Iranian Journal of Organic Chemistry Vol. 12, No.14 (2020) 2811-2814

Catalyst free synthesis of pyrazoles using multicomponent reaction of melderum acid

Sayyed Jalal Shams-Najafi[a*] and Faramarz Rostami-Charati[b]

[a]*Department of Chemistry,Faculty of Sciences, Ferdowsi University of Mashhad, Mashhad 91779-1436, I.R. Iran*
[b]*Research Center for Conservation of Culture Relicst (RCCCR), Research institute of Cultural Heritage &Tourism, Tehran, Iran.*

Received: November 2019; Revised: December 2019; Accepted: January 20120

Abstract: In this research, the reaction between alkyl isocyanides, Meldrum's acid, ketones and hydrazines produced functionalized pyrazols in good yields.

Keywords: Meldrum's acid, Alkyl isocyanides, Four component reaction, Hydrazines, Pyrazole.

Introduction

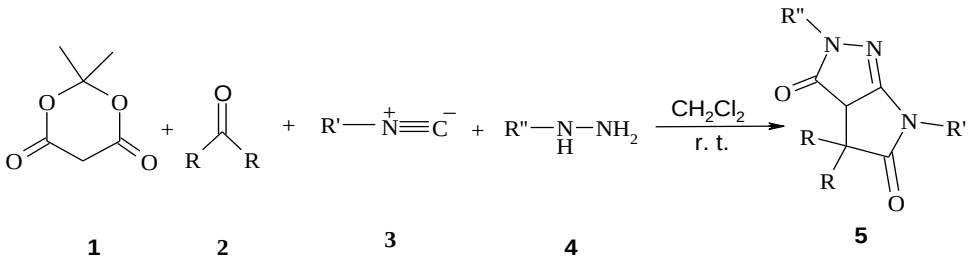
Multicomponent reactions (MCRs), with three or more reactants join in a one-pot procedure to afford a single product [1-3]. They are economically and environmentally useful because multi-step synthesis produce large amounts of trash frequently because of complex isolation actions frequently involving comfortable, toxic, and hazardous solvents after each step [4-7]. MCRs are absolutely suited for combinatorial library synthesis and increased utilize in the finding procedure for new drugs and agrochemicals [8]. They supply a dominant tool toward the one-pot synthesis of diverse and complex compounds as well as small and drug-like heterocycles [9]. Green chemistry move towards hold out significant potential not only for reduction of byproducts, waste produced, and lowering of energy but also in the expansion of new methodologies toward before exclusive materials, using existing technologies [10]. Between existing part of chemistry, medicinal and pharmaceutical chemistry are possibly developed for greening [11].

*Corresponding author: Tel: (+98) 2188006631; Fax: (+98) 2188006544, E-mail: sj.shamsnajafi7148@gmail.com

Synthesis of pyrazole has been a subject of consistent interest because of the wide applications of such heterocycles in pharmaceutical as well as in agrochemical industry [12,13]. Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, antiinflammatory, antipyretic, antibacterial, and sedative-hypnotic activity [14]. 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 and its derivatives have been widely used in organic synthesis [15, 16]. Hence, we investigated a simple four component reaction between alkyl isocyanides, Meldrum's acid, ketones and hydrazines in CH_2Cl_2 at room temperature which afforded pyrazole derivatives **5** in good isolated yield**s** (Scheme **1**).

Results and discussion

Alkyl isocyanides **3** undergo a complex reaction with melderum acid **1** and ketones **2** in the presence of hydrazine **4** in CH_2Cl_2 at room temperature to produce pyrazols **5** in high yields (Scheme 1).

