50% ethanol and titrated with 0.09 M sodium hydroxide. The end points were determined by plotting the volume of titrant against the millivolts which were read directly from a Beckman Zeromatic pH meter.

Registry No.—**1**, 23157-59-7; **2a**, 62076-89-5; **2b**, 62076-90-8; **2c**, 62076-91-9; **4**, 62076-92-0; **5**, 532-96-7; **8**, 17660-82-1; **9**, 36584-22-2; **10**, 62076-93-1; **11**, 62076-95-3; **12**, 62076-96-4; HCl, 7647-01-0; methanesulfonic acid, 75-75-2; periodic acid, 10450-60-9; morpholine, 110-91-8; pyrrolidine, 123-75-1.

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(3) H. Bamberger and J. Grob, *Chem. Ber.*, **34**, 523 (1902).
(4) Salts **2** could not be purified because of their instability to traces of water; elemental analyses proved difficult.
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(6) Solutions of **2c** in Me_2SO-d_6 underwent rapid discoloration and evolved oxides of nitrogen. **2c** was insoluble in the common NMR solvents.
(7) "Nuclear Magnetic Resonance Spectra", Sadtler Research Laboratories, Philadelphia, Pa., No. 9379M, 11175M.
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(10) H. Voswinkel, *Chem. Ber.*, **34**, 2352 (1901).
(11) We should like to thank Mr. S. W. Heinzman for carrying out this experiment.
(12) R. Huisgen, *Tetrahedron*, **17**, 3 (1962).
(13) R. Huisgen, *Angew Chem., Int. Ed. Engl.*, **2**, 571 (1963).
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(16) Compound **4** decolorized at about 80 °C and then decomposed at about 106 °C.

Synthesis and Configurational Assignment of Some 1-*tert*-Butyl-2-aryl 3-Substituted Azetidines[1]

Hiu-Kwong Leung, Shrikant B. Kulkarni, Michael C. Eagen,[1] and Norman H. Cromwell*

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

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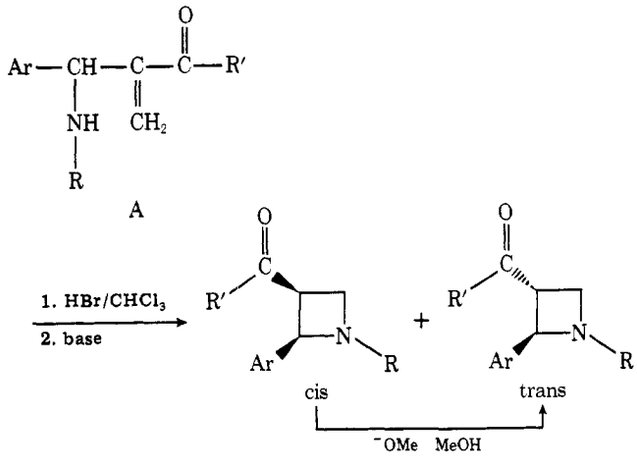
The kinetically favored products, methyl α-(α-*tert*-butylaminobenzyl)acrylates (**2**), from the reaction of *tert*-butylamine with methyl α-(bromomethyl)cinnamates (**1**), upon treatment with hydrogen bromide in chloroform and then triethylamine gave *trans*-1-*tert*-butyl-2-aryl-3-carbomethoxyazetidine (**7**). Similar treatment of the kinetically favored α-(α-*tert*-butylaminobenzyl)acrylonitrile (**5**), of the reaction of *tert*-butylamine with α-(bromomethyl)cinnamonitrile (**4**) gave a mixture of *cis*- and *trans*-1-*tert*-butyl-2-phenyl-3-carbamoylazetidine (**9** and **10**) and *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine (**11**). ^1H NMR spectroscopic studies, base-catalyzed epimerization, deuterium exchange studies, and chemical correlation of the azetidines were employed to assign the configurations. The mechanism and stereochemistry of the reactions leading to these cyclizations to produce the 1-*tert*-butyl-2-aryl 3-substituted azetidines are discussed.

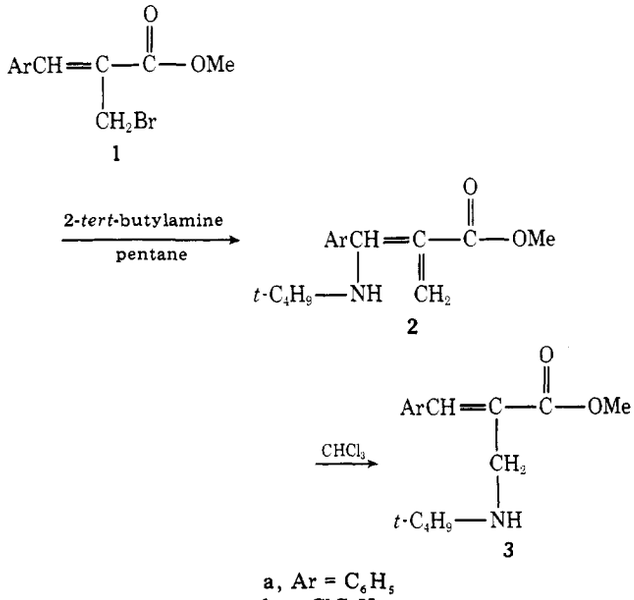
It has been reported[2] that β-carboallylamines A are precursors for the high-yield synthesis of 1-alkyl-2-aryl-3-carboazetidines. The *cis*-azetidine was usually the exclusive or major product, and readily epimerized to the thermodynamically more stable trans isomer in methanol in the presence of sodium methoxide.



