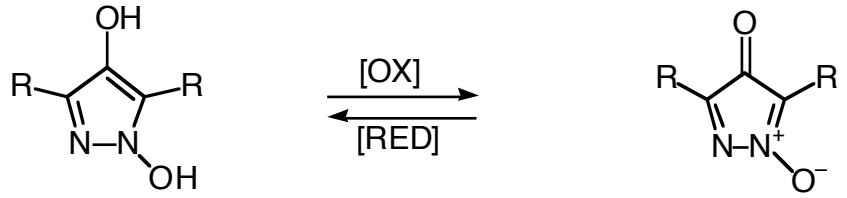
HETEROCYCLES, Vol. 62, 2004, pp. 847 - 849
Received, 25th September, 2003, Accepted, 31st October, 2003, Published online, 14th November, 2003

REDUCTIVE METHYLATION/PHOSPHORYLATION OF 3,4-DIAZACYCLOPENTADIENONE *N*-OXIDES WITH TRIMETHYL PHOSPHITE

Jeremiah P. Freeman* and Marc E. Guay
Department of Chemistry and Biochemistry, University of Notre Dame
Notre Dame, IN 46556, U.S.A.

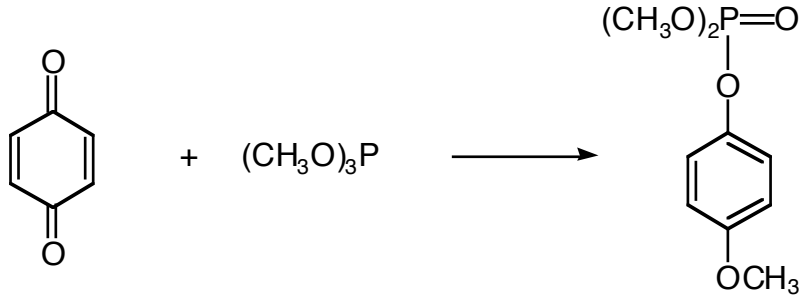
Abstract - Treatment of 2,5-diphenyl-3,4-diazacyclopentadienone 3-oxide and 3,4-dioxide with trimethyl phosphite results in *N*-deoxygenation and methylation and *O*-phosphorylation to produce dimethyl (1-methyl-3,5-diphenyl-4-pyrazolyl) phosphate.

The reversible relationship between 1,4-dihydroxypyrazoles and 3,4-diazacyclopentadienone 3-oxides (**2**)[1] is reminiscent of the hydroquinone-quinone couple. In an effort to find other



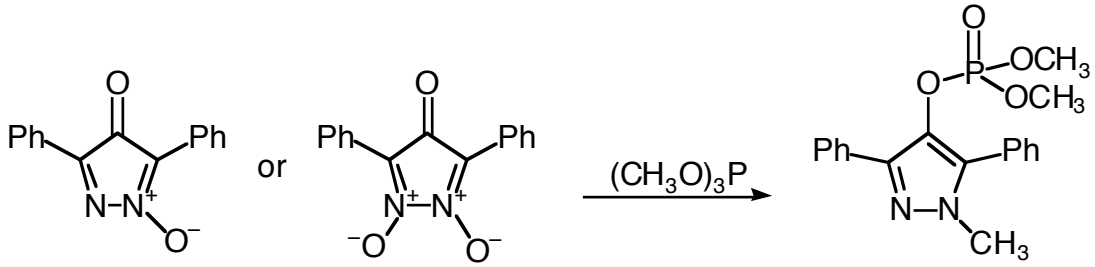
1 **2**

chemical analogies between the two systems, we examined the action of trimethyl phosphite on **2**, R = Ph. Ramirez and co-workers had shown that benzoquinone is converted to dimethyl *p*-methoxyphenyl phosphate by this reagent.[2] On the other hand trisubstituted phosphorus has traditionally been used for the deoxygenation of *N*-oxides.[3]



Heating **2**, R = Ph with trimethyl phosphite in boiling toluene produced dimethyl (1-methyl-3,5-diphenyl-4-pyrazolyl)phosphate (**3**) as the major product. A minor side-product was 1-methyl-3,5-diphenyl-4-hydroxypyrazole, probably formed by adventitious hydrolysis of **3**; the same material was obtained from **3** by treatment with aqueous base. The structure of phosphate (**3**)

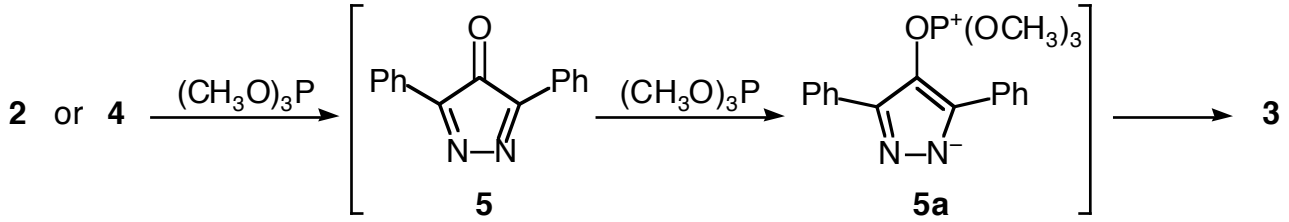
was inferred from its MS spectrum, ^{1}H NMR spectrum, and its ready hydrolysis to 1-methyl-3,5-diphenyl-4-hydroxypyrazole.



