the filter cake was washed with hot dimethylformamide (4 × 10 mL). The filtrate and washings were combined and evaporated to dryness in vacuo. The residue was crystallized from aqueous DMF (water/DMF, 4:6, v/v) to yield 60 mg (69.2%) of 7: mp 250 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 5.10 (t, 1, $H_{2'}$, $J_{2',1'}$ = 6.0 Hz, $J_{2',3'}$ = 6.0 Hz), 6.25 (d, 1, $H_{1'}$, $J_{1',2'}$ = 6.0 Hz), 7.22 (br s, 2, NH_2), 8.22 (s, 1, H_2 or H_5), 8.91 (s, 1, H_5 or H_2).

Anal. Calcd for $C_{13}H_{14}N_6O_5 \cdot 1.5H_2O$ (verified by ^{1}H NMR): C, 43.21; H, 4.71; N, 23.27. Found: C, 43.58; H, 4.47; N, 22.97.

General Procedure.[24] **Method A.** The *o*-aminonitrile was dissolved in pyridine, and 1 mL of liquefied carbonyl sulfide was added to the solution at −70 °C. The reaction mixture was then sealed in a steel vessel and heated for a suitable period of time. The reaction vessel was cooled to room temperature and the excess carbonyl sulfide was allowed to slowly evaporate. The reaction mixture was coevaporated several times with 2-propanol to remove the pyridine. The remaining solid was dissolved in a 1 N NaOH solution, activated charcoal was added, and the resulting mixture was filtered through a Celite bed. The pH of the filtrate was adjusted to 6.0 with a 1 N HCl solution and the solid that separated was collected by filtration. Analytical samples were obtained by one additional reprecipitation.

General Procedure.[24] **Method B.** Carbonyl sulfide was slowly bubbled through a 1 N sodium ethoxide solution for 10 min. The appropriate *o*-aminonitrile was added to this solution and the reaction mixture was heated to reflux temperature. After a suitable period of time, any solid that had formed was dissolved in a small amount of water and the volume of the reaction mixture was concentrated to ca. 4 mL. Activated charcoal was added, the mixture was filtered through a Celite bed, and the pH of the filtrate was adjusted to 6.0 with a 1 N HCl solution. One additional reprecipitation from a basic solution afforded analytical samples of the respective products.

(24) See Tables I and II for the exact quantities used and the results obtained.

Acknowledgment. This investigation was supported by research grant Rol-CA 28381 from the National Cancer Institute, NIH, and by DR & D Research Contract NIH NCI-CM-77142 from DCT, NCI, NIH, and PHS and by CONICIT.

Registry No. 2, 57071-61-1; 3, 74754-48-6; 3 disodium salt, 78479-71-7; 4, 74754-49-7; 5, 73851-57-7; 6, 74754-50-0; 7, 74754-51-1; 10a, 4651-82-5; 10b, 4623-55-6; 11a, 78479-72-8; 11b, 78479-73-9; 12, 16617-46-2; 13, 5334-33-8; 14, 28745-14-4; 15, 28745-15-5.

Metalation of Diazepam and Use of the Resulting Carbanion Intermediate in a New Synthesis of 3-Substituted Diazepam Derivatives[1a,c]

Barbara E. Reitter,[1b] Yesh P. Sachdeva, and James F. Wolfe*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received April 9, 1981

Treatment of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (diazepam, 1) with 1 equiv of LDA in THF–hexane produces an equilibrium mixture consisting of equal amounts of 1 and its monolithio salt 2 as shown by ^{1}H NMR and D_2O quenching. With 2 equiv of LDA, 2 is formed in sufficient concentration to react with alkyl halides, aldehydes, ketones, and esters to give 3-substituted derivatives of 1. ^{1}H NMR studies of THF-d_8 solutions prepared from 1 and 2–3 equiv of LDA indicate partial twofold metalation of 1 in which both hydrogens at C_3 are removed to form dilithio derivative 10. The present metalations provide a convenient new method for direct modification of diazepam, without requiring the more cumbersome ring closure procedures traditionally employed for such syntheses.

