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Short Communication

Catalyst-free one-pot synthesis of 1,4,5-trisubstituted pyrazoles in 2,2,2-trifluoroethanol

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ABSTRACT

A simple, efficient and three component one-pot synthesis of 1,4,5-trisubstituted pyrazoles by condensation of β-dicarbonyls, *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) and hydrazine derivatives in 2,2,2-trifluoroethanol without using any catalyst and activation, is described.

1. Introduction

Pyrazoles have attracted much attention in the last decades as their synthesis has become more accessible and their diverse properties appreciated [1]. Specifically, the pyrazole moiety is present in many pharmacologically and agrochemically important compounds, including those used as inhibitors of HIV-1 reverse transcriptase [2], COX-2 inhibitors [3], sodium hydrogen ion exchanger NHE-1 [4], dipeptidyl peptidase IV (DPP-IV) [5] and in the pesticides such as Cyanopyrafen [6] and Tebufenpyrad [7].

Numerous methods for the synthesis of pyrazole derivatives have been reported in the literature [8–11], for example addition of hydrazines to 1,3-dicarbonyl [12], or α,β-unsaturated carbonyl compounds [13] and 1,3-cycloaddition of diazoalkanes to alkynes [14].

Enaminone derivatives, which are usually prepared from formamide acetals and active methylene ketones [15], are highly reactive intermediates on the synthesis of heterocyclic compounds. Among the different methodologies for the synthesis of the pyrazoles, several examples of the reaction between arylhydrazine derivatives and enaminones have been reported [16], which provide better regioselectivity compared to the former ones. Low yields, acid (HOAc) requirement, two step synthesis and limited substitution patterns have been described in most cases [17–20].

N-methylpyrazoles are also synthesized from methylhydrazine and enaminones, but, the observed regioselectivities reported, are usually low [16a,b,c,21].

On the other hand, fluorinated alcohols have been shown to display unique properties as solvents, cosolvents and additives in organic synthesis due to their CF_3 group. Their high hydrogen bond donating ability, low nucleophilicity, strong ionizing power and ability to solvate water, differentiating them from their non-fluorinated counterparts and other protic solvents [22]. Trifluoroethanol (TFE) modifies the course of reactions when it is used as solvent. Reactions in TFE are generally selective and carried out without using any reagents or catalysts under mild conditions, allowing thus a facile isolation of the product and a recovery of the solvent by distillation [23].

Due to the fact that, most of the aforementioned methods focused on the preparation of mono-and disubstituted pyrazoles and the importance of trisubstituted pyrazoles in recent years, we wish to report here, an efficient, one-pot, regioselective and catalyst-free procedure to prepare 1,4,5-trisubstituted pyrazoles via the condensation of 1,3-dicarbonyls, *N*,*N*-dimethylformamide dimethyl acetal and hydrazines in TFE under mild reaction conditions.

2. Results and discussion

In our work, we initially showed the effectiveness of TFE as a solvent in the preparation of ethyl 5-methyl-1-phenyl-1H-pyrazole-4-carboxylate. 3-Oxo-butyric acid ethyl ester, *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) were treated

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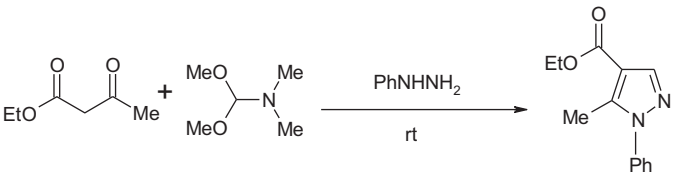
Table 1
Preparation of pyrazoles in different solvents.[a]



Entry	Solvent	Time	Yield (%)[b]
1	THF	5 h	20
2	CH_2Cl_2	5 h	24
3	EtOH	4 h	30
4	MeOH	4 h	35
5	TFE	10 min	98
6	HFIP	10 min	80
7	EtOH/TFE (1:1)	2 h	80

[a] Reactions were performed at room temperature using 1 mmol of 3-oxo-butyric acid ethyl ester, 1.2 mmol DMFDMA and 1.2 mmol of phenylhydrazine.
[b] Yields refer to isolated products.

