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Highly Selective Copper-Catalyzed Ring Expansion of Vinyl Thiiranes: Application to Synthesis of Biotin and the Heterocyclic Core of Plavix

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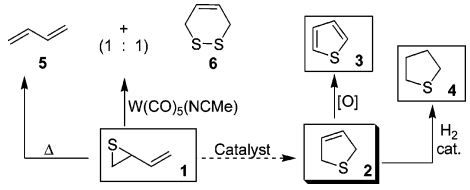
Thiophenes and tetrahydrothiophenes are valuable synthetic building blocks which are essential components of a variety of products, ranging from pharmaceuticals to materials. While much effort has been devoted to the synthesis of thiophenes[1] and tetrahydrothiophenes,[2] dihydrothiophenes have received much less attention even though they are more amenable to further functionalization.[3] Despite new methods using olefin metathesis[4] and gold catalysis,[5] the earliest reductive approach by Birch still remains the most common approach.[6] We envisioned that vinyl thiiranes could serve as very attractive synthons for accessing 2,5-dihydrothiophenes, and in this Communication, we report on the development and study of the first formation of 2,5-dihydrothiophenes from vinyl thiiranes using readily available copper catalysts.

Vinyl thiiranes are underutilized synthons in organic chemistry.[7] Although direct thiiranation of olefins still remains a challenge,[8] vinyl thiiranes can be easily accessed from vinyl oxiranes[9] or by the reduction of enone thiophosphates.[10] There are very few reported ring expansions of vinyl thiiranes (**1**) in the literature (Scheme 1), which is perhaps not surprising given how readily they undergo desulfurization to form conjugated dienes (**5**) when heated.[11] The work of Adams[12] and Alper[13] is most relevant to our pursuit. Adams has shown that vinyl thiiranes can be converted to dihydrodithiins (**6**) along with equimolar amount of dienes (**5**) using a tungsten catalyst, and Alper has used palladium catalysts to ring expand vinyl thiiranes to several four-membered vinyl-substituted heterocycles. To the best of our knowledge, there are no successful examples of the ring expansion of vinyl thiiranes to 2,5-dihydrothiophenes (**2**).[14] The products of such a reaction are particularly attractive synthetic intermediates since it is well-established that they can be readily oxidized or reduced to thiophenes (**3**) and tetrahydrothiophenes (**4**), respectively.

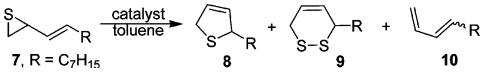
Scheme 1. Vinyl Thiirane Ring Expansions



Encouraged by our recent success in the rearrangement of vinyl oxiranes, we proposed that an analogous reaction might occur with a vinyl thiirane.[15] We realized three main obstacles would need to be overcome for this ring expansion to be successful. Since vinyl thiiranes readily fragment to form dienes (**5**) when heated, the ring expansion would need to occur at lower temperatures than for vinyl oxiranes (150 °C) in order to outcompete undesired sulfur extrusion. Turning over the catalyst, exchanging a 2,5-dihydrothiophene (**2**) for a vinyl thiirane (**1**), might also prove to be particularly challenging since thioethers coordinate to metal catalysts much stronger compared to their ether counterparts. Competing nucleophilic sulfide addition to the metal activated thiirane and resulting intramolecular disulfide formation to form **6**, as observed by Adams, was also of significant concern.

