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Trichloroacetic acid as a solid heterogeneous catalyst for the rapid synthesis of dihydropyrano[2,3-*c*]pyrazoles under solvent-free conditions

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Abstract

A one-pot, three-component reaction of an aromatic aldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one in the presence of a catalytic amount of trichloroacetic acid produces a 6-amino-4-aryl-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole in excellent yield and in a short reaction time.

Keywords: aldehyde; dihydropyranopyrazoles; malononitrile; trichloroacetic acid.

Introduction

Dihydropyrano[2,3-*c*]pyrazole derivatives show useful biological and pharmacological properties (Witte et al., 1986; Bonsignore et al., 1993; Zaki et al., 2006; Abdelrazek et al., 2007). Some 2-amino-4*H*-pyrans can be used as photoactive materials (Armetso et al., 1989). Furthermore, polysubstituted 4*H*-pyrans constitute a structural unit of a series of natural products (Hatakeyama et al., 1988; Kamaljit and Harjit, 1996). Synthesis of 4*H*-pyrano[2,3-*c*]pyrazole from 3-methyl-3-pyrazolin-5-one and arylidenemalononitrile using base catalyst has been attempted (Otto, 1974; Otto and Schmelz, 1979). Recently, three-component one-pot condensation of 3-methyl-1-phenyl-2-pyrazolin-5-one, aldehydes and malononitrile for the construction of 1,4-dihydropyrano[2,3-*c*]pyrazole derivatives has been reported under different conditions (Shi et al., 2004; Jin et al., 2005, 2006; Heravi et al., 2010; Khurana et al., 2011; Kshirsagar et al., 2011). These approaches require harsh reaction conditions, expensive reagents, toxic organic solvents and long reaction times.

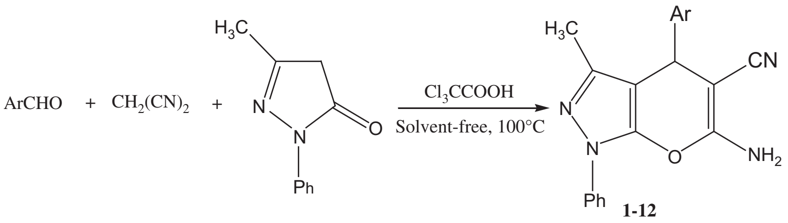
Results and discussion

As part of our ongoing studies devoted to the development of practical, safe, and environmentally friendly procedures for several important organic transformations (Karimi-Jaberi and Amiri, 2010; Karimi-Jaberi and Keshavarzi, 2010; Karimi-Jaberi et al., 2010, Karimi-Jaberi and Arjmandi, 2011), we now describe a simple and efficient protocol for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles (Scheme 1). The approach is based on a three-component reaction of an aromatic aldehyde, malononitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one in the presence of trichloroacetic acid as a solid heterogeneous catalyst under solvent-free conditions. Heterogeneous catalysts are advantageous over conventional homogeneous catalysts in that they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation (Thomas and Thomas, 1997). Trichloroacetic acid is a readily available and inexpensive reagent and can conveniently be handled and removed from the reaction mixture (Karimi-Jaberi et al., 2011).

The conditions were optimized using benzaldehyde for the reaction with 3-methyl-1-phenyl-2-pyrazolin-5-one and malononitrile. The reaction proceeded smoothly under solvent-free conditions in the presence of 10 mol% trichloroacetic acid as a solid heterogeneous catalyst. The yield of **1** was 98% after 3 min at 100°C. Various aldehydes were allowed to react following the optimization to prepare a series of 1,4-dihydropyrano[2,3-*c*]pyrazoles **1–12** (Scheme 1). In all cases, the corresponding products were obtained in low reaction times with good to excellent yields. The reaction was successful with many common aldehydes. However, 4-dimethylaminobenzaldehyde failed to react. It can be suggested that the strongly electron donating dimethylamino group diminishes reactivity of the aldehyde (Jin et al., 2006). It is important to note that the synthesis of dihydropyrano[2,3-*c*]pyrazoles could not be achieved in the absence of trichloroacetic acid. The structures of all products **1–12** were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

Conclusion

Trichloroacetic acid is a simple and efficient solid catalyst for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles through one-pot, three-component reaction of 3-methyl-1-phenyl-2-pyrazolin-5-one, aldehydes and malononitrile under solvent-free conditions. This acid is as an effective catalyst with respect to reaction times and yields when compared to other catalysts used for similar transformations (Shi et al., 2004; Jin et al., 2005, 2006; Heravi et al., 2010; Khurana et al., 2011; Kshirsagar et al., 2011).



