Synthesis of 9-Phenyl-5*H*-2-benzazepines by Ring Expansion of 1-Phenyl-2,3-dihydroisoquinolines

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2-Acetyl-1,1-dibromo-3-phenyl-1a,2,3,7b-tetrahydro-1*H*-cycloprop[*c*]isoquinolines rearrange under the influence of silver trifluoroacetate to provide ring expanded 2-benzazepine derivatives. Remarkably, thermal excitation without the additional metal reagent could not accomplish the transformation. A new method is disclosed for the convenient preparation of the required 1,2-dihydroisoquinoline precursors.

Recently we reported[1] on a mild and convenient ring expansion approach for the synthesis of tetrahydro-2-benzazepines, compounds of considerable pharmacological interest.[2] Our sequence was based on the cyclopropanation and thermal ring expansion of 1,2-dihydroisoquinoline precursors **1** via intermediates **2** and **3** (Scheme I).

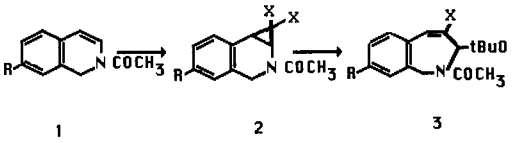
As an extension of this study we desired to prepare 2-benzazepines substituted with the useful aryl pharmacophore in the 1-position. We realized however that such an effort entailed the development of a convenient and general synthetic method for the preparation of the essential 1-aryl-1,2-dihydroisoquinoline precursors **6**, since the hitherto utilized Pomeranz-Fritsch[3] cyclization was anticipated to lack control over the desired regioselectivity of ring closure in this series. In this paper we report on a novel approach for the 1-phenyl-1,2-dihydroisoquinolines and on the ring expansion studies of the derived cyclopropanated derivatives.

Synthesis of *N*-Acetyl-1-phenyl-1,2-dihydroisoquinolines 6. 1,2-Dihydroisoquinolines[4] are unstable species susceptible to air oxidation unless substituted on nitrogen. A number of methods appeared in the literature for these compounds which, in our hands, were found either not applicable to the 1-phenyl derivatives[5] or lack generality on account of the extreme conditions employed.[6]

It appeared to us that a very simple and general approach to the 1-aryl-1,2-dihydroisoquinoline nucleus could be derived from isomerization of the closely related 3,4-dihydroisoquinolines, readily available from Bischler-Napieralski[7] cyclization of benzoylphenethylamines.[8] Further support for this idea could be gained from analogy with dihydroisoquinoline iminium systems[9] which readily underwent double bond migrations to afford isomeric 1-alkylidene structures whenever proton abstraction β to the nitrogen from the 1-substituent was possible. It was expected that in the absence of such protons in **5** stabilization of the iminium intermediates might still occur via proton shifts from C3 and C4, as shown via path a in Scheme II or alternatively via deconjugation of the aromatic ring and subsequent 1,5-proton shift as indicated via path b.[10]

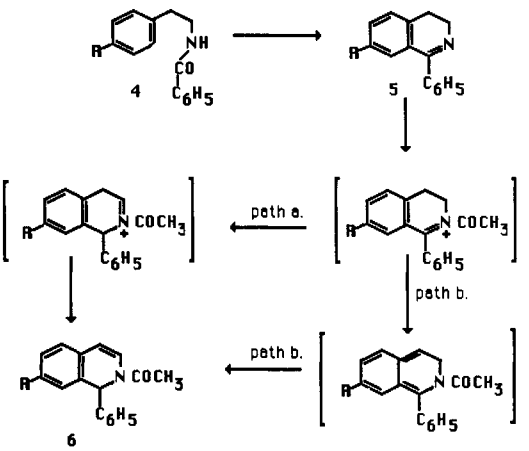
We prepared therefore via standard literature methods[7] 7-substituted 1-phenyl-3,4-dihydroisoquinolines **5a-c** and subjected them to treatment with potassium acetate in refluxing acetic anhydride. Smooth conversion to the desired *N*-acetyl-1,2-dihydroisoquinolines **6a-c** was observed in every instance (Scheme II).

