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Phosphomolybdic acid-catalyzed efficient one-pot three-component aza-Diels–Alder reactions under solvent-free conditions: a facile synthesis of *trans*-fused pyrano- and furanotetrahydroquinolines

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Abstract—*trans*-Fused pyrano- and furanotetrahydroquinoline derivatives have been synthesized via a one-pot three-component aza-Diels–Alder reaction of aryl imines formed in situ from aromatic amines and arylaldehydes with cyclic enol ethers,such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran,in the presence of 1 mol % of phosphomolybdic acid under solvent-free conditions at room temperature in good to excellent yields.

Pyrano- and furanoquinoline derivatives are an important class of natural products and exhibit a wide spectrum of biological activities, such as antiallergic, anti-inflammatory, antipyretic, analgesic, antiplatelet, psychotropic and estrogenic activity.[1] Many biologically active alkaloids, such as simulenoline **1**, huajiaosimuline **2**, zanthodioline **3**, flindersine **4**, teclealbine **5** and flindersiamine **6**, contain pyranoquinoline and furanoquinoline moieties (Fig. 1).[1d,1e,2] Hence, the synthesis of pyranoquinoline and furanoquinoline derivatives is, currently, of much importance. Generally, the pyranoquinoline and furanoquinoline derivatives are prepared by aza-Diels–Alder reactions of imines (derived from various aromatic amines and aromatic aldehydes) with different dienophiles, such as 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran, in the presence of different acid catalysts.[3–6] However, many of these reactions cannot be carried out in a one-pot operation with a carbonyl compound, amine and enol ether, because the amines and water that exist during imine formation can decompose or deactivate the Lewis acids. Thus, more than stoichiometric amounts of the Lewis acids are required because the acids can be trapped by nitrogen of both the reactant and the product.[1] Furthermore, most of the imines are hygroscopic, unstable at high temperatures and are difficult to purify by distillation or column chromatography. One-pot procedures have been developed for this transformation, using lanthanide chlorides[4f] and lanthanide triflates[7] as catalysts. Even though these procedures do not require the isolation of unstable imines prior to the reactions, metal triflates are not easily available or are expensive, and afford a mixture of products with unsatisfactory yields. These limitations prompted us to develop simple, convenient, efficient, economic and environmentally benign approaches for the single step synthesis of pyrano- and furanoquinoline derivatives.

In view of the emerging importance of environmental awareness in chemical and pharmaceutical industries, the development of environmentally benign organic reactions have become a crucial and demanding research area in modern organic chemical research.[8] Due to environmental awareness, chemists are devoted towards 'green chemistry', which by definition is the design, development and implementation of chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment. Heteropolyacids (HPAs) are environmentally friendly and economically feasible solid acids owing to their high catalytic activities and reactivities, ease of handling; they allow cleaner reactions in comparison to conventional catalysts and are non-toxic and,

