Reaction of Hydrazonyl Chlorides and Carboalkoxymethylene Triphenylphosphoranes to Give 5-Alkoxy Substituted Pyrazoles

Albert Padwa* and J. Gavin MacDonald

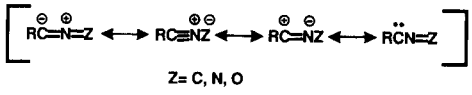
Department of Chemistry, Emory University,
Atlanta, Georgia 30322

Received January 30, 1987

The reaction of ethyl chloroglyoxylate phenyl hydrazone and diphenyl hydrazonyl chloride with several carboalkoxymethylene triphenylphosphoranes has been examined. The products isolated correspond to *N*-phenyl-3-carboalkoxy-5-alkoxy substituted pyrazoles. The mechanism advanced to account for the formation of the products involves the stepwise addition of a nitrile imine intermediate with the Wittig reagent.

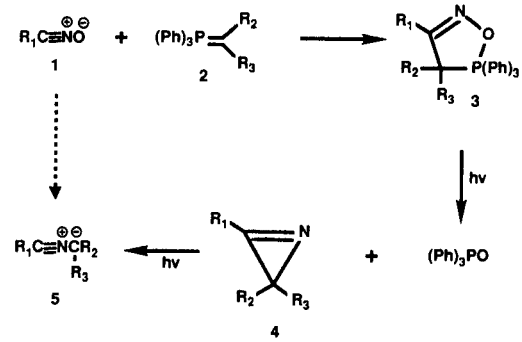
J. Heterocyclic Chem., **24**, 1225 (1987).

The widespread use of the 1,3-dipolar cycloaddition reaction stems in part from the frequent need to synthesize five-membered heterocyclic rings and the customarily high efficiency of such cycloadditions [1]. 1,3-Dipoles can be classified into two major types: (1) those with internal octet stabilization, where a mesomeric formula can be drawn such that the central atom of the dipole has a positive charge and all centers have completely filled valences and (2) those without internal octet stabilization where each mesomeric form has an electron sextet [2]. By far the more common group of dipoles is the former, mainly because the dipoles in the second group are all unstable and must be prepared *in situ*. In recent years our interest has focused on the chemistry of the octet stabilized class of dipoles known as the nitrilium betaines [3]. This class of 1,3-dipoles always contain nitrogen as the middle atom since only this element can supply an unshared electron pair while in the trivalent neutral state. Among the possible geometric forms of a nitrilium betaine, a carbene structure can can be envisaged which makes conceivable a 1,1-cycloaddition of this class of 1,3-dipoles [4]. Results



from our laboratory have shown that there are two pathways by which nitrilium betaines can react with multiple π bonds [5-9]. The most frequently encountered path involves a "parallel plane approach of addends" and can be considered to be an orbital symmetry-allowed [4+2] concerted process. The other path, designated as 1,1-cycloaddition, operates only in certain intramolecular cases. It occurs when the orbitals of the dipolarophile have been deliberately constrained to attack perpendicular to the nitrile ylide plane.

Nitrile ylides are a long known and thoroughly investigated member of the nitrilium betaine family [10]. This class of dipoles has traditionally been prepared by (a) treatment of imidoyl halides with base [11], (2) photolysis of carbene precursors in nitrile solvents [12], (3) desilylation of silyl substituted thioimidates [13] and (4) photolysis of aryl-substituted azirines [14,15]. One of the more interesting methods for generating nitrile ylides involves the photochemical elimination of phosphoric acid esters from 4,5-dihydro-1,3,5-oxazaphospholes **3** [16]. This reaction proceeds *via* the initial formation of a 2*H*-azirine intermediate **4** which is further converted to the nitrile ylide **5** by a photochemical cleavage reaction [17]. The overall process represents a novel conversion of one dipole into another.

