Mobile Keto Allyl Systems. XV.[1] Reaction of Amines with α-(Bromomethyl)benzalacetone and Synthesis of an Acetylazetidine

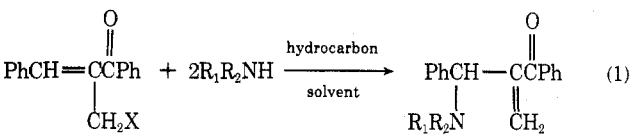
Michael C. Eagen and Norman H. Cromwell*

Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68508

Received September 7, 1973

The synthesis and reaction of α-(bromomethyl)benzalacetone (2) with *tert*-butylamine, morpholine, and piperidine in hydrocarbon solvent is reported. Substitution–rearrangement products 3 were obtained for all amines. The morpholine and piperidine reactions gave 3 as well as normal substitution products 4. The formation of compounds 3 and 4 is discussed in terms of a variant of an S_N2' mechanism. The synthesis and structure determination of *trans*-1-*tert*-butyl-2-phenyl-3-acetylazetidine is described.

Although primary allyl halides react with amines to yield mainly normal substitution products,[2] Cromwell and Rebman observed rearrangement–substitution products (II) upon treating *tert*-butylamine, cyclohexylamine, morpholine, or piperidine with *trans*-α-(bromomethyl)chalcone (Ia) in hydrocarbon solvent.[3] Kinetic studies showed a retardation in the reaction rate of Ia with increasing bulk at the α-carbon atom of the attacking amine.[4] The ratios of reactivities of the bromide Ia and the chloride Ib with cyclohexylamine and triethylcarbinylamine were 3.6 and 5.7, respectively. This small leaving group effect suggested that the reaction of amines with Ia or Ib involved a rate-limiting transition state in which there is only a small extension of the carbon–halogen bond.[4]

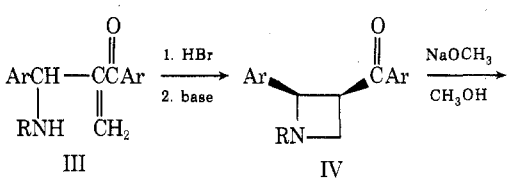


(1)

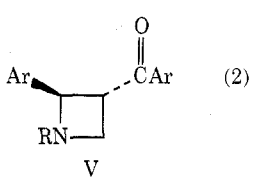
Ia, X = Br
b, X = Cl

II

The β-benzoylallyl amines III are precursors to the high yield synthesis of azetidinyl ketones.[5] A variety of amino derivatives of type III gave the cis azetidine IV, exclusively, in nearly quantitative yield. The cis compounds were readily epimerized to the trans isomers V with sodium methoxide in methanol.



III IV



(2)

V

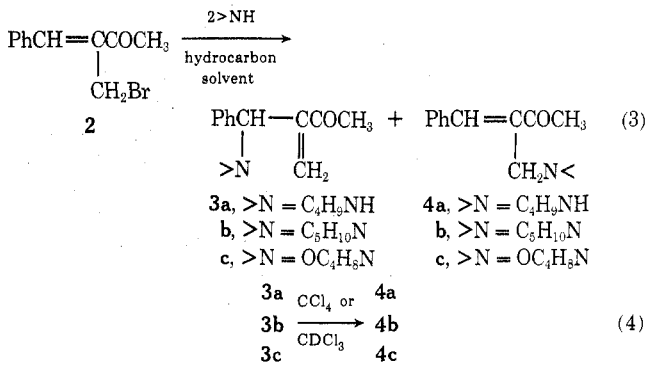
We were interested in studying the reaction of amines with α-(bromomethyl)benzalacetone (2) in hydrocarbon solvent and in utilizing the above procedure for the synthesis of an acetylazetidine.

Results

trans-α-(Methyl)benzalacetone (1) was synthesized in satisfactory yield by the hydrogen chloride catalyzed condensation of benzaldehyde with butanone. Bromination of 1 with *N*-bromosuccinimide in refluxing carbon tetrachloride containing a catalytic amount of benzoyl peroxide yielded *trans*-α-(bromomethyl)benzalacetone (2). Compound 2 was sufficiently soluble in pentane to undergo reaction with amines.