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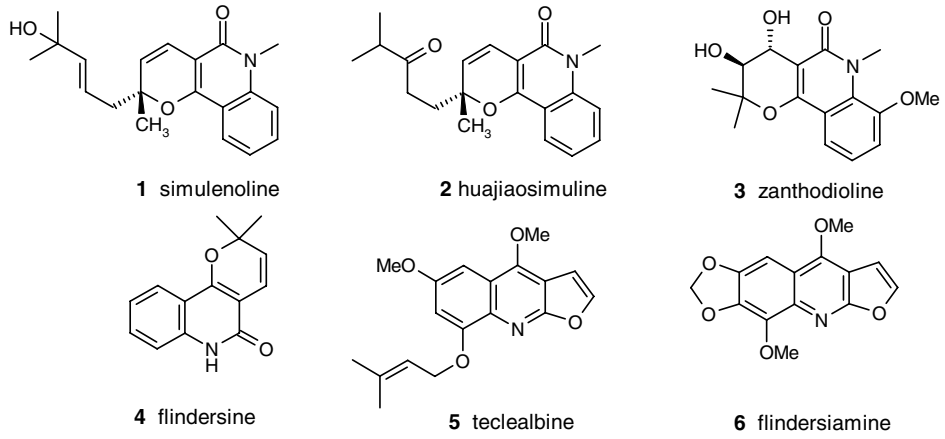
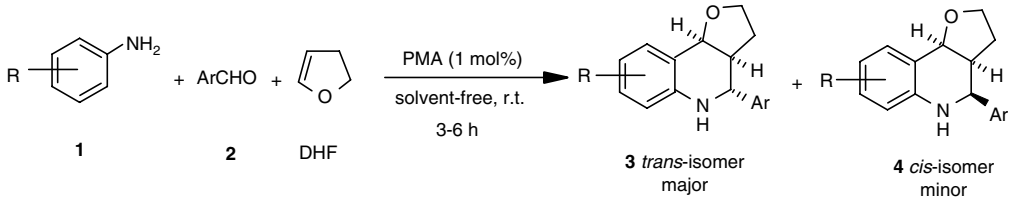
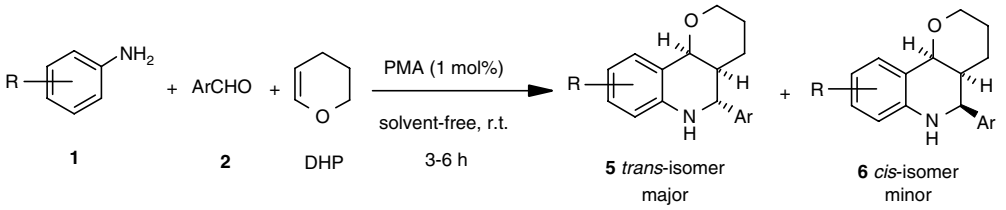


Figure 1.



Scheme 1.



Scheme 2.

hence, are regarded as green catalysts.[9] Also, heteropolyacids are promising redox and bifunctional catalysts in homogeneous as well as heterogeneous conditions.[10] Among the heteropolyacids, phosphomolybdic acid (PMA, $H_3PMO_{12}O_{40}$) is one of the less expensive, commercially available catalysts. Hence, its important catalytic properties in many organic transformations, such as the dehydration of alcohols,[11] tetrahydropyranylation of phenols,[12] Friedel–Crafts *C*-alkylation of aromatic compounds,[13] aziridination of olefins,[14] ring opening of aziridines[15] and in the synthesis of homoallylic amines,[16] have been explored. However, there are no reports on the use of phosphomolybdic acid for the synthesis of pyrano- and furanoquinoline derivatives.

In this letter, we describe a mild and efficient approach for the synthesis of pyrano- and furanoquinoline derivatives via aza-Diels–Alder reactions, using phosphomolybdic acid as catalyst, in good to excellent yields. Accordingly, treatment of anilines **1** and benzaldehydes **2** with 2,3-dihydrofuran (DHF) in the presence of 1 mol % of phosphomolybdic acid under solvent-free conditions gave the corresponding furanoquinolines **3** and **4** in 92% yield (Scheme 1).

In a similar manner, treatment of anilines **1** and benzaldehydes **2** with 3,4-dihydro-2*H*-pyran (DHP) in the presence of 1 mol % of phosphomolybdic acid under solvent-free conditions gave the corresponding pyranoquinolines **5** and **6** in 90% yield (Scheme 2).

