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Application of [Hydroxy(tosyloxy)iodo]benzene in the Wittig-Ring Expansion Sequence for the Synthesis of β-Benzocyclo-alkenones from α-Benzocycloalkenones

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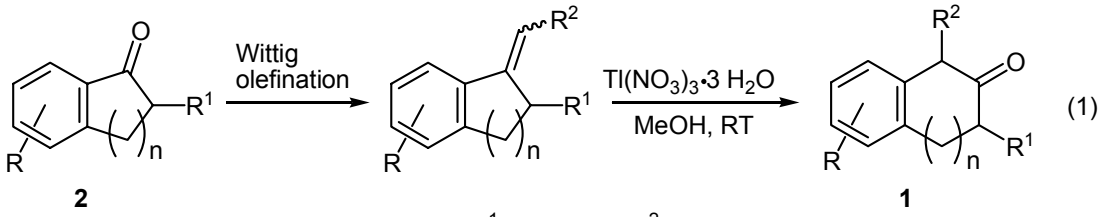
Abstract: The conversion of α-benzocycloalkenones to homologous β-benzocyclo-alkenones containing six, seven and eight-membered rings is reported. This was accomplished *via* a Wittig olefination-oxidative rearrangement sequence using [hydroxy(tosyloxy)iodo]-benzene (HTIB) is the oxidant, that enables the synthesis of regioisomeric pairs of methyl-substituted β-benzocycloalkenones. The incorporation of carbon-13 at C-1 of the β-tetralone nucleus was also demonstrated. The Wittig-HTIB approach is a useful alternative to analogous sequences in which $Tl(NO_3)_3 \cdot 3H_2O$ or the Prevost combination ($AgNO_3/I_2$) are employed in the oxidation step.

Keywords: [Hydroxy(tosyloxy)iodo]benzene, benzocycloalkenones, ring expansion, oxidative rearrangement

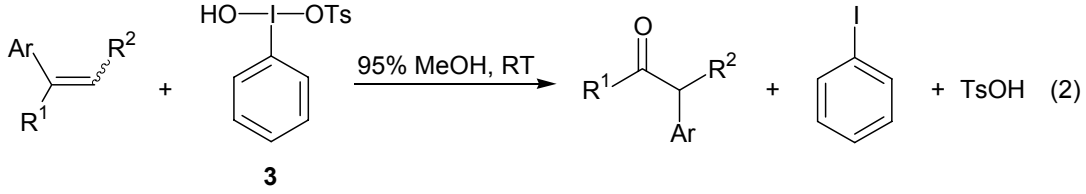
Introduction

Synthetic access to the β-benzocycloalkenones and their ring-substituted derivatives, **1**, was facilitated by the 1977 publication of a two-step protocol involving Wittig olefination of α-benzo-cycloalkenones, **2**, and oxidative ring expansion of the resulting alkenes with thallium(III) nitrate in methanol [1]. This procedure, exemplified by equation 1, enables the regiospecific placement of alkyl groups at the α-carbon atoms of the β-cycloalkenone ring, and affords dimethyl ketals when trimethyl orthoformate is employed as a co-solvent. It was later demonstrated that thallium(III) nitrate can be replaced with the Prevost combination, $AgNO_3$ and I_2, for two-step conversions of α-tetralones (n = 2)

to β-benzosuberones [2], although the experimental procedure is a bit less convenient than the thallium nitrate method.



