SOME REACTIONS WITH 5-CHLORO-3-METHYL-4-NITRO-1-PHENYLPYRAZOLE

Ali Deeb[a]  

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The nucleophilic introduction of ethoxycarbonylmethylthio, 1,2,4-triazolo and azido- groups into 5-chloro-3-methyl-4-nitro-1-phenylpyrazole 1 is described. 5-Azidopyrazole 5 reacts at ambient temperature with phosphines or phosphites 6a-c to yield phosphazenes 7a-c. The use of phosphites leads to "Michaelis-Arbuzov type" rearrangement; thus 5 reacts in boiling 6c and heating of the trimethoxophosphazene 7c in refluxing chlorobenzene gave 9. Compounds 5, 7a,b and 9 can be converted to the corresponding aminopyrazoles. The cyclization of 5 by heating with methanesulfonic acid affords 4H-pyrazolo[5,1-b]benzimidazole derivative.

INTRODUCTION

Several derivatives of pyrazole ring have been found to have biological activities like fungicidal, herbicidal, virucidal and insecticidal. Therefore, it is interesting to synthesize some new pyrazole derivatives that may display pharmacological properties. In continuation of our previous work on pyrazoles the present investigation deals with the synthesis of different substituted pyrazoles.

5-Chloropyrazole can be undergoing nucleophilic substitution but we and other have found that unless activated by other groups the replacement needs vigorous conditions. However the presence of an electro-withdrawing group such as nitro in position four facilitates the substitution by appropriate nucleophiles. By using acetyl nitrate, 5-chloro-3-methyl-1-phenylpyrazole was selectively nitrated to give 5-chloro-3-methyl-4-nitro-1-phenylpyrazole 1.

RESULTS AND DISCUSSION

When compound 1 was heated with ethyl thioglycolate in the presence of potassium carbonate, 5-ethoxycarbonylmethylthiopyrazole 2 was obtained while in the presence of potassium hydroxide; 5-carboxymethylthiopyrazole 3 was obtained.

The 5-chloro group of 1 can also be replaced by 1,2,4-triazolo and azido groups by the reaction with sodium salt of 1,2,4-triazolo and with sodium azide in DMF at room temperature gave 1-(3'-methyl-4'-nitro-1'-phenylpyrazol-5'yl)-1,2,4-triazole 4 and 5-azido-3-methyl-4-nitro-1-phenylpyrazole 5, respectively.

The reaction of a tertiary phosphine with an organic azide to produce an iminophosphorane after nitrogen evolution is known as the Staudinger reaction, which has proved to be a very useful reaction in synthetic organic chemistry. The 5-azidopyrazole 5 thus obtained reacts with triphenylphosphine 6a in ethanol at ambient temperature smoothly to yield 5-methyl-4-nitro-5-triphenylphosphoranylideneamino-1-phenylpyrazole 7a. Tributylphosphine 6b and trimethylphosphite 6c reacted in the same manner yielding 7b and 7c respectively.

In an attempt to perform a similar reaction with the triethyl phosphite 6d this compound is added at room temperature to a stirred ethanolic solution of compound 5.

\[
\text{Me} \quad \begin{array}{c}
\text{N} \\
\text{N} \\
\text{X} \\
\text{Ph}
\end{array} \\
\text{NO}_2
\]

1. \( X = \text{Cl} \)  
2. \( X = \text{SCH}_2\text{COOEt} \)  
3. \( X = \text{SCH}_2\text{COOH} \)  
4. \( X = \text{N}_3 \)  

Scheme 1

Much to our surprise, 5-amino derivative 8 is obtained in excellent yield (95%), not the corresponding triethoxyphosphoranylideneamino derivative (such as compound 7), the mechanism for the formation of amino group have not been elucidated so far.

Hydrolysis of the phosphazenes 7a,b with acetic acid/water (80%) leads to the corresponding amine 8 and phosphine oxide.

The assignment of structure 8 was based on analytical and spectral data. The IR spectrum showed the NH group at 3425, 3315 cm\(^{-1}\) and \(^1\)H-NMR spectrum showed the presence of singlet at \( \delta \) 7.5 for the phenyl protons, a broad singlet at \( \delta \) 5.9 for the NH\(_2\) group and singlet at \( \delta \) 2.5 for the methyl group. Also the structure was assigned by comparison with authentic sample prepared from the hydrogenation of the azide 5 with a catalytic amount of palladium.
The reaction of 5 with an excess of trimethyl phosphite 6c under reflux (b.p. 112°C) gave the isomeric amidophosphonate 9. The first for this rearrangement 8,9 to 9 came from 1H-NMR analysis: there are three different methyl groups present, one singlet at \( \delta \) 2.6 for C-CH\(_3\) and two different doublets in the ratio of 1:2 at \( \delta \) 3.05 (d, 3H, \( J_{3PH} = 7.5 \) Hz, N-CH\(_3\)) and at \( \delta \) 3.25 (d, 3H, \( J_{3PH} = 15 \) Hz, OCH\(_3\)), \( \delta \) 3.70 (d, 3H, \( J_{3PH} = 15 \) Hz, OCH\(_3\)) (Figure 1a), the migration of an alkyl group from oxygen to phosphazyl nitrogen in Staudinger products has been observed previously.\(^{[9,10]}\) Compound 9 when treated with acetic acid-H\(_2\)O (80\%) the corresponding 5-methylamino derivative 10 is obtained. The structure of compound 11 was established from 1H-NMR spectrum which revealed the presence of singlet at \( \delta \) 2.5 for C-CH\(_3\), \( \delta \) 2.65 (d, 3H, \( J = 7.5 \) Hz, NHCH\(_3\)) and \( \delta \) 7.5 (s, 5H, Ph) (Figure 1b).