1: Ar=C_6H_5; **2**: Ar=4-ClC_6H_4; **3**: Ar=4-BrC_6H_4; **4**: Ar=4-FC_6H_4; **5**: Ar= 4-CNC_6H_4; **6**: Ar=4-$NO_2C_6H_4$; **7**: Ar=3-$NO_2C_6H_4$; **8**: Ar=2,6-$Cl_2C_6H_3$; **9**: Ar=2,4-$Cl_2C_6H_3$; **10**: Ar=4-$CH_3C_6H_4$; **11**: Ar=4-$CH_3OC_6H_4$; **12**: Ar=4-OHC_6H_4

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

Experimental

General procedure for the synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles 1–12

To a mixture of aldehyde (2 mmol), malononitrile (132 mg, 2 mmol) and 3-methyl-1-phenyl-2-pyrazolin-5-one (384 mg, 2 mmol), trichloroacetic acid (32 mg, 10 mol%) was added and the mixture was stirred at 100°C for the period of time indicated below. The progress of the reaction was monitored by TLC (ethyl acetate/*n*-hexane, 1:4). After completion of the reaction, the mixture was cooled to 25°C, treated with water (10 mL), and stirred for 10 min. The obtained solid was collected by filtration and crystallized from ethanol to afford pure product **1–12**.

6-Amino-5-cyano-3-methyl-1,4-diphenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (1) Reaction time 3 min; yield 98%; mp 168–170°C; reported mp 168–170°C (Jin et al., 2005).

6-Amino-4-(4-chlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (2) Reaction time 3 min; yield 85%; mp 175–177°C; reported mp 174–175°C (Jin et al., 2005).

6-Amino-4-(4-bromophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (3) Reaction time 1 min; yield 90%; mp 182–184°C; reported mp 183–184°C (Khurana et al., 2011).

6-Amino-4-(4-flourophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (4) Reaction time 2 min; yield 84%; mp 169–171°C; reported mp 167–168°C (Shi et al., 2004).

6-Amino-4-(4-cyanophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (5) Reaction time 2 min; yield 90%; mp 197–199°C; IR (KBr) ν_{max} 3400, 3305, 2234, 2189, 1649, 1491, 1262, 1024, 753 cm^{-1}; ^1H NMR (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); ^{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. 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-4-(4-nitrophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (6) Reaction time 3 min; yield 88%; mp 192–195°C; reported mp 194–196°C (Jin et al., 2006).

6-Amino-4-(3-nitrophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (7) Reaction time 3 min; yield 96%; mp 188–191°C; reported mp 188–190°C (Jin et al., 2006).

6-Amino-4-(2,6-dichlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (8) Reaction time 8 min; yield 70%; mp 205–207°C; IR (KBr) ν_{max} 3321, 3200, 2192, 1654, 1522, 1394, 1269, 1028, 753 cm^{-1}; ^1H 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); ^{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. Anal. Calcd for $C_{20}H_{14}C_{12}N_4O$: C, 60.47; H, 3.55; N, 14.10. Found: C, 60.42; H, 3.51; N, 14.13.

6-Amino-4-(2,4-dichlorophenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (9) Reaction time 3 min; yield 87%; mp 182–184°C; reported mp 182–184°C (Jin et al., 2006).

6-Amino-4-(4-methylphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (10) Reaction time 5 min; yield 88%; mp 172–174°C; reported mp 176–178°C (Jin et al., 2005).

6-Amino-4-(4-methoxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (11) Reaction time 9 min; yield 91%; mp 172–174°C; reported mp 174–176°C (Jin et al., 2005).

6-Amino-4-(4-hydroxyphenyl)-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-*c*]pyrazole (12) Reaction time 4 min; yield 95%; mp 210–212°C; reported mp 211–212°C (Heravi et al., 2010).

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