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ORIGINAL PAPER

One-pot regioselective synthesis of 1,4,5-trisubstituted pyrazoles under solvent-free conditions without catalyst

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Abstract A fast, one pot method with excellent yield has been developed for preparation of 1,4,5-trisubstituted pyrazoles. Treatment of β-dicarbonyl compounds with *N*,*N*-dimethylformamide dimethylacetal and hydrazine derivatives afforded immediately the desired pyrazoles under solvent-free conditions in the absence of catalyst.

Keywords Cyclization · 1,4,5-Trisubstituted pyrazoles · β-Dicarbonyl compounds · *N*,*N*-Dimethylformamide dimethylacetal · Arylhydrazines

Introduction

Pyrazoles have been the subject of chemical and biological studies because of their interesting pharmacology including selective enzyme inhibitory [1], antiviral [2], estrogen receptor agonist [3], anti-inflammatory [4], anticancer [5], antiobesity [6], and antitumor [7] properties.

The synthesis of these compounds has been investigated in depth by use of so-called [2,3]-atom fragments, in which β-difunctional electrophiles, for example enaminones are used as three-atom building blocks and hydrazine derivatives as the two-atom fragment [8]. It is well known that enaminone moieties can be used as starting materials for the preparation of pyrazoles [9], pyrimidines [10], pyrimidones [11], isoxazoles [12], pyrroles [13], etc. Differently substituted β-enaminoketones can be prepared by condensation of the methylene group of β-dicarbonyl compounds with *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) and derivatives [14].

1,4,5-Trisubstituted pyrazoles have usually been prepared by reaction of enaminoketones with hydrazine derivatives in solvent under acid catalysis [15–17]. Recently a microwave-assisted solution phase reaction [18, 19] and a cellulose-based resin [14] were reported for synthesis of these compounds. However, these syntheses are usually carried out in organic solvents, often require acid (AcOH) and two-step synthesis.

One-pot synthesis is a simple and efficient route to target molecules which includes two or more transformation steps in a single operation starting from relatively simple precursors [20]. Compared with reactions in organic solvents, solventless reactions are often rapid, regio or chemoselective, occur in high yields, and have environmental and economic advantages [21].

For these reasons, we decided to pursue one-pot solventless synthesis of 1,4,5-trisubstituted pyrazoles from β-dicarbonyl compounds, DMFDMA, and arylhydrazines without use of a catalyst. Herein we report the results.

Results and discussion

In this study, we first optimized the reaction conditions using acetonylacetone (**1a**), *N*,*N*-dimethylformamide dimethylacetal (**2**), and phenylhydrazine (**3a**) as model substrates. In our preliminary experiments 1 mmol phenylhydrazine was treated with 1 mmol acetonylacetone and 1.5 mmol DMFDMA under solvent-free conditions at 70 °C. The reaction was complete in less than 1 min. After work-up of the reaction mixture, 1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (**4a**) was obtained in excellent yield (95%; Table 1).

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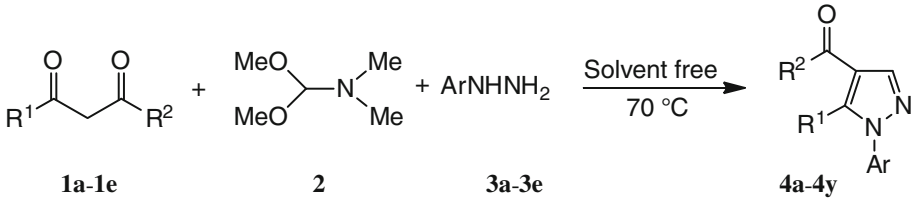
Table 1 Preparation of pyrazole derivatives



1a-1e **2** **3a-3e** **4a-4y**

Prod.	R^1	R^2	Ar	Yield/%[a]	M.p. (lit. m.p.)/°C
4a	Me	Me	Ph	95	103–107 (103 [16])
4b	Me	Me	*p*-$NO_2C_6H_4$	95	88–90 (174–177 [23])
4c	Me	Me	*p*-ClC_6H_4	96	110–113 (110–113 [22])
4d	Me	Me	*o*-ClC_6H_4	95	Oil
4e	Me	Me	*p*-$MeOC_6H_4$	90	86–88 (86–88 [22])
4f	Et	Et	Ph	93	140–142 (153 [16])
4g	Et	Et	*p*-$NO_2C_6H_4$	92	80–85
4h	Et	Et	*p*-ClC_6H_4	94	55–57 (55–57 [22])
4i	Et	Et	*o*-ClC_6H_4	96	Oil
4j	Et	Et	*p*-$MeOC_6H_4$	91	84–89 (84–89 [22])
4k	Me	OEt	Ph	92	49–52 (49 [14])
4l	Me	OEt	*p*-$NO_2C_6H_4$	95	119–124 (116–120 [24])
4m	Me	OEt	*p*-ClC_6H_4	94	60–62 (60–61 [22])
4n	Me	OEt	*o*-ClC_6H_4	96	Oil
4o	Me	OEt	*p*-$MeOC_6H_4$	90	62–64 (63–65 [22])
4p	Me	OCH_2Ph	Ph	95	80–83
4q	Me	OCH_2Ph	*p*-$NO_2C_6H_4$	94	112–114
4r	Me	OCH_2Ph	*p*-ClC_6H_4	96	Oil
4s	Me	OCH_2Ph	*o*-ClC_6H_4	96	Oil
4t	Me	OCH_2Ph	*p*-$MeOC_6H_4$	91	Oil
4u	Me	O*t*-Bu	Ph	97	Oil [17]
4v	Me	O*t*-Bu	*p*-$NO_2C_6H_4$	92	Oil
4w	Me	O*t*-Bu	*p*-ClC_6H_4	95	Oil [22]
4x	Me	O*t*-Bu	*o*-ClC_6H_4	97	Oil
4y	Me	O*t*-Bu	*p*-$MeOC_6H_4$	91	Oil [22]