with phenylhydrazine at room temperature in various solvents (Table 1). As it is clear from this table, high yield of the desired pyrazole is obtained in fluorinated solvents (Table 1, entries 5 and 6). This has further confirmed when TFE was used as a co-solvent with ethanol which significantly reduced the reaction time and increased the yield of the product (Table 1, entries 3 and 7). Reactions in aprotic solvents such as THF and CH_2Cl_2 (Table 1, entries 1 and 2) occur quite slowly and a low yield of the product is formed. The highest yield was achieved in TFE only after 10 min (Table 1, entry 5)

In order to show the generality of this reaction we synthesized different substituted pyrazoles using a variety of β-dicarbonyls and arylhydrazines in TFE as a solvent (Table 2).

Reactions of 3-oxo-butyric acid ethyl ester (1 mmol) and DMFDMA (1.2 mmol) with various arylhydrazines (1.2 mmol) in TFE (1 ml) at room temperature, afforded 4-carboxylate pyrazoles in excellent yields (Table 2, entries 1–3). Similarly other β-keto esters reacted smoothly under reaction conditions to give high yield of the desired pyrazoles (Table 2, entries 4–9).

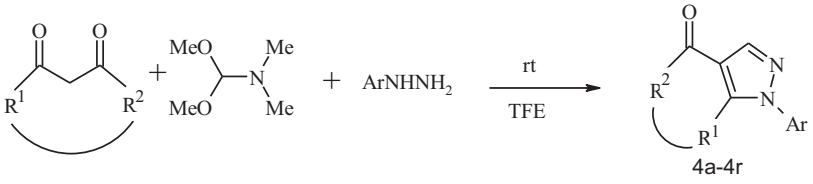
1,3-Cyclohexanedione as cyclic β-diketone required higher temperature (refluxing in TFE) and longer reaction time to afford excellent yield of the corresponding pyrazoles (Table 2, entries 10–12). Reactions of open-chain β-diketones (Scheme 1, 1: R = Me or Et) under optimal reaction conditions produced a mixture of 4-acylpyrazoles (4m–4r) and 3,5-dialkyl-1-aryl pyrazoles (5). However, using an excess amount of DMFDMA (two equivalents), led to formation of the 4-acylpyrazoles as sole product in excellent yields (Table 2, entries 13–18). It is believed that, compounds (4m–4r) are produced through formation of enaminone (2) [19] and trisubstituted pyrazoles (5), are obtained from β-ketoarylhydrazone intermediate (3) [12].

In contrast with arylhydrazines, when methylhydrazine was used as a bidentate nucleophile, a mixture of isomers was formed. This might be due to the close nucleophilicity of both nitrogen atoms in methylhydrazine as, it was reported for similar reactions [16]. In our effort, when 3-oxo-butyric acid ethyl ester and DMFDMA condensed with methylhydrazine under conditions of arylhydrazines at room temperature, a mixture of regioisomers 6a and 7 (3:1) was obtained in 10 min, as determined by NMR spectra (Scheme 2).

In order to improve the selectivity, different reaction conditions were examined. A high selectivity (95:5) was achieved when methylhydrazine (1.2 mmol) was added dropwise to a mixture of DMFDMA (1.2 mmol) and 3-oxo-butyric acid ethyl ester (1 mmol) at 0 °C in TFE (2 ml) and subsequently stirred at room temperature for 10 min.

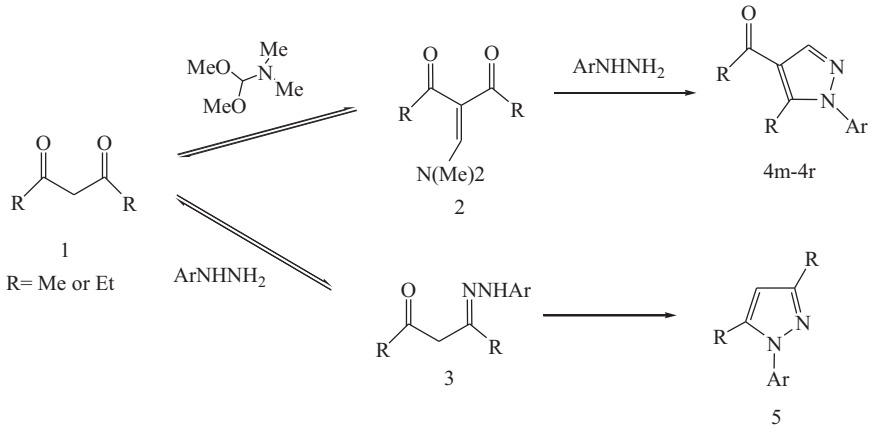
This reaction was extended to cyclic and open-chain 1,3-diketones and in all cases high regioselectivity in favour of 1,4,5-trisubstituted pyrazoles were observed (Table 3, entries 1–6).