Scheme I



1 2 3

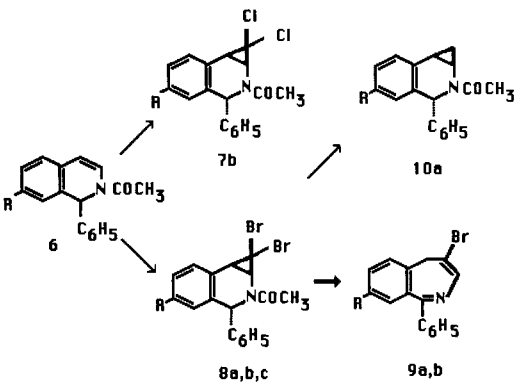
Scheme II



4 5 6

a, R=H; b, R=Cl; c, R=OCH3

Scheme III



7b 10a 6 8a,b,c 9a,b

a, R=H; b, R=Cl; c, R=OCH3

Double bond migration was complete within 6 h and compounds **6a-c** were the only isolable products. Support

† Smith Kline & French Postdoctoral Research Scientist, 1984-1985.

‡ Synthetic Chemistry.

§ Analytical Physical and Structural Chemistry.

(1) Perchonock, C. D.; Lantos, I.; Finkelstein, J. A.; Holden, K. G. *J. Org. Chem.* **1980**, *45*, 1950.

(2) Fuller, R. W.; Perry, K. W.; Hemrick, S. K. *Brain Res.* **1978**, *244*, 240.

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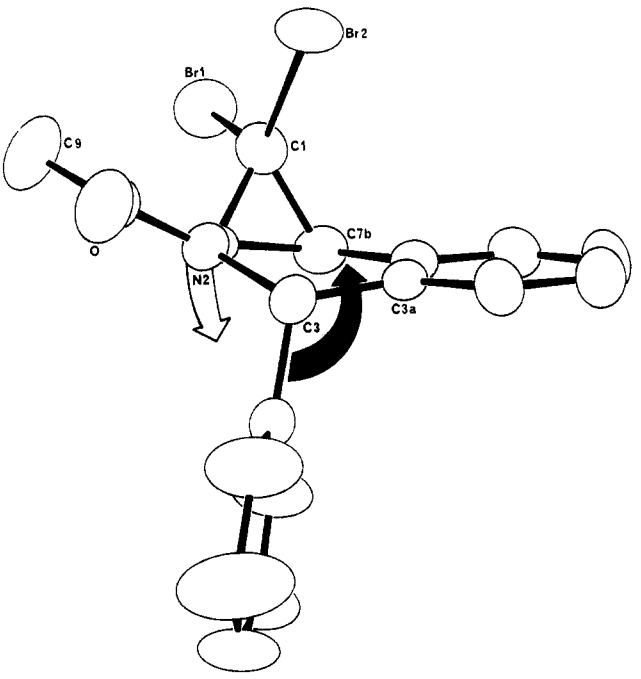

Figure 1. View of **8a** looking down the N2–C1a bond showing the puckered conformation of the six-membered ring and the lack of overlap between the nitrogen lone pair and the C1a–C7b bond.

