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TiO_2 and TiO_2 nanoparticles as efficient and recoverable catalysts for the synthesis of pyran annulated heterocyclic systems

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Abstract TiO_2 catalyzed reactions between various activated CH-acids and tetracyanoethylene are described. This reaction affords the corresponding pyran annulated heterocyclic systems in high yields at room temperature in 3 h. The work-up procedure is very simple, and the products do not require further purification. The catalysts can be recycled and reused several times without observable loss of performance.

Keywords TiO_2 · Pyran · Green chemistry · Nano-particles · Tetracyanoethylene

Introduction

With increasing concern about environmental pollution troubles and the importance of healthy and productive life in harmony with nature, there has been remarkable interest in developing new routes that reduce pollution in chemical synthesis. Water as a solvent and heterogeneous catalysis are keys to successful development of so-called "green chemistry". Therefore, these two factors are widely studied for optimizing reaction conditions [1]. The use of organic solvents required to conduct chemical reactions creates ecological and economic concerns. The hazardous nature of these solvents and the consequence of them in the environment, and their urgent deletion or replacement with H_2O, have been a major emphasis of green chemistry [2–4]. In the last decade, a large number of publications have demonstrated the value of H_2O or aqueous media for chemical reactions [5, 6]. The ease of handling, simple work-up, and regenerability of heterogeneous catalysts induced makes them of great interest in industrial catalytic processes. TiO_2 as a heterogeneous catalyst whas been applied for diverse industrial applications, e.g. in the selective reduction of NO_x in stationary sources, photocatalysis for pollutant elimination or organic

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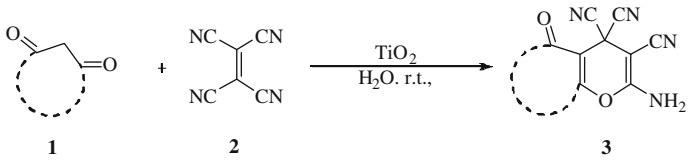


1 2 3

Scheme 1 Reaction between TCNE and CH-acids in the presence of TiO_2 as the catalyst

synthesis, photovoltaic devices, sensors, and paints [7–10]. Nanocrystalline metal oxides have unusual magnetic, physical and surface chemical and catalytic properties [11–15]. These materials can exist with numerous surface sites and enhanced surface reactivity, such as crystal corners, edges or ion vacancies [16]. Nanocrystalline TiO_2 has been applied as a catalyst for the Friedel–Craft's alkylation of indoles with epoxides [17].

Pyrans as naturally-occurring compounds [18, 19] have useful biological activities, such as spasmolytic, diuretic, anti-coagulant, anti-cancer, and anti-anaphylactic [20–23]. They are interesting due to their therapeutic applications such as cognitive enhancers. They are also used for the treatment of neurodegenerative diseases including Alzheimer, amyotrophic lateral sclerosis, Huntington, Parkinson, AIDS-associated dementia and Down's syndrome, as well as for the treatment of schizophrenia and myoclonus [24]. Thus, new methods for the synthesis of pyran derivatives and their optimization is of great interest [25–28].

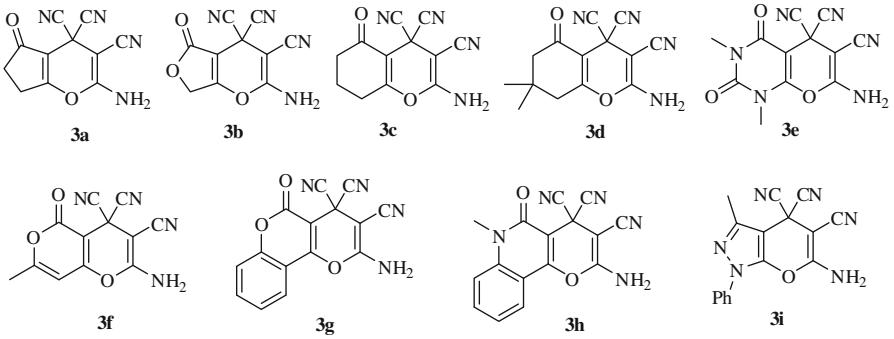
Here, in a greener approach, the synthesis of pyran annulated heterocyclic systems **3a–i** was developed in the presence of TiO_2 as the heterogeneous recyclable catalysts, in H_2O at room temperature (Scheme 1).

