Sergey P. Ivonin, Bohdan B. Kurpil', Oleksandr O. Grygorenko* and Dmitry M. Volochnyuk

Reaction of hydrazones derived from electron-deficient ketones with Vilsmeier-Haack reagent

Abstract: Reaction of hydrazones derived from ketones bearing an acceptor substituent adjacent to the carbonyl group (α,α,α-trifluoroacetone and ethyl pyruvate) with Vilsmeier-Haack reagent was studied. In most cases, the method allows for regioselective preparation of 1,3-disubstituted pyrazole-4-carbaldehydes – the products of initial *C*-electrophilic attack, although in one case, the product resulting from concurrent *N*- and *C*-attacks of the electrophile at the hydrazone moiety is observed. Under analogous conditions, the reaction of *N*-arylhydrazone derived from butanedione leads to the formation of 3-chloro-3-(1-arylpyrazol-3-yl)acrylaldehyde – the product of double formylation at both ketone and hydrazone moieties of the starting material.

Keywords: electrophilic substitution; hydrazones pyrazoles; regioselectivity.

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Introduction

Non-symmetric polysubstituted pyrazoles are challenging targets for regioselective synthesis because the classical method, which relies on the use of *CCC* bis-electrophile and *NN* bis-nucleophile as the starting building blocks (Scheme 1) [1–3], often leads to mixtures of isomers. One of the possible alternative approaches relies on the reaction of *CCNN* bis-nucleophile (e.g., hydrazone of an enolizable ketone) with Vilsmeier-Haack reagent (DMF-$POCl_3$) acting as *C*-electrophile [4–11]. This reaction can lead to several types of products resulting from the initial attack of the electrophilic reagent at either α(α′)-carbon or nitrogen atom of the hydrazone (Scheme 2). As a part of our ongoing interest in such transformations [12–14], we have turned our attention to the reaction of hydrazones **1a–d** (Figure 1) derived from ketones bearing an acceptor substituent adjacent to the carbonyl group (i.e., α,α,α-trifluoroacetone, ethyl pyruvate, and butanedione) with Vilsmeier-Haack reagent. It should be noted that only *N*-aryl hydrazones **1e** and **1f** derived from ethyl pyruvate and 1-phenylpropane-1,2-dione were studied in the literature previously in analogous transformations [15–20]; in this case, a formation of aldehydes **2e,f** was observed (Scheme 3).

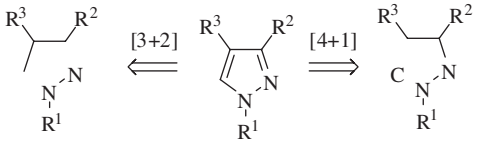
Results and discussion

Since the reaction of *N*-arylhydrazones of ethyl pyruvate (**1e**) with DMF-$POCl_3$ has been described in the literature, we first checked if the method is amendable for their aliphatic counterpart **1a**. We have shown previously [12] that the reactivity of *N*-alkylhydrazones toward Vilsmeier-Haack reagent often contradicts regularities observed for their *N*-aryl analogues. Nevertheless, in the case of **1a**, it was found that the reaction proceeded in expected manner, leading to the formation of aldehyde **2a** in a 71% yield (Scheme 4).

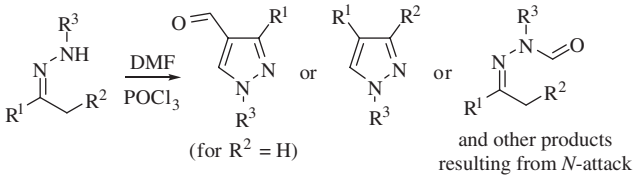
Because the building blocks of the type **2a** look promising in terms of lead-oriented synthesis [21], we have demonstrated their bifunctional reactivity by some representative transformations (Scheme 5). In particular, mild alkaline hydrolysis of **2a** gave carboxylic acid **3a** in 94% yield. Oxidation of **2a** led to the formation of carboxylic acid **4a** (68%). Finally, reaction of **2a** with hydrazine hydrate resulted in the construction of pyrazolo[3,4-*d*] pyridazine ring system of the compounds **5a** (85%).

