Catalytic Alkyne Hydrothiolation with Alkanethiols using Wilkinson's Catalyst

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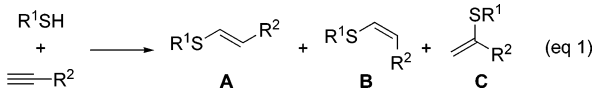
Received August 8, 2007

Summary: We recently discovered that Wilkinson's catalyst ($ClRh(PPh_3)_3$) is an excellent catalyst for alkyne hydrothiolation with alkanethiols to provide linear alkyl (E)-vinyl sulfides, which are valuable synthetic intermediates and precursors to bioactive molecules. Deuterium-labeling studies indicate that the reaction proceeds by thiol oxidative addition, alkyne migratory insertion, and subsequent reductive elimination.

Alkyl (*E*)-vinyl sulfides and their oxidized derivatives are used in a wide range of synthetic transformations, including cross-coupling,[1] Heck reactions,[2] sigmatropic rearrangements,[3] Diels−Alder reactions,[4] and Pauson−Khand reactions[5] and as ligands for a number of transformations,[6] including C−H activation[7] and allylic alkylation.[8] Moreover, benzyl (*E*)-vinyl sulfones, which are readily accessible from alkyl (*E*)-vinyl sulfides,[9] are inhibitors of polo-like kinase 1 (PLK1),[10] MAP kinase,[11] and cysteine protease.[12] Indeed, the PLK1 inhibitor ON01910 is currently in clinical trials for anticancer activity.[10c] In spite of this utility, efficient, regioselective synthesis of alkyl (*E*)-vinyl sulfides has remained a significant challenge.[13−15] Alkyne hydrothiolation with alkanethiols (eq 1, the reaction of a thiol across an alkyne π-system) would provide a direct, atom-economical route to alkyl (*E*)-vinyl sulfides but has yet to be achieved.



Although a number of transition metal complexes are capable of catalyzing hydrothiolation of arenethiols,[16] including Wilkinson's catalyst [$ClRh(PPh_3)_3$],[16c] the use of alkanethiols is rare,[17−20] possibly due to their higher bond strength (both hetero- and homolytic) relative to those of arenethiols. Indeed, it has been reported that both Pd complexes[16a] and Wilkinson's catalyst[16c] are ineffective for hydrothiolation reactions with alkanethiols, even though these same complexes successfully catalyze alkyne hydrothiolation with arenethiols. Nevertheless, we anticipated that an appropriate ligand choice could permit catalytic hydrothiolation of alkanethiols. Toward this end, we recently reported[19] that Tp*Rh(PPh_3)$_2$ (Tp* = hydrotris(3,5-dimethylpyrazyolyl)borate)[21] is an excellent catalyst for alkyne

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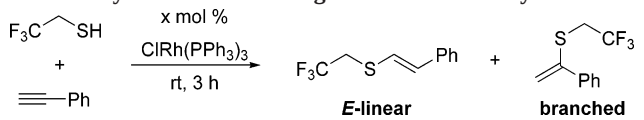
10.1021/om700811e CCC: $37.00
Publication on Web 10/27/2007

Table 1. Optimization of Reaction Conditions for Alkyne Hydrothiolation Using Wilkinson's Catalyst



entry[a]	amt of cat. (mol %)	solvent	yield (%)[b]	lin:br[c]
1	3	DCE	90	9:1
2	3	THF	51	10:1
3	3	$PhCH_3$	70	5:1
4	3	PhH	85	5:1
5	3	hexane	<10	2:1
6	3	EtOH	50	5:1[d]
7	0	EtOH	50	5:1[d]
8	0	DCE	0	N/A

[a] Reaction conditions: 0.3 mmol of alkyne, 0.33 mmol of thiol, 1.8 mL of solvent, and 0.009 mmol (3 mol %) of catalyst. [b] Isolated yields. [c] Ratio of *E*-linear:branched product determined by ^{1}H NMR spectroscopy. [d] *Z* isomer is major product; *E*:*Z* = 1:4.