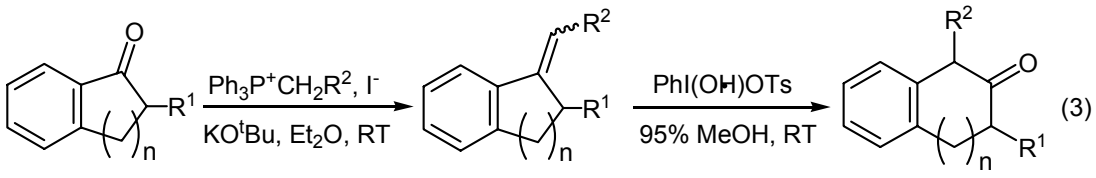
We have recently reported that the treatment of arylalkenes with [hydroxy(tosyloxy)iodo]benzene (**3**, HTIB) in 95% methanol provides a general, regiospecific synthesis of α-aryl ketones (equation 2) [3]. This oxidative rearrangement is fundamentally equivalent to the ring-expansion step depicted in eq. 1, and we now report that HTIB is an excellent alternative to $Tl(NO_3)_3 \cdot 3H_2O$ or $AgNO_3/I_2$ for the two-step synthesis of β-benzocycloalkenones from their lower α-benzocycloalkenone homologs. An obvious advantage of HTIB is its relatively benign character in comparison to $Tl(NO_3)_3 \cdot 3H_2O$ and $AgNO_3$ [4].



Results and Discussion

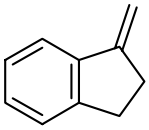
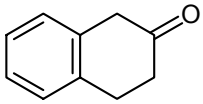
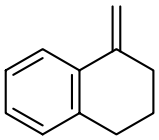
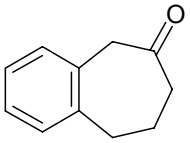
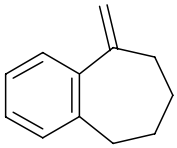
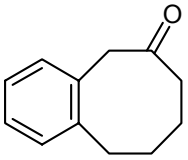
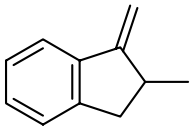
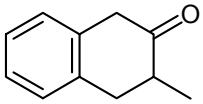
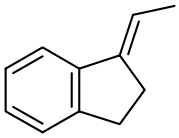
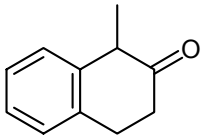
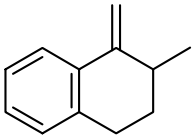
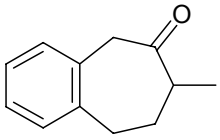
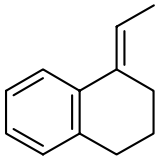
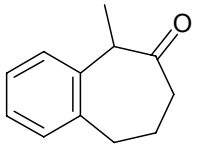
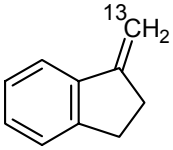
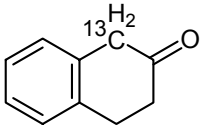
Syntheses of the exocyclic alkenes and β-benzocycloalkenones shown in Table 1 were accomplished as indicated in equation 3. The olefination procedure was adapted from the Fitjer-Quabeck approach, wherein potassium *tert*-butoxide is utilized as the Wittig base in Et_2O or benzene [5]. More specifically, the α-benzocycloalkenones were added to a pre-stirred mixture of potassium *tert*-butoxide and the appropriate alkyltriphenylphosphonium iodide in Et_2O at room temperature. After approximately 4 h, the reaction mixtures were filtered through Celite® and concentrated. Passage of the residual material through silica gel with hexanes gave the exocyclic alkenes (characterized by ^{1}H-NMR) which were used without further purification.

The oxidative ring-expansions were effected by the addition of crystalline HTIB (10 mmol) to a small excess of the alkene in 95% MeOH (mildly exothermic) at room temperature. After about 20 minutes and a preliminary aqueous workup, the resulting β-benzocycloalkenones were isolated by column chromatography in yields (from the alkenes) of 80 to 99%.



