An Improved Synthesis of 5-Ethenyl-4a-methyl-2-oxo-2,3,4,4a,7,8-hexahydronaphthalene and Similar 1,3-Dienes using Palladium Catalyzed Cross-Coupling Methodology

Kollol Pal[1]

Department of Medicinal Chemistry, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06877-0368, USA

Fax +1(617)2250005

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Dedicated to the memory of my colleague Simon J. Coutts (1962–1994).

We report an efficient synthesis of 1,3-dienes from readily available enol triflates and vinyltributyltin using $Pd_2(dba)_3$ and triphenylarsine. Our approach allows for the preparation of these systems at room temperature and thus prevents isomerization to other isomeric dienes. The mild reaction conditions are attributed to the rate acceleration of the cross-coupling reaction due to the weak σ-donation of the triphenylarsine ligand on the palladium catalyst.

As part of an ongoing research program, we recently needed to prepare **2a**, which has been previously prepared from the Wieland Miescher ketone, **1a**.[2] In our hands, the final step of the four-step sequence which involves a lithium bromide promoted 1,4-dehydrobromination at 100 °C led to the formation of variable amounts of the trienone **3**, as a byproduct (Fig. 1). An alternative strategy which would minimize the formation of this byproduct seemed to be the palladium mediated cross-coupling methodology developed by Stille for the regioselective vinylation of enol triflates.[3] A significant drawback of the cross-coupling methodology has been that high reaction temperatures have often been required to effect this transformation, resulting in a decreased yield in some cases (vide infra). However, Farina and co-workers[4] have recently reported that modifications of the ligands on the palladium can lead to dramatic effects in the rate of the reaction. These workers have shown that ligands which result in weak σ-donation to the palladium lead to significant rate accelerations which in turn allow the cross-coupling reaction to be performed under considerably milder conditions.

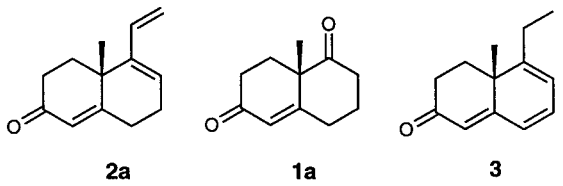
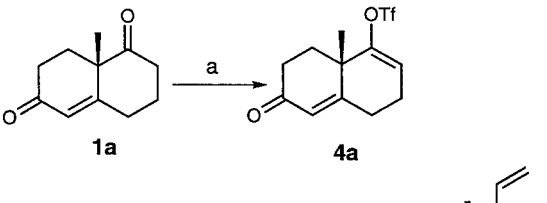


Figure 1

We now report that the enol triflate **4a** of the Wieland Miescher ketone undergoes cross coupling with vinyltributyltin at room temperature when catalyzed with tris(benzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] and triphenylarsine. Our synthetic approach is shown in Scheme 1. The chemoselective formation of the enol triflate of the Wieland Miescher ketone can be easily effected by reaction with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in dichloromethane at 0 °C. The addition of hexane to the crude reaction mixture results in the precipitation of the pyridinium salts which can be removed by filtration to produce the enol triflate. Following purification, treatment of the enol triflate with vinyltributyltin in 1-methyl-2-pyrrolidinone with 2.5 mol% $Pd_2(dba)_3$ and 10 mol% triphenylarsine at room temperature for approximately one hour resulted in the rapid formation of the desired diene, **2a**, which was isolated in 95% yield following chromatographic purification.



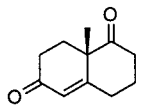
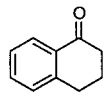
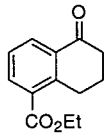
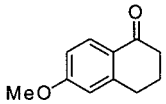
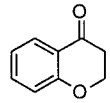
Eq. 1

a. Triflic anhydride, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, 0°C. b. Vinyltributyltin, $Pd_2(dba)_3$, Ph_3As, NMP, 25°C.

Scheme 1

Encouraged by these initial results, we decided to explore the general application of this approach for the preparation of similar 1,3-dienes which are useful reagents in the Diels–Alder reaction. We chose functionalized 1-tetralones as our model system, since these compounds are particularly sensitive to isomerization to the more stable naphthalenes under the thermal dehydrobromination conditions. The results are summarized in Table 1. In the case of 1-tetralone and 5-ethoxycarbonyl-1-tetralone (entries b and c), the enol triflate could be prepared in excellent yield with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (method A) as discussed above. In a few cases these conditions were found to be incompatible with the substrates (entries d and e). In these examples, the enol triflate can also be prepared by treating the ketone with lithium hexamethyldisilazane (LHMDS) and trapping the resulting enolate with *N*-phenyltrifluoromethane sulfonimide (method B). While the enol triflates are often of sufficient purity to be carried on to the cross-coupling protocol directly, they are also remarkably stable and can be readily purified by column chromatography on silica gel. The reaction of the enol triflate with vinyltributyltin was found to be a general approach for the preparation of these sensitive 1,3-diene systems. As shown in Table 1, with the exception of the 4-chro-