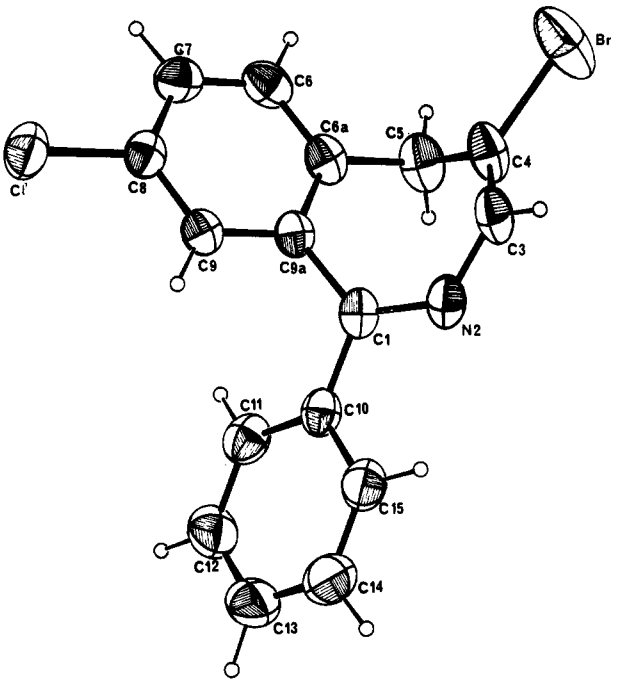

Figure 2. Diagram of **9b** showing the labeling scheme. Principal ellipses are drawn at the 50% probability level; H atoms are shown as small spheres of arbitrary size.

for the structural assignment rests on the presence of signals due to the vinyl protons in the ^{1}H NMR spectra and on the utility of the intermediates in further synthesis (vide infra).

Dihalocarbene Additions and Ring Expansion. With the required precursors for our studies in hand the dihalocarbene addition and ring expansion reactions were explored.

Dichlorocyclopropyl compound **7b** was prepared, as a single isomer in excellent yield, by a route analogous to our previous work on phase-transfer-catalyzed dichlorocarbene additions (Scheme III).[11] Assignment of the anti stereochemistry between the phenyl substituent and the cyclopropyl moiety was gained from direct comparison of the cyclopropyl proton signals at 3.60 and 3.15 ppm with those observed in the spectrum of **8a**, for which the structure has been determined by X-ray crystallography (vide infra).

The stereospecificity of the reaction was not unexpected in view of the steric hindrance of the syn face of the dihydroisoquinoline molecule by the phenyl substituent. It was entirely unexpected, however, that attempted ring expansion of **7b**, in a number of solvents and under diverse reaction conditions (refluxing *t*-BuOH, MeOH/HCl, DMF, dimethyl diglyme) failed to accomplish the desired fragmentation of the cyclopropyl moiety. Only the presence of unchanged starting material was detected in these reactions, and the compound was recovered unchanged even from sublimation at 200 °C. This thermal stability is surprising since compounds lacking substituents in the 1-position easily undergo the transformations under mild conditions.[1]

These results led us to study the behavior of the analogous dibromocyclopropyl intermediates. Their synthesis via a similar phase-transfer procedure with bromoform as the carbene source provided adducts **8a–c**, again with a high degree of stereomeric purity. Detailed structural features of **8a** were determined by an X-ray structural investigation and are shown on Figure 1. The figure in addition to confirming the anti stereochemistry between the substituents on the isoquinoline moiety also shows that the six-membered ring of the isoquinoline moiety adopts a distinctive puckered conformation in which C3 sits 0.283 (6) Å above and N2 sits 0.155 (5) Å below the four-atom plane defined by C3a–C7a–C7b–C1a. This out-of-plane distortion at C3 is toward the side of the ring on which the phenyl substituent lies.

Dibromo compounds **8a–c** showed similar thermal stability, which could be further demonstrated by radical debromination of **8a** to cyclopropyl derivative **10a** in refluxing toluene with tributyltin hydride. In an attempt to alter the mechanism of the fragmentation the reaction was carried out under silver trifluoroacetate catalysis.

These efforts were successful and the desired benzazepines **9a,b**, were secured, albeit in moderate yields. Methoxy compound **8c** was also converted to **9c** in a similar fashion, however the product was not rigorously purified since no appreciable rate acceleration was observed. Single-crystal X-ray diffraction results for **9b** (Figure 2) confirmed the structure for these ring expanded products. Of particular significance are the absence of the *N*-acetyl

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(10) In an effort to differentiate between the proposed mechanistic pathways we are currently investigating the rearrangement of optically active dihydroisoquinolines.

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group and the establishment of the 5-H benzazepine structure which is confirmed by the C3–C4 bond distance of 1.325 Å and the N–Cl bond distance of 1.290 Å.