(3)

Table 1. Oxidative ring expansions of alkylidenebenzocycloalkenes to β-benzocycloalkenones with HTIB in 95% MeOH

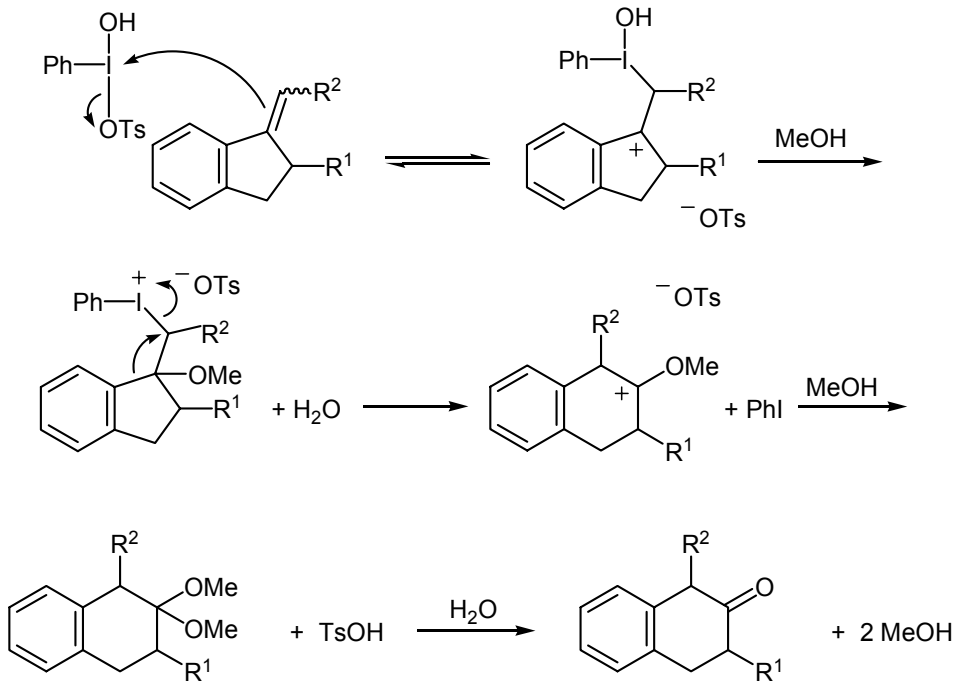
Entry	Alkene	Alkene Yield, %	Product	Isolated Yield, %
1	 **4**	26	 **5**	94
2	 **6**	66	 **7**	99
3	 **8**	91	 **9**	87
4	 **10**	67	 **11**	82
5	 **12**	62	 **13**	92
6	 **14**	90	 **15**	80
7	 **16**	60	 **17**	85
8	 **18**	69	 **19**	91

As indicated in Table 1 (entries 1-3), conversions of unsubstituted α-benzocycloalkenones to homologous β-benzocycloalkenones containing six, seven and eight-membered rings, *via* the Wittig-HTIB sequence, were demonstrated. Furthermore, as with the Tl(III)-induced rearrangements, the proper selection of substrates enables syntheses of regioisomeric pairs of methyl-substituted β-benzocycloalkenones (cf. entries 4-7). For example, the treatment of 2-methyl-1-methylideneindan with HTIB gave 3-methyl-2-tetralone (entry 4), while similar treatment of 1-ethylideneindan gave 1-methyl-2-tetralone (entry 5).

The Wittig-HTIB sequence was also employed for incorporation of a ^{13}C-label into the β-tetralone nucleus (entry 8). To this end, ^{13}C-methyltriphenylphosphonium iodide was prepared from ^{13}C-labeled iodomethane and utilized for the olefination of 1-indanone. Exposure of 1-(^{13}C-methylidene)indan (5.0 mmol) to HTIB (4.54 mmol) in 95% MeOH (25 mL) gave 1-^{13}C-2-tetralone in 91% isolated yield. The location of the label at C-1 in the β-tetralone ring was clearly revealed by NMR analysis. Thus, the singlet at δ 3.58 in the ^{1}H-spectrum of unlabeled β-tetralone appears as a doublet at δ 3.62 (J_{CH} = 128.6 Hz) in the ^{1}H spectrum of the ^{13}C-isotopomer. A ^{13}C-NMR spectrum of the labeled compound, recorded after only 16 scans, exhibits a markedly enhanced singlet at δ 45.03, while the resonances of the remaining carbons are either very weak in comparison or not perceptible.