Reactions were performed at 70 °C using 1 mmol β-dicarbonyl compound, 1.5 mmol DMFDMA, and 1 mmol arylhydrazine

[a] Isolated yield

To demonstrate the generality of the reaction, the substrate scope of the sequence was explored. As shown in Table 1, several substituted hydrazines **3** and β-dicarbonyl compounds **1** (β-ketoesters and β-diketones) were used successfully in this procedure.

The reaction of acetylacetone (**1a**) with a variety of arylhydrazines **3** in the presence of DMFDMA under optimum reaction conditions afforded 4-acylpyrazoles **4a–4e** immediately, in excellent yields. Similarly, heptane-3,5-dione (**1b**) reacted with arylhydrazines and DMFDMA to give the corresponding 4-acylpyrazoles **4f–4j** in 91–96% yields.

This reaction was also successfully performed with β-keto esters in excellent yields. For example, when ethyl acetoacetate (**1c**) and phenylhydrazine were used, the reaction was complete <1 min at 70 °C, giving the desired pyrazole **4k** in 95% yield. Investigation of this method indicated that reaction of ethyl acetoacetate with electron-withdrawing or electron-donating substituted arylhydrazines afforded pyrazoles **4l–4o** under optimum reaction conditions. Similarly, other β-keto esters gave the expected pyrazoles in high yield. When benzyl acetoacetate (**1d**) and *t*-butyl acetoacetate (**1e**) were used, the reactions were

immediately complete at 70 °C, giving the desired compounds **4p**–**4y** in 91–96% yield.

Conclusion

In this study, we have developed a green, one-pot approach for preparation of 1,4,5-trisubstituted pyrazole derivatives starting from different β-ketoesters or β-ketones and a variety of arylhdrazines which is completed immediately, in excellent yields, under solvent free conditions, without use of any catalysts. One-pot and solvent-free conditions are additional eco-friendly attributes of this synthetic procedure.

Experimental

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

General procedure for preparation of 1,4,5-trisubstituted pyrazoles

Hydrazine derivative **3** (1 mmol) was added to a mixture of 1,3-dicarbonyl compound **1** (1 mmol) and *N*,*N*-dimethylformamide dimethylacetal **2** (1.5 mmol) and stirred at 70 °C. All reactions were complete in less than 1 min, indicated by TLC. Ethyl acetate (5 cm^3) was added and the mixture was washed with 10–20 cm^3 H_2O. The organic layer was separated and concentrated under vacuum to give the pure products. If necessary the products were further purified by column chromatography on silica gel with suitable eluents.

1-[1-(2-Chlorophenyl)-5-methyl-1H-pyrazol-4-yl]-ethan-1-one (**4d**, $C_{12}H_{11}ClN_2O$)
Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H, Me), 2.48 (s, 3H, Me), 7.38–7.56 (m, 4H, Ph), 8.03 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.61$, 28.65, 120.44, 127.83, 129.46, 130.42, 131.13, 132.23, 136.10, 142.16, 144.77, 193.43 ppm.

1-[5-Ethyl-1-(4-nitrophenyl)-1H-pyrazol-4-yl]-propan-1-one (**4g**, $C_{14}H_{15}N_3O_3$)
M.p.: 80–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.24$ (t, $J = 7.2$ Hz, 3H, Me), 1.25 (t, $J = 7.6$ Hz, 3H, Me), 2.50 (q, $J = 7.2$ Hz, 2H, CH_2), 3.06 (q, $J = 7.6$ Hz, 2H, CH_2), 7.68 (d, $J = 9.2$ Hz, 2H, Ph), 8.09 (s, 1H, CH), 8.42 (d, $J = 9.2$ Hz, 2H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.06$, 13.32, 19.04, 34.19, 120.61, 124.86, 126.06, 142.46, 143.78, 149.14, 196.09 ppm.