Results and discussion

In a pilot experiment, the reaction of 5,5-dimethylcyclohexane-1,3-dione (**1d**) (1 mmol) with TCNE (**2**) (1 mmol) in the presence of TiO_2 (0.02 g) in H_2O (10 mL) was investigated. This reaction afforded 2-amino-7,7-dimethyl-5-oxo-6,7,8,8a-tetrahydro-4*H*-chromene-3,4,4(4aH,5H)-tricarbonitrile (**3d**) in 75 % yield after 3 h (Scheme 1).

Treatment of various CH-acids **1** such as cyclopentane-1,3-dione (**1a**), tetronic acid (**1b**), cyclohexane-1,3-dione (**1c**), dimedone (**1d**), 1,3-dimethylpyrimidine-2,4,6(1H,3H,5H)-trione (**1e**), 4-hydroxy-6-methyl-2H-pyran-2-one (**1f**), 4-hydroxy-2H-chromen-2-one (**1g**) and 4-hydroxy-1-methylquinolin-2(1H)-one (**1h**) with TCNE (**2**) in the presence of TiO_2 in H_2O at room temperature led to the formation of the corresponding pyran's annulated heterocyclic systems **3a–i** in high yields (Fig. 1).

Next, the reaction was examined in the presence of TiO_2 nanoparticles (NPs) as the catalyst under the same reaction conditions. TiO_2 NPs showed partially good performance rather than TiO_2 and somewhat increased reaction yields. Therefore, we decided to investigate TiO_2 NPs as a catalyst in this reaction for all of the compounds **1**. The results are summarized in Fig. 1 .



Product		3a	3b	3c	3d	3e	3f	3g	3h	3i
Yield[a](%)		75	73	74	75	79	80	80	71	70
Yield[b](%)		80	77	83	81	80	83	86	80	72
M. P (°C)	Found	178-180	186-188	196-198	198-200	210	203	220	219	192-194
	Reported[c]	178-181	186-188	196-197	196-201	210-213	203	220-222	220-222	-

[a]In the presence of TiO_2
[b]In the presence of TiO_2 NPs
[c]Ref [28]

Fig. 1 Structures, melting points [28] and yields of products **3a–i**

Recyclability of the catalysts was also examined. For this reason, catalysts, which were recovered from the reaction between 5,5-dimethylcyclohexane-1,3-dione (**1d**) and TCNE 2 by filtration, washed with CH_2Cl_2 (2 × 5 ml) and dried in the oven (70 °C, 6 h), were used again. This procedure was carried out four times. The results of these successive reactions are shown in Table 1. It is clear that, during successive use of the catalyst, no decrease in the reactivity or performance can be seen for TiO_2, but TiO_2 NPs does not show good recoverability.

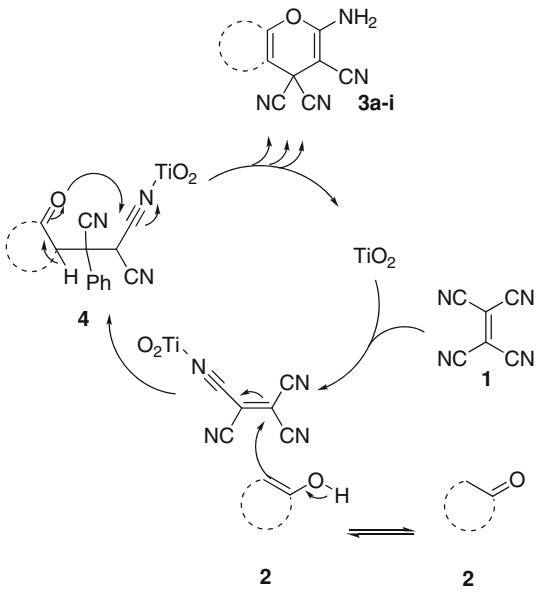
Although no detailed mechanistic studies have been carried out at this point, it is conceivable that the initial event is the activation of TCNE (**2**) via coordination with TiO_2. Then, the cyclic CH-acid **1** undergoes nucleophilic addition to activated TCNE to produce intermediate **4** which, via intramolecular cyclization, afforded products **3a–i** (Scheme 2).

