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Synthesis of important β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives in the presence of γ-alumina catalyst in aqueous medium

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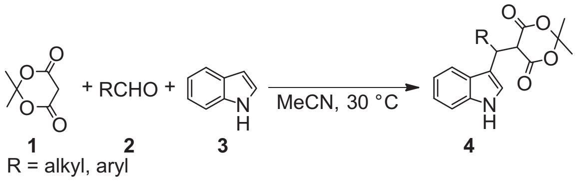
ABSTRACT

The γ-alumina catalyzed synthesis of a new series of β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives by the multi-component reaction of an aldehyde, ethylcyano acetate, and in situ generated 3-methyl-1*H*-pyrazol-5(4*H*)-one obtained from hydrazine monohyrade and ethyl acetoacetate in aqueous medium is described. The present reaction forms an important variant of the Yonemitsu-type multi-component reaction. The salient features of this present environmentally benign method are: recyclability of the catalysts, mild reaction condition, excellent yields of product, and the use of aqueous medium in the reaction.

In recent years synthetic methods involving multi-component reactions (MCRs) have attracted a lot of attention and efforts to improve on these methods are an ongoing process. As a one-pot reaction, MCRs have also become the mainstay in combinatorial chemistry,[1] which has a dramatic impact, especially in the pharmaceutical industries, where libraries of thousands of new complex molecules have been prepared using both solution and solid phase organic synthesis.[2] The synthetic utility of such protocols is further made more attractive when the reactions are carried out in aqueous medium.[3]

Among the various MCRs, Yonemitsu trimolecular condensation which involves Meldrum's acid (**1**), aldehydes/substituted aldehydes (**2**), and indole (**3**) has also gained attention due to its application in the synthesis of various biologically potent molecules (Scheme 1).[4,5] Although, Yonemitsu protocol is effective, the practicability of the reaction is diminished by the fact that the condensation gives the desired product only when Meldrum's acid is employed as the active methylene substrates. Furthermore, few reports are available in the literature on the use of Yonemitsu strategy for the preparation of condensed product with variation in the substrates. Recently the synthesis of substituted indoles, furans, pyrroles, and imidazoles has been reported using the $TiCl_4/Et_3N$ complex as a catalyst.[6] Although, this protocol gives access to important derivatives it has certain disadvantages such as requirement of dry conditions, halogenated solvents, and also organic bases.[5,6] Therefore there is still scope for the design of MCR that involves variation in one or two components in the Yonemitsu trimolecular condensation process and at the same time to develop a method which would remain cost effective and environmentally benign.



Scheme 1. Yonemitsu trimolecular condensation.

In recent years the use of inorganic solid regents has become popular due to their characteristic properties such as enhanced reactivity and selectivity, a straight forward work-up procedure and milder reaction conditions.[2,7] Among these inorganic solid reagents, alumina (Al_2O_3) has been used extensively because of the surface property and well defined porosity, which allows it to act as proficient catalyst and reagent for many important organic reactions. More importantly, alumina is eco-friendly, inexpensive, and easily accessible.

In continuation of the use of γ-alumina (γ-Al_2O_3) as a catalyst for MCRs,[8] we have developed a MCR for the synthesis of β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives by the condensation of ethylcyano acetate other than Meldrums acid,

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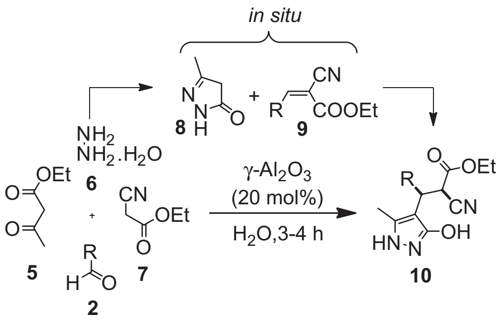
3-methyl-1*H*-pyrazol-5(4*H*)-one (generated in situ) in place of indole and an aldehyde as the reactant in the presence of γ-Al_2O_3 as a catalyst in aqueous medium. The attractiveness of the method is further augmented by the fact that the hitherto unknown β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivative prepared by the present protocol could be a potential precursor for the synthesis of biologically important heterocyclic candidates or β-amino esters.[9,10]

Thus we wish to report herein the synthesis of β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives (**10**) by the four component reaction of an aldehyde (**2**), ethyl acetoacetate (**5**), hydrazine monohydrate (**6**), and ethylcyano acetate (**7**) in the presence of γ-Al_2O_3 (20 mol %) as recyclable catalyst in aqueous medium at 40 °C (Scheme 2).

