*Scientific paper*

# Expeditious, Four-Component Synthesis of 1,4-Dihydropyrano[2,3-c]Pyrazole Derivatives Catalyzed by Trichloroacetic Acid or Ceric Sulfate

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## Abstract

Two efficient and convenient procedures for the synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives based on four-component reaction involving ethyl acetoacetate, phenylhydrazine, malononitrile, and various aromatic aldehydes using trichloroacetic acid or ceric sulfate as heterogeneous catalysts in excellent yields and short reaction times have been described.

**Keywords:** 1,4-Dihydropyrano[2,3-*c*]pyrazole derivatives, Four-component reaction, Trichloroacetic acid, Ceric sulfate, Heterogeneous catalysts

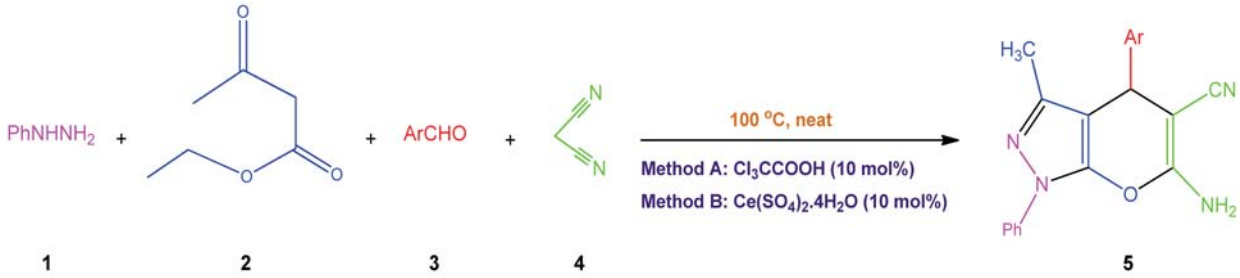
## 1. Introduction

Pyranopyrazoles exhibit appreciable biological activities such as analgesic,[1] anti-tumor, anti-cancer,[2] and anti-inflammatory properties,[3] and also serve as potential inhibitors of human Chk1 kinase.[4] Furthermore, polyfunctionalized 4*H*-pyrans have received considerable attention in synthetic strategies of promising biologically significant compounds.[5–7] These high profile applications and variety of biological activities have promoted extensive studies for the synthesis of 1,4-dihydropyrano[2,3–*c*] pyrazole derivatives employing triethylamine,[8] piperazine[9] and piperidine[10] as a prominent catalysts through a two-component[11–13] or three-component reaction.[14–16] However, one-pot, four-component synthesis[17,18] has also been accomplished and consists of condensation of aldehydes, ethyl acetoacetate, malononitrile and hydrazines. In this context, some methods and catalysts have been used to promote these condensations.[19–23] However, despite the potential utility of the aforementioned routes for the synthesis of substituted 1,4-dihydropyrano[2,3–*c*] pyrazole derivatives, some of them often involve use of excess amounts of acids or hazardous organic solvents, tedious work-up leading to the generation of large amounts of toxic metal-containing waste, and large amounts of solid catalysts, which are not preferred choices in view of green chemistry. Moreover, low yields, long reaction times, and use of expensive reagents are further disadvantages of some of the reported methods. Therefore, to avoid these limitations, the introduction of a new and efficient catalysts with high catalytic activity, short reaction time, recyclability and simple work-up for preparation of 1,4-dihydropyrano[2,3–*c*]pyrazoles under neutral, mild and practical conditions is of prime interest.

With an emphasis on the search for atom-efficient transformations of readily available starting materials into complex organic molecules, reactions with maximal diversity are particularly desirable.[24] In this paper we report on expeditious domino and multicomponent reaction (MCR) as one of the powerful reaction strategies.[25,26]

## 2. Results and Discussion

In conjunction with our interest on the development of environmentally benign synthetic methodologies,[27–30] we report here on two convenient methods for the four-component synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles using trichloroacetic acid or ceric sulfate as heterogeneous catalysts (Scheme 1).