A plausible mechanism for the HTIB-induced ring-expansions reported herein is presented in Scheme 1. It is analogous to that proposed for the oxidative rearrangement of arylalkenes to α-aryl ketones [3], and accounts for the regiochemistry of β-benzocycloalkenone formation. The similarity between iodine(III) and thallium(III) reagents in the context of oxidative rearrangements has been reviewed by Prakash [6] and almost certainly originates from their electrophilic character and capacity for reduction to the respective iodine(I) and thallium(I) oxidation states.

Scheme 1.



Conclusions

In summary, the Wittig-HTIB sequence is a useful method for regiospecific syntheses of β-benzocycloalkenones from α-benzocycloalkenones, and is environmentally preferable to similar protocols based on Tl(III) and Ag(I) reagents.

Experimental

General

NMR spectra were recorded on a Varian model Gemini-300 spectrometer at resonance frequencies of 300 (^{1}H-) and 75 (^{13}C-) MHz. The NMR solvent in all cases was $CDCl_3$; chemical shifts are expressed relative to residual $CHCl_3$ (^{1}H spectra) or to $CDCl_3$ (^{13}C- spectra). Multiplets in ^{1}H-NMR spectra are sometimes specified with a range of chemical shifts corresponding to the highest and lowest lines in the multiplet. IR spectra were recorded on a Bomem MB-100 FT-IR spectrophotometer. IR samples were neat films or a Nujol® mull (Entry 4). The elemental analysis was performed by Midwest Microlab, LTD (Indianapolis, IN). Melting points were recorded on a Thomas-Hoover Unimelt melting point apparatus and are uncorrected. 2-Methyl-1-indanone and 2-methyl-1-tetralone (used for preparation of the alkenes in entries 4 and 6) were prepared by adaptation of literature methods [7, 8]. All other solvents and chemical reagents were obtained from commercial sources and used as received. Flash column chromatography was performed on a 42 mm internal diameter column packed with Kieselgel (230-400 mesh) silica gel purchased from the Aldrich Chemical Company. Thin layer chromatography (TLC) was done with glass backed 250 micron silica gel plates containing a fluorescent indicator and purchased from Alltech. The 95% methanol used as the solvent for the treatment of the substrate alkenes with [hydroxy(tosyloxy)iodo]benzene (HTIB), refers to a 95:5 (v/v) mixture of methanol and water. Consumption of the oxidant was verified prior to work-up by adding a drop of the reaction mixture to 10% KI (aq.) solution. Yields are based on the material used for the spectroscopic data presented in this paper.

Preparation of Hypervalent Iodine Reagents

Typical Synthesis of (Diacetoxyiodo)benzene

A solution of 32% (w/v) peracetic acid (100 mL, 421 mmol) in acetic acid was added dropwise with mechanical stirring to a cooled flask (15 ^{o}C) containing iodobenzene (65.28 g, 320.0 mmol), over a period of 1 hour. The rate of addition was adjusted to keep the temperature of the reaction mixture between 25-30 ^{o}C. Mechanical stirring was continued for 4 hours during which time a white precipitate separated. Water (100 mL) was added to facilitate precipitation and to dilute any remaining oxidant. The solid was isolated by vacuum filtration, washed with water (2 x 100 mL) and ether (150 mL), dried over P_2O_5 in a vacuum dessicator overnight and identified as (diacetoxyiodo)benzene; yield 94.86 g (92%); mp 160-161 °C (lit. [9] mp 159-161 °C).

