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PREPARATION AND USE OF TRITIATED SCHWARTZ' REAGENT ($ZrCp_2Cl^3H$)

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Abstract: Treatment of Li^3H with $ZrCp_2Cl_2$ in THF affords $ZrCp_2Cl^3H$. By the action of $ZrCp_2Cl^3H$ on an acetylene, it is possible to stereo- and regioselectively introduce tritium into the vinylic position, a site which has often proved to be metabolically stable in complex molecules. In addition, $ZrCp_2Cl^3H$ may be used to regioselectively label olefins with tritium.

The radiolabelling of biologically active molecules with carbon-14 or tritium is essential for pharmacokinetic studies. The vinylic proton has often proved to be metabolically stable in such systems;[1] however few methods allow for tritium labelling at this site. Through the use of tritiated Schwartz' Reagent, $ZrCp_2Cl^3H$, incorporation of tritium into vinylic positions is possible. We report a new *in situ* preparation of Schwartz' Reagent (zirconium dicyclopentadienyl hydride chloride, $ZrCp_2ClH$) by the reaction of LiH with $ZrCp_2Cl_2$. The preparation is readily adapted to the synthesis of labelled reagent using freshly prepared Li^2H or Li^3H

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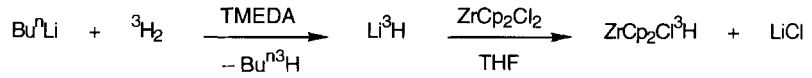
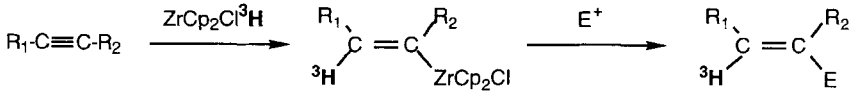
(Scheme 1), allowing for the selective labelling of an acetylene or an olefin substrate.



Scheme 1

Unlabelled Schwartz' Reagent is commercially available, albeit expensive and unstable. The reagent has been prepared *in situ* by the reaction of $ZrCp_2Cl_2$ with $LiAlH_4$, $LiAl(OBu^t)_3H$ (ref. 2) or $LiEt_3BH$.[3] Hydrozirconation of an acetylene proceeds by stereospecific *cis* addition of the metal hydride to afford the *trans*-alkenyl zirconium (Scheme 2).[4] When quenched with an electrophile, this species yields the *trans*-olefin with good tolerance of many functional groups present in the acetylene.[5]



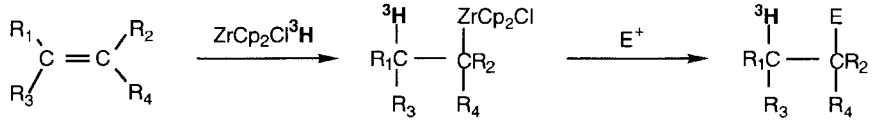
$R_1 > R_2$

Scheme 2

In general, the selective reduction of an acetylene to a *trans*-olefin is difficult, and when reductions are selective [i.e. Lindlar catalyst, nickel (P2) catalyst], the *cis*-olefin is formed and other functional groups that may be present are destroyed.[6] In contrast, reactions of $ZrCp_2ClH$ with acetylenes proceed with high regioselectively, where the zirconium moiety attaches to the site of least steric hindrance,[4,5,7] with selection of electrophile leading to a variety of olefins. Selective carbon-carbon bond formation may also be achieved from

transmetalation reactions between the alkenyl zirconium complex and other metals[5,7,8-10] when quenched with an electropositive carbon species. In the case of the *in situ* prepared reagent, LiCl must be filtered from the solution.

Hydrozirconation also occurs with olefins at elevated temperatures (40 °C) to regioselectively afford the alkyl zirconocene, which may be converted to the corresponding saturated compound by appropriate choice of electrophile (Scheme 3).[4,5,11-14]



Scheme 3

Tritiation experiments (10% tritium/hydrogen) were carried out on phenylacetylene and vinylnaphthalene with N-bromosuccinimide (NBS) as the electrophile. Optimum reaction conditions were established using the hydride and deuteride forms of the reagent and ^{1}H, ^{2}H and ^{3}H NMR spectroscopic techniques were employed to confirm the stereo- and regioselectivity of the addition. Radio-HPLC analyses confirmed the specific activity, radiochemical purity and reaction yields of the tritiated products.

Finely divided and thus very reactive lithium tritide was obtained by the reaction of n-butyllithium and tritium gas in the presence of TMEDA.[15] Upon addition of a concentrated solution of $ZrCp_2Cl_2$ to the lyophilized lithium tritide resuspended in tetrahydrofuran (THF), a brief dissolution was observed before the polymeric Schwartz' Reagent precipitated. Hydride generation was complete within seconds, furnishing a very reactive quality of Schwartz' Reagent.