Careful treatment of 2 with a 2 mol equiv of *tert*-butylamine in pentane at room temperature produced 2-[α-(*tert*-butylamino)benzyl]-1-buten-3-one (3a), exclusively. Upon dissolving 3a in carbon tetrachloride, slow isomerization to 1-(*tert*-butylaminomethyl)benzalacetone (4a) was observed by pmr. Both 3a and 4a were characterized as their hydrohalide salts.

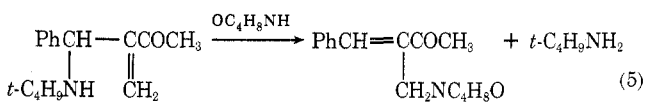
When 2 was treated with a 2 mol equiv of morpholine or piperidine in hexane solvent at room temperature, both rearrangement–substitution (3b and 3c) and substitution (4b and 4c) products were observed. Upon dissolving the reaction mixtures in chloroform-*d*, slow isomerization to the thermodynamically more stable isomers was complete (3b to 4b and 3c to 4c). The lower spectrum in Figure 1[6] is for the products from the reaction of 2 with piperidine after filtering off a 95.3% yield of piperidine hydrobromide. The 6.19- and 6.27-ppm resonances were assigned to the vinylic protons and the 4.49-ppm resonance to the benzyl proton in 3b. The top spectrum in Figure 1 resulted from allowing the product mixture 3b and 4b to stand at room temperature for several days in chloroform-*d*. The 3.32-ppm resonance was assigned to the vinyl methylene protons in 4b. All of the amino ketones (3 and 4) were heat-sensitive oils whose hydrohalide salts were hygroscopic. They were analyzed as their picrates. Attempts to purify the product mixtures on a Florisil chromatography column resulted in decomposition of the compounds.



(3)

(4)

The amino ketone 3a reacted with morpholine in pentane solvent to produce 4c. No evidence for a 1,3-diamino ketone was obtained.

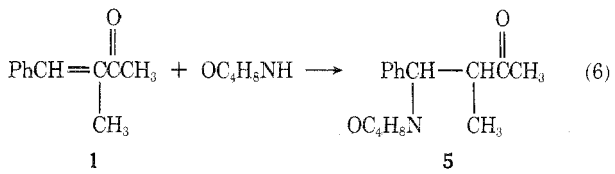


(5)

3a 4c

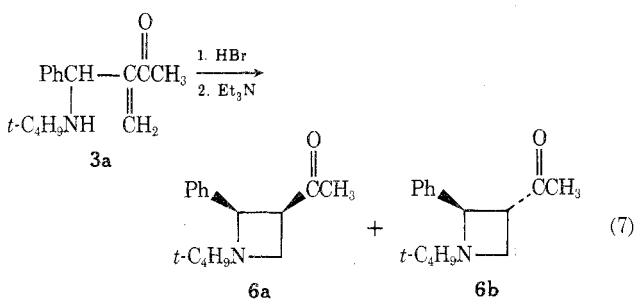
A 20-fold excess of morpholine was allowed to react neat with 1 at room temperature for 13 days. Pmr analysis of the reaction mixture showed unreacted 1 and an 8:1 ratio of the diastereomers of the Michael adduct 5. The diaste-

reomers of 5 were readily identified by the α methyl resonances ($CHCH_3$) appearing as doublets centered at 0.80 and 1.28 ppm. The predominant diastereomer was fractionally crystallized from ether–pentane, mp 90.5–91.5°. When this reaction was carried out for 3.5 months, the diastereomers were present in equal amounts with 30% unreacted starting material remaining.



1 5 (6)

The amino ketone **3a** was dissolved in chloroform saturated with hydrogen bromide at 0° and allowed to reach room temperature after standing several days. Careful neutralization of the reaction mixture with excess triethylamine and subsequent work-up provided a 70% yield of azetidinyl ketones **6a** and **6b** in a 6:1 ratio, respectively (estimated by integration of pmr signals), and some starting material (**3a**).