As part of a program directed toward the preparation of new anticonvulsant agents, we sought a direct, general method for the synthesis of various 3-substituted derivatives of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (diazepam, 1).[2] Current syntheses of such compounds usually involve extensions of methods employed for the preparation of 1 such as condensations of 2-amino-5-chlorobenzophenone with α-substituted α-amino acids (esters)[3] or α-substituted α-haloacyl halides.[3] In these cases, the original α substituent of the acylating agent appears at the 3-position of the resulting diazepinone. Certain 3-substituted 1,4-benzodiazepin-2-ones can also be prepared from 3-hydroxy-1,4-benzodiazepin-2-ones,[4] which are available through reaction of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxides with acetic anhydride followed by hydrolysis,[5] by base-catalyzed cyclization of the syn oximes of 2-(haloacetamido)-5-chlorobenzophenones,[6] and by oxygenation of 1 and related compounds in the presence of potassium *tert*-butoxide.[7]

The present study was based on the concept that 3-substituted diazepams might be available directly from 1 through metalated derivative 2. Subsequent reactions of 2 with electrophilic reagents could then lead to introduction of 3-substituents without requiring construction of the diazepinone ring from acylic precursors each time a dif-

(1) (a) Supported by Grant No. NS 10197 from the National Institute of Neurological and Communicative Disorders and Stroke. (b) Taken in part from the MS thesis of B.E.R., Virginia Polytechnic Institute and State University, Aug 1979. (c) Presented in part at the 181st National Meeting of the American Chemical Society Atlanta GA, Mar 1981; ORGN 15.

(2) (a) Rossi, G. F.; Rocco, C. D.; Maira, G.; Meglio, M. "The Benzodiazepines"; Garattini, S., Mussini, E., Randall, L. O., Eds.; Raven Press: New York, 1973; p 461. (b) For recent references see: Berger, J. G.; Iorio, L. C. In "Annual Reports in Medicinal Chemistry"; Hess, H. J., Ed.; Academic Press: New York, 1979; Chapter 3; 1980, Chapter 3.

(3) (a) Sternbach, L. H.; Fryer, R. I.; Metlesics, W.; Reeder, E.; Sach, G.; Saucy, G.; Stempel, A. *J. Org. Chem.* **1962**, *27*, 3788. (b) Bell, S. C.; Sulkowsti, T. S.; Gochman, C.; Childress, S. J. *Ibid.* **1962**, *27*, 562. (c) Falk, J. L.; Swiss Patent 417 614, 1967; *Chem. Abstr.* **1967**, *67*, 21948. (d) Sunjic, V.; Kajfez, F.; Stomar, I.; Blazevic, N.; Kolbah, D. *J. Heterocycl. Chem.* **1973**, *10*, 591.

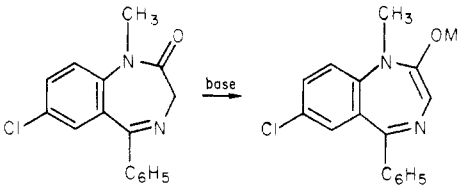
(4) For an example of this approach see: Sellstedt, J. H. *J. Org. Chem.* **1975**, *40*, 1508 and references cited therein.

(5) Bell, S. C.; Gochman, C.; Childress, S. J. *J. Org. Chem.* **1963**, *28*, 3010.

(6) Stempel, A.; Dovan, I.; Reeder, E.; Sternbach, L. H. *J. Org. Chem.* **1967**, *32*, 2417.

(7) Gall, M.; Kamdar, B. V.; Collins, R. J. *J. Med. Chem.* **1978**, *21*, 1290.

0022-3263/81/1946-3945$01.25/0



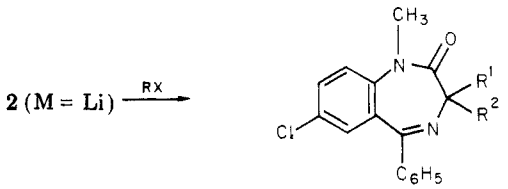
1 2

ferent substituent was desired. Previous attempts to generate metalated intermediate **2** (M = Na or Li) for use in synthetic operations have met with limited success. For example, treatment of **1** with sodium hydride in DMF apparently affords **2** (M = Na) initially, but at temperatures above ambient this salt undergoes rearrangement to afford 5-chloro-*N*-methyl-3-phenyl-1-isoindolecarboxamide.[8] More recently, attempts to hydroxylate **1** by conversion to **2** (M = Li) with 1 equiv of lithium diisopropylamide (LDA) followed by oxygenation gave only 11% of 3-hydroxydiazepam.[7] Although potassium *tert*-butoxide (1.5 equiv) allowed the oxygenation to proceed in better yield, no other reactions were reported with the presumed potassium salt. In a related study, the 3-potassio derivative of 7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide, prepared by means of 1.2 equiv of potassium *tert*-butoxide, was found to undergo alkylation and Michael addition at the 3-position.[9]

Results and Discussion

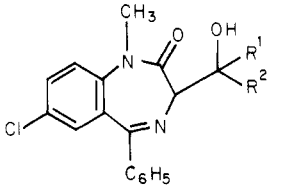
Synthetic Applications. Treatment of **1** with 1 equiv of LDA in THF–hexane followed by quenching with excess D_2O returned **1** containing 0.5–0.6 deuterium atom at C_3 as shown by ^1H NMR. When **1** was allowed to react with excess potassium hydride (KH) in THF at 25 °C until hydrogen evolution ceased and the reaction mixture quenched with D_2O, recovered **1** contained 0.9–1.0 deuterium at C_3. Alkylations of **1** using benzyl chloride and 1 equiv of LDA or excess KH were very slow; yields of **3d** were only 35% and 45%, respectively, after 18 h. In the reaction employing LDA, addition of 4 equiv of hexamethylphosphoramide (HMPA) resulted in ca. an eightfold increase in the rate of consumption of halide, but the yield of **3d** was not improved.

