Use of the Bifunctional Reagent (Z)-4-Iodo-1-(tributylstannyl)but-1-ene: A New Cyclohexenone Annulation Method

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Abstract: A new cyclohexenone annulation method, based on the use of the bifunctional reagent (*Z*)-4-iodo-1-(tributylstannyl)but-1-ene (**6**) and exemplified by conversion of the substrate **8** into the annulated products **13** and **18** and of the starting materials **19–23** into the products **34–38**, respectively, is described.

Functionalized six-membered carbocyclic rings are very common structural features of many classes of natural products and, over the years, a number of methods have been developed for the conversion of ketones into annulated cyclohexenones, as indicated by the generalized transformation of **1** into **2** (Scheme 1).¹⁻⁶ Although the best known of these methods is probably the Robinson annulation,¹⁻⁶ other protocols have also been devised.¹⁻⁵ We report herein a new six-membered ring annulation method that is based on the theoretical combination of the two acceptor–donor⁷ synthons **3** and **4**, followed by oxidative conversion of the resultant tertiary allylic alcohol **5** into the corresponding enone **2**. Clearly, the ketone **1** correlates with the synthon **3**, while we have employed (*Z*)-4-iodo-1-(tributylstannyl)but-1-ene (**6**) as the synthetic equivalent of the synthon **4**.



Scheme 1

The iodide 6^8 was readily prepared by treatment of the corresponding alcohol 7^9 with Ph₃P•I₂ in the presence of imidazole¹⁰ (Equation 1).





The new annulation method is illustrated by the preparation of the enone ketal **13** (Scheme 2). The dimethylhydrazone **8**¹¹ is readily obtained¹² from the corresponding, commercially available ketal ketone. Treatment of **8** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF), followed by addition of hexamethylphosphoramide (HMPA) and the bifunctional reagent **6**, afforded the alkylated product **9**.¹³ Iodo-destannylation¹⁴ of the latter (crude) material afforded **10**, which, upon treatment with buffered acetic acid in THF–water,¹⁵ provided the keto iodide **11**. The conversion of **8** into **11**, which was accomplished

without full characterization of the intermediates **9** and **10**, proceeded in 92% overall yield.





Slow addition of a solution of intermediate **11** in THF to a solution of butyllithium (2.5 equivalents) in cold THF,¹⁶ followed by a reaction time of one hour and workup with aqueous NaHCO₃, produced an excellent yield of the alkenol **12**, which proved to be a mixture of two epimers in a ratio of approximately 1:1. Treatment of this material with pyridinium chlorochromate (PCC)¹⁷ on alumina¹⁸ effected the required rearrangement–oxidation sequence¹⁹ and provided the enone ketal **13** (89%). Thus, the overall yield of the annulation product **13** from the hydrazone **8** was over 75%.

The enone 18, related in structure to 13 but possessing an angular methyl group, was also readily prepared via this methodology (Scheme





3). Hydrolysis (NaOAc, HOAc, H₂O, THF) of the hydrazone **9** gave the ketone **14** (>90% yield). Sequential treatment of the latter material with potassium *tert*-butoxide (THF, 60 °C) and excess MeI (THF, -78°C) produced, as the major product (70% yield),²⁰ the mono-alkylated compound **15**, which was transformed smoothly into the corresponding iodide **16**. Butyllithium–mediated cyclization of **16** provided a single, crystalline (mp 89-91 °C) allylic alcohol **17**,²¹ which, upon reaction with PCC on alumina, afforded the enone **18** in 76% overall yield from the keto stannane **15**.

