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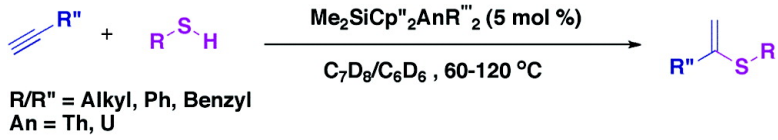

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Organoactinide-Mediated Hydrothiolation of Terminal Alkynes with Aliphatic, Aromatic, and Benzylic Thiols

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Metal-complex-catalyzed hydroelementation is a versatile and atom-efficient method for catalytically installing heteroelements in small molecules and macromolecules.[1] While significant advances have been achieved using amine,[2] phosphine,[3] and alcohol reagents,[4] far less is known about thiols because of the high affinity of sulfur for many "soft" transition metal catalysts.[5] Sulfur is a constituent of many important polymeric materials,[6] natural products,[7] and synthetic reagents,[8] providing impetus to devise efficient catalytic methodologies for sulfur−carbon bond formation. Radical and nucleophilic thiol addition across alkynes in an anti-Markovnikov fashion is well-known;[9] however, Markovnikov addition presents a significant challenge. While some late transition metal catalysts can affect this transformation with aryl and benzyl thiols,[10] few mediate hydrothiolation with aliphatic thiols.[10b,d,g] In this regard, the recent development of lanthanide-mediated hydroalkoxylation[4a,b] raises the question of whether hydrothiolation might be feasible with f-element catalysts. Bond enthalpy considerations[11] for this unexplored reaction predict net exothermicity for RSH addition to alkynes, allenes, and alkenes mediated by organoactinide complexes[12] (Scheme 1). While alkyne insertion into the An−S bond is predicted to be exothermic (step ii, Scheme 1), alkenes are more challenging, with initial insertions predicted to be endothermic. The final protonolysis (step iii, Scheme 1) is estimated to be highly exothermic for all substrates, reflecting the substantial C−H and An−S bond enthalpies.[13] Herein, we report the first use of f-element catalysts to affect the efficient hydrothiolation of terminal alkynes by aromatic, benzylic, and aliphatic thiols, achieving a high degree of Markovnikov selectivity.

While several U(IV) and Th(IV) $Me_2SiCp''NCMe_3$ (CGC), bis(pentamethylcyclopentadienyl), and $U[NEt_2]_4$ complexes exhibit hydrothiolation activity, $Me_2SiCp''_2$ ($Cp'' = Me_4C_5$) complexes[14] were the initial focus because of their stability in the presence of thiol at high temperatures. Other f-element catalysts undergo ligand protonolysis-related precipitation at varying rates. The protonolytic resistance of *ansa* Cp''_2-ligation likely reflects the chelating steric encumbrance around the actinide center. With 5 mol % $Me_2SiCp''_2Th[CH_2TMS]_2$ (**1a**),[14b] the reaction of 1-pentanethiol and 1-hexyne (entry 1, Table 1) proceeds to completion in ∼3.5 h at 90 °C in the presence of excess alkyne.[15] Conversion is clean and quantitative (with the exception of entries 7 and 8, Table 1) in thiol by ^{1}H NMR spectroscopy for a broad range of alkyl, aryl, and benzyl thiols and for alkyl, aryl, and vinyl alkynes (Table 1). Similar transformations are observed for An = U. Kinetic analysis of entry 1 between 60 and 110 °C yields $\Delta H^{\ddagger} = +9.1(0.7)$ kcal/mol and $\Delta S^{\ddagger} = -45(2)$ eu, suggesting a highly ordered transition state and an intermolecular, turnover-limiting step.

While few late transition metal catalysts mediate efficient aliphatic thiol hydrothiolation, the present catalysts affect this transformation with ease. The greater alkyl S−H bond enthalpy has been cited as a possible explanation for this sluggishness observed with late transition metals.[10d] However, the present catalysts appear to be little affected, possibly due to rapid and highly exothermic An−C protonolysis.

The present hydrothiolation processes exhibit a high level of Markovnikov selectivity. This presumably reflects a four-membered transition state (step ii, Scheme 1), with the alkyne insertion regiochemistry dictated by transition state sterics and bond polarity

Scheme 1. Proposed Catalytic Cycle for Organoactinide-Mediated Hydrothiolation of Terminal Alkynes

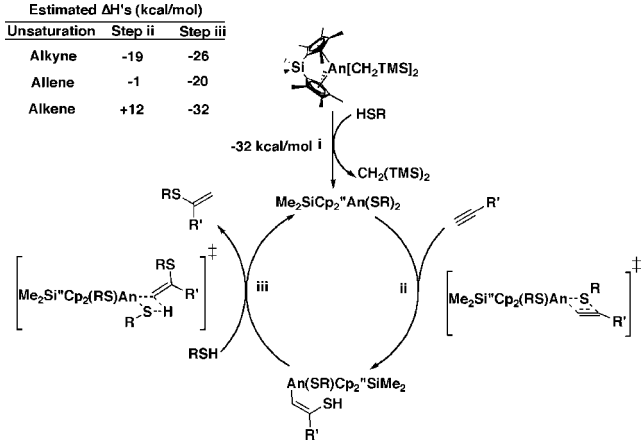

Table 1. $Me_2SiCp''_2Th[CH_2TMS]_2$-Mediated Hydrothiolations in the Presence of Excess Alkyne in Toluene-d_8/Benzene-d_6[a]

