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Short Communication

Iron-catalyzed aerobic oxidative aromatization of 1,3,5-trisubstituted pyrazolines

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ABSTRACT

A simple and high yielding method for the synthesis of tri-substituted pyrazoles *via* iron(III) catalyzed aerobic oxidative aromatization of pyrazolines has been reported. The process demonstrates a variety of functional group tolerance.

1. Introduction

Pyrazoles are an important class of nitrogen heterocycles because of their relevance to pharmaceutical industries and materials.[1–3] The substituted 1*H*-pyrazoles show a broad spectrum of pharmacological activities such as antibacterial, antihyperglycemic, anti-inflammatory, analgesic and hypoglycemic and sedative–hypnotic activities.[4] Several methods have been reported for the synthesis of pyrazoles which include the 1,3-dipolar addition,[5] cyclocondensation of hydrazine derivatives with 1,3-dicarbonyl compounds[6,7] or α,β-unsaturated carbonyl compounds,[8,9] metal-catalyzed intramolecular nucleophilic addition of nitrogen to alkynes[10] and others.[11–15]

Oxidation of pyrazolines is one of the easier methods employed in the preparation of a range of pyrazoles due to its simplicity and versatility. It is well established that the treatment of α,β-unsaturated ketones with hydrazines, in the absence of any metal catalyst, leads to the formation of pyrazolines with regioselectivity.[16,17] These reactions proceed through the formation of hydrazone followed by cyclization to yield 1,3,5-substituted pyrazolines. The oxidation of pyrazolines using reagents such as, lead tetraacetate,[18] manganese dioxide,[19] trichloroisocyanuric acid,[20] iodic acid/iodine pentoxide,[21] silver nitrate,[22] mercury oxide,[23] potassium permanganate,[24] *p*-chloranil,[25] activated carbon/O_2,[26] iodobenzenediacetate,[27] $Zr(NO_3)_2$[28] and DDQ[29] effectively yields pyrazoles. The major disadvantage with most of these methods is the use of stoichiometric or an excess of oxidizing agents. Off late, Hayashi and co-workers have reported the catalytic oxidation of pyrazolines by Pd/C under aerobic condition.[30]

Transition metal catalysts offer an alternative and green way for stoichiometric oxidants in oxidative aromatization and catalytic dehydrogenation reactions.[31–34] High price and toxic nature of heavy and precious metal catalysts have initiated search for alternative and greener catalytic systems. Because of less cost, high abundance and low toxic nature of iron, iron compounds are found to be ideal candidates for efficient, greener and large scale industrial applications. Indeed, use of iron catalysts is accomplishing significance in many organic transformations in recent years.[35] Herein, we report the ferric chloride catalyzed oxidation of several trisubstituted pyrazolines.

2. Experimental section

2.1. General procedure for the synthesis of 1,3-diaryl-2-propen-1-ones

A mixture of appropriate derivatives of both ketone (1.0 equiv.) and aldehyde (1.0 equiv.) was taken in a 100 mL round-bottomed flask in 95% ethanol (25 mL). The mixture was then stirred magnetically and heated gently if necessary until a clear solution is formed. Then a NaOH (1.1 equiv., 10% in EtOH) solution (10 mL) was added slowly. In most of the cases, a yellow precipitate was formed immediately. The solid was collected by filtration, washed with cold water, dried and recrystallized from ethanol. Compounds were characterised using GC-MS and NMR spectroscopy.

2.2. General procedure for the synthesis of pyrazolines

Method A: A mixture of appropriate derivatives of both 1,3-diaryl-2-propen-1-ones (1.0 equiv.) and aryl hydrazine (1.1 equiv.) was taken in a 100 mL round-bottomed flask in 95% ethanol (25 mL). Addition of a drop of H_2SO_4 initiated the precipitation. The reaction mixture was refluxed for 3 to 5 h and cooled to room temperature to form precipitate

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in most of the cases. The residue was filtered, washed with water and dried under vacuum. In some cases where precipitate was not observed after cooling to room temperature, water was added to obtain precipitate.