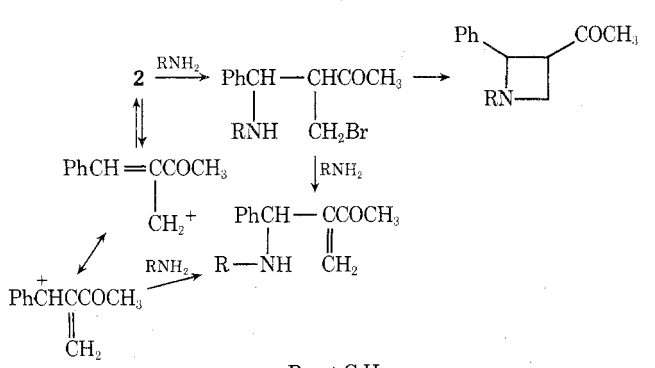
3a 6a 6b (7)

The reaction mixture was eluted with ether–benzene on a silica gel chromatography column. The first band eluted was identified by pmr as **6b** (Figure 2).[6] No other azetidinyl product was collected. Unidentified material was eluted after **6b** and considered to be degradation products of **3a** and **4a**. Compound **6b** was a clear stable oil. Upon treatment with sodium methoxide in methanol-d_1 the acetyl methyl protons and the 3-H ring proton were readily exchanged. The 2-H ring proton signal collapsed from a doublet to a singlet centered at δ 4.39.

Discussion

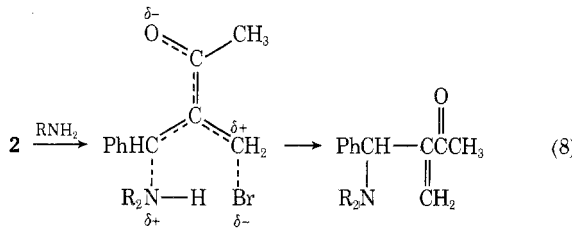
Ionization of the β-carbo allyl bromide **2** and subsequent nucleophilic attack by amine in a nonpolar solvent is not likely.[7] The reaction of **1** in neat morpholine was very slow and incomplete even after 3 months. These data argue against the formation of a 1,4-Michael adduct followed by rapid elimination of hydrogen bromide. If this elimination step was sufficiently slow, then azetidine formation (with *tert*-butylamine) should have been observed since the two reactions are competitive (Scheme I).

Scheme I



R = t-C_4H_9

The formation of rearrangement–substitution products from the reaction of amines with **2** in hydrocarbon solvent is best described by a variant of an S_N2' mechanism. The amine attacks the electron deficient γ-carbon atom of the allyl system with the carbonyl group oxygen atom accepting much of the developing negative charge. The carbon–nitrogen bond formation proceeds ahead of the carbon–bromine bond breakage. The approach of the amine could be aided by hydrogen bonding with the carbonyl oxygen atom[8] or with the bromine atom resulting in a cis orientation of the amine and bromine (eq 8). A cis geometry for the attacking nucleophile to the leaving group was proved for the reaction of piperidine with *trans*-6-alkyl-2-cyclohexen-1-yl-2,6-dichlorobenzoates.[9] We envisage structure A for the transition state of the reaction of amines with **2**.

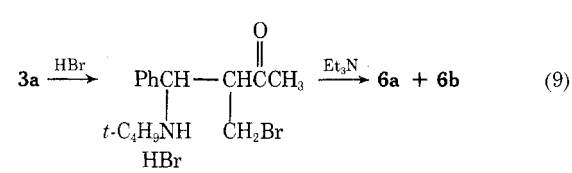


A (8)

The normal substitution products **4b** and **4c** were obtained from reaction of piperidine with **3b** and morpholine with **3c**, respectively, or by self-rearrangement of **3b** and **3c**. The possibility of the former process was demonstrated when **3a** reacted with morpholine to produce **4c** (eq 5).[10] The self-rearrangement process is very slow in pentane or hexane and requires solvents of higher polarity to become important (eq 4).