In the reaction with Vilsmeier-Haack reagent, hydrazone **1b** gave the product **6b** in 82% yield (Scheme 6). It should be noted that we have observed compounds of the type **6b** only as minor products in the reactions of *N*-alkylhydrazones with Vilsmeier-Haack reagent previously [13]. Formation of **6b** can be explained by concurrent attack of the electrophile at the nitrogen atom of the corresponding enhydrazine form **7b**. This can be explained by a stronger electron-withdrawing effect of the

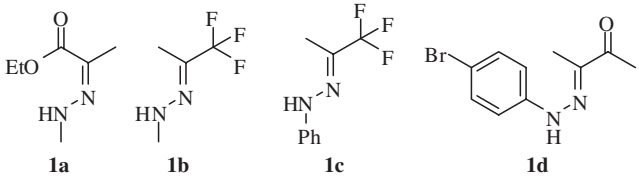
***Corresponding author: Oleksandr O. Grygorenko,** National Taras Shevchenko University of Kyiv, Volodymyrska Street, 64, Kyiv 01601, Ukraine, e-mail: gregor@univ.kiev.ua
Sergey P. Ivonin, Bohdan B. Kurpil' and Dmitry M. Volochnyuk: Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanska Street 5, Kyiv 02660, Ukraine



Scheme 1

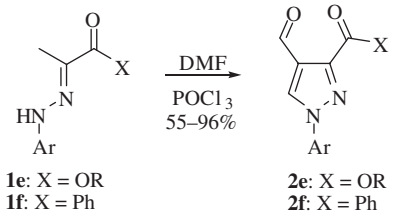


Scheme 2

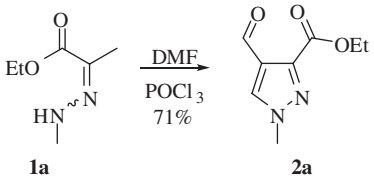


1a **1b** **1c** **1d**

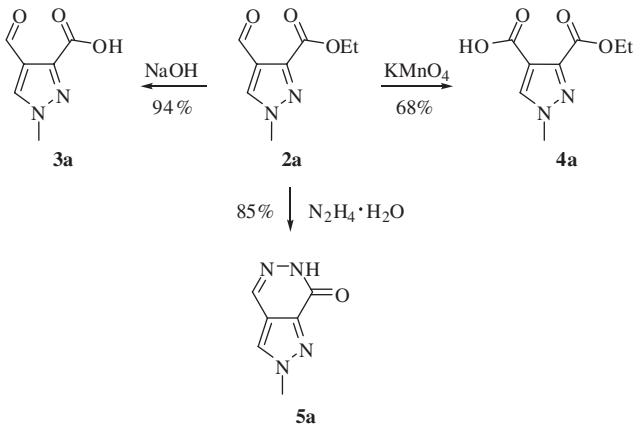
Figure 1 Hydrazones **1a–d** studied in this work.



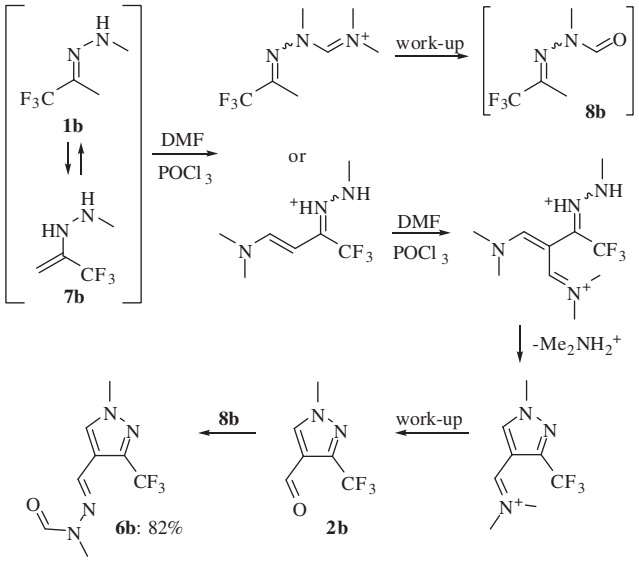
Scheme 3



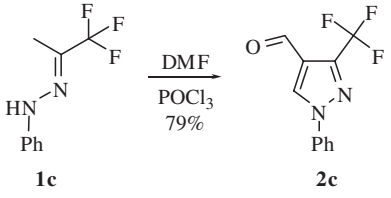
Scheme 4



Scheme 5



Scheme 6

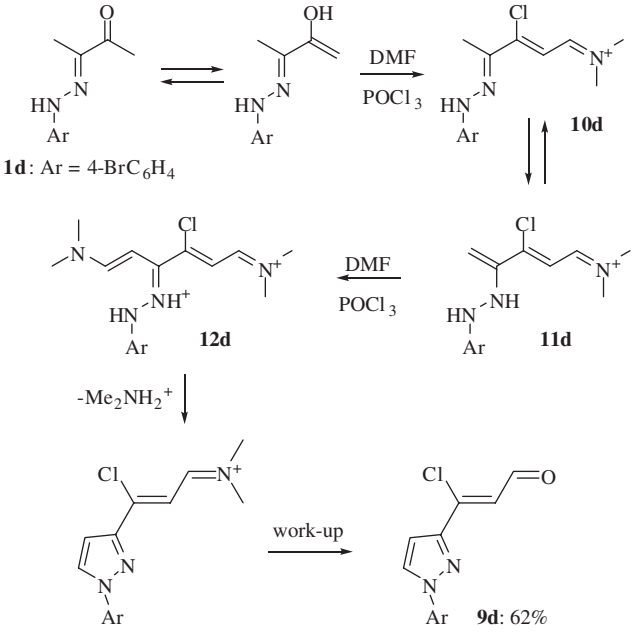


Scheme 7

trifluoromethyl group as compared with ethoxycarbonyl, which lowers the *C*-nucleophilicity of **7b**. The product **8b** resulting from this attack undergoes hydrazone exchange with the product of formal *C*-attack **2b** to give **6b**.

