Tetrahedron Letters No. 22 + 23, pp 1811 - 1814, 1975. Pergamon Press. Printed in Great Britain.

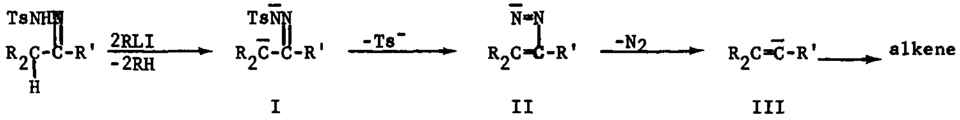
TOSYLHYDRAZONES AND ALKYLLITHIUM REAGENTS: MORE ON THE REGIOSPECIFICITY OF THE REACTION AND THE TRAPPING OF THREE INTERMEDIATES

Robert H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell and L. A. Capuano

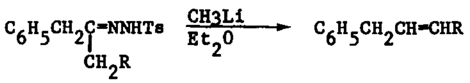
Department of Chemistry, University of Colorado
Boulder, Colorado 80302

(Received in U.S.A. 18 February 1975; received in UK for publication 16 April 1975)

The reaction of tosylhydrazones with alkyllithium reagents has been shown to be a very useful olefin synthesis (1), but very little has been learned about the details of the reaction since its discovery (2,3). In the preceding communication, however, Stemke and Bonds have succeeded in trapping the vinyl anion intermediates produced in several reactions occurring in tetramethylethylenediamine (TMEDA) solvent (4). We have also trapped the vinyl anion (III) as well as two other intermediates, the dianion (I) and the vinyl diimide anion (II), generated during the course of olefin formation.



In addition, we now have evidence that the relative acidities of the two sets of α-hydrogens play a less important role than originally proposed in determining the regiospecificity of the reaction. For example, benzyl methyl ketone tosylhydrazone (IV) yields allylbenzene as the sole olefin when treated with methyllithium in ether at room temperature (5). The benzylic hydrogens in IV are by far more acidic than the methyl hydrogens as determined by deuterium exchange with sodium methoxide in methanol-O-d at 80° in an nmr tube. Similarly, and more surprisingly, benzyl ethyl ketone tosylhydrazone (V) yields only 1-phenyl-2-butene (*cis* and *trans*) under the same reaction conditions.



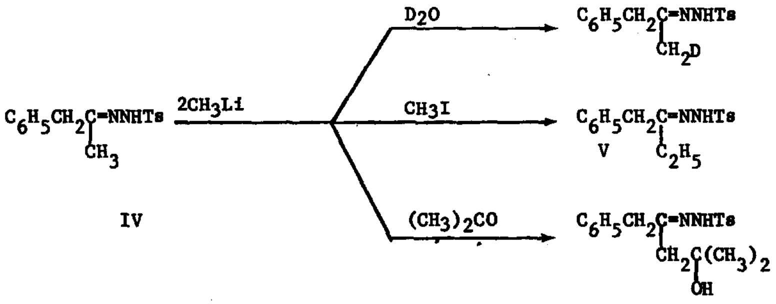
$$C_6H_5CH_2\underset{CH_2R}{C}{=}NNHTs \xrightarrow[Et_2O]{CH_3Li} C_6H_5CH_2CH{=}CHR$$

IV, R=H   R=H, 70%

V, R=CH_3 R=CH_3, 62%

We now believe that the regiospecificity is largely controlled by the configuration of the carbon-nitrogen double bond. Our preliminary results indicate that an α-hydrogen syn to the tosyl group is selectively eliminated. The details of this study will appear in the full paper.

The trapping of the dianion I is effected at reduced temperature with electrophiles such as D_2O, CH_3I and acetone. For example, at -78° for five minutes, IV reacts with two equivalents of CH_3Li to give dianion I (R=H, R'= $CH_2C_6H_5$), which reacts with CH_3I or acetone at the syn α-carbon. The former electrophile will also alkylate nitrogen, but more forcing conditions (40-50° in THF) are required. Monomethylation on nitrogen occurs with one equivalent of CH_3Li followed by addition of CH_3I and warming. Treatment of the cold reaction mixture with D_2O deuteriates I on both carbon and nitrogen, but the deuterium on nitrogen is lost during work-up.



Analogous reactions have been successful with the tosylhydrazones of cyclohexanone, dibenzyl ketone, propiophenone, deoxybenzoin, pinacolone and acetophenone. The tosylhydrazones with secondary α-hydrogens are conveniently converted to dianions which can be trapped at 0°, but those with primary α-hydrogens eliminate too fast at this temperature (6).

The reaction of I with acetone represents a modification of the crossed-aldol condensation, since a tosylhydrazone is quantitatively converted to a ketone by an acid catalyzed exchange with acetone. When this exchange is carried out in acetone containing a trace of p-toluenesulfonic acid at room temperature, dehydration occurs and an α,β -unsaturated ketone is isolated.

