Synthesis of New Pyrazole Derivatives Using Vinamidinium Salts

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Novel pyrazole derivatives 2-7 are synthesized by the reaction of 2-substituted 1,3-bis(dimethylamino)-trimethinium salts with phenyl hydrazine in acetonitrile as the solvent. This method has some advantages of high yields (78-85%), simplicity of the process and easy of control. The ultraviolet spectral behavior of the synthesized compounds is examined in CDCl₃ and their structures were characterized by elemental analysis, FTIR, ¹H and ¹³C NMR and Mass spectra.

Keywords: Trimethinium salts, Pyrazole derivatives, Phenyl hydrazine

INTRODUCTION

Pyrazole derivatives are a class of aromatic heterocyclic compounds which have attracted significant attention in the field of pesticide and medicinal chemistry. They have shown a widespread biological and pharmacological activity such as antitumor, anti-inflammatory, antimicrobial, antidepressant and antifungal [1-10]. Thus these compounds have received significant attention in connection with their synthesis [11-13]. The results of literature survey show that numerous methods have been developed for the synthesis of pyrazole derivatives. However, to the best of our knowledge, there are a few reports on the synthesis of pyrazole derivatives using 2-substituted vinamidinium salts as starting compounds [14]. In this article, we describe the synthesis of six new pyrazole derivatives using the reaction of 2-substituted 1,3-bis (dimethylamino)-trimethinium salts with phenyl hydrazine, and evaluate their molecular structures on the basis of their ultraviolet (UV) absorption, infrared (IR), ¹H and ¹³C NMR and Mass spectra.

RESULTS and DISCUSSION

The novel pyrazole derivatives 2-7 were synthesized using a two-step procedure as shown in Scheme 1: (i) synthesis of the 2-substituted vinamidinium salts 1a-f by Vilsmeier-Arnold formylation as described in our previous works [15-18], and (ii) synthesis of pyrazole derivatives 2-7 using the reaction of the 2-substituted vinamidinium salts 1a-f with phenyl hydrazine in the presence of acetonitrile as solvent. Application of this synthetic route gave derivatives 2-7 in high yields (experimental section). The products are well-defined, stable solids and have a long shelf-life when stored in an anhydrous environment. It is possible to use other solvents such as methanol, however, the best results are obtained in terms of reaction speed and yields in the presence of acetonitrile.

The molecular structures of all six derivatives 2-7 were confirmed by elemental analysis, IR, ¹H and ¹³C NMR. The UV-Vis spectra of 2-7 were measured in CDCl₃. In conclusion, we have established an efficient protocol to access pyrazole derivatives 2-7 using 2-substituted vinamidinium salts as starting compounds. Clearly, this synthetic method has obvious advantages over other synthetic routes such as low time, high yield, no side reaction and a simple procedure. Furthermore, using this method we have been able to synthesize a variety of pyrazole derivatives linked different heterocyclic ring systems at C-4 position.

A possible mechanism for the formation of products
The new pyrazole derivatives (2-7) were obtained (78-85% yields) as shown in Scheme 1, by conversion of acetic acids (a-f) to the 2-substituted vinamidinium salts (1a-f). A

2-7 is shown in Scheme 2. Following the initial attack of hydrazyl group on the vinamidinium salt and subsequent elimination of dimethylamine, a cyclization reaction of the intermediate iminium salt for the formation of the substituted pyrazoles 2-7 occurs.

Scheme 1. Synthesis of the Pyrazole Derivatives 2-7
A possible mechanism for the formation of the substituted pyrazoles 2-7

The Typical Procedure for the Synthesis of Pyrazole Derivatives 2-7

Vinamidinium salt 1a-f (1.0 mmol) was dissolved in CH₂CN (12.0 ml) and then 0.098 ml (1.0 mmol) of phenyl hydrazine was added drop wise to the solution. The reaction mixture was refluxed for 3 h at 50 °C and then for 2 h at room temperature. TLC was used to monitor the progress of the reactions. After cooling in a refrigerator (12 h), the resulting precipitate was filtered, recrystallized from EtOH, and dried in vacuum at 80 °C.

4-Bromo-1-phenyl-1-H-pyrazolo-4-yl (2). Colorless powder; Yield 78%; m.p.: 142-144 °C; IR (KBr): v (cm⁻¹) = 3312, 1596, 1107; ¹H NMR (DMSP): δ (ppm) = 7.34-7.87 (m, 3H, benzyl-H), 8.10-8.33 (m, 2H, benzyl -H), 9.03-9.19 (m, 2H, vinyl-H); ¹³C NMR (DMSP): δ (ppm) = 98.2, 127.3, 128.0, 134.3, 138.5, 143.0, 146.3. λ_max (CDCl₃) (nm) = 267; MS: m/z = 224 [M⁺²], 222[M⁺].

