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PEG-400 as green reaction medium for Lewis acid-promoted cycloaddition reactions with isoeugenol and anethole

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Abstract

A simple and efficient one-pot method for the synthesis of new 2,4-diaryl-1,2,3,4-tetrahydroquinolines using a three-component imino Diels–Alder cycloaddition between *trans*-isoeugenol or *trans*-anethole, anilines, and benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ in PEG-400, a green and reusable solvent, has been developed. Also, $BF_3{\cdot}OEt_2$-catalyzed formal [3+2] cycloaddition reaction of *trans*-isoeugenol or *trans*-anethole with 1,4-benzoquinone in PEG-400 to give dihydrobenzo[*b*]furan derivatives has been described.

Keywords: Multi-component reaction; Imino Diels–Alder reaction; 2,3-Dihydrobenzofuran-5-ols; Tetrahydroquinolines; *trans*-Anethole; *trans*-Isoeugenol; Polyetilenglicol (PEG-400); Benzoquinone

There are numerous natural products that possess tetrahydroquinoline or dihydrobenzofuran ring systems, including simple molecules such as 2,3-dihydro[*b*]benzofurans: derivative **1**, called conocarpan,[1] and derivative **2**, fragnasol B, isolated from *Myristica fragrans* Houtt,[2] both are neolignan molecules, or tetrahydroquinoline derivative **3**, an alkaloid of shrub *Galipea officinalis* Hancock[3] (Fig. 1). In addition, there are many synthetic compounds possessing these skeletons that show significant biological activity.[4] In accordance with the importance of the compounds possessing these skeletons, there have a large number of methods developed for their synthesis, among them, the cycloaddition reactions stand out as powerful and successful reactions to construct rapidly these ring systems. The acid-catalyzed imino Diels–Alder reaction between aldimines and electron-rich alkenes (mainly, vinyl enol ethers and vinyl enamides) or its three-component version is probably the most powerful synthetic tool for the construction of N-containing six-membered heterocyclic compounds, including tetrahydroquinolines.[5–7]

However, the utilization of styrene derivatives as a dienophile in this cycloaddition is poorly studied.[8] Lewis acid-promoted formal [3+2] cycloaddition reactions are also powerful synthetic tool for the preparation of highly

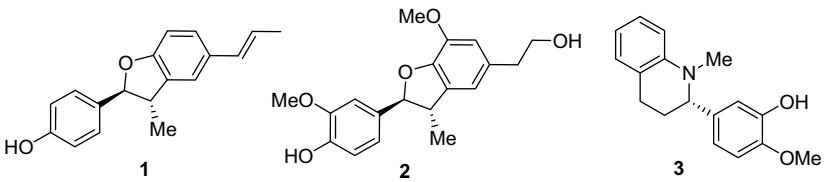

Fig. 1. Heterocyclic skeleton of natural molecules **1**–**3**.

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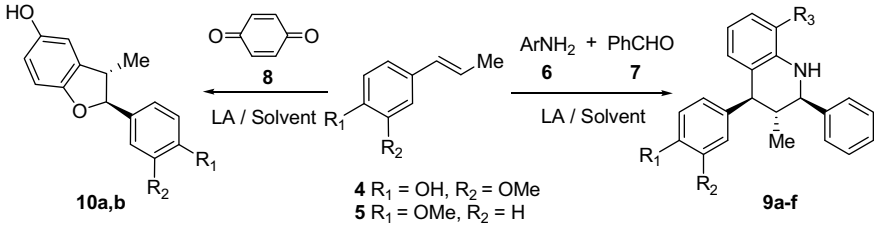
substituted dihydrobenzofurans.[9] More interesting chemical transformation with propenylbenzenes is its cycloaddition with quinones catalyzed by $Fe(ClO_4)_3$, $InCl_3$, or I_2 to give substituted *trans*-2,3-dihydrobenzo[*b*]furans.[10]