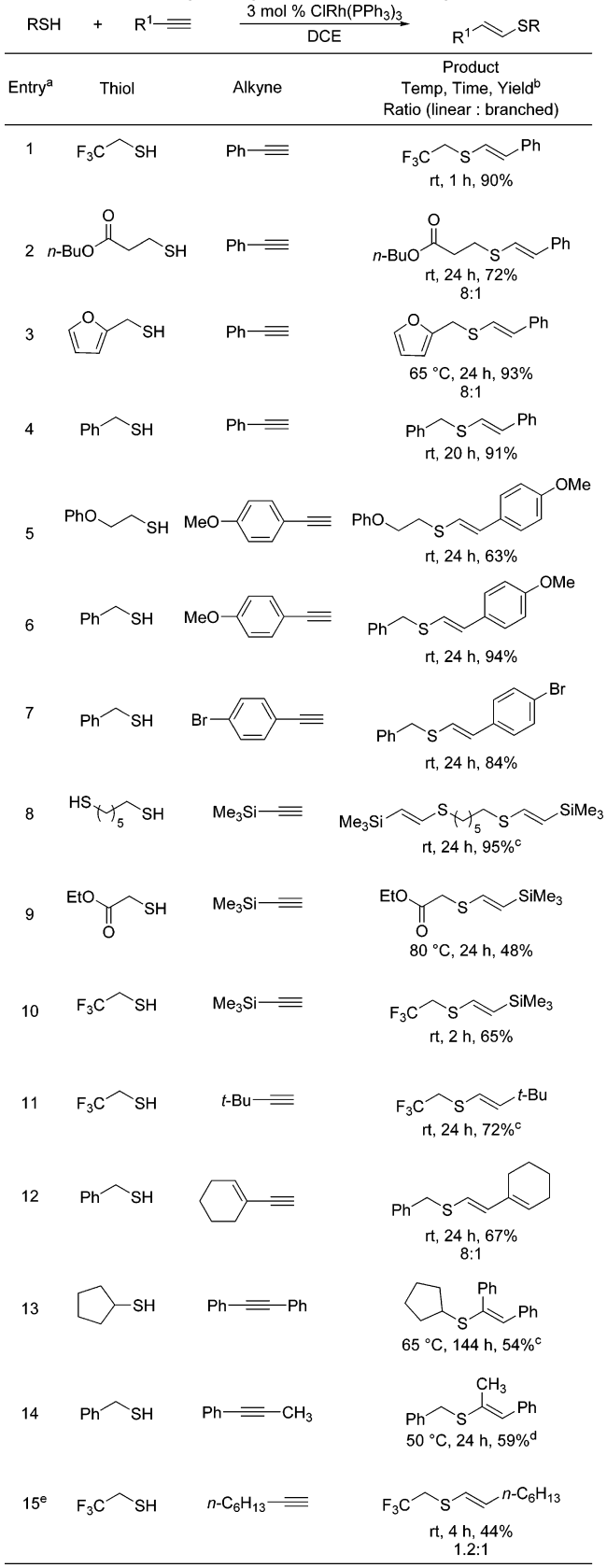
hydrothiolation using alkanethiols, generating the branched products (**C**) regioselectively in high yields.

In the course of these studies, we sought to directly compare the reactivity of Tp*Rh(PPh$_3$)$_2$ with Wilkinson's catalyst in alkyne hydrothiolation with alkanethiols. To our surprise, we discovered that Wilkinson's catalyst is an excellent catalyst for hydrothiolation reactions using alkanethiols, with an appropriate choice of solvent. Of particular significance, alkyl (*E*)-vinyl sulfides are obtained with good-to-excellent regioselectivity, which is complementary to that provided with Tp*Rh(PPh$_3$)$_2$.

For example, the reaction between phenylacetylene and 2,2,2-trifluoroethanethiol with 3 mol % Wilkinson's catalyst in DCE (1,2-dichloroethane) revealed the formation of the *E*-linear and branched isomers in 90% isolated yield as a 9:1 mixture (on the basis of ^{1}H NMR spectroscopy) within 30 min at room temperature (Table 1, entry 1).

A series of solvents were then chosen to explore the possibility that the choice of solvent was crucial to the success of the reaction (Table 1), as Ogawa had reported that alkanethiols did not react when EtOH was used. Of the solvents explored, DCE was found to provide the best yield and selectivity. Interestingly, the *Z* isomer was the main product with EtOH as solvent (entry 6). In the absence of catalyst (entry 7), the same yield and product ratio is obtained as in entry 6, indicating that product formation in EtOH is not metal-catalyzed. In comparison, no background reaction in DCE is observed on the time scale of the catalytic reaction (entry 8). The superior results with DCE as the solvent are possibly due to increased solubility of the catalyst, as Wilkinson's catalyst has higher solubility in chlorinated solvents than in EtOH.[22] Given that an Ir(III) complex with bound DCE has been reported,[23,24] it is possible DCE could play a more significant role in catalysis. Neither the reaction yield nor selectivity is significantly affected by either catalyst loading or temperature.[25] Intrigued by the unexpected success of Wilkinson's catalyst, we then explored a series of eight thiols and nine alkynes (Table 2). In general,

Table 2. Substrate Scope of Alkyne Hydrothiolation Catalyzed by Wilkinson's Catalyst



