Synthesis of *N*-α-Styrylcyclopropane-5-phenylamino-1,2,4-triazoles and Their Conversion to γ-Butyrolactones

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The reaction of cyclopropyl phenyl ketone 1-ureidoethylidenehydrazones **14** with a mixture of triphenylphosphine, carbon tetrachloride, and triethylamine provides a general route to *N*-α-styrylcyclopropane-5-phenylamino-1,2,4-triazoles **17** *via* the thermal reaction of the expected azinocarbodiimide intermediates **15**, and the oxidation of **17** with 3-chloroperoxybenzoic acid affords 1,2,4-triazole substituted γ-butyrolactones **23** directly.

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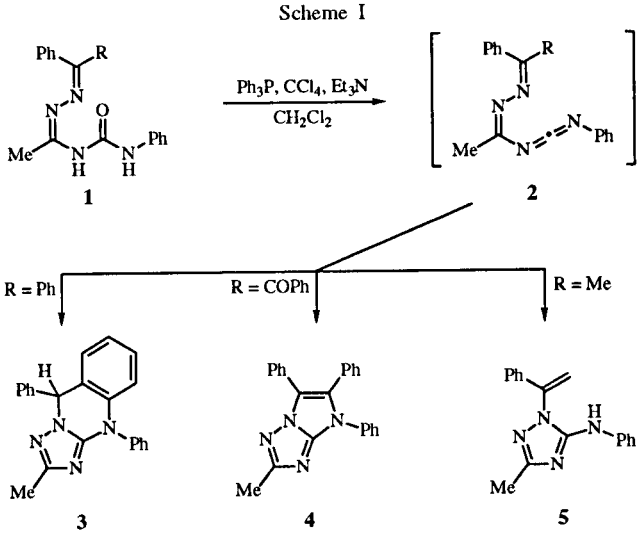
The electrocyclic reaction of conjugated heterocumulenes as a synthetic route to heterocycles [1], prompts us to report on our studies. We recently described a new route to 1,2,4-triazole fused heterocycles such as 5,10-dihydro-1,2,4-triazolo[5,1-*b*]quinazolines **3** [2], 7*H*-imidazo[1,2-*b*][1,2,4]triazoles **4** [3], and monocyclic *N*-α-styryl-5-(phenylamino)-1,2,4-triazoles **5** [4] involving electrocyclization of azinocarbodiimides **2** obtained from the corresponding ureas **1** using Appel's dehydration method [5] (Scheme I).

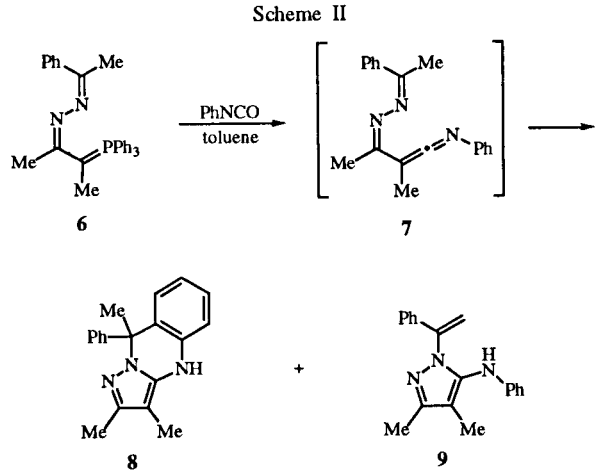
Scheme I



Also, Schweizer and Hayes reported [6] that the thermal electrocyclic reaction of azinoketimine **7**, obtained from phosphorane **6** and an isocyanate could give 4,9-dihydropyrazolo[5,1-*b*]quinazoline **8** as a major product and the *N*-α-styryl-5-(phenylamino)pyrazole **9** as a minor one (Scheme II).

With our continued interest in the reactions of azine substituted heterocumulenes to prepare fused triazolo ring systems, we chose to examine the reaction of cyclopropyl phenyl ketone 1-ureidoethylidenehydrazones **14** with triphenylphosphine, carbon tetrachloride, and triethylamine (Appel's Reagent) to see whether different triazole products such as **17**, **18**, or **19** could be formed, because of the possibility of participation of cyclopropyl or phenyl group in the ring forming step (Scheme IV). Many cyclopropane derivatives were used as synthons or building elements for ring enlargement steps [7].

