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Synthesis of 1-*p*-tolylsulfinyl-1,3-dienes by intramolecular Heck reactions

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Abstract

The first examples of the synthesis of 1,3-dienyl sulfoxides by Heck reactions are described. Both racemic and enantiomerically pure exocyclic 1-*p*-tolylsulfinyl-1,3-dienes **1** are readily prepared by the intramolecular Heck reaction of their corresponding vinyl iodides in the presence of $Pd(OAc)_2$ as catalyst and Ag_2CO_3 as base.

Keywords: Heck reaction; sulfoxides; 1,3-dienes; palladium; cyclization.

During the last two decades the use of sulfoxides as chiral auxiliaries in important C–C forming reactions has been intensively investigated and a wide variety of synthetic applications for the enantioselective synthesis of natural and non-natural products has been reported.[1] For instance, 1,3-dienyl sulfoxides have received considerable attention as chiral dienes in asymmetric Diels–Alder reactions due to the usually very high diastereocontrol promoted by the sulfinyl group.[2] Among the methods for the stereoselective synthesis of 1-sulfinyl-1,3-dienes, the oxidation of appropriate thioether precursors,[3] the condensation of stabilized sulfinyl carbanions with carbonyl compounds[4] (especially the Wadsworth–Emmons olefination between sulfinylmethanephosphonates and α,β-unsaturated carbonyl compounds), and the Stille coupling reaction of vinyl stannanes with β-iodo-α,β-unsaturated sulfoxides,[5] have been the most widely used. As part of an ongoing series of investigations into the applications of sulfoxides in metal-catalyzed reactions,[6] we envisaged that the central C2–C3 bond of 1-sulfinyl-1,3-dienes could be constructed via a Heck type vinylation reaction on simple α,β-unsaturated sulfoxides. In this direction, we report here that the previously unreported exocyclic 1-*p*-tolylsulfinyl-1,3-dienes **1** can be readily prepared by an intramolecular Heck reaction.[7]

The model substrate (*E*)-**2** was prepared in two steps from the readily available 5-iodo-5-hexenal[8] by addition of the α-sulfinylcarbanion of *p*-tolyl methyl sulfoxide (THF, −78°C) and dehydration of the resulting β-hydroxysulfoxide (MsCl, Et_3N; then DBU, CH_2Cl_2) to give the α,β-unsaturated sulfoxide **2** as a 77/23 mixture of *E/Z* isomers, which were easily separated by flash chromatography (60% and

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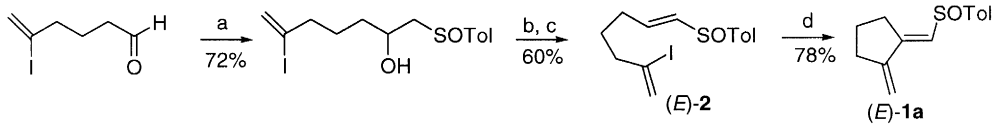
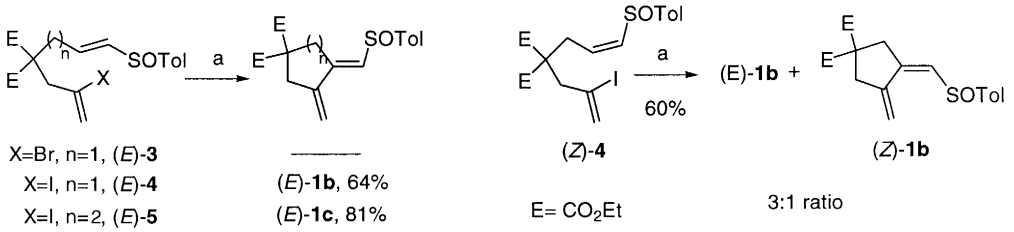
18% yields, respectively). With substrate (*E*)-**2** in hand, extensive experimentation was undertaken in order to find appropriate conditions for its intramolecular Heck reaction. In the presence of $Pd(OAc)_2$ as catalyst, after testing different bases, ligands and solvents, we found that the cyclization occurred mildly using Ag_2CO_3 as base[6b,c] and phosphines as ligands (Scheme 1). As optimal conditions, the reaction of substrate (*E*)-**2** with $Pd(OAc)_2$ 10 mol%, PPh_3 20 mol%, Ag_2CO_3 (2 equiv), in acetonitrile at rt for 24 h afforded cleanly the desired 1-sulfinyl-1,3-diene (*E*)-**1a** (78% yield of crude product), which proved to be rather unstable to chromatographic purification (41% yield after a fast chromatographic purification on deactivated silica gel).[9]



