Evidence for Conformational Isomerism. II. Synthesis of 1-Alkyl-2-carboazetidines Using Organolithium Reagents (1)

Norman H. Cromwell, Kenneth F. Podraza, David S. Soriano and Richard M. Rodebaugh*

Department of Chemistry, University of Nebraska-Lincoln, NE 68588

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Treatment of 1-alkylazetidine-2-carboxylic acids with several organolithium reagents leads to the corresponding 1-alkyl-2-carboazetidines in near quantitative yield. Additional evidence is presented for conformational isomerism in the title compounds on the basis of infrared carbonyl stretching frequencies.

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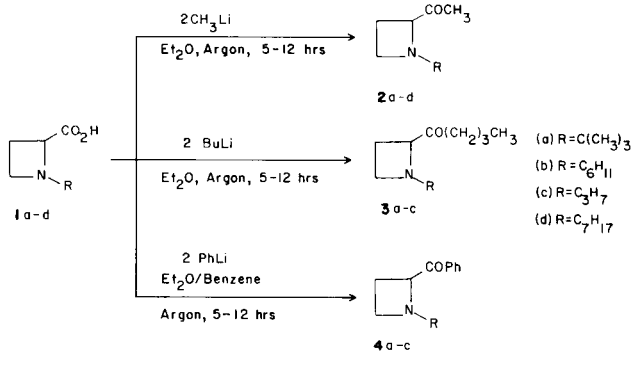
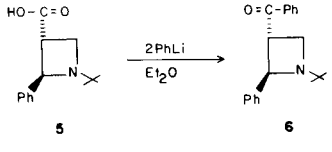
Examination of the literature revealed that the preparative methods for functionally substituted azetidines are relatively few in number. The value of a particular synthetic method depends not only on the yield after the ring closure step, but also on the availability of the precursor. We now report an alternative method of introducing functionality into the azetidine ring by the reaction of 1-alkylazetidine-2-carboxylic acids with organolithium reagents to yield 1-alkyl-2-carboazetidines (Scheme I).

Scheme I



Under an argon atmosphere the 1-alkylazetidine-2-carboxylic acids were suspended in ethereal or benzene-ether solutions and 2 molar equivalents of the appropriate organolithium reagent were added. The mixtures were allowed to stir for 5 to 12 hours, followed by hydrolysis. Only one previous example of an organolithium reagent used in the synthesis of a functionally substituted azetidine exists in the literature, that being reported earlier from this laboratory involving the synthesis of **6** in only a 30% yield (2) (Scheme 2).

Scheme 2



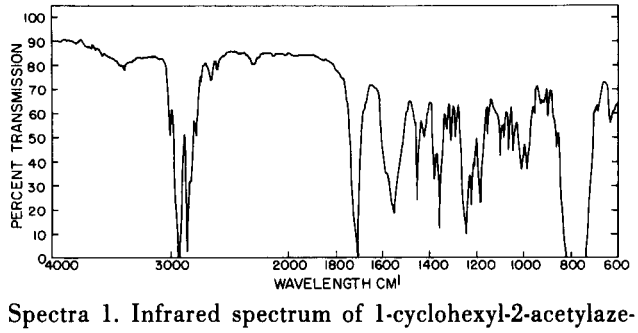
We have found that if the reaction was conducted under normal atmospheric conditions either the desired product was not obtained or was obtained in low yield. However, if the reaction was carried out under an argon atmosphere, the reaction proceeded smoothly in a greater than 90% yield.

Compounds **4a** and **4c** have been previously reported (1,3) being prepared by a different synthetic method. These compounds were found to be unstable, decomposing within 1 hour after isolation as an unidentifiable waxy solid. This prompted us to prepare compounds **4a** and **4c** by another synthetic method.

When looking at the infrared spectra characteristics of the 1-alkyl-2-carboazetidines (**2a-d** and **3a-c**), only one carbonyl stretch was observed, with an occasional shoulder, whereas the 1-alkyl-2-benzoylazetidines (**4a-c**) gave doublet carbonyl stretches (Spectra 1, 2, and 3).

In the case of the 1-alkyl-2-acetylazetidines (**2a-d**) the carbonyl stretching frequencies were nearly identical with an aliphatic model compound (in this case acetone). The 1-alkyl-2-butyrylazetidines (**3a-c**) also had a carbonyl band nearly identical with that of a aliphatic model compound (in this case 2-butanone).

