Pergamon

Tetrahedron Letters 40 (1999) 3119–3122

TETRAHEDRON LETTERS

[1,3] and [3,3] Rearrangements of 3-Amino-1,5-Hexadienes: Solvent Effect on the Regioselectivity

Heather K. Dobson, Richard LeBlanc, Hélène Perrier, Corey Stephenson, Teresa R. Welch and Dwight Macdonald*

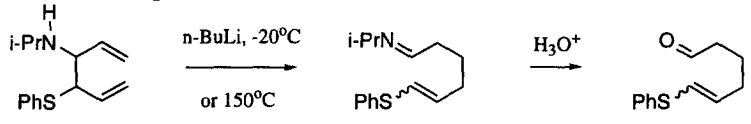
Merck Frosst Centre for Therapeutic Research
P.O. Box 1005, Pointe Claire-Dorval,Québec, Canada, H9R 4P8

Received 19 January 1999; accepted 22 February 1999

Abstract: *3-Amino-1,5-Hexadienes rearrange under anionic conditions to give a [1,3] product in addition to the [3,3] (Cope) product. With some substrates the regioselectivity of the reaction is strongly influenced by the solvent polarity.*

Keywords: aldehydes; amines; dienes; imines; rearrangements; thioethers.

The anionic amino-Cope reaction has come under considerable study in the past few years. Recently Houk and Meyers have published an experimental and *ab initio* study showing that 3-amino-1,5-hexadienes have a potential for fragmentation in addition to the [3,3] rearrangement under anionic conditions.[1] Allin has subsequently reported examples of a highly stereoselective, assymetric, anionic amino-Cope rearrangement which would suggest that a concerted mechanism is operating.[2] Previously we reported, in addition to other cyclic examples, the charge accelerated and thermal rearrangements of **1a** which gave the [3,3] product **2**, after acid workup.[3]



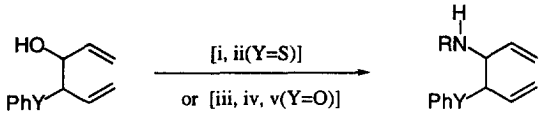
1a **2**

Further investigation of the amino-Cope reaction has led us to the discovery that acyclic 3-amino-1,5-hexadienes such as **1a** rearrange to afford both the [3,3] (Cope) product and the [1,3] product under anionic conditions. This is in sharp contrast to the thermal reaction which yields only the [3,3] product. We have also discovered that with some substrates the ratio of the [3,3] to [1,3] products of the anionic reaction can be controlled by the choice of the solvent. Furthermore, our studies show that the entire diene is necessary for the [1,3] reaction to occur, even though the allyl sulfide unit remains intact in the product.

The 3-amino-1,3-dienes we have used for this study contain either a 3-SPh or a 3-OPh. In the case of the 3-SPh substrate we have also prepared a variety of N-substituents. The

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00455-4

synthesis of 3-SPh substrates was via **3**[4] as shown in Scheme 1 and is similar to that of **1a,** which we have previously reported.[3] The synthesis of the 3-OPh compound is also shown in Scheme 1. Mitsunobu displacement of the known alcohol **4**[4] with phthalimide followed by aminolysis and reductive amination with acetone afforded compound **5**.



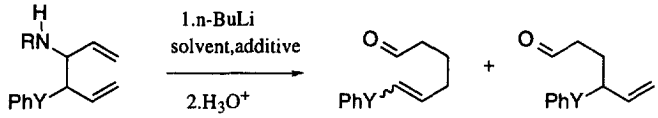
3 (Y=S)
4 (Y=O)

1a-d, 5
mixture of diastereomers

	Y	R	Yield (%)
1a	S	i-Pr	32
1b	S	Me	36
1c	S	t-Bu	51
1d	S	Bn	56
5	O	i-Pr	48

Reagents and conditions: (i) NaH,TsCl,THF; (ii) RNH_2 excess; (iii) PPh_3, t-BuOCON=NCO_2t-Bu, phthalimide, THF; (iv) $MeNH_2$, EtOH; (v) acetone, AcOH, $NaBH_3CN$, MeOH.

