Res Chem Intermed
DOI 10.1007/s11164-012-0991-1

Mild, four-component synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles catalyzed by titanium dioxide nano-sized particles

Hamid Reza Shaterian · Kobra Azizi

Received: 17 December 2012 / Accepted: 20 December 2012

Abstract A convenient and efficient solvent-free procedure is described for preparation of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles by four-component reaction of hydrazine hydrate, ethyl acetoacetate, aryl aldehyde, and malononitrile in the presence of a catalytic amount of titanium dioxide nano-sized particles. Short reaction times, high yields under ambient conditions, simple reaction, clean work-up, and reusability of the nano heterogeneous catalyst are the advantages of this method.

Keywords Nano TiO_2 · Four-component reaction · Solvent-free conditions · 6-Amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles · Hydrazine hydrate

Introduction

1,4-Dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles are important compounds with biological [1], anticancer [1], antimicrobial [2], anti-inflammatory [3], insecticidal [4], and molluscicidal [5] activity. Pyranopyrazole was first synthesized by two-component reaction of 3-methyl-1-phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine [6]. Later, several two-component reactions involving pyran derivatives and hydrazine hydrate [7] or the reaction between 3-methyl-2-pyrazolin-5-one and benzylidenemalononitrile [8] to obtain pyranopyrazoles were used to prepare this class of medicinal compounds.

Several three-component syntheses of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles from pyrazolin-5-one, malononitrile, and aryl

H. R. Shaterian (✉) · K. Azizi
Department of Chemistry, Faculty of Sciences, University of Sistan and Baluchestan, PO Box 98135-674, Zahedan, Iran
e-mail: hrshaterian@chem.usb.ac.ir

Published online: 13 January 2013

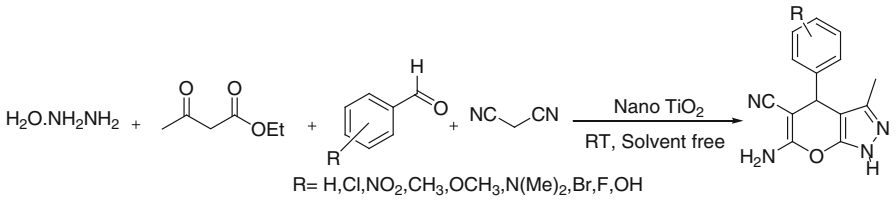
aldehydes, catalyzed by cinchona alkaloid organocatalysts [8] or triethylammonium acetate [9], have been reported in the literature. Recently, per-6-amino-β-cyclodextrin [10], γ-alumina [11], and L-proline [12] have been studied for synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles via four-component reactions from hydrazine hydrate, ethyl acetoacetate, aldehydes, and malononitrile. Despite many reported methods, development of new synthetic strategies using readily accessible heterogeneous catalysts still attracts much attention because of the importance of these molecules, especially if the new methods can overcome the disadvantages of reported procedures.

Efficient and environmentally benign chemical processes and methods in the presence of heterogeneous recyclable catalysts under mild and solvent-free conditions are a major challenge for chemists in organic synthesis [13]. In continuation of our research on solid heterogeneous catalysts [14–18], herein we report a facile, general, and efficient method for preparation of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles by four-component reaction of hydrazine hydrate, ethyl acetoacetate, aryl aldehydes, and malononitrile, using titanium dioxide nano-sized particles as an expedient and recyclable catalyst under mild, solvent-free conditions (Scheme 1). The reaction has several advantages over other reported methods.

Nanocatalysts have attracted the attention of researchers working on catalysis and nanoparticles, because their high surface-to-volume ratio results in high efficiency and selectivity [19, 20]. Titanium dioxide nano-sized particles have been proved to be a good catalyst because of their high activity, non-toxicity, ready availability, reusability, strong oxidizing power, and long-term stability [21, 22].

Experimental

All reagents were purchased from Merck and Sigma-Aldrich and used without further purification. Nano-TiO_2 ellipsoids of size <3 nm (95 % anatase, 5 % brokite; CAS no. 1317-70-0) were purchased from Merck. All yields refer to isolated products after purification. Products were characterized by comparison of physical data with those of authentic samples and by use of spectroscopic data (IR and NMR). NMR spectra were recorded on a Bruker Avance DPX 400-MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a Jasco FT-IR 460 Plus spectrophotometer. Melting



Scheme 1 Preparation of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles by a four-component reaction using titanium dioxide nano-sized particles as recyclable catalyst under solvent-free conditions

points were determined in open capillaries with a Buchi 510 melting point apparatus. TLC was performed on Polygram silica–gel SILG/UV 254 plates.