The comparison of the 1-alkyl-2-benzoylazetidines (**4a-c**) with a model compound, acetophenone, revealed two carbonyl stretches, one of the peaks at a considerably higher frequency than that of the corresponding model compound, while the other stretching frequency was significantly lower.



Spectra 1. Infrared spectrum of 1-cyclohexyl-2-acetylazetidine (in carbon tetrachloride).

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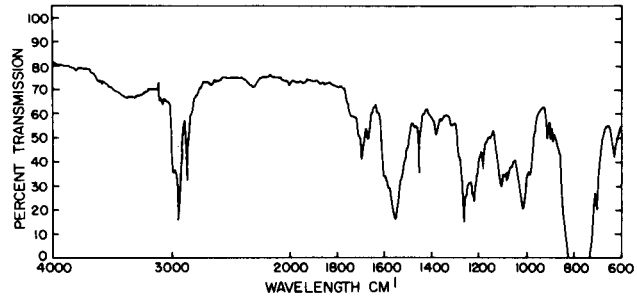
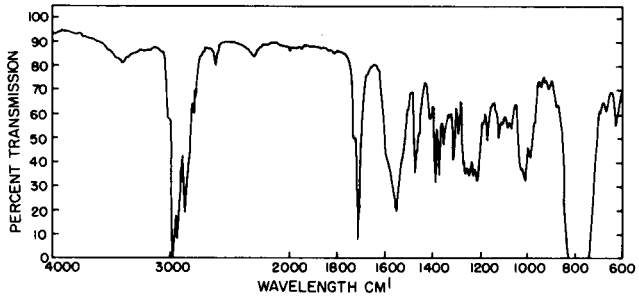
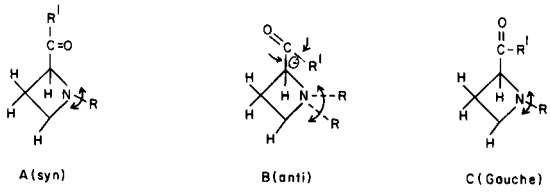


Spectra 2. Infrared spectrum of 1-cyclohexyl-2-benzoylazetidine (in carbon tetrachloride).



Spectra 3. Infrared spectrum of 1-isopropyl-2-butyrylazetidine (in carbon tetrachloride).

As pointed out in a previous publication (1), this suggests that both dipole-dipole and steric interactions are important in these systems, thus implying that rotation of the carbonyl moiety is partially hindered and that three conformers A, B, and C are of varying importance.



The syn conformer (A) has the ring nitrogen and carbonyl oxygen nearly eclipsed. The dipole-dipole interactions would be expected to increase the carbonyl stretching accounting for the high frequency band. Other studies (4) have shown that such eclipsed conformers involving a dipole-dipole interaction often represent the most stable arrangement for functional groups in the molecule and inspection of the infrared spectrum indicates that the high frequency band is predominant in intensity and thus represents the most stable arrangement for the functional groups present in the azetidine ring.

Conformer B, anti, arises from A by 180° bond rotation of the carbonyl moiety. When the *N*-substituent is oriented in a position *cis* to the carbonyl moiety in the anti conformer B nonbonded repulsive interactions may occur between R and R^1. An increase in the angle Θ would relieve steric compression and result in increased s-character in the C-C bond and increased *p*-character in the C-O bond with a subsequently lower energy stretching frequency than that observed in aliphatic model compounds. Such a steric interaction is expected when *N*-alkyl groups are bulky and no such interaction should occur with small R groups.

Neither dipole-dipole interaction nor significant steric interactions are expected to be present in the gauche conformer (C) in which the carbonyl bond's axis is perpendicular to the plane of the azetidine ring. The nitrogen atom would be expected to have little effect upon the position of the absorption maximum since through bond inductive effects of other electronegative groups have been shown to be negligible (5). Conformer C therefore gives rise to carbonyl stretching frequencies near those of the model compounds.

In addition to the above, it was concluded that Fermi resonance is not likely the cause of the doublet absorptions observed above because of the fact that several analogous compounds (such as **2d**) show a single syn carbonyl band.

Reports of doublet infrared carbonyl stretching absorption which have ascribed to conformational isomerism are numerous in the literature (5-13).