Phenylacetylene was exclusively converted to β-bromostyrene in 16% yield with theoretical specific activity (S.A.; 2.8 Ci/mmol) as determined by HPLC. The ^{3}H NMR spectrum in Figure 1A confirms the reaction to be highly regioselective as all the tritium is found to be at the α-position, while the proton coupled ^{3}H NMR spectrum (Figure 1B) establishes the product as a *trans*-olefin with $J_{H\text{-}T}$ = 14.53 Hz.

Vinylnaphthalene was converted to β-bromoethylnaphthalene and ethylnaphthalene in a 1:1.3 mass ratio (combined yield of 41%). As seen in Figure 2, the products of this reaction were found to contain tritium in both α and β positions. In β-bromoethylnaphthalene, the ratio of tritium in the α vs. β position was 25:1 while in ethylnaphthalene, the ratio was 1:1. It is interesting to note that when this reaction was repeated at room temperature, the ratio of β-bromoethylnaphthalene to ethylnaphthalene increased to 1.4:1; however, as expected, the overall conversion decreased.

We have demonstrated a novel procedure using $Li^{3}H$ for the generation of tritiated Schwartz' Reagent. The reaction of this new tritide reducing agent with an acetylene enables the stereo- and regioselective incorporation of tritium into the vinylic position of a *trans*-olefin at high specific activity. In addition, use of this reagent with an olefin regioselectively affords the corresponding tritium labelled saturated compound. We expect that radiolabelling using tritiated Schwartz' Reagent may also be extended to more complex molecules such as FKANAL, an analog of the immunosuppressant, FK506, where use of Schwartz' Reagent is an existing, late step in the synthesis.[16]

Experimental:

When required, all glassware, syringes and syringe needles were oven-dried prior to use. All NMR spectra were recorded on a Bruker 300 MHz NMR

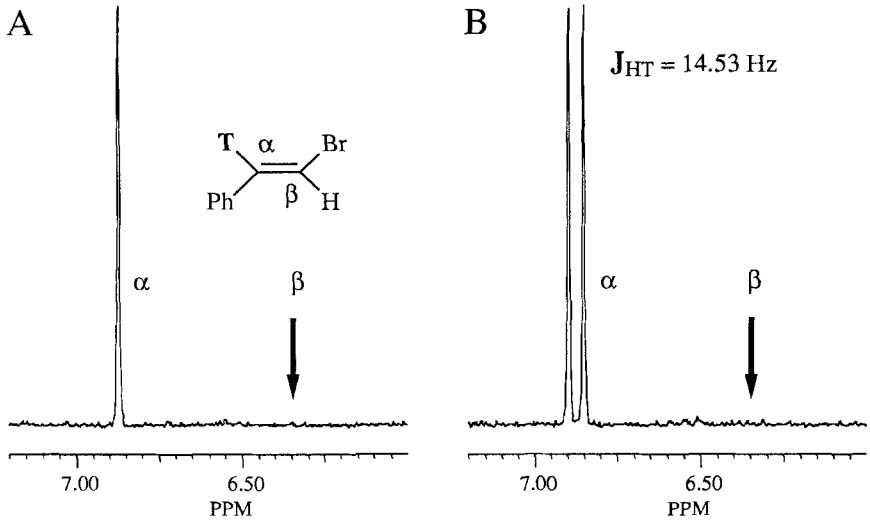


FIG. 1

320 MHz ^{3}H NMR spectra of β-Bromostyrene reaction product in C_6D_6, (7.2–6.0 ppm). A. Proton decoupled tritium spectrum, B. Proton coupled tritium spectrum.

