Heterocyclization Reactions of Azinoisocyanates. Synthesis of 2*H*-1,2,4-Triazol-3(4*H*)-one Derivatives

Kee-Jung Lee*, Jin Lyang Kim, Mun Ki Hong and Jung Yong Lee

Department of Industrial Chemistry, Hanyang University, Seoul 133-791, Korea

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The reaction of 1-aminoethylidenehydrazones **9** with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine led to the corresponding azinoisocyanates **10**, which underwent thermal rearrangement under the reaction conditions to give 4-(*tert*-butoxycarbonyl)-5-methyl-2*H*-1,2,4-triazol-3(4*H*)-ones **14**. However, amidrazone **17** gave 2-(2-*tert*-butoxycarbonyloxy-2-phenyl)ethyl-4-(*tert*-butoxycarbonyl)-5-methyl-2*H*-1,2,4-triazol-3(4*H*)-one **22** and *N*-aziridinyliminocarbamate **18** under the similar conditions.

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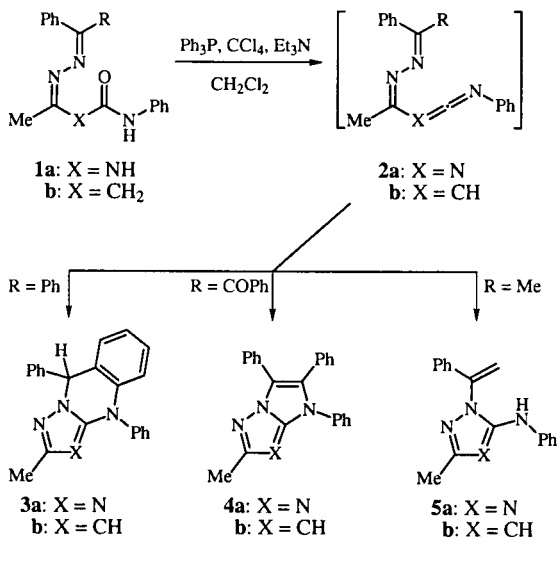
Isocyanates are an important class of compounds in organic chemistry [1]. They are used in the synthesis of heterocyclic derivatives and some isocyanates have found applications in the synthesis of biologically active compounds. Isocyanates have been mainly prepared by the phosgenation of amines [2], thermolysis of carbamates [3], and 4-dimethylaminopyridine catalyzed reaction of the amine with di-*tert*-butyl dicarbonate [4] in recent progress.

We described a new route to 1,2,4-triazole-fused heterocycles such as 5,10-dihydro-1,2,4-triazolo[5,1-*b*]-quinazolines **3a** [5], 7*H*-imidazo[1,2-*b*][1,2,4]-triazole **4a** [6], and monocyclic *N*-α-styryl-5-(phenylamino)-1,2,4-triazole **5a** [7] involving electrocyclization of azinocarbodiimides **2a** obtained from the corresponding ureas **1a** using Appel's dehydration method [8]. Also, we reported [9] that azinoketimines **2b**, which were obtainable from the corresponding amides **1b** in the similar condition, gave pyrazole-fused heterocycles such as 4,9-dihydropyrazolo[5,1-*b*]quinazoline **3b**, 1*H*-imidazo[1,2-*b*]pyrazole **4b**, and monocyclic *N*-α-styryl-5-(phenylamino)-pyrazole **5b** by thermal rearrangement (Scheme I).

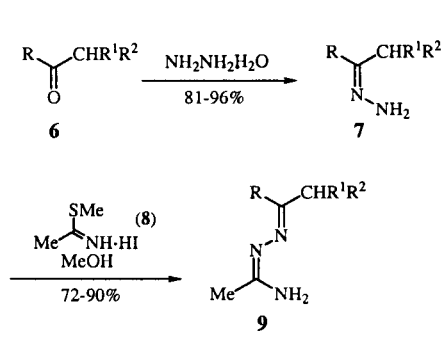
Scheme I



We now wish to report that azinoisocyanates **10**, which are obtainable from the 4-dimethylaminopyridine catalyzed reaction of the 1-aminoethylidenehydrazones **9** with di-*tert*-butyl dicarbonate [$(Boc)_2O$] [4], give 2*H*-1,2,4-triazol-3(4*H*)-one derivatives **14** by thermal rearrangement. The 1,2,4-triazolone nucleus is present in a wide variety of compounds with biological activity. They have been shown to exhibit antibacterial [10], antifungal [11], antiinflammatory [12], anticonvulsant [13], and herbicidal activity [14] and this justifies continuous efforts in developing more general and versatile synthetic methodologies to this class of compounds [15]. Some modern triazolone syntheses involve amidrazone intermediates formed through rearrangements of cyanates [16] and isocyanates generated in the Curtius rearrangement [17] are reported.