R = alkyl
R′ = Ar or CH_3

The cis and trans isomers of the azetidines can be distinguished readily from each other by the ^1H NMR spectra.[2b] Compared to that of the trans isomer, the benzylic (C-2) proton of the cis isomer usually resonates as a doublet at a higher frequency.

In a previous publication,[3] it was reported that the reaction of 2 molar equiv of *tert*-butylamine with β-carbomethoxyallyl bromides **1** gave the substitution–rearrangement products **2**

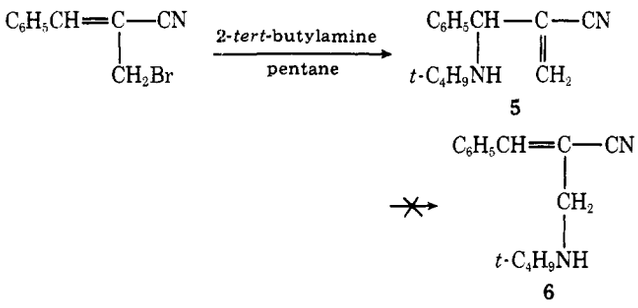


a, Ar = C_6H_5
b, *p*-ClC_6H_4

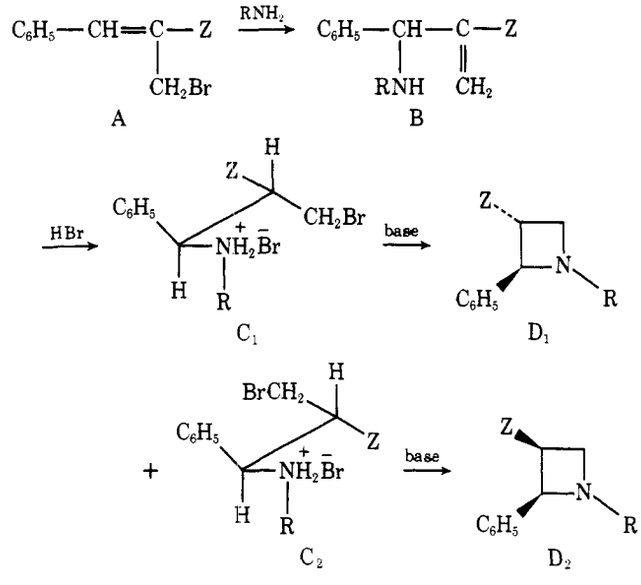
exclusively. Compounds **2** isomerized to **3** autocatalytically on prolonged standing in a polar solvent.

It has also been reported[4] that the reaction of *tert*-butylamine with α-(bromomethyl)cinnamonitrile (**4**) yielded the

substitution rearrangement product **5** exclusively. Conversion of **5** to **6** either autocatalytically or in the presence of excess amine was too slow to be detectable in chloroform.



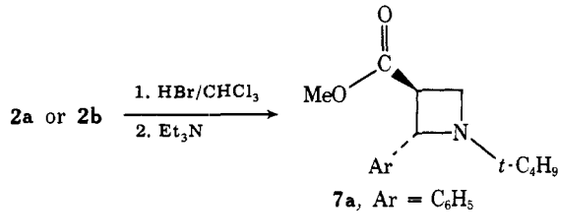
In conjunction with our integrated program of comparative studies of the chemistry of aziridines and azetidines, synthesis of azetidines with different substituents at various positions is under investigation. It seemed important to explore fully the steric controls[2b] operating during the addition of hydrogen bromide to the allylamines B to form the threo (C_1) and



erythro (C_2) γ-bromoamines when the activating group Z in A is varied from benzoyl to acetyl to carbomethoxy to cyano. Ring closures of the γ-bromoamines are stereospecific processes to produce the trans (D_1) and cis (D_2) substituted azetidines.[2] It is premature to attempt to discuss the various factors of asymmetric induction involved in the addition of hydrogen bromide to these several systems. Previously brief mention was made of this matter when Z is the benzoyl group.[2b] In this publication we wish to report the cyclization of **2** and **5** by a method developed for the synthesis of 1-alkyl-2-aryl-3-carboazetidines,[2] and to discuss in a preliminary manner the stereochemistry and mechanism for the reactions involved in the synthesis of these stereoisomeric substituted azetidines.