General procedure for synthesis of 6-amino-4-aryl-3-methyl-1, 4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile derivatives

A mixture of hydrazine hydrate (1 mmol) and ethyl acetoacetate (1 mmol) was stirred at room temperature until 3-methyl-2-pyrazolin-5-one was precipitated and its formation was complete (5 min). The mixture was cooled to 0 °C then aryl aldehyde (1 mmol), malononitrile (1 mmol), and titanium dioxide nano-sized particles (0.25 mmol) were added at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was washed with ethyl acetate and filtered to recover the catalyst. The filtrate solution was evaporated and the crude product was recrystallized from ethanol to afford the pure pyranopyrazole derivatives in 81–96 % yields.

The desired pure products were characterized by comparison of their physical data with those of known compounds [11, 23].

6-Amino-1,4-dihydro-3-methyl-4-(2-nitrophenyl)pyrano[2,3-c]pyrazole-5-carbonitrile (Table 2, entry 10)

(KBr, cm^{-1}): 1076, 1169, 1348, 1407, 1527, 1600, 1653, 2196, 2932, 3118, 3217, 3469; ^{1}H NMR (400 MHz, (DMSO-d_6): δ (ppm) = 1.92 (s, 3H, CH_3), 4.79 (s, 1H, 4H), 6.20 (s, 2H, NH_2), 7.55 (t, 1H, J = 8.0 Hz, Ar–H), 7.62 (d, 1H, J = 7.6 Hz, Ar–H), 8.00–8.03 (m, 2H, Ar–H), 11.34 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 9.70, 29.0, 56.5, 112.6, 120.2, 123.2, 128.4, 128.6, 135.7, 141.3, 146.3, 151.3, 154.6, 160.9.

Results and discussion

In our initial experiments, condensation of hydrazine hydrate, ethyl acetoacetate, benzaldehyde, and malononitrile (molar ratio 1:1:1:1) was performed in the presence of different amounts of the catalyst at room temperature under solvent-free conditions. The results (Table 1) clearly indicate that 0.25 mmol (0.02 g) nano-TiO_2 is an effective amount of catalyst for this transformation.

We also used bulk TiO_2 for synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles (Table 1, entry 6). The reaction was not complete after 3 h; almost 50 % of the starting materials were intact and the desired product was obtained in low yield. Thus, it is necessary to use titanium dioxide nano-sized particles.

Under these optimized reaction conditions, the scope and efficiency of the reaction were investigated for synthesis of a wide variety of substituted 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles. The results are summarized in Table 2.

Table 1 Optimization of the amount of titanium dioxide nano-sized particles used as catalyst in the reaction of hydrazine hydrate, ethyl acetoacetate, benzaldehyde, and malononitrile under solvent-free conditions at room temperature

Entry	Catalyst (mmol)	Time (min)	Yield (%)[a]
1	0.1	25	75
2	0.15	12	78
3	0.2	7	87
4	0.25	3	96
5	0.3	3	95
6	0.25	3 h	50[b]

[a] Yields refer to isolated pure product

[b] The reaction was performed in the presence of bulk TiO_2 for synthesis

Table 2 Four-component synthesis of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles