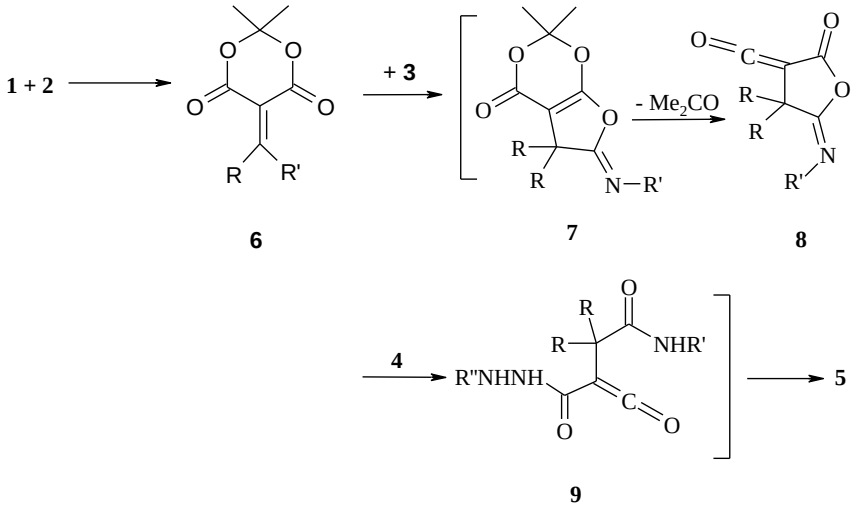


1 **2** **3** **4** **5**

5	R	R'	R"	Yield (%)
a	CH_3	^{t}Bu	Ph	85
b	CH_3	^{t}Bu	2,4-dinitrophenyl	85
c	CH_3	1,1,3,3-tetramethylbutyl	2,4-dinitrophenyl	83
d	$(CH_2)_5$	^{t}Bu	2,4-dinitrophenyl	68

Scheme 1: Synthesis of pyrazole 5.

The structures **5a-5d** was corroborated by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. For example, the ^{1}H NMR spectrum of **5a** in $CDCl_3$ showed four sharp singlets arising from CMe3 (δ(H) 1.36), two methyl groups of CMe2 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 **5a** shows thirteen distinct resonances in agreement with the proposed structure. A plausible mechanism for the formation of products **5** is proposed in Scheme 2. On the basis of the well-established chemistry of isocyanides [16-17] the reaction starts from [4+1] cycloadition of the isocyanide to the electron deficient heterodiene moiety of alkylydene melderum acid to form intermediate iminolactone **7** [18]. This intermediate first losses acetone to give acylketene 8 and then the hidrazine may attack 8 to produce **9**. With hidrazine, as NH-acid/nucleophile, the reaction leads to the pyrazol **4** (Scheme 2).



6 **7** **8** **9**

Scheme 2: Proposed mechanism for the formation of **5**.

Conclusion

In summary, the reaction between alkyl isocyanides and alkylidene Meldrum's acid in the presence of hydrazines leads 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; 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* analyzer.

General Procedure for the Preparation of Compounds 5:

To a magnetically stirred solution of Meldrum's acid (1 mmol) and ketones (1 mmol) after 30 min 0.11 g, hydrazine (1 mmol) in 15 mL CH_2Cl_2 was added. After 5min 0.12 mL *tert*-butyl isocyanide (1 mmol) at 0 °C was added. 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 (5a):

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*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 $C_{17}H_{23}N_3O_3$ (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-dioxo tetrahydro-1H-pyrazol-4-yl]-2-methylpropanamide (5b):

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*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 $C_{17}H_{21}N_5O_7$ (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-(1,1,3,3-tetramethyl butyl)propanamide (5c):

Yield: 0.43 g (94%). Red powder, m.p.90-92 °C. IR (KBr): 3410, 3210; 1711, 1653 (C=O); 1348, 1291. ^{1}H NMR: 1.05 (*s*, CMe_3); 1.44 (*s*, 2 CH_3); 1.62 (*s*, CH_2); 1.42 (*s*, CH_3); 1.47 (*s*, CH_3); 3.44 (*s*, CH); 6.93 (*s*, NH); 8.02 (*d*, $^3J_{HH}$ = 9.1 Hz, CH); 8.50 (*dd*, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 2.1 Hz CH); 8.81 (*d*, $^4J_{HH}$ = 2.1 Hz, CH); 9.13 (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 $C_{21}H_{29}N_5O_7$ (463.5): C 54.42, H 6.31, N 15.11; Found: C 54.21, H 6.35, N 15.09.

N^1-(tert-Butyl)-1-[1-(2,4-dinitrophenyl)-3,5-dioxo-1-phenyltetrahydro-1H-pyrazol-4-yl)-1-cyclohexanecarboxamide (5d):

Yield: 0.25 g (56%). Yellow powder, m.p.170-172 °C. IR (KBr): 3400, 3150; 1731 and 1685 (C=O), 1531, 1342 (C-O). ^{1}H NMR: 0.92-0.95 (*m*, 2 CH_2); 1.59-1.74 (*m*, 3 CH_2); 1.38 (*s*, 3 CH_3); 3.44 (*s*, CH); 5.63 (*s*, NH); 8.04 (*d*, $^3J_{HH}$ = 9.1 Hz, CH); 8.47 (*dd*, $^3J_{HH}$ = 9.1 Hz, $^4J_{HH}$ = 2.5 Hz CH); 8.79 (*d*, $^4J_{HH}$ = 2.0 Hz, CH); 10.9 (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 $C_{20}H_{25}N_5O_7$ (447.4): C53.69, H 5.62, N 15.65; Found: C 53.74, H 5.54, N 15.47.