Initially the reaction condition was optimized by heating a pre-stirred (10 min, 23 °C) mixture of ethyl acetoacetate (**5**) (5.0 mmol), hydrazine monohydrate (**6**), (5.2 mmol) and a mixture of 4-methylbenzaldehyde (**2b**) (5.0 mmol) and ethylcyano acetate (**7**) (5.0 mmol) in ethanol (1 mL) and water (9 mL) in the presence of γ-alumina (10 mol %) at 40 °C. The reaction mixture resulted in the formation of **10b** in 60% yield after 5 h. The same reaction mixture with 15 mol % of catalyst gave **10b** with an increased yield (80%). Further optimization resulted in the formation of the product **10b** in 90% overall yield within 3 h when 20 mol % of the catalyst was used (Table 1 and Fig. 1). However, the same reaction mixture in the absence of the catalyst did not give the desired product rather only compound **8** and trace amount of compound **9** were obtained, thus indicating the importance of the catalyst in the reaction. On the other hand, the use of other heterogeneous catalysts such as silica or aluminosilicates for example zeolites also did not give the desired product. The structure of **10b** was assigned based on the IR, ^{1}H, and ^{13}C NMR spectroscopy. Finally the molecular structure was confirmed by single-crystal X-ray diffraction studies (Fig. 2).

The ^{1}H, ^{13}C NMR spectroscopic data clearly indicate the mixture of two diastereomers in almost 1:1 ratio. It may be noted that partial crystallization of the mixture from dichloromethane:ethanol (1:1) yielded a single crystal of diastereomers.

The recyclability of the catalyst was ascertained, when the catalyst recovered from the reaction after filtration and washing with boiling ethanol was dried and reused for the condensation of ethyl acetoacetate (**5**), hydrazine monohydrate (**6**), 4-methylbenzaldehyde (**2b**), and ethylcyano acetate (**7**). Interestingly, the reaction proceeded efficiently to furnish **10b** in 89% yield with no change in the reaction time. The reusability of the catalyst was further confirmed when it was found to exhibit good activity even after the fourth run with no major drops in the yield of the product (Table 2).



Scheme 2.

Table 1
Optimization of reaction condition with **7b**

Entry	Reaction conditions	Yield[a] (%)
1	Without catalyst, 5 h, at 40 °C	–
2	γ-Al_2O_3 (10 mol %), 5 h, at 40 °C	60
3	γ-Al_2O_3 (15 mol %), 5 h, at 40 °C	80
4	γ-Al_2O_3 (20 mol %), 3 h, at 40 °C	90
5	γ-Al_2O_3 (20 mol %), 5 h, at 40 °C	89

[a] Isolated yields.

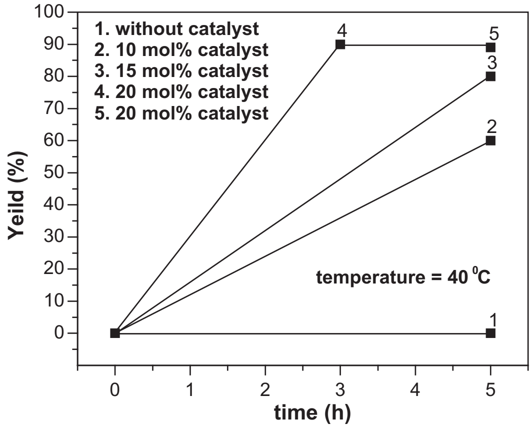


Figure 1. Plot showing the variation in yield (%) of product **10b** versus time at different catalyst loads (mol %).

