5 H, aromatics), 3.58 (s, 2 H, $C_6H_5CH_2N<$), 3.32 (d, 2 H, J = 2 Hz, $>NCH_2C{\equiv}C-$), 2.33 (s, 3 H, $>NCH_3$), 2.25 (t, 1 H, J = 2 Hz, $HC{\equiv}C-$). The NMR spectrum was identical with that of authentic pargyline.[14] Treatment of **1c** in dry ether with HCl followed by crystallization from MeOH–ether gave 0.007 g of **1c** HCl, mp 158.5–159 °C (lit.[15] mp 154–155 °C).

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Registry No.—**1a,** 17780-72-2; **1a** HCl, 17780-75-5; **1b,** 14611-51-9; **1b** HCl, 14611-52-0; **1c,** 555-57-7; **1c** HCl, 306-07-0; **2a** HCl, 62505-88-8; **2b,** 33817-09-3; **2b** HCl, 826-10-8; **2c** HCl, 13426-94-3; **3a,** 62505-89-9; **3b,** 62505-90-2; **3c,** 62505-91-3; 2-methyl-3-butyn-2-ol, 115-19-5; L-*N*-formyl-1-phenyl-2-aminopropane, 62532-67-6.

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α-Alkylation and Michael Addition of Amino Acids—a Practical Method

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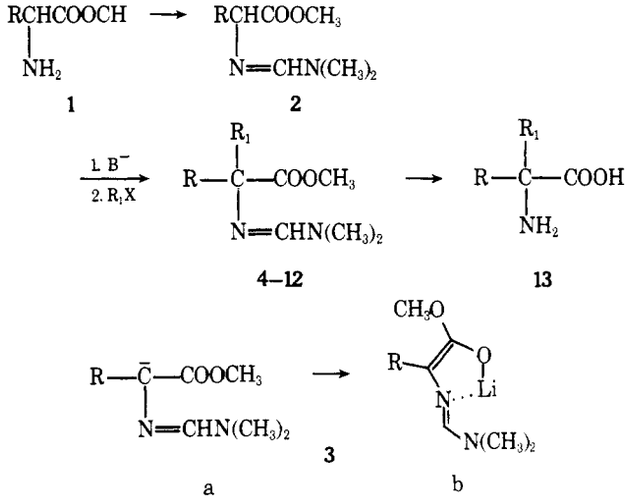
In recent years various methods have been developed to effect alkylation of amino acid derivatives at their α carbon.[1] One of the more versatile variants is the alkylation of deprotonated α-isocyano esters developed by Schöllkopf.[1a] Yet most of these procedures—the latter one included—suffer from the drawback of a multistep procedure necessary to sequentially protect carboxylic acid and amine functions in order to prepare a derivative suitable for α-deprotonation. We here wish to report a new and practical approach which is general for *all* α-amino acids and obviates the need for a laborious sequential protection.

The treatment of carboxylic acids in general and N-protected amino acids in particular with the acetals of dimethylformamide is known as an efficient and high-yielding method to prepare the corresponding esters.[2–6] Aminolysis of these reagents, on the other hand, particularly with primary aromatic amines, leads to substituted formamidines.[7–9] The simultaneous application of these two reactions for the conversion of a free amino acid into its α-formamidine methyl ester has not been used previously for preparative synthetic purposes.[10] Our results indicate that such ester formamidines are ideally suited as intermediates for α-alkylations.

By refluxing any α-amino acid **1** in 2–2.5 equiv of dimethylformamide dimethyl acetal (cf. ref 10) for 1–6 h, an essentially quantitative conversion to the distillable and reasonably stable[11] amidino esters **2** is achieved.[12] As we have discovered