Treatment of **1** with 2 equiv of LDA followed by D_2O quenching produced **1** containing 1 deuterium at C_3.[10] Subsequent reactions of solutions prepared from **1** and 2 equiv of LDA with a series of alkyl halides provided 3-alkyl derivatives **3a–f** in good yields. In all cases the reactions were complete in 3 h or less. Attempts to prepare 3,3-dialkyldiazepams by treatment of **3a** or **3d** with 2 equiv of LDA followed by methyl iodide failed to afford isolable amounts of the desired 3,3-dialkyl derivatives, even in the presence of HMPA. Quenching with D_2O indicated that metalation was <10% complete. In view of these results, it was surprising that when *n*-butyl iodide was employed in the normal procedure for alkylating **1**, both mono- and dibutyl derivatives **3g** and **3h** were isolated. Similar mixtures of mono- and dialkylated products were also observed with *n*-propyl iodide.

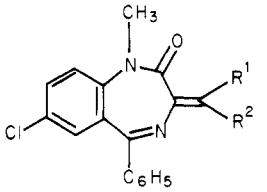


3a, $R^1 = CH_3$; $R^2 = H$
b, $R^1 = C_2H_5$; $R^2 = H$
c, $R^1 = CH(CH_3)_2$; $R^2 = H$
d, $R^1 = CH_2C_6H_5$; $R^2 = H$
e, $R^1 = CH_2C_6H_4OCH_3$-*p*; $R^2 = H$
f, $R^1 = CH_2C_6H_4Cl$-*p*; $R^2 = H$
g, $R^1 = n$-C_4H_9; $R^2 = H$
h, $R^1 = R^2 = n$-C_4H_9

Since the D_2O quenching and alkylation experiments indicated that formation of anion **2** (M = Li) was satisfactory with 2 equiv of LDA, similar conditions were employed in testing several other carbon–carbon bond forming reactions. Thus, aldol condensations of lithio derivative **2** with benzophenone, acetophenone, acetone, cyclohexanone, and benzaldehyde gave 3-(hydroxyalkyl)diazepams **4a–e**. The modest yields of carbinols **4b** and **4c** apparently result from competing enolization of acetophenone and acetone by either anion **2** or LDA. With cyclohexanone and benzaldehyde, carbinols **4d** and **4e** were obtained when the respective reaction mixtures were neutralized within several minutes after addition of the carbonyl compound. Longer reaction times lead to exclusive formation of alkylidene derivatives **5a** and **5b**, respectively.

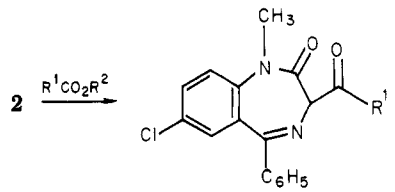


4a, $R^1 = R^2 = C_6H_5$
b, $R^1 = CH_3$; $R^2 = C_6H_5$
c, $R^1 = R^2 = CH_3$
d, $R^1,R^2 = -(CH_2)_5-$
e, $R^1 = H$; $R^2 = C_6H_5$



5a, $R^1,R^2 = -(CH_2)_5-$
b, $R^1 = H$; $R^2 = C_6H_5$

Reaction of **2** with ethyl acetate and methyl benzoate afforded 3-acyl derivatives **6a,b**.



6a, $R^1 = CH_3$
b, $R^1 = C_6H_5$

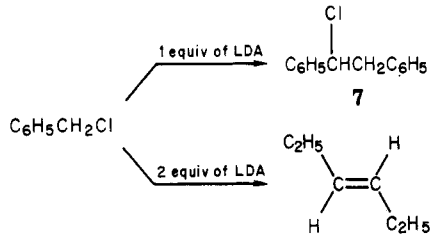
Nature of the Metalation Process with LDA. Incomplete deuteration of **1** in the presence of 1 equiv of LDA was initially taken as evidence for unfavorable equilibrium formation of anion **2** (eq 1). This was further

$$1 + LiNR_2 \rightleftarrows 2 + R_2NH \quad (1)$$

supported by the results of D_2O quenches when 2 equiv of LDA were employed in the metalation process. However, since others[11,12] have observed that α metalations of carboxylate salts with LDA do not exhibit characteristics of a simple equilibrium phenomenon, we conducted several additional experiments aimed at defining the nature of the present metalations. Thus, the first series of reactions involving anion **2** were carried out with benzyl chloride in