Vinyl thiirane **7** was chosen as a model substrate, and it was determined that the nucleophilic dihydrothiin (**9**) formation and extrusion of sulfur as the pathways (both of which lead to diene **10**) in competition with the rearrangement to a 2,5-dihydrothiophene (**8**). Further studies revealed that the product distribution of these three pathways was also affected by the catalyst electronics (Table 1). Of catalysts studied to date, only copper catalysts have been shown to rearrange vinyl thiirane **7** to 2,5-dihydrothiophene **8**. Competing dihydrodithiine (**9**) formation turns also out to be a major challenge, but we were able to suppress this intermolecular reaction by using lower concentration. As expected, suppressing the undesired desulfurization (**10**) pathway proved to be the main obstacle we needed to overcome. Most copper catalysts did not facilitate the formation of **8** to any appreciable extent (entries 2−9). Our studies revealed that fluorinated copper(II) acetylacetonate (acac) catalysts improved formation of 2,5-dihydrothiophene **8** as the major product (entries 10−11), and copper(II) hexafluoroacetylacetonate in particular proved to be superior by successfully suppressing both diene (**10**) and dihydrodithiine (**9**) formation while favoring the catalytic ring expansion of **7**−**8** (entry 11).

Table 1. Copper-Catalyzed Ring Expansion of Vinyl Thiiranes



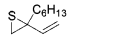
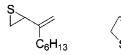
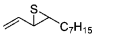
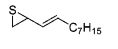
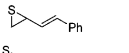
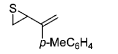
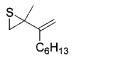
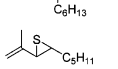
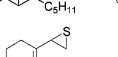
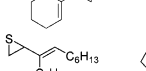
entry	catalyst	time (h)[a]	8/9/10[b]
1	none	12	0:0:1
2	Cu	12	0:0:1
3	CuBr	2	1:9:10
4	$Cu(OAc)_2$	2	0:1:3
5	$Cu(TFA)_2$	2	0:1:1
6	Cu(thiophene 2-carboxylate)	2	0:2:3
7	$Cu(cyclohexanebutyrate)_2$	2	1:4:8
8	$Cu(2\text{-ethylhexanoate})_2$	2	1:3:4
9	$Cu(acac)_2$	3	1:6:8
10	$Cu(tfacac)_2$	3	2:0:3
11	**$Cu(hfacac)_2$**	**1**	**11:0:1**

[a] For a 100% conversion at 5 mol % catalyst, 120 °C and 0.01 M in toluene. [b] Ratio determined by analyzing ^1H NMR spectra of unpurified mixture.

This ring expansion is not only limited to vinyl thiirane **7**, but also proves to be tolerant of many substitution patterns. Several monosubstituted vinyl thiiranes are shown to be competent (entries 1−6), and as can be seen from entries 1−4, regioisomeric vinyl thiiranes can be used to access the same 2,5-dihydrothiophene product.[16](Table 2). The substrate shown in entry 1 was used to study the effects of catalyst loading and temperature. We were able to use a catalyst loading of 0.1 mol % to achieve full conversion in less than 2 h. At room temperature, the reaction was found to

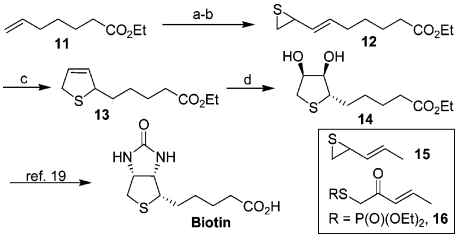
10.1021/ja069059h CCC: $37.00

Table 2. Copper-Catalyzed Synthesis of 2,5-Dihydrothiophenes*

entry	substrate	product	mol %	t (h)	T (°C)	yield[a]
1			1	0.5	80	93%
			0.1	1.7	80	95%[b]
			10	40	25	95%[b]
2			1	1	100	95%
3[c]			5	3	120	85%
4[c]			5	1.5	120	78%
5[c,d]			10	2	110	91%
6			2	2	80	85%
7			10	20	80	75%
8			10	20	80	92%
9[c]			30	24	100	35%[f]
10			10	4.5	80	65%

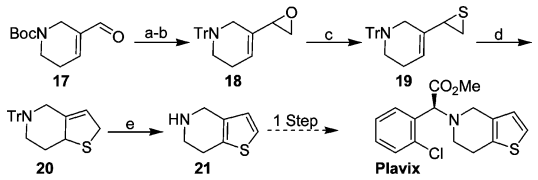
*Conditions: $Cu(hfacac)_2$, C_6H_6, 0.1 M. [a] Isolated yield. [b] Yield based on molar ratios from ^1H NMR integration [c] Concentration = 0.01 M. [d] Toluene. [e] $Cu(tfacac)_2$. [f] Volatile product.