It has been shown by previous work that the same general phenomenon occurs with aziridinyl ketones and decided to be due to three-ring carbonyl hyperconjugation and conformational isomerism (7). Bellamy observed that same phenomenon and suggested it to be due to dipole-dipole interaction, as well as three-ring electrostatic factors (10).

Other studies, (8,9,11) have shown that doublet carbonyl bands are dependent upon solvent polarity, and the intensity of the high frequency band increases at the expense of the low frequency band, which is reasonable since the more polar solvent should favor the conformer of highest dipole moment.

In a previous publication (1), an nmr temperature study was conducted on an analogous ester, and it was concluded that the conformational isomerism could not be detected due to the relatively slow time scale of the nmr.

Application of additional organolithium reagents toward the synthesis of other functionalized azetidines is currently being explored.

Acknowledgment.

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EXPERIMENTAL

Boiling points were determined at pressures recorded on a standard

Virtis gauge and are uncorrected. Elemental analysis were performed by Micro-Tech Laboratories, Skokie, Illinois. Infrared spectra were recorded on a Beckman Acculab 4 Spectrometer. The chemical shifts and coupling constants (J) are reported in δ and Hertz respectively, using a Varian A60-D nmr, with TMS as the internal standard. Mass spectra were determined on a AEI-MS5076 spectrometer by Dr. Phil Lyon.

Synthesis of 1-Isopropylazetidine-2-carboxylic Acid (**1c**).

A sample of 1-isopropyl-2-carbomethoxy azetidine (14) was added dropwise to a solution containing 0.5 molar equivalent of barium hyroxide octahydrate in a minimum quantity of water heated to 90°. After addition of the ester, the heated solution was stirred for 30 minutes during which time the barium salt precipitated. Water was then added and carbon dioxide was passed through the hot mixture until no further precipitation occurred. The precipitated barium carbonate was removed by filtration. The water was evaporated *in vacuo* yielding a white solid, recrystallized from chloroform-ethyl ether, m.p. 177-179°; ir (chloroform): (ionic carboxylate ν C=O) 1630 cm^{-1}; nmr (deuterium oxide): δ 4.7 (1H, s, HOD), 4.55 (1H, t, J = 9.4 Hz, C_2), 4.0-3.7 (2H, m, C_4), 3.3 (1H, septet, J = 6.5 Hz, $CH(CH_3)_2$, 2.7-2.0 (2H, m, C_3), 1.1 and 1.05 (3H (each), two d, J = 6.5 Hz, non equivalent isopropyl methyl protons).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.70; H, 9.16; N, 9.75.

Synthesis of compounds **1a, 1b** and **1d** have been published previously (14).

General Procedure for the Preparation of 1-Alkyl-2-carboazetidines.

To a suspension of 1-alkylazetidine-2-carboxylic acid in the appropriate solvent 2 molar equivalents of the organolithium reagent was added dropwise and the solution was allowed to stir for 5 to 12 hours, the above steps being conducted under an argon atmosphere. The solution was then hydrolyzed with 5% ammonium chloride, the layers were separated, the ether layer was dried over magnesium sulfate, filtered, and the ether was evaporated. The crude liquid was then purified according to the procedure indicated for each azetidine.

The compounds reported here have been found to be thermally unstable and therefore correct elemental analyses could not be obtained for many of them. Their approximate stability is indicated for each azetidine.

Synthesis of 1-*t*-Butyl-2-acetylazetidine (**2a**).

A 2.5 g. sample of **1a** was reacted with the appropriate quantity of methyl lithium. Evaporation of the ether layer as described above yielded a pale yellow liquid. This pale yellow liquid required no further purification; ir (carbon tetrachloride): (ketone ν, C=O) 1710 cm^{-1} and (ketone shoulder ν_2, C=O) 1725 cm^{-1}; nmr (deuteriochloroform): δ 4.0 (1H, t, J = 8.0 Hz, C_2), 3.15-3.5 (2H, m, C_4), 2.28 (3H, s, $COCH_3$), 2.25-1.88 (2H, m, C_3), 0.95 (9H, s, *t*-butyl protons); ms: exact mass measurement calcd. for $C_9H_{17}NO$: 155.131. Found: 155.131 (±0.001).

This compound is stable for approximately 2 days at room temperature.

Synthesis of 1-Cyclohexyl-2-acetylazetidine (**2b**).

