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FORMATION OF 3-PYRROLIN-2-ONES *VIA* 5-*ENDO-TRIG* CYCLIZATION

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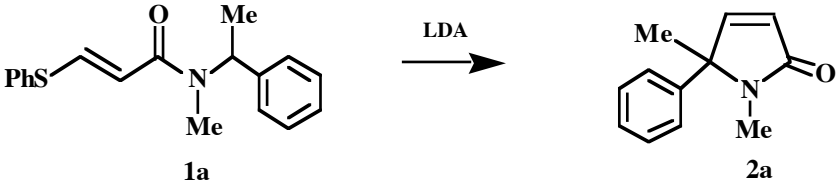
Abstract - Anionic cyclization of *N*-benzyl-3-phenylsulfanyl-2-propenamide derivatives gave the corresponding 3-pyrrolin-2-ones. Mechanistic investigation using deuterated starting materials revealed this cyclization proceeds *via* a 5-*endo-trig* process.

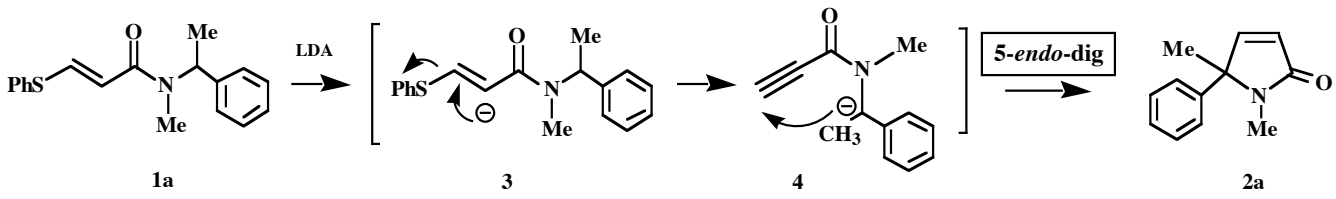
In the course of our studies on the chemistry of amide homoenolates,[1] we have examined the behavior of various *N*-benzyl-3-phenylsulfanyl-2-propenamide derivatives under basic conditions, and found that LDA treatment of (3-phenylsulfanyl)propenamide derivative (**1a**) at -20°C gave 3-pyrrolin-2-one (**2a**) in 80% yield. Having been interested in the mechanism, we looked into this reaction in detail.



1a **2a**

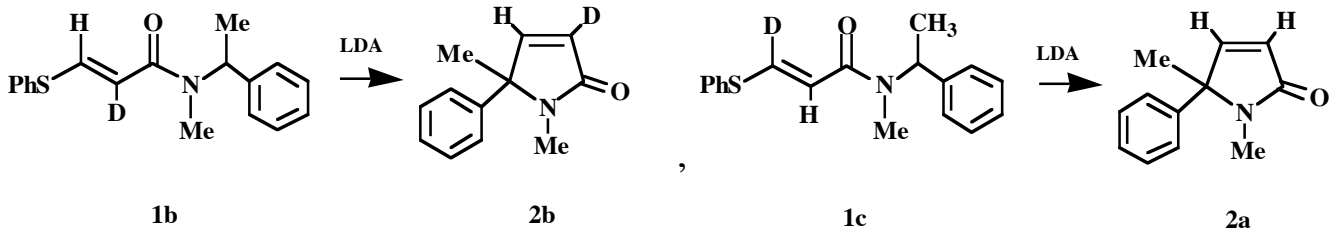
Scheme 1

According to the Baldwin's rules, 5-*endo-dig* cyclizations are favorable processes whereas 5-*endo-trig* cyclizations are disfavorable.[2] Therefore, we assumed that the above reaction should have proceed *via* the 5-*endo-dig* process as shown below (Scheme 2).