Typical Synthesis of [Hydroxy(tosyloxy)iodo]benzene (*HTIB,* **3**)

A solution of (diacetoxyiodo)benzene (40.26 g 125.0 mmol) in boiling acetonitrile (120 mL) was added at once to a solution of *p*-toluenesulfonic acid monohydrate (24.72 g, 130.0 mmol) in boiling acetonitrile (80 mL), with magnetic stirring, to give a yellow-green solution. The solution was allowed to cool to room temperature, and the crystalline [hydroxy(tosyloxy)iodo]benzene that separated was isolated by vacuum filtration and washed with acetonitrile (100 mL) and ether (100 mL); yield, 45.39 g (93%); mp 136-7 ^{o}C, dec. (lit.[10] mp 136-138.5 ^{o}C).

Representative Procedure - Reaction of HTIB with 1-Methylideneindan (**4**) *(Entry 1).*

Crystalline HTIB (3.92 g, 10.0 mmol) was added to a stirred solution of 1-methylideneindan (1.43 g, 11.0 mmol) in 95% methanol (40 mL). The solid dissolved rapidly (~15 sec) with the evolution of heat (41 ^{o}C) to give a colorless solution. The solution was stirred at room temperature for 20 minutes and the solvent was removed *in vacuo* to give an oily mixture. This mixture was partitioned between CH_2Cl_2 (40 mL) and H_2O (25 mL) and transferred to a separatory funnel. The organic layer was separated, washed with H_2O (2 x 25 mL) and brine (1 x 30 mL), dried over $MgSO_4$, and concentrated *in vacuo* to a bright yellow oil (1.51 g), which was subjected to flash column chromatography on silica gel (hexanes; 5 % ethyl acetate/hexanes) to give *β-tetralone* (**5**) as a light yellow oil (R_f = 0.29, 5 % ethyl acetate/hexanes); yield, 1.38 g (94 %); ^{1}H-NMR δ 2.54 (t, *J* = 6.6, 2H), 3.06 (t, *J* = 6.6, 2H), 3.58 (s, 2H), 7.11-7.15 (m, 1H), 7.20-7.24 (m, 3H); ^{13}C-NMR δ 28.13, 37.95, 44.91, 126.80, 126.87, 127.58, 128.19, 133.28, 136.71, 210.71; IR (C=O) 1719 cm^{-1}.

Summary of Purification, Yield and Spectral Data for β-benzocycloalkenones (Entries 2-7)

Conversion of Alkene **6** *to Ketone* **7** *(Entry 2)*

Flash column chromatography of the oil on silica gel (petroleum ether; 10% ethyl acetate/petroleum ether) gave *2-benzosuberone* (**7**) as a colorless oil; yield, 1.58 g (99%); ^{1}H-NMR δ 1.99 (m, 2H), 2.57 (dd, *J* = 6.9, 6.9, 2H), 2.95 (m, 2H), 3.73 (s, 2H), 7.14-7.22 (m, 4H); ^{13}C-NMR δ 26.11, 32.85, 43.56, 50.04, 127.14, 127.59, 129.24, 129.60, 133.61, 140.51, 208.90; IR (C=O) 1710 cm^{-1}; 2,4-dinitrophenylhydrazone, mp 174-176 °C (lit. [11] mp 169-170 °C).

Conversion of Alkene **8** *to Ketone* **9** *(Entry 3)*

Flash column chromatography of the oil on silica gel (hexanes; 5% ethyl acetate/hexanes) gave *7,8,9,10-tetrahydro-5H-benzocyclooctan-6-one* (**9**) as a colorless oil (R_f = 0.32, 5% ethyl acetate/ hexanes); yield, 1.51 g (87%); ^{1}H-NMR δ1.76 (m, 2H), 1.87 (m, 2H), 2.35 (m, 2H), 2.84 (m, 2H), 3.82 (s, 2H), 7.14-7.30 (m, 3H) [12]; ^{13}C-NMR δ 24.63, 31.14, 32.98, 40.87, 48.58, 126.73, 127.99, 129.98, 130.27, 133.66, 141.13, 212.05; IR (C=O) 1700 cm^{-1}; oxime, mp 128-129 °C (lit.[13] mp 130-131 °C).