Discussion

Much has been published on the utility of cyclopropyl ring fragmentations in synthesis.[12] The method has been extensively used in both carbocyclic and heterocyclic ring expansions.[13] In addition, fused [n.1.0]bicyclic amines have been utilized by Kuhne and King[14] as α-methyl ketone precursors providing a regiospecific alternative to the use of enolates for alkylation of cyclic ketones. Much less is known, however, of the conformational restrictions that determine the ease or direction of the carbon–carbon bond fragmentation (i.e. central vs. edge bond cleavage).

From the results described in this and in our previous report it appears that the conformationally rigid 2-azabicyclo[4.1.0]heptane system is particularly well suited to study the impact of conformational changes in the ring as induced by the 1-substituent on the rate of fragmentation of the cyclopropyl moiety. The facility of ring opening in the unsubstituted system implies to us that the stereoelectronic requirements for the central carbon–carbon bond fragmentation are exceptionally well met by the heterocyclic framework.

On the other hand, the sizable thermal stability observed for **8a–c** we believe to be of conformational origin caused by diminished assistance from the lone pair of electrons on the endocyclic amido nitrogen. Support for this suggestion can be gained from the X-ray structure of **8a** (Figure 1) showing incomplete overlap between the lone pair of electrons on the nitrogen and the C1a–C7b Walsh orbitals.[15] The rigidity of the azaheptane system prevents the double inversion of the acetyl and phenyl moieties to take place and the achievement of the orbital alignment necessary for the ring expansion.[16]

The silver-assisted reaction proceeds via a completely different mechanism. Fragmentation in this instance is initiated at the halogen, and no assistance from the nitrogen is required. Furthermore, the loss of the acetyl moiety appears to be the result of a cleavage from the ring expanded iminium acetate, facilitated by the trifluoroacetate nucleophile. It is clear that the steric arguments will need to be substantiated by additional experiments with analogues of **8**, for which the syn and anti isomers are available with substituents of varying steric demand. These results will be reported in future papers.

Experimental Section

All melting points are uncorrected. NMR spectra were obtained in 0.01 M $CDCl_3$ solutions on a Hitachi Perkin-Elmer R-24 spectrophotometer and are reported in ppm downfield from internal Me_4Si. IR spectra were taken as Nujol mulls on a Perkin-Elmer Infracord spectrophotometer. The usual workup conditions involved dichloromethane extraction, washing the extract with water and brine, and drying over anhydrous $MgSO_4$. Evaporation of the organic solution at reduced pressure yielded the crude product.

Preparation of 1-Phenyl-3,4-dihydroisoquinolines (5). The 1-(benzoylamino)-2-arylethane (50 mmol) was dissolved in 200 mL of xylene. P_2O_5 (14.5 g, 100 mmol) and $POCl_3$ (40 mL, 158 mmol) were added, and the mixture was heated to reflux. Heating was continued for a specific period, and the solution was allowed to cool to room temperature. The solvent was decanted, and the residual solid was carefully triturated to neutrality with 10% NaOH solution. The resultant aqueous mixture was treated by the usual workup to obtain oily crude products.

1-(Benzoylamino)-2-phenylethane, after 3 h of reflux, afforded a 90% yield of 1-phenyl-3,4-dihydroisoquinoline (**5a**) which was crystallized as the hydrobromide salt from *i*-PrOH–Et_2O–HBr, mp 216–218 °C. Anal. Calcd for $C_{15}H_{13}N$·HBr: C, 62.51; H, 4.90; N, 4.86. Found: C, 62.45; H, 4.89; N, 4.81. IR 2500, 1626, 1438, 1408, 1300, 1219, 1190, 1156, 917, 800 cm^{-1}; NMR 8.10–7.50 (9 H, m), 4.15 (2 H, t, J = 8 Hz), 3.25 (2 H, t, J = 8 Hz).

1-(Benzoylamino)-2-(4-chlorophenyl)ethane, after 6 h of reflux, afforded a 40% yield of 1-phenyl-7-chloro-3,4-dihydroisoquinoline (**5b**), which was crystallized from Et_2O and recrystallized as the hydrobromide from EtOH–HBr, mp 245–247 °C. Anal. Calcd for $C_{15}H_{12}NCl$·HBr: C, 55.84; H, 4.06; N, 4.34. Found: C, 55.75; H, 4.09; N, 4.31. IR 2500, 1626, 1450, 1360, 1342, 1300, 1162, 1090, 957, 862 cm^{-1}; NMR 7.9–7.3 (8 H, m), 4.10 (2 H, t, J = 8 Hz), 3.15 (2 H, t, J = 8 Hz).

