



Pergamon

Tetrahedron Letters 41 (2000) 1363–1367

TETRAHEDRON
LETTERS

Palladium and nickel catalyzed thio-Claisen rearrangements of chiral bicyclic thiolactams (via *N,S*-ketene acetals)

Daniel J. Watson, Paul N. Devine and A. I. Meyers *

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

Received 17 November 1999; revised 6 December 1999; accepted 9 December 1999

Abstract

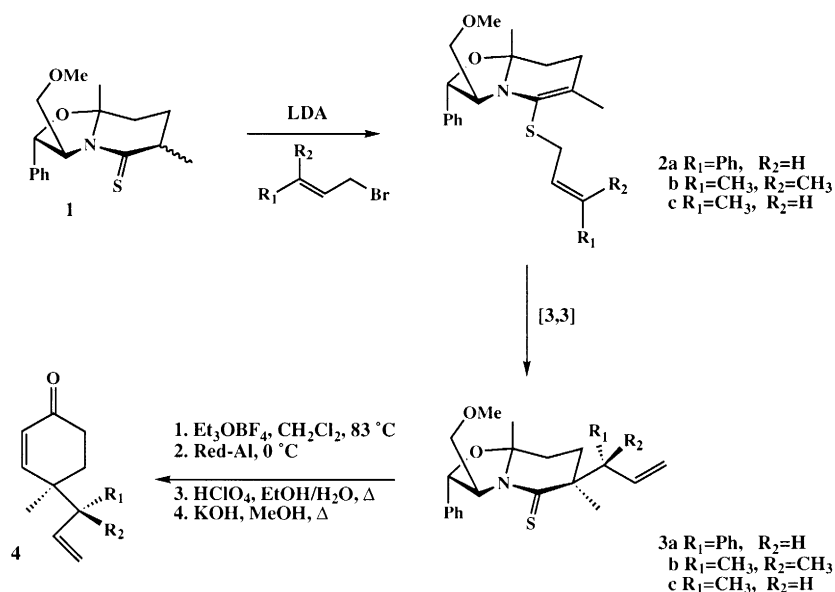
Pd, Ni, and Lewis acid catalyzed rearrangements occur under milder conditions than the thermal version of the titled rearrangements. © 2000 Elsevier Science Ltd. All rights reserved.

Recently, we reported¹ the highly stereoselective thio-Claisen rearrangement starting from **1** and a number of allylic halides to generate *N,S*-ketene acetals **2a–c** (Scheme 1). The resulting thiolactams **3a–c** bearing vicinal stereogenic quaternary centers or quaternary–tertiary centers were then transformed into 4,4-disubstituted cyclohexenones, **4**.

Further application of this thio-Claisen rearrangement has led to the first asymmetric synthesis of the sesquiterpene (–)-trichodiene,² as well as providing an asymmetric route to chiral cyclohexenones with spiro-connected cyclopentenones.³ Based upon our early work, Rawal has recently achieved highly diastereoselective thio-Claisen rearrangements employing a *C*₂-symmetric amine as the chiral auxiliary.^{4a} Apart from the classical thermal version of [3,3]-sigmatropic rearrangements^{4b–f} there has been increasing interest in the use of transition metals (Hg^{II}, Pd^{II}) to catalyze these transformations under mild conditions.⁵ Although extensive studies are known in the transition metal catalyzed [3,3]-sigmatropic rearrangements, we have found no examples of metal catalyzed thio-Claisen rearrangements. We now describe, in preliminary form, our findings that *N,S*-ketene acetals **2a** and **2b** undergo both Lewis acid and transition metal promoted [3,3]-sigmatropic rearrangements, under mild conditions, to afford thiolactams **3a** and **3b**, a process which would significantly enhance its synthetic utility.

Although Lewis acids are known to accelerate aromatic and aliphatic *O*-Claisen rearrangements,⁶ the thio-Claisen rearrangement of **2a** to **3a** has failed in our hands using common Lewis acids. TiCl₄, Bu₂BOTf and ZnCl₂ resulted in cleavage of the *S*-allylic-C bond in **2b** affording the starting α -methylated thiolactam **1**. Alkylaluminums implemented the thio-Claisen rearrangement at room temperature and although the diastereomeric ratio of the newly formed quaternary center in **3** was poor (<3:1), we obtained significantly higher yields (68–78%) than those obtained in the thermal rearrangement. When

* Corresponding author.



Scheme 1.

prenyl bromide was used to prepare the *N,S*-ketene acetal **2b**, Me₃Al provided the rearranged product **3b** in 75% yield when heated in ethylene dichloride at 83°C.

