Synthesis of Pyrazolo-fused Heterocycles by a Tandem Appel's Dehydration/Electrocyclization Methodology

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The hydrazones of benzophenone, benzil, and acetophenone were allowed to react with acetoacetanilide to give azinoamides **18**, and the reaction of **18** with Appel's dehydrathon contiditons (triphenylphosphine/carbon tetrachloride/triethylamine) led to the corresponding azinoketimines **19**, which underwent elctrocyclic ring closure under the reaction conditions to give pyrazolo-fused heterocycles. Azinoamide **18a** gave a 4,9-dihydropyazolo-[5,1-*b*]quinazoine **21**, while **18b** yielded 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-2-one **26** and 1*H*-imidazo[1,2-*b*]-pyrazole **29**. Compound **18c** gave a monocyclic *N*-α-styryl-5-(phenylamino)pyrazole **32**.

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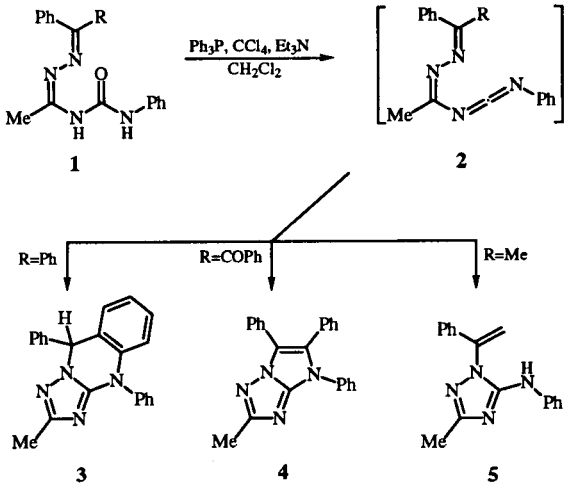
The electrocyclic reaction of conjugated heterocumulenes as a synthetic route to heterocycles [1], prompts us to report our studies. We recently described a new route to 1,2,4-triazole-fused heterocycles such as 5,10-dihydro-1,2,4-triazolo[5,1-*b*]quinazoline **3** [2], 7*H*-imidazo[1,2-*b*]-[1,2,4]triazole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

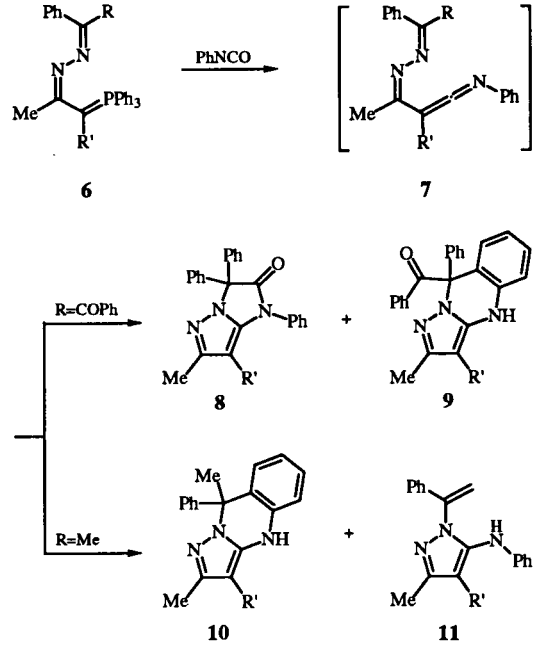
Scheme I



Also, Schweizer and co-workers reported that the thermal rearrangement of azinoketimines **7**, obtained from phosphoranes **6** and an isocyanate could give pyrazolo-fused heterocycles such as 2,3-dihydro-1*H*-imidazo-[1,2-*b*]pyrazol-2-one **8** [6], 4,9-dihydropyrazolo[5,1-*b*]-quinazolines **9** [6] and **10** [7], and the *N*-α-styryl-5-(phenylamino)pyrazole **11** [7] (Scheme II).