1-(Benzoylamino)-2-(4-methoxyphenyl)ethane was refluxed for 4 h, affording a 65% yield of 1-phenyl-7-methoxy-3,4-dihydroisoquinoline (**5c**), which was crystallized from EtOH–HBr, mp 251–253 °C. IR 2564, 1626, 1562, 1449, 1315, 1250, 1150, 854 cm^{-1}; NMR 8.0–7.0 (8 H, m), 4.10 (2 H, t, J = 8 Hz), 3.80 (3 H, s), 3.15 (2 H, t, J = 8 Hz); mass spectrum, m/e 237 ($C_{16}H_{15}NO$).

Preparation of *N*-Acetyl-1-phenyl-1,2-dihydroisoquinolines (6). The 3,4-dihydroisoquinolines (29 mmol) obtained from the previous experiment were refluxed in 120 mL of acetic anhydride with potassium acetate (3.0 g, 30 mmol) for 6 h. The excess acetic anhydride was removed at reduced pressure, and the residual oil was thoroughly triturated with 10% Na_2CO_3 solution. The resultant residual solid was subjected to the usual workup conditions.

Compound **5a** afforded a 63% yield of *N*-acetyl-1-phenyl-1,2-dihydroisoquinoline (**6a**), crystallized from *i*-PrOH, mp 137–138 °C. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.88; H, 6.46; N, 5.49. IR 3448, 1658, 1613, 1449, 1333, 1227, 930, 781 cm^{-1}; NMR 7.05 (9 H, s), 6.78 (1 H, s), 6.53 (1 H, d, J = 8 Hz), 5.86 (1 H, d, J = 8 Hz), 2.16 (3 H, s).

Compound **5b** afforded a 58% yield of *N*-acetyl-7-chloro-1-phenyl-1,2-dihydroisoquinoline (**6b**), after crystallization from *i*-PrOH, mp 121–122 °C. Anal. Calcd for $C_{17}H_{14}ClNO$: C, 71.96; H, 4.97; N, 4.94. Found: C, 72.01; H, 5.02; N, 5.04. IR 1667, 1621, 1481, 1333, 1227, 1087, 930, 833 cm^{-1}; NMR 7.20 (8 H, m), 6.80 (1 H, s), 6.33 (1 H, d, J = 8 Hz), 5.90 (1 H, d, J = 8 Hz), 2.20 (3 H, s).

Compound **5c** afforded a 65% yield of *N*-acetyl-7-methoxy-1-phenyl-1,2-dihydroisoquinoline **6c**, mp 80–82 °C, after silica gel chromatography (CH_2Cl_2 solvent) and *i*-PrOH crystallization. IR 1660, 1620, 1485, 1370, 1250, 1225, 1120, 1050, 900, 820 cm^{-1}; NMR 7.20 (8 H, s), 6.90 (1 H, m), 6.70 (3 H, q, J = 9.0 Hz), 6.43 (1 H, d, J = 8.0 Hz), 5.86 (1 H, d, J = 8 Hz), 3.70 (3 H, s), 2.15 (3 H, s); mass spectrum, m/e 279 ($C_{18}H_{17}NO_2$).