independently, the conditions for deprotonation to **3** as well as its reactivity are very similar to those recently reported by Stork[1b] for the benzylidene derivative of glycine ethyl ester. Deprotonation can be achieved either with lithium diisopropylamide in THF at temperatures ranging from 0 to −70 °C or in certain instances with potassium *tert*-butoxide in CH_3OH. The anion **3** is sufficiently reactive toward alkylating agents such as alkyl iodides, allylic halides and even epoxides to give the products **4–12** in good to excellent yields[13] (see Table I). We have reason to believe that deprotonation of **2** initially leads to **3a** which readily tautomerizes to the lithium enolate **3b,** highly favored by the chelating effect of the unshared pair of electrons of the amidine nitrogen. In the case of the phenylglycine derivative **2c** (R = C_6H_5), low-temperature (−78 °C) deprotonation by LDA produces an intense red-orange color, characteristic of stabilized benzylic anions, gradually fading to a light orange-yellow. The infrared spectrum of the anionic species **3** (in CH_3CN) indicates no ester absorption but instead a strong band at 1630 cm^{-1} (C=N and C=C).[14]

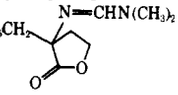
The high degree of chelation in **3** appears to be the reason for its unusually soft character (cf. ref 1b): in sharp contrast to the reactivity of the α-isocyano esters,[15,16] **3** does not react with ketones (benzophenone), and only sluggishly with benzaldehyde. This reactivity pattern is ideal for 1,4-additions which indeed occur readily either in aprotic or protic solvents (cf. ref 1b) (see Table I). Hydrolysis of the products **4–12** can be achieved in refluxing concentrated hydrochloric acid to produce the amino acids **13–15.** Unlike the imine functionality (cf. ref 1b), the dimethylformamidine moiety appears to be remarkably stable toward dilute mineral acids at room temperature.

Thus, we have outlined a practical method which permits the effective α-alkylation of any α-amino acid in a total of three steps: (1) simultaneous protection of both functional groups with dimethylformamide dimethyl acetal, (2) α-alkylation (or Michael addition), (3) acidic hydrolysis.

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); IR spectra on a Perkin-Elmer 521; mass spectra on a AEI MS 902 by direct in-

Table I

Compd	(±)-Amino acid 1 R	Amidino ester 2[13] Yield, %	Amidino ester 2[13] Bp, °C (mmHg)	Electrophile	Product[13] R_1	Isold yield, %	Mp or bp, °C (mmHg)
a	H	80	71 (0.4)	Cinnamyl bromide	4 $C_6H_5CH{=}CHCH_2$	65	118[a]
				Dimethyl *p*-chlorobenzalmalonate	5 *p*-$ClC_6H_4CH(CO_2CH_3)_2CH$	63[b]	128
				Nitrostyrene	6 $C_6H_5CHCH_2NO_2$	(90)[c]	
b	$CH_3SCH_2CH_2$	94	128 (0.55)	*p*-Chlorobenzyl chloride	7 *p*-$ClC_6H_4CH_2$	84[d]	124
c	C_6H_5	86	128 (0.55)	Methyl iodide	8 CH_3	83	130 (0.4)
				Methyl acrylate	9 $CH_2CH_2CO_2CH_3$	88	61
d	$C_6H_5CH_2$	90	124 (0.6)	Methyl iodide	10 CH_3	84	130 (0.2)
				n-Propyl iodide	11 $CH_3CH_2CH_2$	80	135 (0.2)
				Ethylene oxide	12 	60[e]	178

[a] Isolated as fumarate salt. [b] Crude yield of diastereomeric mixture is >95%; 63% is of pure major isomer. [c] Crude yield as judged by NMR; product is unstable. [d] As CH_3SO_3H salt. [e] As cyclohexylsulfamic acid salt.

sertion; NMR spectra on a Varian A-60 using Me_4Si as internal standard. The following abbreviations are used: (b) broad, (w) weak, (ex) exchangeable with D_2O, (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet.

***dl*-Methyl *N*-(Dimethylaminomethylene)phenylglycinate (2c).** A suspension of 15.1 g (0.1 mol) of *dl*-α-phenylglycine in 75 mL (0.55 mol) of dimethylformamide dimethyl acetal was refluxed under N_2 for 3.0 h. Excess reagent was removed in vacuo. The residue was dissolved in ether and filtered through Celite. The oil from the ether was distilled to give 19.0 g (86.4%) of **2c**: bp (0.55 mm) 128–131 °C; NMR ($CDCl_3$) δ 2.88 (s, 6 H), 3.68 (s, 3 H), 4.93 (s, 1 H), 7.20–7.63 (m, 6 H); IR (CH_3CN) 1740, 1640 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 66.52; H, 7.37; N, 12.62.