The starting compounds, 1-aminoethylidenehydrazones **9** employed in this study, were prepared from ketones **6** in two steps as depicted in Scheme II. Ketones **6** were reacted with excess hydrazine monohydrate at reflux temperature to give hydrazones **7** in 81-96% yields. Hydrazones **7** were treated with *S*-methylthioacetimidate hydroiodide **8** [18] in refluxing methanol followed by neutralization with aqueous sodium hydrogen carbonate to give 1-aminoethylidenehydrazones **9** in 72-90% yields. The reaction of **9** with di-*tert*-butyl dicar-

Scheme II

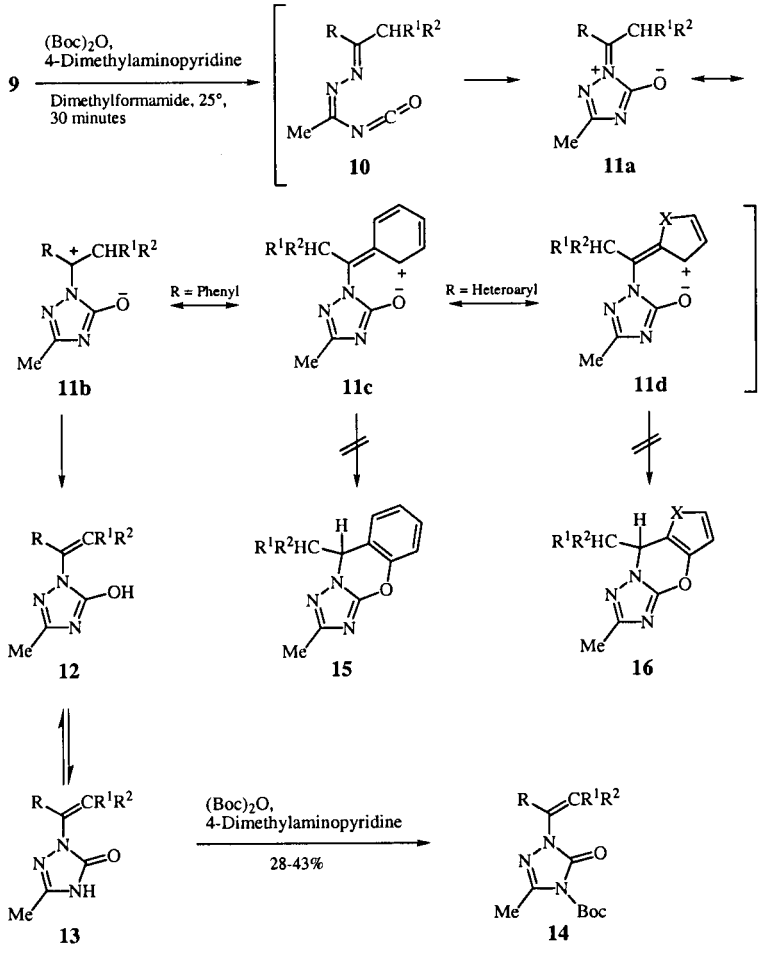


bonate in the presence of 4-dimethylaminopyridine in *N,N*-dimethylfomamide at room temperature led to 4-(*tert*-butoxycarbonyl)-2*H*-1,2,4-triazol-3(4*H*)-ones **14** within 30 minutes in 28-43% yields. In the case of **9f**, 1-(*tert*-butoxycarbonyl)-2-pyrrolytriazolone **14f** was obtained. Neither compounds **15** nor **16** were obtained. Determination of the structure of triazolinones **14** was accomplished on the basis of microanalyses and spectral data. The infrared spectrum of **14a** showed strong broad absorptions at 1760 cm^{-1} due to the carbonyl group. The ^1H nmr spectrum showed peaks at δ = 1.63, 2.43, 5.49 and 5.63 as four singlets assignable to the *tert*-butyl, C5-methyl and two exo methylene protons, respectively. In the ^{13}C nmr spectrum peaks at δ = 149.1 (NCO_2), 146.7 (C5), 142.4 (C3), 141.2 (PhC=), 109.5 ($=CH_2$), 86.1 (O-C-*tert*-butyl), 27.8 (*tert*-butyl) and 15.5 (C5-methyl) in addition to the aromatic peaks characterized 4-(*tert*-butoxycarbonyl)-5-methyl-2-(1-phenylethenyl)-2*H*-1,2,4-triazol-3(4*H*)-one (**14a**).

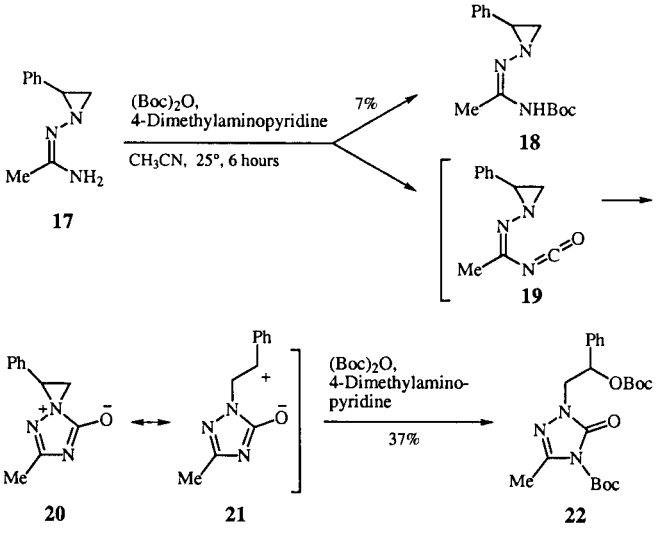
