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STEREOSPECIFICITY IN ALKYLATION OF ANIONS OF KETONE DIMETHYLHYDRAZONES: KINETIC ANTI PREFERENCE, THERMODYNAMIC SYN PREFERENCE

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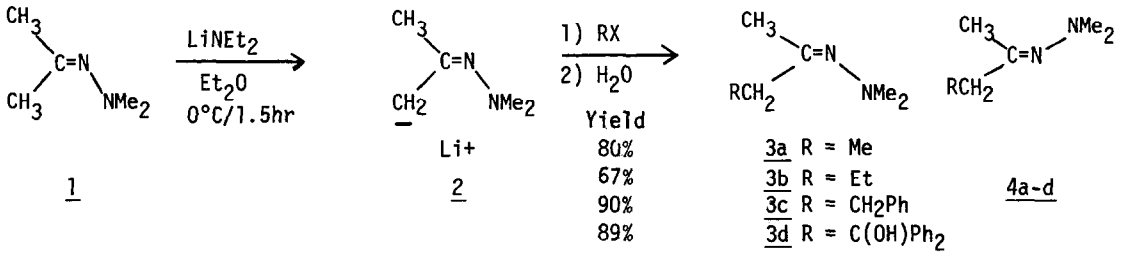
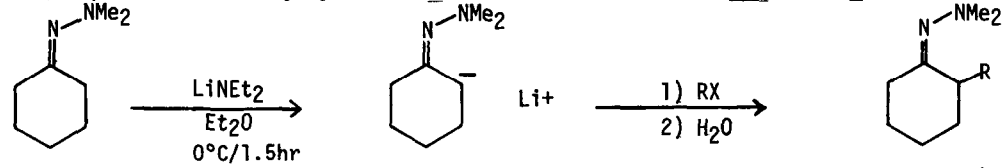
The high acidity of protons α to the carbonyl in ketones, aldehydes and their derivatives has made available a variety of stable carbanions which have been of immense value in organic synthesis. Lately studies in our laboratory and several others have shown that certain carbonyl derivatives exhibit total stereospecificity in deprotonation reactions.[1] The dianions of oximes,[1abk] tosyl hydrazones,[1c] and allyl mercaptans,[1de] and the monoanions of oxime ethers,[1fg] allylic ethers,[1hi] and nitrosamines[1jk] all have shown a clean preference for formation in the syn-orientation. Most recently Corey[2a] has reported similar syn-stereospecificity in the functionalization of anions of ketone dimethylhydrazones. This is in apparent contrast to an earlier publication from the same group[2b] which reported clean stereospecificity toward the less substituted carbon in the alkylation of the dimethylhydrazones of methyl ketones. These recent publications prompt us to report our own results on the stereospecificity in alkylation of anions of ketone dimethylhydrazones.

Treatment of acetone dimethylhydrazone 1 with one equivalent of lithium diethylamide in diethyl ether at 0°C for 1.5 hr resulted in the formation of exclusively the syn anion 2. Treatment with methyl iodide at 0°C for 1.5 hr and workup in the cold[3] afforded only the syn 2-butanone dimethylhydrazone 3a in 80% yield.[4] The NMR spectrum of 3a in benzene was identical to that reported by Karabatsos for this compound, which could be prepared only as the minor isomer (18%) of the syn-anti mixture from the reaction of dimethylhydrazine and 2-butanone.[5] Substitution of ethyl iodide, benzyl bromide, or benzophenone for methyl iodide in the reaction with 2 also affords exclusively the syn alkylated products 3b-d in good yields.[4] The assignment of the syn geometry was based on the chemical shift of the allylic methylene protons in the ^{1}H NMR spectra of these compounds 3b-d.[6] In all cases this chemical shift is about 0.2 - 0.4δ downfield from the chemical shift of these

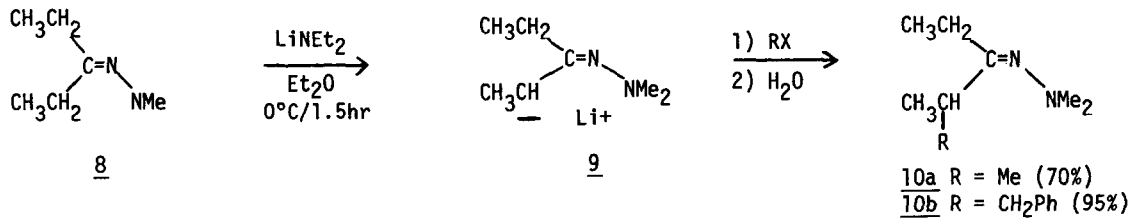


protons in the anti isomers 4a-d. All of the syn isomers 3a-d rearrange on standing to an equilibrium mixture which consists predominately of the more stable anti isomers 4a-d. This same equilibrium mixture is also available via direct dimethylhydrazone formation from the corresponding ketones.