Scheme II



The starting compounds, cyclopropyl phenyl ketone 1-ureidoethylidenehydrazones **14** employed in this study, were prepared from cyclopropyl phenyl ketone **10** in three steps as depicted in Scheme III. Ketone **10** was reacted with excess hydrazine monohydrate at reflux

Scheme III

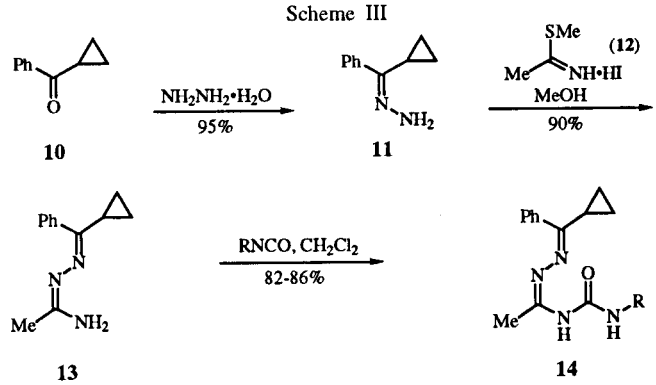


Table 1
Cyclopropyl Phenyl Ketone 1-Ureidoethylidenehydrazones **14**

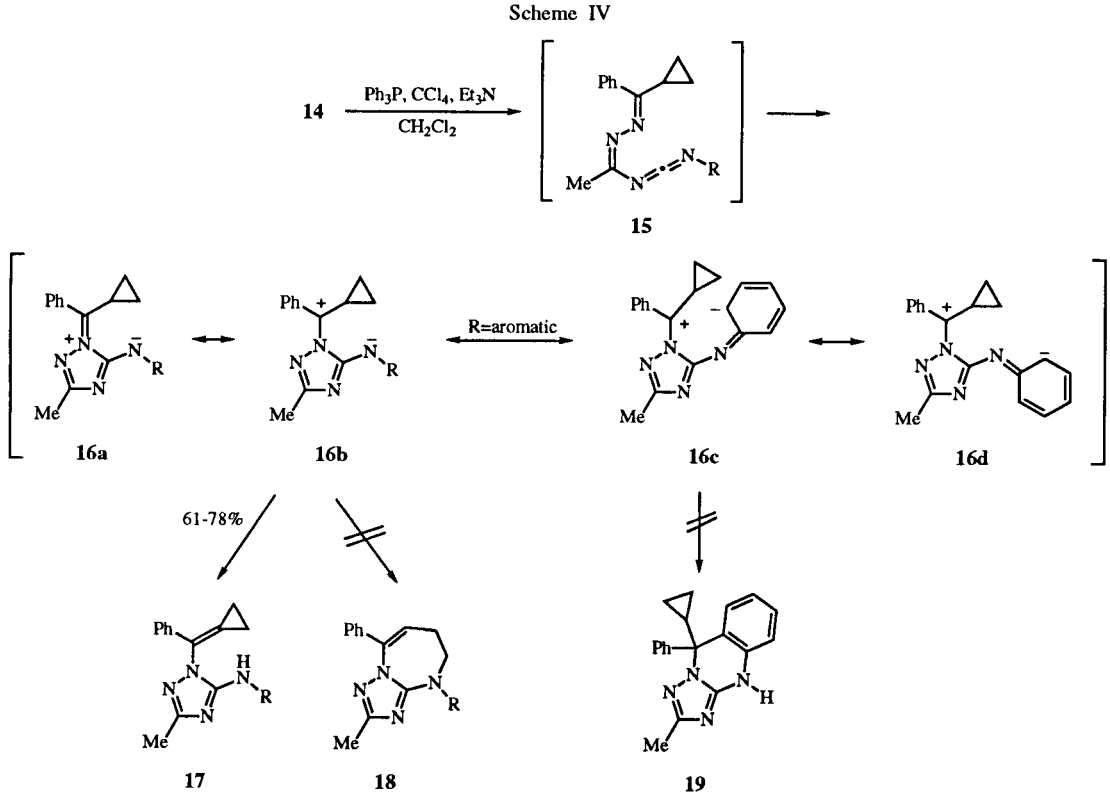
Product No.	R	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
14a	C_6H_5	82	158-159	$C_{19}H_{20}N_4O$	71.23	6.29	17.49
				(320.39)	71.05	6.13	17.27
14b	4-ClC_6H_4	86	178-180	$C_{19}H_{19}ClN_4O$	64.31	5.40	15.79
				(354.84)	64.13	5.29	15.58
14c	2-FC_6H_4	84	166-167	$C_{19}H_{19}FN_4O$	67.44	5.66	16.56
				(338.38)	67.19	5.60	16.29
14d	4-$CH_3OC_6H_4$	86	170-171	$C_{20}H_{22}N_4O_2$	68.55	6.33	15.99
				(350.42)	68.38	6.21	15.80