Table 1 Recycle of catalysts

Cycle	TiO_2 (g)	Yield (%)[a]	TiO_2 NPs (g)	Yield (%)[a]
1	0.018	75	0.016	81
2	0.017	75	0.012	80
3	0.015	73	0.011	80
4	0.015	71	0.010	79

Reaction conditions: 5,5-dimethylcyclohexane-1,3-dione (**1d**) (1 mmol), TCNE (**2**) (1 mmol), H_2O (10 mL), room temperature, 3 h

[a] Isolated yield



Scheme 2 The proposed mechanism for the formation of pyrans **3a–i** in the presence of TiO_2

Here, we want to solve two problems. The first problem is when using the homogeneous catalyst, such as separation and regeneration, and the second problem is the application of organic solvent. Successively, we overcame these problems by using a heterogeneous catalyst in H_2O. The separation of TiO_2 and TiO_2 NPs from the reaction medium was easily carried out by filtration. After drying, it was reused for subsequent reactions (Table 1). Thus, this process could be interesting for large-scale synthesis.

Conclusions

In conclusion, we have developed a rapid and efficient approach for the synthesis of pyran annulated heterocyclic systems under mild reaction conditions in H_2O in the presence of TiO_2 and TiO_2 NPs with fairly good yields. The present method has the advantages that not only can the catalysts be recycled and reused for several times without loss of performance but also the substances can be mixed without any modification. The work-up procedures are very simple, and the products do not require further purification. The simplicity of the present procedures and the environmental friendliness of this route makes it an interesting alternative to other approaches.

Experimental

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded in KBr on a Shimadzu IR-470 spectrometer.

^1H NMR Spectra were recorded on a Bruker DRX-300 Avance spectrometer 300.13 MHz. The ^{13}C NMR spectra were recorded at 75.47 MHz; for all NMR spectra data, chemical shifts (δ scale) are reported in parts per million (ppm). The elemental analyses were performed with an Elementar Analysensysteme VarioEL. The chemicals used in this work were purchased from Merck and Fluka Chemical. TiO_2 NPs were purchased from Aldrich with particle size <100 nm.

Typical procedure for preparation of 6-amino-3-methyl-1-phenylpyrano[2,3-c]pyrazole-4,4,5(1H)-tricarbonitrile (**3i**)

To a magnetically stirred solution of tetracyanoethylene (0.13 g, 1.0 mmol) in H_2O (10 ml), TiO_2 (0.02 g) and 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (0.17 g, 1.0 mmol) was added at room temperature and the reaction mixture was stirred for 3 h. After completion of the reaction, the solvent was removed under reduced pressure. Then, CH_2Cl_2 was added to the residue and the solid catalyst was separated from the reaction mixture by filtration. Then, crystallization from CH_2Cl_2/*n*hexane 1:2 afforded **3i** as a white powder (0.21 g, yield 70 %); Mp 192–194 °C; IR: 3,421, 3,329, 2,210, 1,747, 1,656, 1,536, 1,413 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 2.11 (s, 3H, CH_3), 7.31–7.47 (m, 5H, Ar–H), 8.63 (br s, 2H, NH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 37.26, 56.7, 91.2, 111.4, 117.3, 121.6, 122.1, 126.7, 129.1, 140.1, 142.3, 148.3, 160.9; Anal. calcd. for $C_{16}H_{10}N_6O$: C 63.57, H 3.33, N 27.80; Found $C_{16}H_{10}N_6O$: C 63.56, H 3.33, N 27.83.