The proposed mechanism for the formation of **14** is shown in Scheme III. The presumed intermediate azinoisocyanates **10** were too unstable to isolate, so the thermal reaction of **10** would give the resonance-stabilized zwitterionic intermediates **11a-d**. Proton abstraction by the exocyclic oxy anion in **11b** would produce vinyl alcohols **12**, which were converted to the 4-(*tert*-butoxycarbonyl)-2*H*-1,2,4-triazol-3(4*H*)-ones **14** by the reaction of excess di-*tert*-butyl dicarbonate [19] directly or *via* the keto form **13**.

On the other hand, the thermal reaction of *N*-aziridinyliminoisocyanate **19** derived from the reaction of the known amidrazone **17** [20] under similar conditions led to the formation of two products which were separated by column chromatography. The first product was the simple *N*-aziridinyliminocarbamate **18** (7%) and the second one was isolated as a white solid and assigned as the 2-(2-*tert*-butoxycarbonyloxy-2-phenyl)ethyl-4-(*tert*-butoxycarbonyl)-5-methyl-2*H*-1,2,4-triazol-3(4*H*)-one (**22**, 37%) on the basis of the following spectral data. Compound **22** exhibited strong bands at 1795 (C=O), 1743 (C=O) and 1600 cm^{-1}(C=N) in its infrared spectrum. In the ^1H nmr spectrum peaks at δ = 1.42 and 1.61 ppm characterized two *tert*-butyl protons. Also two *tert*-butoxycarbonyl groups were indicated by peaks at δ = 27.7 and 27.8 (*tert*-butyl),

Scheme III



Scheme IV



δ = 82.4 and 85.8 (O-C-*tert*-butyl), δ = 150.3 (NCO_2) and 152.6 (OCO_2) in the ^{13}C nmr spectrum. There were also a C5-methyl absorption at δ = 15.4, as well as peaks at δ = 146.9 (C5) and 142.2 (C3) for the 1,2,4-triazolinone ring.

Although the isolation of isocyanate **19** was unsuccessful under the reaction conditions, we believe that the mechanistic sequence may involve an electrocyclization of the *N*-aziridinyliminoisocyanate **19** to give the zwitterionic aziridinum ion **20** followed by aziridine ring opening and reaction of di-*tert* butyl dicarbonate with the resultant betaine **21** to give product **22**.