The cyclization of ortho-phenylazidoarenes or heteroarenes to indole derivatives is a known reaction and the mechanistic studies have that a singlet nitrene intermediate is involved in these reactions.\(^{[11]}\) Accordingly compound 5 was cyclized in methanesulfonic acid at 120°C to afford 2-methyl-3-nitro-4H-pyrazolo[5,1-b]benzimidazole 11.
The most salient feature of IR and H-NMR are given under experimental. Further studies are in progress in our laboratory on the application of the methods to the synthesis of other organic compounds.

EXPERIMENTAL SECTION


5-Ethoxycarbonylmethylthio-3-methyl-4-nitro-1-phenylpyrazole 2

To a solution of compound 1 (2.0 g, 8.0 mmol) and ethyl thioglycolate (1.0 g, 8.0 mmol) in methanol (20 ml) potassium carbonate (1.0 g, 7.2 mmol) was added. The reaction mixture was refluxed for 10 min., the solvent was evaporated under reduced pressure until dryness, and water (100 ml) was added. The precipitate was filtered, washed with water, dried and recrystallized from ether (2.1 g, 78%), mp 127-128°C; i.r.: 3000, 1635, 1535, 1350 cm-1; H-NMR (CDCl3): δ 2.55 (s, 3H, CH3), 3.7 (d, 9H, 3JPh = 8.7 Hz, OCH3), 7.2-7.5 (m, 5H, Ph). Anal. Calcd for C12H10N6O2: C, 49.40; H, 3.88; N, 14.30. Found: C, 49.31; H, 3.45; N, 14.37.

5-Carboxymethylthio-3-methyl-4-nitro-1-phenylpyrazole 3

To a stirred solution of compound 1 (2.0 g, 8.0 mmol) and ethyl thioglycolate (1.0 g, 8.0 mmol) in methanol (20 ml) a solution of potassium hydroxide (1.0 g) in water (5 ml) was added drop wise at room temperature. Nitrogen evolution started instantly, the stirring was continued for 30 min. then the reaction mixture was poured onto water (100 ml) and the precipitated product was filtered, dried and recrystallized from the appropriate solvent.

3-Methyl-4-nitro-5-triphenylphosphoranylideneamino-1-phenylpyrazole 7a

Yield 2.7 g (95%), mp 63-64°C (methanol); i.r.: 2990, 1605, 1530, 1420, 1400, 1290, 1050 cm-1; H-NMR (CDCl3): δ 2.6 (s, 3H, CH3), 3.6 (d, 9H, 3JPh = 8.7 Hz, OCH3), 7.2-8.0 (m, 15H, Ph), 7.6-7.8 (m, 5H, Ph). Anal. Calcd for C25H24N2O2P: C, 70.44; H, 5.11; N, 11.42. Found: C, 70.44; H, 5.11; N, 11.42.

3-Methyl-4-nitro-5-tri-n-butylphosphoranylideneamino-1-phenylpyrazole 7b

Yield 2.6 g (95%), mp 89-90°C (ethanol); i.r.: 2990, 1605, 1530, 1420, 1400, 1290, 1050 cm-1; 1H-NMR (CDCl3): δ 2.6 (s, 3H, CH3), 3.7 (d, 9H, 3JPh = 8.7 Hz, OCH3), 7.3-7.6 (m, 5H, Ph). Anal. Calcd for C25H24N2O2P: C, 45.88; H, 5.03; N, 16.27. Found: C, 45.94; H, 5.17; N, 16.50.

5-Amino-3-methyl-4-nitro-1-phenylpyrazole 8

Method A. A solution of phosphoranylideneamino pyrazole 7a,b (10 mmol) in acetic acid (80%, 30 ml) was heated under refluxed for 20 min. After cooling to room temperature, water (20 ml) was added and the solution was extracted with ethyl acetate (2 x 25 ml). The aqueous layer was evaporated to dryness under reduced pressure and the oily residue was triturated with ether. The precipitate was filtered off and recrystallized from ethanol, (1.6 g, 78%), mp 171-172°C; i.r.: 3425, 3315, 1610, 1540, 1285 cm-1; 1H-NMR (CDCl3): δ 2.5 (s, 3H, CH3), 5.9 (br, 2H, NH2), 7.5 (s, 5H, Ph). Anal. Calcd for C10H9N2O2: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.07; H, 4.62; N, 25.71.