Table 2
Preparation of arylpyrazole derivatives.[a]

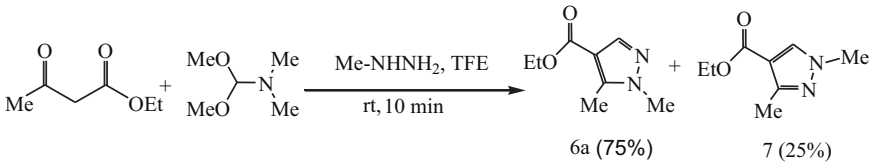


Entry	R^1	R^2	Ar	Time (min)	Product	Yield (%)[b]
1	Me	OEt	Ph	10	4a	98
2	Me	OEt	p-ClC_6H_4	15	4b	95
3	Me	OEt	p-$OMeC_6H_4$	10	4c	97
4	Me	O*t*-Bu	Ph	10	4d	93
5	Me	O*t*-Bu	p-ClC_6H_4	16	4e	94
6	Me	O*t*-Bu	p-$OMeC_6H_4$	10	4f	98
7	*i*-Pr	OEt	Ph	60	4g	94
8	*i*-Pr	OEt	p-ClC_6H_4	80	4h	94
9	*i*-Pr	OEt	p-$OMeC_6H_4$	30	4i	97
10[c]	$-(CH_2)_3-$	–	Ph	60	4j	91
11[c]	$-(CH_2)_3-$	–	p-ClC_6H_4	180	4k	92
12[c]	$-(CH_2)_3-$	–	p-$OMeC_6H_4$	30	4l	90
13[d]	Me	Me	Ph	5	4m	94
14[d]	Me	Me	p-ClC_6H_4	10	4n	95
15[d]	Me	Me	p-$OMeC_6H_4$	5	4o	93
16[d]	Et	Et	Ph	5	4p	92
17[d]	Et	Et	p-ClC_6H_4	5	4q	93
18[d]	Et	Et	p-$OMeC_6H_4$	5	4r	95

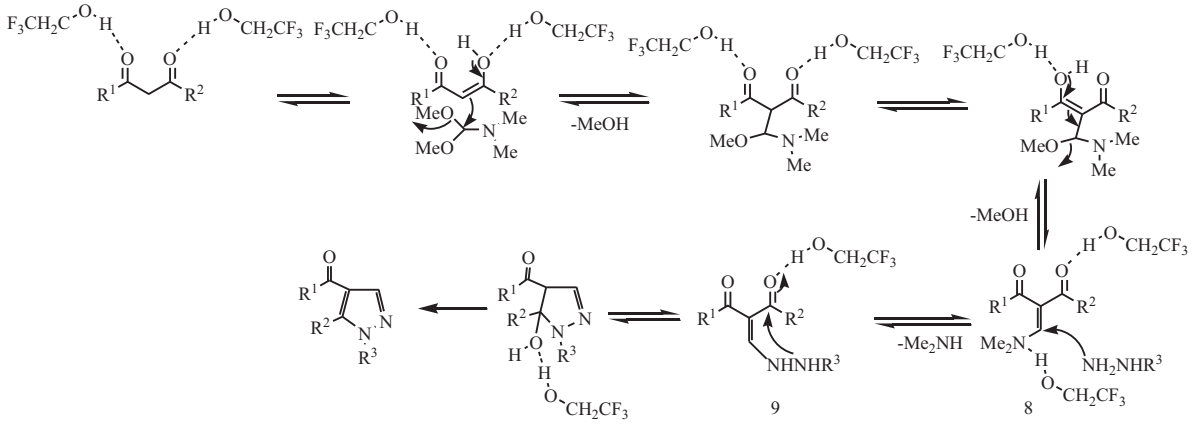
[a] Reactions were performed using β-dicarbonyls (1 mmol), DMFDMA (1.2 mmol) and arylhydrazines (1.2 mmol) at room temperature.
[b] Isolated yield.
[c] Reaction was carried out under reflux conditions.
[d] 2 mmol of DMFDMA was used.