We then examined metal salts of Pd and Ni, which have been shown to catalyze a wide variety of [3,3]-sigmatropic rearrangements. Yoshida⁷ has reported several examples of the regioselective S→N allylic rearrangement of *S*-allylthioimidates into *N*-allylthioamides catalyzed by palladium(II) chloride. In addition, rearrangements such as the *O*-allyl thiocarboxylate rearrangement⁸ and the *O*-allyl phosphorothionate (C–O→C–S) rearrangement⁹ have also been reported to proceed under mild conditions. To our knowledge, none of these metals have ever been utilized in the thio-Claisen rearrangement.¹⁰

N,S-Ketene acetal **2a**, when treated with 10 mol% of the palladium(II) catalyst resulted in the rearrangement at 25°C to produce the desired thiolactam **3a**. The rearrangement of **2a** occurred with a variety of palladium(II) catalysts at room temperature whereas the thermal rearrangement of **2a** required heating at 140°C (Table 1). Initially, the use of PdCl₂(MeCN)₂, PdCl₂(PPh₃)₂ and Pd(OAc)₂ (Table 1, entries 2–4) provided thiolactam **3a** as a 3:1 mixture of *exo* (β) and *endo* (α) diastereoisomers, respectively. When palladium(0) was employed as a potential catalyst for this rearrangement it was found that Pd(PPh₃)₄ (entry 6) catalyzed the rearrangement at 25°C and afforded a diastereomeric ratio of 3.4:1 in favor of the *exo* (β) diastereomer **3a**. However, the best result came from a Pd₂(dba)₂ catalyzed rearrangement of **2a** to provide **3a** in a diastereomeric ratio of 5.6:1 (entry 7). Although moderate diastereoselectivity was observed under catalytic conditions it is important to note that the isolated yield of the major *exo* diastereomer **3a** was somewhat higher than that obtained during the thermal rearrangement (entry 1).

NiCl₂(Ph₃P)₂ also effected the rearrangement at room temperature affording the thiolactam **3a** as a 4:1 mixture of *exo:endo* diastereoisomers, respectively, (entry 8). However, with tetrakis(triphenylphosphine)-nickel(0) reagent prepared from the treatment of a nickel(II) salt with either zinc metal or *n*BuLi,¹¹ the ratio of *exo* to *endo* diastereomers decreased (2:1 and 2.6:1, respectively, entries 9 and 10). The Lewis acid by-products, from the preparation of these catalysts were shown to render them ineffective in the thio-Claisen rearrangement and thus the Ni(PPh₃)₄ suffers from the same limitations as the Lewis acid catalysis. Ni(COD)₂ effected the rearrangement much the same as

Table 1
Thio-Claisen rearrangement of *N,S*-ketene acetal **2a** to thiolactam **3a** with palladium and nickel catalysts

Entry	Catalyst (10 mol %)	Temp (°C)	Time (h)	d.r. ^a <i>exo:endo</i> 3a	Yield ^b of 3a (%)
1	no catalyst	140		>99:1 ^c	48
2	PdCl ₂ (MeCN) ₂	25	28	3.0:1	65
3	PdCl ₂ (Ph ₃ P) ₂	25	18	3.2:1	57
4	Pd(OAc) ₂	25	18	3.3:1	54
5	PdCl ₂ (dppf)	25	17	3.0:1	64
6	Pd(Ph ₃ P) ₄	25	17	3.4:1	64
7	Pd ₂ (dba) ₃	25	15	5.6:1	58
8	NiCl ₂ (Ph ₃ P) ₂	25	16	4:1	58
9	Ni(Ph ₃ P) ₄ /LiCl	25	24	2.6:1	46
10	Ni(Ph ₃ P) ₄ /ZnCl ₂	25	24	2:1	59
11	Ni(COD) ₂	25	16	3.3:1	63

^aRatio determined by ¹H NMR, ^bIsolated Yield of the major *exo* diastereomer, ^cRatio determined by GC.

palladium to provide the thiolactam **3a** in a 3.3:1 mixture of *exo:endo* diastereomers (entry 11). Solvent changes resulted in little change in product ratios.

The prenyl bromide derived *N,S*-ketene acetal **2b** underwent a [3,3]-sigmatropic rearrangement with both palladium and nickel catalysts to afford thiolactam **3b** bearing vicinal quaternary stereogenic centers. In all the examples the rearrangement occurred with high diastereoselectivity (>20:1, *exo:endo*) and good chemical yield although heating to 65°C in THF was required (Table 2, entries 2–5 and 8). The ¹H NMR spectrum derived from the crude mixture indicated the presence of a single diastereomer corresponding to the rearrangement to the *exo* (β) face of the bicyclic system. Again, in the case of the Ni(PPh₃)₄ (entries 6 and 7), the ratio of *exo:endo* diastereomers decreased dramatically due to the presence of Lewis acid by-products. However, it is noteworthy that in entries 6 and 7 the rearrangement occurred at room temperature.