Table 2
N-α-Styrylcyclopropane-5-phenylamino-1,2,4-triazoles **17**

Product No.	R	Yield (%)	Mp (°C)	Molecular Formula	Analysis (%) Calcd./Found C	H	N
17a	C_6H_5	78	172-173	$C_{19}H_{18}N_4$	75.47	5.60	18.53
				(302.38)	75.70	5.45	18.44
17b	4-ClC_6H_4	68	175-176	$C_{19}H_{17}ClN_4$	67.75	5.09	16.63
				(336.82)	67.91	5.04	16.47
17c	2-FC_6H_4	61	118-119	$C_{19}H_{17}FN_4$	71.23	5.35	17.49
				(320.37)	71.27	5.31	17.41
17d	4-$CH_3OC_6H_4$	70	165-166	$C_{20}H_{20}N_4O$	72.27	6.06	16.86
				(332.40)	72.33	6.06	16.72

temperature to give hydrazone **11** in 95% yield. Hydrazone **11** was treated with *S*-methylthioacetimidate hydroiodide **12** [8] in refluxing methanol followed by neutralization with aqueous sodium hydrogen carbonate

Scheme IV



to give cyclopropyl phenyl ketone 1-aminoethylidenehydrazone **13** in 90% yield. Compound **13** was reacted with an equivalent of isocyanates in dichloromethane at room temperature to afford the desired cyclopropyl

Table 3

1,2,4-Triazole Substituted γ-Butyrolactones **23**

Product No.	R	Yield (%)	Mp (°C)	IR (cm^{-1}) ν [a] C=O/NH	Molecular Formula	Analysis (%) Calcd./Found C	H	N
23a	C_6H_5	83	98-99	1807	$C_{19}H_{18}N_4O_2$	68.25	5.43	16.76
				3427	(334.38)	68.31	5.41	16.65
23b	4-ClC_6H_4	75	83-84	1807	$C_{19}H_{17}ClN_4O_2$	61.88	4.65	15.19
				3422	(368.82)	61.97	4.75	14.94
23c	2-FC_6H_4	79	125-126	1807	$C_{19}H_{17}FN_4O_2$	64.76	4.86	15.90
				3427	(352.37)	64.91	4.99	15.61
23d	4-$CH_3OC_6H_4$	70	64-65	1807	$C_{20}H_{20}N_4O_3$	65.92	5.53	15.38
				3396	(364.40)	66.01	5.49	15.14

[a] Determined by using potassium bromide pellets.

Table 4

^{1}H NMR Data of Compounds **14** [a], **17** [b] and **23** [b]

14a 0.58 (m, 2H, cyclopropyl), 0.97 (m, 2H, cyclopropyl), 2.22 (br s, 4H, CH_3 and cyclopropyl), 7.07-7.70 (m, 10H, phenyl), 9.63 (s, 1H, NH), 11.76 (s, 1H, NH)

14b 0.57 (m, 2H, cyclopropyl), 0.96 (m, 2H, cyclopropyl), 2.20 (s, 3H, CH_3), 2.21 (m, 1H, cyclopropyl), 7.25-7.78 (m, 9H, phenyl), 9.65 (s, 1H, NH), 11.84 (s, 1H, NH)