The formation of **4b** and **4c** in hydrocarbon solvent was not expected in view of the reaction of morpholine and piperidine with Ia to produce only abnormal substitution products under the conditions of eq 1 and 3. We rationalize that compounds **3b** and **3c** are able to compete with **2** for unreacted amine while II cannot compete with Ia. It is known that the reactivity of amines toward Ia and II is influenced by the bulkiness of the attacking amine and, for Ia, interaction between substituents at the α-carbon atom of the attacking amine and the γ-phenyl ring of the allyl system.[3,10] It now appears necessary to consider the substituent on the β-carbonyl group of the allyl system as a product controlling factor.

The addition of hydrogen bromide to **3a** probably formed a γ-bromo amine B which cyclized to the cis azetidinyl ketone **6a**.[5a] Approximately 30% of unchanged starting material was observed by pmr (Figure 2)[6] and was considered to arise from elimination of hydrogen bromide from B rather than incomplete addition of hydrogen bromide to **3a**.[11] The reaction is further complicated by the production of a small amount of the trans azetidinyl ketone **6b**.



B (9)

The cis azetidine **6a** results from a stereospecific intramolecular nucleophilic displacement of halogen by nitrogen from the erythro form of B.[5] The trans azetidine **6b** is derived from the threo form of B or by epimerization of **6a** in the presence of excess triethylamine.

Configuration assignments were based on pmr spectra and were compared with known 3-carbo azetidines.[5] Ex-

amination of the spectra in Figure 2[6] shows the C-2 benzyl doublet of **6b** (J = 6.6 Hz) centered at 4.39 ppm compared to 4.69 ppm for **6a** (J = 8.3 Hz).

The benzyl proton of trans 3-carbo azetidines (V) typically resonate at higher field than in the cis isomer (IV).[5c] Also, the trans isomers of V show a smaller coupling constant for the benzyl proton than the cis compounds IV. Lastly, the relative chemical shifts of the acetyl methyl protons in **6a** and **6b** suggest that the assignments were correct. For **6a**, the acetyl methyl protons are cis to the phenyl ring and resonate at 1.37 ppm. In **6b**, a trans configuration exists and the singlet now resonates at lower field at 1.91 ppm.

Experimental Section

Melting points were determined from a Mel-Temp or a Hoover capillary tube device and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Models 237 and 621 spectrophotometers and a Beckman IR-18. The pmr spectra were obtained from Varian Models A-60, A-60D, and HA-100 spectrometers utilizing tetramethylsilane as an internal standard. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

trans-α-**(Methyl)benzalacetone (1).**[12] A 53-g (0.5 mol) sample of benzaldehyde and 36 g (0.5 mol) of butanone were stirred magnetically at 0° while anhydrous hydrogen chloride was bubbled in until saturated. The mixture was stirred overnight to leave a red oil followed by evaporation of water and hydrogen chloride *in vacuo* with heating. The resulting mass was taken up in 400 ml of 95% ethanol containing 70 g (0.5 mol) of K_2CO_3 and 49 g (0.5 mol) of KOAc and refluxed 4 hr. The solvent was evaporated and the residue taken up in ether and filtered, and the ether evaporated to leave a yellow oil. The oil was distilled through a 6-in. Vigreux column collecting 48 g (60%): bp 80–93° (~1 mm); pmr (CCl_4) δ 7.1–7.4 (m, 6, C_6H_5CH), 2.33 (s, 3, $COCH_3$), and 1.96 (d, 3, J = 1.5 Hz, vinyl CH_3); $\nu_{C=O}$ (CCl_4) 1670 cm^{-1}.

trans-α-**(Bromomethyl)benzalacetone (2).** A 48-g (0.30 mol) sample of **1** dissolved in 500 ml of CCl_4 containing 53.4 g (0.30 mol) of *N*-bromosuccinimide and a catalytic amount (*ca.* 0.05 g) of benzoyl peroxide were refluxed 14 hr, cooled to room temperature, and filtered; the solvent evaporated *in vacuo* to leave an oil. The oil was dissolved in 100 ml of ether–hexane (1:1, v/v) and cooled for crystallization of 54.6 g (76%) of **2.** Upon recrystallization it showed mp 49–50°; pmr (CCl_4) δ 7.1–7.6 (m, 6, C_6H_5CH), 4.22 (s, 2, CH_2Br), and 2.38 (s, 3, $COCH_3$); $\nu_{C=O}$ (CCl_4) 1686 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}BrO$: C, 55.23; H, 4.68; Br, 33.44. Found: C, 55.18; H, 4.82; Br, 33.29.

