Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Tungstophosphoric Acid-Catalyzed Imino-Diels-Alder Reaction: An Efficient One-Pot Synthesis of Pyrano- and Furanoquinoline Derivatives

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Version of record first published: 07 Oct 2009.

To cite this article: Biswanath Das , P. Balasubramanyam , Maddeboina Krishnaiah & Boyapati Veeranjaneyulu (2009): Tungstophosphoric Acid-Catalyzed Imino-Diels-Alder Reaction: An Efficient One-Pot Synthesis of Pyrano- and Furanoquinoline Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:21, 3825-3832

To link to this article: http://dx.doi.org/10.1080/00397910902838946

Synthetic Communications®, 39: 3825–3832, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910902838946

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Tungstophosphoric Acid–Catalyzed Imino-Diels–Alder Reaction: An Efficient One-Pot Synthesis of Pyrano- and Furanoquinoline Derivatives

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Abstract: Tungstophosphoric acid has been found to be an efficient catalyst for the synthesis of pyranos- and furanoquinolines through the Imino-Diels–Alder reaction involving one-pot coupling of benzaldehydes, anilines, and 3,4-dihydro-2 H-pyran or 2,3-dihydrofuran. The products are formed at room temperature in excellent yields in a short period of time.

Keywords: Imino-Diels–Alder reaction, pyrano- and furanoquinolines, tungstophosphoric acid

INTRODUCTION

Pyrano- and furanoquinolines have attracted much attention because of their broad spectra of biological properties[1–4] and occurrence in several bioactive natural alkaloids.[5] These compounds are generally prepared[6–12] by aza-Diels–Alder reaction of imines (derived from aldehydes and amines) with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran employing Lewis acids as catalysts. However, the use of expensive catalysts, formation of mixtures of

Received December 1, 2008.
Part 176 in the series "Studies on novel synthetic methodologies."
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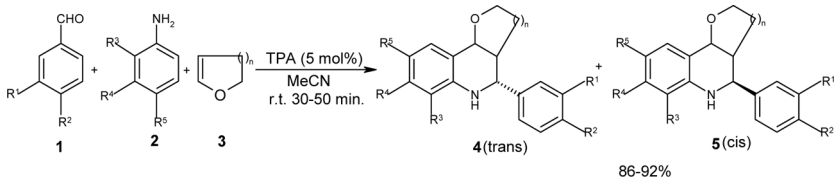
products, unsatisfactory yields, and long reaction times are the drawbacks in several of these methods. Many of the imines are also hygroscopic, unstable, and difficult to purify, and thus the preparation of these compounds separately is not advantageous. Another problem is that several Lewis acids cannot be employed for one-pot coupling of aldehydes, amines, and enol ethers because they will be decomposed or deactivated by the amines and water formed in the intermediate imine-formation step. Thus, few methods for single-step coupling of these three components have been developed. Here we report the catalytic activity of a heteropoly acid for such a reaction for the preparation of pyrano- and furanoquinolines.

RESULTS AND DISCUSSION

In continuation of our work[13–15] on the discovery of useful and improved synthetic methodologies, we have observed that the one-pot coupling of benzaldehydes **1**, anilines **2**, and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran **3** can efficiently be carried out using tungstophosphoric acid (TPA) as a catalyst (Scheme 1).

Initially the conversion was conducted with benzaldehyde, aniline, and 3,4-dihydro-2*H*-pyran in the presence of different amounts of TPA in MeCN at room temperature (Table 1). Considering the yields and reaction times, 5 mol% of the catalyst was considered to be suitable to carry out the reaction. Different solvents such as MeCN, tetrahydrofuran (THF), CH_2Cl_2, and toluene were utilized for this reaction, but MeCN was preferred because the yield of the corresponding quinoline was greatest.

A series of pyrano- and furanoquinolines were prepared from various benzaldehydes and anilines (Table 2). The conversion was complete within 30–50 min, and the quinoline derivatives were formed in excellent yields. The products were the mixtures of *trans*- and *cis*- isomers, which were separated by column chromatograph over silica gel. The *trans*-isomer **4** was the major isomer, whereas the *cis*-isomer **5** was the minor one in each case. The ratio of these two isomers was determined by ^{1}H



Scheme 1. Synthesis of pyrano- and furanoquinolines using TPA.