(8) Fryer, R. I.; Earley, J. V.; Sternbach, L. H. *J. Org. Chem.* **1969**, *34*, 649.
(9) Walser, A.; Silverman, G.; Fryer, R. I. *J. Org. Chem.* **1973**, *38*, 3502.
(10) The rate of H/D exchange observed when **1** was treated with 1–2 equiv of lithium deuterioxide in D_2O–THF–hexane was much too slow to account for the amount of deuterium incorporation observed in the quenching experiments described above.
(11) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396.
(12) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M. *J. Org. Chem.* **1972**, *37*, 451.

anticipation that this halide could serve as both a reactive electrophile and a probe for the presence of LDA in the presumed equilibrium mixture. This approach was based on the observation that reaction of benzyl chloride with 1 equiv of LDA in THF–hexane at 25 °C results in complete consumption of the halide within 15 min to form 1-chloro-1,2-diphenylethane (7). Under similar conditions,



2 equiv of LDA converts benzyl chloride to *trans*-stilbene (8) at a similar rate.[13] Surprisingly, addition of benzyl chloride to reaction mixtures containing 1 and 1, 2, or 3.5 equiv of LDA failed to yield detectable amounts of 7 or 8. Instead, 3-benzyl derivative **3d** accumulated at a rate much slower than that observed for formation of either 7 or 8 with LDA alone. If it is assumed that formation of 7 and 8 from benzyl chloride requires generation of at least a small equilibrium quantity of α-halo carbanion **9**[13] (eq 2), then perhaps the diisopropylamine present in reaction

$$C_6H_5CH_2Cl + LiNR_2 \rightleftarrows \underset{\mathbf{9}}{C_6H_5CHCl^-} + R_2NH \quad (2)$$

mixtures of 1 and LDA prevents halide dimerization by suppressing such ionization. This premise was tested by adding benzyl chloride to a mixture of 1 equiv of LDA and 1 equiv of diisopropylamine; however, 7 was formed just as fast as it had been without excess amine. Although we still do not have a satisfactory rationale for the apparent inhibition of benzyl chloride dimerization in reactions involving 1 and LDA, it is obvious that this halide is a poor indicator for excess LDA, even when the rate of carbanion alkylation is relatively slow. However, this unexpected occurrence enhances the synthetic utility of the present approach to functionalization of 1 by allowing excess LDA to be used with benzylic halides without competing consumption of the alkylating agent through self-condensation.

In addition to the D_2O quenching experiments, compelling support for equilibrium controlled formation of anion 2 was obtained from ^1H NMR spectra of 1 and varying molar amounts of LDA in THF-d_8 (Figure 1). Addition of 1 equiv of LDA causes the original spectrum of 1 (trace a) to assume the features shown in trace b within 5 min, after which time there were no significant changes. This spectrum is characterized by a decrease in the intensity of the doublet of doublets arising from the diastereotopic C_3 protons and the singlet at δ 3.40 for the N_1-methyl protons of 1.[14] At the same time, new signals attributable to the C_3-vinyl and N_1-methyl protons of anion 2 appear at δ 5.78 and 2.90, respectively. The latter peak is superimposed on the methine multiplet of diisopropylamine. Integration of the spectrum revealed that the ratio of 1 to 2 to diisopropylamine was 1:1:1. In other words, 50% of 1 remains unionized under these conditions. Addition of a second equivalent of LDA caused complete

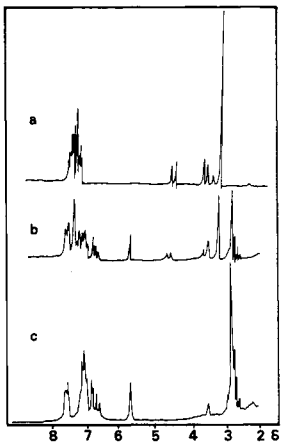
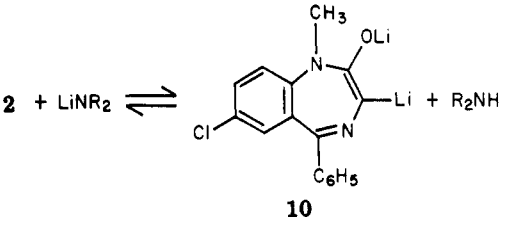