Conversion of Alkene **10** *to Ketone* **11** *(Entry 4)*

Flash column chromatography on silica gel (5% ethyl acetate/hexanes; 10% ethyl acetate/hexanes) gave a yellow oil (R_f = 0.78, 10% ethyl acetate in hexanes). Kugelrohr distillation of this oil gave *3-methyl-2-tetralone* (**11**) as white rosettes; yield, 1.31 g (82%); mp 38-40 °C (lit. [14] mp 37-40 °C); ^{1}H-NMR δ 1.20 (d, J = 6.9, 3H), 2.54 (m, 1H), 2.84 (dd, *J* = 15.4, 11.0, 1H), 3.08 (dd, *J* = 15.4, 5.8, 1H), 3.61 (s, 2H), 7.12-7.26 (m, 4H); ^{13}C-NMR δ 14.89, δ 36.73, δ 42.31, δ 44.07, δ 126.76, δ 126.87, δ 127.80, δ 128.13, δ 133.51, δ 136.24, δ 212.28; IR (C=O) 1722 cm^{-1}.

Conversion of Alkene **12** *to Ketone* **13** *(Entry 5)*

Flash column chromatography of the oil on silica gel (hexanes; 5% ethyl acetate/hexanes) gave *1-methyl-2-tetralone* (**13**) as a colorless oil (R_f = 0.24, 5% ethyl acetate/hexanes); yield, 1.48 g (92%); ^{1}H- NMR δ 1.48 (d, J = 6.9, 3H), 2.43-2.69 (overlapping m's, 2H), 3.08 (m, 2H), 3.54 (quartet, *J* = 6.9, 1H), 7.21-7.29 (m, 4H); ^{13}C-NMR δ 13.74, 27.70, 36.82, 47.12, 125.72, 126.36, 126.73, 127.18, 136.56, 137.63, 211.83; IR (C=O) 1714 cm^{-1}; Anal. Calcd. for $C_{11}H_{12}O$: C: 82.46%, H: 7.55 %, Found: C 82.35 %, H 7.60%.

Conversion of Alkene **14** *to Ketone* **15** *(Entry 6)*

Flash column chromatography of the oil on silica gel (hexanes; 5% ethyl acetate/hexanes) gave *3-methyl-2-benzosuberone* (**15**) as a colorless oil (R_f = 0.27, 5% ethyl acetate/hexanes); yield, 1.40 g (80%); ^{1}H-NMR δ 1.03 (d, *J* = 6.3, 3H), 1.56 (m, 1H), 2.13 (m, 1H), 2.80 (m, 1H), 2.92 (m, 2H), 3.72 (AB doublet pair, *J* = 54.9, 15.4, 2H), 7.14-7.26 (m, 4H); ^{13}C-NMR δ 10.80, 27.94, 30.75, 41.69, 45.15, 122.57, 122.98, 124.46, 125.00, 129.39, 136.17, 206.11; IR (C=O) 1708 cm^{-1}.

Conversion of Alkene **16** *to Ketone* ***17*** *(Entry 7)*

Flash column chromatography of the oil on silica gel (hexanes; 5% ethyl acetate/hexanes; 10% ethyl acetate/hexanes) gave *1-methyl-2-benzosuberone* (**17**) as a colorless oil (R_f = 0.26, 5% ethyl acetate/hexanes); yield, 1.47 g (85%); ^{1}H-NMR δ 1.45 (d, *J* = 7.1, 3H), 1.92 (m, 1H), 2.08 (m, 1H), 2.47 (m, 1H), 2.66 (m, 1H), 2.79 (m, 1H), 2.95 (m, 1H), 3.88 (quartet, 6.9, 1H), 7.12-7.26 (m, 4H); ^{13}C-NMR δ 14.50, 27.07, 32.33, 42.21, 50.80, 127.12, 127.16, 127.21, 129.40, 138.61, 139.65, 211.89; IR (C=O) 1709 cm^{-1}; 2,4-dinitrophenylhydrazone, mp 144-146 °C (lit. [15] mp 150-151 °C).