Scheme 1.

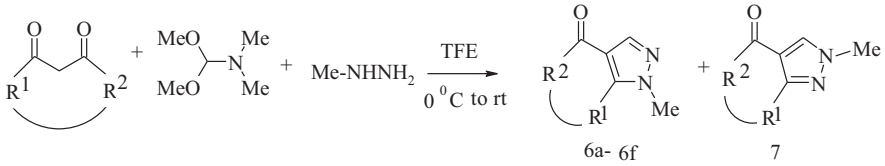


Scheme 2.



Scheme 3.

Table 3
Preparation of methylpyrazole derivatives.[a]



Entry	R^1	R^2	Time (min)	Product	Yield (%)[b]
1	Me	OEt	10	6a	95:5 (98)
2	Me	O*t*-Bu	15	6b	96:4 (96)
3	*i*-Pr	OEt	30	6c	92:8 (96)
4[c]	$-(CH_2)_3-$	–	5	6d	100:0 (90)
5[d]	Me	Me	5	6e	95:5 (97) (90[e])
6[d]	Et	Et	5	6f	97:3 (98)

[a] Reactions were performed using β-dicarbonyls (1 mmol), DMFDMA (1.2 mmol) and methylhydrazines (1.2 mmol) at 0 °C to room temperature.
[b] Isolated yield.
[c] Reaction was carried out under reflux conditions.
[d] 2 mmol of DMFDMA was used.
[e] After recrystallization from anhydrous diethyl ether.

It is believed that, the electrophilic character of the carbonyl groups is enhanced by high hydrogen bond donating ability of the CF_3CH_2OH [22a] which facilitate the in situ generation of the enaminone 8. Subsequent Michael addition of the terminal amino group of the substituted hydrazines to enaminone 8 forms the acyclic species 9 which undergoes an intramolecular cyclodehydration to afford the pyrazole derivative (Scheme 3) [16a,19].

3. Conclusion

In this study, we have developed a simple, mild and regioselective one pot approach for the preparation of 1,4,5-trisubstituted pyrazoles starting from different β-keto esters or β-diketones and various hydrazines in TFE which are completed in excellent yields without use of any catalyst or additive.

4. Experimental

4.1. General

Materials were purchased from Fluka and Merck companies. Products were characterized by comparison of their spectroscopic data (^{1}H NMR, ^{13}C NMR) and elemental analysis (CHN).

4.2. General procedure for preparation of the arylpyrazole derivatives

Arylhydrazine (1.2 mmol) in TFE (0.5 ml) was slowly added to a solution of β-dicarbonyl (1.2 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.2 mmol) in TFE (0.5 ml) at room temperature. The progress of reactions was monitored by TLC. After completion of the reaction solvent was evaporated under reduced pressure, and water (10 ml) was added to the residue and extracted with ethylacetate (2× 10 ml). The organic layer was successively washed with sodium hydrogen carbonate solution and water, and then dried with magnesium sulfate. Evaporation of the solvent afforded 4-carboxylate pyrazole. If necessary the products were further purified by column chromatography on silica gel.

Reactions with 1,3-cyclohexanedione were carried out at reflux temperature (Table 2, entries 10–12). In the case of open-chain β-diketones, under optimal reaction conditions two equivalents of DMFDMA were used (Table 2, entries 13–18).

Spectral data of all products are as follows.

4.2.1. 5-Methyl-1-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester 4a (Table 1, entry 1)

mp 49–52 °C [18]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.40 (t, J = 7.2 Hz, 3H, Me), 2.59 (s, 3H, Me), 4.35 (q, J = 7.2 Hz, 2H, CH_2) 7.28–7.55 (m, 5H, Ph), 8.05 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 11.96, 14.45, 59.98, 112.97, 125.52, 128.64, 129.26, 138.86, 141.92, 143.54, 163.87. Calcd. For $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.83; H, 6.12; N, 12.17.