Figure 1. ^1H NMR spectra in 0.25 mL of THF-d_8 at 34 °C of (a) 0.2 mmol of 1, (b) 0.2 mmol of 1 and 0.2 mmol of LDA, and (c) 0.2 mmol of 1 and 0.4 mmol of LDA.

disappearance of the original N_1-methyl and C_3 proton signals of 1 (trace c).[15] Comparison of the integrated intensities of the aromatic and vinyl proton signals indicated that formation of 2 was essentially complete. The absence of signals other than those assigned to 2 demonstrates that the anionic species presumed to accompany rearrangement of 2 (M = Na)[8] are not present. When a sample of 1 was allowed to stand at room temperature for several hours with 2 equiv of LDA, the ratio of aromatic to vinyl hydrogen signals increased from 8:1 to 16.7:1. When 1 was treated with 3 equiv of LDA, the ratio of aromatic to vinyl hydrogens increased to 17.1:1 within 8 min. Although there was some obvious decomposition of this solution, a D_2O quench afforded 1 containing 1.3 deuterium atoms at C_3. When this deuterated sample was reexposed to LDA (2 equiv), the resulting spectrum had all the characteristics of that obtained from nondeuterated 1, except that the resonance at δ 5.78 was reduced in intensity by approximately 60%. This experiment confirmed the assignment of the peak at δ 5.78 to the C_3-vinyl hydrogen of anion 2. The decrease in vinyl proton intensity upon treatment of 1 with 3 equiv of LDA suggests that dilithio salt 10 may be present under such conditions. The



10

existence of 10 raises the possibility that the successful alkylations and carbonyl condensations which take place in the presence of 2 or more equiv of LDA may not result only from a shift of the equilibrium from 1 to 2 and that perhaps 10 is a key intermediate in these reactions.

Experimental Section

All reactions were carried out under an argon atmosphere. Tetrahydrofuran (THF) was purified by distillation from sodium benzophenone ketyl under nitrogen. Diisopropylamine was distilled from calcium hydride and stored under argon. Standardized (1.6 M) *n*-butyllithium in hexane and THF-d_8 were obtained from Aldrich Chemical Co. *p*-Methoxybenzyl chloride was prepared from *p*-hydroxybenzyl chloride by following a literature procedure.[16] All other chemicals were commercial grade and were

(13) For a discussion of the mechanisms of formation of 7 by means of *n*-butyllithium see: Hoeg, D. F.; Lusk, D. I. *J. Organomet. Chem.* **1966**, *5*, 1.

(14) Wade, P. C.; Vogt, B. R.; Toeplitz, B.; Puar, M. S.; Gougoutas, J. S. *J. Org. Chem.* **1979**, *44*, 88.

(15) The peak at δ 3.55 in the spectrum shown in trace c of Figure 1 is caused by residual THF in the THF-d_8 used as solvent.

Table I. Reactions of Anion 2 with Electrophiles

electrophile	reaction time	product	yield, %	mp, °C	chromatography solvent(s)	recrystallization solvent(s)
CH_3I	2 h	3a	75	110-112	cyclohexane-benzene-diisopropylamine (15:6:2)	$CHCl_3$-hexane
C_2H_5I	3 h	3b	60	180-181	benzene	CH_2Cl_2-petroleum ether (40-60 °C)
i-C_3H_7I	3 h	3c	50	193-194	benzene	$CHCl_3$-petroleum ether
$C_6H_5CH_2Cl$	2 h	3d	53	151-152	benzene-hexane (1:1)	hexane
p-$MeOC_6H_4CH_2Cl$	3 h	3e	56	121-122	benzene	pentane-ether
p-$ClC_6H_4CH_2Cl$	2 h	3f	60	167-168	MeOH-ether (3:97)	hexane
n-C_4H_9I	2.5 h	3g	22	159-160	CH_2Cl_2-hexane (9:1)	pentane-ether
		3h	10	137-138	CH_2Cl_2-hexane (9:1)	CH_2Cl_2-hexane
$(C_6H_5)_2CO$	2 h	4a	60	201-204	hexane-benzene-diisopropylamine (15:6:2)	$CHCl_3$-hexane
$C_6H_5COCH_3$	2 h	4b	22	216-219	CH_2Cl_2-EtOAc (19:1)	CH_2Cl_2-hexane
CH_3COCH_3	2.5 h	4c	16	165-168	CH_2Cl_2-EtOAc (4:1)	$CHCl_3$-hexane
cyclohexanone	2 min	4d	75	214-215	CH_2Cl_2-EtOAc (9:1)	$CHCl_3$-hexane
C_6H_5CHO	2 min	4e	44	170-171	benzene-EtOAc (2:1)	$CHCl_3$-hexane
cyclohexanone	3 h	5a	58	154-157	hexane-benzene-diisopropylamine (15:6:2)	CH_2Cl_2-hexane
C_6H_5CHO	3 h	5b	67	189-191[a]	CH_2Cl_2-EtOAc (99:1)	MeOH
CH_3CO_2Et	1 h	6a	12	148	hexane-EtOAc (4:1)	pentane
$C_6H_5CO_2Me$	1 h	6b	20	199-200	hexane-EtOAc (1:1)	$CHCl_3$-hexane

[a] Lit.[9] mp 189-192 °C.

purified by distillation or crystallization prior to use.