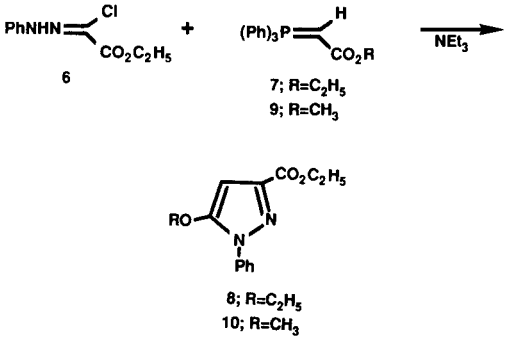


In searching for new routes to interconvert 1,3-dipoles, we became interested in studying the reaction of Wittig reagents with hydrazonyl chlorides. By analogy to the results encountered with nitrile oxides, we hoped that the reaction of a nitrile imine with a Wittig reagent would generate a 1,3-diazophosphole. Elimination of triphenyl phosphine oxide was expected to proceed analogously to the results encountered in the oxygen series and produce a nitrile ylide intermediate. This would then constitute a method for converting nitrile imines into nitrile ylides.

Results and Discussion.

As our first model we chose to investigate the reaction of the nitrile imine derived from ethyl chloroglyoxylate phenylhydrazone (**6**) with carboethoxymethylene triphenylphosphorane (**7**). In contrast to the reaction of nitrile oxides with methylene triphenylphosphoranes, no signs of a phosphorous adduct could be detected in this reaction. Instead, the only material isolated (84%) was identified as *N*-phenyl-3-carboethoxy-5-ethoxypyrazole (**8**), mp 86-87°;

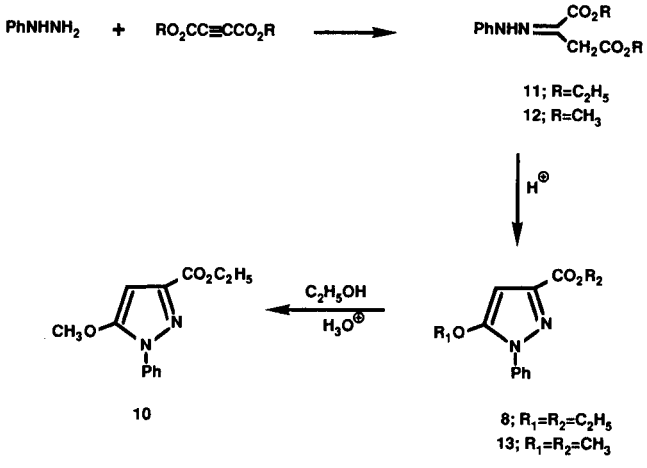
nmr (deuteriochloroform, 90 MHz): δ 1.48 (t, 3H, J = 6.0 Hz), 1.51 (t, 3H, J = 6.0 Hz), 4.26 (q, 2H, J = 6.0 Hz), 4.49 (q, 2H, J = 6.0 Hz), 6.25 (s, 1H) and 7.3-7.9 (m, 5H). Structure **8** was verified by an independent synthesis which



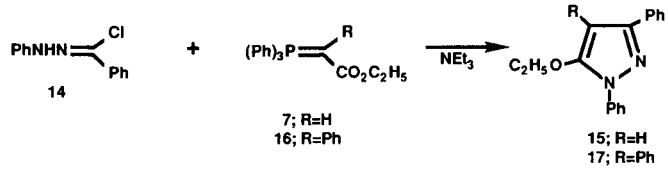
involved the treatment of diethyl acetylenedicarboxylate with phenylhydrazine. The conjugate addition product **11** was subjected to an acid induced cyclization reaction to give pyrazole **8**.

In order to provide some information regarding the mechanism of the reaction, we needed to distinguish between the two carboethoxy groups on the pyrazole ring. This was accomplished by studying the reaction of the closely related carbomethoxymethylene triphenylphosphorane **9** with the nitrile imine derived from **6**. The only product obtained from this reaction was identified as *N*-phenyl-3-carbomethoxy-5-methoxypyrazole (**10**). The structure of this material was assigned on the basis of its spectral properties and by comparison with an independently synthesized sample. The cyclized pyrazole **13** derived from the reaction of phenyl hydrazine and dimethyl acetylenedicarboxylate was converted to **10** by the hydrolysis-esterification sequence outlined in Scheme I.