**Scheme 1.** Synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole.

At the onset of this work, we investigated a variety of conditions with the model reaction involving benzaldehyde (2 mmol), ethyl acetoacetate (2 mmol) phenylhydrazine (2 mmol), and malononitrile (2 mmol) using trichloroacetic acid (TCAA) as catalyst to afford the dihydropyranopyrazole product. The best results were obtained by carrying out the reaction at 100 °C for 5 min with 10 mol% TCAA as a catalyst, without any solvent. In addition, we also studied the influence of the amount of TCAA on the reaction yield and found that the yield is not significantly affected by different amounts of TCAA, and that excessive amounts of catalyst do not increase the yield remarkably.

These results promoted us to investigate the scope and generality of this new four-component protocol for various aldehydes under optimized conditions. A variety of aromatic aldehydes bearing both electron-donating groups (such as alkyl, alkoxyl, and hydroxyl) and electron-withdrawing groups (such as halide, nitro, and cyano) were reacted with ethyl acetoacetate, phenylhydrazine and malononitrile in the presence of a catalytic amount of TCAA at 100 °C, in order to give the corresponding products in good to excellent yields (Table 1, Method A). However, 4-dimethylaminobenzaldehyde (Entry 13, Table 1) failed to give the corresponding product under the same conditions. The explanation for this result may be due to the strong electron-donating dimethylamino group, which reduces the reactivity of aldehyde.[30]

Moreover, we also turned our attention to other catalysts for this reaction, such as ceric sulfate ($Ce(SO_4)_2 \cdot 4H_2O$), which is readily available and inexpensive catalyst, and can be handled and conveniently removed from the reaction mixture. Indeed, good reaction yields were obtained by treatment of benzaldehyde with ethyl acetoacetate, phenylhydrazine and malononitrile in the presence of catalytic amount of ceric sulfate under solvent-free conditions. To show the generality and scope of the ceric sulfate-promoted 1,4-dihydropyranopyrazole synthesis, the reaction was examined with various structurally diverse aromatic aldehydes. Very similar results were obtained for the above mentioned four-component reaction (see Table 1, Method B). All products are known compounds and their IR and NMR spectroscopic data, together with melting points, were compared with already reported values.[19–23]

It is interesting to mention that the same four-component reaction using aliphatic aldehydes failed to give

**Table 1.** Synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives.

| Entry | Ar | Method A[a] | | Method B[b] | | Mp (°C) | |
|---|---|---|---|---|---|---|---|
| | | Time (min) | Yield (%) | Time (min) | Yield (%) | Found | Reported[Ref] |
| 1 | $C_6H_5$ | 5 | 85 | 5 | 80 | 168–170 | 168–170[30] |
| 2 | 4-$ClC_6H_4$ | 3 | 80 | 4 | 80 | 175–177 | 174–175[19] |
| 3 | 4-$BrC_6H_4$ | 2 | 87 | 5 | 85 | 182–184 | 183–184[21] |
| 4 | 4-$FC_6H_4$ | 5 | 90 | 7 | 87 | 169–171 | 167–168[30] |
| 5 | 4-$CNC_6H_4$ | 5 | 90 | 5 | 80 | 197–199 | 197–199[30] |
| 6 | 4-$NO_2C_6H_4$ | 7 | 80 | 8 | 80 | 192–195 | 194–196[30] |
| 7 | 3-$NO_2C_6H_4$ | 7 | 80 | 7 | 80 | 188–191 | 188–190[19] |
| 8 | 2,6-$Cl_2C_6H_3$ | 9 | 85 | 12 | 85 | 205–207 | 205–207[30] |
| 9 | 2,4-$Cl_2C_6H_3$ | 3 | 90 | 4 | 86 | 182–184 | 182–184[21] |
| 10 | 4-$CH_3C_6H_4$ | 9 | 85 | 6 | 83 | 172–174 | 176–178[21] |
| 11 | 4-$CH_3OC_6H_4$ | 5 | 91 | 10 | 80 | 172–174 | 174–176[30] |
| 12 | 4-$OHC_6H_4$ | 3 | 85 | 5 | 82 | 210–212 | 211–212[30] |
| 13 | 4-$(CH_3)_2NC_6H_4$ | No reaction | | | | | |

