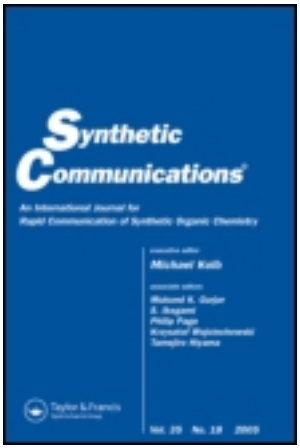

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Abstract: Semicarbazone derivatives **3** of 1,3-diphenylpyrazole-4-carboxaldehyde have been synthesized in high yields through a one-pot procedure involving acetophenone phenylhydrazones **1** subjected to Vilsmeier double formylation and workup under new conditions (i.e., treatment with semicarbazide followed by sodium bicarbonate). This method is even suitable for preparing other derivatives (i.e., thiosemicarbazones **4** and hydrazones **5**) in high yields.

Keywords: Acetophenone, 1,3-diphenylpyrazole-4-carboxaldehyde, phenylhydrazones, semicarbazones, thiosemicarbazones, Vilsmeier–Haack reaction

INTRODUCTION

Vilsmeier reaction was initially used for the formylation of activated aromatic and carbonyl compounds;[1] it is now used as a powerful synthetic tool for the construction of many heterocyclic compounds[2] such as quinolines, indoles, quinozolines, and pyridine. Synthesis of 4-formylpyrazoles from the double formylation of hydrazones using Vilsmeier–Haack reagent was first reported by Kira et al. in 1969.[3] The formyl group present on the pyrazole ring opens up the possibility of carrying

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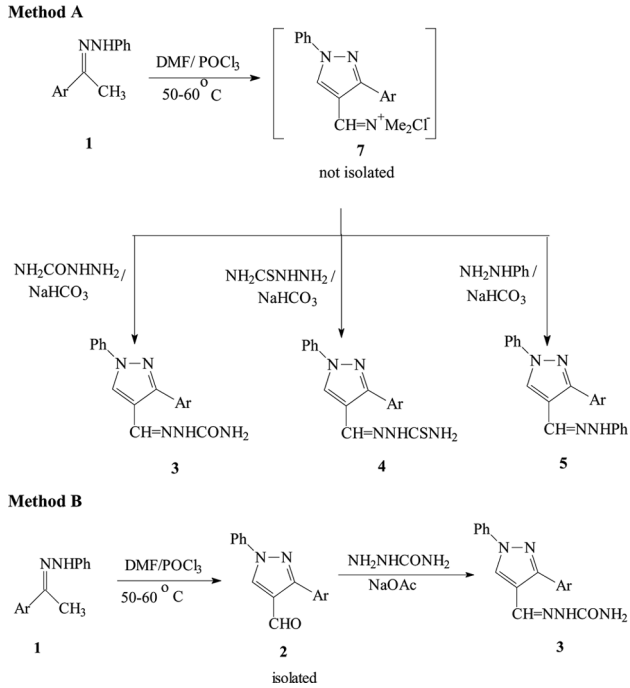
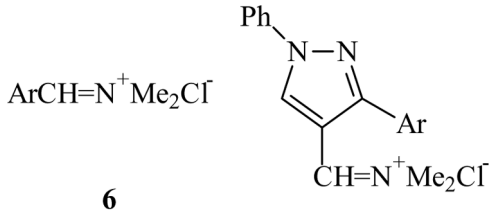
out a diverse range of functional group transformations and is an important protocol for the construction of heterocyclic compounds. In the recent literature, various aryl semicarbazones with established pharmacophore requirement have been reported to possess a novel class of anticonvulsant agent with fewer central nervous system side effects and less hepatotoxicity.[4] More recently, research on the interaction of DNA and thiosemicarbazone has received significant attention.[5] In the context of developing libraries of biologically active pyrazoles,[6] particularly directed toward the search for new biologically active ligands, we envisioned a versatile access to new aldehyde derivatives (i.e., semicarbazones, thiosemicarbazones, and hydrazones of 4-formylpyrazoles). Hydrazone derivatives have been claimed to possess interesting antibacterial,[7] anticonvulsant,[8] and antituberculosis activities.[9] The possible biological activities of semicarbazones, thiosemicarbazones, and hydrazones make it attractive to report a facile, efficient, and one-pot synthesis of some new derivatives of pyrazole-4-carboxaldehyde from acetophenone