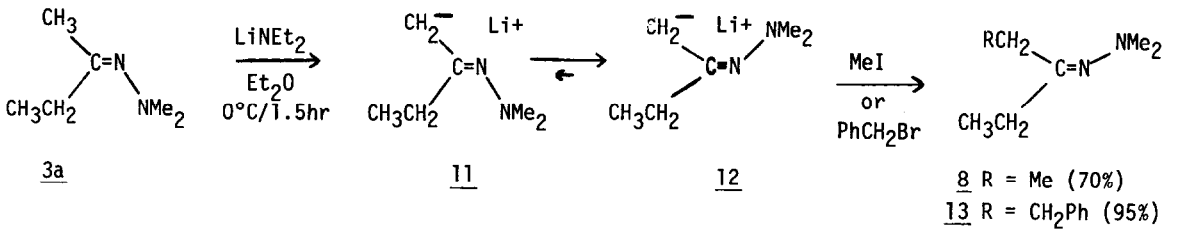
The dimethylhydrazones of other symmetrically substituted ketones also show this same syn-stereospecificity in alkylation reactions. For example, cyclohexanone dimethylhydrazone 5 was converted exclusively into the syn anion 6 upon similar treatment. Alkylation with methyl iodide or benzyl bromide furnished cleanly the syn alkylation products 7ab, respectively, in good yield.[4] In addition, 3-pentanone dimethylhydrazone 8 was converted into the syn anion 9 under similar conditions



and then the anion alkylated (methyl iodide, benzyl bromide) to afford compounds 10ab.[4] The syn geometry of all of these alkylation products, 7ab and 10ab, was again assigned by NMR measurements.[6]



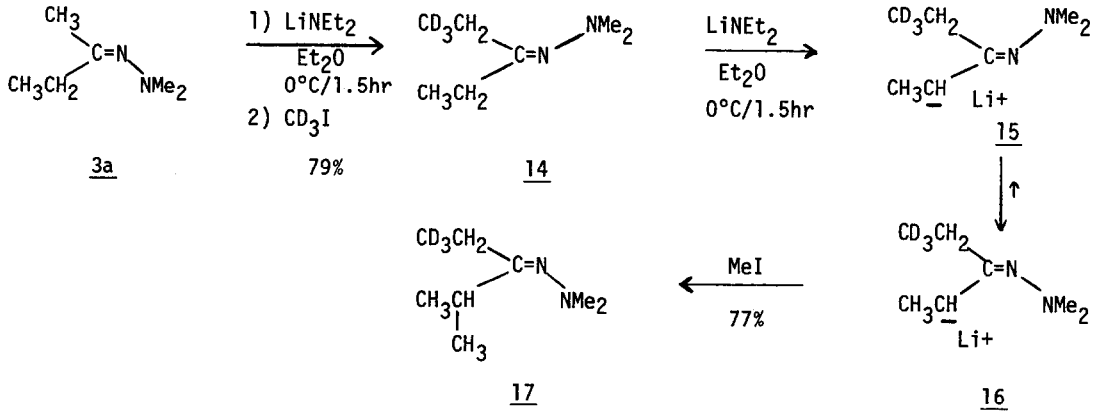
In an attempt to extend this stereospecific alkylation procedure to the preparation of a secondary syn carbanion in preference to a primary anti carbanion, which occurs in the case of oxime dianions,[1a] syn 2-butanone dimethylhydrazone 3a was treated with lithium diethylamide in ether at 0°C followed by alkylation. Methylation afforded 3-pentanone dimethylhydrazone 8 while the use of benzyl bromide as the alkylating agent produced cleanly syn 1-phenyl-3-pentanone dimethylhydrazone 13.[4] These results imply that the following mechanistic pathway is occurring: formation of the anti anion 11, facile and complete rearrangement of this anion to the syn isomer 12 by



isomerization at nitrogen, and alkylation of 12 to afford 8 and 13. The same products 8 and 13 could be formed starting with either pure isomer, 3a or 4a, or from the equilibrium mixture of the two. Thus one always obtains the primary carbanion in preference to the secondary one, independent of the hydrazone stereochemistry, as Corey has reported.[2b]

The production of only the isomer with Me_2N syn to the new alkyl group implies a large thermodynamic preference for the syn anion 11 versus the anti one 12.[7] This is the first clear demonstration of a thermodynamic stereochemical preference in these systems rather than a kinetic one. The energy difference between 11 and 12 must be fairly large ($\geq$ 3 kcal), and the barrier to isomerization fairly low, since none of the product resulting from alkylation of 11 can be seen by NMR.

In order to test the kinetic preference for deprotonation of the dimethylhydrazones of symmetrically substituted ketones, we prepared the syn trideuteromethyl derivative 14 by alkylation of 3a.[4] Anion formation and methylation of 14 afforded the syn isopropyl trideuteroethyl compound 17,[4] implying initial anti deprotonation to give anti anion 15, rearrangement to the syn isomer 16, and finally alkylation to produce 17.[8] Thus there is a clear kinetic preference for anti deprotonation in symmetrically substituted systems. This is not unexpected since the large steric bulk of the NMe_2 group should hinder deprotonation syn but not anti to it. The two alkyl groups of the



dimethylamino function seem to be necessary to cause this steric preference for kinetic anti deprotonation since oxime ethers and oxime anions are kinetically deprotonated syn to the oxygen.