However, this method has some drawbacks in that the ylide **6** contains no α-proton to the triphenylphosphonium moiety. This is a necessary condition for the preparation of ketimines from ylides and isocyanates [8], and alkylation of phosphoranes have been reported [9]. The reactions of

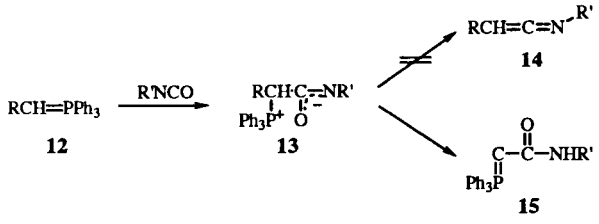
Scheme II



isocyanates with ylides **12** with α-protons give betamines **13** which do not decompose to ketimines **14** but transfer a proton to give stable phosphoranes **15** [10] (Scheme III). Therefore, the ylide **6** (R' = H) must be alkylated in order to acquire a suitable substituted phosphorane to use in the preparation of azinoketimines **7**. But, many ylides **6** when alkylated with a variety of alkylating agents gave predominantly *N*-alkylated products, not the hoped for *C*-alkylated products depending upon R substituent [11].

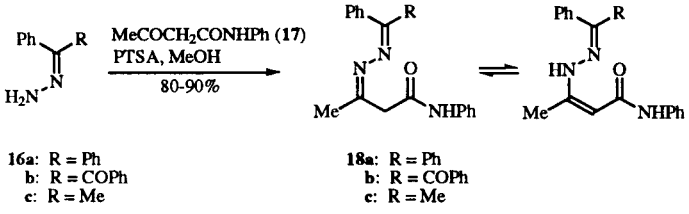
On the other hand, it is well known that ketimines [12] are readily obtained from dehydration of amides with triphenylphosphine dibromide [13], phosphorus pentoxide [14] and dehydrochlorination of imino chlorides [15] produced from amides with phosphorus pentachloride. We now wish to report that azinoketimines, which are obtainable from the corresponding amides in the Appel's dehydration condition, give pyrazolo-fused heterocycles by thermal rearrangement.

Scheme III



The starting compounds, 1-(phenylcarbamoyl)-2-propylidenehydrazones **18** employed in this study, were prepared from condensation of hydrazones **16** with acetoacetanilide (**17**) in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing methanol (Scheme IV). Thin layer chromatography (tlc) showed one spot, however, ^{1}H nmr showed a mixture of imine/enamine structures, and the ratios based on ^{1}H nmr of methyl protons found were 6/4 for the azinoamide **18a**, and 4/6 for **18c**. But azinoamide **18b** existed exclusively as the imine form. Treatment of **18a** with triphenylphosphine, carbon tetrachloride, and triethylamine in refluxing dichloromethane, the only product obtained was

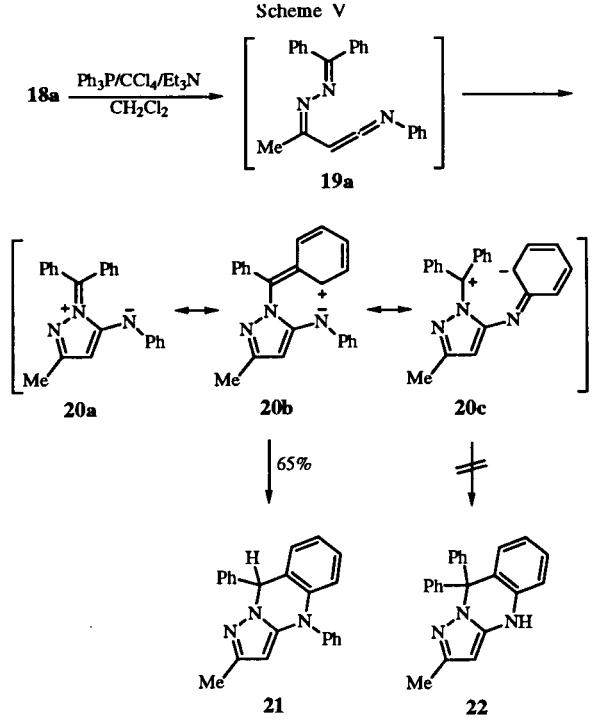
Scheme IV



the 4,9-dihydropyrazolo[5,1-*b*]quinazoline **21** in 65% yield. The proposed mechanism [2] for formation of **21** is shown in Scheme V. The presumed intermediate azinoketimine **19a** was too unstable to isolate, so the thermal reaction of **19a** would give the resonance-stabilized zwitterionic intermediates **20a-c** followed by ring closure and rearomatization to give the product. Presumably unfavorable steric hindrance of resonance form **20c** prohibited production of regioisomer **22**.