References

[1] Do¨mling, A. *Comb. Chem. High Throughput Screening* **1998**, *1*, 1.

[2] Do¨mling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169.

[3] Weber, L. *Drug Discovery Today* **2002**, *7*, 143.

[4] Multicomponent Reactions; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, **2005**.

[5] Wipf, P.; Kendall, C. *Chem. Eur. J.* **2002**, *8*, 1779.

[6] Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101.

[7] Jacobi von Wangelin, A.; Neumann, H.; Gordes, D.; Klaus, S.; Strubing, D.; Beller, M. *Chem. Eur. J.* **2003**, *9*, 4286.

[8] (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (b) Ugi, I.; Domling, A. *Endeavour* **1994**, *18*, 115; (c) Heck, S.; Domling, A. *Synlett* **2000**, 424.

[9] Weber, L. *Curr. Med. Chem.* **2002**, *9*, 2085.

[10] Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Chem. Commun*. **2001**, 2159.

[11] Sheldon, R. A. *Chem. Ind.* **1997**, 12.

[12] Elguero, J. *In Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C. W. Rees, E. F. V. Scriven, , Eds.; Pergamon Press: Oxford, **1996**; Vol. 3, p 1; A. N. Kost, I. I. Grandberg, *In Advances in Heterocyclic Chemistry*; A. R. Katritzky, A. J. Boulton, , Eds.; Academic Press: New York, **1966**; Vol. 6, p 347.

[13] For leading references for synthesis and biological activity, see: a) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V. *J. Org. Chem.* **2001**, 66, 6787; b) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2003**, 44, 6737; c) Sakya, S. M.; Rast, B. *Tetrahedron Lett.* **2003**, *44*, 7629; d) Kees, K. L.; Fitzgerald, J. J.; Steiner, K. E.; Mattes, J. F.; Mihan, B.; Tosi, T.; Mondoro, D.; McCaleb, M. L. *J. Med. Chem.***1996**, *39*, 3920; e) Manfredini, S.; Bazzanini, R.; Baraldi, P. G.; Guarneri, M.; Simoni, D.; Marongiu, M. E.; Pani, A.; Tramontano, E.; Colla, P. L. *J. Med. Chem.* **1992**, *35*, 917; f) Jungheim, L. N. *Tetrahedron Lett.* **1989**, *30*, 1889; g) Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem*. **2001**, *44*, 3039; h) Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem.* **1997**, *40*, 1347; i) Bauer, V. J.; Dalalian, H. P.; Fanshawe, W. J.; Safir, S. R.; Tocus, E. C.; Boshart, C. R. *J. Med. Chem.* **1968**, *11*, 981.

[14] a) Meegalla, S. K.; Doller, D.; Liu, R.; Sha, D.; Soll, R. M.; Dhanoa, D. S. *Tetrahedron Lett.* **2002**, *43*, 8639; b) Dannhardt, G.; Laufer, S. *Curr. Med. Chem.* **2000**, *7*, 1101; c) Ashton, W. T.; Hutchins, S. M.; Greenlee, W. J.; Doss, G. A.; Chang, R. S. L.; Lotti, V. J.; Faust, K. A.; Chen, T.-B.; Zingaro, G. J.; Kivlighn, S. D.; Siegl, P. K. S. *J. Med. Chem.* **1993**, *36*, 3595.

[15] Genin, M. J.; Biles, C.; Keiser, B. J.; Poppe, S. M.; Swaney, S. M.; Tarpley, W. G.; Yagi, Y.; Romero D. L. *J. Med. Chem.* **2000**, *43*, 1034.

[16] a) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833; b) Fink, B. E.; Mortensen, D. S.; Stauffer, S. R.; Aron, Z. D.; Katzenellenbogen, J. A. *Chem. Biol.* **1999**, *6*, 205; c) Stauffer, S. R.; Katzenellenbogen, J. A. *J. Comb. Chem*. **2000**, *2*, 318; d) Astead, G. M.; Carlson, K. E.; Katzenellenbogen, J. A. *Steroids* **1997**, *62*, 268; e) Stauffer, S. R.; Huang, Y.; Coletta, C. J.; Tedesco, R.; Katzenellenbogen, J. A.; *Bioorg. Med. Chem.* **2001**, *9*, 141.