4.2.2. 1-(4-Chloro-phenyl)-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester 4b (Table 1, entry 2)

mp 60–61 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, J = 7.2 Hz, 3H, Me), 2.57 (s, 3H, Me), 4.33 (q, J = 7.2 Hz, 2H, CH_2) 7.37 (d, J = 11.6 Hz, 2H, Ph), 7.46 (d, J = 11.6 Hz, 2H, Ph), 8.032 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 11.93, 14.42, 60.05, 113.29, 126.67, 129.46, 134.51, 137.35, 142.14, 143.55, 163.66. Calcd. For $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 58.94; H, 4.97; N, 10.60.

4.2.3. 1-(4-Methoxy-phenyl)-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester 4c (Table 1, entry 3)

mp 63–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, J = 7.2 Hz, 3H, Me), δ 2.51 (s, 3H, Me), 3.85 (s, 3H, Me), 4.31 (q, J = 7.2 Hz, 2H, CH_2), 6.99 (d, J = 15.6 Hz, 2H, Ph), 7.30 (d, J = 15.6 Hz, 2H, Ph), 8.00 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 11.81, 14.43, 55.55, 59.89, 114.33, 120.99, 126.88, 131.83, 141.58, 143.59, 159.64, 163.87. Calcd. For $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.65; H, 6.18; N, 10.70.

4.2.4. 5-Methyl-1-phenyl-1H-pyrazole-4-carboxylic acid tert-butyl ester 4d (Table 1, entry 4)

Oil [21a]. ^{1}H NMR (400 MHz, $CDCl_3$): 1.58 (s, 9H, Me), 2.53 (s, 3H, Me), 7.39–7.51 (m, 5H, Ph), 7.97 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 11.94, 28.40, 80.42, 114.36, 125.51, 128.52, 129.20, 138.93, 142.01, 143.02, 163.26. Calcd. For $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.73; H, 7.05; N, 10.85.

4.2.5. 1-(4-Chloro-phenyl)-5-methyl-1H-pyrazole-4-carboxylic acid tert-butyl ester 4e (Table 1, entry 5)

Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (s, 9H, Me), 2.54 (s, 3H, Me), 7.37 (d, J = 14.2 Hz, 2H, Ph), 7.55 (d, J = 14.4 Hz, 2H, Ph) 7.97, (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 11.94, 28.39, 80.59, 114.70, 126.70, 129.42, 134.40, 137.46, 142.29, 143.04, 163.08. Calcd. For $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57. Found: C, 61.50; H, 5.79; N, 9.55.

4.2.6. 1-(4-Methoxy-phenyl)-5-methyl-1H-pyrazole-4-carboxylic acid tert-butyl ester 4f (Table 1, entry 6)

Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.57 (s, 9H, Me), δ 2.48 (s, 3H, Me), 3.84 (s, 3H, Me), 6.97 (d, J = 12.4 Hz, 2H, Ph), 7.29 (d, J = 12 Hz, 2H, Ph), 7.93 (s, 1H, CH). ^{13}C NMR (400 MHz, $CDCl_3$): 11.82, 28.40, 55.54, 80.34, 114.31, 120.98, 126.91, 131.91, 141.71, 143.11, 159.58, 163.31. Calcd. For $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.67; H, 6.94; N, 9.73.

4.2.7. 5-Isopropyl-1-phenyl-1H-pyrazole-4-carboxylic acid ethyl ester 4g (Table 1, entry 7)

mp 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (d, J = 6.8 Hz, 6H, Me), 1.38 (t, J = 7.2, 3H, Me), 3.24–3.31 (m, 1H, CH), 2.25 (q, J = 7.2, 2H CH_2) 7.35–7.52 (m, 5H, Ph), 8.04 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 14.41, 20.07, 26.38, 60.00, 111.56, 126.63, 129.15, 129.20, 139.46, 142.99, 152.81, 163.36. Calcd. For $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.72; H, 7.04; N, 10.81.