Scheme 1. Method A: One-pot synthesis of some new carbonyl derivatives (**3**, **4**, and **5**) of 4-formylpyrazole under new work-up condition of Vilsmeier–Haack condition; Method B: Typical procedure for the synthesis of carbonyl derivative (**3**) of 4-formylpyrazole.

phenylhydrazones **1** under Vilsmeier–Haack (VH) conditions (Scheme 1). Recently it has been shown that the intermediate iminium salt **6** formed in VH formylation of aromatic substrates can be converted into groups other than aldehydes such as oximes, using a modified workup procedure that involves hydroxylamine in one pot.[10] We envisaged that treatment of the acetophenone phenylhydrazones **1** with VH reagent would lead to iminium salt of the type **7** followed by semicarbazide to afford desired pyrazole-4-carboxaldehyde derivatives of the type **3** as shown in method A of Scheme 1.



6 **7**

To test the feasibility of the proposed scheme, acetophenone phenylhydrazone (**1a**) was subjected to VH conditions using $POCl_3$ and *N,N*-dimethylformamide (DMF); the product mixture was worked up under new conditions using $NH_2CONHNH_2$ followed by $NaHCO_3$ to give the substituted pyrazole (**3a**) in 78% yield. The chemical structure of the pure product (recrystallized from ethanol) was confirmed by elemental analysis and spectral data [IR, ^{1}H NMR, and mass (MS-ES)] data. The –CH = and –NH signals of newly synthesized compound appeared as singlets at 8.55 and 9.67 ppm, respectively. The signals of aromatic protons were also observed at the expected chemical shift. For comparing the outcome of the present study with that of the reported procedure and also to characterize the new compounds, the synthesis of **3** was carried out by a conventional route (method B) which involved the isolation of aldehyde. The yields obtained by new workup (method A) procedure are much better than the established route (method B), employing the isolation of aldehyde. Encourgaged by the successful results, we studied the scope of new method for the synthesis of thiosemicarbazones **4** and hydrazones **5**. The VH reaction of hydrazones 1 using new workup conditions indeed afforded the new aldehyde derivatives (i.e., thiosemicarbazones **4** and hydrazones **5**) in good yields (Table 1).

In conclusion, the present study provides an easy access to synthesize carbonyl derivatives of 4-formylpyrazole under a new workup procedure. The synthetic route described here is simple, high-yielding, and a one-pot procedure. Because these compounds contain pyrazole, carbazone, and hydrazone functions in their structure, they seem to be suitable

Table 1. Physical data of semicarbazone (3), thiosemicarbazone (4), and hydrazone (5) derivatives of 4-formylpyrazoles prepared according to Scheme 1

Compounds	Ar	Mp (°C)	Yields[a] (%)	
			Method A	Method B
3a	C_6H_5	110–112	78	52
3b	4-$OMeC_6H_4$	194	75	50
3c	4-MeC_6H_4	193–195	79	54
3d	4-ClC_6H_4	189	82	45
3e	4-BrC_6H_4	192–194	84	48
3f	4-FC_6H_4	203	86	56
3g	4-$NO_2C_6H_4$	195	79	40
4a	C_6H_5	213	75	52
4b	4-$OMeC_6H_4$	174–176	78	57
5a	C_6H_5	143	70	57
5b	4-$OMeC_6H_4$	150–152	78	50

[a]Yields of the isolated products **2** and **3** with regard to **1**.

candidates for further chemical modification and may be pharmacologically active and useful as ligands in coordination chemistry.

EXPERIMENTAL

All reagents were purchased from commercial sources and were used without further purification. Melting points were taken in open capillaries in an electrical apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker 300-MHz instrument using TMS as an internal standard. Infrared (IR) spectra were recorded on a Perkin-Elmer 1800 Fourier transform infrared (FT-IR) spectrophotometer.

