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Synthesis of pyrazole derivatives from multicomponent reaction of arylhydrazines in the presence of Vanadium oxytrichloride as catalyst

Narges Ghasemi*

National Petrochemical Company (NPC), petrochemical Research and Technology Company, Arak Center, Iran

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Abstract: The reaction between alkyl isocyanides and isopropylidene Meldrum's acid in the presence of arylhydrazines leads to functionalized 1-aryl-3,5-dioxo-tetrahydro-1*H*-pyrazols in good yields.

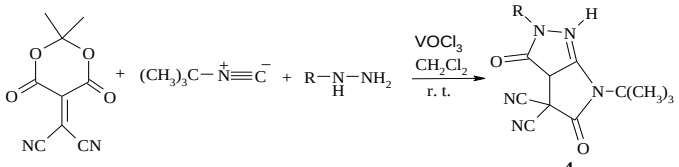
Keywords: Isocyanide, Meldrum's acid, Arylhydrazine, Three-component reaction.

Introduction

Synthesis of pyrazole and its *N*-aryl analogues has been a subject of consistent interest because of the wide applications of such heterocycles in pharmaceutical as well as in agrochemical industry [1, 2]. Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, antiinflammatory, antipyretic, antibacterial, and sedative-hypnotic activity [2]. The 1-phenylpyrazole motif is present in several drug candidates for treatment of various diseases such as cyclooxygenase-2 (Cox-2) inhibitors, IL-1 synthesis inhibitors, and protein kinase inhibitors [3]. Similarly a few of the 1,5-diarylpyrazole derivatives have been shown to exhibit nonnucleoside HIV-1 reverse transcriptase inhibitory activities [4] along with Cox-2 inhibitor [2]. The corresponding 1,3,5-triaryl-4-alkylpyrazoles have been recently identified as efficient ligands for estrogen receptor, displaying high binding affinities and selective transcriptional efficacy for ERR subtype [5]. Therefore, continuous efforts have been devoted to the development of more general, efficient, and regioselective methods for the synthesis of this class of compounds.

*Corresponding author: Tel: +98 8633677201-9; Fax: +98 8633677203, E-mail: naghasemi.16@gmail.com

As versatile reagents and important intermediates, Meldrum's acid (isopropylidene malonate) and its derivatives have been widely used in organic synthesis [6, 7]. In the context of our recent studies [8] on the reactivity of isopropylidene Meldrum's acid (**1**), we ventured into an exploration of the reaction between **1**, and alkyl isocyanides in the presence of arylhydrazine proton sources and Vanadium oxytrichloride (Scheme **1**).



4	R	Yield (%)
a	Ph	95
b	2,4-dinitrophenyl	90

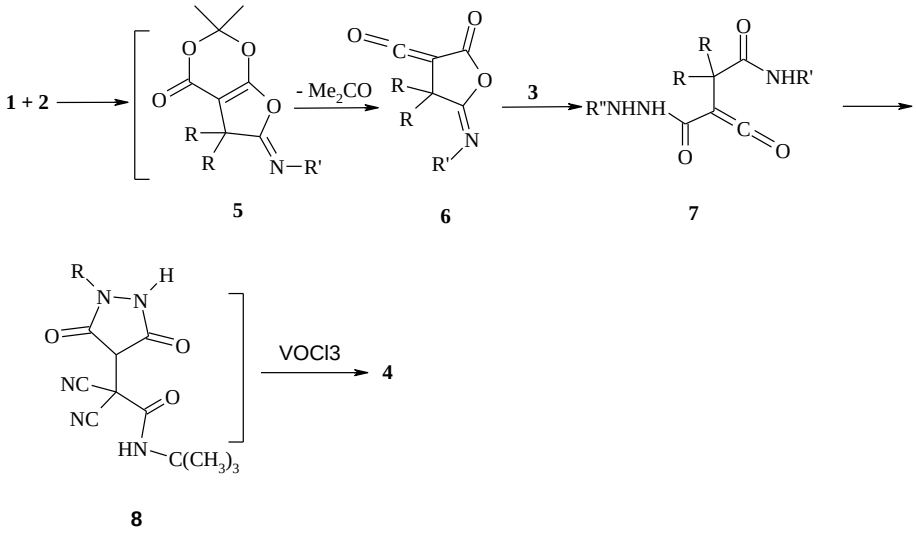
Scheme 1: Synthesis of pyrazol derivatives

Result and Discussion

Alkyl isocyanides undergo a complex reaction with **1** in the presence of hydrazine **3** and Vanadium

oxytrichloride in CH_2Cl_2 at room temperature to produce 1*H*-pyrazol derivatives **4** in high yields (Scheme **1**). The structures **4a-4b** were corroborated by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, **t**he ^{1}H NMR spectrum of **4a** in $CDCl_3$ showed four sharp singlets arising from C*Me*$_3$ (δ(H) 1.36), two methyl groups of CMe_2 moiety are diastereotopic (δ(H) 1.51, 1.61) and methine (δ(H) 3.34) protons. multiplets at (δ(H) 7.22-7.71) for the aromatic moiety, together with two signals at (δ(H) 5.60) and 8.30 for the NH protons. The ^{13}C NMR spectrum of **4a** shows thirteen distinct resonances (see *Exper. Part*) in agreement with the proposed structure.