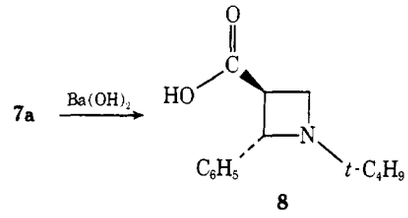
Results

The syntheses of 1-*tert*-butyl-2-phenyl-3-carbomethoxyazetidine (**7a**) and 1-*tert*-butyl-2-*p*-chlorophenyl-3-carbomethoxyazetidine (**7b**) were accomplished in excellent yield by treatment of **2a** and **2b** with hydrogen bromide in chloroform, followed by neutralization with triethylamine.

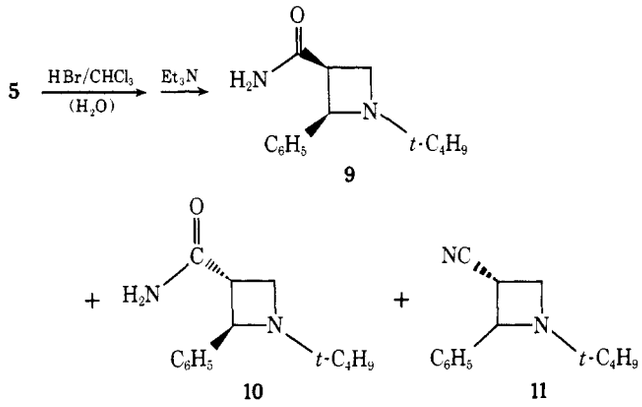


The existence of the azetidine ring in **7** was readily determined by the typical ^{1}H NMR absorption of benzylic, C-3, and C-4 protons.[2] The azetidinyl esters **7** were found to be exclusively of one configuration, which were later shown to be trans. Treatment of azetidinyl esters **7** with strong base did not effect epimerization, and no deuterium exchange could be observed when the reaction was carried out in methanol-d_1.

Base-catalyzed hydrolysis of azetidinyl ester **7a** with barium hydroxide yielded azetidinyl acid **8**, which later was assigned the trans configuration. The ^{1}H NMR spectrum displayed the benzylic proton as a doublet (J_{HH} = 8.4 Hz) at δ 5.31 in D_2O. The mass spectrum showed a weak molecular ion at *m/e* 233 (calcd 233). The M + 1/M ratio corresponded to C/N ratio of 14:1, which is in agreement with the structure of **8**.

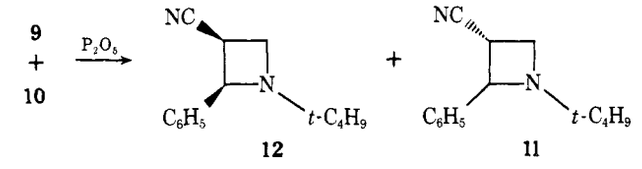


Treatment of aminonitrile **5** with hydrogen bromide in chloroform and then triethylamine yielded three products. Apparently small amounts of moisture were present in these solutions.



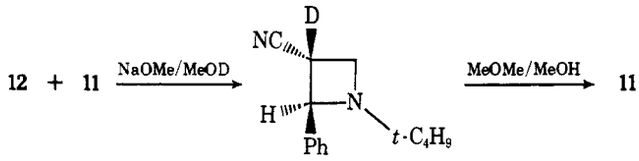
Carbamoylazetidines **9** and **10** crystallized together as a 60:40 (**9/10**) mixture from the pentane solution. Chromatography of the mother liquor yielded in addition to **9** and **10**, cyanoazetidine **11**. The ^{1}H NMR spectrum of the mixture of **9** and **10** displayed the benzylic protons as two doublets, respectively, at δ 4.72 (J_{HH} = 8 Hz) and 4.43 (J_{HH} = 8 Hz).

Dehydration of amidoazetidines **9** and **10** with phosphorus pentoxide yielded a mixture of *cis*- and *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine (**12/11**, 50:50). The ^{1}H NMR spectrum of the mixture displayed the benzylic protons of the two isomers as two doublets at δ 4.55 (J_{HH} = 7 Hz) and 4.45 (J_{HH} = 8 Hz). The unreacted amidoazetidine was found to consist of only the trans isomer **10**.



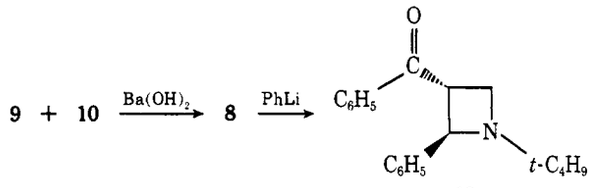
Cyanoazetidine mixture **12** and **11** was refluxed with sodium methoxide in methanol-d_1. The ^{1}H NMR spectrum of the product **11a** after working up indicated that deuterium had become incorporated into the compound. Refluxing com-

pound **11a** with sodium methoxide in methanol yielded *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine **11**.



11a

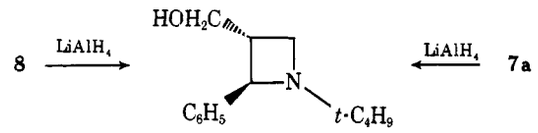
Base-catalyzed hydrolysis of amidoazetidine mixture **9** and **10** with barium hydroxide produced the azetidinylcarboxylic acid, which was spectrally identical with **8**. The ^1H NMR spectrum of the crude product did not reveal the presence of any other isomer of the acid.