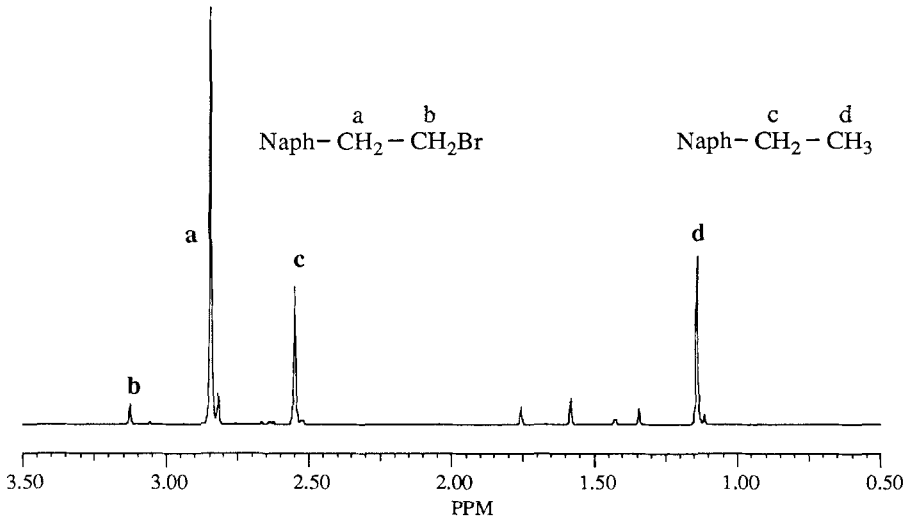


FIG. 2

Proton-decoupled 320 MHz ^{3}H NMR spectrum of the products from the reaction of Schwartz Reagent with vinylnaphthalene, dissolved in C_6D_6. The integral ratios of the peaks were: a/b = 25/1 and c/d = 1/1.

spectrometer in deuteriobenzene (C_6D_6) which was used as an internal standard (δ = 7.15 ppm. (s)). HPLC analyses were performed on a Supelco LC-18 column with a mobile phase of CH_3OH/H_2O.

Tritiation of Phenylacetylene. A mixture of 10% tritium/hydrogen was admitted into a side-arm flask containing a Teflon stirbar to a final pressure of 83 kPa. A solution of n-butyllithium (1.6 M in hexanes; 125 μL; 0.20 mmol) was added, followed by injection of tetramethylethylenediamine (TMEDA; 36 μL; 0.20 mmol) into the rapidly stirred liquid, after which a creamy, white precipitate (Li^3H) immediately began to form. After 30 min. of stirring, the solvents and butane were removed by lyophilization and THF (100 μL) was added to resuspend the Li^3H. $ZrCp_2Cl_2$ (0.20 mmol; 59 mg) in THF (900 μL) was then added and a creamy, beige precipitate formed. The color darkened slightly upon addition of phenylacetylene (0.20 mmol; 22 μL), but after 20 min. of stirring, a deeper beige color was observed. NBS (0.20 mmol; 36 mg) in THF (600 μL) was added, the color became a cloudy, pale yellow, and a dark burgundy solution was obtained after a further 35 min. HCl (1.5 mL; 1.0 N) was added 2.5 h after introduction of NBS in order to quench the reaction. The mixture was extracted with dichloromethane and the organic phase was dried by static lyophilization. Hexane was added and the product was filtered through a Pasteur pipette containing glass wool. Hexane was removed via static lyophilization to afford 5.9 mg of β-bromostyrene (16% yield; S.A. = 2.8 Ci/mmol); ^1H NMR (C_6D_6): δ 6.97 (m, 3H, meta and para H's), 6.85 (d, 1H, PhC<u>H</u>=CHBr, J = 14.04 Hz), 6.83 (m, 2H, ortho H's), 6.34 (d, 1H, PhCH=C<u>H</u>Br, J = 14.03 Hz); ^3H NMR (C_6D_6): δ 6.87 (d, 1H, PhC^3<u>H</u>=CHBr, $J_{H\text{-}T}$ = 14.53 Hz).

Tritiation of Vinylnaphthalene. To a THF solution of $ZrCp_2Cl^3H$ (0.20 mmol), prepared as above, was added vinylnaphthalene (0.20 mmol; 31 mg) in THF and the color became bright yellow. The reaction mixture was heated at 40 °C for 20 min. after which time a rust brown solution had formed. The reaction was allowed to cool to room temperature and NBS (0.20 mmol; 36 mg) in THF (600 μL) was added. A cloudy, pale yellow color developed and after 35 min., a dark purple, brown solution was obtained. The reaction and workup were completed as above to give 6.5 mg of β-bromoethylnaphthalene (14% yield); ^1H NMR (C_6D_6): δ 7.62-7.24 (m, 6H, naphthyl H's-1-6), 6.89 (d, 1H, naphthyl H-7), 3.14 (t, 2H, $PhCH_2C\underline{H}_2Br$), 2.87 (t, 2H, $PhC\underline{H}_2CH_2Br$); ^3H NMR (C_6D_6): δ 3.12 (q, 1H, $PhCH_2CH^3\underline{H}Br$), 2.84 (m, 1H, $PhCH^3\underline{H}CH_2Br$) and 8.6 mg of ethylnaphthalene (27% yield); ^1H NMR (C_6D_6): δ 7.64-7.20 (m, 6H, naphthyl H's-1-6), 7.14 (d, 1H, naphthyl H-7), 2.55 (q, 2H, CH_2), 1.12 (t, 3H, CH_3); ^3H NMR (C_6D_6): δ 2.53 (m 1H, $CH^3\underline{H}$), 1.13 (m, 1H, $CH_2{}^3\underline{H}$).

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