A plausible mechanism for the formation of products **4** is proposed in Scheme **2**. On the basis of the well-established chemistry of isocyanides [9-11] the reaction starts from [4+1] cycloadition of the isocyanide to the electron deficient heterodiene moiety of **1** to form intermediate iminolactone **5 [**8]. This intermediate first losses acetone to give acylketene **6** and then the hidrazine may attack **6** to produce **7**. With hidrazine, as NH-acid/nucleophile, the reaction leads to the pyrazol **8** that in the presence of $VOCl_3$ produce product **4** (Scheme **2**).



Scheme 2: Proposed mechanism for the synthesis of **4**

Conclusion

In summary, the reaction between alkyl isocyanides and alkylidene *Meldrum*'s acid in the presence of hydrazines and VOCl3leads to functionalized pyrazols. The presented reactions carry the advantage that not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification.

Experimental

General

Isopropylidene Meldrum's acid was prepared by addition of Meldrum's acid to acetone in presence of piperidine and glacial acetic acid [6]. Melting points were measured on an *Electrothermal 9100* aparatus.

Further purification. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H-and ^{13}C-NMR spectra: *Bruker DRX-500 AVANCE* instrument; in $CDCl_3$ at 500.1 and 125.7 MHz, resp; *Finnigan-MAT-8430* mass spectrometer, in m/z. Elemental analyses (C, H, N) were performed with a *Heraeus CHN-O-Rapid* analyzer.

General Procedure for the Preparation of Compounds 4:

To a magnetically stirred solution of 0.18 g, isopropylidene Meldrum's acid (1 mmol) and 0.11 g, hydrazine (1 mmol) in 15 mL CH_2Cl_2 was added 0.12 mL *tert*-butyl isocyanide (1 mmol) at 0 °C over 5 min. The reaction mixture was then stirred for 24 h. The solvent was removed under reduced pressure and the viscous residue was purified by diethyl ether.

N^1-(tert-Butyl)-2-(3,5-dioxo-1-phenyltetrahydro-1H-pyrazol-4-yl)-methylpropanamide (**4a**).

Yield: 0.31 g (98%). Yellow powder, m.p.140-142 °C. IR (KBr): 3355, 3055; 1727, 1697 (C=O); 1361, 1297. ^{1}H NMR: 1.36 (*s*, 3 CH_3); 1.51, 1.61 (2*s*, 2 CH_3); 3.34 (*s*, CH); 5.60 (*s*, NH); 7.22 (*t*, $^3J_{HH}$ = 7.4 Hz, CH); 7.41 (*t*, $^3J_{HH}$ = 7.7 Hz, 2 CH); 7.71 (*d*, $^3J_{HH}$ = 7.9 Hz, 2 CH); 8.30 (broad *s*, NH). ^{13}C NMR: 24.5, 24.6 (2 CH_3); 28.8 (C*M*e$_3$); 46.9 (C); 52.1 (*C*Me$_3$); 53.3 (CH); 119.8 (2 CH); 125.9 (CH); 129.6 (2 CH); 136.7 (C); 166.7, 170.7, 175.5 (3 C=O). EI-MS: 317 (M^+, 5), 217 (10), 88 (100), 77 (20), 59 (40), 39 (27). Anal. Calc. for $C_{17}H_{23}N_3O_3$ (317.4): C 64.33, H 7.30, N 13.24; Found: C 63.93, H 7.08, N 13.20.

N^1-(tert-Butyl)-2-[1-(2,4-dinitrophenyl)-3,5-dioxotetrahydro-1H-pyrazol-4-yl]-2-methylpropanamide **(4b)**.

Yield: 0.40 g (98%). Red powder, m.p.184-186 °C, IR (KBr): 3410, 3075; 1714, 1652 (C=O), 1368, 1342. ^{1}H NMR: 1.30 (*s*, 3 CH_3); 1.52, 1.63 (2 *s*, 2 CH_3); 3.47 (*s*, CH); 6.62 (*s*, NH); 8.11 (*d*, $^3J_{HH}$ = 9.1 Hz, CH); 8.63 (*dd*, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 2.5 Hz, CH); 8.76 (*d*, $^4J_{HH}$ = 2.5 Hz, CH); 10.9 (broad *s*, NH). ^{13}C NMR: 23.7, 24.1 (2 CH_3); 28.2 (C*M*e$_3$); 48.3 (C); 51.7 (*C*Me$_3$); 51.8 (CH); 121.4, 123.9, 128.2 (3 CH); 135.2, 142.4, 144.4 (C); 169.2, 170.0, 176.1 (3 C=O) . EI-MS: 407 (M^+, 5), 307 (5), 84 (72), 59 (84), 58 (100). Anal. Calcd for $C_{17}H_{21}N_5O_7$ (407.4): C 50.12, H 5.20, N 17.19; Found: C 50.21, H 5.12, N 17.30.

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