1-(1-Phenyl-1-H-pyrazolo-4-yl)pyrimidinium (3).

Yellow powder; Yield 82%; m.p.: 163-164 °C; IR (KBr): v (cm⁻¹) = 314, 1631, 1096; ¹H NMR (DMSP): δ (ppm) = 7.33-7.76 (m, 5H, benzo-H), 8.15-8.58 (m, 4H, pyridine-H, NCH), 9.11-9.40 (m, 3H, pyridine-H); ¹³C NMR (DMSP): δ (ppm) = 103.3, 127.5, 128.5, 134.7, 146.5, 146.6, 147.9, 148.8, 162.2; UV: λ_max (CDCl₃) (nm) = 267.

4-Tert-butyl-1-(1-phenyl-1-H-pyrazolo-4-yl)pyrimidinium (4). Yellow powder; Yield 85%; m.p.: 194-196 °C; IR (KBr): v (cm⁻¹) = 3118, 1660, 1092; ¹H NMR (CDCl₃): δ (ppm) = 1.45 (s, 9H, CH₃), 7.47 (t, J = 8 Hz, 1H, H-benzyl), 7.46 (t, J = 8 Hz, 2H, H-benzyl), 7.90 (d, J = 8 Hz, 2H, H-benzyl), 8.36 (d, J = 8 Hz, 2H, H-pyridinium), 8.59 (s, 1H, H-vinyl), 9.35 (d, J = 8 Hz, 2H, H-pyridinium), 9.52 (s, 1H, H-vinyl); ¹³C NMR (DMSP): δ (ppm) = 30.0, 37.2, 98.9, 107.4, 110.1, 122.5, 123.1, 145.7, 146.1, 147.9, 148.4; UV: λ_max (CDCl₃) (nm) = 267.

2-(1-Phenyl-1-H-pyrazolo-4-yl)isoquinolinium (5).

Brown powder; Yield 78%; m.p.: 214-216 °C; IR (KBr): v (cm⁻¹) = 3110, 1637, 1095; ¹H NMR (DMSP): δ (ppm) = 7.45 (t, J = 8 Hz, 1H, H-benzyl), 7.60 (t, J = 8 Hz, 2H, H-benzyl), 7.93 (d, J = 8 Hz, 2H, H-benzyl), 7.97-9.38 (m, 9H, H-isoquinolinium); ¹³C NMR (DMSP/CDCl₃): δ (ppm) = 120.5, 124.5, 128.0, 128.6, 129.6, 130.9, 132.4, 133.2, 134.3, 135.0, 139.0, 140.2, 148.2; UV: λ_max (CDCl₃) (nm) = 267.

3,5-Dimethyl-1-(1-phenyl-1-H-pyrazolo-4-yl)pyrimidinium (6).

Brown powder; Yield 85%; m.p.: 162-164 °C; IR (KBr): v (cm⁻¹) = 3110, 1660, 1092 cm⁻¹; ¹H
NMR (CDCl₃): δ (ppm) = 2.58 (s, 6H, CH₃), 6.41-6.57 (m, 5H, Ar-H), 6.92-6.96 (m, 3H, Ar-H), 7.26-8.34 (m, 2H, Ar-H), 8.81-9.10 (m, 1H); ¹³C NMR (DMSO): δ (ppm) = 18.3, 98.2, 127.3, 128.6, 134.4, 138.5, 143.4, 143.1, 146.4, 147.9, 146.6; UV: λ_{max} (CDCl₃) (nm) = 267.

1-(1-Phenyl-1-H-pyrazolo-4-yl) quinolinium (7). Yellow powder; Yield 85%; m.p.: 214-216 °C; IR (KBr): ν (cm⁻¹) = 3110, 1632, 1097 cm⁻¹; ¹H NMR (DMSO): δ (ppm) = 6.74-7.52 (m, 5H, Ar-H), 7.75-8.56 (m, 5H, Ar-H), 8.56-9.36 (m, 4H, Ar-H); ¹³C NMR (DMSO): δ (ppm) = 103.2, 120.6, 122.1, 122.9, 125.8, 125.4, 128.4, 128.5, 128.6, 129.6, 130.9, 141.0, 145.5, 145.6, 152.7, 154.5; UV: λ_{max} (CDCl₃) (nm) = 267.

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