In conclusion, the present method demonstrated that thermal reaction of azinoisocyanate or *N*-aziridinyliminoisocyanate, obtained from the reaction of 4-dimethylaminopyridine catalyzed reaction of the corresponding amidrazone with di-*tert*-butyl dicarbonate, provides a new entry to the synthesis of 2*H*-1,2,4-triazol-3(4*H*)-one derivatives.

Table 1

Hydrazones **7**

	R	R^1	R^2	Yield (%)	Mp (°)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
7a	Phenyl	H	H	93	24-25	$C_8H_{10}N_2$ (134.18)		[a]	
7b	Phenyl	CH_3	H	91	55-57	$C_9H_{12}N_2$ (148.21)		[b]	
7c	Phenyl	-CH_2-CH_2-		95	57-58	$C_{10}H_{12}N_2$ (160.22)		[c]	
7d	2-Furyl	H	H	81	48-50	$C_6H_8N_2O$ (124.14)	58.05 58.22	6.50 6.66	22.57 22.77
7e	2-Thienyl	H	H	96	76-78	$C_6H_8N_2S$ (140.21)	51.39 51.45	5.75 5.63	19.98 20.27
7f	2-Pyrrolyl	H	H	95	85-87	$C_6H_9N_3$ (123.16)	58.51 58.84	7.37 7.75	34.12 34.07

[a] Reference [21]. [b] Reference [22]. [c] Reference [7b].

Table 2

1-Aminoethylidenehydrazones **9**

	R	R^1	R^2	Yield (%)	Mp (°)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
9a	Phenyl	H	H	79	76-77	$C_{10}H_{13}N_3$ (175.23)		[a]	
9b	Phenyl	CH_3	H	72	88-90	$C_{11}H_{15}N_3$ (189.26)	69.81 70.16	7.99 7.98	22.20 22.53
9c	Phenyl	-CH_2-CH_2-		90	oil	$C_{12}H_{15}N_3$ (201.27)		[b]	
9d	2-Furyl	H	H	87	74-75	$C_8H_{11}N_3O$ (165.19)	58.16 58.02	6.71 6.35	25.44 25.65
9e	2-Thienyl	H	H	78	76-78	$C_8H_{11}N_3S$ (181.26)	53.01 52.69	6.12 6.47	23.18 23.06
9f	2-Pyrrolyl	H	H	88	148-149	$C_8H_{12}N_4$ (164.21)	58.52 58.18	7.37 7.75	34.12 34.19

[a] Reference [7a]. [b] Reference [7b].

Table 3

4-(*tert*-Butoxycarbonyl)-5-methyl-2*H*-1,2,4-triazol-3(4*H*)-ones **14**

	R	R^1	R^2	Yield (%)	Mp (°)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
14a	Phenyl	H	H	34	71-73	$C_{16}H_{19}N_3O_3$ (301.35)	63.77 64.29	6.36 6.81	13.94 14.10
14b	Phenyl	CH_3	H	30	180-181	$C_{17}H_{21}N_3O_3$ (315.37)	64.75 64.75	6.71 7.04	13.32 13.08
14c	Phenyl	-CH_2 - CH_2-		28	oil	$C_{18}H_{22}N_3O_3$ (328.39)	65.84 65.61	6.75 6.41	12.80 12.82
14d	2-Furyl	H	H	43	oil	$C_{14}H_{17}N_3O_4$ (291.31)	57.72 58.04	5.88 5.68	14.43 14.07
14e	2-Thienyl	H	H	40	oil	$C_{14}H_{17}N_3O_3S$ (307.37)	54.71 55.08	5.57 5.92	13.67 13.33
14f	1-Boc-2-Pyrrolyl	H	H	35	oil	$C_{19}H_{26}N_4O_5$ (390.44)	58.45 58.17	6.71 7.02	14.35 13.98