^1H NMR spectra were recorded on a Varian EM-390 spectrometer at 90 MHz with Me_4Si as an internal reference. ^{13}C NMR spectra were obtained on a JEOL FX-200 NMR spectrometer. Chemical shifts are given as parts per million (δ) downfield from Me_4Si. IR spectra were recorded either on a Beckman IR-20A-X or on a Perkin-Elmer 710B infrared spectrophotometer. Microanalyses were determined in this department by Jorge I. Bedia and T. E. Glass on a Perkin-Elmer 240 elemental analyzer and by Galbraith Laboratories. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator (Eastman Kodak No. 6060). Column chromatography was carried out by using 60–200-mesh silica gel from Davison Chemicals. The solvents for chromatography were dried over molecular sieves.

General Procedure for Generation of Anion 2. To a flame-dried, argon-flushed, 125-mL, three-necked flask, equipped with a thermometer, a magnetic stirrer, and an argon inlet and containing 20 mL of anhydrous THF, was added 1.6 g (16 mmol) of diisopropylamine. The solution was cooled to −60 °C, and 11.2 mL (16 mmol) of 1.6 M n-butyllithium solution in hexane was added via syringe. The solution was stirred for 10–15 min and then warmed to room temperature during 20–25 min. After the mixture was cooled back to −60 °C, a 5-mL THF solution of 1 (2.3 g, 8 mmol) was added through a syringe and the reaction mixture was brought to room temperature over 25 min. The resulting dark red solution of 2 was used in specific reactions described below and in Table I. In aldol condensations and acylations, 4 mmol of 2 was used.

Preparation of Anion 2 for NMR Experiments. For these experiments, 60 mg (0.2 mmol) of 1 was dissolved in 0.25 mL of THF-d_8. A stock solution of LDA (2 mmol) was prepared by adding 1.3 mL of 1.6 M n-butyllithium solution in hexane to 0.5 mL of THF-d_8 containing 0.2 mL of diisopropylamine. For 1 equiv of LDA, 0.2 mL (0.2 mmol) of this solution was syringed out and added to the NMR tube. The spectra were recorded at 34 °C. Experiments employing 2 and 3 equiv of LDA were conducted in a similar fashion. Examination of ^{13}C NMR spectra of samples prepared in this manner provided limited information concerning the extent of metalation and the structure of anion 2. On the basis of previous reports[17,18] of ^{13}C NMR spectra of 1, it was possible to determine that the resonance for C_3, which originally appears at δ 57.6 in the spectrum of 1, is shifted downfield to δ 103.8 in anion 2. Assignment of this resonance was done by off-resonance proton decoupling.

General Procedure for Reactions of Anion 2 with Electrophiles. Before adding any electrophilic reagent to anion 2, the solution was cooled to −20 °C. The electrophile (normally a molar quantity equal to the amount of 2) was then added as a solution in 5 mL of THF, and the reaction mixture was allowed to come to room temperature. The progress of the reaction was followed by ^1H NMR and TLC. In general, after the reaction was completed, saturated aqueous sodium chloride solution was added, and the mixture was extracted with dichloromethane (3 × 100 mL). The extracts were dried ($MgSO_4$) and concentrated. The resulting residues were chromatographed on silica gel and then recrystallized from appropriate solvents. The specific experiments described below for the preparation of deuterated **1**, **3a**, **3g-h**, **4a**, and **6a** are representative of typical procedures. Reaction conditions and yields for the preparation of **3a–f**, **4a–e**, **5a,b** and **6a,b** are summarized in Table I (see the paragraph at the end of the paper about supplementary material).

7-Chloro-1-methyl-5-phenyl-2*H*-1,3-dihydro-1,4-benzodiazepin-2-one-*3-d*. A solution of anion 2, prepared from 1.15 g (4 mmol) of 1 and 8 mmol of LDA, was quenched with 1.2 mL (0.12 mol, 15 equiv) of D_2O. The THF layer was decanted, and the remaining paste was extracted several times (8 × 30 mL) with ether. The ethereal and THF layers were combined and dried. Evaporation of the solvent gave a dark brown oil. Chromatography on silica gel gave, on elution with hexane–chloroform (7:3, 600 mL) 0.3 g (26%) of 1: mp 123–124 °C (after crystallization from hexane–chloroform); ^1H NMR ($CDCl_3$) δ 7.71–7.20 (m, 8 H, aromatic), 4.80 (s, 0.5 H, H_3), 3.74 (s, 0.5 H, H_3), 3.4 (s, 3 H, NCH_3); IR (CCl_4) 1690 (s), 1610 (s), 1490 cm^{-1} (s).