Unlike **1b**, *N*-phenylhydrazone **1c** was transformed to the product of *C*-attack of the electrophile **2c** (79%) upon treatment with DMF-$POCl_3$ (Scheme 7). Obviously, decreased nucleophilicity of nitrogen atom of the hydrazone moiety in **1c**, due to the effect of the phenyl substituent, prevented *N*-attack of the electrophile.

An unexpected product **9d** (62%) was obtained in the reaction of hydrazone **1d** with the Vilsmeier-Haack reagent (Scheme 8). Obviously, in this case, chloroformylation at the ketone moiety resulting from the initial



Scheme 8

attack at α′-CH_3 group occurs first; the intermediate **10d** thus obtained undergoes second electrophilic attack to give **11d**. Because **11d** is a dication, it does not react with an additional mole of Vilsmeier-Haack reagent but undergoes cyclization to pyrazole **12d**, which is transformed into aldehyde **9d** upon workup.

Conclusions

In most cases, reaction of hydrazones derived from ketones bearing an acceptor substituent adjacent to the carbonyl group (e.g., COOR, CF_3, C(O)R) with Vilsmeier-Haack reagent is a powerful method for the preparation of the corresponding 1,3-disubstituted pyrazole-4-carbaldehydes, resulting from initial *C*-electrophilic attack. In particular, both *N*-alkyl- and *N*-arylhydrazones derived from pyruvic acid esters give 1-substituted 4-formylpyrazole-3-carboxylates, which are promising bifunctional building blocks for organic synthesis. The reactions of *N*-arylhydrazones of α,α,α-trifluoroacetone also lead to 1-aryl-3-trifluoromethylpyrazole-4-carbaldehydes. On the contrary, the corresponding *N*-alkylhydrazones are prone to both *N*- and C-formylation. This behavior is obviously related to the strong inductive electron-withdrawing effect of the trifluoromethyl group. Finally, treatment of *N*-arylhydrazones of butanedione gives the pyrazole-derived β-chlorovinyl aldehydes resulting from double *C*-electrophilic attack at both ketone and hydrazone moieties of the starting compound. This result is contrary to the literature data for *N*-arylhydrazones of 1-phenylpropane-1,2-dione (giving the expected 1,3-disubstituted pyrazole-4-carbaldehyde), because analogous reaction is impossible in that case.

Experimental

Solvents were purified according to the standard procedures. Hydrazones **1a–d** were prepared using reported procedures [13, 14]. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 spectrometer at 400 and 100 MHz, respectively. Elemental analyses (C, H, N, S, Cl, Br) were conducted at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Electrospray ionization mass spectra were recorded on an Agilent 1200 LCMSD SL instrument.

General procedure for the reaction of hydrazones 1 with Vilsmeier-Haack reagent

$POCl_3$ (0.1 mol) was added dropwise to DMF (20 mL) at 0°C. After 1 h, a solution of hydrazone **1** (0.05 mol) in DMF (10 mL) was added dropwise at 0°C. The mixture was stirred at 0°C for 1 h and at 80°C for 1 h, then cooled to ambient temperature and poured onto ice (100 g). The resultant precipitate was filtered to give the product **2a**, **2c**, **6b**, or **9d.**

Ethyl 4-formyl-1-methyl-1*H*-pyrazole-3-carboxylate (2a): Yield 71%; mp 107–108°C; ^{1}H NMR ($CDCl_3$): δ 10.39 (s, 1H), 7.98 (s, 1H), 4.49 (q, *J* = 7.2 Hz, 2H), 4.03 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 185.6, 160.9, 142.4, 134.3, 123.6, 60.8, 39.8, 13.9; MS: *m/z* 183 (MH^+). Anal. Calcd for $C_8H_{10}N_2O_3$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.97; H, 5.26; N, 15.50.