Analogously, reaction of 11.3 g (0.15 mol) of glycine with dimethylformamide dimethyl acetal gave 17.2 g (79.6%) of **2a**: bp (0.4 mm) 71–74 °C; NMR ($CDCl_3$) δ 2.88 (s, 6 H), 3.69 (s, 3 H), 4.01 (s, 2 H), 7.30 (s, 1 H).

Reaction of 29.8 g (0.2 mol) of *dl*-methionine with dimethylformamide dimethyl acetal gave 40.8 g (93.6%) of **2b**: bp (0.55 mm) 124–128 °C; NMR ($CDCl_3$) δ 1.91–2.22 (m, 2 H), 2.06 (s, 3 H), 2.33–2.67 (m, 2 H), 2.86 (s, 6 H), 3.66 (s, 3 H), 3.70–3.98 (m, 1 H), 7.28 (s, 1 H).

Reaction of 16.5 g (0.1 mol) of *dl*-β-phenylalanine with dimethylformamide dimethyl acetal gave 21.0 g (89.7%) of **2d**: bp (0.6 mm) 124–126 °C; NMR ($CDCl_3$) δ 2.77 (s, 6 H), 2.80–3.39 (m, 2 H), 3.66 (s, 3 H), 3.71–4.02 (m, 1 H), 6.99 (s, 1 H), 7.20 (s, 5 H); IR (CH_2Cl_2) 1738, 1643 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.99; H, 7.85; N, 11.71.

Methyl 2-(Dimethylaminomethyleneamino)-5-phenyl-4-pentenoate (4). To a solution of 8 mmol of LDA (lithium diisopropylamide) in 10 mL of dry THF [prepared by adding dropwise 5 mL (8 mmol) of a 1.6 M *n*-butyllithium solution in hexane to 1.5 mL of diisopropylamine in 10 mL of dry THF at 0 °C under N_2] cooled to −70 °C under N_2 was added dropwise a solution of 1.04 g (7.2 mmol) of amidino ester **2a** in 3 mL of dry THF. After 1.25 h at −70 °C a solution of 1.7 g (8.6 mmol) of cinnamyl bromide in 3 mL of dry THF was added. After 3.0 h at room temperature the reaction mixture was partitioned between ether and ice-cold diluted Na_2CO_3 solution. The ether was washed with basic (Na_2CO_3) brine, dried, and evaporated to give 1.89 g of **4** as an oil: NMR ($CDCl_3$) δ 2.52–2.68 (m, 2 H), 2.80 (s, 6 H), 3.66 (s, 3 H), 3.70–3.95 (m, 1 H), 5.78–6.60 (m, 2 H), 7.0–7.35 (m, 6 H). This oil was dissolved in acetone and treated with 1 equiv of fumaric acid, to give 1.76 g (65.2%) of **4** fumarate salt: mp 116–119 °C dec; IR (Nujol) 1750, 1708, 1655, 1595 cm^{-1}; MS *m/e* 260 (M^+).

Anal. Calcd for $C_{15}H_{20}N_2O_2{\cdot}C_4H_4O_4{\cdot}H_2O$: C, 57.86; H, 6.64; N, 7.10. Found: C, 57.47; H, 6.52; N, 7.20.

Dimethyl 2-(Dimethylaminomethyleneamino)-3-(4-chlorophenyl)-4-(methoxycarbonyl)pentanedioate (5). To a solution of 55 mmol of LDA in 125 mL of dry THF at −70 °C under N_2 was added a solution of 7.2 g (50 mmol) of amidino ester **2a** in 25 mL of dry THF dropwise. After 1 h at −70 °C a solution of 12.8 g (50 mmol) of dimethyl *p*-chlorobenzalmalonate in 20 mL of dry THF was added at a fast drop rate. After 18 h at room temperature, the reaction mixture was partitioned between ether and ice water. The ether layer was washed with basic (NaOH) brine, dried, and evaporated to give 20 g of compound **5** as an oily diastereomeric mixture. Crystallization from ether afforded 12.5 g (62.7%) of a pure major isomer: mp 128–129 °C; NMR ($CDCl_3$) δ 2.88 (s, 6 H), 3.49 (s, 6 H), 3.66 (s, 3 H), 3.90–4.13 (m, 3 H), 7.24 (s, 4 H), 7.35 (s, 1 H); IR (Nujol) 1748, 1721, 1646 cm^{-1}.