13

Reaction of azetidinyl acid **8** with phenyllithium yielded *trans*-1-*tert*-butyl-2-phenyl-3-benzoylazetidine **13**, which was spectrally equivalent to an authentic sample.[2b] This result, however, is of no use in assigning the configuration of **8**, since phenyllithium is itself a strong base.[5]

Reaction of azetidinyl acid **8** with lithium aluminum hydride gave the corresponding alcohol **14**. The ^1H NMR spectrum of alcohol **14** displayed the benzylic signal at δ 4.13 as a doublet (J_{HH} = 7 Hz). The same alcohol **14** was also obtained by the reaction of ester **7a** with lithium aluminum hydride. Lithium aluminum hydride is not expected to catalyze epimerization in the azetidine nucleus in either case,[6] so azetidinyl ester **7a** and azetidinyl acid **8** are expected to have the same configuration.



14

X-ray crystallographic studies of the picrate of **7b**[7] showed that azetidinyl esters **7** have a trans configuration. Therefore, azetidinyl acid **8** and azetidinyl alcohol **14** are also assigned a trans configuration.

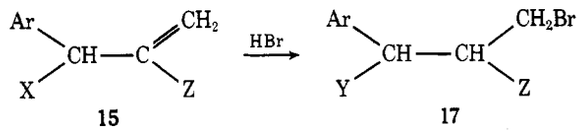
Discussion

Treatment of aminoester **2** or aminonitrile **5** with hydrogen bromide followed by triethylamine yielded the appropriate azetidine. The conversion can be rationalized as a two-step process. The first involves a hydrobromination of the alkenes and the second is the cyclization of the γ-haloamines.[8]

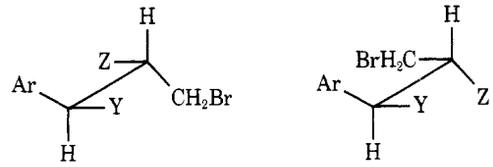
The addition of hydrogen bromide to **15** gives **17**, which can exist in two diastereomeric forms, **17a** for the threo, and **17b** for the erythro.

As pointed out by Grob,[9] Vaughan,[10] and later by Cromwell,[2b] the cyclization of these γ-haloamines should be treated as a conformational problem. Therefore **17a** would give *trans*-azetidine **18a** and **17b** would give *cis*-azetidine **18b**. When Z is carbomethoxy, the reaction sequence goes through **15** → **17a** → **18a**. For the case when Z is cyano, **15** goes to **17a** and **17b**, giving **18a** and **18b** rather nonselectively.

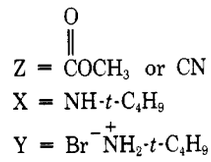
Epimerization of the *cis*-2-carbomethoxyazetidine to its trans isomer is unlikely in an acidic medium. In one experiment, the reaction of **2a** with HBr/$CHCl_3$ was interrupted purposely before it went to completion, and was then treated with triethylamine. However, no signal corresponding to the

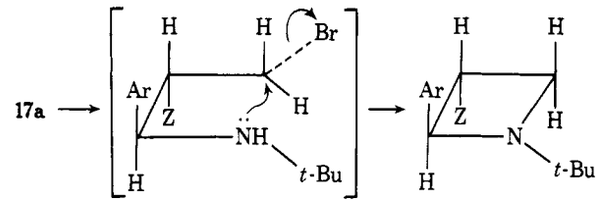


15 **17**

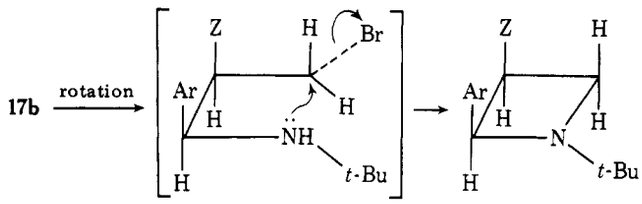


17a, threo **17b**, erythro





18a



18b

cis-arylcarbomethoxyazetidine could be observed in the ^1H NMR spectrum of the reaction mixture, thus it seems improbable that **2a** produced any of the cis product in this reaction sequence.

Experimental Section

Melting points were determined from a Mel-Temp apparatus, and were uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 621 Spectrophotometer. The proton magnetic resonance spectra were determined on a Varian Model A-60 spectrometer, utilizing tetramethylsilane as an internal standard. Elementary analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The low-resolution mass spectra were obtained from a Hitachi RMU-60 spectrometer, and the high-resolution spectra from a AEI MS-50 spectrometer.