2-[α-(*tert*-Butylamino)benzyl]-1-buten-3-one (3a). A 4.78-g (0.02 mol) sample of **2** dissolved in 400 ml of pentane was treated with 3.00 g (0.04 mol) of *tert*-butylamine in 20 ml of the same solvent. The contents were stirred 43 hr while stoppered at room temperature and filtered to remove 2.95 g (96.4%) of *tert*-butylamine hydrobromide. The pentane was evaporated *in vacuo* at room temperature to leave **3a** as an oil: pmr (CCl_4) δ 7.15–7.5 (m, 5, C_6H_5), 6.15 and 6.4 (m, 1 each, $C=CH_2$), 5.06 (m, 1, C_6H_5CH), 2.2 (s, 3, CH_3), and 1.05 (s, 10, NH and t-C_4H_9); $\nu_{C=O}$ ($CHCl_3$) 1673 cm^{-1}; hydrobromide (methanol–ether) mp 191.5–192.5°.

Anal. Calcd for $C_{15}H_{22}BrNO$: C, 57.68; H, 7.13; Br, 25.58; N, 4.48. Found: C, 57.86; H, 7.25; Br, 25.36; N, 4.40.

1-(*tert*-Butylaminomethyl)benzalacetone (4a). A small amount (*ca.* 0.1 ml) of **3a** was dissolved in *ca.* 0.3 ml of CCl_4 at room temperature. After 2 days isomerization of **3a** to **4a** was quantitative: pmr (CCl_4) δ 7.17–7.7 (m, 6, C_6H_5CH), 3.4 (s, 2, CH_2N), 2.5 (s, 3, $COCH_3$), 1.28 (NH), and 1.13 (s, 9, *tert*-C_4H_9); $\nu_{C=O}$ ($CHCl_3$) 1657 cm^{-1}; hydrochloride (methanol–ether) mp 157–158°.

Anal. Calcd for $C_{15}H_{22}ClNO$: C, 70.45; H, 9.34; Cl, 10.95; N, 4.32. Found: C, 70.35; H, 9.37; Cl, 11.02; N, 4.32.

2-[α-(Piperidino)benzyl]-1-buten-3-one (3b) and 1-(Piperidinomethyl)benzalacetone (4b). A 1.20-g (0.005 mol) sample of **2** dissolved in 100 ml of hexane was treated with 0.85 g (0.01 mol) of piperidine in 50 ml of hexane. The contents were stirred 23 hr while stoppered at room temperature and filtered to remove 0.79 g (95.3%) of piperidine hydrobromide. The hexane was evaporated to *ca.* 3 ml and the solution analyzed by pmr to show **3b** and **4b** in a 1:1 ratio. Upon standing in $CDCl_3$ slow isomerization of **3b** to **4b** was quantitative: **3b** pmr, δ 6.27 and 6.19 (s, 1 each, $C=CH_2$), and 4.49 (s, 1, C_6H_5CH); **4b,** δ 7.25–7.7 (m, 6, C_6H_5CH), 3.32 (s, 2, CH_2N), 2.43 (s, 3, $COCH_3$), 2.20–2.55 (m, 4, CH_2NCH_2), and 1.3–1.7 [m, 6, $(CH_2)_3$]; $\nu_{C=O}$ ($CHCl_3$) 1668 cm^{-1}; picrate (ethanol) mp 146–147°.

Anal. Calcd for $C_{22}H_{24}N_4O_8$: C, 55.93; H, 5.12; N, 11.86. Found: C, 55.83; H, 5.05; N, 12.06.