Table 4

^{1}H NMR Data [a] of Compounds **7**, **9** and **14**

7a 2.13 (s, 3 H, CH_3), 5.35 (br s, 2 H, NH_2), 7.26-7.38 (m, 3 H, aromatic), 7.63-7.66 (m, 2 H, aromatic)
7b 1.14 (t, 3 H, J = 7.6 Hz, CH_3), 2.60 (q, 2 H, J = 7.8 Hz, CH_2), 5.42 (br s, 2 H, NH_2), 7.26-7.39 (m, 3 H, aromatic), 7.62-7.65 (m, 2 H, aromatic)
7c 0.58 (m, 2 H, cyclopropyl), 1.06 (m, 2 H, cyclopropyl), 1.54 (m, 1 H, cyclopropyl), 5.88 (br s, 2 H, NH_2), 7.24-7.35 (m, 3 H, aromatic), 7.65-7.68 (m, 2 H, aromatic)
7d 2.03 (s, 3 H, CH_3), 5.38 (br s, 2 H, NH_2), 6.39 (dd, 1 H, J = 3.3 and J = 0.9 Hz, aromatic), 6.48 (d, 1 H, J = 3.3 Hz, aromatic), 7.39 (d, 1 H, J = 0.9 Hz, aromatic)
7e 2.15 (s, 3 H, CH_3), 5.23 (br s, 2 H, NH_2), 6.97-7.21 (m, 3 H, aromatic)
7f 2.04 (s, 3 H, CH_3), 5.08 (s, 2 H, NH_2), 6.17 (m, 1 H, aromatic), 6.32 and 6.75 (s, 1 H each, aromatic), 9.45 (br s, 1 H, NH)
9a 2.10 (s, 3 H, CH_3), 2.40 (s, 3 H, CH_3), 5.29 (br s, 2 H, NH_2), 7.27-7.46 (m, 3 H, aromatic), 7.80-7.87 (m, 2 H, aromatic)
9b 1.12 (t, 3 H, J = 7.6 Hz, CH_3), 2.09 (s, 3 H, CH_3), 2.99 (q, 2 H, J = 7.6 Hz, CH_2), 5.22 (br s, 2 H, NH_2), 7.35-7.40 (m, 3 H, aromatic), 7.78 -7.82 (m, 2 H, aromatic)
9c 0.69 (m, 2 H, cyclopropyl), 0.92 (m, 2 H, cyclopropyl), 2.07 (s, 3 H, CH_3), 2.51 (m, 1 H, cyclopropyl), 5.15 (br s, 2 H, NH_2), 7.32-7.40 (m, 5 H, aromatic)
9d 2.10 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 5.42 (br s, 2 H, NH_2), 6.45 (m, 1 H, aromatic), 6.74 (d, 1 H, aromatic), 7.47 (s, 1 H, aromatic)
9e 2.06 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 5.34 (br s, 2 H, NH_2), 6.97-7.29 (m, 3 H, aromatic)
9f 2.02 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 5.28 (br s, 2 H, NH_2), 6.20 (s, 1 H, aromatic), 6.51 (d, 1 H, J = 2.6 Hz, aromatic), 6.79 (s, 1 H, aromatic), 9.78 (br s, 1 H, NH)
14a 1.63 (s, 9 H, *tert*-butyl), 2.43 (s, 3 H, CH_3), 5.49 (s, 1 H, vinyl), 5.63 (s, 1 H, vinyl), 7.35 (s, 5 H, aromatic)
14b 1.61 (s, 9 H, *tert*-butyl), 1.85 (d, 3 H, J = 7.3 Hz, CH_3), 2.39 (s, 3 H, CH_3), 6.16 (q, 1 H, J = 7.3 Hz, vinyl), 7.27-7.37 (m, 5 H, aromatic)
14c 1.45 (m, 2 H, cyclopropyl), 1.59 (m, 2 H, cyclopropyl), 1.64 (s, 9 H, *tert*-butyl), 2.47 (s, 3 H, CH_3), 7.26-7.46 (m, 5 H, aromatic)
14d 1.63 (s, 9 H, *tert*-butyl), 2.47 (s, 3 H, CH_3), 5.53 (s, 1 H, vinyl), 5.76 (s, 1 H, vinyl), 6.41 (s, 2 H, aromatic), 7.41 (s, 1 H, aromatic)
14e 1.63 (s, 9 H, *tert*-butyl), 2.46 (s, 3 H, CH_3), 5.53 (s, 1 H, vinyl), 5.60 (s, 1 H, vinyl), 6.99, 7.09 and 7.26 (s, 1 H each, aromatic)
14f 1.46 (s, 9 H, *tert*-butyl), 1.60 (s, 9 H, *tert*-butyl), 2.35 (s, 3 H, CH_3), 5.09 (s, 1 H, vinyl), 5.85(s, 1 H, vinyl), 6.16, 6.35 and 7.28 (m, 1 H each, aromatic)

[a] Deuteriochloroform.