[a] Method A: Trichloroacetic acid (10 mol%) as catalyst. [b] Method B: $Ce(SO_4)_2 \cdot 4H_2O$ (10 mol%) as catalyst.

**Table 2**. Comparison of different reaction conditions for preparation of 6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile from benzaldehyde.

| Entry | Conditions | Time (min) | Yield (%) | Reference |
|---|---|---|---|---|
| 1 | L-proline (10 mol %), [Bmim]$BF_4$, 50 °C | 10 | 90 | 19 |
| 2 | Mg/Al HT (0.1 g), Ethanol, rt | 1 h | 87 | 20 |
| 3 | nanosized MgO (50 mg), Acetonitrile, rt | 10 | 97 | 21 |
| 4 | γ-alumina (30 mol %), $H_2O$, reflux | 50 | 80 | 22 |
| 5 | TCAA (10 mol %), solvent free, 100 °C | 5 | 85 | This paper |
| 6 | $Ce(SO_4)_2$ (10 mol %), solvent free, 100 °C | 5 | 80 | This paper |

the corresponding products under the same reaction conditions.

In order to compare the current protocol with previously published methods for the synthesis of 1,4-dihydropyranopyrazoles, we carried out some additional studies (Table 2). The comparison of results clearly demonstrates that TCAA is a good catalyst in terms of reaction times and yields of obtained products.

# 3. Conclusions

Two new methods for the synthesis of 6-amino-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives have been developed through a four-component one-pot reaction of ethyl acetoacetate, phenylhydrazine, malononitrile, and various aromatic aldehydes, using commercially available trichloroacetic acid or ceric sulfate as an efficient heterogeneous catalysts. The developed methodology is simple, novel and highly efficient, which afford various 1,4-dihydropyrano [2,3-*c*]pyrazoles in good to excellent yields under mild and solvent free conditions. Clean conversions, higher yields compared to the other similar methods, very short reaction times, and avoidance of the tedious work-up, are some of the additional advantages of these protocols.

# 4. Experimental

## 4. 1. General

All chemicals were purchased from Aldrich and Merck chemical companies with high-grade quality, and used without further purification. Melting points were determined in open capillary tubes and are uncorrected. IR measurements were carried out using KBr pellets on FTIR spectrometer. The NMR spectra were run on Bruker-250 MHz instrument, using $CDCl_3$ as solvent and referenced to TMS. All products are known compounds and were characterized by comparison of their spectral and physical data with literature values. The monitoring of the progress of all reactions was carried out by TLC using aluminum plates with silica gel 60 $F_{254}$ (Merck).

## 4. 2. General Procedure for the Synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles

**Method A**: To a pre-stirred mixture of ethyl acetoacetate (0.260 g, 2 mmol) and phenylhydrazine (0.214 g, 2 mmol) in trichloroacetic acid (0.032 g, 10 mol%) was added aromatic aldehyde (2 mmol) and malononitrile (0.132 g, 2 mmol), and stirred at 100 °C for the appropriate time. The reaction progress was monitored by TLC (ethyl acetate/n-hexane = 1/4). After completion of the reaction, the reaction mixture was cooled to 25 °C with addition of water (10 ml) and stirred for 10 min. The obtained solid was collected by filtration and purified by recrystallization from ethanol to afford the pure product.