Dihalocarbene Additions. Preparation of 2-Acetyl-1,1,5-trichloro-3-phenyl-1a,2,3,7b-tetrahydro-1*H*-cycloprop[*c*]isoquinoline (7b). To a solution of **6b** (1.0 g, 3.5 mmol) in 20 mL $CHCl_3$ was added benzyltriethyl ammonium chloride (0.5 g, 2.2 mmol). The solution was stirred vigorously for 4 h with 20 mL of 40% NaOH solution. The organic phase was separated and was worked up in the usual manner to afford a 55% yield of **7b**, crystallized from Et_2O–petroleum ether, mp 129–130 °C. Anal. Calcd for $C_{18}H_{14}Cl_3NO$: C, 58.96; H, 3.84; N, 3.82. Found: C, 58.69; H, 3.75; N, 3.79. IR 1653, 1481, 1307, 1053, 890, 855 cm^{-1}; NMR 7.25 (8 H, m), 6.55 (1 H, s), 3.60 (1 H, d, J = 10 Hz), 3.15 (1 H, d, J = 10 Hz), 2.27 (3 H, s).

Preparation of 2-Acetyl-1,1-dibromo-3-phenyl-5-substituted-1a,2,3,7b-tetrahydro-1*H*-cycloprop[*c*]isoquinolines (8). The *N*-acetyl-1,2-dihydroisoquinolines (3.50 mmol) were dissolved in 10 mL of $CHBr_3$ and benzyltriethylammonium chloride (0.5 g, 2.2 mmol) was added. The resultant solution was slowly added to 10 mL of 40% NaOH solution. The two-phase mixture was

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(15) Dauben, W. G., Wolf, R. E. *J. Org. Chem.* **1973**, *38*, 304.

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vigorously stirred for 4.5 h, and the organic phase was separated from the alkaline solution and was thoroughly washed with H_2O. The product was isolated by silica gel chromatography with CH_2Cl_2–Et_2O (1:1) solvent.

Compound **6a** resulted in a 60% yield of **8a**, which was crystallized from MeOH, mp 176–178 °C. Anal. Calcd for $C_{18}H_{15}Br_2NO$: C, 51.34; H,3.59; N, 3.33. Found: C, 51.83; H, 3.29; N, 3.52. IR 1653, 1481, 1370, 1307, 1111, 1053, 1031, 935, 885, 870 cm^{-1}; NMR 7.50 (9 H, s), 6.53 (1 H, s), 3.58 (1 H, d, J = 10 Hz), 3.25 (1 H, d, J = 10 Hz), 2.27 (3 H, s).

Compound **6b** resulted in a 60% yield of **8b**, which was crystallized from petroleum ether–Et_2O, mp 130–132 °C. Anal. Calcd for $C_{18}H_{14}Br_2ClNO$: C, 47.46; H, 3.10; N, 3.07. Found: C, 47.62; H, 3.25; N, 3.11. IR 1667, 1493, 1316, 1042, 893, 877, 830 cm^{-1}; NMR 7.20 (8 H, m), 6.50 (1 H, s), 3.60 (1 H, d, J = 9 Hz), 3.15 (1 H, d, J = 9 Hz), 2.30 (3 H, s).

Compound **6c** resulted in a 52% yield of **8c**, obtained as an oil. IR 1665, 1450, 1375, 1315, 1240, 1120, 1050, 1030, 870, 820 cm^{-1}; NMR 7.40 (1 H, d, J = 9 Hz), 7.16 (5 H, s), 6.83 (1 H, q, J = 3 and 9 Hz), 6.60 (1 H, d, J = 3 Hz), 6.43 (1 H, s), 3.70 (3 H, s), 3.53 (1 H, d, J = 10 Hz), 3.13 (1 H, d, J = 10 Hz), 2.26 (3 H, s); mass spectrum, m/e 450 ($C_{19}H_{17}Br_2NO_2$).

Preparation of 2-Acetyl-3-phenyl-1a,2,3,7a-tetrahydrocycloprop[*c*]isoquinoline (10). A solution of **8a** (0.42 g, 1 mmol) and tributyltin hydride (0.58 g, 2 mmol) in 10 mL toluene was refluxed for 28 h with the aid of a 200-W sunlamp. The reaction afforded three products; the major product was isolated in 50% yield by silica gel chromatography and identified spectroscopically as **10**, and the minor products have so far not been purified and identified. IR 1650, 1450, 1370, 1370, 1310, 1270, 1230, 1070, 1030, 840 cm^{-1}; NMR 7.20 (9 H, m), 6.60 (1 H, s), 2.26 (3 H, s), 1.36 (2 H, m), 0.85 (2 H, m); mass spectrum, m/e 263 ($C_{18}H_{17}NO$).