General Procedure for the Preparation of Semicarbazone (3), Thiosemicarbazone (4), and Hydrazone (5) Derivatives of 1,3-Diphenylpyrazole-4-carboxaldehyde

Method A: One-Pot Synthesis of **3** from **1**

Acetophenone phenylhydrazone (**1a**, 0.84 g, 4 mmol) was added to a cold solution of DMF (10 ml) and phosphorus oxychloride (0.5 ml, 6 mmol), and the mixture was stirred at 50–60 °C for 5–6 h, cooled to room temperature, and then poured into an ice-cold solution of semicarbazide

hydrochloride and sodium bicarbonate. The reaction mixture was stirred overnight. The solid product thus obtained was filtered, washed with water, and recrystallized from ethanol to give 1,3-diarylpyrazole-4-caboxyaldehyde semicarbazone (**3a**) in 78% yield.

Method B: Synthesis of **3** from **1** *via* Isolation of **2**

Step I: Synthesis of 1,3-diphenylpyrazole-4-carboxyaldehyde 2 from 1. To a cold solution of DMF (10 ml) and phosphorus oxychloride (0.5 ml, 6 mmol), acetophenone phenylhydrazone (**1a**, 0.84 g, 4 mmol) was added. The mixture was stirred at 50–60 °C for 5–6 h, cooled to room temperature, and then poured into ice-cold water. A saturated solution of sodium bicarbonate was added to neutralize the mixture to give formylpyrazole **2a**, isolated by filtration followed by washing with water (0.8 g yield 80%).

Step II: Synthesis of 3 from 2. Semicarbazide hydrochloride (20 mmol) and sodium acetate (30 mmol) were added to formylpyrazole (**2a**, 2.4 g, 10 mmol) in 25 ml ethanol, and the reaction mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid thus obtained was filtered, washed with water, and recrystallized from ethanol to get **3a** (2.10 g, yield 69%, overall yield of step I and step II: 55%).

Characterization Data of 1,3-Diarylpyrazole-4-carboxyaldehyde Semicarbazones

1,3-Diphenylpyrazole-4-carboxaldehyde Semicarbazone **(3a)**

IR (KBr): 1682, 1591, 3200, 3345, 3472.2 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 6.28 (s, 2H, NH_2), 7.2–7.7 (m, 10H, Ar–H), 8.2 (s, 1H, C_5H), 8.58 (s, 1H, CH=N), 9.67 (s, 1H, NH). Anal. calcd. for $C_{17}H_{15}N_5O$: C, 66.8; H, 4.91; N, 22.95. Found:C, 66.5; H, 4.85; N, 23.12.

1-Phenyl-3-(4-methylphenyl)pyrazole-4-carboxaldehyde Semicarbazone **(3b)**

IR (KBr): 1694, 1595, 3207, 3355, 3451 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.5 (s, 1H, CH_3), 5.8 (s, 2H, NH_2), 7.2–7.8 (m, 9H, Ar–H), 8.2 (s, 1H, C_5H), 8.5 (s, 1H, CH=N), 9.0 (s, 1H, NH). Anal. calcd. for $C_{18}H_{17}N_5O$: C, 67.7; H, 5.3; N, 21.94. Found:C, 68.02; H, 5.1; N, 21.8.

1-Phenyl-3-(4-methoxyphenyl)pyrazole-4-carboxaldehyde Semicarbazone **(3c)**

IR (KBr): 1698, 1603, 3188, 3357, 3458.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 3.6 (s, 3H, OCH_3), 6.08 (s, 2H, NH_2), 7.4–7.8 (m, 9H, Ar–H), 8.314 (s, 1H, C_5H), 8.59 (s, 1H, CH=N), 9.59 (s, 1H, NH). Anal. calcd. for $C_{18}H_{17}N_5O_2$: C, 64. 4; H, 5.0; N, 20.89. Found:C, 64.32; H, 4.89; N, 20.73.

1-Phenyl-3-(4-bromophenyl)pyrazole-4-carboxaldehyde Semicarbazone **(3d)**

IR (KBr): 1700, 1595, 3189, 3357, 3484.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 6.0 (s, 2H, NH_2), 7.2–7.8 (m, 9H, Ar–H), 8.314 (s, 1H, C_5H), 8.71 (s, 1H, CH=N), 9.69 (s, 1H, NH). Anal. calcd. for $C_{17}H_{14}N_5OBr$: C, 53.12; H, 3.64; N, 18.22. Found:C, 53.13; H, 3.6; N, 18.17.