Scheme 1



1, 5 [3,3] [1,3]

R	Y	Solvent	Additive	T(°C)	Time (min.)	[3,3]/[1,3]	cis/trans [3,3]	% Yield[a]
i-Pr	S	THF	-----	-78	10	1/2	1/5	54
			TMEDA	-70	30	1/2	1/9	57
			HMPA	-78	30	1/5	1/10	43[b]
		TOLUENE	-----	-20	60	1/1	2/1	50
			TMEDA	-78	30	8/1	3/1	49[b]
			HMPA	-60	60	3/2	2/1	27
		HEXANE	-----	-20	60	2/1	2/1	31
			TMEDA	-78	30	10/1	4/1	37
			HMPA	-60	60	4/1	3/1	43
i-Pr	O	THF	TMEDA	25	45	3/1	1/2	20
			HMPA	25	45	2/1	1/1	36
		TOLUENE	TMEDA	25	45	4/1	1/3	13
Me	S	THF	TMEDA	-78	15	1/3	1/3	69
t-Bu			TMEDA	-78	30	1/3	1/2	63
CH_2Ph			TMEDA	-78	15	1/2	2/3	73
Me	S	TOLUENE	TMEDA	-20	30	4/1	2/1	33
t-Bu			TMEDA	-20	30	7/1	3/1	25
CH_2Ph			TMEDA	-20	30	2/1	1/1	20

a) No starting material or other easily identifyable products were obtained except for small amounts of the cleavage product allyl phenyl sulfide.
b) A 6% yield of allyl phenyl sulfide was obtained in these two examples.

Table 1[5]

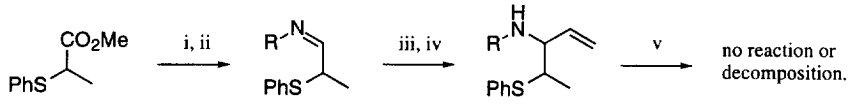
When **1a** is treated with n-BuLi in a non-polar solvent, such as hexane, the [3,3] product predominates (Table 1). However when a polar solvent like THF is used, the [1,3] product is predominant in a very facile reaction at -78°C. Addition of a coordinating additive

such as HMPA or TMEDA results in a more facile reaction, particularly with toluene or hexane as solvent (-78 vs -20°C). The coordinating additives also increase the solvent effects on the regioselectivity of the reactions. For example, TMEDA increases the selectivity for the [3,3] product in toluene and hexane while HMPA increases the selectivity for the [1,3] product in THF. The [1,3] product is also observed when the OPh diene **5** is used (Table 1). In the case of **5**, however, the [3,3] product predominates even when THF is used as solvent. The PhS in **1a** has a significant effect on the reactivity of the system because this substrate reacts at -78°C under the same reaction conditions in which the PhO substituted compound **5** requires 25°C. The PhS in **1a** also has a significant directing effect on the course of the reaction, allowing the regioselectivity of the reaction to be strongly controlled toward either the [3,3] or the [1,3] reaction depending on the choice of solvent. The PhO substrate **4** does not allow the same degree of flexability; the ratio of [3,3] to [1,3] can only be varied from 4:1 to 2:1 by using non-polar and polar solvents.

The ratio of the cis/trans [3,3] products bears an interesting relation to the reaction conditions in the case of the PhS substrates. The non-polar solvent favors the cis product while the polar solvent favors the trans product.

The N-substituent on **1** has little effect on the reaction. Polar and non-polar conditions yield similar product ratios with **1a, b, c** and **d** (Table 1).

The allyl amines **6a** and **6b** were prepared (Scheme 2) to determine if it is possible to completely direct the reaction toward a [1,3] process by replacing the allyl sulfide part with an alkyl sulfide. Treatment of the imines **7a** and **7b** with boron trifluoride etherate in THF at -78°C followed by vinyl magnesium bromide then warming to 25°C provided compounds **6a** and **6b**. Placing **6a** and **6b** under similar conditions to those used for the rearrangements of compounds **1** and **5** gave only recovered starting material or decomposition. Thus the complete diene is required for the [1,3] reaction. It may be possible to achieve a [1,3] reaction with another activating group to replace the alkene, but this is the subject of further investigation.