On the other hand, the reaction of **18b** under Appel's conditions led to the formation of two products which were separated by column chromatography. The first product was isolated as a white solid and assigned as the 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-2-one **26** (45%) on the basis of the following spectral data [6]. Compound **26** exhibited strong bands at 1737 (γ-lactam C=O), 1598 (C=N) and 1622 cm^{-1} (C=C) in its infrared spectrum. In the ^{13}C nmr spectrum [16] peaks at δ 172.2 (C=O), 152.2 (C7a), 144.1 (C6), 86.7 (C7), and 74.2 ppm (C3) characterized the 2,3-dihydro-1*H*-imidazo[1,2-*b*]pyrazol-2-one **26**. The second product was the 1*H*-imidazo[1,2-*b*]-pyrazole **29** (36%). Compound **29** showed bands at 1594

Scheme V

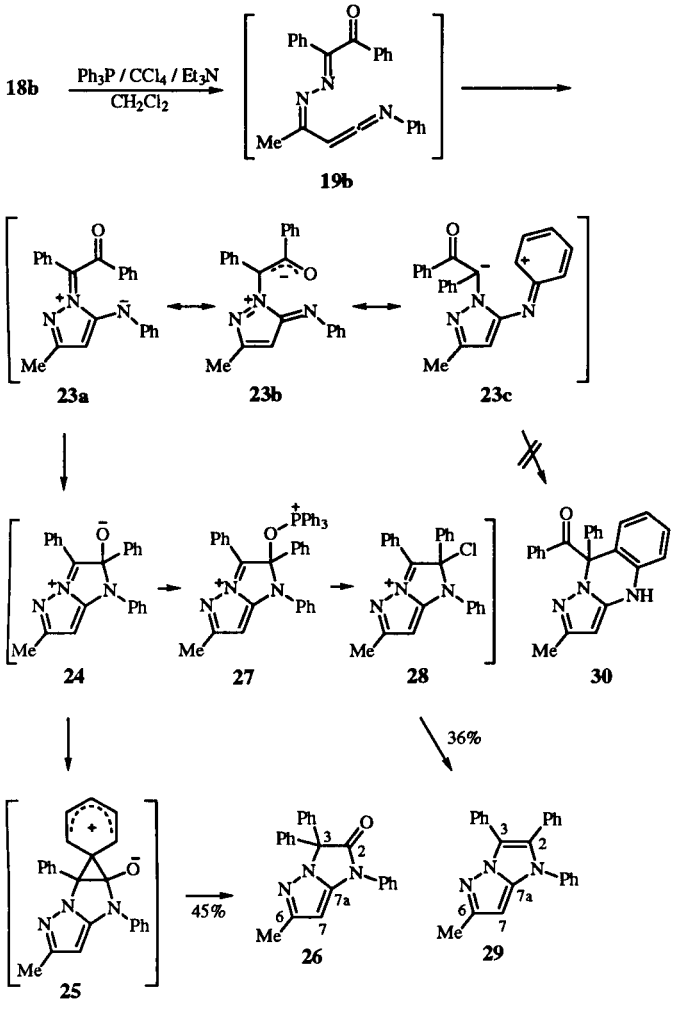


and 1627 cm^{-1} assignable to the C=N and C=C bonds in its infrared spectrum. The ^{13}C nmr spectrum [16] showed peaks at δ 153.3 (C7a), 143.4 (C6), and 80.5 ppm (C7) assignable to the pyrazole ring in addition to the aromatic and methyl peaks.