4.2.8. 1-(4-Chloro-phenyl)-5-isopropyl-1H-pyrazole-4-carboxylic acid ethyl ester 4h (Table 1, entry 8)

mp 62–65 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (d, J = 6.8 Hz, 6H, Me), 1.39 (t, J = 6.8, 3H, Me), 3.21–3.28 (m, 1H, CH), 4.33 (q, J = 6.8, 2H, CH_2) 7.37 (d, J = 8.8 Hz, 2H, Ph), 7.49 (d, J = 8.8 Hz, 2H, Ph), 8.03 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 14.40, 20.08, 26.41, 60.12, 111.87, 127.9, 129.45, 135.16, 137.90, 143.24, 152.93, 163.21. Calcd. For $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 12.11. Found: C, 61.53; H, 5.84; N, 12.11.

4.2.9. 5-isopropyl-1-(4-Methoxy-phenyl)-1H-pyrazole-4-carboxylic acid ethyl ester 4i (Table 1, entry 9)

mp 63–66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.34 (d, J = 6.8 Hz, 6H, Me), 1.38 (t, J = 7.2, 3H, Me), 3.23–3.30 (m, 1H, CH), 3.22 (q, J = 7.2, 2H CH_2), 3.87 (s, 3H, Me), 6.99 (d, J = 8.8 Hz, 2H, Ph), 7.27 (d, J = 8.8 Hz, 2H, Ph), 8.01 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 14.41, 20.08, 26.35, 55.57, 59.95, 111.26, 114.35, 127.87, 132.40, 124.72, 152.97, 156.00, 163.42. Calcd. For $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.63; H, 6.96; N, 9.72.

4.2.10. 1-Phenyl-1,5,6,7-tetrahydro-4H-indazol-4-one 4j (Table 1, entry 10)

mp 77–80 °C [19]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16–2.22 (m, 2H, CH_2), 2.57 (t, J = 6.4, 2H, CH_2), 3.00 (t, J = 6.4, 2H, CH_2), 7.43–7.53 (m, 5H, Ph), 8.09 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 23.28,

23.64, 37.91, 120.53, 123.62, 128.25, 120.41, 138.51, 138.7, 149.13, 193.30. Calcd. For $C_{13}H_{12}N_2O$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.55; H, 5.73; N, 13.22.

4.2.11. 1-(4-Chloro-phenyl)-1,5,6,7-tetrahydro-4H-indazol-4-one 4k (Table 1, entry 11)

mp 94–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.19–2.22 (m, 2H, CH_2), 2.57 (t, J = 6, 2H, CH_2), 2.99 (t, J = 6, 2H, CH_2), 7.48 (d, J = 9.2 Hz, 2H, Ph), 7.52 (d, J = 9.2 Hz, 2H, Ph), 8.09 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 23.28, 23.59, 37.84, 120.76, 124.75, 129.61, 134.08, 137.23, 138.77, 149.09, 193.11. Calcd. For $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.29; H, 4.46; N, 11.37.

4.2.12. 1-(4-Methoxy-phenyl)-1,5,6,7-tetrahydro-4H-indazol-4-one 4l (Table 1, entry 12)

mp 142–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.14–2.19 (m, 2H, CH_2), 2.55 (t, J = 6, 2H, CH_2), 2.92 (t, J = 6, 2H, CH_2), 3.88 (s, 3H, Me), 7.02 (d, J = 9.2 Hz, 2H, Ph), 7.24 (d, J = 9.2 Hz, 2H, Ph), 8.05 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 2.99, 23.58, 37.91, 55.62, 114.5, 120.14, 125.17, 131.73, 138.16, 149.10, 159.41, 193.39. Calcd. For $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.40; H, 5.79; N, 11.58.

4.2.13. 1-(5-Methyl-1-phenyl-1H-pyrazol-4-yl)ethan-1-one 4m (Table 1, entry 13)

mp 103–107 °C [21b]. ^{1}H NMR (400 MHz, $CDCl_3$): 2.48 (s, 3H, Me), 2.57 (s, 3H, Me), 7.39–7.49 (m, 5H, Ph), 8.00 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.40, 28.71, 121.09, 125.54, 128.82, 129.30, 138.54, 141.94, 142.99, 193.57. Calcd. For $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.94; H, 6.03; N, 13.94.