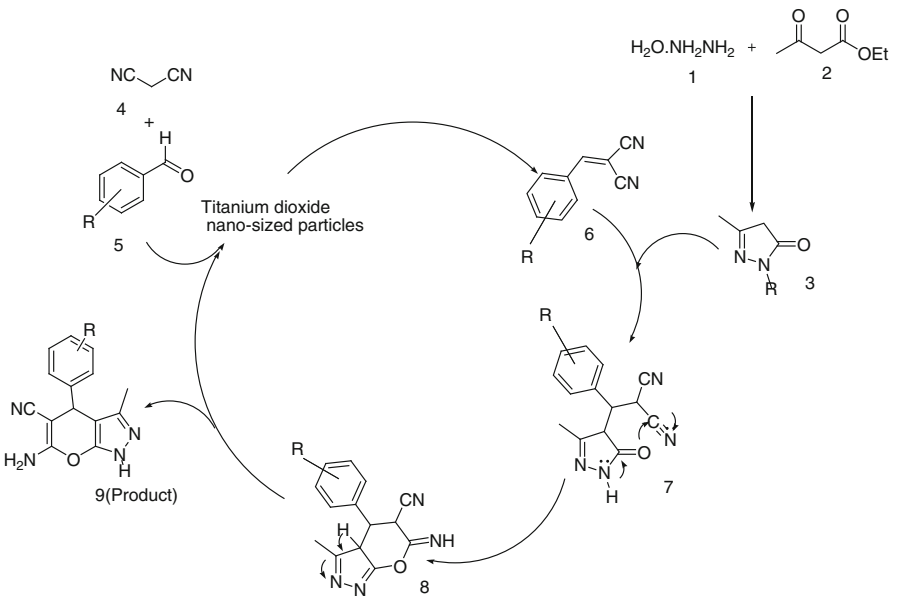
Entry	R	Time (min)	Yield (%)[a]	Found M.P. (°C)/[Lit. M.P (°C)] [Ref.]
1	H	3	96	245–247 [245–247] [11, 23]
2	3-CH_3O-4-HO	6	81	235–237 [235–237] [11, 23]
3	4-Cl	4	93	234–235 [234–235] [11, 23]
4	4-CH_3O	5	89	159–160 [157–159] [11, 23]
5	4-NO_2	4	87	244–245 [245–247] [11, 23]
6	2,4-Cl_2	4	85	235–237 [235–237] [11, 23]
7	4-Br	5	86	178–180 [178–180] [11, 23]
8	3-Br	3	86	223–225 [222–224] [11, 23]
9	2-Cl	5	85	146–148 [146–148] [11, 23]
10	2-NO_2	2	82	221–223 [221–223] [11, 23]
11	2,4-Cl_2	4	87	183–185 [183–185] [11, 23]
12	4-F	5	87	173–175 [173–175] [11, 23]
13	4-CH_3	4	85	207–209 [206–208] [11, 23]
14	2,5-$(CH_3O)_2$	5	85	212–213 [210–212] [11, 23]
15	3,4$(CH_3O)_2$	5	82	192–194 [193–195] [11, 23]
16	3,4,5-$(CH_3O)_3$	6	84	209–211 [209–211] [11, 23]
17	4-HO	6	81	225–227 [224–226] [11, 23]
18	4-N$(CH_3)_2$	6	81	167–169 [167–169] [11, 23]
19	3-NO_2	4	92	194–196 [193–195] [11, 23]

[a] Yields refer to the isolated pure products. The products were characterized by comparison of their physical data (melting points, and IR and ^1H and ^{13}C NMR spectra) with those of known compounds [11, 23]

Interestingly, a variety of aryl aldehydes with electron-withdrawing or releasing substituents (*ortho*, *meta*, and *para*-substituted) participated well in this reaction and gave the 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in good to excellent yield.

On the basis of the literature [23], we propose following mechanism for synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles in the presence of titanium dioxide nano-sized particles as catalyst. First, pyrazolone 3 is formed by reaction of 1 and 2. Knoevenagel condensation of 4 and 5 produced 2-benzylidenemalononitrile (6), Michael addition of 3 and 6, and subsequent cyclization and tautomerization afforded the corresponding product (Scheme 2).

In Table 3 the results obtained in this work are compared with those recently reported in the literature for use of such catalysts as L-proline [12], γ-alumina [11], cinchona alkaloids [8], and nano-sized magnesium oxide MgO [23] to prepare 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles. The table



Scheme 2 Proposed mechanism for synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitriles in the presence of titanium dioxide nano-sized particles as catalyst

Table 3 Comparison of results obtained by use of titanium dioxide nano-sized particles as catalyst for synthesis of 1,4-dihydropyrano[2,3-*c*]pyrazoles with those obtained by use of L-proline, γ-alumina, cinchona alkaloids, and nano-sized magnesium oxide MgO

Entry	Catalyst	Time	Yield (%)[a]
1	L-Proline	10 min	90
2	γ-Alumina	50 min	80
3	Cinchona alkaloids	12 h	84
4	Nano-sized magnesium oxide MgO	10 min	97
5	Nano-sized titanium dioxide TiO_2	3 min	96 (Present work)

[a] Based on reaction of hydrazine hydrate, ethyl acetoacetate, benzaldehyde, and malononitrile

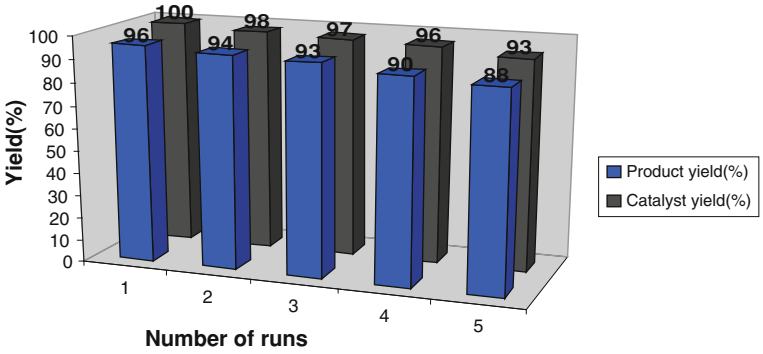


Fig. 1 Reusability of titanium dioxide nano-sized particles as catalyst

shows that titanium dioxide nano-sized particles are the most efficient catalyst with regard to reaction time. Yield is equivalent to that reported for the other catalysts.