1-*tert*-Butyl-2-phenyl-3-carbomethoxyazetidine (7a). A 5.10-g (0.02 mol) sample of methyl α-(bromomethyl)cinnamate[3] (**1a**) dissolved in 250 mL of pentane was treated with 2.92 g (0.04 mol) of *tert*-butylamine in a closed vessel. The tightly stoppered contents were stirred magnetically at room temperature for 76.5 h. The *tert*-butylamine hydrobromide thus produced was removed by filtration. The filtrate was subjected to rotary evaporation at reduced pressure to leave an oil which was taken up in ca. 100 mL of chloroform saturated with hydrogen bromide gas at 0 °C. The reactants were kept tightly stoppered in a flask while warmed to room temperature over a period of 15 days. The chloroform and excess hydrogen bromide were evaporated under reduced pressure with warming and the residue was taken up in another 100 mL of chloroform. To this solution was added excess triethylamine and the contents stirred for 1 h. Evaporation of the solvent and excess triethylamine left a solid residue, which was extracted with boiling hexane. After being subjected to filtration, the hexane was evaporated to leave an oil (quantitative) which was shown to be **7a**: IR ν (C=O) ($CHCl_3$) 1723 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.10–7.70 (m, 5 H, aromatic), 4.51 (d, J_{HH} = 7.2 Hz, 1 H, PhC**H**), 3.50 (s, 3 H, CH_3) 2.70–3.50 (m, 3 H, other azetidine ring protons), 1.06 (s, 9 H, *tert*-butyl). The compound was analyzed as its picrate, mp 160.5–162 °C.

Anal. Calcd for $C_{21}H_{24}N_4O_9$: C, 52.94; H, 5.08; N, 11.76. Found: C, 53.14; H, 5.12; N, 11.63.

Attempted Deuterium Exchange with 7a. (1) A 0.025-g sample of **7a** was dissolved in 1 mL of methanol-d_1, to which was added a catalytic amount of sodium methoxide. The contents were allowed to stand at room temperature for 46 h. Evaporation of the solvent under reduced pressure with warming left an oil which was analyzed by ^{1}H NMR spectroscopy to be unchanged starting material.

(2) A 0.95-g sample of **7a** was dissolved in 4 mL of methanol-d_1, to which was added 0.21 g of sodium methoxide. The mixture was refluxed for 88 h. Evaporation of the solvent gave a residue, the ^{1}H NMR spectrum of which indicated the presence of unchanged starting material together with a small amount of unidentifiable impurities.

(3) A 0.025-g sample of **7a** was dissolved in 2 mL of *tert*-butyl alcohol containing a catalytic amount of potassium *tert*-butoxide. The mixture was allowed to stand at room temperature for 40 h, followed by the addition of 1 mL of deuterium oxide. The mixture was allowed to stand for several minutes, and the solvent evaporated under reduced pressure to leave a residue which was taken up in ether. The ethereal solution was filtered and subjected to rotary evaporation. The residue was analyzed by ^{1}H NMR spectroscopy, indicating the complete destruction of the starting material.

1-*tert*-Butyl-2-(4-chlorophenyl)-3-carbomethoxyazetidine (7b). A 4.0-g (0.011 mol) sample of the hydrobromide of methyl α-(α-*tert*-butylamino-4-chlorobenzyl)acrylate (**2b**)[3] was dissolved in 500 mL of chloroform saturated with anhydrous hydrogen bromide at 0 °C. The reaction mixture was tightly stoppered in a flask while warming to room temperature, and allowed to stand for 14 days. The solvent and excess hydrogen bromide were removed under reduced pressure to leave a solid residue, which was taken up in 75 mL of chloroform. The solution was treated with excess triethylamine. The mixture was allowed to stand for another 6 h and the solution then filtered. Excess triethylamine and the solvent were evaporated under reduced pressure. The residue was taken up in boiling hexane and the hexane solution again filtered. Rotary evaporation under reduced pressure yielded an oil (quantitative), which was identified to be **7b**: IR ν (C=O) ($CHCl_3$) 1726 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.15–7.65 (m, 4 H, aromatic), 4.53 (d, J = 7.0 Hz, 1 H, ArC**H**), 3.66 (s, 3 H, OCH_3), 2.60–3.60 (m, 3 H, the remaining azetidine ring protons), 0.90 (s, 9 H, *tert*-butyl). The compound was analyzed as its picrate, mp 181–182.5 °C.

Anal. Calcd for $C_{21}H_{23}ClN_4O_9$: C, 49.37; H, 4.52; Cl, 6.94; N, 10.97. Found: C, 49.15; H, 4.42; Cl, 6.94; N, 10.79.

Attempted Deuterium Exchange with 7b. A small amount of **7b** was dissolved in methanol-d_1 which contained a catalytic amount of sodium methoxide. The contents were allowed to stand at room temperature for 19 h. Evaporation of the solvent under reduced pressure with mild warming gave a residue, which was analyzed by ^{1}H NMR spectroscopy to be unchanged starting material.