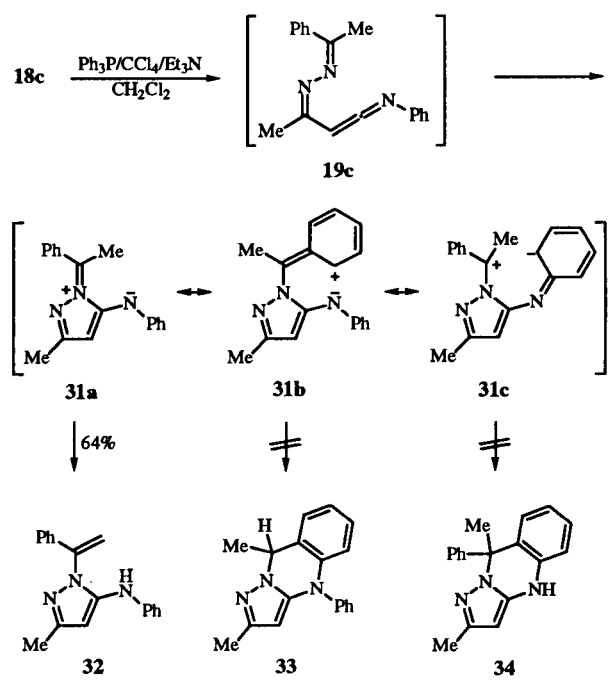
A reasonable mechanism based on the literature for the transformation of **18b** into **26** [6] and **29** [3] is shown in Scheme VI. The thermal reaction of the keto azinoketimine **19b** would give the resonance-stabilized azomethine imine **23a-c**. In **23a**, the exocyclic anionic nitrogen would attack the carbonly group and phenyl migration, *via* phenonium ion **25**, would give compound **26**; while in **24**, the oxy anion might react with chlorotriphenylphosphonium ion to give alkoxyphosphonium ion **27**, which is converted to the chloride **28** by loss of triphenylphosphine oxide and subsequent elimination of chlorine by triphenylphosphine would give compound **29**. However, 4,9-dihydropyrazolo[5,1-*b*]quinazoline **30** as previously reported [6] was not produced in this reaction.

Finally, we have investigated the reaction of **18c** under the Appel's conditions, and the only product obtained was the *N*-α-styryl-5-(phenylamino)pyrazole **32** in 64% yield, but neither the 4,9-dihydropyrazolo[5,1-*b*]quinazolines **33** nor **34**. Compound **32** showed bands at 3249 (NH), and both 1635 and 925 cm^{-1} assignable to the exo double bond [17] in its infrared spectrum. The proposed mechanisim [4,7] for formation of pyrazole **32** is shown in Scheme VII. The thermal reaction of azinoketimine **19c** would give the resonance-stabilized zwitterionic intermediates **31a-c**.

Scheme VI



Scheme VII



Proton abstraction by the exocyclic nitrogen anion in **31a** would produce **32**.

In conclusion, the present method demonstrates that the tandem Appel's dehydration/electrocyclization methodology of azinoamides, complementary to the Wittig/electrocyclic ring closure strategy, provides a new entry to the sysnthesis of pyrazolo-fused heterocycles.

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. The mass spectra were recorded on a Shimadzu model QP-5000 spectrometer with an electron beem energy of 70 eV. 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 acetophenone hydrazone was prepared following the literature procedure [18]. Benzophenone hydrazone, benzil monohydrazone, and acetoacetanilide were purchased from Aldrich Chemical Company.

Benzophenone 1-(Phenylcabamoyl)-2-propylidenehydrazone (**18a**).

A solution of benzophenone hydrazone (**16a**, 0.78 g, 4 mmoles) and acetoacetanilide (**17**, 0.71 g, 4 mmoles) in 20 ml of methanol in the presence of catalytic amount of *p*-toluenesulfonic acid was stirred at reflux temperature for 5 hours. After cooling, the precipitated solid, which gradually separated during the reaction, was filtered, washed with petroleum ether to give 1.28 g (90%) of **18a**, mp 165-167°; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.04 (s, 3 H, CH_3), 2.25 (s, 3 H, CH_3), 3.53 (s, 2 H, CH_2), 4.81 (s, 1 H, CH), 6.89-7.66 (m, 15 H, phenyl), 9.46 (s, 1 H, NH), 11.97 (s, 1 H, NH); ir (potassium bromide): 3323, 1639, 1602, 1533, 1488, 1435, 1309, 1268, 1113 cm^{-1}.

Anal. Calcd. for $C_{23}H_{21}N_3O$: C, 77.72; H, 5.95; N, 11.82. Found: C, 77.58; H, 5.85; N, 11.60.

Benzil 1-(Phenylcabamoyl)-2-propylidenehydrazone (**18b**).