Table 1. Preparation of Enol Triflates and 1,3-Dienes

Entry	Ketone (1)	Method	Yield Enol Triflate(%)[a] (4)	Yield 1,3-Diene(%)[a,b] (2)
a		A	70	95 (87)[1]
b		A	100	82 (NA)[6]
c		A	82	91 57[c]
d		A B	39 98	– 74 (41)[7]
e		B	100	41 (22)[8]

[a] Isolated yields NA = not available.
[b] Literature yields in parentheses.
[c] Bis(triphenylphosphine)palladium(II) dichloride, lithium chloride, DMF, 90 °C.

manone example, the yields of the cross-coupling reaction are quite good. For comparison we also prepared **2c** in 57% yield using standard Stille conditions [bis(triphenylphosphine)palladium(II) dichloride, lithium chloride, DMF, 90 °C]. While we did not detect any of the isomerized naphthalene in the crude reaction mixture, a lower yield was obtained at the elevated reaction temperature.

All reactions were performed in flame-dried glassware under an atmosphere of dry argon. ^{1}H NMR spectra were measured at 270 MHz and ^{13}C NMR were measured at 67.9 MHz on a Bruker WM-270 instrument using $CDCl_3$ as solvent and tetramethylsilane as the internal standard. Mass spectra were recorded on a Finnigan 4023 GC/MS/DC spectrometer. Elemental analyses were performed by Midwest Microlabs (Indianapolis, Indiana) or Oneida Research Services (Whitesboro, New York) and are within 0.4% of theoretical values. Preparative radial chromatography was performed on a Chromatotron (Harrison Research, Palo Alto, California). Silica gel coated rotor plates were purchased from Analtech (Newark, Delaware). Triflic anhydride, 2,6-di-*tert*-butyl-4-methylpyridine, 1-tetralone, 6-methoxy-1-tetralone, 4-chromanone and vinyltributyltin were commercially available and were used without further purification. Commercial grade CH_2Cl_2 was used as received. THF was distilled from sodium and benzophenone immediately prior to use.

Enol Triflate 4c (Method A):
A solution of tetralone[5] (0.5 g, 2.3 mmol) in CH_2Cl_2 (12 mL) was cooled to 0 °C and then 2,6-di-*tert*-butyl-4-methylpyridine (0.988 g, 4.8 mmol) and triflic anhydride (1.28 g, 4.4 mmol) were added to the reaction mixture. After warming to r.t. over 90 min, hexane was added to the reaction mixture and the pyridinium salts were removed by filtration through a pad of Celite. The solids were washed with EtOAc, and the combined organic layer was concentrated to afford a tan solid which was immediately chromatographed (silica gel; EtOAc–hexanes) to afford 0.65 g (82%) of **4c** as a yellow oil which was used in the next step in the reaction sequence.

^{1}H NMR ($CDCl_3$): δ = 7.83 (d, 1H, J = 7.9 Hz), 7.52 (d, 1H, J = 7.7 Hz), 7.32 (t, 1H, J = 7.8 Hz), 6.10 (t, 1H, J = 4.8 Hz), 4.37 (q, 2H, J = 7.1 Hz), 3.26 (t, 2H, J = 7.9 Hz), 2.46–2.54 (m, 2H), 1.4 (t, 3H, J = 7.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 167.4, 145.4, 137.7, 130.8, 129.6, 126.4, 124.5, 123.6, 118.5 (q, J = 318.9 Hz), 118.2, 61.33, 23.7, 21.9, 14.2.

Compound **4a**:
^{1}H NMR ($CDCl_3$): δ = 6.13 (br s, 1H), 5.85 (t, 1H, J = 4.2 Hz), 2.32–2.85 (m, 6H), 2.05–2.13 (m, 1H), 1.62–1.73 (m, 1H), 1.24 (s, 3H).

^{13}C NMR ($CDCl_3$): δ = 212.9, 148.0, 136.3, 127.3, 119.3, 118.5 (q, J = 321.8 Hz), 35.0, 28.7, 24.9, 24.7 22.5, 22.2.