Preparation of ^{13}C-Methyltriphenylphosphonium Iodide

A solution of ^{13}C-labeled iodomethane [16] (5.00 g, 35.0 mmol) in benzene (20 mL) was added dropwise to a cooled (-4 to 0 °C) solution of triphenylphosphine (8.39 g, 32.0 mmol) in benzene (50 mL) over one hour. A white solid began to separate after 40 minutes. This mixture was allowed to warm to room temperature and stirred for a period of 4 hours. The white solid was collected by vacuum filtration and identified by melting point as ^{13}C-methyltriphenylphosphonium iodide; yield, 12.60 (97%); melting point, 182-184 °C (lit. [17] mp 183-184 °C).

Preparation of ^{13}C-Methylideneindan (**18**)

Potassium *tert*-butoxide (1.35 g, 12.0 mmol) was added at once under argon to a mechanically stirred mixture of ^{13}C-methyltriphenylphosphonium iodide (4.86 g, 12.0 mmol) in dry ether (50 mL) to give a canary yellow mixture. This mixture was vigorously stirred for 30 minutes. A solution of 1-indanone (1.32 g, 10.0 mmol) in dry ether (20 mL) was added to the mixture over a period of 5 minutes. The color of the mixture gradually became a vivid blue as it was stirred overnight (14 hours). The resulting mixture was filtered through Celite® (10 g), and the filtrate was concentrated *in vacuo* to give a light yellow oil. The oil was eluted with hexanes through a pad of silica gel (30 g) on a sintered glass funnel under aspirator vacuum. The eluant was concentrated *in vacuo* to give *1-(^{13}C-methylidene)indan* (**18**) as a colorless oil; yield, 0.91 g (69%); ^{1}H-NMR δ 2.97 (m, 2H), 3.14 (m, 2H), 5.16 (dt, J_{HH} = 2.1, J_{HC} = 127.20, 1H), 5.68 (dt, J_{HH} = 2.1, J_{HC} = 125.4, 1H), 7.34-7.44 (m, 3H), 7.66 (d, J = 6.9, 1H); ^{13}C-NMR δ 12.93, 30.01, 31.10, 102.73 (enhanced), 120.50, 120.53, 125.24, 126.31, 128.13, 128.15; IR (^{12}C=^{13}C) 1715 cm^{-1}.

Reaction of ^{13}C Labeled Methylideneindan with HTIB (Entry 8)

Crystalline HTIB (1.78 g, 4.54 mmol) was added to a stirred solution of 1-(^{13}C-methylidene)indan (**18**, 0.66 g, 5.0 mmol) in 95% methanol (25 mL). The solid dissolved rapidly with the evolution of heat to give a colorless solution. The solution was stirred at room temperature for 20 minutes, and the solvent was removed *in vacuo* to give an oily mixture. This mixture was partitioned between CH_2Cl_2 (25 mL) and H_2O (25 mL). The organic layer was washed with H_2O (2 x 25 mL) and brine (1 x 20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a bright yellow oil (0.79 g). Flash column chromatography of the oil on silica gel (hexanes; 5 % ethyl acetate/ hexanes) gave *1-^{13}C-β-tetralone* (**19**) as a light yellow oil (R_f = 0.30, 5 % ethyl acetate/hexanes); yield, 0.61 g (91 %); ^{1}H-NMR δ 2.58 (t, J = 6.6, 2H), δ 3.10 (t, J = 6.6, 2H), δ 3.62 (d, J_{HC} = 128.6, 2H), δ 7.15-7.19 (m, 4H); ^{13}C-NMR, (16 transients) δ 45.03; IR (C=O) 1718 cm^{-1}.

References and Notes

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Sample Availability: Not available.