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References

1. B.K. Min, C.M. Friend, Chem. Rev. **107**, 2709 (2007)
2. G. Nagendrappa, Resonance **7**, 59 (2002)
3. R.S. Varma, V.V. Namboodiri, Pure Appl. Chem. **73**, 1309 (2001)
4. R.S. Varma, Green Chem. **1**, 43 (1999)
5. P.A. Grieco, *Organic Synthesis in Water* (Blackie, New York, 1998)
6. D.J. Adams, P.J. Dyson, S.J. Tavener, *Chemistry in Alternative Reaction Media* (Wiley, New York, 2003)
7. H. Bosh, F. Janssen, Catal. Today **2**, 369 (1988)
8. P. Forzatti, Catal. Today **62**, 51 (2000)
9. M.R. Hoffman, S.T. Martin, W. Choi, D.W. Bahnemann, Chem. Rev. **95**, 69 (1995)
10. A. Maldoti, A. Molinari, R. Amadeni, Chem. Rev. **102**, 3811 (2002)
11. H. Itoh, S. Utamapanya, J.V. Stark, K.J. Klabunde, J.R. Schlup, Chem. Mater. **5**, 71 (1993)
12. Y. Jiang, C. Decker, C. Mohs, K.J. Klabunde, J. Catal. **180**, 24 (1998)
13. J. Guzman, B.C. Gates, Nano Lett. **1**, 689 (2001)
14. B.M. Choudary, R.S. Mulukutla, K.J. Klabunde, J. Am. Chem. Soc. **125**, 2020 (2003)
15. B.M. Choudary, M.L. Kantam, K.V.S. Ranganath, K. Mahender, B. Sreedhar, J. Am. Chem. Soc. **126**, 3396 (2004)
16. R. Richards, W. Li, S. Decker, C. Davidson, O. Koper, V. Zaikovski, A. Volodin, T. Rieker, J. Am. Chem. Soc. **122**, 4921 (2000)
17. M.L. Kantam, S. Laha, J. Yadav, B. Sreedhar, Tetrahedron Lett. **47**, 6213 (2006)
18. J.A. Ciller, N. Martin, C. Seoane, J.L. Soto, J. Chem. Soc. Perkin Trans. **1**, 2581 (1985)
19. S. Hatakeyama, N. Ochi, H. Numata, S. Takano, J. Chem. Soc. Chem. Commun. 1202 (1988)

20. L.L. Andreani, E. Lapi, Boll. Chim. Farm. **99**, 583 (1960)
21. L. Bonsignore, G. Loy, D. Secci, A. Calignano, Eur. J. Med. Chem. **28**, 517 (1993)
22. E.C. Witte, P. Neubert, A. Roesch, Chem. Abstr. **104**, 224915f (1986)
23. Y.L. Zhang, B.Z. Chen, K.Q. Zheng, M.L. Xu, L.Z. Zhang, X.H. Lei, Acta Pharm. Sin. **17**, 17 (1982)
24. C.S. Konkoy, D.B. Fick, S.X. Cai, N.C. Lan, J.F.W. Keana, PCT Int. Appl. WO oo75123 (2000)
25. P. Li, L.L. Luo, X.S. Li, J.W. Xie, Tetrahedron **66**, 7590 (2010)
26. W.B. Chen, Z.J. Wu, Q.L. Pei, L.F. Cun, X.M. Zhang, W.C. Yuan, Org. Lett. **12**, 3132 (2010)
27. M.A. Khalilzadeh, Z. Hossaini, M.M. Baradarani, A. Hasanni, Tetrahedron **66**, 8464 (2010)
28. A. Shaabani, A.H. Rezayan, A. Sarvary, A. Rahmati, H.R. Khavasi, Catal. Commun. **9**, 1082 (2008)