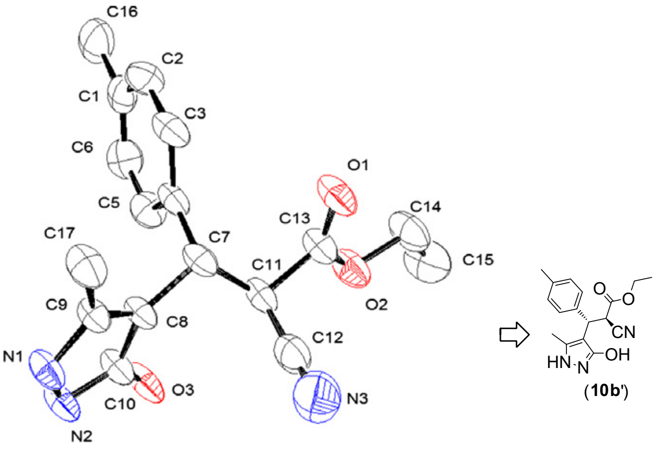


Figure 2. Ortep image of (2R,3S)-ethyl 2-cyano-3-(3-hydroxy-5-methyl-1*H*-pyrazol-4-yl)-3-(*p*-tolyl)propanoate (**10b**′).

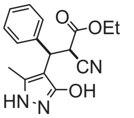
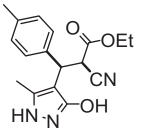
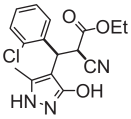
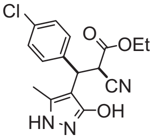
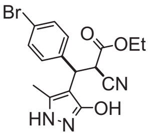
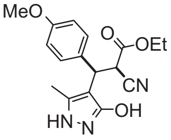
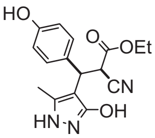
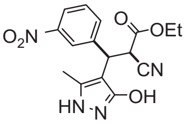
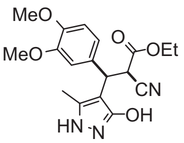
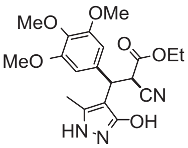
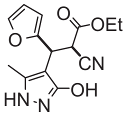
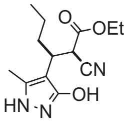
Table 2
Reusability test of the catalyst with **10b**

Entry	Reaction conditions	Yield[a] (%)
1	γ-Al_2O_3 (20 mol%, recycled once), 3 h, at 40 °C	89
2	γ-Al_2O_3 (20 mol%, recycled twice), 3 h, at 40 °C	85
3	γ-Al_2O_3 (20 mol%, recycled three times), 3 h, at 40 °C	82
4	γ-Al_2O_3 (20 mol%, recycled four times), 4 h, at 40 °C	79

[a] Isolated yields.

Subsequently, a series of β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives (entries 1, 3–10, Table 3) were prepared by adding a pre-stirred mixture (5 min at 23 °C) of ethyl acetoacetate (**5**) (5.0 mmol), hydrazine monohydrate (**6**) (5.2 mmol) to a mixture of aldehydes (**2**) (5.0 mmol) and ethylcyanoaceate (**7**) (5.0 mmol) in ethanol (1 mL) and water (9 mL). Then, to this reaction mixture was added γ-alumina (20 mol %) and heated at 40 °C for 3–4 h. The reaction mixture was then allowed to cool, filtered

Table 3
γ-Al_2O_3 catalyzed synthesis of β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives

Entry	Substrate **2** (*R*)	Time (h)	Product **10**[b]	Yield[a] (%)
1	C_6H_5 (**2a**)	3	 (**10a**)	91
2	4-$CH_3C_6H_4$ (**2b**)	3	 (**10b**)	90
3	2-ClC_6H_4 (**2c**)	3	 (**10c**)	92
4	4-ClC_6H_4 (**2d**)	3	 (**10d**)	91
5	4-BrC_6H_4 (**2e**)	3	 (**10e**)	89
6	4-$CH_3OC_6H_4$ (**2f**)	3	 (**10f**)	88
7	4-HOC_6H_4 (**2g**)	4	 (**10g**)	72
8	3-$NO_2C_6H_4$ (**2h**)	4	 (**10h**)	93
9	3,4-$(CH_3O)_2C_6H_3$ (**2i**)	3	 (**10i**)	87
10	3,4,5-$(CH_3O)_3C_6H_2$ (**2j**)	3	 (**10j**)	84
11	Furanyl (**2k**)	3	 (**10k**)	89
12	Propionyl (**2l**)	4	 (**10l**)	78[c]