2 **4** **3**

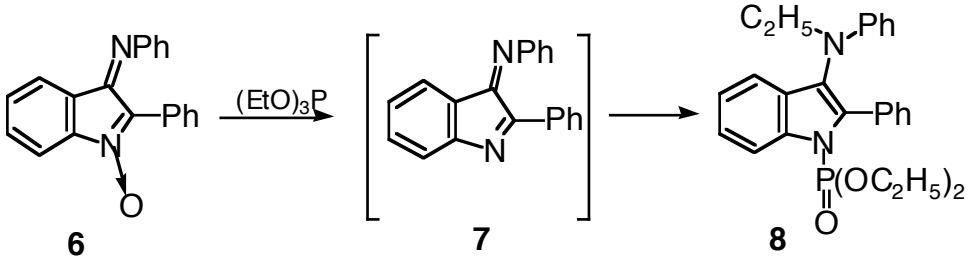
Phosphate (**3**) was also obtained when 2,5-diphenyl-3,4-diazacyclopentadienone 3,4-dioxide (**4**) was heated with trimethyl phosphite. Again a small amount of the 4-hydroxypyrazole was obtained and, in one experiment, a trace of 4-methoxy-3,5-diphenylpyrazole. Interestingly, the two methylated hydroxypyrazoles could easily be distinguished by their MS spectra: the *N*-methyl compound exhibited its principal peak at m/z 118 ($PhC^+{=}NCH_3$), whereas the *O*-methyl isomer had its principal peak at m/z 104 ($PhC_+{=}NH$).

Thus the reaction of these *N*-oxides does not exactly parallel the quinone reaction, but appears to begin with nitrogen deoxygenation to the diazadienone (**5**). Conversion of **5** to **3** then parallels the quinone methylation. The difference observed here is probably related to the



5 **5a**

relatively weak N-O bond. The fact that the dioxide gives the same product supports the suggestion that nitrogen deoxygenation occurs so that intermediate (**5**) is common to both reactions. (It had previously been shown that **5** is reduced to 4-hydroxy-3,5-diphenylpyrazole by triphenylphosphine; an intermediate analogous to **5a** was suggested). In a somewhat related investigation,[5] 2-phenyl-3-phenyimino-3*H*-indole *N*-oxide (**6**) was found to be converted principally to 1-diethylphosphoryl-2-phenyl-3-(*N*-ethyl-*N*-phenylamino)-1*H*- indole (**8**) by triethyl phosphite, presumably by way of the deoxygenation product (**7**). Again reductive alkylation/phosphorylation was observed in this related system.



6 **7** **8**

EXPERIMENTAL

*2,5-Diphenyl-3,4-diazacyclopentadienone 3,4-Dioxide (**4**) or 2,5-Diphenyl-3,4-diazacyclopentadienone 3-Oxide (**2**) and Trimethyl Phosphite*. A mixture of 5 g (0.02 mol) of either **2** or **4** and 3 mL of trimethyl phosphite in 50 mL of toluene was heated under nitrogen overnight at reflux. At this point the original red or orange color of the starting *N*-oxides had faded and the solution was bright yellow. The solution was cooled and washed several times to remove trimethyl phosphate, dried, and concentrated to a yellow oil. The oil was dissolved in ether and washed with 10% sodium hydroxide solution and water. The dried ether solution was subjected to GLC analysis, which revealed the presence of a trace of benzonitrile. The remaining ether solution was chromatographed on silica.

Ether-hexane (3:1) eluted 1-methyl-3,5-diphenyl-4-hydroxypyrazole as a pale yellow solid (0.5 g), mp 175-177°C (lit.,[4] 175-177°C); MS spectrum, m/z: M^+250 (52), 118 (100), 103 (40), 77 (38); ^{1}H NMR (300 MHz, $CDCl_3$), □: 3.60, s, 3 H; 7.33, m, 6 H; 7.80, m, 4 H.. It was identical to an authentic sample.[4] Acetylation with acetic anhydride produced 1-methyl-3,5-diphenyl-4-acetoxypyrazole as a white solid, mp 108-110°C (lit.,[4]109-111°C).

Further elution with ether-ethyl acetate produced several fractions containing a yellow oil that was rechromatographed to give 3.7 g (54%) of dimethyl (1-methyl-3,5-diphenyl-4-pyrazolyl)-phosphate as a pale yellow oil; MS spectrum, m/z: M^+, 358 (100), 118 (80), 103 (12), 77 (16); ^{1}H NMR (300 MHz, $CDCl_3$), □: 3.28 (d, J = 11 Hz, 6 H, P-OCH_3); 3.72 (s, 3 H, N-CH_3); 7.48 (m, 6 H); 7.96 (m, 4 H).

A solution of 1.4 g of this phosphate in 10 mL of 10% NaOH was heated under reflux for an hour. The solution was neutralized by addition of 10% HCl and extracted with ether. After drying, the ether extracts were concentrated to yield a white solid, mp 175-176°C, identical to 1-methyl-3,5-diphenyl-4-hydroxypyrazole.

In one experiment with **4**, further elution of the column with ethyl acetate yielded a trace of a white solid, mp 160-162°C, identical to an authentic sample of 4-methoxy-3,5-diphenylpyrazole (lit.,[4] mp 161-163°C).

REFERENCES

1. D. L. Surbey, J. J. Gannon, and J. P. Freeman, *J. Org. Chem.*, 1969, **34**, 187.

2. F. Ramirez, E. H. Chen, and S. Dershowitz, *J. Am. Chem. Soc.*, 1959, **81**, 4338.

3. For example, see C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, 1965, **30,** 2077.

4. P. J. Fagen, E. E. Neidert, M. J. Nye, M. J. O'Hare, and W.-P. O'Hare, *Can. J. Chem.*, 1979, 57.

5. S. Canaestrari, A. Mar'in, P. Sgarabotto, L. Righi, and L. Greci, *J. Chem Soc., Perkin Trans. 2*, 2000, 833.