1-*tert*-Butyl-2-phenylazetidine-3-carboxylic Acid (8). A 2.0-g (8.1 mmol) sample of **7a** was dissolved in 40 mL of dioxane/water mixture (v/v, 1:1) to which was added 1.5 g (4.0 mmol) of barium hydroxide octahydrate. The mixture was refluxed for 8 h. Carbon dioxide was bubbled through the reaction mixture to precipitate barium carbonate, which was removed by filtration. Evaporation of the solvents under reduced pressure with heating gave a solid residue. Recrystallization from an ethanol/ether mixture yielded 1 g (53%) of a white flaky solid, which was identified to be **8**: mp 156–157 °C; IR ν (C=O) (Nujol) 1590 cm^{-1}; ^{1}H NMR δ (D_2O with acetone as internal standard at 125 Hz), 7.40–7.75 (m, 5 H, aromatic), 5.31 (d, J = 8.4 Hz, 1 H, PhC**H**), 3.50–4.10 (m, 3 H, other azetidine ring protons), 1.12 (s, 9 H, *tert*-butyl); MS M$^+$ 233.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.05; H, 8.21; N, 6.01. Found: C, 72.03; H, 8.31; N, 6.02.

***cis*- and *trans*-1-*tert*-Butyl-2-phenyl-3-amidoazetidine (9 and 10).** To a solution of 11.9 g (0.0536 mol) of α-(bromomethyl)cinnamonitrile (**4**)[4] in 900 mL of pentane was added 7.89 g (0.11 mol) of *tert*-butylamine. The solution was allowed to stand for 41.5 h. The amine salt thus produced was removed by filtration. Removal of the solvent yielded an oil, dissolved in 125 mL of chloroform. The solution was then saturated with hydrogen bromide gas. After standing for 7 days at room temperature, the hydrogen bromide in excess and the solvent were evaporated. To the residue was added another 125 mL of chloroform. The solution was neutralized by excess triethylamine. The amine salt produced upon replacement of chloroform with ether was removed by filtration. The residue was washed well with ether, and the combined washings were subjected to rotary evaporation. The residual oil was extracted with hot pentane. The pentane extract was collected and the solvent evaporated. Recrystallization of the residue yielded 2.4 g (20%) of a white solid, which was identified to be a 60:40 mixture of *cis*- and *trans*-1-*tert*-butyl-2-phenyl-3-amidoazetidine (**9** and **10**): IR (Nujol) ν (NH) 3360, 3191 (hydrogen bending), ν (C=O) 1660 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.20–7.60 (m, 5 H, aromatic), 4.72, 4.43 (2 d, J_{HH} = 8 Hz, 1 H, benzylic proton of the cis and trans epimers), 2.37–3.50 (m, 3 H, the remaining azetidine ring protons), 0.92, 0.90 (2 s, 9 H, *tert*-butyl protons of the two epimers).

Anal. Calcd for $C_{14}H_{20}N_2O$: C, 72.41; H, 8.62; N, 12.06. Found: C, 72.21; H, 8.74; N, 12.03.

The mother liquor of the previously described recrystallization yielded a residual oil upon evaporation of the solvent. Preparative thin-layer chromatographic separation of the residual oil gave three compounds. The first (30 mg) was identified to be the unreacted starting material by ^{1}H NMR spectroscopy. The second (100 mg, 0.9%) was identified to be *trans*-1-*tert*-butyl-2-phenyl-3-cyanoazetidine (**11**). (Identification was made by comparing the ^{1}H NMR spectrum with that of an authentic sample obtained by an independent route.) A third compound (250 mg) was identified to be a 10:90 mixture of the **9** and **10**.

1-*tert*-Butyl-2-phenylazetidine-3-carboxylic Acid (8) from a Mixture of 9 and 10. To a solution of 750 mg of barium hydroxide octahydrate in 20 mL of 1:1 (v/v) mixture of dioxane and distilled water was added 700 mg (0.003 mol) of a 60:40 mixture of **9** and **10**. The mixture was refluxed for 11 h. Excess carbon dioxide was added to precipitate barium carbonate, which was removed by filtration. Evaporation of the solvent yielded 580 mg (83%) of a white solid. Recrystallization from methanol/ether mixture gave flaky white crystals, spectrally equivalent to 1-*tert*-butyl-2-phenylazetidine-3-carboxylic acid (**8**) prepared by the previously described independent route.

***trans*-1-*tert*-Butyl-2-phenyl-3-benzoylazetidine (13).** To a solution of 220 mg (0.0009 mol) of **8** in 10 mL of dry tetrahydrofuran at the temperature of ice was added 2.6 mL of 1.72 M phenyllithium in benzene. The solution was stirred for 2.75 h while warming to room temperature. Aqueous ammonium chloride solution was added. The mixture was then extracted with ether. After being dried over anhydrous magnesium sulfate, the solution was subjected to rotary evaporation. The ^{1}H NMR spectrum of the residual oil showed that in the region of the benzylic protons, only one doublet was present. Preparative thin-layer chromatography on the residual oil yielded two compounds. The first was a polyphenyl compound which was not further investigated. The second (80 mg, 30%) was a yellow oil, which was identified to be **13**:[2b] ^{1}H NMR δ ($CDCl_3$) 7.10–7.72 (m, 5 H, aromatic), 4.67 (d, 1 H, J_{HH} = 7.8 Hz, benzylic), 3.33–4.00 (m, 3 H, the other azetidine ring protons), 0.92 (s, 9 H, *tert*-butyl).