[a] Reaction conditions: 0.5 mmol of alkyne, 0.55 mmol of thiol, 5 mL of solvent, and 0.015 mmol (3 mol %) of catalyst. [b] Isolated yields. [c] Yield determined by ^{1}H NMR spectroscopy in $CDCl_3$. [d] 10 mol % of catalyst used. [e] Additional 3 mol % of catalyst added after 2 h.

the reactions proceeded in good-to-excellent yields and selectivities for the *E*-linear isomer. In comparison, Tp*Rh(PPh$_3$)$_2$

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(25) Details of these experiments are provided in the Supporting Information.

provides access to the branched isomer regioselectively. Consequently, we are able to generate either regioisomer, depending on the choice of ligand.

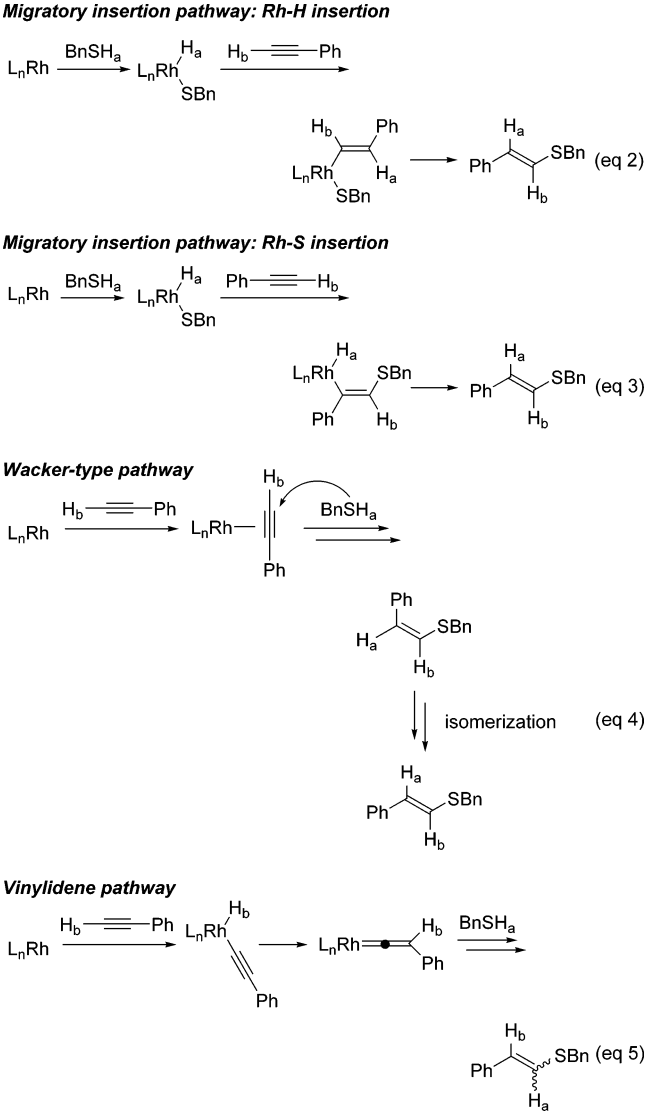
Substrates bearing halogens, ethers, esters, alkenes, and silanes all participated efficiently in the reaction. For example, 2,2,2-trifluoroethanethiol, butyl 3-mercaptopropionate, furfuryl mercaptan, and benzenethiol all reacted with phenylacetylene in high yields and selectivities ranging from 5:1 to >19:1 (entries 1−4). Both electron-donating and electron-withdrawing para substitution of aryl alkynes are tolerated, with all reactions proceeding with selectivity (entries 4−7). The olefinic products obtained from use of a silylated alkyne (entries 8−10) can be further functionalized in Hiyama coupling[26] or deprotected to yield the terminal alkene. The product of entry 12 and its oxidized derivatives are potential Diels−Alder substrates. Internal alkynes react (entries 13 and 14) but require considerably longer reaction times. An unsubstituted aliphatic alkyne generates a 1.2:1 mixture of *E*-linear and branched isomers, presumably due to the lower steric requirements (entry 15).