**Method B**: To a pre-stirred mixture of ethyl acetoacetate (0.260 g, 2 mmol) and phenylhydrazine (0.214 g, 2 mmol) in ceric sulfate (0.080 g, 10 mol%) was added aromatic aldehyde (2 mmol) and malononitrile (0.132 g, 2 mmol), and stirred at 100 °C for the appropriate time. The reaction progress was monitored by TLC (ethyl acetate/n-hexane = 1/4). After completion of the reaction, the reaction mixture was cooled to 25 °C with addition of ethanol (10 ml) and the catalyst recovered by filtration. The filtrate was concentrated and allowed to crystallize the desired product.

**6-Amino-4-(4-bromophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile**

White solid, mp: 182–184 °C, IR (KBr) $\nu_{max}$ 3450, 3324, 2197, 1660, 1518, 1396, 1127, 1069, 752 $cm^{-1}$; $^1H$ NMR (250MHz, $CDCl_3$): δ 1.89 (s, 3H, $CH_3$), 4.64 (s, 1H, C–H), 4.68 (s, 2H, $NH_2$), 7.12–7.66 (m, 9H, ArH) ppm.

**6-Amino-4-(4-cyanophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile**

White solid, mp: 197–199 °C, IR (KBr) $\nu_{max}$ 3400, 3305, 2234, 2189, 1649, 1491, 1262, 1024, 753 $cm^{-1}$; $^1$HNMR (250 MHz, $CDCl_3$): δ 1.88 (s, 3H, $CH_3$), 4.74 (s, 1H, C–H), 4.76 (s, 2H, $NH_2$), 7.26–7.69 (m, 9H, ArH) ppm; $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ 12.9, 37.5, 62.5, 97.1, 111.7, 118.5, 121.3, 127.1, 128.3, 128.71, 129.3, 131.9, 132.3, 132.8, 146.0, 147.2, 158.4 ppm. Anal. Calcd For $C_{21}H_{15}N_5O$: C, 71.38; H, 4.28; N, 19.82; Found: C, 71.30; H, 4.25; N, 19.78.

**6-Amino-3-methyl-4-(3-nitrophenyl)-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile**

White solid, mp: 188–191 °C, IR (KBr) $\nu_{max}$ 3438, 3298, 2194, 1652, 1517, 1352, 1068, 755cm$^{-1}$; $^1$H NMR (250MHz, $CDCl_3$): δ 1.89 (s, 3H, $CH_3$), 4.78 (s, 1H, C–H), 4.81 (s, 2H, $NH_2$), 7.26–8.19 (m, 9H, ArH) ppm.

**6-Amino-4-(2,6-dichlorophenyl)-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile**

White solid, mp: 205–207 °C, IR (KBr) $\nu_{max}$ 3321, 3200, 2192, 1654, 1522, 1394, 1269, 1028, 753 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): δ 1.90 (s, 3H, $CH_3$), 5.80 (s, 1H, C–H), 4.80 (s, 2H, $NH_2$), 7.14–7.64 (m, 8H, ArH) ppm; $^{13}$C NMR (62.5 MHz, $CDCl_3$): δ 12.4, 33.2, 59.4, 96.1, 118.6, 121.3, 126.8, 129.2, 130.77, 134.4, 135.6, 136.4, 137.5, 144.4, 145.7, 159.9 ppm. Anal. Calcd For $C_{20}H_{14}C_{l2}N_4O$: C, 60.47; H, 3.55; N, 14.10; Found: C, 60.42; H, 3.51; N, 14.13.

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## Povzetek

V prispevku sta opisana dva enostavna in učinkovita postopka priprave derivatov 6-amino-3-metil-1,4-difenil-1,4-dihidropirano[2,3-*c*]pirazol-5-karbonitrila s pomočjo štiri-komponentne reakcije med etil acetoacetatom, fenilhidrazinom, malononitrilom in različnimi aromatskimi aldehidi. Avtorji so v reakciji uporabili triklorocetno kislino, oziroma cerijev sulfat kot heterogena katalizatorja in pri tem dobili odlične izkoristke v kratkih reakcijskih časih.