Carbon Elongations with 1,5-Diazapentadienium Salts: Reaction with Aralkyl Ketones

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Carbonyl compounds play a central role in carbon-carbon bond elaboration. For this reason, reaction sequences that result in carbon chain elongation are especially significant. Although numerous methods are available for the conversion of ketones into higher homologs involving unsaturation attendant with one and two carbon chain extension, the methodology for such three carbon elaborations of these structures is very limited[1]. We have discovered recently[2] that 1,5-diazapentadienium or vinamidinium salts react selectively with enolates of alicyclic ketones, esters, lactones, and lactams to give products with conjugated three-carbon elongation at the α-position of the original compound.

This paper reports on the utilization of the vinamidinium salt **1** for the carbon elongation of aralkyl ketones (**2**–**5**). The multifunctional dienaminones (**6**–**9**) produced can be regarded as potential synthetic intermediates for a number of natural products including maytansinoids[3,4], gibberelins[5,6], steroids[7,8], and colchicines[9,10]. The vinamidinium salt **1** was prepared from β-(dimethylamino)-acrolein[11] as previously described[2]. When the salt **1** was treated with enolates generated *in situ* by reaction of sodium hydride or lithium diisopropylamide with the aralkyl ketones **2**–**5** in triethylamine, multifunctional dienaminones **6**–**9** were isolated in good to excellent yields (Table).

Method A involves the reaction with enolates generated *in situ* by reaction with sodium hydride and Method B used lithium diisopropylamide as base. There was no significant difference in yields between the two methods. However, dramatic reductions in reaction times were observed in all cases when lithium diisopropylamide was used. Determination of reaction times was carried out by U.V.-visible spectral methods. The substrates absorb at wavelengths shorter than that for **1** (which has a λ_{max} at 309 nm), and the products absorb at wavelengths longer than that for **1** (in the range of 360–440 nm). Optimization of the transformation required that a 2:1 ratio of **1** and ketone be used.

The stereochemistry of the dienaminones were determined by high-field ^{1}H-N.M.R. data which showed that these compounds were exclusively the (*E,E*)-(*s-trans*)-geometric isomers. The stereospecificity of the reaction was further confirmed by ^{13}C-N.M.R. data. ^{13}C-Chemical shift assignments were aided by delayed decoupling experiments. The mass spectra of all of the dienaminones gave parent ions and fragmentation patterns consistent with their structures.

Carbon Elongation Reactions; General Procedures:

Method A: The carbonyl compound (2.0 mmol) in tetrahydrofuran (3 ml) is added dropwise with stirring to 1,1,5,5-tetramethyl-1,5-diazapentadienium chloride (**1**; 4.0 mmol) and sodium hydride (3.0 mmol) in triethylamine (7 ml). The mixture is stirred over 4-A molecular sieves (0.3 g) at 0°C for 30 min. It is then warmed to room temperature and progress of reaction is monitored by ultraviolet-visible spectroscopy. On completion, the mixture is worked up by carefully pouring it into saturated sodium chloride solution (40 ml) followed by extraction with dichloromethane (4 × 40 ml). The combined organic layers are dried with sodium sulfate. After removal of

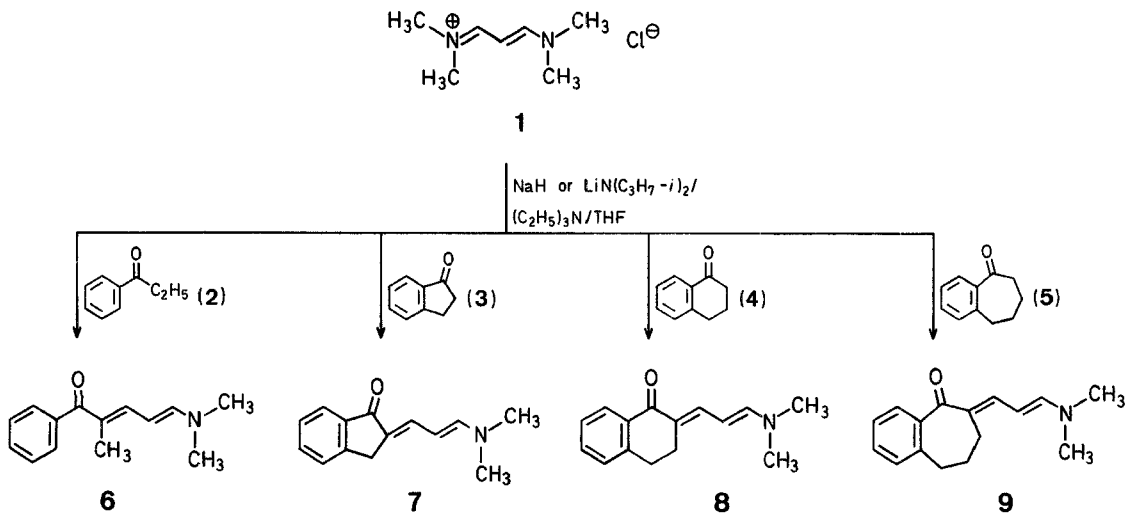

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Table. Products from the Reaction of Vinamidinium Salt **1** with Aralkyl Ketones