Attempts to trap anions II and III were carried out using butyllithium in hexane and TMEDA either as the solvent or as a cosolvent with benzene. Alkyl halides were used primarily as the trapping agent, but in some cases D_2O was used, confirming the results of Stemke and Bond (4). The alkyl halides were not ideal electrophiles, but the results with them demonstrated the existence of II and III. Methyl iodide reacts with TMEDA to form a quaternary ammonium salt, which does, in fact, alkylate the anionic intermediates but because of the salt's insolubility efficient stirring is difficult. Ethyl and propyl bromide, which do not appear to react with TMEDA under the reaction conditions, appear to undergo some elimination and protonate the vinyl anion. The dianion I is generated at -78° and the mixture is then allowed to warm before addition of electrophile. When the reaction mixture is allowed to come to room temperature and remain there for 1/2-1 hr., only III is trapped (7). If the reaction is quenched at lower temperatures, a mixture of II and III are trapped, although the yield of the unsaturated azo compound resulting from II is low. The same tosylhydrazones used in dianion trapping experiments were used in this study. All gave the expected products, except IV since the vinyl anion generated from it seems to undergo rapid rearrangement to the 1-phenylallyl anion which undergoes alkylation at both ends of the allylic system. The Table lists some of the systems studied.

TABLE

Vinyl Anion Trapping Experiments

Tosylhydrazone of:	Electrophile	Product(s)	Yield[a]
Cyclohexanone	Ethyl Bromide	1-Ethylcyclohexene Cyclohexene	76% 24%
Cyclohexanone	n-Propyl Bromide	1-n-Propylcyclohexene Cyclohexene	67% 33%
Acetophenone	Ethyl Bromide[b]	2-Phenyl-1-butene Styrene	50% 50%
Pinacolone	n-Butyl Bromide	2-tert-Butyl-1-hexene	66%
Propiophenone	Methyl Iodide[b]	2-Phenyl-2-butene (cis:trans, 1:1)	>95%
Deoxybenzoin	Methyl Iodide	1,3-Diphenylpropene (cis:trans, 4:13)	85%

Table (continued)

Tosylhydrazone of:	Electrophile	Product(s)	Yield[a]
Isobutyrophenone	Methyl Iodide	2-Phenyl-3-methyl-2-butene	63%
		3-Phenyl-2-methylheptane[c]	21%
Isobutyrophenone	D_2O	1-Phenyl-2-methyl-propene-1-$\underline{d}_1$	55%
		3-Phenyl-2-methylheptane-3-$\underline{d}_1$[c]	45%
Phenylacetone (IV)	Methyl Iodide	3-Phenyl-1-butene	55%
		1-Phenyl-1-butene (*cis*:*trans*, 19:26)	45%

a. GLC ratio of products where sum equals 100%; otherwise yield.
b. Benzene used as the solvent with 6 equivalents of TMEDA added.
c. Substitution product (6).

References & Notes

1. For review see R. H. Shapiro, Org. Reactions, **23**, in press.

2. R. H. Shapiro and M. J. Heath, *J. Am. Chem. Soc.*, **89**, 5734 (1967).

3. G. Kaufman, F. Cook, H. Schechter, J. Bayless and L. Friedman, *J. Am. Chem. Soc.*, **89**, 5736 (1967).

4. J. E. Stemke and F. T. Bond , *Tetrahedron Lett.* preceding communication. We thank Professor Bonds for making his results available to us and for delaying publication of them.

5. Some substitution product, isobutylbenzene, is also produced (allylbenzene: isobutylbenzene=7:3). The allylbenzene slowly isomerizes to a mixture of *cis*- and *trans*-propenylbenzene if left in the reaction mixture for long periods. The substitution reaction is completely inhibited if TMEDA is added, but then the isomerization of allylbenzene occurs very much faster.

6. Tosylhydrazones containing only tertiary α-hydrogens react very slowly with alkyllithium reagents (1,8,9). TMEDA accelerates the reaction significantly, but substitution still occurs at the carbon-nitrogen double bond (10). With CH_3Li in Ether/TMEDA substitution is completely inhibited, but the ether protonates the vinyl anion III. See Table for an example with isobutyrophenone.

7. Nitrogen is evolved during the warming period. If electrophile is added before nitrogen evolution is complete, then some II is trapped.

8. Y. Chretien-Bessiere and J.-P. Bras, *C. R. Acad. Sci., Paris*, Ser. C, **268**, 2221 (1969).

9. K. Mori and M. Matsui, Tetrahedron, 26, 2801 (1970), *Tetrahedron Lett.*, **1969**, 2729.

10. J. E. Herz and C. V. Ortiz, *J. Chem. Soc., C*, 2294 (1971).