14c 0.53 (m, 2H, cyclopropyl), 0.92 (m, 2H, cyclopropyl), 2.20 (s, 3H, CH_3), 2.20 (m, 1H, cyclopropyl), 7.32-7.60 (m, 8H, phenyl), 8.14 (t, 1H, J = 8.1 Hz, phenyl), 9.76 (s, 1H, NH), 11.70 (s, 1H, NH)

14d 0.55 (m, 2H, cyclopropyl), 0.95 (m, 2H, cyclopropyl), 2.18 (m, 1H, cyclopropyl), 2.20 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.91 (d, 2H, J = 8.8 Hz, phenyl), 7.37-7.40 (m, 5H, phenyl), 7.63-7.65 (m, 2H, phenyl), 9.58 (s, 1H, NH), 11.64 (s, 1H, NH)

17a 1.39 (t, 2H, J = 7.5 and 8.8 Hz, cyclopropyl), 1.76 (t, 2H, J = 7.5 and 8.8 Hz, cyclopropyl), 2.39 (s, 3H, CH_3), 6.09 (s, 1H, NH), 6.97 (t, 1H, J = 7.2 Hz, phenyl), 7.23-7.43 (m, 9H, phenyl)

17b 1.41 (t, 2H, J = 7.7 and 8.9 Hz, cyclopropyl), 1.79 (t, 2H, J = 7.6 and 9.0 Hz, cyclopropyl), 2.40 (s, 3H, CH_3), 5.99 (s, 1H, NH), 7.22-7.40 (m, 9H, phenyl)

17c 1.46 (t, 2H, J = 7.9 and 8.8 Hz, cyclopropyl), 1.81 (t, 2H, J = 7.8 and 8.9 Hz, cyclopropyl), 2.43 (s, 3H, CH_3), 6.38 (s, 1H, NH), 6.91-7.45 (m, 8H, phenyl), 8.42 (t, 1H, J = 8.2 Hz, phenyl)

17d 1.42 (t, 2H, J = 7.7 and 8.9 Hz, cyclopropyl), 1.78 (t, 2H, J = 7.7 and 8.8 Hz, cyclopropyl), 2.38 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 5.85 (s, 1H, NH), 6.84 (d, 2H, J = 9.0 Hz, phenyl), 7.30-7.45 (m, 7H, phenyl)

23a 2.36 (s, 3H, CH_3), 2.41-2.52 (m, AA'BB', 1H, CH), 2.70-2.79 (m, AA'BB', 1H, CH), 2.98-3.11 (m, AA'BB', 1H, CH), 3.87-3.95 (m, AA'BB', 1H, CH), 6.21 (s, 1H, NH), 6.91-6.96 (m, 1H, phenyl), 7.17-7.44 (m, 9H, phenyl)

23b 2.35 (s, 3H, CH_3), 2.42-2.53 (m, AA'BB', 1H, CH), 2.72-2.81 (m, AA'BB', 1H, CH), 2.98-3.11 (m, AA'BB', 1H, CH), 3.88-3.95 (m, AA'BB', 1H, CH), 6.21 (s, 1H, NH), 7.16-7.44 (m, 9H, phenyl)

23c 2.37 (s, 3H, CH_3), 2.42-2.53 (m, AA'BB', 1H, CH), 2.71-2.80 (m, AA'BB', 1H, CH), 3.01-3.11 (m, AA'BB', 1H, CH), 3.88-3.96 (m, AA'BB', 1H, CH), 6.54 (s, 1H, NH), 6.84-6.96 (m, 2H, phenyl), 7.06 (t, 1H, J = 7.8 Hz, phenyl), 7.41-7.47 (m, 5H, phenyl), 8.20 (t, 1H, J = 7.8 Hz, phenyl)

23d 2.33 (s, 3H, CH_3), 2.40-2.51 (m, AA'BB', 1H, CH), 2.70-2.79 (m, AA'BB', 1H, CH), 2.99- 3.11 (m, AA'BB', 1H, CH), 3.72 (s, 3H, OCH_3), 3.85-3.94 (m, AA'BB', 1H, CH), 6.03 (s, 1H, NH), 6.76 (d, 2H, J = 7.7 Hz, phenyl), 7.09 (d, 2H, J = 8.2 Hz, phenyl), 7.35-7.43 (m, 5H, phenyl)

[a] Dimethyl-d_6 sulfoxide. [b] Deuteriochloroform.