In another experiment the reaction mixture prepared from 1.15 g (4 mmol) of 1 and 12 mmol of LDA was quenched with excess D_2O. The reaction was worked up in the manner used above. Integration of the ^1H NMR spectrum of the purified sample showed incorporation of 1.34 deuterium atom at C_3 of 1.

7-Chloro-1,3-dimethyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3a). To a solution of 8 mmol of anion 2 was added, via syringe, 5 mL of a THF solution containing 1.2 g (8 mmol) of methyl iodide. The reaction mixture was stirred for 2 h. After the usual workup, the resulting oil was chromatographed. Elution with a mixture of cyclohexane–benzene–diisopropylamine (15:6:2, 600 mL) gave 1.8 g (75%) of **3a**, which was crystallized from hexane–chloroform: mp 110–112 °C (lit.[3d] mp (R enantiomer) 47–50 °C; mp (S enantiomer) 48 °C). An authentic sample of racemic **3a**[8] had the following: mp 106–109 °C; mmp 105–107 °C. The ^1H NMR and IR spectra of **3a** were identical with those of an authentic sample.

7-Chloro-3-*n*-butyl(and 3,3-di-*n*-butyl)-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (3g,h). Re-

(16) Dankova, T. F.; Evdokimova, L.-G.; Stepanov, I. I.; Preobrazhenski, N. A. *Zh. Obshch. Khim.* **1948**, *18*, 1724; *Chem. Abstr.* **1949**, *43*, 2607a.
(17) Sarrazin, M.; Faure, R.; Aubert, C.; Vincent, E. J. *J. Chim. Phys.* **1980**, *77*, 91.
(18) Singh, S. P.; Parmar, S. S.; Farnum, S. A.; Stenberg, V. I. *J. Heterocycl. Chem.* **1978**, *15*, 1083.

action of 8 mmol of 2 with 2.2 g (12 mmol) of *n*-butyl iodide for 2.5 h gave a semisolid crude product which was chromatographed. Elution with dichloromethane–hexane (9:1, 700 mL) gave 0.32 g (10%) of **3h**.[19] Further elution with the same solvent mixture 1.2 L) gave 0.6 g (22%) of **3g**.

7-Chloro-3-(diphenylhydroxymethyl)-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (4a). To 4 mmol of anion 2 was added 0.73 g (4 mmol) of benzophenone in 5 mL of THF. The reaction was stirred for 2 h, decomposed with dilute HCl (pH of aqueous layer was 6–7), and extracted with ether. The oil obtained after evaporation of the dried extract was passed through a column of silica gel.

3-Acetyl-7-chloro-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (6a). To 4 mmol of 2 was added 0.35 g (4 mmol) of ethyl acetate in 5 mL of THF, and the mixture was stirred for 1 h. The solution was treated with dilute HCl to pH 6–7. The reaction mixture was extracted with ether (500 mL). The oil, obtained after evaporation of the dried ethereal extract, was chromatographed. Elution with hexane–ethyl acetate (4:1, 200 mL) gave traces of an oil (unidentified). Further elution with the same solvent mixture (150 mL) gave a thick oil, which was crystallized from pentane to give 0.15 g (12%) of **6a**.

Reactions of Benzyl Chloride with LDA. To 4 mmol of LDA in THF was added 0.48 g (4 mmol) of benzyl chloride as a solution in 5 mL of THF. After 15 min at 25 °C the reaction was processed in the usual fashion to yield 1-chloro-1,2-diphenylethane (7) as a light yellow oil (homogeneous by TLC): ^{1}H NMR ($CDCl_3$) δ 7.61–7.15 (m, 10 H, aromatic), 4.96 (t, 1 H, CH), 3.24 (d, 2 H, CH_2).

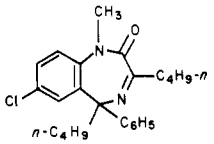
In a similar experiment employing 4 mmol of benzyl chloride and 8 mmol of LDA, *trans*-stilbene (8, mp 123–124 °C) was isolated as the major product. A mixture melting point with an authentic sample was not depressed. The ^{1}H NMR spectrum was identical with that of an authentic sample of 8.

Acknowledgment. We are grateful to Dr. W. E. Scott of Hoffman-La Roche Inc. for providing us with samples of diazepam (1) and racemic 3-methyldiazepam (**3a**) and to Mr. T. C. Glass for his help with the NMR experiments.

