A synthesis of 1-aryl-3,5-dioxo-tetrahydro-1*H*-pyrazols from reaction of alkyl isocyanides, isopropylidene Meldrum's acid and arylhydrazines

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

Keywords: isocyanide, Meldrum's acid, arylhydrazine, three-component reaction

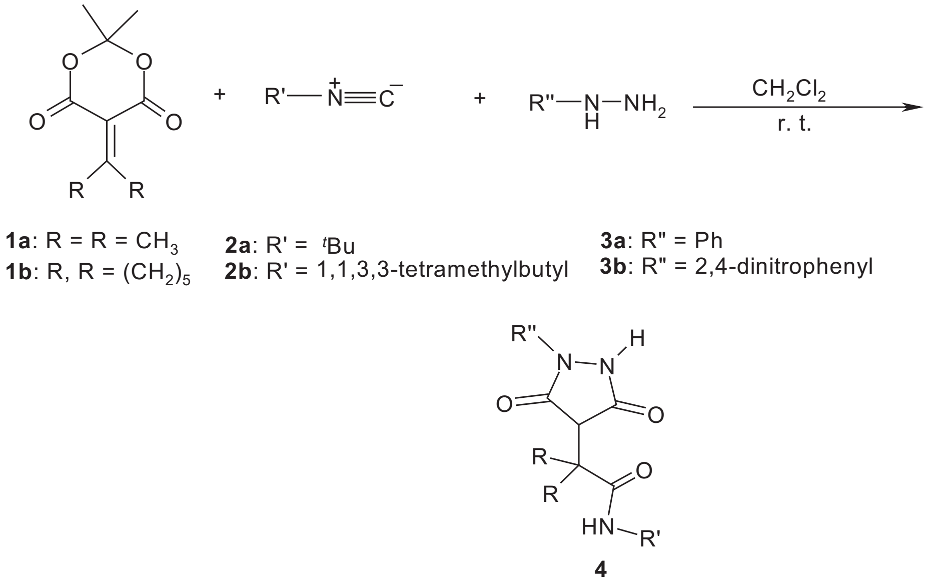
Synthesis of pyrazole and its *N*-aryl analogues has been the subject of consistent interest because of the wide applications of such heterocycles in pharmaceutical as well as in agrochemical industry.[1,2] Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, 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.

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 studied the reaction between **1**, and alkyl isocyanides in the presence of arylhydrazines.

Alkyl isocyanides undergo a complex reaction with **1** in the presence of hydrazine **3** in CH_2Cl_2 at room temperature to produce *N*-(alkyl)-2-(3,5-dioxo-1-aryltetrahydro-1*H*-pyrazol-4-yl)- propanamides **4** in high yields (Scheme 1).

The structures **4a–4d** were corroborated by IR, ^1H NMR, ^{13}C NMR and mass spectral data. For example, the ^1H NMR spectrum of **4a** in $CDCl_3$ showed four sharp singlets arising from C*Me*$_3$ ($\delta = 1.36$), two methyl groups of CMe_2 moiety are diastereotopic ($\delta = 1.51, 1.61$) and methine ($\delta = 3.34$) protons. multiplets at ($\delta = 7.22$-7.71) for the aromatic moiety, together with two signals at ($\delta = 5.60$) and 8.30 for the NH protons. The ^{13}C NMR spectrum of **4a** shows 13 distinct resonances (see Experimental) 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[9,10] 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 arylhidrazine attacks **6** to produce **7**, which undergoes ring closure to produce the pyrazol **4** (Scheme 2).



1a: R = R = CH_3
1b: R, R = $(CH_2)_5$
2a: R' = ^{t}Bu
2b: R' = 1,1,3,3-tetramethylbutyl
3a: R" = Ph
3b: R" = 2,4-dinitrophenyl

4

2, 3, 4	R	R'	R"	Yield/%
a	CH_3	^{t}Bu	Ph	98
b	CH_3	^{t}Bu	2,4-dinitrophenyl	98
c	CH_3	1,1,3,3-tetramethylbutyl	2,4-dinitrophenyl	94
d	$(CH_2)_5$	^{t}Bu	2,4-dinitrophenyl	56

Scheme 1

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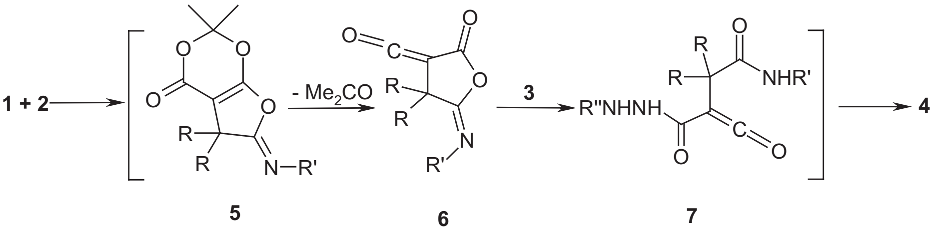

Scheme 2

In summary, the reaction between alkyl isocyanides and alkylidene Meldrum's acid in the presence of arylhydrazines leads to functionalised 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] M.p.: Electrothermal-9100 apparatus. 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, respectively; δ in ppm, *J* in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in *m/z*. Elemental analyses (C, H, N) were performed with a Heraeus CHN–O–Rapid analyser.

General procedure for the preparation of compounds **4**.