Method B: A mixture of appropriate derivatives of both 1,3-diaryl-2-propen-1-ones (1.0 equiv.) and hydrazine (1.1 equiv.) was taken in a 100 mL round-bottomed flask along with acetic acid. A drop of H_2SO_4 was added to this mixture, immediate precipitate was observed. The reaction mixture was refluxed for 3 h and cooled to room temperature to give precipitate. The precipitate was filtered, washed consecutively with water and petroleum ether (bp range: 60–85 °C) and the residue was dried under vacuum. In some cases where precipitate was not observed after cooling to room temperature, water was added to obtain precipitate. Compounds were characterised using GC-MS and NMR spectroscopy.

2.3. General procedure for the synthesis of pyrazoles

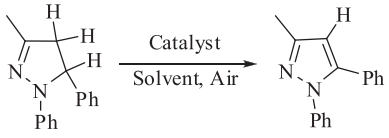
A 10 mL screw capped tube was charged with pyrazoline (1 equiv.), acetic acid (2 mL), and $FeCl_3$ (10 mol%). The mixture was stirred at 120 °C for 6–10 h. After confirmation of the complete consumption of pyrazoline by GC-MS analysis, the reaction mixture was cooled to room temperature, neutralized with saturated aqueous Na_2CO_3 and extracted with ethyl acetate (10 mL × 3). After usual work-up (see Supporting data), the residue obtained was passed through a small pad of silica gel using ethyl acetate to give analytically pure substituted pyrazoles.

3. Results and discussion

Our initial efforts were focused on identifying a suitable catalytic system for the aromatization of substituted pyrazolines into substituted pyrazoles. Initially 3-methyl-1,5-diphenyl-1*H*-pyrazoline was used as a model substrate to optimize the reaction conditions. The reaction was completed within 4 h when $Pd(OAc)_2$ (2 mol%) was used as catalyst (Table 1, entry 1), in refluxing acetic acid under aerobic conditions. On decreasing the catalyst loading to 1 mol% under similar reaction conditions also led to complete conversion but in 6 h (Table 1, entry 2). In order to explore a better and economic catalytic system, catalysts such as Ag_2CO_3, $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$, $Ni(OAc)_2 \cdot 4H_2O$, $NiCl_2 \cdot 6H_2O$, $FeCl_2$, and anhydrous $FeCl_3$ (Table 1, entries 5–13) were also tested under similar reaction conditions. The conversions were excellent when $FeCl_3$ (10 mol%) was used as a catalyst (Table 1, entry 13) (Scheme **1**). The degree of hydration of $FeCl_3$ did not show any substantial effect on the reaction (Table 1, entry 16). The reactions carried out using high purity $FeCl_3$ (>99.9%) also did not show any significant change in the conversion rates or yields (Table 1, entries 14 and 15). This confirms that the trace metal impurities often found in iron salts have no effect on aromatization reactions carried out in the present investigation. It was observed that the acetic acid is necessary for the reaction to proceed.[30] The yield was lowered considerably when other solvents were used (Table 1, entry 17). Air was used as an effective oxidant and in its absence yields were lowered significantly (Table 1, entries 18 and 20).

Under these optimized reaction conditions (Table 1, entry 13 with $FeCl_3$ (>98%)), various substituted pyrazolines were subjected to oxidative aromatization reaction, and the results obtained are summarized in Charts 1 and 2. The electron donating, electron withdrawing and hetero aromatic substituents on pyrazolines were effective substrates in this catalytic system. The reaction time was usually 6–7 h in case of electron donating substituents. Interestingly, electron withdrawing nitro- (Chart 1, **8**, **17** and Chart 2, **25**) and halo- (Chart 1, **7**, **9**–**14** and Chart 2, **20**, **22**) substituted pyrazolines also gave good to excellent yield, but took longer time for the completion of reaction (8–10 h). The electronic effects of the substituents on pyrazolines are not pronounced under these conditions. It is noteworthy that, alkene (Chart 1, **15**–**18**) and methoxy (Chart 1, **5**, **6** and Chart 2, **23**, **24**) functionalities were also tolerated and the corresponding products were isolated in excellent yield. The generality of the reaction was further established by investigating the reactivity of hetero-aromatic substituents like furan and thiophene on pyrazolines (Chart 2). For example, 1-phenyl-3,5-di(thiophen-2-yl)-1*H*-pyrazole (**19**) was obtained in 96% yield from 1-phenyl-3,5-di(thiophen-2-yl)-1*H*-pyrazoline. Various combinations of heteroaromatic with methoxy-, nitro-, and halo-substituted pyrazolines were also successfully tested under the reaction conditions (Chart 2, **20**–**27**).