1-[1-(2-Chlorophenyl)-5-ethyl-1H-pyrazol-4-yl]propan-1-one (**4i**, $C_{14}H_{15}ClN_2O$)
Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.06$ (t, $J = 7.6$ Hz, 3H, Me), 1.22 (t, $J = 7.6$ Hz, 3H, Me), 2.86 (q, $J = 7.6$ Hz, 2H, CH_2), 2.67 (q, $J = 7.6$ Hz, 2H, CH_2), 7.37–7.58 (m, 4H, Ph), 8.06 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 8.08$, 12.74, 18.87, 33.90, 119.14, 127.65, 129.59, 130.51, 131.15, 132.68, 136.29, 141.73, 150.19, 196.18 ppm.

1-(2-Chlorophenyl)-5-methyl-1H-pyrazole-4-carboxylic acid ethyl ester (**4n**, $C_{13}H_{13}ClN_2O_2$)
Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$ (t, $J = 7.2$ Hz, 3H, Me), 2.40 (s, 3H, Me), 4.34 (q, $J = 7.2$ Hz, 2H, CH_2), 7.40–7.58 (m, 4H, Ph), 8.07 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.16$, 14.43, 60.01, 112.37, 127.79, 129.59, 130.41, 131.02, 132.39, 136.41, 143.30, 145.31, 163.74 ppm.

5-Methyl-1-phenyl-1H-pyrazole-4-carboxylic acid benzyl-ester (**4p**, $C_{18}H_{16}N_2O_2$)
M.p.: 80–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.59$ (s, 3H, Me), 5.35 (s, 2H, CH_2), 7.34–7.54 (m, 10H, Ph), 8.09 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.04$, 65.74, 112.63, 125.52, 128.11, 128.17, 128.60, 128.71, 129.29, 136.34, 142.00, 143.85, 163.59 ppm.

5-Methyl-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylic acid benzyl ester (**4q**, $C_{18}H_{15}N_3O_4$)
M.p.: 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.70$ (s, 3H, Me), 5.35 (s, 2H, CH_2), 7.37–7.47 (m, 5H, Ph), 7.70 (d, $J = 12$ Hz, 2H, Ph), 8.13 (s, 1H, CH), 8.39 (d, $J = 12$ Hz, 2H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.35$, 66.03, 114.07, 124.82, 125.50, 128.18, 128.31, 128.65, 136.05, 143.08, 143.75, 144.10, 147.01, 163.12 ppm.

1-(4-Chlorophenyl)-5-methyl-1H-pyrazole-4-carboxylic acid benzyl ester (**4r**, $C_{18}H_{15}ClN_2O_2$)
Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.59$ (s, 3H, Me), 5.35 (s, 2H, CH_2), 7.39–7.53 (m, 9H, Ph), 8.08 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.01$, 65.8, 112.96, 126.69, 128.12, 128.20, 128.61, 129.49, 134.59, 136.25, 137.30, 142.24, 143.84, 163.41 ppm.

1-(2-Chlorophenyl)-5-methyl-1H-pyrazole-4-carboxylic acid benzyl ester (**4s**, $C_{18}H_{15}ClN_2O_2$)
Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.42$ (s, 3H, Me), 5.35 (s, 2H, CH_2), 7.23–7.59 (m, 9H, Ph), 8.12 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.25$, 65.79, 112.04, 127.81, 128.17, 128.19, 128.61, 129.59, 130.44, 131.08, 132.37, 136.29, 136.35, 142.30, 145.63, 163.49 ppm.

1-(4-Methoxyphenyl)-5-methyl-1H-pyrazole-4-carboxylic acid benzyl ester (**4t**, $C_{19}H_{18}N_2O_3$)
Oil; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.53$ (s, 3H, Me), 3.87 (s, 3H, Me), 5.30 (s, 2H, CH_2), 7.01 (d, $J = 12$ Hz,

2H, Ph), 7.32 (d, $J = 12$ Hz, 2H, Ph), 7.33–7.47 (m, 5H, Ph), 8.05 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.91$, 55.59, 65.68, 112.25, 114.38, 126.91, 128.08, 128.14, 128.59, 131.13, 136.37, 141.70, 143.94, 159.71, 163.62 ppm.

5-Methyl-1-(4-nitrophenyl)-1H-pyrazole-4-carboxylic acid t-butyl ester (**4v**, $C_{15}H_{17}N_3O_4$)
Oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.59$ (s, 9H, Me), 2.65 (s, 3H, Me), 7.67 (d, $J = 9.2$ Hz, 2H, Ph), 8.01 (s, 1H, CH), 8.38 (d, $J = 9.2$ Hz, 2H, Ph) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 12.28$, 28.36, 80.97, 115.81, 124.77, 125.44, 143.18, 143.30, 143.94, 146.87, 163.74 ppm.

1-(2-Chlorophenyl)-5-methyl-1H-pyrazole-4-carboxylic acid t-butyl ester (**4x**, $C_{15}H_{17}ClN_2O_2$)
Oil; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.57$ (s, 9H, Me), 2.35 (s, 3H, Me), 7.35–7.54 (m, 4H, Ph), 7.99 (s, 1H, CH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.16$, 28.40, 80.48, 113.73, 127.76, 129.62, 130.36, 130.94, 132.37, 136.47, 142.31, 144.79, 163.14 ppm.

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