Product	Yield [%][a]	m.p. [°C]	Molecular Formula[b]	M.S. *m/e* (rel. intens. %)	U.V.(C_2H_5OH) λ_{max} (ε)	^{1}H-N.M.R.($CDCl_3$) δ [ppm]	^{13}C-N.M.R. ($CDCl_3$) δ [ppm]
6	52[c]	100–102°	$C_{14}H_{17}NO$ (215.3)	215 (M^+, 45.4); 200 (7.2); 186 (1.3); 171 (100); 157 (9.5)	249 (9104); 387 (42166)	1.98 (s, 3H); 2.89 (s, 3H); 5.17 (t, 1H, J = 11.9 Hz); 6.54 (d, 1H, J = 11.9 Hz); 6.90 (d, 1H, J = 11.9 Hz); 7.40 (m, 5H)	11.7; 40.6; 95.3; 123.6; 127.8; 128.6; 129.5; 141.2; 148.9; 150.7; 197.4
7	67	153–155°	$C_{14}H_{15}NO$ (213.3)	213 (M^+, 100); 198 (10.5); 184 (22.8); 169 (71.3); 156 (7.4)	273 (18954); 438 (69804)	2.85 (s, 6H); 3.54 (s, 2H); 5.06 (t, 1H, J = 12.3 Hz); 6.74 (d, 1H, J = 12.3 Hz); 7.35 (d, 1H, J = 12.3 Hz); 7.43 (m, 3H); 7.79 (d, 1H, J = 6.6 Hz)	30.8; 40.6; 95.5; 123.2; 123.8; 125.8; 126.8; 132.3; 138.0; 141.2; 148.3; 152.6; 192.0
8	93	145–147°	$C_{15}H_{17}NO$ (227.3)	227 (M^+, 24.6); 212 (1.9); 198 (1.9); 183 (100); 170 (1.7)	274 (23374); 438 (48823)	2.76 (m, 2H); 2.91 (m, 2H); 2.94 (s, 6H); 5.20 (t, 1H, J = 12.3 Hz); 6.84 (d, 1H, J = 12.3 Hz); 7.29 (m, 3H); 7.62 (d, 1H, J = 12.3 Hz); 8.07 (d, 1H, J = 7.7 Hz)	24.8; 28.7; 40.7; 95.1; 121,3; 126.5; 127.5; 127.6; 131.6; 135.1; 140.8; 142.9; 152.2; 185.8
9	65	90–93°	$C_{16}H_{19}NO \cdot H_2O$ (259.3)	241 (M^+, 32.7); 226 (2.0); 212 (3.2); 197 (100); 184 (5.6)	267 (11285); 418 (38546)	1.90 (m, 2H); 2.32 (m, 2H); 2.71 (m, 2H); 2.83 (s, 6H); 5.18 (t, 1H, J = 12.3 Hz; 6.78 (d, 1H, J = 12.3 Hz); 7.31 (m, 4H); 7.40 (d, 1H, J = 12.3 Hz)	24.2; 27.0; 31.6; 40.6; 94.5; 124.6; 126.5; 128.2; 128.4; 130.7; 139.1; 141.2; 141.3; 152.2; 196.1

[a] The yields quoted are averaged yields from small and large scale experiments. Only small variations were found between these runs.
[b] Satisfactory microanalyses obtained: C ±0.20, H ±0.38, N ±0.44; exception: **9**, C +0.7.
[c] Yield based on recovered starting material; the yield of isolated product is 27%.

the solvent, the products are purified by preparative layer chromatography on E. Merck aluminum oxide 60-PF-254 plates with chloroform/ethyl acetate as the eluting solvent. Crystallizations are performed from hexane.

Method B: The carbonyl compound (2.0 mmol) in dry triethylamine (5 ml) is added dropwise to a stirred solution of lithium diisopropylamide [generated by adding 1.5 molar *n*-butyllithium solution (2.0 ml) to dry diisopropylamine (3.0 mmol) in dry tetrahydrofuran (7 ml) at 0 °C and stirring the mixture at 0 °C for 20 min after the addition is complete]. To this is added 1,1,5,5-tetramethyl-1,5-diazapentadienium chloride (**1**; 2.0 mmol). The mixture is stirred at 0 °C for 30 min and then at room temperature for 2 h. At this stage, another portion of (2.0 mmol) is added. Progress of reaction is monitored by ultraviolet-visible spectroscopy. The mixture is worked up by carefully pouring it into saturated sodium chloride solution (40 ml) followed by extraction with dichloromethane (4 × 40 ml). The combined organic layers are dried with sodium sulfate. After removal of the solvent, the products are purified as described in Method A.

Method C (Large Scale Procedure): The carbonyl compound (10.0 mmol) in dry triethylamine (10 ml) is added dropwise to a stirred solution of lithium diisopropylamide [generated by adding 1.5 molar *n*-butyllithium solution (10.0 ml) to dry diisopropylamine (15 mmol) in dry tetrahydrofuran (30 ml) at 0 °C and stirring the mixture at 0 °C for 20 min after the addition is complete]. To this is added 1,1,5,5-tetramethyl-1,5-diazapentadienium chloride (**1**; 10.0 mmol). The mixture is stirred at 0 °C for 30 min and then at room temperature for 2 h. At this stage, another portion of **1**

(10.0 mmol) is added. Progress of reaction is monitored by ultraviolet-visible spectroscopy. The mixture is worked up by carefully pouring it into saturated sodium chloride solution (100 ml) followed by extraction with dichloromethane (4 × 100 ml). The combined organic layers are dried with sodium sulfate. After removal of the solvent, the products are purified by column chromatography on activated alumina (80–325 mesh) with mixtures of chloroform and ethyl acetate as the eluting solvent. They are crystallized from hexane.

Note: The lithium diisopropylamide method is much more convenient for larger scale reactions than the procedure using sodium hydride.

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