The appropriate quantity of methyllithium was reacted with 5.0 g. of **1b**. This compound was distilled under vacuum yielding a pale yellow liquid, b.p. 65-67°/0.1mm; ir (carbon tetrachloride): (ketone ν, C=O) 1707 cm^{-1} and (ketone shoulder ν_2 C=O) 1728 cm^{-1}; nmr (deuteriochloroform): δ 3.8-3.15 (1H, m, C_2), 3.13-2.65 (2H, m, C_4), 2.2 (3H, s, $COCH_3$), 2.32-1.95 (2H, m, C_3), 1.9-0.95 (10H, m, cyclohexyl protons); ms: exact mass measurement calcd. for $C_{11}H_{19}NO$: 181.146. Found: 181.146 (±0.0002).

This compound is stable for approximately 2 days at room temperature.

Synthesis of 1-Isopropyl-2-acetylazetidine (**2c**).

A 1.0 g. sample of **1c** was treated with the appropriate quantity of methyllithium. This compound was then chromatographed on florisil and eluted with acetonitrile yielding a pale yellow liquid; ir (carbon tetrachloride): (ketone ν, C=O) 1710 cm^{-1} and (ketone shoulder ν_2 C=O) 1740 cm^{-1}; nmr (deuteriochloroform): δ 3.6 (1H, t, J = 8.5 Hz, C_2), 3.35-2.65 (2H, m, C_4), 2.2 (3H, s, $COCH_3$), 2.5-1.95 (2H, m, C_3), 1.15-0.8 (7H, bm, isopropyl protons); ms: exact mass measurement calcd. for $C_8H_{15}NO$: 141.115. Found: 141.115 (±0.0002).

Anal. Calcd. for $C_8H_{15}NO$: C, 68.05; H, 10.71; N, 9.92. Found: C, 68.10; H, 11.00; N, 9.83.

Synthesis of 1-Benzyl-2-acetylazetidine (**2d**).

A 1.0 g. sample of **1d** was reacted with the appropriate amount of methyllithium. Evaporation of the ether layer as described previously yielded a pale yellow liquid. This pale yellow liquid required no further purification; ir (carbon tetrachloride): (ketone ν, C=O) 1710 cm^{-1}; nmr (deuteriochloroform): δ 7.25 (7H, s, $CH_2C_6H_5$), 4.1-2.5 (5H, complex m, C_2 and C_4 and benzyl protons), 2.45-1.65 (2H, m, C_3), 2.0 (3H, s, $COCH_3$); ms: m/e (M^+) 189.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 75.95; H, 7.98; N, 7.43.

Synthesis of 1-*t*-Butyl-2-butyrylazetidine (**3a**).

A 1.0 g. sample of **1a** was reacted with the appropriate quantity of butyllithium. This pale yellow liquid required no further purification; ir (carbon tetrachloride): (ketone ν, C=O) 1705 cm^{-1} and (ketone shoulder ν_2 C=O) 1725 cm^{-1}; nmr (deuteriochloroform): δ 3.9 (1H, t, J = 8.5 Hz, C_2), 3.6-2.9 (2H, m, C_4), 2.75-2.35 (2H, m, $COCH_2$), 2.25-1.75 (2H, m, C_3), 1.6-1.05 (4H, m, $(CH_2)_2$), 1.05 (3H, s, CH_3), 0.95 (9H, s, *t*-butyl protons); ms: exact mass measurement calcd. for $C_{12}H_{23}NO$: 197.1779. Found: 197.1779 (±0.00002).

This compound is stable for approximately 2 days at room temperature.

Synthesis of 1-Cyclohexyl-2-butyrylazetidine (**3b**).

The appropriate quantity of butyllithium was reacted with 1.0 g. of **1b**. Evaporation of the ether layer as described previously yielded a pale yellow liquid. No further purification was required for this pale yellow liquid; ir (carbon tetrachloride): (ketone ν, C=O) 1708 cm^{-1} and (ketone shoulder ν_2 C=O) 1730 cm^{-1}; nmr (deuteriochloroform): δ 3.55 (1H, t, J = 8.0 Hz, C_2), 3.35-2.28 (4H, complex m, C_4 and $COCH_2$), 2.25-1.85 (2H, m, C_3), 1.83-0.65 (14H, complex m, $(CH_2)_2$ and cyclohexyl protons 0.82 (3H, s, CH_3); ms: exact mass measurement calcd. for $C_{14}H_{25}NO$: 223.193. Found: 223.193 (±0.001).