Method B. To a stirred solution of compound 5 (1.0 g, 4.0 mmol) in ethanol (20 ml), triethylphosphite 6d (0.7 g, 4.0 mmol) was added drop wise at room temperature. Nitrogen gas was then passed into the reaction mixture, the residue was filtrated and the filtrate was evaporated under reduced pressure, the residue was triturated with ether. The precipitate was filtered, dried and recrystallized from petroleum ether (2.1 g, 78%), mp 171-172°C; i.r.: 3425, 3315, 1610, 1540, 1285 cm-1; 1H-NMR (CDCl3): δ 2.5 (s, 3H, CH3), 5.9 (br, 2H, NH2), 7.5 (s, 5H, Ph). Anal. Calcd for C10H9N2O2: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.07; H, 4.62; N, 25.71.


983

Section A-Research Paper
gas evolution started instantly. The solvent was evaporated under reduced pressure and the residue was crystallized from ethanol, (0.85 g, 95%), it was identical with that prepared by method A.

Method C. The azidopyrazole 5 (2.0 g, 8.0 mmol) was dissolved in ethanol (30 ml). After the addition of 5% Pd/C (100 mg) H₂ was bubbled through the stirred mixture at room temperature, till no starting material was detected by TLC (30 minutes). The mixture was filtered, the filtrate was evaporated to dryness under reduced pressure and the residue was recrystallized from ethanol, (1.67 g, 100%), it was identical with that prepared by method A.

3-Methyl-4-nitro-5-(N-methylidimethylethylphosphonoamino)-1-phenylpyrazole, 9

Method A. Compound 5 (2.0 g, 8.0 mmol) was added in portion-wise to trimethyl phosphate (20 ml) at room temperature while stirring, nitrogen gas evolution started instantly. The reaction mixture was stirred for additional 30 min., and then heated under reflux for 12 h. The reaction mixture was evaporated under reduced pressure, the residue was triturated with light petroleum (40-60°C), the precipitate was filtered and recrystallized from ether, (2.0 g, 72%), mp 101-102°C; ir: 2980, 1600, 1560, 1500, 1430, 1370, 1280, 1025, 900 cm⁻¹; ¹H-NMR (CDCl₃): δ 2.6 (s, 3H, CH₃), 3.25 (d, 3H, J = 15 Hz, OCH₃), 3.70 (d, 3H, JₚH = 15 Hz, OCH₃), 7.5 (s, 5H, Ph). Anal. Calcd for C₁₉H₁₅N₄O₃P: C, 56.88; H, 5.21; N, 24.12. Found: C, 56.69; H, 5.04; N, 25.92.

Method B. A solution of 7c (1.0 g) in chlorobenzene (20 ml) was heated to reflux for 3h. The reaction mixture was evaporated under reduced pressure to dryness. Recrystallization from ether, (1.9 g, 69%) it was identical with that prepared by method A.

3-Methyl-5-methylamino-4-nitro-1-phenylpyrazole, 10

Compound 9 (1.0 g, 2.9 mmol) was refluxed with a mixture of acetic acid/H₂O (20 ml, 80%) for 1 h. The reaction mixture was evaporated under reduced pressure, the residue was triturated with water, the precipitate was filtered and recrystallized from ethanol, (0.44 g, 65%), mp 84-85°C; ir: 3340, 2940, 1600, 1555, 1500, 1430, 1370, 1280 cm⁻¹; ¹H-NMR (CDCl₃): δ 2.5 (s, 3H, CH₃), 2.65 (d, 3H, J = 7.5 Hz, NHCH₃), 7.5 (s, 5H, Ph). Anal. Calcd for C₁₉H₁₅N₄O₂: C, 56.88; H, 5.21; N, 24.12. Found: C, 56.69; H, 5.04; N, 23.88.

2-Methyl-3-nitro-4H-pyrazolo[5, 1-d]benzimidazole, 11

Compound 5 (1.0 g, 4.0 mmol) was heated slowly to 102°C with methanesulfonic acid (15 ml), nitrogen being evolved. After 10 min. Heating was continued for further 10 min. at 125°C. The cooled reaction mixture was poured onto water (100 ml), the precipitated product was collected by suction and recrystallized from DMF, (0.58 g, 66%), mp 115-117°C; ir: 3345, 3000, 1600, 1535, 1430, 1335 cm⁻¹. Anal. Calcd for C₁₀H₇N₄O₂: C, 55.55; H, 3.73; N, 25.92. Found: C, 55.70; H, 3.60; N, 25.85.

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REFERENCES