2-[α-(Morpholino)benzyl]-1-buten-3-one (3c) and 1-(Morpholinomethyl)benzalacetone (4c). A 1.20-g (0.005 mol) sample of **2** dissolved in 100 ml of hexane was treated with 0.87 g (0.01 mol) of morpholine in 50 ml of hexane. The contents were stirred 23 hr while stoppered at room temperature and filtered to remove 0.78 g (92.9%) of morpholine hydrobromide. The hexane was evaporated to *ca.* 3 ml, and the solution was analyzed by pmr to show **3c** and **4c** in a 2:1 ratio, respectively. Upon standing in $CDCl_3$ slow isomerization of **3c** to **4c** was quantitative: **3c** pmr, δ 6.22 and 6.33 (s, 1 each, $C=CH_2$) and 4.47 (s, 1, C_6H_5CH); **4c,** δ 7.0–7.6 (m, 6, C_6H_5CH), 3.5–3.7 (m, 4, CH_2OCH_2), 3.38 (s, 2, CH_2N), 2.47 (s, 3, $COCH_3$), and 2.2–2.5 (m, 4, CH_2NCH_2); $\nu_{C=O}$ ($CHCl_3$) 1670 cm^{-1}; picrate (ethanol) mp 186–187°.

Anal. Calcd for $C_{21}H_{22}N_4O_9$: C, 53.16; H, 4.67; N, 11.81. Found: C, 53.16; H, 4.64; N, 11.98.

2-Acetyl-1-morpholino-1-phenylpropane (5). A 3.20-g (0.02 mol) sample of **1** was dissolved in 34.8 g (0.4 mol) of morpholine at room temperature and stirred magnetically for 13 days. The morpholine was evaporated under a stream of nitrogen (2 days) to leave a yellow residue. Pmr analysis showed a 1:8 ratio of the diastereomers of **5.** The mixture was crystallized from 50 ml of ether–pentane (1:1, v/v) to yield 2.22 g (45%) of the diastereomer in greater yield: mp 90.5–91.5°; pmr ($CDCl_3$) δ 6.9–7.4 (m, 5, C_6H_5), 3.1–3.8 (m, 6, CH_2OCH_2 and C_6H_5CHCH), 2.1–2.5 (m, 4, CH_2NCH_2), 1.9 (s, 3, $COCH_3$), and 1.28 (d, 3, J = 6.2 Hz, CCH_3); $\nu_{C=O}$ ($CHCl_3$) 1709 cm^{-1}; picrate (ethanol) mp 171–171.5°.

Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 52.98; H, 4.95; N, 11.58.

In another experiment 3.20 g (0.02 mol) of **1** was dissolved in 1.74 g (0.02 mol) of morpholine at room temperature. The contents stood for 3.5 months and were analyzed by pmr (CCl_4) to show a 1:1 ratio of the diastereomers of **5:** CCH_3, δ 1.20 (d, J = 6 Hz) and 0.80 (d, J = 6 Hz). Approximately 30% of **1** was unreacted.

trans-**1-*tert*-Butyl-2-phenyl-3-acetylazetidine (6b).** A 4.78-g (0.02 mol) sample of **2** was dissolved in 350 ml of pentane followed by treatment with 2.92 g (0.04 mol) of *tert*-butylamine. The contents were stirred magnetically at room temperature while tightly stoppered for 31.5 hr, and filtered to remove *tert*-butylamine hydrobromide; the solvent evaporated *in vacuo* to leave an oil which was dissolved in 125 ml of $CHCl_3$ saturated with anhydrous HBr at 0°. The reaction was tightly stoppered and allowed to stand while warming to room temperature over a period of 13 days. Excess HBr and solvent were removed *in vacuo* with warming to leave a solid, which was taken up in 60 ml of $CHCl_3$ followed by slow addition (30 min) of 25 ml of Et_3N, and then filtered. The solvent and Et_3N were removed to leave a residue which was taken up in boiling pentane and filtered; the pentane was evaporated to leave an oil analyzed by pmr to show 70% of **6a** and **6b** (6:1 ratio, respectively) and **3a.** A portion of the product mixture was chromatographed on a silica gel column using ether–benzene (1:1, v/v) as eluent. The first band eluted was **6b** and the only azetidinyl product collected: pmr ($CDCl_3$) 7.1–7.7 (m, 5, C_6H_5), 4.39 (d, J = 6.6 Hz, 1, C_6H_5CH), 2.9–3.5 (m, 3, $CHCH_2$), 1.91 (s, 3, CH_3), and 0.88 (s, 9, t-C_4H_9); $\nu_{C=O}$ 1712 cm^{-1} (CCl_4); picrate (ethanol) mp 165.5–166.5°.