Table 2
Thio-Claisen rearrangement of *N,S*-ketene acetal **2b** to thiolactam **3b** with palladium and nickel catalysts

Entry	Catalyst (10 mol %)	Temp (°C)	Time (h)	d.r. ^a (<i>exo:endo</i>) 3b	Yield ^b of 3b (%)
1	no catalyst	140		>99:1 ^c	68
2	PdCl ₂ (MeCN) ₂	65	36	>20:1	65
3	PdCl ₂ (dppf)	65	48	>20:1	66
4	Pd ₂ (dba) ₃	65	36	>20:1	50
5	NiCl ₂ (Ph ₃ P) ₂	65	37	>20:1	62
6	Ni(Ph ₃ P) ₄ /LiCl	65	24	2.2:1	40
7	Ni(Ph ₃ P) ₄ /ZnCl ₂	65	24	3:1	63
8	Ni(COD) ₂	65	44	>20:1	70

^aRatio determined by ¹H NMR, ^bIsolated yield of major *exo* diastereomer, ^cRatio determined by GC.

The stereochemistry of products **3a** was shown to be identical to that observed from the thermal [3,3]-sigmatropic rearrangement indicating palladium(II) most likely catalyzes the rearrangement through a chair transition state.¹² Rationale for the stereoselective outcomes is presented below (Figs. 1 and 2). The palladium(II) pathway⁵ (Fig. 1) coordinates to the double bond of **2a** and subsequent nucleophilic attack of the thioenol ether provides a six-membered palladated intermediate **5** which undergoes elimination

of Pd(II) to afford the [3,3] rearranged thiocarbonyl **3a**. The palladium(0) pathway (Table 1, entry 6) is shown in Fig. 2. The low selectivity shown by *N,S*-ketene acetal **2a** may be due to the proximity of Pd and the phenyl group in **5** (Fig. 1), or the regioselectivity in thioenolate addition to the π -allyl complex in **6** (Fig. 2).¹³

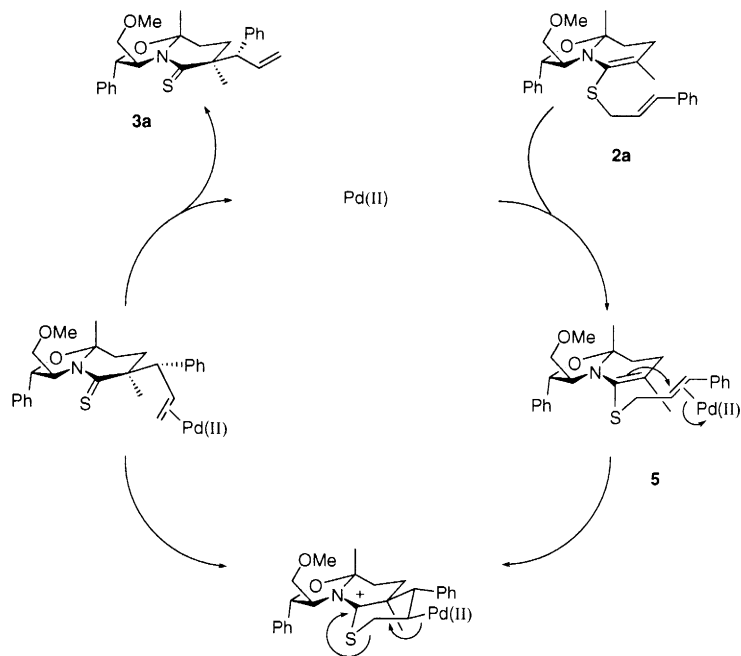


Fig. 1.

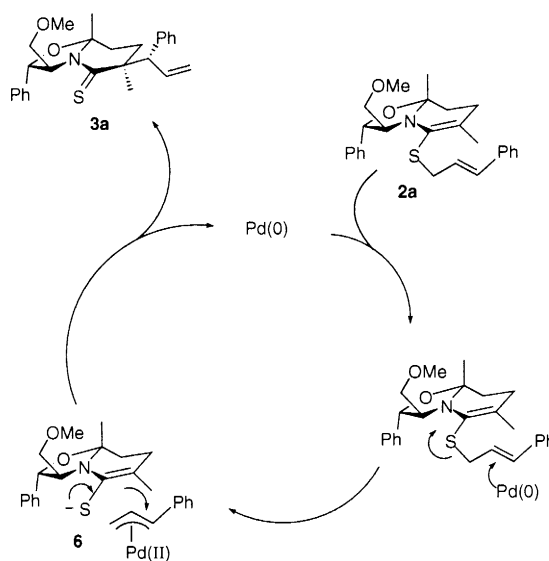


Fig. 2.

Thio-Claisen rearrangements derived from a thioketone have been reported to be reversible.¹⁴ However, [3,3]-sigmatropic rearrangements from thioamides are rarely reversible.² When we subjected both the 3:1 mixture and the pure *endo* diastereomer **3a** to thermal conditions (xylenes, 140°C, 12 h), we