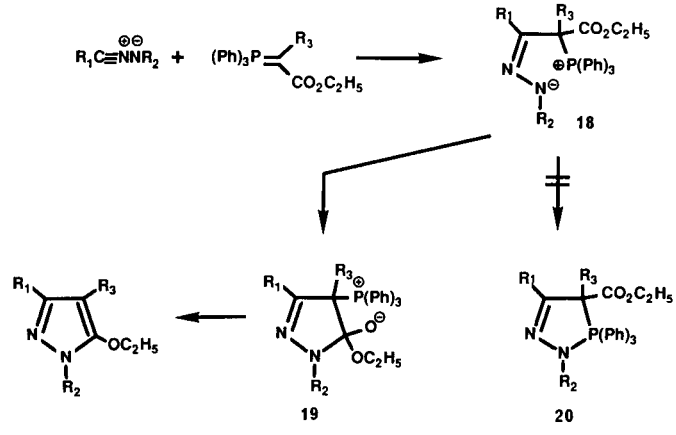
Scheme I



Attention was next turned to the reaction of diphenylhydrazonyl chloride (**14**) and carboethoxymethylene triphenylphosphorane (**7**). The major product isolated in 88% yield was identified as 1,3-diphenyl-5-ethoxypyrazole (**15**) on the basis of its spectroscopic data (see Experimental Section). A similar reaction occurred when **14** was treated with phenyl carboethoxymethylene triphenylphosphorane (**16**) in the presence of triethyl amine. The only product isolated here was pyrazole **17** in 90% isolated yield. Attempts to obtain other pyrazoles from the reaction of hydrazonyl chlorides **6** or **14** with a series of nonstabilized methylene phosphoranes failed.



All of the above reactions can be rationalized in terms of a mechanism which involves the stepwise attack of the phosphorane onto the intially generated nitrile imine intermediate. The hydrazonyl anion portion of the resulting zwitterion ion **18** attacks the adjacent carbonyl group



to give intermediate **19**. This is followed by elimination of triphenylphosphine oxide and generation of the pyrazole ring. The reason why zwitterion **18** does not collapse to produce diazophosphole **20** is presumably related to the weakness of the developing nitrogen-phosphorus bond.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin Elmer Model 283 infrared spectrometer. Proton nmr spectra were obtained on a Varian EM-390 and Jeol 100-MHz spectrometer. The ^{13}C-nmr spectra were recorded on an IBM-200 MHz spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, Ga. Mass spectra were determined with a Finnegan 4000 mass spectrometer at an ionizing voltage of 70 eV.

Treatment of Carboethoxy (**7**) and Carbomethoxymethylene Triphenylphosphorane (**9**) with Ethyl Chloroglyoxylate Phenylhydrazone (**6**) in the Presence of Triethylamine.

To a stirred solution containing 1.5 mmoles of carbomethoxymethylene triphenylphosphorane (**9**) and 1.5 mmoles of ethyl chloroglyoxylate phenylhydrazone (**6**) in 30 ml of benzene at 25° was added 1 ml of triethylamine and the solution was allowed to stir for 6 hours. Filtration of the reaction mixture followed by evaporation of the solvent gave a light yellow oil which was subjected to silica gel chromatography using a 10% ethyl acetate in hexane as the eluent. The major fraction contained a crystalline solid which was recrystallized from ether-hexane mixture to give a 93% yield of *N*-phenyl-3-carboethoxy-5-methoxypyrazole (**10**) as a white solid, mp 58-59°; ir (potassium bromide): 3080, 3030, 3000, 2950, 1722, 1600, 1570, 1510, 1460, 1425, 1235, 1165, 1110, 1050, 1030, 990, 765, 700 and 670 cm^{-1}; nmr (deuteriochloroform, 90 MHz): δ 1.40 (t, 3H, J = 6.0 Hz), 4.00 (s, 3H), 4.34 (q, 2H, J = 6.0 Hz), 6.20 (s, 1H) and 7.3-7.8 (m, 5H).