Benzil 1-(phenylcabamoyl)-2-propylidenehydrazone (**18b**) was prepared in 80% yield from benzil monohydrazone (**16b**) for 7 hours by the aforementioned procedure; purification was achieved by recrystallization from ethanol, mp 185-186°; ^1H nmr (dimethyl-d_6 sulfoxide): δ 2.04 (s, 3 H, CH_3), 3.34 (s, 2 H, CH_2), 6.97-7.59 (m, 13 H, phenyl), 7.93-7.96 (m, 2 H, phenyl), 9.76 (s, 1 H, NH); ir (potassium bromide): 3355, 1627, 1537, 1488, 1427, 1349, 1272, 1215, 1174, 1080 cm^{-1}.

Anal. Calcd. for $C_{24}H_{21}N_3O_2$: C, 75.18; H, 5.52; N, 10.96. Found: C, 74.89; H, 5.31; N, 10.72.

Acetophenone 1-(Phenylcabamoyl)-2-propylidenehydrazone (**18c**).

Acetophenone 1-(phenylcabamoyl)-2-propylidenehydrazone (**18c**) was prepared in 84% yield from acetophenone hydrazone (**16c**) for 4 hours by the aformentioned procedure; purification was achieved by chromatography on silica gel column and eluting with hexane-ethyl acetate 5:1, mp 101-103° (ether-petroleum ether); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.07 (s, 3 H, CH_3), 2.28 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 2.33 (s, 3 H, CH_3), 3.51 (s, 2 H, CH_2), 4.67 (s, 1 H, CH), 6.88-7.88 (m, 10 H, phenyl), 9.35 (br s, 1 H, NH), 12.31 (s, 1 H, NH); ir (potassium bromide): 3249, 1631, 1606, 1537, 1492, 1431, 1329, 1264, 1137 cm^{-1}.

Anal. Calcd. for $C_{18}H_{19}N_3O$: C, 73.70; H, 6.53; N, 14.32. Found: C, 73.59; H, 6.51; N, 14.22.

4,9-Dihydro-4,9-diphenyl-2-methylpyrazolo[5,1-*b*]quinazoline (**21**).

To a stirred solution of the azinoamide **18a** (1.06 g, 3.0 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 for 3 hours. 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 6:1 to give 0.66 g (65%) of **21**, mp 128-130°(ether); ^{1}H nmr (deuteriochloroform): δ 2.11 (s, 3 H, CH_3), 5.01 (s, 1 H, CH), 6.45 (m, 1 H, phenyl), 6.56 (s, 1 H, CH), 6.85-7.61 (m, 13 H, phenyl); ^{13}C nmr (deuteriochloroform): δ 149.2, 143.8, 143.3, 140.1, 137.6, 130.5, 129.6, 128.9, 128.6, 128.1, 127.8, 126.7, 121.3, 121.2, 113.8, 87.9, 62.6, 14.1; ir (potassium bromide): 1594, 1566, 1529, 1492, 1451, 1398, 1325 cm^{-1}; ms: m/z 337 (M$^+$,45), 261 (20), 260 (100), 244 (10), 218 (10), 77 (9).

Anal. Calcd. for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68; N, 12.45. Found: C, 81.69; H, 5.73; N, 12.21.

2,3-Dihydro-6-methyl-1,3,3-triphenyl-1*H*-imidazo[1,2-*b*]pyrazol-2-one (**26**) and 6-Methyl-1,2,3-triphenyl-1*H*-imidazo[1,2-*b*]-pyrazole (**29**).

To a stirred solution of the azinoamide **18b** (1.14 g, 3.0 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 for 16 hours. 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 dichloromethane-hexane 4:1 to give 0.49 g (45%) of **26** and 0.38 (36%) of **29** in the order of elution.

Compound **26** had mp 195-196°(ethanol); ^{1}H nmr (deuteriochloroform): δ 2.41 (s, 3 H, CH_3), 5.83 (s, 1 H, CH), 7.34-7.71 (m, 15 H, phenyl); ^{13}C nmr (deuteriochloroform): δ 172.2 , 152.2, 144.1, 138.4, 129.8, 129.5, 128.7, 128.2, 127.8, 127.4, 122.6, 86.7, 74.2, 14.9; ir (potassium bromide): 1737, 1622, 1598, 1570, 1499, 1447, 1344, 1166, 1126 cm^{-1}; ms: m/z 365 (M$^+$,46), 336 (100), 260 (11), 165 (31), 77 (47).

Anal. Calcd. for $C_{24}H_{19}N_3O$: C, 78.88; H, 5.24; N, 11.50. Found: C, 78.69; H, 5.14; N, 11.22.