Table 1. Optimisation of the catalytic and solvent conditions on the reaction of aniline **1 g**, benzaldehyde **2 g** and 3,4-dihydro-2*H*-pyran[a]

Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[b]	Product[c] *trans:cis*
1	CH_2Cl_2	1.0	12	60	57:43
2	$CHCl_3$	1.0	12	62	60:40
3	1,2-Dichloroethane	1.0	12	69	65:35
4	CH_3CN	1.0	12	71	68:32
5	*n*-Hexane	1.0	12	75	75:25
6	None	None	24	—	—
7	None	1.0	3	92	90:10
8	None	2.0	3	87	88:12
9	None	5.0	3	75	85:15
10	None	10.0	3	72	82:18

[a] Reaction conditions: Benzaldehyde (1 mmol), aniline (1 mmol), 3,4-dihydro-2*H*-pyran (2 mmol), solvent (5 ml) or no solvent.
[b] Isolated and unoptimized yields.
[c] Ratio of the products was determined from the crude ^{1}H NMR spectra.

Initially, a systematic study was carried out for the catalytic evaluation of phosphomolybdic acid in the reaction of aniline **1g** and benzaldehyde **2g** with 3,4-dihydro-2*H*-pyran (DHP) with different solvents and catalytic loads (Table 1). The best result was obtained with 1 mol % of the catalyst under solvent-free conditions in terms of reaction times, yields and diastereoselectivity. However, in the absence of the catalyst, the reaction did not proceed even after a longer reaction time (24 h).

To investigate the scope of the phosphomolybdic acid catalysed synthesis of pyrano- and furanoquinolines, several aldimines (formed in situ from aromatic aldehydes and anilines in acetonitrile) were examined, and the results are summarized in Table 2. Various imines, generated in situ from aldehydes and amines, immediately react with dihydrofuran or dihydropyran afforded furano- and pyranoquinolines via one-pot without the need of preformation of the imines. In most cases, the product was obtained as a mixture of cis- and trans-isomers favoring the trans-isomer. In all cases, the products were obtained in good yields with high diastereoselectivity. The diastereomers could be easily separated by column chromatography on silica gel. The ratio of the diastereomers was determined from ^{1}H NMR spectra of the crude products, and the structures were established from the spectral (^{1}H NMR and MS) data of the pure compounds. This method is equally effective

Table 2. Phosphomolybdic acid catalyzed synthesis of pyrano- and furanoquinolines[a]

Entry	R	Ar	Enol ether	Time [h]	Yield [%][b]	Product *trans*/*cis*[c]
a	H	C_6H_5		3.0	92	8:12
b	H	4-$MeOC_6H_4$		4.0	90	87:13
c	H	4-FC_6H_4		3.0	89	85:15
d	4-Me	4-ClC_6H_4		3.5	85	78:22
e	4-MeO	H		4.5	87	88:12
f	4-MeO	4-FC_6H_4		4.0	92	75:25
g	H	C_6H_5		3.5	90	90:10
h	H	4-ClC_6H_4		3.0	87	85:15
i	H	4-FC_6H_4		3.5	89	88:12
j	4-Me	C_6H_5		5.0	83	83:17
k	4-Me	4-$MeOC_6H_4$		6.0	80	80:20
l	2-Me	C_6H_5		4.5	81	82:18
m	4-MeO	C_6H_5		4.0	85	78:22
n	4-F	C_6H_5		3.5	87	85:15
o	1-Naphthyl	C_6H_5		6.0	90	73:27
p	1-Naphthyl	4-FC_6H_4		4.0	89	75:25

[a] Reaction conditions: aldehyde (1 mmol), amine (1.5 mmol), enol ether (2 mmol), PMA (1 mol %), solvent-free.
[b] All products were characterized by ^{1}H and ^{13}C NMR, IR and mass spectroscopy.
[c] Product ratio was determined from the ^{1}H NMR spectra of the crude products.

for both electron-rich as well as electron deficient aryl imines. Also, this method offers several advantages, such as higher yields, shorter reaction times, high trans-selectivity, cleaner reaction profiles and simple experimental and work-up procedures. All the products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data and also by comparison with authentic samples.[17]

In conclusion, we have described a simple, mild and efficient protocol for the synthesis of *trans*-fused furano- and pyranoquinolines via a three-component one-pot aza-Diels–Alder reaction of aldehydes, amines and cyclic enol ethers, using 1 mol % of commercially available and cheap phosphomolybdic acid (PMA) as catalyst.