Table 5

^{13}C NMR [a] and IR [b] Data of 4-(*tert*-Butoxycarbonyl)-5-methyl-2*H*-1,2,4-triazol-3(4*H*)-ones **14**

	^{13}C NMR (ppm)	IR (cm^{-1})
14a	15.5, 27.8, 86.1, 109.5, 126.9, 128.2, 128.8, 135.2, 141.2, 142.4, 146.7, 149.1	2988, 1760, 1638, 1459, 1375, 1312, 1159, 1069
14b	13.9 (d), 15.4 (d), 27.8 (d), 85.8, 123.5 (d), 127.8, 128.4, 128.7, 129.2, 134.1, 142.0, 146.9, 149.3	2988, 1791, 1759, 1601, 1364, 1312, 1153, 1074
14c	3.2, 5.3, 15.7 (d), 27.9 (d), 85.9, 124.4 (d), 125.9 (d), 127.6, 128.0, 128.5, 135.3, 142.5, 146.8, 149.3	2977, 1749, 1717, 1607, 1438, 1370, 1311, 1159, 1070
14d	15.4, 27.8, 86.2, 108.3, 109.5, 111.3, 131.8, 142.6, 142.9, 146.7, 148.6, 149.0	2986, 1795, 1750, 1603, 1463, 1303 1143, 1013

Table 5 (continued)

^{13}C NMR [a] and IR [b] Data of 4-(*tert*-Butoxycarbonyl)-5-methyl-2*H*- 1,2,4-triazol-3(4*H*)-ones **14**

	^{13}C NMR (ppm)	IR (cm^{-1})
14e	15.4, 27.8, 86.2, 109.3, 126.1, 126.6, 127.2, 135.2, 138.2, 142.5, 146.7, 149.0	2985, 1795, 1754, 1620, 1365, 1146 1006
14f	15.2, 27.7, 27.8, 83.5, 85.8, 104.3, 110.1, 116.6, 122.5, 128.6, 134.5, 141.7, 146.8, 148.3, 148.4	2975, 1794, 1745, 1635, 1475, 1375, 1149, 1087

[a] Deuteriochloroform. [b] Determined by using potassium bromide pellets or KRS-5 cells.

EXPERIMENTAL

All reagents and solvents were reagent grade or were purified by standard methods before use and the reactions were routinely carried out under an inert atmosphere. Silica gel 60 (70-230 mesh ASTM) used for column chromatography was supplied by E. Merck. Analytical thin layer chromatography (tlc) was performed on silica gel with fluorescent indicator coated on aluminium sheets. Melting points were taken using an Electrothermal melting point apparatus and are uncorrected. Microanalyses were obtained using a Carlo Erba EA 1180 element analyzer. Infrared spectra were recorded on a Nicolet Magna 550 FTIR spectrometer. The ^1H and ^{13}C nmr spectra were measured on a Gemini 300 spectrometer. All chemical shifts are reported in parts per million (δ) relative to tetramethylsilane.

The *S*-methylthioacetimidate hydroiodide [18], acetophenone hydrazone [21], propiophenone hydrazone [22], cyclopropyl phenyl ketone hydrazone [7b] and amidrazone **17** [20] were prepared following the literature procedures. Acetophenone, propiophenone, cyclopropyl phenyl ketone, 2-acetylfuran, 2-acetylthiophene, 2-acetylpyrrole, di-*tert*-butyl dicarbonate, and 4-dimethylaminopyridine were purchased from Aldrich Chemical Company.

Hydrazones **7**. General Procedure.

A solution of the appropriate ketone **6** (15 mmoles) and 30 ml of excess 85% hydrazine monohydrate was stirred at reflux temperature for 3 hours. After cooling to room temperature dichloromethane (50 ml) was poured into the reaction mixture and was partitioned between water and dichloromethane. The dichloromethane layer was washed with water and the solvent was removed after drying over magnesium sulfate, and the residue was crystallized with petroleum ether–ethyl ether to give **7** as a white to yellowish solid.

The physical and spectral data of compounds **7** prepared by this general method are listed in Table 1 and Table 4.