Additional examples of the new annulation method are summarized in the Table. The hydrazones **19–23** were converted into the corresponding iodo ketones **24–28** via three-step protocols very similar to that outlined in Scheme 2 for the transformation of **8** into **11**. Thus, in each case, the starting material was alkylated with the iodide **6**, the crude product was immediately subjected to iododestannylation, and the resultant hydrazone–iodide was hydrolyzed to the required iodo ketone. The intermediate products (corresponding to **9** and **10** in Scheme 2) were used as crude materials and were not fully characterized. The yields of **24–28** given in the Table represent overall yields from the hydrazones **19–23**, respectively. It should be noted that the iodo ketone derived from the hydrazone **21** consisted of a mixture of epimers with respect to the stereochemical orientation of the newly introduced side chain. Equilibration (NaOMe, MeOH, room temperature) of this material provided **26**.

Butyllithium-mediated cyclization of each of the iodo ketones 24-28 was accomplished as outlined earlier for the conversion $11\rightarrow12$ (Scheme 2). The bicyclo[5.4.0]undecenol 33 (cyclization of 28) was obtained as a mixture of diastereomers,²² while each of the allylic alcohols 29-32 proved to be a single (racemic) substance. Although the relative configuration of the carbinol stereogenic center in each of 29-32 was not definitively established, molecular modelling suggests that the newly formed ring fusion in 29 and 30 should be *cis*, while that in 31 and 32 is likely to be *trans.*²³

Although the conversions $11\rightarrow 12$, $16\rightarrow 17$, and $26\rightarrow 31$ were very clean and produced no detectible byproducts, the allylic alcohols 29, 30, 32, and 33 were accompanied by minor amounts (~8%, 17%, 14%, and 6%, respectively) of the corresponding uncyclized materials in which the iodine in the starting material had been replaced by a hydrogen. Fortunately, these substances were readily separated from the required alcohols by means of silica gel chromatography.

Oxidation of the tertiary allylic alcohols **29–33** with PCC on alumina provided the corresponding cyclohexenones **34–38** in moderate to excellent yields. The volatility of **34** probably accounts for the lower yield in this case. The reaction involving substrate **32** produced a number of minor byproducts. Since the tertiary hydroxyl group in **32** is also both allylic and benzylic, it is likely that this material is quite susceptible to conversion into a carbocation. The observed occurrence of minor processes in competition with the desired oxidation reaction is, therefore, not unexpected.

In summary, a new cyclohexenone annulation method has been developed. The efficacy of the method has been demonstrated by the annulation of substrates containing five- (19, 20), six- (8, 21, 22), and seven-membered rings (23). This protocol should find useful applications in the synthesis of structurally complex molecules.

Experimental Section

Preparation of the ketal alcohols 12: To a cold (-78 °C), stirred solution of BuLi (1.4 mmol) in dry THF (28 mL, argon atmosphere) was added dropwise, via a Teflon[®] cannula, a solution of the keto iodide **11**

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(217 mg, 0.574 mmol) in dry THF (2 mL). The reaction mixture was stirred at -78 °C for 1 h and then was treated with saturated aqueous NaHCO3 (15 mL). The mixture was warmed to room temperature, diluted with diethyl ether (15 mL) and water (15 mL), and the layers were separated. The aqueous layer was extracted three times with diethyl ether. The combined organic extracts were washed with brine, dried (MgSO₄), and concentrated. The ¹H NMR spectrum of the crude oil indicated a 1:1 mixture of epimeric alcohols 12, as determined by the integration of the vinyl signals for each diastereomer. Flash chromatography (10 g TLC-grade silica gel, 1:1.5 petroleum etherdiethyl ether) of this material afforded, after concentration of the appropriate fractions and removal of traces of solvent (vacuum pump), the allylic alcohols 12 (140 mg, 96%), as a viscous semi-solid. Subjection of a sample of this material to flash chromatography (TLCgrade silica gel, 1:1.5 petroleum ether-diethyl ether) led to the isolation of a small amount of each diastereomer. The compound that eluted first was an off-white solid that exhibited mp 123-125 °C; ¹H NMR (CDCl₃, 400 MHz): δ 0.91 (s, 3H), 0.98 (s, 3H), 1.15-1.21 (m, 1H), 1.37-1.70 (m, 6H), 1.75 (ddd, 1H, J = 13.5, 13.5, 4.4 Hz), 1.88-1.93 (dm, 1H, J for d = 9.7 Hz), 2.03-2.11 (m, 2H), 2.16-2.24 (dm, 1H, J for d = 13.5 Hz), 3.42-3.58 (m, 4H), 5.66 (br d, 1H, J = 9.8 Hz), 5.73 (ddd, 1H, J = 9.8, 3.1, 3.1