Table 5

^{13}C NMR Data [a] of Compounds **17** and **23**

17a	2.9,5.9, 14.6, 117.5, 122.2, 125.1, 125,2, 125.8, 128.7, 128.8, 129.2, 134.9, 139.2, 151.6, 158.8
17b	2.9, 6.0, 14.6, 118.7, 125.0, 125.4, 125.8, 127.1, 128.8, 128.9, 129.1, 134.7, 137.8, 151.3, 158.7
17c	3.1, 5.8, 14.5, 114.5 (d), 118.7, 121.9 (d), 124.4, 124.8 (d), 125.1, 126.0, 127.7, 128.8, 134.8, 149.9, 150.9, 153.1, 158.7
17d	2.9, 5.5, 14.5, 55.5, 114.4, 120.1, 125.0, 125.1, 125.8, 128.6, 128.8, 132.4, 134.9, 152.4, 155.4, 158.6
23a	15.1, 29.6, 37.1, 97.0, 118.6, 123.0, 125.1, 129.5, 130.1, 130.5, 139.2, 139.3, 152.9, 158.3, 175.3
23b	15.1, 29.7, 37.2, 96.4, 119.9, 125.1, 128.0, 129.6, 130.2, 130.7, 138.0, 139.1, 152.7, 158.4, 175.4
23c	15.0, 29.6, 37.1, 96.8, 115.1 (d), 119.6, 122.7 (d), 125.0, 127.9 (d), 130.2, 130.5, 138.8, 150.5, 152.1, 153.8, 158.3, 175.3
23d	15.1, 29.7, 37.2, 56.1, 97.0, 114.8, 121.3, 125.1, 130.0, 130.4, 132.5, 139.2, 153.8, 156.1, 158.3, 175.5

[a] Deuteriochloroform.