Scheme 2. Formal Racemic Total Synthesis of Biotin



Conditions: (a) **16**, Grubbs second, CH_2Cl_2, 40 °C, 70%; (b) $NaBH_4$, MeOH, 10 °C, 83%; (c) 5% $Cu(hfacac)_2$, benzene, 120 °C, 1.5 h, 0.01 M, 80%; (d) AD-mix α, *t*-BuOH, H_2O, room temp, 50% (80% based on recovered starting material).

Scheme 3. Synthesis of the Thiophene Core of Plavix



Conditions: (a) TFA, CH_2Cl_2, room temp then TrCl, Et_3N, room temp, 93%; (b) $ClCH_2I$, *n*-BuLi, THF, −78 °C to room temp; (c) KSCN, Et_3N, CH_2Cl_2−MeOH, room temp, (40%, two steps); (d) 5 mol % $Cu(tfacac)_2$, C_6H_6, 100 °C, 52%; (e) SO_2Cl_2, Et_3N, CH_2Cl_2, 0 °C, then 1 M HCl, THF, room temp, 65%.

proceed in 2 days with 10 mol % catalyst. Furthermore, entry 8 was found to proceed best with the less electrophilic $Cu(tfacac)_2$ catalyst. Similarly, disubstituted vinyl thiiranes (entries 7−10) are also excellent substrates for this reaction. The synthetic utility of this new method has been demonstrated in the synthesis of biotin and Plavix, as detailed in Schemes 2 and 3.

Biotin (vitamin H) is an important biocatalyst involved in carbon dioxide transport, which has remained a synthetic challenge since its isolation 70 years ago.[17] Our synthetic method can be used to access the tetrahydrothiophene moiety from commercially available ethyl 6-heptenoate (**11**, Scheme 2). Although attempts to form vinyl thiirane **12** in a single step by cross metathesis of **11** with **15** were unsuccessful, cross metathesis with enone thiophosphate **16** followed by a selective reduction with $NaBH_4$ and in situ cyclization did afford **12** in good yield. In our key synthetic step, vinyl thiirane **12** rearranged to give the desired 2-substituted 2,5-dihydrothiophene (**13**), which then underwent a chemoselective and substrate controlled dihydroxylation[18] affording diol **14**, an intermediate in Ohrui's synthesis[19] of biotin, in only four steps from ester **11**.

Plavix is an antiplatelet medication used to reduce the risk of heart attack and stroke.[20] Our copper catalyzed vinyl thiirane rearrangement can be used to access its fused heterocyclic core (**21**) in a few steps as illustrated in Scheme 3. The amino group of **17**[21] was first protected, and the aldehyde was then converted in a single step to epoxide **18**, which was then thiiranated using potassium thiocyanate. Thiirane **19** ring expanded to 2,5-dihydrothiophene **20** in the presence of $Cu(tfacac)_2$. Oxidation using sulfuryl chloride[22] proceeded smoothly to a fused thiophene product, which upon deprotection afforded **21**. This synthetic building block has been utilized to access Plavix in one additional step.[23]

In summary, we have demonstrated that vinyl thiiranes can be selectively converted to 2,5-dihydrothiophenes in excellent yields using commercially available electrophilic copper(II) catalysts. This new methodology provides a mild new entry into the thiophene framework as illustrated by our synthetic approaches to biotin and Plavix. Further studies on the mechanism and scope of this new catalytic ring expansion are currently underway.

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Supporting Information Available: Experimental details and physical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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