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17. *Experimental procedure*: A mixture of aryl amine **1** (1.0 mmol), aromatic aldehyde **2** (1.0 mmol), 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran (2.0 mmol) and phosphomolybdic acid (PMA) (18 mg, 1 mol %), under solvent-free conditions, was stirred at ambient temperature for the appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion, the reaction mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromatography over silica gel to yield the corresponding furano- and pyranoquinolines. All products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopic data and also by comparison with authentic samples. The spectroscopic data of known products were identical with the data reported in the literature.[3–6] Spectral data for selected products:
Compound **3a:** *trans-4-Phenyl-2,3,3a,4,5,9b-hexahydro-furo-[3,2-c]quinoline:* viscous oil, IR (KBr): ν_{max}: 3329, 2952, 1610, 1055 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.72 (m, 1H), 2.00 (m, 1H), 2.45 (m, 1H), 3.85 (m, 3H), 4.10 (m, 1H), 4.60 (d, $J = 5.2$ Hz, 1H), 6.64 (d, $J = 8.2$ Hz, 1H), 6.80 (td, $J = 7.9$, 0.9 Hz, 1H,), 7.18 (td, $J = 7.9$, 0.9 Hz, 1H), 7.24–7.46 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.5, 141.6, 131.0, 128.9, 128.6, 128.2, 128.0, 120.0, 118.0, 114.4, 76.0, 65.2, 57.4, 43.3, 28.6. EIMS (EI, 70 eV): *m/z*: 251 M$^+$, 206.
Compound **4a:** *cis-4-Phenyl-2,3,3a,4,5,9b-hexahydro-furo-[3,2-c]quinoline:* white solid, mp 93–95 °C; IR (KBr): ν_{max}: 3350, 2975, 2855, 1612, 1485, 1072 cm^{-1}, ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55 (m, 1H), 2.25 (m, 1H), 2.75 (m, 1H), 3.82 (m, 3H), 4.70 (d, $J = 2.9$ Hz, 1H), 5.25 (d, $J = 8.2$ Hz, 1H), 6.60 (d, $J = 8.2$ Hz, 1H), 6.80 (d, $J = 8.2$ Hz, 1H), 7.05 (t, $J = 8.2$ Hz, 1H), 7.35–7.55 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.7, 142.3, 130.0, 128.7, 128.2, 127.5, 126.2, 122.5, 119.0, 114.8, 75.8, 66.6, 57.4, 45.7, 24.4. EIMS (EI, 70 eV): *m/z*: 251 M$^+$, 206, 174, 130, 91. Anal. Calcd for $C_{17}H_{17}NO$ (251.32): C, 81.24; H, 6.82; N, 5.57. Found: C, 81.27; H, 6.85; N, 5.60.
Compound **5g:** *trans-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline:* Pale yellow oil; IR (KBr): ν_{max}: 3325,

2940, 2864, 1605, 1480, 1080 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 1.25–1.60 (m, 3H), 1.80–1.90 (m, 1H), 2.00–2.10 (m, 1H), 3.75 (dt, $J = 11.5$, 2.5 Hz, 1H), 4.00–4.10 (m, 2H), 4.40 (d, $J = 2.5$ Hz, 1H), 4.75 (d, $J = 10.8$ Hz, 1H), 6.50 (d, $J = 8.0$ Hz, 1H), 6.70 (t, $J = 7.5$ Hz, 1H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.25 (d, $J = 8.0$ Hz, 1H), 7.45–7.55 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 144.5, 142.2, 130.9, 129.5, 128.5, 127.9, 127.7, 120.5, 117.2, 114.2, 74.5, 69.2, 55.0, 39.2, 24.2, 22.2. EIMS (EI, 70 eV): *m/z*: 265 M^+, 205, 150, 109, 77, 43. Anal. Calcd for $C_{18}H_{19}NO$ (265.35): C, 81.48; H, 7.22; N, 5.28. Found: C, C, 81.51; H, 7.24; N, 5.34.