Anal. Calcd for $C_{18}H_{23}N_2O_6Cl$: C, 54.21; H, 5.81; N, 7.02. Found: C, 54.51; H, 5.93; N, 6.71.

Methyl 2-(Dimethylaminomethyleneamino)-4-nitro-3-phenylbutanoate (6). To a solution of 11 mmol of LDA in 25 mL of dry THF at −70 °C under N_2 a solution of 1.45 g (10 mmol) of amidino ester **2a** was added dropwise. After 1 h a solution of 1.5 g (10 mmol) of ω-nitrostyrene in 10 mL of dry THF was added. After 1 h at −70 °C, 1 mL of acetic acid was added and the reaction mixture partitioned between ether and ice-cold $NaHCO_3$ solution (twice). The ether layer was dried and evaporated to give 2.8 g (95%) of compound **6**, an unstable oil: NMR ($CDCl_3$) δ 2.82 (s, 6 H), 3.53 (s, 3 H), 3.95–4.21 (m, 2 H), 4.80–5.16 (m, 2 H), 7.25 (s, 1 H), 7.29 (s, 5 H). Yield as judged by NMR is 90%.

***dl*-2-(4-Chlorobenzyl)-*N*-dimethylaminomethylene Methionine Methyl Ester (7).** To a solution of 24 mmol of LDA in 30 mL of dry THF at −70 °C under N_2 atmosphere was added dropwise a solution of 4.71 g (21.6 mmol) of amidino ester **2b** in 10 mL of dry THF. After 1 h at −70 °C, 4.2 mL (24.5 mmol) of hexamethylphosphoric triamide (HMPT) was added dropwise. After 15 min a solution of 3.85 g (24 mmol) of α-*p*-dichlorotoluene in 10 mL of dry THF was added. After 18 h at room temperature the reaction mixture was partitioned between ether and cold diluted Na_2CO_3 solution. The ether layer was washed with basic(Na_2CO_3) brine, dried, and evaporated to give 7.35 g of **7** as an oil: NMR ($CDCl_3$) δ 1.80–2.24 (m, 2 H), 2.05 (s, 3 H), 2.35–2.70 (m, 2 H), 2.79 (s, 6 H), 2.97–3.12 (m, 2 H), 3.67 (s, 3 H), 7.15 (s, 4 H), 7.33 (s, 1 H). This oil was dissolved in acetone and treated with 1 equiv of methanesulfonic acid to give 7.93 g (83.7%) of **7** methanesulfonate salt: mp 125–128 °C; IR (Nujol) 1740, 1697 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}ClN_2O_2S{\cdot}CH_4O_3S$: C, 46.51; H, 6.20; N, 6.38. Found: C, 46.43; H, 6.37; N, 6.17.

2-(4-Chlorobenzyl)methionine (15). A solution of 1.3 g (3.8 mmol) of **7** in 25 mL of 2.0 N HCl was refluxed for 72 h. The reaction mixture was decanted from a small amount of insoluble gum and cooled in an ice bath. Neutralization with concentrated NH_4OH followed by filtration of the crystalline solid gave 690 mg (66.4%) of **15**: mp 245–248 °C dec; IR (Nujol) 2030, 1625, 1600 cm^{-1}; MS *m/e* 274 (M^+).

Anal. Calcd for $C_{12}H_{16}ClNO_2S$: C, 52.64; H, 5.89; N, 5.11. Found: C, 52.57; H, 5.41; N, 4.72.