Table 1. Optimization of catalyst loading[a]

Entry	Catalyst loading (mol%)	Time (min)	Isolated yield (%)
a	1	40	55
b	5	40	92
c	10	40	93
d	15	40	93
e	20	40	94
f	0	180	0

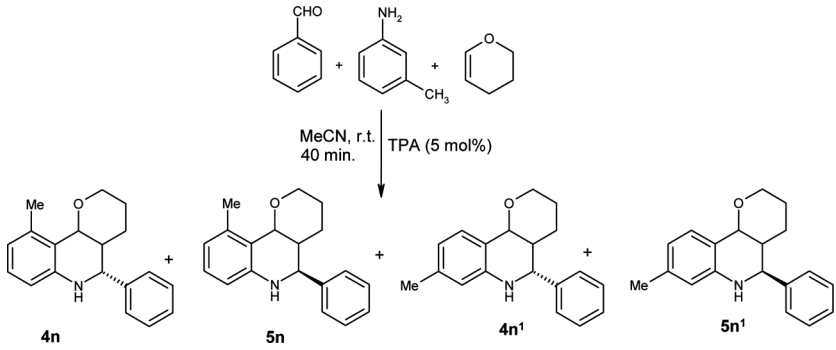
[a]The reaction of benzaldehyde, aniline, and 3,4-dyhydro-2*H*-pyran was conducted using different amounts of PTA in MeCN at room temperature.

NMR spectra of the crude products, and their structures were established from the spectral (^{1}H NMR and MS) and analytical data of the pure compounds. The four isomeric products (two sets of *trans*- and *cis*- isomers) from the reaction of benzaldehyde, m-methyl aniline, and 3,4-dihydro-2*H*-pyran (Scheme 2) were successfully isolated and characterized.

Table 2. Synthesis of pyrano- and furanoquinolines using TPA

	Benzaldehyde (**1**)		Aniline (**2**)						
Entry	R^1	R^2	R^3	R^4	R^5	Olefin (**3**)	Time (min)	Isolated yield (%)	Product ratio (**4:5**)[a]
a	H	H	H	H	H	2	30	92	62:38
b	H	H	H	H	Cl	2	40	91	61:39
c	H	H	H	H	F	2	45	89	63:37
d	H	H	OMe	H	H	2	40	87	60:40
e	H	Cl	H	H	H	2	40	93	62:38
f	H	Ome	H	H	H	2	50	86	59:41
g	H	H	H	H	Me	2	40	94	60:40
h	H	H	Me	H	H	2	40	89	61:39
i	H	H	H	H	H	1	30	90	59:41
j	H	H	Ome	H	H	1	45	89	62:38
k	H	H	H	H	Cl	1	40	88	61:39
l	H	Cl	H	H	F	1	50	86	59:41
m	H	H	H	H	OMe	1	45	90	63:37
n	H	H	H	H	Me	1	45	88	64:36

[a]The ratio of **4** and **5** was determined by ^{1}H NMR spectra of the crude products, and their structures were determined from the spectra (^{1}H NMR and MS) and analytical data of the pure compounds.



Scheme 2. Synthesis of pyranoquinolines using TPA.

The conversion can be explained by in situ formation of imines (by condensation of benzaldehydes and anilines), which act as heterodienes to undergo aza-Diels–Alder reactions with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the presence of tungstophosphoric acid (TPA) to produce the corresponding pyrano- or furnaoquinolines.

The catalyst, TPA, is a commercially available important heteropoly acid. In recent years, several heteropoly acids have gained much importance as catalysts for the synthesis of fine chemicals, flavones, and pharmaceuticals.[16] They are also frequently employed to conduct various useful industrial processes.[17,18] Among the heteropolyacids, polytungstic acids are most widely used as catalysts. In the present conversion, tungstophosphoric acid has been found to be a highly effective catalyst for the preparation of pyrano- and furanoquinolines. In the absence of TPA, no products were formed under the present experimental conditions.

In conclusion, we have applied heteropoly acid, TPA, at room temperature for the convenient and efficient one-pot preparation of pyrano- and furanoquinolines in excellent yields. The mild reaction conditions, operational simplicity, and short reaction times are the advantages of the present method.