4.2.14. 1-(1-(4-Chlorophenyl)-5-methyl-1H-pyrazol-4-yl)ethan-1-one 4n (Table 1, entry 14)

mp 110–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.51 (s, 3H, Me), 2.60 (s, 3H, Me), 7.39 (d, J = 12 Hz, 2H, Ph), 7.46 (d, J = 12 Hz, 2H, Ph), 8.02 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.37, 28.73, 121.29, 126.73, 129.51, 134.74, 137.04, 142.13, 143.01, 193.45. Calcd. For $C_{12}H_{11}ClN_2O$: C, 61.41; H, 4.72; N, 11.94. Found: C, 61.47; H, 4.70; N, 11.90.

4.2.15. 1-(1-(4-Methoxyphenyl)-5-methyl-1H-pyrazol-4-yl)ethan-1-one 4o (Table 1, entry 15)

mp 86–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.50 (s, 3H, Me), 2.55 (s, 3H, Me), 3.88 (s, 3H, Me), 7.02 (d, J = 8.8 Hz, 2H, Ph), 7.3 (d, J = 8.8 Hz, 2H, Ph), 8.00 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 12.30, 28.65, 55.60, 114.4, 120.83, 126.90, 131.51, 141.69, 143.06, 159.77, 193.54. Calcd. For $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.82; H, 6.15; N, 12.20.

4.2.16. 1-(5-Ethyl-1-phenyl-1H-pyrazol-4-yl)-propan-1-one 4p (Table 1, entry 16)

Oil [21b]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7.6 Hz, 3H, Me), 1.95 (t, J = 7.2 Hz, 3H, Me), 2.65 (q, J = 7.2 Hz, 2H, CH_2), 2.94 (q, J = 7.6 Hz, 2H, CH_2), 7.28–7.51 (m, 5H, Ph), 8.00 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 8.18, 13.23, 18.91, 33.91, 119.59, 125.89, 129.02, 129.29, 138.69, 141.44, 148.88, 196.26. Calcd. For $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.62; H, 7.06; N, 12.28.

4.2.17. 1-(1-(4-Chloro-phenyl)-5-ethyl-1H-pyrazol-4-yl)-propan-1-one 4q (Table 1, entry 17)

mp 55–57 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, J = 7.6 Hz, 3H, Me), 1.22 (t, J = 7.2 Hz, 3H, Me), 2.87 (q, J = 7.2 Hz, 2H, CH_2), 2.96 (q, J = 7.6 Hz, 2H, CH_2), 7.36 (d, J = 8.8 Hz, 2H, Ph), 7.49 (d, J = 8.8 Hz, 2H, Ph), 8.02 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 8.15, 13.26, 18.91, 33.98, 119.82, 127.11, 129.54, 134.98, 137.22, 141.67, 148.97, 169.20. Calcd. For $C_{14}H_{15}ClN_2O$: C, 64.00; H, 5.75; N, 10.66. Found: C, 64.08; H, 5.73; N, 10.60.

4.2.18. 1-(5-Ethyl-1-(4-methoxy-phenyl)-1H-pyrazol-4-yl)-propan-1-one 4r (Table 1, entry 18)

mp 84–89 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 1.14 (t, J = 7.6 Hz, 3H, Me), 1.22 (t, J = 7.2 Hz, 3H, Me), 2.67 (q, J = 7.2 Hz, 2H, CH_2), 2.91 (q, J = 7.6 Hz, 2H, CH_2), 3.88 (s, 3H, Me), 7.01 (d, J = 8.8 Hz, 2H, Ph), 7.31 (d, J = 8.8 Hz, 2H, Ph), 8.00 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 8.22, 13.24, 18.93, 33.87, 55.59, 114.39, 119.36, 127.26, 131.63, 141.21, 149.05, 159.92, 196.30. Calcd. For $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.70; H, 7.09; N, 10.80.