Table 1
Optimization of reaction conditions.

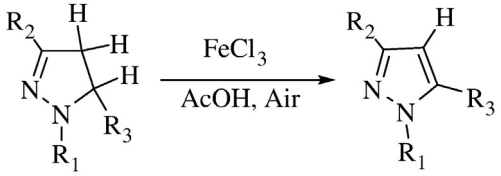


Entry	Catalyst	Solvent	Time (h)	Conv[a] (%)
1	$Pd(OAc)_2$ (2 mol%)	AcOH	4	100 (98[b])
2	$Pd(OAc)_2$ (1 mol%)	AcOH	6	99
3	$Pd(OAc)_2$ (2 mol%)	Acetone	6	36
4	$Pd(OAc)_2$ (2 mol%)	AcOH:H_2O (1:1)	6	48
5	Ag_2CO_3 (2 mol%)	AcOH	4	96
6	$[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ (2 mol%)	AcOH	4	100
7	$Ni(OAc)_2 \cdot 4H_2O$ (5 mol%)	AcOH	6	75
8	$NiCl_2 \cdot 6H_2O$ (5 mol%)	AcOH	6	90
9	$NiCl_2 \cdot 2H_2O$ (5 mol%)	AcOH	6	55
10	$Ni(OAc)_2 \cdot 4H_2O$ (10 mol%)	AcOH	6	99
11	$FeCl_3$ (5 mol%)	AcOH	6	75
12	$FeCl_2$ (>99.8%) (10 mol%)	AcOH	6	98
13	$FeCl_3$ (>98%)(10 mol%)	AcOH	6	100 (98[b])
14	$FeCl_3$ (>99.9% pure) (5 mol%)	AcOH	6	72
15	$FeCl_3$ (>99.9% pure) (10 mol%)	AcOH	6	100
16	$FeCl_3 \cdot 6H_2O$ (10 mol%)	AcOH	6	97
17	$FeCl_3$ (10 mol%)	Acetone	6	39
18	$FeCl_3$ (10 mol%)[c]	AcOH	6	61
19	No catalyst	AcOH	6	46
20	No catalyst[c]	AcOH	6	34

[a] Conversion based on GC analysis with dodecane as internal standard.
[b] Isolated yields.
[c] The reactions were carried out under nitrogen atmosphere.

4. Conclusions

In conclusion, we have developed an easy and greener process for the preparation of pyrazoles *via* Fe(III) catalyzed oxidative aromatization reaction. Current method utilizes $FeCl_3$ as a catalyst, which makes the reaction more economical and productive (Scheme **2**). All the products are obtained in pure form without the use of column chromatography. The method is high yielding and shows variety of functional group tolerance.



Scheme 1. Synthesis of pyrazole via iron catalyzed oxidation of pyrazoline.

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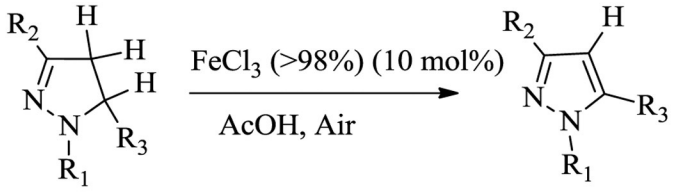