Methyl 2-(Dimethylaminomethyleneamino)-2-phenylpropionate (8). To a solution of 8.0 mmol of LDA in 8 mL of dry THF at − 70 °C under N_2 was added a solution of 1.58 g (7.2 mmol) of amidino ester **2c** in 5 mL of dry THF dropwise. After 10 min at −70 °C the reaction mixture was warmed to 0 °C and 1.53 g (10.8 mmol) of methyl iodide added neat. After 1 h at room temperature the reaction mixture was partitioned between ether and basic (NaOH) brine

(twice). The ether layer was dried and evaporated and the residue distilled to give 1.4 g (83.3%) of compound **8**: bp (0.6 mm) 130–135 °C; NMR ($CDCl_3$) δ 1.70 (s, 3 H), 2.88 (s, 6 H), 3.65 (s, 3 H), 7.13–7.67 (m, 6 H); IR (film) 1721, 1634 cm^{-1}.

Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.39; H, 7.79; N, 11.89.

Dimethyl 2-(Dimethylaminomethyleneamino)-2-phenylpentanedioate (9). To a solution of 2.2 g (10 mmol) of amidino ester **2c** in 30 mL of anhydrous MeOH at room temperature under N_2, 300 mg (2.5 mmol) of potassium *tert*-butoxide was added. After 15 min 1.72 g (20 mmol) of methyl acrylate was added and the solution refluxed for 24 h. The solvent was removed in vacuo and the residue dissolved in ether, dried, and filtered through Celite. The oily residue crystallized from ether/hexane to give 2.69 g (87.9%) of compound **9**: mp 61–63 °C; bp (0.7 mm) 166–169 °C; NMR ($CDCl_3$) δ 2.19–2.45 (m, 4 H), 2.89 (s, 6 H), 3.59 (s, 3 H), 3.68 (s, 3 H), 7.19–7.60 (m, 6 H); IR (CH_2Cl_2) 1720, 1633 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 63.04; H, 7.38; N, 9.19.

Methyl 2-(Dimethylaminomethyleneamino)-2-methyl-3-phenylpropionate (10). To a solution of 27.5 mmol of LDA in 50 mL of dry THF at −70 °C under N_2 was added dropwise a solution of 5.85 g (25 mmol) of amidino ester **2d** in 50 mL of dry THF. The reaction mixture was warmed to 0 °C and 5.3 g (37.5 mmol) of methyl iodide added neat. After 1 h at room temperature, the reaction mixture was partitioned between ether and basic (NaOH) brine (twice). The ether layer was dried and evaporated. The residue was distilled to give 5.2 g (84%) of compound **10**: bp (0.2 mm) 130 °C; NMR ($CDCl_3$) δ 1.29 (s, 3 H), 2.81 (s, 6 H), 3.08 (s, 2 H), 3.67 (s, 3 H), 7.20 (s, 6 H); IR (film) 1721, 1638 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.66; H, 7.88; N, 11.17.

Methyl 2-Benzyl-2-(dimethylaminomethyleneamino)pentanoate (11). To a solution of 16.5 mmol of LDA in 30 mL of dry THF at −70 °C under N_2 was added a solution of 3.5 g (15 mmol) of amidino ester **2d** in 30 mL of THF. The reaction mixture was warmed to 0 °C and 3.83 g (22.5 mmol) of *n*-propyl iodide added neat. After 6 h at room temperature the reaction mixture was partitioned between ether and basic (NaOH) brine (twice). The ether layer was dried and evaporated and the residue distilled to give 3.32 g (80%) of compound **11**: bp (0.2 mm) 135–140 °C; NMR ($CDCl_3$) δ 0.70–1.95 (m, 7 H), 2.74 (s, 6 H), 3.01–3.11 (m, 2 H), 3.64 (s, 3 H), 6.98 (s, 1 H), 7.11 (s, 5 H); IR (film) 1723, 1638 cm^{-1}.

Anal. Calcd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.40; H, 8.62; N, 10.14.

α-Propylphenylalanine (13). A solution of amidino ester **11** (1.38 g, 5 mmol) in 10 mL of concentrated HCl was refluxed for 24 h. On cooling, the hydrochloride salt of **13** crystallized from the solution. Filtration afforded 1.1 g (90.2%), mp 235 °C dec.

Anal. Calcd for $C_{12}H_{17}NO_2$·HCl: C, 59.14; H, 7.44; N, 5.74. Found: C, 59.51; H, 7.67; N, 6.08.