1-Aminoethylidene Hydrazones **9**. General Procedure.

To a solution of hydrazones **7** (40 mmoles) in 100 ml of methanol was added *S*-methylthioacetimidate hydroiodide (**8**, 9.55 g, 44 mmoles) and this solution was stirred at reflux temperature for 3 hours. After cooling to room temperature the solvent was removed on a rotavapor and the residue was partitioned between aqueous sodium hydrogen carbonate solution and dichloromethane. The dichloromethane layer was washed with water and the solvent was removed after drying over magnesium sulfate, and the residue was crystallized with petroleum ether-ethyl ether to give **9** as a yellowish solid or an oil.

The physical and spectral data of **9** prepared by this general method are listed in Table 2 and Table 4.

4-(*tert*-Butoxycarbonyl)-5-methyl-2*H*-1,2,4-triazol-3(4*H*)-ones **14**.

General Procedure.

To a stirred solution of di-*tert*-butyl dicarbonate (1.96 g, 9 mmoles) and 4-dimethylaminopyridine (0.12 g, 1 mmole) in 10 ml of *N,N*-dimethylformamide was added the appropriate 1-aminoethylidenehydrazone **9** (3 mmoles). The solution was stirred at room temperature for 30 minutes. The reaction mixture was partitioned between water and ethyl ether (15 ml x 2), combined and the solvent was removed after drying over magnesium sulfate. The residue was chromatographed on a silica gel column and eluted with hexane-ethyl acetate 4:1 to give product **14** as a white solid or as an oil.

The physical and spectral data of compounds **14** prepared by this general method are listed in Table 3, Table 4, and Table 5.

N-Aziridinyliminocarbamate **18** and 2-(2-*tert*-Butoxycarbonyloxy-2-phenyl)ethyl-4-(*tert*-butoxycarbonyl)-5-methyl-2*H*-1,2,4-triazol-3(4*H*)-one **22**.

To a stirred solution of di-*tert*-butyl dicarbonate (1.87 g, 8.56 mmoles) and 4-dimethylaminopyridine (0.21 g, 1.71 mmoles) in 15 ml of acetonitrile was added 5 ml of acetonitrile solution of amidrazone **17** (0.60 g, 3.42 mmoles) and this solution was stirred at room temperature for 6 hours. The solvent was removed on a rotavapor and the residue was chromatographed on silica gel column and eluted with hexane-ethyl acetate 8:1 to give 0.07 g (7%) of **18** and 0.53 g (37%) of **22** in the order of elution.

Compound **18** had mp 84-85°; ^1H nmr (deuteriochloroform): δ 1.44 (s, 9 H, *tert*-butyl), 2.26 (s, 3 H, CH_3), 2.34 (d, 1 H, J = 4.9 Hz, CH), 2.37 (d, 1 H, J = 7.6 Hz, CH), 2.93 (dd, 1 H, J = 4.9 and J = 7.5 Hz, CH), 7.24-7.36 (m, 5 H, aromatic), 8.52 (br s, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 19.4, 28.1, 40.0, 43.9, 81.3, 126.4, 127.3, 128.4, 138.4, 151.0, 154.6.

Anal. Calcd. for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.31. Found: C, 65.23; H, 7.46; N, 15.36.

Compound **22** had mp 82-83°; ^1H nmr (deuteriochloroform): δ 1.42 (s, 9 H, *tert*-butyl), 1.61 (s, 9 H, *tert*-butyl), 2.40 (s, 3 H, CH_3), 3.98 (dd, 1 H, J = 14.5 and J = 9.0 Hz, CH), 5.94 (dd, J = 9.0 and J = 4.0 Hz, CH), 7.29-7.44 (m, 5 H, aromatic); ^{13}C nmr (deuteriochloroform): δ 15.4, 27.6, 27.8, 49.9, 75.8, 82.4, 85.8, 126.5, 128.6, 128.7, 136.9, 142.2, 146.9, 150.3, 152.6; ir (potas-

sium bromide): 2979, 1795, 1743, 1600, 1457, 1361, 1303, 1255, 1153, 1091, 846.

Anal. Calcd. for $C_{21}H_{29}N_3O_6$: C, 60.13; H, 6.97; N, 10.02. Found: C, 60.21; H, 7.35; N, 9.89.

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