1-Phenyl-3-(trifluoromethyl)-1*H*-pyrazole-4-carbaldehyde (2c): Yield 79%; mp 105–106°C; ^{1}H NMR ($CDCl_3$): δ 10.05 (s, 1H), 8.51 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (DMSO"-d_6): δ 182.4, 140.5 (q, *J* = 37.5Hz), 137.9, 135.5, 129.6, 128.4, 122.2, 121.7, 119.7; ^{19}F NMR (75 MHz): δ -62.08; MS: *m/z* 241 (MH^+). Anal. Calcd for $C_{11}H_7F_3N_2O$: C, 55.01; H, 2.94; N, 11.66. Found: 55.16; H, 3.08; N, 11.47.

(*E*)-*N*-methyl-*N*′-((1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-methylene)formohydrazide (6b): Yield 82%; mp 143–144°C; ^{1}H NMR ($CDCl_3$): δ 8.70 (s, 1H), 7.86 (s, 1H), 7.73 (s, 1H), 3.97 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 164.5, 137.9 (q, *J* = 37.5 Hz), 132.9, 132.5, 123.6, 120.1, 39.9, 27.1; ^{19}F NMR (75 MHz): δ -61.28; MS: *m/z* 235 (MH^+). Anal. Calcd for $C_8H_9F_3N_4$: C, 41.03; H, 3.87; N, 23.92. Found: C, 40.83; H, 3.99; N, 24.06.

3-(1-(4-Bromophenyl)-1*H*-pyrazol-3-yl)-3-chloroacrylaldehyde (9d): Yield 62%; mp 109–110°C; ^{1}H NMR (DMSO-d_6): δ 9.98 (s, 1H), 9.32 (s, 1H), 7.88 (d, *J* = 9.0 Hz, 2H), 7.74 (d, *J* = 9.0 Hz, 2H), 6.54 (d, *J* =

1.8 Hz, 1H), 6.00 (d, J = 1.8 Hz, 1H); ^{13}C NMR (DMSO-d_6), δ 183.8, 148.7, 137.3, 135.7, 132.5, 129.0, 122.2, 121.1, 121.0, 120.5; MS: m/z 312 (MH^+). Anal. Calcd for $C_{12}H_8BrClN_2O$: C, 46.26; H, 2.59; N, 8.99; (Br+Cl) 37.03. Found: C, 46.15; H, 2.52; N, 9.04; (Br+Cl) 36.73.

4-Formyl-1-methyl-1*H*-pyrazole-3-carboxylic acid (3a): NaOH (0.40 g, 0.01 mol) was dissolved in MeOH (20 mL), then pyrazole **2a** (1.82 g, 0.01 mol) was added. The resulting solution was stirred at room temperature for 1 h, then concentrated, diluted with water (20 mL), and acidified to pH=3. The resultant precipitate was filtered and dried on air to give the product **3a** (1.45 g): Yield 94%; mp 215–217°C; ^{1}H NMR (DMSO-d_6): δ 13.46 (br s, 1H), 10.22 (s, 1H), 8.44 (s, 1H), 3.95 (s, 3H); ^{13}C NMR (DMSO-d_6): δ 186.1, 162.4, 143.4, 134.2, 123.6, 39.5; MS: m/z 155 (MH^+). Anal. Calcd for $C_6H_6N_2O_3$: C, 46.76; H, 3.92; N, 18.18. Found: C, 46.94; H, 3.76; N, 17.95.

3-(Ethoxycarbonyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid (4a): To a mixture of pyrazole **2a** (1.82 g, 0.01 mol) and water (20 mL), $KMnO_4$ (1.58 g, 0.01 mol) was added at room temperature upon stirring. The resulting mixture was stirred at room temperature for 3 h. Then the solid was filtered off and washed with water (3×10 mL). The combined filtrates were acidified to pH=3, and the precipitate formed was filtered to give carboxylic acid **4a** (1.34 g): Yield 68%; mp 188–189°C; ^{1}H NMR (DMSO-d_6): δ 12.6 (br s, 1H), 8.28 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6): δ 162.6, 162.5, 143.0, 135.7, 114.7, 61.1, 39.2, 13.9; MS: m/z 198 (MH^+). Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.74; H, 4.82; N, 14.07.

2-Methyl-2*H*-pyrazolo[3,4-*d*]pyridazin-7(6*H*)-one (5a): A solution of pyrazole **2** (1.82 g, 0.01 mol) and hydrazine hydrate (0.01 mol) in *i*-PrOH (10 mL) was stirred under reflux for 2 h. Then the mixture was concentrated, and the residue was crystalized from MeOH to give the product **5** (1.27 g): Yield 85%; mp 280–282°C; ^{1}H NMR (DMSO-d_6), δ 13.24 (br s, 1H), 8.44 (s, 1H), 8.27 (s, 1H), 4.15 (s, 3H); ^{13}C NMR (DMSO-d_6), δ 156.5, 141.8, 133.0, 128.1, 118.5, 40.1; MS: m/z 151 (MH^+). Anal. Calcd for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.78; H, 4.30; N, 37.26.

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