Mixture of diastereomers

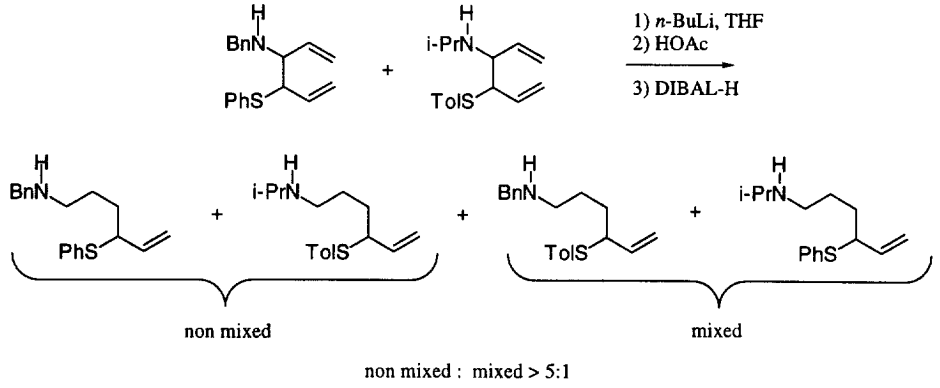
7a R = $CH(CH_3)_2$ **6a** 12%
7b R = CH_2Ph **6b** 46%

Reagents and conditions: (i) DIBAL-H, hexane, -78 °C; (ii) RNH_2, AcOH, $MgSO_4$, ether, RT; (iii) $BF_3.Et_2O$, THF, -78°C; (iv) CuI, vinylmagnesium bromide, -30°C to RT (R=i-Pr) or: vinylmagnesium bromide, -78°C to RT (R=Bn); (v) BuLi, additive, THF (additive = none, HMPA, t-BuOK).

Scheme 2

The influence of the solvent on the regioselectivity of the reactions may be due to a fragmentation pathway being favored by the polar solvent while the non-polar solvents favor the concerted pathway. The effect of the solvent on the cis/trans [3,3] product selectivity may

be due to the cis [3,3] product being preferentially formed by a concerted mechanism while the trans [3,3] product is formed preferentially by a fragmentation pathway. In order to further examine the mechanism of these rearrangements, we performed the mixing experiment shown in Scheme 3, where we found that there is very little or no mixing of the starting material substituents in the products. This result would suggest that either a concerted pathway is operating, to form the [1,3] product, or that it is a very rapid fragmentation-recombination pathway. We are currently studying the stereoselectivity of the [1,3] and the [3,3] rearrangements, on stereochemically pure substrates, in order to more clearly understand the mechanism and also to evaluate the synthetic potential of the reactions.



Scheme 3

In conclusion, we have discovered that 3-amino-1,5-hexadienes undergo anionically mediated [1,3] rearrangements in addition to the usual [3,3] processes previously reported. In the case of the 3-SPh substrate, the conditions of the reaction strongly influence the [1,3] to [3,3] regioselectivity. These products may arise from either a concerted pathway or a rapid fragmentation-recombination process.

References and Notes

1. Yoo, Y.H.; Houk, K.N.; Lee, J.K.; Scialdone, M.A.; Meyers, A.I. *J. Am. Chem. Soc.*, **1998**;*120*:205-206.
2. Allin, S.M.; Button, M.A.C. *Tetrahedron Lett.*, **1998**;*39*:3345-3348; Allin, S.M.; Button, M.A.C.; Baird, R.D. *Synlett*, **1998**:1117-1119.
3. Sprules, T.J.; Galpin, J.D.; Macdonald, D. *Tetrahedron Lett.*, **1993**;*34*:247-250.
4. Evans, D.A.; Baillargeon, D.J.; Nelson, J.V. *J. Am. Chem. Soc.*, **1978**;*100*:2242-2244.
5. Typical Procedure: To the amino-diene (0.4 mmol) and the additive (0.48 mmol) in the solvent (15 mL) at -78 °C, under an argon atmosphere, was added n-BuLi (1.6 M in hexanes, 0.48 mmol). The reaction mixture was then raised to the required temperature for the time indicated followed by quenching with acetic acid (1.2 mmol). Citric acid (20% aqueous, 5 mL) was then added and the mixture was stirred at 25 °C for 1hr. Extractive workup followed by purification on chromatography afforded a mixture of the [1,3] and [3,3] products. The product ratios were determined by ^{1}H-NMR. Complete characterization of the individual products was obtained by reduction to the alcohols with sodium borohydride then HPLC separation followed by ^{1}H-NMR, ^{13}C-NMR, IR, MS and elemental analysis.