Compound **29** had mp 158-159°(ethanol-ether); ^{1}H nmr (deuteriochloroform): δ 2.47 (s, 3 H, CH_3), 5.69 (s, 1 H, CH), 7.13-7.34 (m, 13 H, phenyl), 7.68-7.72 (m, 2 H, phenyl); ^{13}C nmr (deuteriochloroform): δ 153.3, 143.4, 138.0, 131.7, 130.0, 129.8, 129.3, 129.2, 129.1, 128.9, 128.2, 127.2, 125.7, 121.0, 117.2, 80.5, 15.7; ir (potassium bromide): 1627, 1594, 1566, 1496, 1451, 1329, 1133 cm^{-1}; ms: m/z 349 (M$^+$,100), 348 (28), 308 (15), 307 (32), 207 (9), 77 (25).

Anal. Calcd. for $C_{24}H_{19}N_3$: C, 82.49; H, 5.48; N, 12.03. Found: C, 82.34; H, 5.39; N, 11.82.

3-Methyl-*N*-α-styryl-5-(phenylamino)pyrazole (**32**).

To a stirred solution of the azinoamide **18c** (0.88 g, 3.0 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 for 2 hours. 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 give 0.53 g (64%) of **32**, mp 124-126° (ether-petroleum ether); ^{1}H nmr (deuteriochloroform): δ 2.30 (s, 3 H, CH_3), 5.31 (br s, 1 H, NH), 5.49 (s, 1 H, vinyl), 5.68 (s, 1 H, vinyl), 5.94 (s, 1 H, CH), 6.79-6.90 (m, 3 H, phenyl), 7.17-7.36 (m, 7 H, phenyl); ^{13}C nmr (deuteriochloroform): δ 149.3, 143.9, 142.5, 142.4, 135.9, 129.3, 128.8, 126.5, 126.4, 120.9, 116.1, 111.6, 94.3, 14.3; ir (potassium bromide): 3249, 1635, 1610, 1553, 1500, 1455, 1268, 1023, 925 cm^{-1}; ms: m/z 275 (M$^+$,54), 274 (100), 77 (26).

Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.52; H, 6.22; N, 15.26. Found: C, 78.38; H, 6.11; N, 15.09.

Acknowledgements.

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REFERENCES AND NOTES

* Author to whom correspondence should be addressed.

[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).

[4a] K.-J. Lee, Y.-S. Lee and D.-H. Song, *Bull. Korean Chem. Soc.*, **16**, 1037 (1995); [b] K.-J. Lee and D.-W. Kim, *J. Heterocyclic Chem.*, **34** (1997), in press.

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

[6] E. E. Schweizer and K.-J. Lee, *J. Org. Chem.*, **49**, 1964 (1984).

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

[8] H. Staudinger and J. Meyer, *Chem. Ber.*, **53**, 72 (1920).

[9a] G. Wittig and M. Rieber, *Liebigs Ann. Chem.*, **562**, 177 (1949); [b] H. J. Bestmann, E. Vilsmaier and G. Graf, *Liebigs Ann. Chem.*, **704**, 109 (1967).

[10] S. Trippett and D. M. Walker, *J. Chem. Soc.*, 3874 (1959).

[11] J. C. Boring, M. S. Thesis, University of Delaware, Newark, DE, June, 1984.

[12] For a review on synthesis and reactions of ketimines, see: G. R. Krow, *Angew. Chem.*, **83**, 455 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 435 (1971).

[13a] H. J. Bestmann, J. Lienert and L. Mott, *Liebigs Ann. Chem.*, **718**, 24 (1968); [b] T. Aoyama, T. Nakano, K. Marumo, Y. Uno and T. Shioiri, *Synthesis*, 1163 (1991).

[14] C. L. Stevens and G. H. Singhal, *J. Org. Chem.*, **29**, 34 (1964).

[15] C. L. Stevens and J. C. French, *J. Am. Chem. Soc.*, **76**, 4398 (1954).

[16] The numbering systems are shown in Scheme VI.

[17] D. L. Pavia, G. M. Lampman and G. S. Kriz, Jr., Introduction to Spectroscopy, W. B. Saunders Company, Philadelphia, PA, 1979, p 36.

[18] G. Lock and K. Stach, *Chem. Ber.*, **77B**, 293 (1944).