Compound **6g:** *cis-5-Phenyl-3,4,4a,5,6,10b-hexahydro-2H-pyrano[3,2-c]quinoline:* White solid, mp 128–129 °C; IR (KBr): ν_{max}: 3340, 2970, 2850, 1610, 1490, 1090 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (m, 1H), 1.50–1.70 (m, 3H), 2.15–2.20 (m, 1H), 3.40 (dt, $J = 11.3$, 2.4 Hz, 1H), 3.55 (dd, $J = 11.3$, 2.4 Hz, 1H), 3.80 (br s, NH, 1H), 4.70 (d, $J =$ 2.7 Hz, 1H), 5.30 (d, $J = 5.6$ Hz, 1H), 6.55 (d, $J = 8.0$ Hz, 1H), 6.78 (t, $J = 8.0$ Hz, 1H), 7.05 (t, $J = 7.8$ Hz, 1H), 7.25–7.45 (m, 6H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 145.2, 141.2, 128.2, 128.0, 127.7, 127.5, 126.9, 120.4, 118.0, 114.4, 72.8, 60.7, 59.3, 39.0, 25.7, 18.2. EIMS (EI, 70 eV): *m/z*: 265 M^+, 234, 220, 194, 129, 117, 91, 77. Anal. Calcd for $C_{18}H_{19}NO$ (265.35): C, 81.48; H, 7.22; N, 5.28. Found: C, C, 81.50; H, 7.24; N, 5.30.

Compound **5p:** *trans-12-(4-Fluoro-phenyl)-2,3,4a,11,12,12a hexahydro-1H-4-oxa-11-aza-chrysene:* Brown solid, mp 179–181 °C; IR (KBr): ν_{max}: 3378, 2947, 2870, 1668, 1575, 1468, 1081 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 1.30–1.45 (m, 2H), 1.60–1.80 (m, 2H), 2.10 (m, 1H), 3.75 (dt, $J = 11.5$, 2.7 Hz, 1H), 4.10 (d, $J = 2.7$ Hz, 1H), 4.452 (d, $J = 2.7$ Hz, 1H), 4.65 (br s, NH, 1H), 4.80 (d, $J = 10.8$ Hz, 1H), 7.05–7.15 (m, 2H), 7.20–7.40 (m, 4H), 7.45–7.50 (m, 2H), 7.70–7.80 (m, 2H). Anal. Calcd for $C_{22}H_{20}FNO$ (333.40): C, 79.26; H, 6.05; F, 5.70, N, 4.20. Found: C, 79.28; H, 6.10; F, 5.74, N, 4.22.

Compound **6p:** *cis-12-(4-Fluoro-phenyl)-2,3,4a,11,12,12a-hexahydro-1H-4-oxa-11-aza-chrysene:* Brown solid, mp 138–140 °C; IR (KBr): ν_{max}: 3370, 2945, 2860, 1665, 1570, 1465, 1080 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ 1.20–1.35 (m, 2H), 1.40–1.55 (m, 2H), 2.10 (m, 1H), 3.25 (dt, $J = 11.5$, 2.5 Hz, 1H), 3.50 (dd, $J = 11.5$, 2.5 Hz, 1H), 4.00 (br s, NH, 1H), 4.70 (d, $J = 2.7$ Hz, 1H), 5.40 (d, $J = 5.7$ Hz, 1H), 7.00 (m, 2H), 7.20 (m, 1H), 7.35 (m, 2H), 7.40–7.50 (m, 3H). 7.65 (m, 2H). Anal. Calcd for $C_{22}H_{20}FNO$ (333.40): C, 79.26; H, 6.05; F, 5.70; N, 4.20. Found: C, 79.30; H, 6.09; F, 5.76; N, 4.24.