An 80-mg sample of **13** was refluxed in a solution of 50 mg of sodium methoxide in 10 mL of methanol-d_1 for 12 h. The solvent was evaporated in vacuo and the residue was extracted with hot pentane. The hot extract was evaporated in vacuo. The solid residue left was identified to be **13** deuterated at C-3: ^{1}H NMR δ ($CDCl_3$) 7.10–7.72 (m, 10 H, aromatic), 4.66 (s, 1 H, benzylic), 3.52 (s, 2 H, NCH_2–), 0.92 (s, 9 H, *tert*-butyl).

***cis*- and *trans*-1-*tert*-Butyl-2-phenyl-3-cyanoazetidine (12 and 11).** A 200-mg (0.00086 mol) sample of a 60:40 mixture of **9** and **10** was refluxed in a suspension of 1.97 g of phosphorus pentoxide in 70 mL of benzene for 48 h. The P_2O_5 in excess was destroyed by adding water and the solution was neutralized with sodium bicarbonate solution. The organic layer was separated and dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo yielded a yellow oil, preparative thin-layer chromatography of which gave three compounds. The first was a carbonyl compound: IR ν_{max} 1745 cm^{-1}, which was not further investigated due to the small quantity obtained. The second was a 50:50 mixture of **12** and **11** (100 mg, 54.6%): IR (CCl_4) ν (CN) 2242 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 7.16–7.64 (m, 5 H, aromatic), 4.55, 4.45 (2 d, 1 H, J_{HH} = 7, 8 Hz, benzylic proton of respectively the cis and trans epimers), 2.50–3.53 (m, 3 H, the remaining azetidine ring protons), 0.89 (s, 9 H, *tert*-butyl). The third compound was **10**: ^{1}H NMR δ ($CDCl_3$) 7.15–7.76 (m, 5 H, aromatic), 4.43 (d, 1 H, J_{HH} = 8 Hz, benzylic), 2.50–3.50 (m, 3 H, remaining azetidine ring protons), 0.90 (s, 9 H, *tert*-butyl).

A 100-mg sample of the mixture of **12** and **11** (50:50) was refluxed in a solution of 200 mg of sodium methoxide in 10 mL of methanol-d_1 for 18 h. The solvent was then evaporated in vacuo. The solid residue was extracted with boiling pentane, and the organic solution was separated from the inorganic residue. Evaporation of the solvent in vacuo yielded a yellow solid: ^{1}H NMR δ ($CDCl_3$) 7.20–7.62 (m, 5 H, aromatic), 4.33–4.59 (1 H, m, benzylic), 3.37 (br s, 2 H, NCH_2–), 0.89 (s, 9 H, *tert*-butyl). The deuterium incorporated compound was refluxed in a solution of 200 mg of sodium methoxide in 10 mL of methanol. Similar workup as above yielded a yellow solid (100 mg,

quantitative). Recrystallization from pentane gave a yellow crystalline solid, which was identified to be **11**: mp 119–119.5 °C; IR (CCl_4) ν (CN) 2242 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.20–7.62 (m, 5 H, aromatic), 4.45 (d, 1 H, J_{HH} = 8 Hz, benzylic), 2.70–3.55 (m, 3 H, remaining azetidine ring protons), 0.89 (s, 9 H, *tert*-butyl).

The compound was analyzed as its picrate derivative, mp 181–181.5 °C.

Anal. Calcd for $C_{20}H_{21}N_5O_7$: C, 54.18; H, 4.74; N, 15.80. Found: C, 53.98; H, 4.70; N, 15.57.

***trans*-1-*tert*-Butyl-2-phenyl-3-hydroxymethylazetidine (14).** A 0.6-g (0.0025 mol) sample of **8** was refluxed in a suspension of 1 g of lithium aluminum hydride in a mixture of 15 mL of dioxane and 60 mL of ether for 57 h. The $LiAlH_4$ in excess was destroyed by adding water to it. The organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic extract was dried over anhydrous magnesium sulfate. Evaporation of the solvent in vacuo yielded 490 mg (89%) of a slightly yellow oil, which was identified to be **14**: IR ν (OH) 3400 cm^{-1}; ^1H NMR δ ($CDCl_3$) 7.10–7.58 (m, 5 H, aromatic), 4.13 (d, 1 H, J_{HH} = 7 Hz, benzylic), 3.66 (d, 2 H, J_{HH} = 5.5 Hz, $-CH_2OH$), 2.20–3.50 (m, 3 H, remaining azetidine ring protons), 0.89 (s, 9 H, *tert*-butyl); high-resolution MS M^+ 219.1620; molecular weight, calcd for $C_{14}H_{21}NO$ = 219.1623.