CONCLUSION

In conclusion, we have developed a convenient and efficient method for the synthesis of pyrano- and furanoquinolines using TPA as a heterogeneous catalyst. The method provides simple access for the preparation of various pyrano- and furanoquinoline derivatives of biological importance.

EXPERIMENTAL

General Procedure for the Synthesis of Pyrano- and Furanoquinolines

TPA (5 mol %) was added to a mixture of benzaldehyde (1 mmol) and aniline (1.1 mmol) in MeCN (5 mL). The mixture was stirred at room temperature for 10 min followed by addition of dihydropyran or dihydrofuran (1.2 mmol). The stirring was continued, and the reaction was monitored by thin-layer chromatography (TLC). After completion, the reaction was quenched with water (5 ml), and the mixture was extracted with CH_2Cl_2 (3×5 ml). The combined organic layer was washed with water (2×10 ml), dried, and concentrated. The residue was purified by column chromatography to obtain pure pyrano- or furanoquinoline.

Spectral Data for Selected Compounds

The spectral (^{1}H NMR and MS) and analytical data of the unknown products are given here.

Product **4d** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.49–7.21 (5 H, m), 6.82 (1 H, dd, $J = 8.0$, 2.0 Hz), 6.71–6.60 (2 H, m), 4.65 (1 H, d, $J = 10.0$ Hz), 4.45 (1 H, brs), 4.36 (1 H, d, $J = 2.0$ Hz), 4.06 (1 H, m), 3.78 (3 H, s), 3.69 (1 H, m), 2.02 (1 H, m), 1.92–1.28 (4 H, m). FABMS m/z: 296 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12; N, 4.75%. Found: C, 77.34; H, 7.24; N, 4.78%.

Product **5d** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.46–7.21 (5 H, m), 7.01 (1 H, dd, $J = 8.0$, 2.0 Hz), 6.72–6.60 (2 H, m), 5.30 (1 H, d, $J = 3.0$ Hz), 4.66 (1 H, d, $J = 2.0$ Hz), 4.25 (1 H, brs), 3.84 (3 H, s), 3.52 (1 H, m), 3.41 (1 H, m), 2.13 (1 H, m), 1.60–1.38 (4 H, m). FABMS m/z: 296 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{21}NO_2$: C, 77.29; H, 7.12; N, 4.75%. Found: C, 77.23; H, 7.18; N 4.82%.

Product **4j** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.54–7.21 (5 H, m), 6.97 (1 H, dd, $J = 8.0$, 2.0 Hz), 6.75–6.61 (2 H, m), 5.25 (1 H, d, $J = 10.0$ Hz), 4.64 (1 H, d,

$J = 2.5$ Hz), 4.32 (1 H, brs), 3.82 (3 H, s), 3.80–3.62 (2 H, m), 2.74 (1 H, m), 2.21 (1 H, m), 1.52 (1 H, m). FABMS m/z: 282 ($M^+ + 1$). Anal. calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98%. Found: C, 76.73; H, 6.84; N, 4.89%.

Product **5j** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.50–7.29 (5 H, m), 6.99 (1 H, dd, $J = 8.0$, 2.0 Hz), 6.74–6.62 (2 H, m), 4.60 (1 H, d, $J = 2.0$ Hz), 4.58 (1 H, d, $J = 3.0$ Hz), 3.98 (1 H, m), 3.81 (3 H, s), 3.80–3.66 (2 H, m), 2.42 (1 H, m), 2.01 (1 H, m), 1.72 (1 H, m). FABMS m/z: 282 ($M^+ + 1$). Anal. calcd. for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98%. Found: C, 76.92; H, 6.79; N, 5.06%.

Product **4l** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.42–7.27 (4 H, m), 6.83–6.74 (2 H, m), 6.42 (1 H, m), 4.62 (1 H, d, $J = 10.0$ Hz), 4.30 (1 H, d, $J = 2.0$ Hz), 4.01 (1 H, brs), 3.66 (1 H, m), 3.18 (1 H, m), 2.01 (1 H, m), 1.48–1.10 (2 H, m). FABMS m/z: 304 306 ($M^+ + 1$). Anal. calcd. for $C_{17}H_{15}ClFNO$: C, 67.33; H, 4.95; N, 4.62%. Found: C, 67.28; H, 4.87; N, 4.71%.