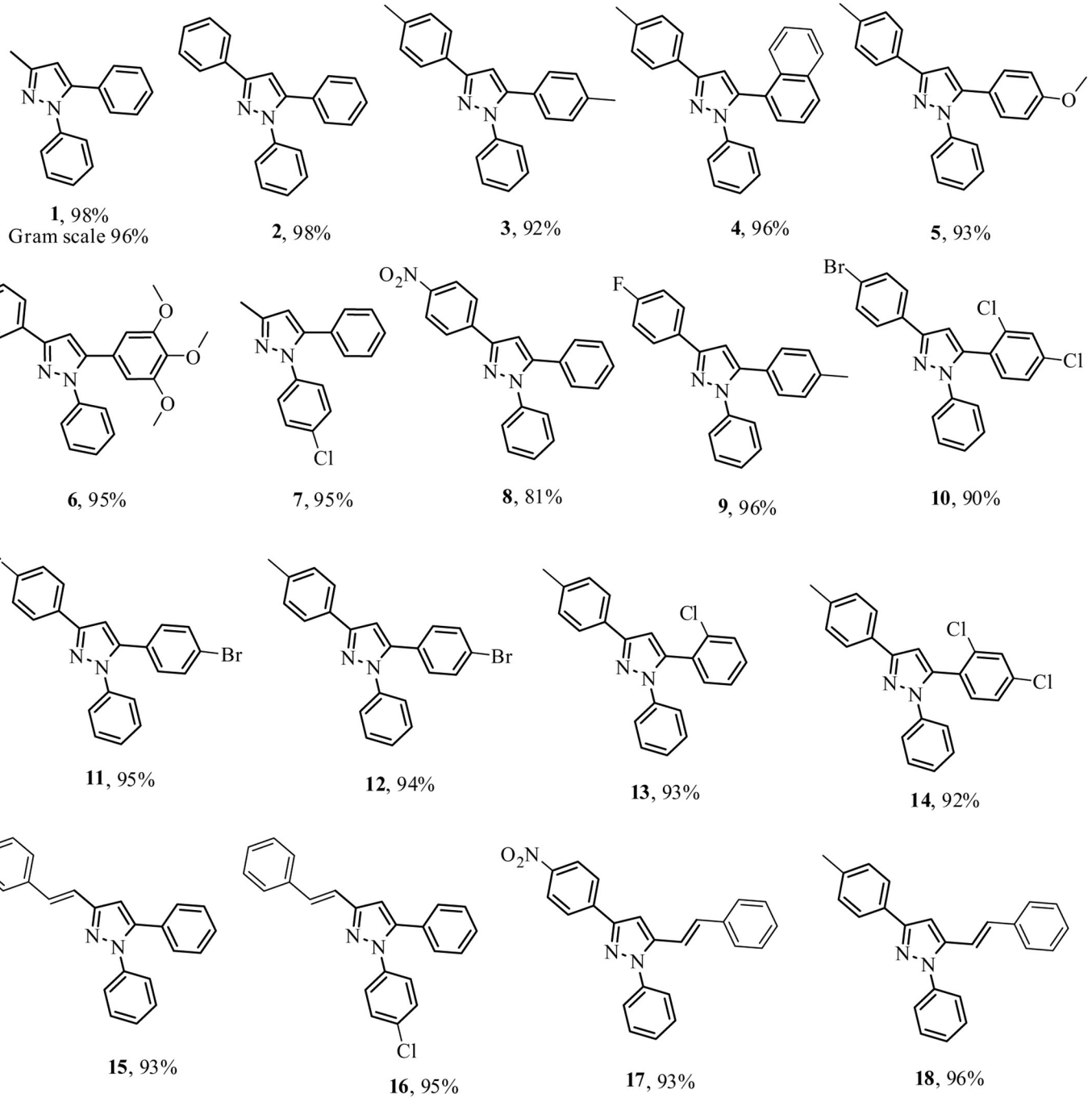

Chart 1. Substrate scope for the aromatization of pyrazolines.