Registry No. 1, 439-14-5; 2, 78498-73-4; **3a**, 50882-52-5; **3b**, 40918-46-5; **3c**, 78498-74-5; **3d**, 29580-36-7; **3e**, 78498-75-6; **3f**, 78498-76-7; **3g**, 78498-77-8; **3h**, 78498-78-9; **4a**, 78498-79-0; **4b**, 78498-80-3; **4c**, 78498-81-4; **4d**, 78498-82-5; **4e**, 78498-83-6; **5a**, 78498-84-7; **5b**, 78498-85-8; **6a**, 78498-86-9; **6b**, 78498-87-0; 7, 4714-14-1; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; isopropyl iodide, 75-30-9; benzyl chloride, 100-44-7; 4-methylbenzyl chloride, 824-94-2; 4-chlorobenzyl chloride, 104-83-6; butyl iodide, 542-69-8; diphenylmethanone, 119-61-9; 1-phenylethanone, 98-86-2; 2-propanone, 67-64-1; cyclohexanone, 108-94-1; benzaldehyde, 100-52-7; ethyl acetate, 141-78-6; methyl benzoate, 93-58-3.

Supplementary Material Available: ^{1}H NMR, IR, and analytical data for compounds **3a–h**, **4a–e**, **5a,b**, and **6a,b** (2 pages). Ordering information is given on any current masthead page.

(19) A referee has suggested that dibutyl derivative **3h** could have the 1,5-dihydro structure i. This alternative structure is ruled out by the observations that **3h** possesses the characteristic IR bands at 1680, 1610, and 1410 cm^{-1} for 1,3-dihydro-1,4-benzodiazepinones, while i would be expected to have strong absorption below 1650 cm^{-1}.[20]



i

(20) Ogata, M.; Matsumoto, H.; Hirose, K. *J. Med. Chem.* 1977, *20*, 776.

Pyrimidine Derivatives and Related Compounds. 39.[1] A Novel Cycloaromatization Reaction of 5-Formyl-1,3-dimethyluracil with Three-Carbon Nucleophiles. Synthesis of Substituted 4-Hydroxybenzoates

Kosaku Hirota,* Yukio Kitade, and Shigeo Senda

Gifu College of Pharmacy, 6-1, Mitahora-higashi 5 Chome, Gifu 502, Japan

Received April 13, 1981

Treatment of 5-formyl-1,3-dimethyluracil (1) with α-substituted acetone derivatives (C–C–C type nucleophiles) such as acetylacetone, acetoacetamide, ethyl acetoacetate, and phenylacetone in basic media affords the corresponding 4-hydroxybenzoates (4). On the other hand, treatment of 1 with cyanoacetamide, a C–C–N type nucleophile, gives the nicotinate 8. A mechanism for this cycloaromatization was proposed on the basis of reaction of 5-formyl-1,3-dimethyluracil-d_1 (6) with acetylacetone.

Uracil derivatives constituted of a urea part (N_1–C_2–N_3) and a three-carbon fragment (C_4–C_5–C_6) can be used as a source of formyl acetate.[2a] In fact, when uracils are allowed to react with the reagents containing two nucleophilic sites, various heterocyclic compounds are obtained.[2-5] For example, uracils are converted into the corresponding pyrazolones and isoxazolones by treatment with hydrazine and hydroxylamine, respectively.[3] Watanabe et al. and we[4] have also found that the reaction of 1,3-disubstituted uracils with 1,3-bifunctional nucleophiles such as guanidine

(1) For part 38, see M. Yogo, K. Hirota, and S. Senda, *J. Heterocycl. Chem.*, in press.
(2) (a) E. G. Lovett and D. Lipkin, *J. Org. Chem.*, 43, 3073 (1978); (b) *ibid.*, 42, 2574 (1977).
(3) F. Lingens and H. Schneider-Bernlöhr, *Justus. Liebigs Ann. Chem.*, 686, 134 (1965); D. H. Hayes and F. Hayes-Baron, *J. Chem. Soc. C*, 1528 (1967).
(4) K. Hirota, K. A. Watanabe, and J. J. Fox, *J. Heterocycl. Chem.*, 14, 537 (1977); *J. Org. Chem.*, 43, 1193 (1978); K Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. J. Fox, *J. Am. Chem. Soc.*, 101, 4423 (1979); K. Hirota, Y. Kitade, and S. Senda, *Heterocycles*, 14, 407 (1980); K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. J. Fox, *J. Org. Chem.*, 46, 846 (1981).
(5) K. Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.*, 33, 892 (1968).

0022-3263/81/1946-3949$01.25/0