Anal. Calcd for $C_{21}H_{24}N_4O_8$: C, 54.78; H, 5.25; N, 12.17. Found: C, 54.52; H, 5.31; N, 12.23.

The Reaction of 2-[α-(*tert*-Butylamino)benzyl]-1-buten-3-one (3a) with Morpholine. Approximately 1.2 g (0.005 mol) of **3a** in 25 ml of hexane was treated with 1.5 g (0.015 mol) of morpholine. The contents stood at room temperature several days followed by complete evaporation of solvent and excess amine. The resulting oil was analyzed by pmr to show only **4c.**

Acknowledgment. We gratefully acknowledge financial support from Grant No. CA-02931 of the National Cancer Institute, U. S. Public Health Service, and the University of Nebraska Damon Runyon Memorial Fund for Cancer Research.

Registry No.—**1,** 42968-14-9; **2,** 42967-97-5; **3a,** 42967-98-6; **3a** HBr, 42967-99-7; **3b,** 42968-00-3; **3c,** 42968-01-4; **4a,** 42968-02-5; **4a** HCl, 42968-03-6; **4b,** 42968-04-7; **4b** picrate, 42968-05-8; **4c,** 42968-06-9; **4c** picrate, 42968-07-0; **5** isomer A, 42968-08-1; **5** iso-

mer B, 42968-09-2; **5** picrate, 42968-10-5; **6a**, 42968-11-6; **6b**, 42968-12-7; **6b** picrate, 42968-13-8; benzaldehyde, 100-52-7; 2-butanone, 78-93-3; *tert*-butylamine, 78-81-9; piperidine, 110-89-4; morpholine, 110-91-8.

Supplementary Material Available. Full nmr data in Figures 1 and 2 will appear following this article in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-911.

References and Notes

(1) For paper XIV in this series, see G. Glaros and N. H. Cromwell, *J. Org. Chem.*, **38**, 4226 (1974).
(2) (a) F. G. Bordwell and D. A. Schexnayder, *J. Org. Chem.*, **33**, 3240 (1968); (b) G. Valkanas and E. S. Waight, *J. Chem. Soc.*, 531 (1964); (c) R. H. DeWolfe and W. G. Young, "The Chemistry of Alkenes," Vol. 1, S. Patai, Ed., Wiley, New York, N. Y., 1964, p 681.
(3) (a) R. P. Rebman and N. H. Cromwell, *Tetrahedron Lett.*, 4833 (1965); (b) *J. Org. Chem.*, **32**, 3830 (1967).
(4) A. Denise George, E. Doomes, and N. H. Cromwell, *J. Org. Chem.*, **36**, 3918 (1971).
(5) (a) N. H. Cromwell and E. Doomes, *Tetrahedron Lett.*, 4037 (1966); (b) J. L. Imbach, E. Doomes, R. P. Rebman, and N. H. Cromwell, *J. Org. Chem.*, **32**, 78 (1967); (c) E. Doomes and N. H. Cromwell, *ibid.*, **34**, 310 (1969); (d) M. F. Stevens and N. H. Cromwell, *J. Heterocycl. Chem.*, **8**, 253 (1971); (e) M. C. Eagen, R. H. Higgins, and N. H. Cromwell, *ibid.*, **8**, 851 (1971).
(6) See paragraph at end of paper for supplementary material available.
(7) J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill, New York, N. Y., 1968, Chapter 5.
(8) (a) P. L. Southwick and R. J. Shozda, *J. Amer. Chem. Soc.*, **81**, 5435 (1959); (b) N. H. Cromwell and D. J. Cram, *ibid.*, **65**, 301 (1943).
(9) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).
(10) N. H. Cromwell, K. Matsumoto, and A. D. George, *J. Org. Chem.*, **36**, 272 (1971).
(11) J. A. Moore in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part II, A. Weissburger, Ed., Interscience, New York, N. Y., 1964, p 885.
(12) J. D. Geltler and L. P. Hammet, *J. Amer. Chem. Soc.*, **65**, 1824 (1943).