Azetidine 14 from 7a. A 500-mg (0.0021 mol) sample of **7a** was stirred in a suspension of 350 mg of lithium aluminum hydride in 75 mL of anhydrous ether for 46.5 h at room temperature. The $LiAlH_4$ in excess was destroyed by adding water to the mixture. The organic layer was separated and the aqueous layer was extracted several times with ether. The combined ethereal extract was dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded 300 mg (65.2%) of a light yellow oil, which was spectrally equivalent to **14** prepared by a different method as described in the previous section.

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Registry No.—**1a**, 53059-43-1; **2b** HBr, 62029-87-2; **4**, 59728-94-8; **7a**, 62029-88-3; **7a** picrate, 62029-89-4; **7b**, 62029-90-7; **7b** picrate, 62029-91-8; **8**, 62029-92-9; **9**, 62029-93-0; **10**, 62029-94-1; **11**, 62029-95-2; **11** picrate, 62029-96-3; **11a**, 62059-32-9; **12**, 62029-97-4; **13**, 10235-75-3; **13-*d***, 13943-11-8; **14**, 62029-98-5; *tert*-butylamine, 75-64-9.

References and Notes

(1) Presented at the 172nd National Meeting of the American Chemical Society, New Orleans, La., March 1977.
(2) (a) N. H. Cromwell and E. Doomes, *Tetrahedron Lett.*, **No. 34**, 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); (f) M. C. Eagen and N. H. Cromwell, *J. Org. Chem.*, **39**, 911 (1974).
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(4) N. H. Cromwell and H.-K. Leung, *J. Org. Chem.*, **41**, 3241 (1976).
(5) Under basic condition *cis*-1-*tert*-butyl-2-phenyl-3-benzoylazetidine epimerizes to its trans isomer.[2b]
(6) Compared to sodium methoxide and potassium *tert*-butoxide in the appropriate alcohol which fail to catalyze epimerization or deuterium exchange of azetidinyl ester **7**, lithium aluminum hydride and the bases produced during hydrolysis are much weaker. Therefore, under the condition described, base-catalyzed epimerization of azetidinyl ester **7a**, acid **8**, and alcohol **14** is unlikely.
(7) A report on the x-ray crystallographic studies of the picrates of the series of 1-*tert*-butyl-2-phenyl 3-substituted azetidines is under preparation and will be published elsewhere. A preliminary report was presented at the 12th Midwest Regional Meeting (Organic) of the American Chemical Society, University of Missouri, Kansas City, Mo., October 1976.
(8) The ring closure of a γ-haloamine in the presence of base is one of the most commonly used methods for the synthesis of azetidines. This reaction involves an internal nucleophilic displacement by an amino group of the halogen atom at the γ position of a three-carbon chain. For a review, see J. A. Moore in "Heterocyclic Compounds with Three and Four-Membered Rings", Part II, A. Weissberger, Ed., Interscience, New York, N.Y., 1964, p 885.
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Excess Azide Method of Peptide Synthesis

Manohar A. Tilak* and James A. Hoffmann

Lilly Research Laboratories, Division of Eli Lilly and Company, Indianapolis, Indiana 46206

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A new procedure of peptide synthesis using a large excess of protected amino acid azide is described. The azide solution in CH_2Cl_2 (or DMF) is added to the amino component dissolved in DMF. Methylene chloride (if used) can then be evaporated in vacuo at low temperatures. The excess azide is subsequently hydrolyzed at 0 °C by treatment of the DMF solution with $KHCO_3/H_2O$ *in a homogenous phase*. The procedure permits isolation of analytically pure peptides in high yields. Syntheses of several dipeptides and Z-Gly-Gly-Gly-OEt are reported.

Summary

Analytically pure peptides were synthesized in excellent yields by a procedure employing a large excess of the amino acid azide component. Two equivalents of the protected amino acid azides were reacted with the amino group of a carboxyl protected amino acid or peptide in DMF. Consistent 85–90% yields of the coupled peptide were obtained. The excess azide components were eliminated during product isolation by rapid hydrolysis in a homogeneous potassium bicarbonate/H_2O/DMF solution. The large excess may reduce side reactions by permitting a low reaction temperature (0 °C or lower) during a relatively short time period (27 h). The relative freedom from racemization, an outstanding feature of azide couplings, was retained in this procedure. Additional purification steps were generally not required after the simple isolation of the product. Hydroxyl protective groups for serine and threonine were not needed, but side reactions occurred with the unprotected phenolic group of tyrosine. This procedure offers a convenient approach to the stepwise synthesis of many peptide sequences and may be of help in optimizing the yields of longer peptides.

Discussion

There have been recent successful applications of the excess mixed anhydride method[1,2] for the synthesis of peptides, such as secretin.[3] This has encouraged us to extend the advantages of the excess amino acid derivative concept to the development of new peptide synthesis procedures. The acid azide method of peptide synthesis has proven to be adaptable to procedural modifications, similar to the excess mixed anhydride method.

The azide method of peptide synthesis, in use for over 70 years, is held in high regard by peptide chemists due to several advantages. The starting materials (hydrazides) are easy to