Given the remarkable influence of ligand choice on hydrothiolation regioselectivity, coupled with the limited amount of mechanistic data for transition metal-catalyzed reactions of thiols, we sought to investigate the mechanism of this reaction. A number of possible mechanisms to form the *E*-linear isomer can be envisioned on the basis of other late-transition metal-catalyzed reactions of alkenes and alkynes with heteroatom nucleophiles (Scheme 1). For example, one possibility is that the reaction proceeds by initial oxidative addition of the thiol, followed by alkyne insertion into either the Rh−H (eq 2) or Rh−S bond (eq 3). After insertion, subsequent reductive elimination would give the vinyl sulfide product with syn addition of the thiol across the alkyne (i.e., H_a and SBn are on the same side of the alkene). Ogawa postulated that this mechanism was operable for arenethiols using Wilkinson's catalyst.[16c]

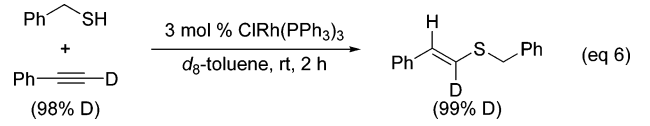
Alternatively, alkyne coordination could precede nucleophilic attack by thiol or thiolate, similar to the Wacker oxidation[27] and related reactions.[28] This mechanism, if operable in hydrothiolation, would occur with anti addition of the thiol across the alkyne, generating the *Z*-linear isomer (eq 4). Although we observe only the *E*-linear product, the *Z* isomer might be formed initially and subsequently converted to the *E* isomer. If isomerization is fast, the observed reaction product would be that of syn addition and would thus be indistinguishable from eqs 2 and 3.

An additional possibility involves oxidative addition of the alkyne to generate a rhodium hydrido acetylide species, which could then isomerize to the corresponding vinylidene (eq 5).[29] Attack by thiol or thiolate would lead to the linear product. This process involves migration of the terminal alkynyl proton to the same carbon as the other alkynyl substituent (i.e., H_a and SBn would be attached to the same carbon) and thus could be readily distinguished from the other possible mechanisms by use of deuterium-labeled alkyne.

Scheme 1. Possible Mechanistic Pathways



We thus explored the reaction between deuterium-labeled phenylacetylene (98% deuterium) with benzenethiol (eq 6).[30]



Only the product with syn addition, rather than migration, is observed, thereby excluding the vinylidene pathway depicted in eq 5.

This result does not differentiate the migratory insertion pathways (eqs 2 and 3) from the Wacker-type pathway (eq 4). To do so, we explored the possibility of product isomerization; if isomerization occurs readily, eq 4 would be feasible. If isomerization were slow or did not occur, eq 4 could be excluded as a possible mechanism. Accordingly, a sample enriched in the *Z* isomer (2.3:1 *Z*:*E*) was subjected to the catalytic reaction conditions, in the presence of both thiol and alkyne. No evidence for isomerization was observed on the time scale of the catalytic

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(30) No evidence of deuterium exchange between alkyne and thiol was observed.

reaction, thereby excluding the Wacker-type mechanism depicted in eq 4.[31]

Distinguishing between eqs 2 and 3 is more challenging. Insertion into the Rh−S bond (eq 3) would be more sterically hindered than insertion into the Rh−H bond (eq 2), as the alkynyl substituent in the mechanism shown in eq 3 must point toward the hindered metal center in order to produce the *E*-linear product. It seems unlikely that the more sterically demanding path would predominate, although we cannot as yet rule out the mechanistic pathway shown in eq 3. In addition, although insertion into Rh−S bonds has been documented,[32] insertion of an alkyne into M−H bonds is typically favored over insertion into M−X bonds (X = heteroatom).[33] Notable exceptions include the modified Chalk−Harrod mechanism for hydrosilylation[34] and Pt-mediated hydroamination.[35]

In summary, we have discovered that Wilkinson's catalyst is an excellent catalyst for alkyne hydrothiolation using alkanethiols. The reactions generally proceeded with good-to-excellent yields and regioselectivities. Deuterium-labeling studies indicate that $ClRh(PPh_3)_3$ operates by an oxidative addition, alkyne migratory insertion, reductive elimination pathway. On the basis of steric arguments, we suggest that the reactions involve alkyne insertion into an Rh−H bond. Exploration of other rhodium complexes, the detailed reaction mechanism, and the synthetic utility of this process are underway.

Acknowledgment. We thank the following for support of this research: University of British Columbia, NSERC (Discovery Grant, Research Tools and Instrumentation Grants, PGS-D for S.S.), the Canada Foundation for Innovation (New Opportunities Grant), and the British Columbia Knowledge Fund.

Supporting Information Available: Text and figures giving complete experimental details, including ^1H and ^{13}C NMR spectra, for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OM700811E

(31) Thiol and alkyne were allowed to react in the absence of Wilkinson's catalyst to 54% conversion (38% *Z* and 16% *E*). Catalyst was then added. The reaction proceeded to 92% conversion (38% *Z*, 52% *E*, 2% branched), consistent with our data that the catalytic reaction proceeds with 19:1 *E*:branched selectivity.

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