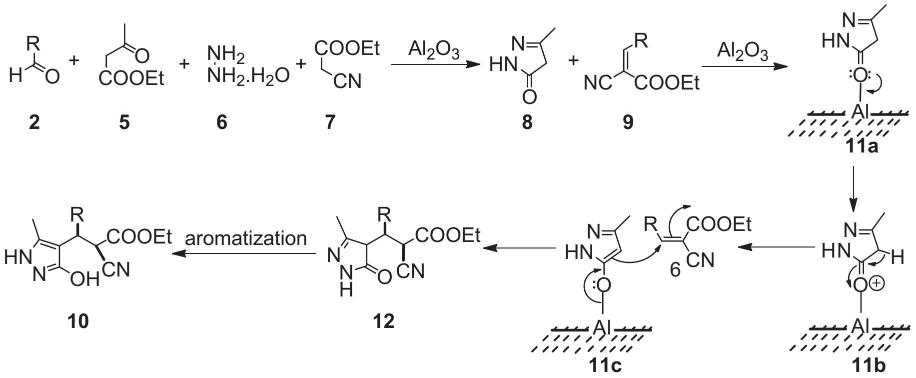
[a] Isolated yields.
[b] Products have been characterized by recording their IR, ^1H NMR and ^{13}C NMR spectra.
[c] Purified by column chromatography.

through a sintered funnel, and washed thoroughly with boiling ethanol (3 × 20 mL). The combined filtrate was reduced to 10 mL by volume. The precipitate formed was filtered and washed with water to give solid crude product mass, which was further purified by precipitation from a concentrated solution of product mass in ethanol to obtain pure compound **10**. Irrespective of the presence of electron withdrawing or donating substituents in the ortho, meta, or para positions on the ring of various aromatic aldehydes the reactions proceeded smoothly to furnish the desired products in good to excellent yields. Similarly, the aromatic aldehydes with deactivating substituent such as, 3-nitrobenzaldehyde (**2h**) gave excellent yield of the product **10h** (Table 3, entry 8). However, 4-hydroxybezaldehyde (**2g**) afforded the desired product in 72% yield even after continuing the reaction for 4 h at 40 °C (Table 3, entry 7). Notably, the reaction of heterocyclic aldehydes such as furan-2-carbaldehyde (**2k**) afforded **10k** in 89% yield under the experimental conditions (Table 3, entry 11). The methodology was also found to be effective for butyraldehyde (**2l**) which reacted cleanly with substrates **5**, **6**, and **7** to give β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivative **10l** in 78% yield (Table 2, entry 12). The products obtained were fully characterized by ^1H, ^{13}C NMR, IR, mass spectral, and elemental analyses.[11] In each case ^1H, ^{13}C NMR study showed the presence of two diastereomer peaks.

It may be mentioned that in all the reactions no cyclized products were formed as is usually expected to occur in this type of condensations.[8,9]

Although the mechanistic details remain ambiguous, it is presumed that the amphoteric nature and high surface area of alumina allow compound **8** to adsorb on its surface to give complex **11c** which facilitates the Michael addition of **11c** to the Knoevenagel product **9** to give intermediate **12**. Subsequently aromatization of the intermediate **12** affords product **10** (Scheme 3).

In summary, γ-alumina was found to be an efficient and recyclable inorganic solid catalyst for the synthesis β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives in aqueous medium which is an important variant of the Yonemitsu-type of multi-component reaction. The present reaction involved aldehydes, ethylcyano acetate, and in situ generated 3-methyl-1*H*-pyrazol-5(4*H*)-one obtained from hydrazine monohydrate and ethyl acetoacetate as the reactants to provide the titled compounds in excellent yields under mild reaction conditions and environment friendly procedures. More importantly, the unknown β-functionalized 5-methyl-1*H*-pyrazol-3-ol derivatives synthesized by the present protocol could be potential precursors for the synthesis of heterocyclic candidates with potentials for biological activities or β-amino esters.