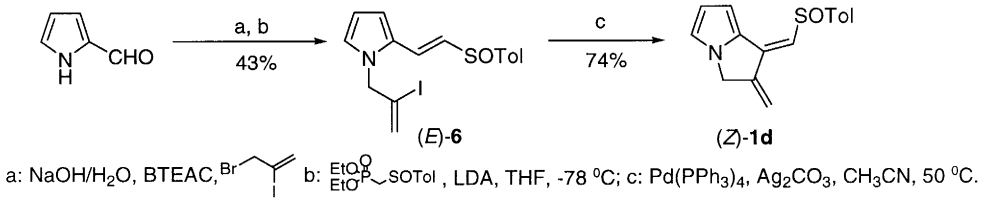
Scheme 1. (a) MeSOTol, LDA, THF, −78°C; (b) MsCl, Et_3N, CH_2Cl_2, rt; (c) DBU, rt; (d) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, CH_3CN, rt

To investigate the generality of this kind of Heck reaction the malonate derivatives (*E*)-**3**, (*E*)-**4** and (*E*)-**5** were readily prepared from diethyl malonate following straightforward synthetic sequences based on successive alkylations and further Wadsworth–Emmons olefinations of the corresponding aldehydes with ethyl *p*-tolysulfinylmethanephosphonate.[10] The Heck reactions were carried out under the optimal conditions found for (*E*)-**2** [$Pd(OAc)_2$, PPh_3, Ag_2CO_3, CH_3CN, rt] and we found that, although no reaction at all was observed from the bromo derivative (*E*)-**3**, the iodo derivatives (*E*)-**4** and (*E*)-**5** reacted mildly at rt to give the expected 1,3-dienes (*E*)-**1b** and (*E*)-**1c** in better yields (64% and 81%, respectively after chromatographic purification) than in the case of the synthesis of (*E*)-**1a** probably due to their significantly higher stability. We also investigated the Heck reaction of the olefin (*Z*)-**4**[10] under the same experimental conditions. The cyclization took place at a similar rate to that observed for the isomer (*E*)-**4**, but the process was not stereospecific, affording a 3:1 mixture of both *E*:*Z* 1,3-dienes **1b** (60% yield) instead of the exclusive formation of the expected isomer (*Z*)-**1b**[11] (Scheme 2).



Scheme 2. (a) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, CH_3CN, rt

As a synthetically more elaborate case, that could eventually be used in the stereoselective synthesis of pyrrolizidines,[12] the pyrrole derivative (*E*)-**6** was readily prepared from pyrrole 2-carboxaldehyde by *N*-allylation with 3-bromo-2-iodopropene under basic conditions (50% $NaOH/CH_2Cl_2$, benzyltriethylammonium chloride, rt) and subsequent olefination with ethyl *p*-tolysulfinylmethanephosphonate to give a 67/33 mixture of *E*/*Z* isomers (82% yield), which were separated by flash chromatography (Scheme 3). However, the pyrrole (*E*)-**6** failed to react under the usual Heck reaction conditions [$Pd(OAc)_2$, PPh_3, Ag_2CO_3, CH_3CN, rt], its lack of reactivity probably being due to the strain associated with the formation of the bicyclic 1,3-diene (*Z*)-**1d**. After some experimentation, we found that the Heck reaction of (*E*)-**6** occurred under somewhat harsher conditions: $Pd(PPh_3)_4$ (20 mol%), Ag_2CO_3 (2 equiv.) in acetonitrile at 50°C for 5 h, furnishing after chromatographic purification the diene (*Z*)-**1d** in 44% yield (74% based on converted product) along with 40% of starting (*E*)-**6**.



Scheme 3.

Having developed a new approach to the stereoselective synthesis of 1-sulfinyl-1,3-dienes, in order to apply this methodology to asymmetric synthesis the preparation of this type of diene in enantiomerically pure form was required. To this end, applying the same synthetic procedures, but starting with the readily available optically pure (*S*)-ethyl *p*-tolylsulfinylmethylphosphonate[13] instead of its racemic form, the optically pure substrate (*E*)-**4** of (*R*) configuration at sulfur was prepared (ee>98%, HPLC, Daicel Chiralpack AS). Heck reaction of (*R*)-(*E*)-**4** under the usual conditions afforded the 1,3-diene (*R*)-(*E*)-**1b**[14] without any loss of optical purity (ee>99%, HPLC, Daicel Chiralpack AS), proving that there is no racemization at sulfur under the experimental conditions of the Heck reaction.

