 117.4, 134.3, 174.4 ; Mass spectrum *m/z* : 250 (M^+) ; Elemental Analysis: Calcd. for $C_{15}H_{22}O_3$: C, 71.95 , H, 8.86 %, Found C, 72.10, H, 8.71 % .

***Data for compound* 10**

Yield : 60% ; IR(CCl_4) cm^{-1}: 3520 (OH), 1730(ester carbonyl), 1690(cyclic carbonyl) and 1620(double bond) ; ^1H NMR(200.1 MHz): δ 4.8-5.0(m, 2H, *exomethylene*), 4.2(q, 2H, *J*=7.33, $CO_2CH_2CH_3$), 2.5(m, 2H, *methylenes*), 1.2-1.8(m, 11H, *methylenes*), 0.9(t, 3H, *J*=7.33, $CO_2CH_2CH_3$); ^{13}C NMR(50.3 MHz): δ 209.2, 166.1, 140.3, 133.6, 121.2, 110.4, 103.8, 80.3, 64.5, 59.7, 28.8, 22.9, 17.0, 13.8 ; Mass Spectrum *m/z* : 236 (M^+) ; Elemental Analysis: Calcd for $C_{14}H_{20}O_3$: C, 71.14 , H, 8.54 %, Found C, 71. 10, H, 8.47 %.

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