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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.

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## 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 $\alpha,\beta$-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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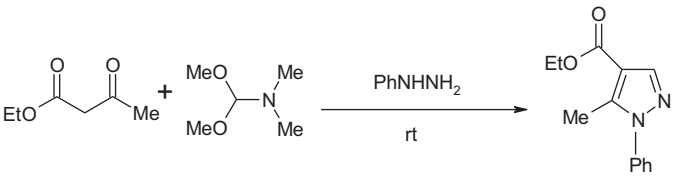
**Table 1**
Preparation of pyrazoles in different solvents.[a]




| 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 $\beta$-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 $\beta$-keto esters reacted smoothly under reaction conditions to give high yield of the desired pyrazoles (Table 2, entries 4–9).

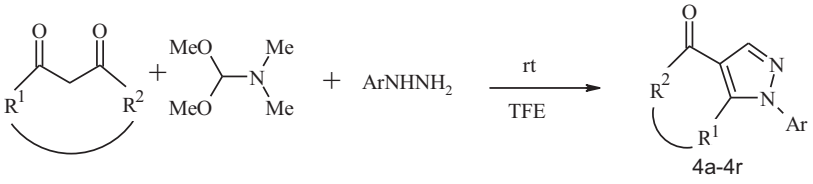
1,3-Cyclohexanedione as cyclic $\beta$-diketone required higher temperature (refluxing in TFE) and longer reaction time to afford excellent yield of the corresponding pyrazoles (Table 2, entries 10–12). Reactions of open-chain $\beta$-diketones (Scheme 1, 1: R = Me or Et) under optimal reaction conditions 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 $\beta$-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 $\beta$-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.

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