We also investigated recycling of the catalyst under solvent-free conditions using, as model reactants, hydrazine hydrate, ethyl acetoacetate, benzaldehyde, and malononitrile. After completion of the reaction, the crude solid product was dissolved in ethyl acetate. The mixture was filtered for separation of the catalyst. The catalyst was washed twice with ethyl acetate (2 × 5 mL). The recovered catalyst was dried under vacuum and was used for subsequent catalytic runs (Table 2, entry 1). The recovered catalyst was reused five times without any loss of activity (Fig. 1).

Conclusion

We have developed an environmentally benign and straightforward procedure for synthesis of 6-amino-4-aryl-3-methyl-1,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitriles using titanium dioxide nano-sized particles as catalyst under solvent-free and ambient conditions. This procedure has several advantages over previously reported catalysts, for example milder and cleaner reactions, easier workup, reduced reaction times, reusable catalyst, and eco-friendly promising strategy.

Acknowledgments We are thankful to Sistan and Baluchestan University Research Council for partial support of this research.

References

1. E.S. El-Tamany, F.A. El-Shahed, B.H. Mohamed, J. Serb. Chem. Soc. **64**, 9 (1999)
2. M.E.A. Zaki, H.A. Soliman, O.A. Hiekal, A.E.Z. Rashad, Naturforsch. C. **61**, 1 (2006)
3. Z.H. Ismail, G.M. Aly, M.S. El-Degwi, H.I. Heiba, M.M. Ghorab, Egypt. J. Biot. **13**, 73 (2003)
4. F.M. Abdelrazek, P. Metz, N.H. Metwally, S.F. El- Mahrouky, Arch. Pharm. **339**, 456 (2006)
5. N. Oloppe, L.M. Fisher, R. Howes, A. Potter, G.S. Robertson Alan, A.E. Surgenor, Bioorg. Med. Chem. **14**, 4792 (2006)
6. H. Junek, H. Aigner, Chem. Ber. **106**, 914 (1973)

7. Y. Peng, G. Song, R. Dou, Green Chem. **8**, 573 (2006)
8. S. Gogoi, C.G. Zhao, Tetrahedron Lett. **50**, 2250 (2009)
9. R.S Balaskar, S.N. Gavade, M.S. Mane, B.B. Shingate, M.S. Shingare, D.V. Mane, Chin. Chem. Lett. **21**, 1175 (2010)
10. K. Kanagaraj, K. Pitchumani, Tetrahedron Lett. **51**, 3312 (2010)
11. H. Mecadon, M.R. Rohman, M. Rajbangshi, B. Myrboh, Tetrahedron Lett. **52**, 2523 (2011)
12. H. Mecadon, M.R. Rohman, I. Kharbangar, B.M. Laloo, I. Kharkongor, M. Rajbangshi, B. Myrboh, Tetrahedron Lett. **52**, 3228 (2011)
13. M.M. Heravi, F. Derikvand, L. Ranjbar, F.F. Bamoharram, J. Mol. Catal. Chem. A. **261**, 156 (2007)
14. H.R. Shaterian, H. Yarahmadi, Tetrahedron Lett. **49**, 1297 (2008)
15. H. R Shaterian, H. Yarahmadi, Arkivoc **2**, 105 (2008)
16. H.R. Shaterian, M. Ghashang, A. Hassankhani, Dyes Pigments. **76**, 564 (2008)
17. H.R. Shaterian, A. Hosseinian, M. Ghashang, Synth. Commun. **38**, 4097 (2008)
18. H.R Shaterian, A. Hosseinian, M. Ghashang, Synth. Commun. **19**, 3375 (2008)
19. S. Yamazaki, Bull. Chem. Soc. Jpn. **69**, 2955 (1996)
20. H.J. Reich, F. Chow, S.L. Peake, Synthesis **2**, 299 (1978)
21. I. Mohammadpoor-Baltork, M. Moghadama, S. Tangestaninejada, V. Mirkhani, Z. Eskandari, H. Salavati, J. Iran. Chem. Soc. **8**, 17 (2011)
22. S. Tangestaninejada, M. Moghadama, V. Mirkhani, I. Mohammadpoor-Baltork, H. Salavati, J. Iran. Chem. Soc. **7**, 161 (2010)
23. M. Babaie, H. Sheibani, Arab. J. Chem. **4**, 159 (2010)