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CARBANION-ACCELERATED CLAISEN REARRANGEMENTS 5. STUDIES ON STEREOCONTROL WITH PHOSPHORUS-STABILIZED ANIONS

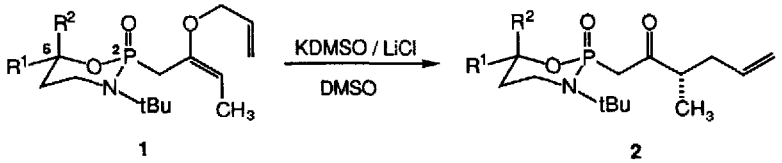
Scott E. Denmark*, G. Rajendra† and John E. Marlin

Roger Adams Laboratory, Department of Chemistry
University of Illinois, Urbana, IL 61801

Summary: The allyl vinyl ethers **1** undergo facile and highly diastereoselective carbanionic Claisen rearrangements. The selectivity of the reaction depends on the counterion and the size of the group on the 1,3,2-oxazaphosphorinane nitrogen atom. The origin of the high selectivity is discussed.

We recently described a method for achieving high diastereoselectivity in the carbanionic Claisen rearrangement[1a] by the use of chiral phosphorus-stabilized anions, Scheme I.[1b] Both the racemic (R^1=R^2=CH_3)

Scheme I



1 **2**

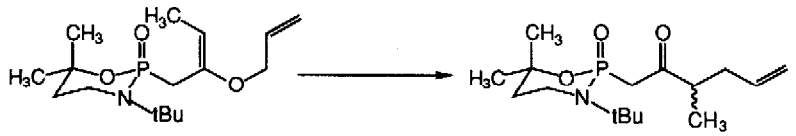
and optically active (R^1=CH_3, R^2=H, R^1=H, R^2=CH_3) 1,3,2-oxazaphosphorinanes **1** underwent rapid Claisen rearrangement with potassium dimsylate as the base, but the presence of lithium chloride was found to be essential for good diastereoselectivity (90:10). This Letter describes an improvement in the selectivity and experiments aimed at clarifying the role of the auxiliary in controlling the structure of the anion.

The first series of experiments addressed the effects of counterion and solvent on diastereoselectivity. The substrate for this study **1a** was prepared as previously described[1b] and rigorously purified to remove traces of the α,β-unsaturated tautomer **1a'**. This was necessary since this isomer rearranges with opposite selectivity (*vide infra*). The results of rearrangement experiments are collected in Table I. Our initial experiments employing potassium dimsylate in DMSO showed a dramatic counterion effect with selectivity increasing to >90:10 with added lithium chloride. By using freshly prepared lithium dimsylate[2] the selectivity could be improved to ~95:5 (entry 3).[3] The effect of solvent was briefly examined (entries 3-5) and, as expected, the rate of reaction follows solvent polarity. We were interested in evaluating lithium *diisopropyl*sulfoxylate (entry 6) for several reasons: 1) it should be a stronger base than DMSO by 2-3 pK_a units,[4] and 2) if the sulfoxide is a ligand for lithium the increased bulk may influence stereoselectivity. As shown in Table I, the rate did increase (compare entry 4) but the selectivity was unaffected. From these experiments it appears that the rate of the reaction is primarily solvent

† Deceased, July 13, 1988

dependent, but that stereoselectivity is primarily counterion dependent. The results obtained with *n*BuLi as the base in THF (entry 7) were consistent with this conclusion, i.e. slow reaction but high selectivity. Our current

Table I. Claisen Rearrangement of Oxazaphosphorinane **1a**[a]