In conclusion, we have demonstrated that 1-*p*-tolylsulfinyl-1,3-dienes **1** can be readily synthesized in both racemic and optically pure form by formation of the C2–C3 bond via an intramolecular Heck reaction. The reactivity of the exocyclic dienes **1** in asymmetric Diels–Alder reactions is currently being investigated in our laboratory.

Acknowledgements

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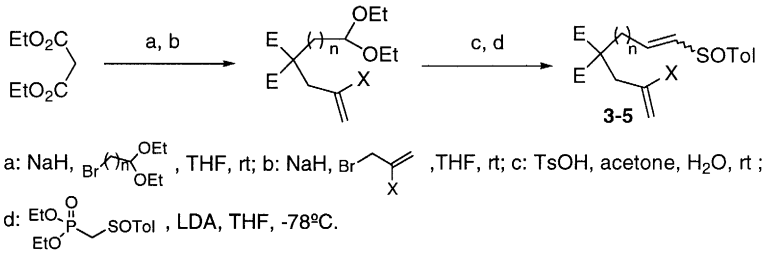
8. 5-Iodo-5-hexenal was readily prepared from commercially available 5-hexyn-1-ol by iodination at the triple bond (TMSCl, NaI, H_2O, CH_3CN, rt) and PCC oxidation (celite, CH_2Cl_2, rt).
9. Diene (*E*)-**1a** was very prone to suffer isomerization of the exocyclic methylenic double bond to the endocyclic position and other side reactions. This compound must be rapidly purified by flash chromatography on deactivated silica gel (previously treated with a 9:1 solution of hexane:Et_3N) and kept in the freezer under an argon atmosphere.
10. The malonate derivatives (*E*)-**3**, (*E*)-**4** and (*E*)-**5** were readily prepared from diethyl malonate as indicated below (for the synthesis of related acyclic precursors, see: Chatani, N.; Morimoto, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc*. **1998**, *120*, 5335). The Wadsworth–Emmons olefination was in all cases moderately stereoselective, affording mixtures of *E/Z* isomers which were easily separated by chromatography.



11. The stereochemical assignment of isomers *E/Z* **1b** was unequivocally established from the important observed NOEs between the olefinic protons of both double bonds in (*E*)-**1b**. As possible mechanistic hypotheses, the low stereoselectivity in the cyclization of (*Z*)-**4** could be due to either a thermodynamically *Z/E* palladium catalyzed isomerization of the α,β-unsaturated sulfinyl moiety [in either the starting compound (*Z*)-**4** or the product **1b**] or to the epimerization of the α-alkylpalladium intermediate generated after the *syn*-insertion step (for an example of epimerization of an α-alkylpalladium species in a Heck reaction, see: Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047).
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13. Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczynska, A. *J. Org. Chem.* **1978**, *43*, 473. Alternatively, this optically pure phosphonate can be prepared by phosphorylation of the carbanion of (*R*) *p*-tolyl methyl sulfoxide with diethyl chlorophosphate.
14. General procedure: Synthesis of (*R*)-(*E*)-**1b**. To a suspension of $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), PPh_3 (5.4 mg, 0.02 mmol) and Ag_2CO_3 (32 mg, 0.12 mmol) in 4 mL of dry CH_3CN, was added 1,3 diene (*R*)-(*E*)-**4** (50 mg, 0.1 mmol) in 2 mL of CH_3CN under an argon atmosphere. The mixture was vigorously stirred at rt for 20 h, filtered over Celite and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate, 5/1) to afford 1,3 diene (*R*)-(*E*)-**1b** (24 mg, 64%). $[\alpha]_D$=−26 (c 1, acetone); ee>99% (HPLC, Daicel Chiralpack AS, 75:25 hexane:isopropanol). ^{1}H NMR ($CDCl_3$): 1.25 (t, *J*=7.1 Hz, 3H), 1.28 (t, *J*=7.1 Hz, 3H), 2.39 (s, 3H), 2.97 (dt, *J*=16.7 and 2.1 Hz, 1H), 3.15 (dt, *J*=16.7 and 2.1 Hz, 1H), 3.45 (d, *J*=2.1 Hz, 2H), 4.20 (m, *J*=7.1 Hz, 4H), 5.17 (t, J=1.7 Hz, 1H), 5.47 (t, *J*=2.1 Hz, 1H), 6.44 (t, *J*=2.1 Hz, 1H), 7.31 and 7.40 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$): 13.9, 21.2, 38.7, 40.2, 57.7, 61.7, 110.8, 124.0, 126.5, 129.8, 141.0, 143.2, 147.7, 169.7, 170.4. HRMS: (EI) *m/z* calcd for M^+: 376.1351, found: 376.1345.