Part of the explanation for the observed thermodynamic preference for the syn anion probably lies in the attractive through-space non-bonded interaction which stabilizes the syn but not the anti anion.[9] Further experiments must be performed to evaluate the importance of chelation of the lithium ion to the observed energy difference in this system.

References and Notes

1. a) M. E. Jung, P. A. Blair, and J. A. Lowe, Tetrahedron Lett., 1439 (1976); b) W. G. Kofron and M.-K. Yeh, J. Org. Chem., 41, 439 (1976); c) R. H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell, and L. A. Capuano, Tetrahedron Lett., 1811 (1975); d) K. H. Geiss, B. Seuring, R. Pieter, and D. Seebach, Angew. Chem., 86, 484 (1974); J. Hartmann, R. Muthukrishnan, and M. Schlosser, Helv. Chim. Acta, 57, 2261 (1974); f) T. A. Spencer and C. W. Leong, Tetrahedron Lett., 3889 (1975); g) R. R. Fraser and K. L. Dhawan, Chem. Commun., 674 (1976); h) D. A. Evans, G. C. Andrews, and B. Buckwalter, J. Am. Chem. Soc., 96, 5560 (1974); i) W. C. Still and T. L. Macdonald, ibid., 96, 5561 (1974); j) R. R. Fraser, T. B. Grindlev, and S. Passannanti, Can. J. Chem., 53, 2473 (1975); k) R. E. Lyle, J. E. Saavedra, G. G. Lyle, H. M. Fribush, J. L. Marshall, W. Lijinsky, and G. M. Singer, Tetrahedron Lett., 4431 (1976).

2. a) E. J. Corey and S. Knapp, ibid., 4687 (1976); b) E. J. Corey and D. Enders, ibid., 3 (1976).

3. In order to avoid syn-anti isomerization of the products, the temperature during the workup was kept as low as possible, i.e., washing with ice water, cold brine solution, drying over magnesium sulfate at 0°C, and finally evaporating the solvent at low pressures at 25°C.

4. Satisfactory spectral data (NMR, IR, MS) have been obtained for all new compounds reported.

5. G. J. Karabatsos and R. A. Taller, Tetrahedron, 24, 3923 (1968).

6. NMR of 3b: δ(PhH) 2.38, s (6H); 2.35, t, J=7 (2H); 1.75, s (3H); 1.2-0.7, m (5H).
   NMR of 3c: δ(PhH) 2.68, s (4H); 2.40, s (6H); 1.8, s (3H).
   NMR of 3c: δ(CCl_4) 7.2, s (5H); 2.72, s (4H); 2.3, s (6H); 1.85, s (3H).
   NMR of 3d: δ(CCl_4) 7.5-7.0, m (10H); 6.1, br s (1H); 3.15, s (2H); 2.4, s (6H); 1.35, s (3H).
   NMR of 7a: δ(PhH) 3.7, m, J=7 (1H); 2.4, s, (6H); 2.2-1.9, m (2H); 1.6-1.2, m, (6H); 0.98, d, J=7 (3H).
   NMR of 7b: δ(PhH) 3.3, m, J=6 (1H); 2.7-2.5, m (2H); 2.3, s (6H), 1.7-0.8, m (8H).
   NMR of 7b: δ(CCl_4) 7.2, s (5H); 4.0-3.6, m, J=7 (1H); 2.75, d, J=7 (2H); 2.2, s (6H); 1.9-1.0, m (8H).
   NMR of 10a: δ(PhH) 3.8, m, J=6 (1H); 2.4, s (6H); 2.1, q, J=7 (2H); 1.2, t, J=7 (3H); 0.9, d, J=7 (6H).
   NMR of 10b: δ(CCl_4) 7.1, s (5H); 3.9, p, J=7 (1H); 2.6, m (2H); 2.2, s (6H); 2.15, q, J=7 (2H); 1.05, t, J=7 (3H); 0.95, d, J=7 (3H).
   NMR of 13: δ(PhH) 2.65, s (4H); 2.35, s (6H); 2.1, q, J=7 (2H); 1.05, t, J=7 (3H).
   NMR of 13: δ(CCl_4) 7.2, s (5H); 2.65, br s (4H); 2.25, s (6H); 2.20, q, J=6 (2H); 1.05, t, J=6 (3H).
   NMR of 14: δ(PhH) 2.4, s (6H); 2.35, m (2H); 2.05, q, J=7 (2H); 1.05, t, J=7 (3H).
   NMR of 17: δ(PhH) 3.8, m, J=7 (1H); 2.4, s (6H); 2.0, m (2H); 0.9, d, J=7 (6H).

7. The alternative explanation for the complete formation of the syn alkylated product -- a much faster rate of alkylation of the syn anion 12 than of the anti anion 11 -- seems unlikely here since the transition state for alkylation of 12 is likely to be more hindered than that for 11.

8. The secondary deuterium isotope effects in this system can not be ignored. However, they are unlikely to be very large and thus should not be very important in initial anion formation.

9. For a more detailed explanation of this argument see reference 1a and N. D. Epiotis, J. Am. Chem. Soc., 95, 3087 (1973).