1-Phenyl-3-(4-chlorophenyl)pyrazole-4-carboxaldehyde semicarbazone **(3e)**

IR (KBr): 1702, 1596, 3195, 3375, 3471.3 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 6.16 (s, 2H, NH_2), 7.2–7.7 (m, 9H, Ar–H), 8.2 (s, 1H, C_5H), 8.58 (s, 1H, CH=N), 9.89 (s, 1H, NH). Anal. calcd. for $C_{17}H_{14}N_5OCl$: C, 60.17; H, 4.12; N, 20.6. Found:C, 60.11; H, 4.36; N, 20.2. Mass: M^+341.

1-Phenyl-3-(4-fluorophenyl)pyrazole-4-carboxaldehyde Semicarbazone **(3f)**

IR (KBr): 1708, 1593, 3200, 3331, 3470 cm^{-1}; ^1H NMR (DMSO, 300 MHz): 6.28 (s, 2H, NH_2), 7.3–8.3 (m, 10H, Ar–H), 8.8 (s, 1H, CH=N), 10.13 (s, 1H, NH). Anal. calcd. for $C_{17}H_{14}N_5OF$: C, 63.15; H, 4.33; N, 21.6. Found:C, 63.11; H, 4.54; N, 21.57.

1-Phenyl-3-(4-nitrophenyl)pyrazole-4-carboxaldehyde Semicarbazone **(3g)**

IR (KBr): 1708, 1595, 3220, 3330, 3470 cm^{-1}; ^1H NMR (DMSO, 300 MHz): 6.28 (s, 2H, NH_2), 7.5–8.5 (m, 10H, Ar–H), 8.78 (s, 1H, CH=N), 10.03 (s, 1H, NH). Anal. calcd. for $C_{17}H_{14}N_6O_3$: C, 58.28; H, 4.00; N, 24.0. Found:C, 58.28; H, 4.35; N, 24.2.

1,3-Diphenylpyrazole-4-carboxaldehyde Thiosemicarbazone **(4a)**

IR (KBr): 1620, 3159, 3333, 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 5.0 (s, 2H, NH_2), 6.7–7.2 (m, 10H, Ar–H), 8.0 (s, 1H, C_5H), 8.3 (s, 1H, CH=N), 8.9 (s, 1H, NH). Anal. calcd. for $C_{17}H_{15}N_5S$: C, 63.35; H, 4.6; N, 21.80. Found:C, 63.30; H, 4.96; N, 21.8. Mass: M^+321.

1-Phenyl-3-(4-methoxyphenyl)pyrazole-4-carboxaldehyde Thiosemicarbazone **(4b)**

IR (KBr): 1614, 3200, 3315, 3400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 3.8 (s, 3H, OMe), 5.28 (s, 2H, NH_2), 6.8–7.4 (m, 10H, Ar–H), 8.3 (s, 1H, C_5H), 8.5 (s, 1H, CH=N), 9.8 (s, 1H, NH). Anal. Calcd. for $C_{18}H_{17}N_5OS$: C, 61.5; H, 4.84; N, 19.9. Found:C, 61.57; H, 4.9; N, 20.1.

1,3-Diphenylpyrazole-4-carboxaldehyde Hydrazone **(5a)**

IR (KBr): 1603, 3321 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 7.2–7.7 (m, 11H, Ar–H). Anal. calcd. for $C_{23}H_{20}N_4O$: C, 78.10; H, 5.32; N, 16.5. Found:C, 78.26; H, 5.44; N, 16.24.

1-Phenyl-3-(4-methoxyphenyl)pyrazole-4-carboxaldehyde Hydrazone **(5b)**

IR (KBr): 1600, 3321 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 3.8 (s, 3H, OMe), 7.2–7.7 (m, 10H, Ar–H). Anal. calcd. for $C_{23}H_{20}N_4O$: C, 75.0; H, 5.43; N, 15.2. Found:C, 75.17; H, 5.44; N, 15.24.

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