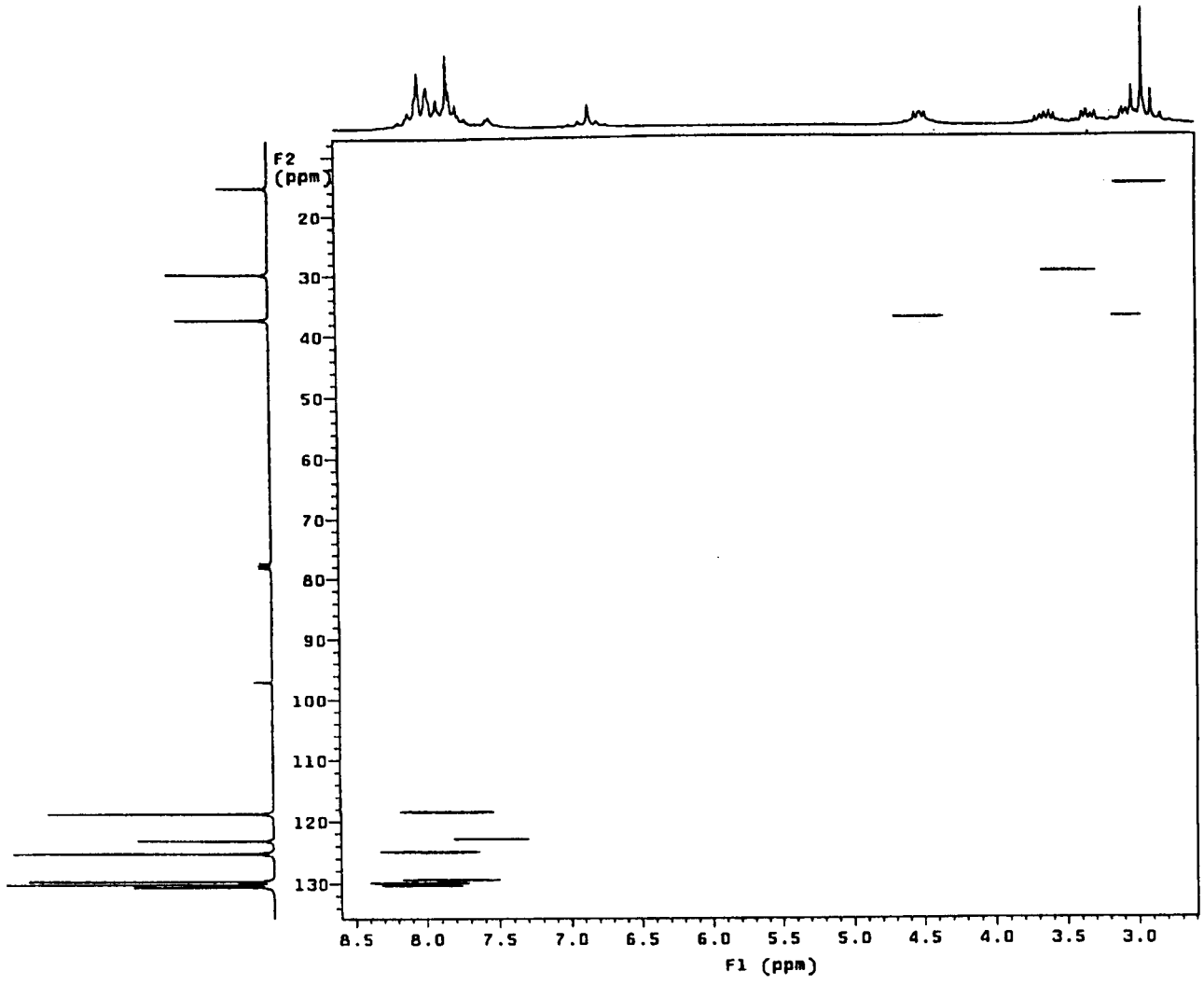


Figure 1. ^{1}H-^{13}C HETCOR nmr spectrum of **23a**. The ^{1}H nmr spectrum is shown in horizontal and the ^{13}C nmr spectrum is shown in vertical.

phenyl ketone 1-ureidoethylidenehydrazones **14** in 82-86% yields (Table 1).

We anticipated on the basis of the literature work [6,7] that the intramolecular cycloaddition reaction of azinocarbodiimides **15**, which were readily obtainable from the azinoureas **14** in Appel's conditions, could give the resonance stabilized zwitterionic intermediates **16a-d**. Proton abstraction, or cyclopropane ring opening by the exocyclic nitrogen atom in resonance form **16b** could produce **17**, or **18**, while addition of the anion in the *ortho* position to the carbocation in resonance form **16c** and rearomatization could yield **19**. However, when azinoureas **14** were treated with Appel's reagent in refluxing dichloromethane, the only product obtained was the *N*-α-styrylcyclopropane-5-phenylamino-1,2,4-triazoles **17** in 61-78% yields (Table 2), neither 4*H*-5,6-dihydro-1,2,4-triazolo[2,3-*a*][1,3]diazepines **18** nor 5,10-dihydro-1,2,4-triazolo[5,1-*b*]quinazolines **19** (Scheme IV).

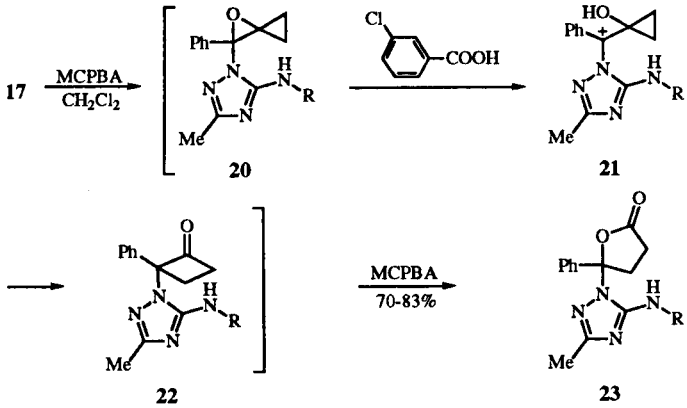
In an attempt to make oxaspiropentanes **20** by the oxidation of **17** using three equivalents of 3-chloroperoxybenzoic acid in dichloromethane, the only product obtained was the γ-butyrolactones **23** in 70-83% yields (Table 3). Using one equivalent of 3-chloroperoxybenzoic acid in the reaction of **17a**, γ-butyrolactone **23a** was obtained in 21% yield again, and 43% yield of unchanged *N*-α-styrylcyclopropanetriazole **17a** was recovered.