Synthetic Applications of Trimethylsilyl Cyanide. An Efficient Synthesis of β-Aminomethyl Alcohols

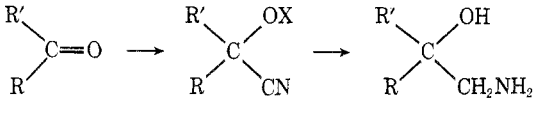
David A. Evans,*[1] Gary L. Carroll, and Larry K. Truesdale

Contribution No. 3220 from the Department of Chemistry, University of California, Los Angeles, California 90024

Received September 17, 1973

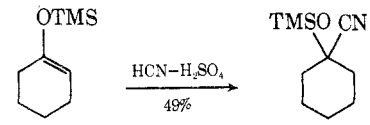
The use of trimethylsilyl cyanide (TMSCN) as a reagent for the direct formation of trimethylsilyl cyanohydrin ethers **3** from ketones is reported. The advantages in using TMSCN as opposed to hydrogen cyanide are illustrated by the formation of cyanohydrin ethers of ketones that do not form stable cyanohydrins. The reduction of derivatives **3** with lithium aluminum hydride is reported to afford β-aminomethyl alcohols **4** in good yield. The combined carbonyl derivatization-reduction sequence should afford a general synthesis of **4** useful in executing ring expansion reactions.

A great deal of attention has been devoted to the conversion of ketones to β-aminomethyl alcohols **4**. Interest in these derivatives has largely centered around their use in the Tiffeneau–Demjanov ring expansion of cycloalkanones.[2] The major difficulty in this general homologation process has been associated with the lack of reliable routes to β-aminomethyl alcohols.

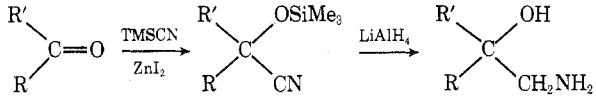


1 **2**, X = H; **3**, X = $SiMe_3$ **4**

The two classical methods for effecting this transformation have involved the formation and subsequent reduction of either ketone cyanohydrins[3] **2** or β-nitromethyl alcohols.[4] Both procedures have suffered from lack of generality and low overall yields for the desired transformation.[5] For the more widely used homologation sequence proceeding through ketone cyanohydrins, the yield of β-amino alcohol **4** is directly dependent upon the stability of the cyanohydrin **2**, the formation of which is highly dependent upon the steric and strain factors in the ketone.[6] Recently Parham and coworkers have shown that cyanohydrin ethers can be prepared by the acid-catalyzed addition of HCN to both alkyl[7a] and trimethylsilyl enol ethers,[7b,c] and that the resultant cyanohydrin derivatives can be reduced with $LiAlH_4$ to the desired β-amino ethers or alcohols. Although this approach results in the synthesis of derivatives of unstable cyanohydrins, the sequence requires the synthesis of the appropriate enol derivative, thus lengthening as well as restricting the homologation sequence to those systems for which enol ethers are easily prepared.



In conjunction with our interest[8] in exploring the utility of trimethylsilyl cyanide (TMSCN)[9] as a useful reagent in organic synthesis, we would like to report on its advantages in effecting carbonyl aminomethylation *via* the α-silyloxy nitriles **3** (eq 1).



(1)

1 **3** **4**

Our previous studies have shown that, in contrast to the substrate sensitivity of HCN–carbonyl addition reactions, the addition of TMSCN to both ketones and aldehydes is a general, high-yield process.[8] Apparently this is a consequence of the alteration in the ΔH for the carbonyl addi-