Compound **4b**:
^{1}H NMR ($CDCl_3$): δ = 7.12–7.39 (m, 4H), 6.03 (t, 1H, J = 4.8 Hz), 2.88 (t, 2H, J = 7.7 Hz), 2.53 (dt, 2H, J = 4.8, 7.7 Hz).

^{13}C NMR ($CDCl_3$): δ = 146.4, 136.3, 129.2, 128.7, 127.8, 127.0, 121.3, 118.7 (q, J = 323.2 Hz), 117.8, 26.9, 22.4.

Enol Triflate 4d (Method B):
A solution of 6-methoxytetralone (0.5 g, 2.8 mmol) in THF (14 mL) was cooled to – 78 °C and a solution of LHMDS (4.3 mL, 4.3 mmol, 1 M in THF) was added dropwise to the reaction mixture. After stirring for 1 h, *N*-phenyltrifluoromethane sulfonimide (1.52 g, 4.3 mmol) was added in one portion and the reaction mixture was allowed to warm to r.t. over 1 h. The reaction was quenched by the addition of water, extracted with EtOAc, and the organic layer was sequentially washed with sat. aq NH_4Cl, sat. aq NaCl, dried ($MgSO_4$), filtered, and concentrated to produce 1.38 g of a yellow oil. Column chromatography (silica gel; 5% EtOAc–hexanes) afforded 0.93 g (100%) of a clear colorless oil which was used immediately in the following step.

^{1}H NMR ($CDCl_3$): δ = 7.20 (d, 1H, J = 7.5 Hz), 6.67–6.72 (m, 2H), 5.79 (t, 1H, J = 4.78), 3.75 (s, 3H), 2.77 (apparent t, 2H, J = 7.9, 8.3 Hz), 2.37–2.45 (m, 2H).

^{13}C NMR ($CDCl_3$): δ = 160.2, 146.4, 138.8, 122.8, 121.7, 118.6 (q, J = 318.9 Hz), 114.8, 114.3, 111.3, 55.4, 27.4, 22.3.

Compound **4e**:
^{1}H NMR ($CDCl_3$): δ = 7.39–7.41 (m, 1H), 7.20–7.25 (m, 1H), 6.93–6.98 (m 1H), 6.81–6.85 (m, 1H), 5.74 (t, 1H, J = 4.1 Hz), 4.95 (d, 2H, J = 4.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 155.1, 143.2, 131.6, 131.0, 130.0, 121.9, 121.7, 118.9 (q, J = 325.0 Hz), 116.3, 65.1.

1-Ethenyl-5-ethoxycarbonyl-3,4-dihydronaphthalene (2c):
The enol triflate **4c** was dissolved in 1-methyl-2-pyrrolidinone (9 mL), and triphenylarsine (0.057 g, 0.2 mmol) and $Pd_2(dba)_3$ (0.042 g, 0.05 mmol) were added to the reaction mixture. After degassing, the brown solution was allowed to stir for 10 min during which period the reaction mixture turned to a yellow solution. Vinyltributyltin (0.67 g, 2.1 mmol) was added and the reaction mixture was allowed to stir at r.t. for 1 h. Addition of 5 mL of 2 M aq KF resulted in the formation of a precipitate. The reaction mixture was stirred vigorously for 30 min, filtered through a pad of Celite, and washed with EtOAc. The combined washings were then washed with sat. aq NaCl, dried ($MgSO_4$), and filtered through a pad of silica gel. Concentration afforded a yellow oil which was purified on a Chromatotron (5% EtOAc–hexanes) to afford 0.384 g (91%) of the diene.

^{1}H NMR ($CDCl_3$): 7.68 (d, 1H, J = 7.8 Hz), 7.47 (d, 1H, J = 7.7 Hz), 7.23 (t, 1H, J = 7.8 Hz), 6.58 (dd, 1H, J = 10.0, 17.3 Hz), 6.25 (t, 1H, J = 4.8 Hz), 5.5 (dd, 1H, J = 1.6, 17.3 Hz), 5.20 (dd, 1H, J = 1.9, 10.0 Hz), 4.36 (q, 2H, J = 7.1 Hz), 3.09 (t, 2H, J = 7.6 Hz), 2.23–2.31 (m, 2H), 1.39 (t, 3H, J = 7.1 Hz).

^{13}C NMR ($CDCl_3$): δ = 167.9, 137.9, 136.1, 135.4, 135.1, 129.8, 128.5, 127.2, 127.1, 125.5, 115.4, 60.7, 24.8, 22.6, 14.2.

CI-MS (NH_3): m/z = 229 (MH^+).

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(1) Present address: Mitotix, Inc., 1 Kendall Square, Building 600 Cambridge, Massachusetts 02139, USA.
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