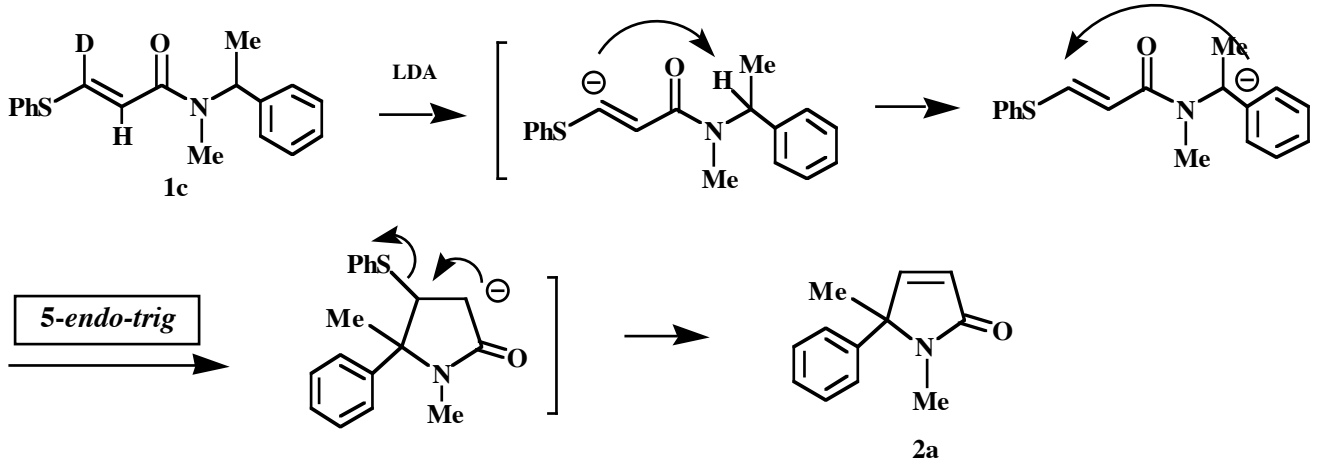
Scheme 2

To confirm the assumption, deuterium was introduced into the starting material (**1a**). Thus, α-deuterated (**1b**) and β-deuterated compound (**1c**) were prepared and subjected to the cyclization. To our surprise, α-deuterium of **1b**, which should disappear during the 5-*endo-dig* process, remained in the product (**2b**) and β-deuterium of **1c**, which should be untouched, disappeared (Scheme 3).



Scheme 3

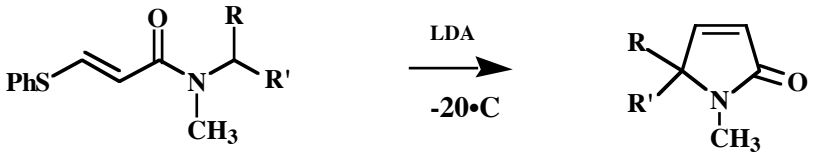
On the bases of these results we concluded that this cyclization reaction proceeds *via* the 5-*endo-trig* process as shown below (Scheme 4).



Scheme 4

Despite the disfavored nature of a 5-*endo-trig* mode,[2] reports of examples continue to appear in the literature.[3-5] However, to our best knowledge, most of the anionic 5-*endo-trig* cyclizations reported so far include the nucleophilic addition of heteroatoms.[3,4] Therefore, the above reaction is one of the rare examples which proceeds *via* the 5-*endo-trig* process with an sp^3 carbon nucleophile.[5]

To assess the applicability of this type of cyclization, some 3-phenylsulfanyl-2-propenamide derivatives were subjected to the reaction. The results are summarized in Table 1.



1 **Scheme 5** 2

Table 1. Cyclization of (3-phenylsulfanyl)propenamides.

entry	1	R	R'	time (min)	2	yield 2 (%)
1	(*S*)-1a	Me	Ph	60	(+)-2a	80
2	(*R*)-1a	Me	Ph	60	(-)-2a	78
3	1b (α-D)	Me	Ph	60	2b	76
4	1c (β-D)	Me	Ph	60	2a	72
5	1d	H	Ph	45	2d	46
6	1e	Me	*p*-Me-C_6H_4	60	2e	64
7	1f	Me	1-naphthyl	45	2f	78
8	1g	Ph	Ph	60	2g	47
9	1h	Me	CO_2Et	30	2h	57

When **1d** (R=H) was used (entry 5), the yield was low and the product was contaminated with a small amount of impurities. Presumably side reaction occurs due to the high acidity of the γ-hydrogen of the product. In the other cases the corresponding pure products were isolated in good yields. Ester derivative (**1h**) also gave the corresponding cyclized product in good yield (entry 9).

It should be noteworthy that optically active starting materials [(*S*)-**1a** and (*R*)-**1a**] gave the corresponding optically active products [(+)-**2a**: $[\alpha]_D$ +278° (*c* 2.8, $CHCl_3$) and (-)-**2a**: $[\alpha]_D$ -273° (*c* 1.5, $CHCl_3$)] (entries 1 and 2).[6] The optical purity was determined by HPLC on CHIRALCEL OJ-R and found to be >98% ee.

A typical procedure: To a cooled (-20°C) THF solution (20 mL) of LDA (1.3 mmol) was added a THF solution (5 mL) of **1a** (1 mmol), and then the mixture was stirred at that temperature for 60 min. Usual workup followed by purification by flash column chromatography (hexane:AcOEt=1:1) gave **2a** in 80% yield.

Further studies to explore the scope and limitations of the above reaction are currently in progress.

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