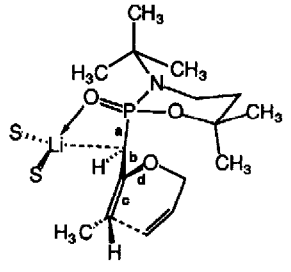


1a **2a**

entry	base[b]	solvent	tine, h	yield, %	d.s.[c]
1[d]	KDMSO	DMSO/THF (3:1)	0.25	77	52 : 48
2[d]	KDMSO (LiCl)[e]	DMSO/THF (3:1)	0.25	81	91 : 9
3	LiDMSO[f]	DMSO/THF (1:1)	0.25	73	95 : 5
4	LiDMSO	THF	0.50	64	94 : 6
5	LiDMSO	Et_2O	1.0	31	90 : 10
6	LiDIPSO	THF	0.25	68	94 : 6
7	*n*BuLi	THF	1.75	51	95 : 5

[a] All rearrangements carried out at r.t. [b] Usually 2.0-2.5 equiv of base used. [c] Diastereoselectivity determined by ^{31}P NMR or ^{1}H NMR (500 MHz). [d] Ref. 1a. [e] Six equiv LiCl. [f] Prepared with *n*-BuLi. The reagent was insoluble in THF but dissolved upon addition of **1a**.

picture of the allyl anion which is consistent with these results is shown in Figure 1. Independent spectroscopic and computational studies support the view of an sp^2 hybridized anion strongly complexed with lithium.[5] For high selectivity in the rearrangement to be observed all degrees of freedom about bonds **a-d** must be controlled. The suspected control elements for these bonds are included in Figure 1. The following studies provide experimental support for the assertion of steric control of bond **a** and slow rotation about the allyl anion.



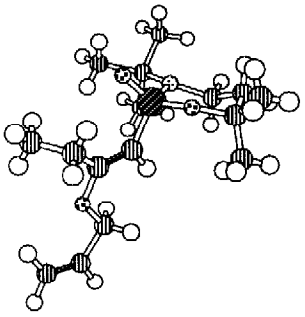
conformational control elements

bond **a**: steric - O vs. NtBu fixed by Li^+ coordination
bond **b**: steric - O/O vs. O/ethylidene
bond **c**: high barrier to rotation about allyl anion
bond **d**: stereoelectronic (anti S_E') or steric

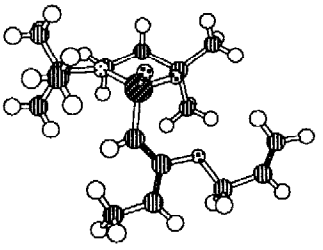
Figure 1. Proposed structure for anion Li^+**1a**$^-$.

Rotation about bond **a** would generate severe non-bonded interactions with the N-*t*-butyl group. Indeed, X-ray crystallographic analysis of several N-alkyl 1,3,2-oxazaphosphorinane-2-oxides confirms the axial or pseudoaxial positioning of the phosphonyl moiety.[6] Figure 2 contains a presentation of the X-ray structure of **1a'** (the α,β-unsaturated isomer) as illustrative. The nitrogen atom is nearly planar and the allyl vinyl ether stands axially despite the 1,3-diaxial interaction with the CH_3-C(6).[6] The role of the N-*t*-butyl group in controlling

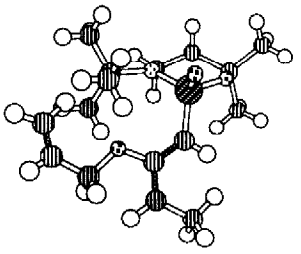
rotation about bond **a** is illustrated by the two "anion" structures in Figure 2. These artificial constructs[8] were generated using the X-ray structure of **1a'** and modifying the allyl vinyl ether according to the proposal in Figure 1. Clearly in the "favored anion" the allyl vinyl ether appendage effectively avoids the *t*-butyl group even though it is axially oriented.



1a' (α,β-unsaturated isomer)



"favored anion"



"unfavored anion"

Figure 2. X-ray crystallographic structure of **1a'** and hypothetical anions.

To probe the importance of this type of interaction we have prepared and studied the N-adamantyl (**1b**) and N-methyl (**1c**) derivatives.[9] The result of rearrangements with these substrates are collected in Table II.