This compound is stable for approximately 2 days at room temperature.

Synthesis of 1-Isopropyl-2-butyrylazetidine (**3c**).

A 2.0 g. sample of **1c** was reacted with the appropriate quantity of butyllithium. This pale yellow liquid required no further purification; ir (carbon tetrachloride): (ketone ν, C=O) 1710 cm^{-1} and (ketone shoulder ν_2 C=O) 1730 cm^{-1}; nmr (deuteriochloroform): δ 3.55-3.05 (1H, m, C_2), 3.0-2.25 (4H, m, C_4 and $COCH_2$), 2.23-1.65 (2H, m, C_3), 1.6-1.05 (4H, m, $(CH_2)_2$), 1.0 (3H, s, CH_3), 0.95-0.65 (7H, bm, isopropyl protons); ms: exact mass measurement calcd. for $C_{11}H_{21}NO$: 183.162. Found: 183.162 (±0.001).

This compound is stable for approximately 2 days at room temperature.

Synthesis of 1-*t*-Butyl-2-benzoylazetidine (**4a**).

A 2.0 g. sample of **1a** was reacted with the appropriate quantity of phenyllithium. The crude liquid was purified by chromatography on florisil and eluted with ether. The colorless fraction after the first pale yellow band was collected; ir (carbon tetrachloride): (ketone ν, C=O/% abs) 1697 cm^{-1}/85 and (ketone ν_2 C=O/% abs) 1668 cm^{-1}/71; nmr (deuteriochloroform): δ 8.0-7.2 (5H, complex m, aromatic protons), 4.8 (1H, t, J = 8.5 Hz, C_2), 3.4-3.1 (2H, m, C_4), 2.45-1.95 (2H, m, C_3), 1.0 (9H, s, *t*-butyl protons); ms: exact mass measurement calcd. for $C_{14}H_{19}NO$: 217.146. Found: 217.146 (±0.001).

The preparation of this compound has been reported previously (1,3).

This compound is stable for approximately 2 days at room temperature.

Synthesis of 1-Cyclohexyl-2-benzoylazetidine (**4b**).

A 2.0 g. sample of **1b** was reacted with the appropriate quantity of phenyllithium. The crude liquid was purified by chromatography on florisil and eluted with ether. The colorless fraction after the first pale yellow band was collected; ir (carbon tetrachloride): (ketone ν, C=O/% abs) 1700 cm^{-1}/80 and (ketone ν_2 C=O/% abs) 1670 cm^{-1}/20; nmr (deuteriochloroform): δ 8.5-7.1 (5H, complex m, aromatic protons), 4.45 (1H, t, J = 8.0 Hz, C_2), 3.65-3.4 (2H, m, C_4), 2.55-2.1 (2H, m, C_3), 1.95-0.95 (10H, m, cyclohexyl protons); ms: exact mass measurement calcd. for $C_{16}H_{21}NO$: 243.162. Found: 243.162 (±0.001).

This compound is stable for approximately 2 days at room temperature.

Synthesis of 1-Isopropyl-2-benzoylazetidine (**4c**).

A 2.0 g. sample of (**1c**) was reacted with the appropriate quantity of phenyllithium. It was purified by column chromatography on florisil and eluted with ether. The colorless fraction after the first pale yellow band was collected; ir (carbon tetrachloride): (ketone ν, C=O/% abs) 1699 cm^{-1}/52 and (ketone ν_2 C=O/% abs) 1669 cm^{-1}/41; nmr (deuteriochloroform): δ 8.2-7.4 (5H, m, aromatic protons), 4.6 (1H, t, J = 8.5 Hz, C_2), 3.8-2.85 (3H, m, C_4 and isopropyl methine), 2.8-2.1 (2H, m, C_3), 1.1-0.93 (6H, 2d, J = 6.1 Hz, nonequivalent isopropyl methyls); ms: exact mass measurement calcd. for $C_{13}H_{17}NO$: 201.115. Found: 201.115 (±0.0002).

The preparation of this compound has been reported previously (1,3). It is stable for approximately 2 hours at room temperature.

REFERENCES AND NOTES

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