Anal., Calcd. for $C_{13}H_{14}N_2O_3$: 63.40; H, 5.73; N, 11.38. Found: C, 63.39; H, 5.74; N, 11.38.

An authentic sample of **10** was prepared by the following method. To an ether solution (50 ml) containing 1.3 g of dimethyl acetylenedicarboxylate was slowly added 1.00 g of phenylhydrazine in 10 ml of ether [18]. The mixture was stirred for 1 hour at 25° and the solvent was then removed under reduced pressure. The yellow solid (**12**) that remained was taken up in 25 ml of tetrahydrofuran and the mixture was heated at reflux for 1 hour after the addition of several drops of concentrated hydrochloric acid. Removal of the solvent left a yellow oil which was purified by silica gel chromatography using a 4:1 hexane-ether mixture as the eluent to give 0.86 g (92%) of a crystalline solid, mp 75-76°, whose structure was assigned as methyl 5-methoxy-*N*-phenylpyrazole-3-carboxylate (**8**). This material was saponified to the corresponding carboxylic acid by heating in a basic aqueous methanol solution. The resulting carboxylic acid was taken up in ethanol and heated with a trace of concentrated hydrochloric acid to give *N*-phenyl-3-carboethoxy-5-methoxypyrazole (**10**), mp 58-59°, which was identical in every detail with the reaction of Wittig reagent **9** and the hydrazonyl chloride **6**.

A similar set of reaction conditions were used to prepare *N*-phenyl-3-carboethoxy-5-ethoxypyrazole (**8**) in 84% yield, mp 86-87°; ir (potassium bromide): 3080, 3030, 2990, 2950, 2900, 1735, 1600, 1570, 1510, 1460, 1405, 1240, 1160, 1040, 905, 775 and 700 cm^{-1}; nmr (deuteriochloroform, 90 MHz): δ 1.48 (t, 3H, J = 6.0 Hz), 1.51 (t, 3H, J = 6.0 Hz), 4.26 (q, 2H, J = 6.0 Hz), 4.49 (q, 2H, J = 6.0 Hz), 6.25 (s, 1H) and 7.3-7.9 (m, 5H).

Anal., Calcd. $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.63; H, 6.22; N, 10.76.

An authentic sample of this material was prepared by treating diethyl acetylenedicarboxylate with phenylhydrazine and then subjecting the resulting adduct **11** to an acid catalyzed cyclization using the method described for the preparation of pyrazole **13**.

Treatment of Diphenyl Hydrazonyl Chloride (**14**) with Carboethoxymethylene Triphenylphosphorane (**7**) in the Presence of Triethylamine.

To a stirred mixture containing 1.5 mmoles of carboethoxymethylene triphenylphosphorane **7** and 1.5 mmoles of diphenyl hydrazonyl chloride (**14**) in 30 ml of benzene at 25° was added 1 ml of triethylamine. The solution was allowed to stir for 6 hours and was filtered. The residue which was obtained on removal of the solvent was purified by silica gel chromatography to give 1,3-diphenyl-5-ethoxypyrazole (**15**) in 88% yield; ir (potassium bromide): 3070, 3040, 2990, 2940, 2910, 1600, 1565, 1500, 1450, 1400, 1300, 1250, 1155, 1100, 1045, 835, 750 and 700 cm^{-1}; nmr (deuteriochloroform, 90 MHz): δ 1.50 (t, 3H, J = 6.0 Hz), 4.26 (q, 2H, J = 6.0 Hz), 6.00 (s, 1H) and 7.2-7.8 (m, 10H).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.18; H, 6.09; N, 10.62.

Treatment of Dihenyl Hydrazonyl Chloride (**14**) with Phenyl Carboethoxymethylene Triphenylphosphorane (**16**) in the Presence of Triethylamine.