A plausible mechanism for the transformation of **17** into **23** is shown in Scheme V. Under epoxidation conditions, *N*-α-styrylcyclopropanetriazoles **17** reacted with 3-chloroperoxybenzoic acid to give oxaspiropentanes **20**, and subsequently rearranged to the cyclobutanones **22** by the resulting 3-chlorobenzoic acid [9], and further oxidized to the γ-butyrolactones **23** by the Baeyer-Villiger oxidation [10].

Determination of the structure of lactones **23** was accomplished on the basis of microanalyses and spectral data. The

infrared spectra of **23** showed strong absorptions at 1807 cm^{-1} and 3396-3427 cm^{-1} due to the carbonyl group and secondary amino group. In the ^{13}C nmr spectra, the signal of the lactone carbonyl was characteristically found at δ = 175.3-175.5 and the other signals of the carbons were in good agreement with previous reported values [4]. In the ^1H nmr spectra, the characteristic chemical shift of the NH was found at δ = 6.03-6.54, and four methylene protons of lactone moiety were observed as four multiplets (AA'BB' system), respectively. Interestingly, the chemical shift of two α-hydrogens of lactones were shown at δ = 2.40-2.53 and 3.85-3.96, and proved to be correlated to the α-carbon atom (δ = 37.1 ppm) by the two dimensional carbon-proton heteronuclear correlation spectroscopy (HETCOR) of **23a** (Figure 1).

Scheme V



We have thus worked out a simple method for the synthesis of *N*-α-styrylcyclopropane substituted 1,2,4-triazoles **17** from azinoureas **14** using Appel's dehydration conditions and for the synthesis of 1,2,4-triazole substituted γ-butyrolactones **23** simply by oxidation of **17** using excess 3-chloroperoxybenzoic acid.

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 was prepared following the literature procedure [8]. Cyclopropyl phenyl ketone, 3-chloroperoxybenzoic acid, and isocyanates were purchased from Aldrich Chemical Company.

Cyclopropyl Phenyl Ketone Hydrazone **11**.

A solution of 2.19 g (15 mmoles) of cyclopropyl phenyl ketone (**10**) 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 2.28 g (95%) of **11**, mp 57-58°; ^1H nmr (deuteriochloroform): δ 0.58 (m, 2 H, CH_2), 1.06 (m, 2 H, CH_2), 1.54 (m, 1 H, CH), 5.88 (br s, 2 H, NH_2), 7.24-7.35 (m, 3 H, phenyl), 7.65-7.68 (m, 2 H, phenyl).

Anal. Calcd. for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.91; H, 7.62; N, 17.35.

Cyclopropyl Phenyl Ketone 1-Aminoethylidenehydrazone **13**.

To a solution of cyclopropyl phenyl ketone hydrazone (**11**, 2.40 g, 15 mmoles) in 40 ml of methanol was added *S*-methylthioacetimidate hydroiodide (**12**, 3.26 g, 15 mmoles) and this solution was stirred at reflux temperature for 10 minutes. 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 to give 2.53 g (90%) of **13** as an oil, ^1H nmr (deuteriochloroform): δ 0.69 (m, 2 H, CH_2), 0.92 (m, 2 H, CH_2), 2.07 (s, 3 H, CH_3), 2.51 (m, 1 H, CH), 5.15 (br s, 2 H, NH_2), 7.32-7.40 (m, 5 H, phenyl).

Anal. Calcd. for $C_{12}H_{15}N_2$: C, 76.97; H, 8.07; N, 14.96. Found: C, 77.15; H, 8.11; N, 14.68.