Product **5l** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.40–7.28 (4 H, m), 7.11 (1 H, dd, $J = 8.0$, 2.0 Hz), 6.76 (1 H, m), 6.48 (1 H, m), 5.21 (1 H, d, $J = 3.0$ Hz), 4.61 (1 H, d, $J = 2.0$ Hz), 3.58 (1 H, m), 3.37 (1 H, m), 2.07 (1 H, m), 1.53–1.41 (2 H, m). FABMS m/z: 304 306 ($M^+ + 1$). Anal. calcd. for $C_{17}H_{15}ClFNO$: C, 67.33; H, 4.95; N, 4.62%. Found: C, 67.42; H, 4.84; N, 4.68%.

Product **4n** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.45–7.23 (5 H, m), 6.91 (1 H, t, $J = 8.0$ Hz), 6.51 (1 H, d, $J = 8.0$ Hz), 6.32 (1 H, d, $J = 8.0$ Hz), 4.65 (1 H, d, $J = 10.0$ Hz), 4.42 (1 H, d, $J = 2.0$ Hz), 4.10 (1 H, m), 3.94 (1 H, brs), 3.64 (1 H, m), 2.32 (3 H, s), 2.0 (1 H, m), 1.91–1.25 (4 H, m). FABMS m/z: 280 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02%. Found: C, 81.95; H, 7.44; N, 5.11%.

Product **5n** (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.49–7.21 (5 H, m), 6.99 (1 H, t, $J = 8.0$ Hz), 6.58 (1 H, d, $J = 8.0$ Hz), 6.43 (1 H, d, $J = 8.0$ Hz), 5.28 (1 H, d, $J = 3.0$ Hz), 4.55 (1 H, d, $J = 2.0$ Hz), 3.90 (1 H, brs), 3.52 (1 H, m), 3.30 (1 H, m), 2.38 (3 H, s), 2.24 (1 H, m), 1.81 (1 H, m), 1.52–1.23 (3 H, m). FABMS m/z: 280 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02%. Found: C, 81.85; H, 7.64; N, 5.14%.

Product **4n**[1] (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.43–7.25 (5 H, m), 7.02 (1 H, d, $J = 8.0$ Hz), 6.49 (1 H, d, $J = 8.0$ Hz), 6.25 (1 H, s), 4.63 (1 H, d, $J = 10.0$ Hz), 4.30 (1 H, d, $J = 2.0$ Hz), 4.03 (1 H, m), 3.91 (1 H, brs), 3.63 (1 H, m), 2.22 (3 H, s), 2.01 (1 H, m), 1.88–123 (4 H, m). FABMS m/z: 280 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02%. Found: C, 81.82; H, 7.61; N, 5.09%.

Product **5n**[1] (Table 2)

^{1}H NMR ($CDCl_3$, 200 MHz) δ: 7.42–7.28 (5 H, m), 7.25 (1 H, d, $J = 8.0$ Hz), 6.60 (1 H, d, $J = 8.0$ Hz), 6.39 (1 H, s), 5.27 (1 H, d, $J = 3.0$ Hz), 4.65 (1 H, d, $J = 2.0$ Hz), 3.73 (1 H, brs), 3.55 (1 H, m), 3.41 (1 H, m), 2.28 (3 H, s), 2.12 (1 H, m), 1.62–1.21 (4 H, m). FABMS m/z: 280 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02%. Found: C, 81.68; H, 7.59; N, 5.07%.

ACKNOWLEDGMENTS

The authors thank the Council of Scientific and Industrial Research and the University Grants Commission, New Delhi for financial assistance.

REFERENCES

1. Johnson, J. V.; Rauckman, B. S.; Beccanari, P. D.; Roth, B. 2,4-Diamino-5-benzylpyrimidines and analogs as antibacterial agents, 12: 1,2-Dihydroquinolylmethyl analogs with high activity and specificity for bacterial dihydrofolate reductase. *J. Med. Chem.* **1989**, *32*, 1942.
2. Yamada, N.; Kadowaki, S.; Takahashi, K.; Umeza, K. MY-1250, a major metabolite of the anti-allergic drug repirinast, induces phosphorylation of a 78-kD a protein in rat mast cells. *Biochem. Pharmacol.* **1992**, *44*, 1211.