4.3. General procedure for preparation of the methylpyrazoles

Methylhydrazine (1.2 mmol) in TFE (1 ml) was slowly added to a solution of β-dicarbonyl (1 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (1.2 mmol) in TFE (1 ml) at 0 °C and then the mixture was stirred at room temperature. The reaction was monitored by TLC. After completion of the reaction, water (10 ml) was added to the mixture and extracted with ethylacetate (2× 10 ml). The ethylacetate was washed with sodium hydrogen carbonate solution and water, then dried and evaporated the solvent to give desired product. The percent of regioisomers 3 and 4 was identified by ^{1}H NMR spectroscopy (Table 3, entries 1–3, 5–6).

Reaction with 1,3-cyclohexanedione was carried out at reflux temperature (Table 3, entry 4). In the case of open-chain β-diketones, under optimal reaction conditions required two equivalents of DMFDMA under optimal reaction conditions required two equivalents of DMFDMA.

Spectral data of all products are as follows.

4.3.1. 1,5-Dimethyl-1H-pyrazole-4-carboxylic acid ethyl ester 6a (Table 2, entry 1)

Oil [21a]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 3H, Me), 2.51 (s, 3H, Me), 3.78 (s, 3H, Me), 4.26 (q, J = 7.2 Hz, 2H, CH_2), 7.80 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 10.50, 14.37, 36.26, 59.72, 111.80, 140.54, 142.94, 163.83. Calcd. For $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.66. Found: C, 57.10; H, 7.20; N, 16.64.

4.3.2. 1,5-Dimethyl-1H-pyrazole-4-carboxylic acid tert-butyl ester 6b (Table 2, entry 2)

Oil [21a]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 9H, Me), 2.48 (s, 3H, Me), 3.78 (s, 3H, Me), 7.73 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 10.51, 28.36, 38.81, 80.14, 113.23, 134.48, 140.65, 163.29. Calcd. For $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.25; H, 8.24; N, 14.25.

4.3.3. 5-Isopropyl-1-methyl-1H-pyrazole-4-carboxylic acid ethyl ester 6c (Table 2, entry 3)

Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2, 3H, Me), 1.37 (d, J = 7.2 Hz, 6H, Me), 3.68–3.72 (m, 1H, CH), 3.88 (s, 3H, Me), 4.25 (q, J = 7.2, 2H, CH_2) 7.80 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 14.35, 19.71, 25.06, 38.98, 59.68, 110.85, 141.3, 151.44, 163.54. Calcd. For $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.27. Found: C, 61.25; H, 8.23; N, 14.25.

4.3.4. 1-Methyl-1,5,6,7-tetrahydro-4H-indazol-4-one 6d (Table 2, entry 4)

mp 94–99 °C [21b]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.17–2.24 (m, 2H, CH_2), 2.48 (t, J = 6.4, 2H, CH_2), 2.83 (t, J = 6.4, 2H, CH_2), 3.84 (s, 3H, Me), 7.89 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 21.45, 29.70, 32.99, 38.44, 127.31, 134.66, 167.29, 196.72. Calcd. For C8H10N2O: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.96; H, 6.70; N, 18.66.

4.3.5. 1-(1,5-Dimethyl-1H-pyrazol-4-yl)-ethan-1-one 6e (Table 2, entry 5)

mp 54–56 °C [21b]. ^{1}H NMR (400 MHz, $CDCl_3$): 2.43 (s, 3H, Me), 2.57 (s, 3H, Me), 3.81 (s, 3H, Me), 7.81 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 10.91, 28.45, 36.10, 120.32, 140.76, 142.46, 193.39. Calcd. For $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.27. Found: C, 60.83; H, 7.33; N, 20.25.

4.3.6. 1-(5-Ethyl-1-methyl-1H-pyrazol-4-yl)-propan-1-one 6f (Table 2, entry 6)

Oil [21b]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13–1.18 (m, 6H, Me), 2.75 (q, J = 7.2 Hz, 2H, CH_2), 2.99 (q, J = 7.6 Hz, 2H, CH_2), 3.8 (s, 3H, Me), 7.79 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): 8.16, 12.56, 18.32, 33.62, 35.88, 118.94, 140.21, 147.89, 196.19. Calcd. For $C_9H_{14}N_2O$: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.05; H, 8.49; N, 16.84.

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