Cyclopropyl Phenyl Ketone 1-Ureidoethylidenehydrazones **14**. General Procedure.

To a stirred solution of aminoethylidenehydrazone (**13**, 1.87 g, 10 mmoles) in 20 ml of dichloromethane was added isocyanates (10 mmoles) at room temperature. The white solid was precipitated as soon as addition was completed. After stirring for 20 minutes at ambient temperature, the precipitated solid was separated by filtration, washed with petroleum ether-hexane to give **14**.

The physical and spectral data of **14** prepared by this general method are listed in Table 1, Table 4, and Table 5.

N-α-Styrylcyclopropane-5-phenylamino-1,2,4-triazoles **17**. General Procedure.

To a stirred solution of the appropriate urea **14** (3 mmoles) in 30 ml of dichloromethane was added triphenylphosphine (1.18 g, 4.5 mmoles), carbon tetrachloride (1.16 ml, 12 mmoles), and triethylamine (0.63 ml, 4.5 mmoles) and the mixture was heated to reflux temperature. After 1 hour, the same amount of triphenylphosphine, carbon tetrachloride, and triethylamine was added once more, and the mixture was refluxed for 2 hours further. After cooling to room temperature the reaction mixture was partitioned between water and dichloromethane (15 ml x 2), and combine each other, and the solvent was removed after drying over magnesium sulfate. The residue was chromatographed on silica gel column and eluted

with hexane-ethyl acetate 5:1 to yield the product **17** as a white solid.

The physical and spectral data of **17** prepared by this general method are listed in Table 2, Table 4, and Table 5.

1,2,4-Triazole Substituted γ-Butyrolactones **23**. General Procedure.

To a solution of the appropriate *N*-α-styrylcyclopropanetriazoles **17** (1.5 mmoles) in 20 ml of dichloromethane was added 3-chloroperoxybenzoic acid (0.78 g, 4.5 mmoles) and the mixture was stirred at room temperature for 4 hours. The reaction mixture was poured into saturated aqueous sodium hydrogen carbonate solution and extracted with dichloromethane (20 ml x 2). The combined extracts were dried over anhydrous magnesium sulfate, concentrated to dryness, and crystallized from ethyl ether-petroleum ether to give **23** as a white or yellowish solid **23**.

The physical and spectral data of **23** prepared by this general method are listed in Table 3, Table 4, and Table 5.

Acknowledgements.

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REFERENCES AND NOTES

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[1a] J. Barluenga and F. Palacios, *Org. Prep. Proced. Int.*, **23**, 1 (1991); [b] N. I. Gusar, *Russ. Chem. Rev.*, **60**, 146 (1991); [c] Y. G. Gololobov and L. Kasukin, *Tetrahedron*, **48**, 1353 (1992); [d] S. Eguchi, Y. Matsushita and K. Yamashita, *Org. Prep. Proced. Int.*, **24**, 209 (1992).

[2] K.-J. Lee, S. H. Kim, S. Kim, H. Park, Y. R. Cho, B. Y. Chung and E. E. Schweizer, *Synthesis*, 1057 (1994).

[3] K.-J. Lee, D.-H. Song, D.-J. Kim and S.-W. Park, *J. Heterocyclic Chem.*, **33**, 1877 (1996).

[4] K.-J. Lee, Y.-S. Lee and D.-H. Song, *Bull. Korean Chem. Soc.*, **16**, 1037 (1995).

[5] R. Appel, R. Kleinstück and K. D. Ziehn, *Chem. Ber.*, **104**, 1335 (1971).

[6] E. E. Schweizer and J. E. Hayes, *J. Org. Chem.*, **53**, 5562 (1988).

[7] H.-U. Reißig, Small Ring Compounds in Organic Synthesis III, A. de Meijere, eds, Springer-Verlag, Berlin Heidelberg 1988, p 73.

[8] H. Bredereck, R. Gompper and H. Seiz, *Chem. Ber.*, **90**, 1837 (1957).

[9] B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, **95**, 5321 (1973).

[10] G. R. Krow, Organic Reactions, Vol **43**, L. A. Paquette, ed, John Wiley and Sons, Inc. New York, 1993, p 251.