3. Wood, E.; Crosby, R. M.; Dickerson, S.; Frye, S. V.; Griffin, R.; Hunter, R.; Jung, D. K.; McDonald, O. B.; McNutt, R.; Mahony, W. B.; Peel, M. R.; Ray, J. A prodrug approach to the design of cRaf1 kinase anhibitors with improved cellular activity. *Anti-Cancer Drug Des.* **2001**, *16*, 1.
4. Ramesh, M.; Mohan, P. S.; Shanmugam, P. A convenient synthesis of flindersine, atanine, and their analogues. *Tetrahedron* **1984**, *40*, 4041.
5. Quraishi, M. A.; Thakur, V. R.; Dhawan, S. N. Synthesis of 6-(4-chlor phenyl)-7H-indeno[2,1-C] quinolines and their biological activity. *Indian J. Chem.* **1989**, *28B*, 891.
6. Boger, D. L.; Weinreb, S. M. *Hetero-Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chaps. 2 and 9.
7. Weinreb, S. M. In *Comprehensive Organic Synthesis*; B. M. Trost, and I. Fleming (Eds.); Pergamon, Oxford, 1991; vol. 5, p. 401.
8. Babu, G.; Perumal, P. T. Convenient synthesis of pyrano[3,2-c] quinolines and indeno[2,1-c] quinolines by imino Diels–Alder reaction. *Tetrahedron Lett.* **1998**, *39*, 3225.
9. Ma, Y.; Qian, C.; Xie, M.; Sun, J. Lanthanide chloride–catalyzed imino Diels–Alder reaction one-pot synthesis of pyrano[3,2-c]-and furo[3,2-c] quinolines. *J. Org. Chem.* **1999**, *64*, 6462.
10. Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Madhuri, C.; Ramalingam, T. Lithium perchlorate/diethylether–catalyzed aza-Diels–Alder reaction: An expeditious synthesis of pyrano, indeno quinolines and phenanthridines. *Synlett* **2001**, 240.
11. Yadav, J. S.; Reddy, B. V. S.; Sunitha, V.; Reddy, K. S. Novel use of Selectfluor for the synthesis of *cis*-fused pyrano- and furanotetrahydroquinolines. *Adv. Synth. Catal.* **2003**, *345*, 1203.
12. Zhou, Z.; Xu, F.; Han, X.; Zhou, J.; Shen, Q. Stereoselective synthesis of pyrano[3,2-*c*]- and furano[3,2-*c*]quinolines: Samarium diiodide–catalyzed one-pot aza-Diels–Alder reactions. *Eur. J. Org. Chem.* **2007**, 5265.
13. Das, B.; Reddy, K. R.; Ramu, R.; Thirupathi, P.; Ravikanth, B. Iodine as an efficient catalyst for one-pot multicomponent synthesis of β-acetamido ketones. *Synlett* **2006**, 1756.
14. Das, B.; Reddy, V. S.; Tehseen, F.; Krishnaiah, M. Catalyst-free highly regio- and stereo-selective ring opening of epoxides and aziridines with sodium azide using poly(ethylene glycol) as an efficient reaction medium. *Synthesis* **2007**, 666.
15. Das, B.; Krishnaiah, M.; Balasubramanyam, P.; Veeranjaneyulu, B.; Kumar, D. N. A remarkably simple N-formylation of anilines using polyethylene glycol. *Tetrahedron Lett.* **2008**, *49*, 2225.
16. Pizzio, L. R.; Cáceres, C. V.; Blanco, M. N. Acid catalysts prepared by impregnation of tungstophospohoric acid solutions on different supports. *Appl. Catal. A.* **1998**, *167*, 283.
17. Soeda, H.; Okuhara, T.; Misono, M. Selective alkylation of *p*-xylene with 2-methylpropene by 12-tungstophosphoric acid. *Chem. Lett.* **1994**, 909.
18. Kozhevnikov, I. V. Heteropoly acids and related compounds as catalysts for fine chemical synthesis. *Catal. Rev. Sci. Eng.* **1995**, *37*, 311.