Hz); ¹³C NMR (CDCl₃, 75.3 MHz): δ 22.5, 22.7, 23.7, 25.7, 26.9, 30.0, 34.0, 34.6, 37.8, 66.9, 69.8 (2 carbons), 98.0, 130.1, 133.0. Exact Mass calcd. for C₁₅H₂₄O₃: 252.1726; found: 252.1724. *Anal.* calcd.: C 71.39, H 9.59; found: C 71.47, H 9.61 (determined on the 1:1 mixture of the alcohols **12**).

The compound that eluted second was an off-white solid that exhibited mp 94-95 °C; ¹H NMR (CDCl₃, 400 MHz): δ 0.92 (s, 3H), 0.98 (s, 3H), 1.15-1.27 (m, 1H), 1.32 (ddd, 1H, *J* = 13.3, 13.3, 4.1 Hz), 1.40-1.57 (m, 2H), 1.63-1.79 (m, 2H), 1.88-2.08 (m, 5H), 2.12-2.20 (dm, 1H, *J* for d = 13.3 Hz), 3.43-3.53 (m, 4H), 5.52 (dd, 1H, *J* = 10.1, 1.1 Hz), 5.83 (ddd, 1H, *J* = 10.1, 2.9, 2.9 Hz); ¹³C NMR (CDCl₃, 75.3 MHz): δ 21.6, 22.5, 22.6, 22.7, 28.5, 30.0, 33.4, 34.6, 37.2, 68.8, 69.7, 70.1, 97.5, 130.9, 131.3. Exact Mass calcd. for C₁₅H₂₄O₃: 252.1726; found: 252.1717.

Preparation of the annulation product 13: To a stirred solution of the allylic alcohol 12 (105 mg, 0.42 mmol, 1:1 mixture of epimers) in dry CH₂Cl₂ (4.0 mL, argon atmosphere) at room temperature was added PCC on basic alumina (1.06 g, 21.5 wt. % PCC, 1.04 mmol) and the dark brown mixture was stirred at room temperature for 3.5 h. Dry diethyl ether (20 mL) was added, the mixture was stirred under an atmosphere of argon for 1 h, and then was filtered through a column of Florisil® (~10 g). The column was eluted with diethyl ether and then with ethyl acetate until no uv active product could be detected in the eluate. The combined eluate was concentrated under reduced pressure. The crude product was purified by flash chromatography (10 g TLCgrade silica gel, 2.3:1 petroleum ether-diethyl ether). The oil thus obtained was distilled (bulb-to-bulb, 175-185 °C/0.15 Torr) to afford the enone 13 (92 mg, 89%) as a colourless, viscous oil that displayed ¹H NMR (CDCl₃, 400 MHz): δ 0.94 (s, 3H), 1.00 (s, 3H), 1.24 (dd, 1H, J = 12.9, 12.9 Hz), 1.40-1.50 (m, 1H), 1.56-1.68 (m, 1H), 2.03-2.11 (m, 1H), 2.23-2.63 (m, 7H), 3.46-3.58 (m, 4H), 5.83 (s, 1H); ¹³C NMR (CDCl₃, 75.3 MHz): δ 22.4, 22.6, 29.0, 30.1, 30.8, 30.9, 33.8, 36.5, 39.5, 70.1 (2 carbons), 96.8, 124.6, 164.9, 199.5. Exact Mass calcd. for C15H22O3: 250.1569; found: 250.1563. Anal. calcd.: C 71.97, H 8.86; found: C 71.83, H 9.01.

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