Table II. Rearrangements of **1b** and **1c**[a]

1 **2**

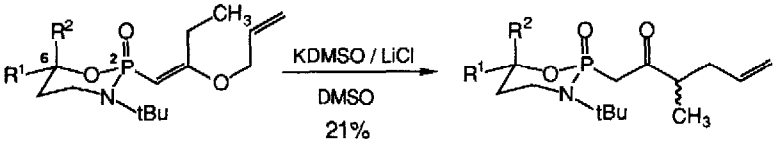
entry	R	base[b]	solvent	time, h	yield, %	d.s.[c]
1	adamantyl	none	toluene[d]	2.0	93	60 : 40
2	adamantyl	LiDMSO	THF	0.25	58	94 : 6
3	adamantyl	LiDMSO	DMSO/THF (1:1)	0.25	74	94 : 6
4	methyl	none	toluene[d]	2.5	86	53 : 47
5	methyl	LiDMSO	THF	0.25	62	52 : 48

[a] All anionic rearrangements were carried out at r.t. [b] Usually 2.5 equiv of base used. [c] Diastereoselectivity determined by ^{1}H NMR (500 MHz). [d] Reaction run at 110°C.

Claisen rearrangements (entries 1 and 4) proceeded unselectively demonstrating the lack of an intrinsic stereodirecting effect due to the ligand alone. However, anionic rearrangement of **1b** proceeded with the same high selectivity seen with **1a**. On the other hand, anionic rearrangement of **1c** was rapid but unselective (entry 5). Therefore, a critical role of steric bulk of the N-substituent in the stereocontrol mechanism is demonstrated.

Finally, we have addressed the issue of the relative heights of the barriers to rotation about bonds **b** and **c** in the anion versus rearrangement. Exposure of substrate **1a'** to the standard reaction conditions afforded the

Scheme II



1a' **2a** (30:70)

rearrangement product **2a**, Scheme II. Remarkably, the major diastereomer from this rearrangement had the opposite configuration to that derived from **1a**.[10] This can be understood in terms of a change in the configuration of the allyl anion at either (but not both)[11] bonds **b** and **c**. Since **1a** and **1a'** gave distinctly different diastereomer mixtures, the anions leading to these diastereomers cannot readily interconvert. Since **1a'** is an *E*-configured enol ether it is not possible to unambiguously identify whether bond **b** or **c** has changed. We suspect bond **c** is different based on the analogy to sulfonyl allyl anions[12] which have higher barriers to rotation of bond **c** than bond **b**.

Further studies on the structure and reactions of chiral phosphorus-stabilized anions are in progress.

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(2) Chaykovsky, M. *J. Org. Chem.* **1975**, *40*, 145.

(3) Control experiments showed that diastereomerically enriched **2a** (93:7) was recovered unchanged from treatment with 2.5 equiv LiDMSO (93% recovery).

(4) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456 (c.f. ref. 25).

(5) Cramer, C. J.; Denmark, S. E., manuscript submitted.

(6) Three allyl vinyl ethers and two P-benzyl derivatives show this behavior crystallographically. ^{1}H NMR data also support the axial nature of the benzyl group in the latter case.

(7) Bentrude has come to the same conclusion based on careful solution NMR analysis. (a) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Chandresekaran, S.; Ashby, M. T. *J. Am. Chem. Soc.* **1988**, *100*, 7119. (b) Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *Ibid.* **1985**, *107*, 2083. See also: (c) Spossor, S. L.; Lyapova, M. J.; Ivanova, M. E. *Phosphorus and Sulfur* **1988**, *37*, 199.

(8) Generated from the X-ray crystallographic coordinates of **1a'** using the Chem 3D® program.

(9) These were prepared by modification of the synthesis described for **1a**,[1b] using adamantylamine and N-methylacetamide.

(10) The diastereomers of **2a** have characteristic ^{31}P NMR resonances at 15.8 and 15.9 ppm (121.4 MHz).

(11) If the configuration of both bonds **b** and **c** change the major diastereomer should be the same.

(12) Gais, H.-J.; Vollhardt, J.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 932.

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