To a magnetically stirred solution of isopropylidene Meldrum's acid (0.18 g, 1 mmol) and phenylhydrazine (0.11 g, 1 mmol) in CH$_2$Cl$_2$ (15 ml) was added *tert*-butyl isocyanide (0.12 ml, 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-(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 (NH); 1727, 1697 (C=O); 1361, 1297. ^{1}H NMR: 1.36 (9 H, *s*, CMe$_3$); 1.51, 1.61 (6 H, 2 s, 2 Me); 3.34 (1 H, *s*, CH); 5.60 (1 H, *s*, NH); 7.22 (1 H, *t*, $^3J_{HH}$ = 7.4, CH); 7.41 (2 H, *t*, $^3J_{HH}$ = 7.7, 2 CH); 7.71 (2 H, *d*, $^3J_{HH}$ = 7.9, 2 CH); 8.30 (1 H, broad *s*, NH). ^{13}C NMR: 24.5, 24.6 (2 Me); 28.8 (C*Me*$_3$); 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$_3$O$_3$ (317.4): C 64.33, H 7.30, N 13.24; Found: C 63.93, H 7.08, N 13.20.

N-(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 (NH); 1714, 1652 (C=O), 1368, 1342. ^{1}H NMR: 1.30 (*9 H, s*, CMe$_3$); 1.52, 1.63 (6 H, 2 *s*, 2 CH$_3$); 3.47 (1 H, *s*, CH); 6.62 (1 H, *s*, NH); 8.11 (1 H, *d*, $^3J_{HH}$ = 9.1, CH); 8.63 (1 H, *dd*, $^3J_{HH}$ = 9.1, $^4J_{HH}$ = 2.5, CH); 8.76 (1 H, *d*, $^4J_{HH}$ = 2.5, CH); 10.9 (1 H, broad *s*, NH). ^{13}C NMR: 23.7, 24.1 (2 CH$_3$); 28.2 (C*Me*$_3$); 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$_5$O$_7$ (407.4): C 50.12, H 5.20, N 17.19; Found: C 50.21, H 5.12, N 17.30.

2-[1-(2,4-Dinitrophenyl)-3,5-dioxotetrahydro-1H-pyrazol-4-yl]-2-methyl-N-(1,1,3,3-tetramethylbutyl)propanamide (**4c**): Yield: 0.43 g (94%). Red powder, m.p. 90–92°C. IR (KBr): 3410, 3210 (NH); 1711, 1653 (C=O); 1348, 1291. ^{1}H NMR: 1.05 (9 H, *s*, CMe$_3$); 1.44 (6 H, *s*, 2 Me); 1.62 (2 H, *s*, CH$_2$); 1.42 (3 H, *s*, Me); 1.47 (3 H, *s*, Me); 3.44 (1 H, *s*, CH); 6.93 (1 H, *s*, NH); 8.02 (1 H, *d*, $^3J_{HH}$ = 9.1, CH); 8.50 (1 H, *dd*, $^3J_{HH}$ = 9.1, $^4J_{HH}$ = 2.1 Hz CH); 8.81 (1 H, *d*, $^4J_{HH}$ = 2.1, CH); 9.13 (1 H, broad *s*, NH). ^{13}C NMR: 23.1, 23.9 (2 CH$_3$); 29.6 (C*Me*$_2$); 32.0 (C*Me*$_3$); 35.2, 46.3 (2 *C*Me$_2$); 52.0 (*C*Me$_3$); 52.5 (CH$_2$); 57.2 (CH); 121.7, 124.7, 128.2 (3 CH); 134.6, 142.1, 144.4 (3 C); 166.6, 168.2, 177.7 (3 C=O). EI–MS: 463 (M$^+$, 5), 266 (48), 198 (52), 157 (100), 57 (52). Anal. Calcd for C$_{21}$H$_{29}$N$_5$O$_7$ (463.5): C 54.42, H 6.31, N 15.11; Found: C 54.21, H 6.35, N 15.09.

N-(tert-butyl)-1-[1-(2,4-dinitrophenyl)-3,5-dioxo-1-phenyltetrahydro-1H-pyrazol-4-yl)-1-cyclohexanecarboxamide (**4d**): Yield: 0.25 g (56%). Yellow powder, m.p. 170–172°C. IR (KBr): 3400, 3150 (NH); 1731 and 1685 (C=O), 1531, 1342 (C-O). ^{1}H NMR: 0.92–0.95 (4 H, *m*, 2 CH$_2$); 1.59–1.74 (6 H, *m*, 3 CH$_2$); 1.38 (9 H, *s*, CMe$_3$); 3.44 (1 H, *s*, CH); 5.63 (1 H, *s*, NH); 8.04 (1 H, *d*, $^3J_{HH}$ = 9.1, CH); 8.47 (1 H, *dd*, $^3J_{HH}$ = 9.1, $^4J_{HH}$ = 2.5, CH); 8.79 (1 H, *d*, $^4J_{HH}$ = 2.0, CH); 10.9 (1 H, broad *s*, NH). ^{13}C NMR: 25.2 (CH$_2$); 28.5 (C*Me*$_3$); 28.6, 28.8, 29.6, 30.7 (4 CH$_2$); 41.9 (C); 52.7 (*C*Me$_3$); 65.3 (CH); 121.1, 123.6, 127.7 (3 CH); 134.5, 142.2, 144.2 (3 C); 168.3, 170.9, 174.1 (3 C=O). EI-MS: 447 (M$^+$, 2), 127 (65), 73 (100), 86 (55), 57 (32). Anal. Calcd for C$_{20}$H$_{25}$N$_5$O$_7$ (447.4): C53.69, H 5.62, N 15.65; Found: C 53.74, H 5.54, N 15.47.

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