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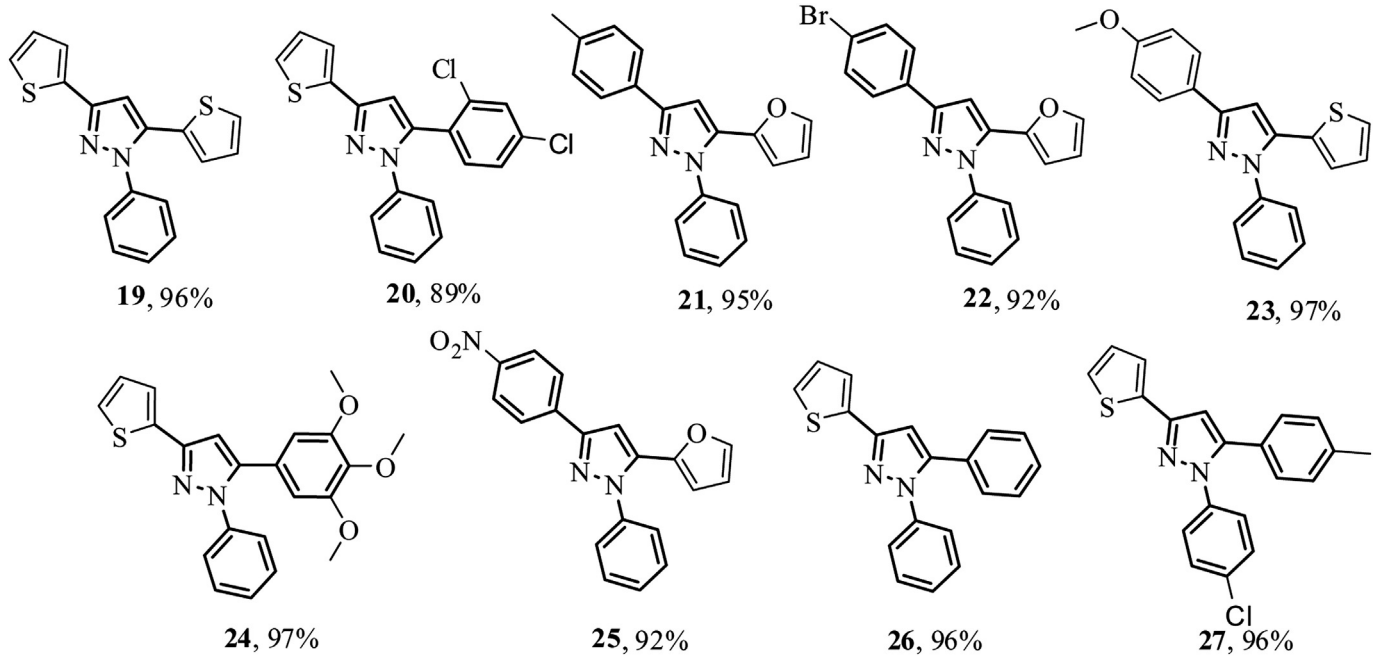
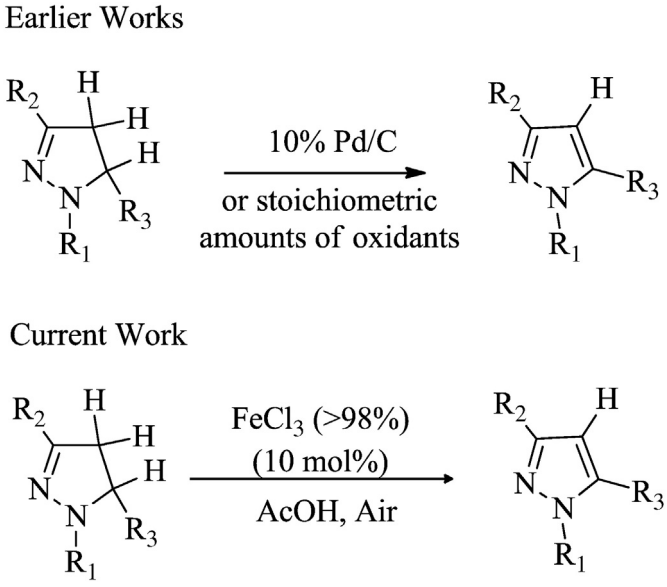


Chart 2. Aromatization of hetero-aromatic substituted pyrazolines.



Scheme 2. Comparisons of previous reports and our methodology for the synthesis of trisubstituted pyrazoles.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.09.002.

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