Preparation of 8-Substituted 4-Bromo-1-phenyl-5*H*-2-benzazepines (9). The dibromocyclopropyl compound **8a** (0.4 g, 0.95 mmol) and silver trifluoroacetate (0.5 g, 2.2 mmol) were refluxed in 15 mL of α-picoline for 20 h. The solvent was evaporated at reduced pressure, and the residue was chromatographed on silica gel with cyclohexane. The product **9a** eluted in the first fraction in about 20% yield. IR 1590, 1540, 1460, 1380, 1320, 1000, 955, 860 cm^{-1}; NMR 7.0 (10 H, m), 3.4 (2 H, s); mass spectrum, m/e 297 ($C_{16}H_{12}BrN$).

Dibromocyclopropyl compound **8b** (1.0 g, 2.20 mmol) and silver trifluoroacetate were refluxed in 25 mL of α-picoline overnight under a blanket of nitrogen. The solution was allowed to cool to room temperature and was diluted with 100 mL of Et_2O. The ethereal solution was washed with H_2O (3 × 50 mL) and with saturated brine, and after drying over magnesium sulfate the organic solvent was evaporated, first at reduced pressure and then in vacuo. The oily residue was chromatographed on silica gel with CH_2Cl_2–petroleum ether (3:7). The product, **9b**, was obtained in 28% yield and was recrystallized from petroleum ether, mp 112–113 °C. Anal. Calcd for $C_{16}H_{11}BrClN$: C, 57.77; H, 3.33; N, 4.21. Found: C, 58.14; H, 3.15; N, 4.21. IR 1575, 1527, 1471, 1439, 1307, 1299, 1250, 1124, 1093, 1010, 962, 847, 820 cm^{-1}; NMR 7.50 (9 H, m), 3.50 (2 H, s).

Acknowledgment. We acknowledge our gratitude to Ms. Edith Reich of the Analytical, Physical and Structural Chemistry Department for the elemental analyses.

Supplementary Material Available: Positional parameters, anisotropic thermal parameters, and bond length and angles for compounds **8a** and **9b** (19 pages). Ordering information is given on any current masthead page.

Facile and Efficient Syntheses of Carboxylic Anhydrides and Amides Using (Trimethylsilyl)ethoxyacetylene†

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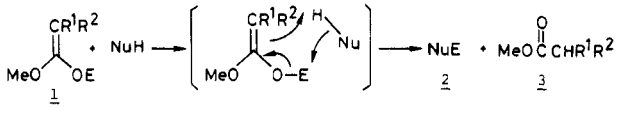
(Trimethylsilyl)ethoxyacetylene, a stable and easy-handling reagent, serves as an excellent dehydrating agent for the synthesis of carboxylic anhydrides and amides from the corresponding carboxylic acids. By means of this reagent, various types of acid-sensitive carboxylic anhydrides and amides were obtained almost in quantitative yields. Twenty-two examples of carboxylic anhydrides and 12 examples of amides were presented.

In organic synthesis, reagents are required which are able under neutral or nearly neutral conditions to bring about the desired reactions in high yields with easy isolation and especially seem to be quite significant for the synthesis of complicated compounds having multifunctional groups such as natural products. For this purpose, ketene acetal derivatives **1** were suitably introduced as the reagents for alkoxy (or aryloxy) carbonylation,[1] silylation,[2] silylenation,[3] Semmler–Wolff aromatization,[4] and Pummerer-type rearrangement[5] from this laboratory. The reactions using these reagents were generally carried out in an inert solvent such as methylene chloride, chloroform, tetrahydrofuran or acetonitrile and usually brought to completion at low temperature for a short period to give the desired products (**2**) in high yields accompanied by a volatile ester (**3**) as a single side product (Scheme I).

Scheme I



E=acyl or silyl group

In connection with this study, we have recently communicated[6] an extremely facile and efficient method for

† Dedicated to Professor George Büchi on the occasion of his 65th birthday.

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