Entry	Thiol	Alkyne	Product	N_i(h^{-1},°C)
1.	2	6	10	5(90)
2.	2-D	6	10 + 6-D	--
3.	3	6	11	1(110)
4.	4	6	12	14(90) 27(110)
5.	5	6	13	4(110)
6.	2	7	14	5(90)
7.	5	7	15	8(110)
8.	2	8	16	16(110)
9.	2	9	17	14(110)
10.	4	9	18	16(90)

[a] $[Catalyst]_o$ = 3.5−7.7 mM, $[alkyne]_o$ = 0.8−3.0 M, $[thiol]_o$ = ∼120 mM.

10.1021/ja808764q CCC: $40.75

orientation. Additional competing, noncatalytic, anti-Markovnikov products are occasionally detected under the present reaction conditions and presumably arise via a known radical mechanism.[9b,c] These products are formed in negligible quantities except for entries 7 and 8 (Table 1).[16] Despite formal similarities to the proposed insertion/protonolysis mechanisms of several Pd and Ni catalysts,[10f] double-thiolated side-products are not observed in the present case, presumably reflecting Th(IV) resistance to 2-electron reductive elimination.

Thiol architecture has a substantial impact on **1a**-mediated hydrothiolation rates, with sterics appearing to dominate over electronics. Changing from primary to secondary aliphatic thiols (entries 1−3, Table 1), results in significant rate depression, consistent with steric impediments in the turnover-limiting alkyne insertion (step ii, Scheme 1). On switching to a benzyl mercaptan (**4**), N_t increases nearly 3× (entries 1−4). The enhanced reactivity of aryl- and benzyl-thiols likely reflects electronic factors. However, for benzenethiol (**5**), any electronic gain is offset by increased sterics versus 1-pentanethiol (**2**). The 4-methylbenzyl mercaptan (**4**) yields the largest thiol substrate N_t, likely reflecting a combination of favorable electronics and sterics.

Alkyne substituents have a more minor effect on catalytic activity with less pronounced dependence on sterics. In sharp contrast to thiol effects, increasing alkyne encumbrance (entries 4−10 and 1−6) results in only minor changes in rate. Changing to an α-disubstituted alkyne (**9**) has little impact on N_t, even with a conjugated enyne (**8**).

In situ monitoring of the reaction reveals that complex **1a** undergoes rapid Th-CH_2TMS protonolysis (step i, Scheme 1) in the presence of excess thiol, without the aid of an additional activator.[10f] Kinetic studies reveal entry 1 to be first-order in [**1a**] (at ≳7.7 mM), first-order in [alkyne] at lower alkyne concentrations, zero-order at higher [alkyne],[17] and zero-order in [thiol] (eq 1). These findings are consistent with the catalytic cycle of Scheme 1 and with turnover-limiting alkyne insertion into the An−S bond.

$$\text{rate} = k[\text{catalyst}]^1[\text{alkyne}]^x[\text{thiol}]^0 \qquad (1)$$

To determine a possible kinetic isotope effect, the reaction of 1-pentaneSD (**2-D**) with excess 1-hexyne (**6**) was monitored by ^{1}H and ^{2}H NMR spectroscopy. Exchange of deuterium between the thiol and terminal alkyne C−H group is observed (entry 2, Table 1) with excess alkyne effectively diluting the product deuteration. When the reaction is carried out in a stoichiometric thiol:alkyne ratio, deuterium is equally distributed between the E and Z positions. This presumably reflects reversible alkyne C−H activation, similar to that observed by Eisen with organoactinide complexes.[12b,18] As a result, deuterium distributed between the thiol and alkyne results in partial deuteration of both the E and Z positions.

In summary, we have demonstrated efficient and highly Markovnikov selective organoactinide-catalyzed addition of aryl, benzyl, and aliphatic thiols to terminal alkynes yielding a variety of vinyl sulfides. Further studies are underway to explore scope and mechanism.[19]

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Supporting Information Available: Experimental details and kinetic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) [Alkyne]≳ 2.7×10^{-1} M. Excess alkyne is not required but is employed in this study to increase the reaction rate and induce a pseudozero-order reaction.

(16) Anti-Markovnikov side products in entry 7 can be suppressed via addition of the radical inhibitor γ-terpinene. See Supporting Information for side product ratios.

(17) The rate with respect to [alkyne] exhibits Michaelis−Menten-like kinetics. See Supporting Information.

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(19) Hydrothiolation has also been successfully carried out with organolanthanide catalysts. Reports will be forthcoming.

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