To a stirred solution containing 1.5 mmoles of diphenyl hydrazonyl chloride (**14**) and 1.5 mmoles of carboethoxymethylene triphenylphosphorane (**16**) in 30 ml of benzene at 25° was added 1 ml of triethylamine. The solution was allowed to stir for 6 hours and was filtered. The residue obtained upon removal of the solvent under reduced pressure was subjected to silica gel chromatography. The major fraction contained a white crystalline solid, mp 141-142° (90% yield), whose structure was assigned as 1,3,4-triphenyl-5-ethoxypyrazole (**17**); ir (potassium bromide): 3070, 3030, 2990, 2940, 1600, 1490, 1440, 1370, 1320, 1240, 1200, 1100, 1000, 975, 755 and 700 cm^{-1}; nmr (deuteriochloroform, 90 MHz) δ 0.85 (t, 3H, J = 6.0 Hz), 3.93 (q, 2H, J = 6.0 Hz) and 7.0-7.8 (m, 15H).

Anal. Calcd. for $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92; N, 8.23. Found: C, 81.10; H, 5.90; N, 8.22.

Acknowledgement.

We wish to thank the National Cancer Institute, DHEW, for generous support of this work. Aid in the purchase of the nmr spectrometer used in this work was provided by the NSF *via* an equipment grant.

REFERENCES AND NOTES

[1] A. Padwa, "1,3-Dipolar Cycloaddition Chemistry", Wiley-Interscience, New York, Vol **1** and **2**, 1984.

[2] R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1973).

[3] A. Padwa, *Acc. Chem. Res.*, **9**, 371 (1976).

[4] R. Huisgen, R. Sustmann and K. Bunge, *Chem. Ber.*, **105**, 1324 (1972).

[5] A. Padwa and P. H. J. Carlsen, *J. Am. Chem. Soc.*, **97**, 3682 (1975).

[6] A. Padwa, A. Ku, A. Mazzu and S. I. Wetmore, *J. Am. Chem. Soc.*, **98**, 1048 (1976).

[7] A. Padwa, P. H. J. Carlsen and A. Ku, *J. Am. Chem. Soc.*, **99**, 2798 (1977).

[8] A. Padwa, S. Nahm and E. Sato, *J. Org. Chem.*, **43**, 1664 (1978).

[9] A. Padwa and S. Nahm, *J. Org. Chem.*, **46**, 1402, (1981).

[10] H. J. Hansen and H. Heimgartner in "1,3-Dipolar Cycloaddition Chemistry", Vol **1**, Chapter 2, A. Padwa, ed, Wiley-Interscience, New York, 1984.

[11] R. Huisgen, H. Stangle, H. J. Sturm and H. Wagenhofer, *Angew. Chem.*, **74**, 31 (1962).

[12] D. Griller, C. R. Montgomery, J. C. Scaiano, M. S. Platz and L. Hadel, *J. Am. Chem. Soc.*, **104**, 6813 (1982).

[13] A. Padwa, J. R. Gasdaska, M. Tomas, N. J. Turro, Y. Cha and I. R. Gould, *J. Am. Chem. Soc.*, **108**, 6739 (1986).

[14] P. Gilfen, H. Heimgartner, H. Schmid and H. J. Hansen, *Heterocycles*, **6**, 143 (1977).

[15] A. Padwa and P. H. J. Carlsen in "Reactive Intermediates", R. A. Abramovitch ed, Plenum Press, New York, Vol **2**, p 55, 1982.

[16] K. Burger and J. Fehn, *Chem. Ber.*, **105**, 3814 (1972).

[17] A. Padwa, J. K. Rasmussen and A. Tremper, *J. Am. Chem. Soc.*, **98**, 2605 (1976).

[18] S. Sugiura, A. Ohno, O. Ohtani, K. Izumi, T. Kitamikado, H. Asai, K. Kao, M. Hori and H. Fijimura, *J. Med. Chem.*, **20**, 80 (1977).