2-Benzyl-2-(dimethylaminomethyleneamino)butyrolactone (12). To a solution of 24 mmol of LDA in 40 mL of dry THF at −70 °C under N_2 was added a solution of 5.04 g (21.6 mmol) of amidino ester **2d** in 20 mL of dry THF. After 1 h at −70 °C the solution was saturated with ethylene oxide, and the bath removed and stirred at room temperature. After 2 days the solvent was removed in vacuo. The residue was dissolved in ether, decolorized with charcoal, dried, and filtered through Celite. The filtrate was evaporated to give 4.18 g of **12** as an oil: NMR ($CDCl_3$) δ 2.03–2.17 (m, 2 H), 2.91 (s, 6 H), 2.96–3.02 (m, 2 H), 3.91–4.13 (m, 2 H), 7.09 (s, 5 H), 7.51 (s, 1 H). This oil was dissolved in acetone and treated with 1 equiv of cyclohexylsulfamic acid to give 5.42 g (60%) of **12**, cyclohexylsulfamate salt: mp 178–180 °C; IR (Nujol) 1768, 1705 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}N_2O_2 \cdot C_6H_{13}NO_3S$: C, 56.46; H, 7.34; N, 9.88. Found: C, 56.31; H, 7.55; N, 9.89.

2-Amino-2-benzylbutyrolactone (14). A solution of 3.63 g (14.7 mmol) of **12** in 25 mL of *p*-dioxane and 25 mL of 5 N HCl was refluxed for 18 h. The reaction mixture was concentrated to one-half volume and extracted with ether (twice). The aqueous layer was further concentrated yielding 950 mg (28.5%) of compound **14** HCl: mp 251–254 °C dec; ir (Nujol) 2010, 1775 cm^{-1}; MS *m/e* 192 ($M^+ + 1$).

Anal. Calcd for $C_{11}H_{13}NO_2$·HCl: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.01; H, 6.43; N, 6.02.

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Registry No.—**1a,** 56-40-6; **1b,** 59-51-8; **1c,** 2835-06-5; **1d,** 150-30-1; **2a,** 62448-39-9; **2b,** 62448-40-2; **2c,** 62448-41-3; **2d,** 62448-42-4; **4,** 62448-43-5; **4** fumarate, 62448-44-6; **5** isomer a, 62460-38-2; **5** isomer b, 62448-45-7; **6,** 62448-46-8; **7,** 62448-47-9; **7** methanesulfonate, 62448-48-0; **8,** 62448-49-1; **9,** 62448-31-1; **10,** 62448-32-2; **11,** 62448-33-3; **12,** 62448-34-4; **12** cyclohexylsulfamate, 62448-35-5; **13,** 62448-36-6; **14,** 62448-37-7; **15,** 62448-38-8; dimethylformamide dimethyl acetal, 4637-24-5; cinnamyl bromide, 4392-24-9; fumaric acid, 110-17-8; dimethyl-*p*-chlorobenzalmalonate, 52927-44-3; ω-nitrostyrene, 102-96-5; α-*p*-dichlorotoluene, 104-83-6; methanesulfonic acid, 75-75-2; methyl iodide, 74-88-4; methyl acrylate, 96-33-3; *n*-propyl iodide, 107-08-4; ethylene oxide, 75-21-8.

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Electronic Structure and Nitrogen Hybridization in β-Aminovinylphosphonium Salts by Carbon-13 Nuclear Magnetic Resonance

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We have previously examined the ^{13}C NMR for a number of β-vinyl substituted phosphonium salts.[1] Current synthetic work in this laboratory has dealt with β-aminovinylphosphonium salts, and thus, a more detailed study of their spectra was undertaken. The following is a report on that study.

Compounds **2–7** were prepared by addition of the corresponding amine to 2-propynyltriphenylphosphonium bromide. The ^{13}C chemical shifts and ^{13}C–^{31}P nuclear couplings of these compounds are listed in Tables I and II, respectively, and their ^1H NMR spectra in Table III. Assignments of the carbons and the stereochemistry of the compounds were made by analogy with previous work.[1] In all cases, the *E* form (as shown) was indicated.