Scheme 3. Plausible mechanism.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.073.

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11. *Spectroscopic analytical data: Ethyl* 2-*cyano*-3-(3-*hydroxy*-5-*methyl*-1*H*-*pyrazol*-4-*yl*)-3-(*p*-*tolyl*)*propanoate* (**10b**). White solid; mp 162–164 °C. IR (KBr film): 3456, 3397, 2986, 2925, 2217, 1725, 1598, 1515, 1447, 1367, 1272, 1209, 1191 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ 7.36/7.23 (d,‡ J = 8.0 Hz, 2H), 7.02/6.98 (d,‡ J = 8.0 Hz, 2H), 4.62/4.61 (d,‡ J = 11.6 Hz, 1H), 4.29–4.23 (m, 1H), 4.03–3.93/3.91–3.82 (m,‡ 2H), 2.31/2.16 (s,‡ 3H), 2.03/1.93 (s,‡ 3H), 0.96/0.87 (t,‡ J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ 166.5, 161.1/161.0, 139.2/139.1, 138.5, 137.7/137.6, 130.0, 128.9/128.6, 117.4/117.3, 101.6/101.1, 63.0/62.9, 43.3/43.2, 42.6, 42.5/42.0, 14.0, 10.2 ppm; MS (ES+) calcd for $C_{17}H_{19}N_3O_3$ 313.1, found *m*/*z* 314.0 [M+H]$^+$, 336.1 [M+Na]$^+$; Anal. Calcd for $C_{17}H_{19}N_3O_3$: C, 65.16; H, 6.11; N, 13.41%; Found: C, 65.30; H, 6.19; N, 13.36%.
    Ethyl 2-cyano-3-(furan-2-yl)-3-(3-hydroxy-5-methyl-1H-pyrazol-4-yl)propanoate (**10k**). Off white solid; 141–143 °C. IR (KBr film): 3326, 2925, 2651, 2263, 1746, 1604, 1536, 1310, 1231, 1159, 1015 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.04 (s br s, 1H), 10.20 (s br s, 1H), 7.60–7.56 (m, 1H), 6.42–6.25 (m, 2H), 4.71–4.70/4.63–4.61 (m,‡ 1H), 4.57–4.51 (m, 1H), 4.12–4.10/4.09–4.03 (m,‡ 2H), 2.00/1.86 (s,‡ 3H), 1.13/1.07 (t,‡ J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.4/166.1, 159.7/159.4, 152.4/152.1, 142.4, 138.0, 116.8/116.6, 110.6, 107.1/107.0, 97.2/97.0, 62.5/62.4, 41.3/41.0, 34.9/34.8, 13.7, 10.4/10.1 ppm; Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53%; Found: C, 58.26; H, 5.30; N, 14.47%.
    Ethyl 2-*cyano*-3-(3-*hydroxy*-5-*methyl*-1*H*-*pyrazol*-4-*yl*)*hexanoate* **(10l)**. Yellow solid; mp 84–87 °C. IR (KBr film): 3362, 2961, 2928, 2868, 2247, 1745, 1607, 1523, 1465, 1370, 1218, 1178, 1111, 1029 cm^{-1}.^{1}H NMR (400 MHz, DMSO-d_6): δ 11.10 (s br, 1H), 9.73 (s br, 1H), 4.18–4.12/4.11–4.03 (m,‡ 2H), 4.02–3.98 (m, 1H), 3.08–3.03 (m, 1H), 2.10/2.05 (s,‡ 3H), 1.89–1.86/1.76–1.73 (m,‡ 2H), 1.60–1.58/1.47–1.46 (m,‡ 2H), 1.20/1.05 (t,‡ J = 7.2 Hz, 3H), 0.85–0.80 (m, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.1/165.8, 159.9, 137.8, 128.4, 117.3/117.0, 100.0/97.5, 62.2/61.9, 42.7/42.5, 35.6/35.4, 33.1/32.6, 20.0, 13.8/13.6, 10.3/10.0 ppm; Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84%; Found: C, 58.96; H, 7.18; N, 15.79%.
    ‡ = Double signals: Isomers.