Typically, these traditional syntheses employ the use of toxic and volatile organic solvents. The replacement of these hazardous solvents as with the environmentally benign solvents is one of the key areas of Green Chemistry. Among these so-called green solvents, supercritical carbon dioxide ($scCO_2$) and ionic liquid solvents are the most popular.[11] PEG, poly(ethylene glycol), is known to be inexpensive, thermally stable, recoverable, biological compatible, and non-toxic.[12] PEG is most commonly employed as a support or a phase-transfer catalyst in various organic transformations.[13] Its use as a reaction medium in organic reactions is relatively recent.[14] This is despite the fact that the toxicity data of some alternative solvent (ionic liquid solvents) are for the most part unknown, while complete toxicity profiles are available for a range of PEG molecular weights; some of them are already approved for internal consumption by the US FDA.[12] It is important to note the *trans*-isoeugenol or *trans*-anethole in the [4+2] or [3+2] cycloaddition reactions in PEG-400 has not been used in the preparation of polyfunctionalized tetrahydroquinolines, dihydrobenzo[*b*]furanols. Bearing these results in mind and in the continuation of our recent work on the tetrahydroquinolines synthesis in supercritical fluid medium ($scCO_2$),[15] we wanted to explore another alternative environmentally benign condition for Lewis acid-promoted formal [4+2] or [3+2] cycloaddition reactions with the *trans*-isoeugenol (*trans*-anethole). Herein, we wish to describe our study on a three-component condensation between *trans*-isoeugenol (*trans*-anethole), anilines, and benzaldehyde, which resulted in a simple preparation of new polyfuncionalized 2,4-diaryl-3-methyl-l-1,2,3,4-tetrahydroquinolines, interesting rigid molecules in pharmacological studies. Also, we wish to report the new stereoselective synthesis of 2-aryl-2,3-dihydrobenzo[*b*]-furan-5-ols under green conditions. Both cycloaddition reactions were successfully realized in PEG-400, a green, commercially available, and easily degradable solvent. In our initial study, we have investigated three-component imino Diels–Alder cycloaddition (Povarov reaction) between *trans*-isoeugenol **4** (*trans*-anethole **5**), anilines **6a–c**, and benzaldehyde **7** to afford the tetrahydroquinolines **9a–f** (Scheme 1, Table 1) using different conditions. Following our experience on imino Diels–Alder reactions[16] and after several experiments we found that this condensation occurred only at high temperature (60 °C) in MeCN in the presence of $BF_3{\cdot}OEt_2$ in 10–14 h to give the solid products **9a–f**.

^1H NMR and ^{13}C NMR analyses of the tetrahydroquinoline products indicated that the structure of major diastereoisomers **9** was *cis*-(2e,4e)-form (given in Scheme 1). The large vicinal coupling constants $J_{2a,3a}$ and $J_{3a,4a} = 9.9–11.0$ Hz for this form indicate an axial–axial (trans) relationship and the aryl groups on C-2 and C-4 are both pseudo-equatorial and are located in cis-configuration.[17] In addition, this stereochemistry was confirmed by homonuclear and inverse-detected 2D NMR. The configuration of the minor diastereoisomer **9** was judged to be *trans*-(2a,4e)-form.[18]

In order to make these cycloaddition reactions 'greener', PEG-400 was replaced the conventional toxic organic solvent (MeCN). During these experiments we found that three-component imino Diels–Alder reactions occurred



Scheme 1. Synthesis of new tetrahydroquinolines **9a–f** and dihydrobenzofuran derivatives **10a,b**.

Table 1
Comparative physicochemical parameters of [4+2] or [3+2] cycloaddition reactions in MeCN and in PEG-400

Compd	R_1	R_2	R_3	Mp (°C)	Yield (%)		Reaction time (h)		Volume of solvent (mL)	
					MeCN	PEG	MeCN	PEG	MeCN	PEG
9a	OH	OMe	H	173–175	68	54	12	6	30	5
9b	OH	OMe	CN	219–220	86	78	11	4	30	5
9c	OH	OMe	NO_2	241–242	90	75	14	5	30	5
9d	OMe	H	H	152–153	52	39	10	8	30	5
9e	OMe	H	CN	183–184	59	50	10	8	30	5
9f	OMe	H	NO_2	160–161	68	60	10	8	30	5
10a	OH	OMe	—	Reddish oil	51[a]	68	16[a]	14	30[a]	7
10b	OMe	H	—	Reddish oil	41[a]	56	16[a]	14	30[a]	7

[a] Synthesis was realized in dichloromethane, using 10 mol % $BF_3{\cdot}OEt_2$.

smoothly in this nonhalogenated solvent in the presence of 1 equiv $BF_3{\cdot}OEt_2$ to give the same products **9a**–**f**. Although the yields of desired products were somewhat less than that in MeCN, reaction time and volume of solvent were reduced considerably (Table 1). Moreover, isolation of final products became easy without the necessity of common work-up (basic treatment and extraction), using only a column chromatography separation.[19]

Inspired with our findings, we continued our study toward Lewis acid-promoted formal [3+2] cycloaddition reactions with the same propenylbenzenes **4**, **5**. In a similar fashion, we investigated Lewis acid-promoted [3+2] cycloaddition reactions between *trans*-isoeugenol or *trans*-anethole **5** and 1,4-benzoquinone **8** to afford the corresponding *trans*-2,3-dihydrobenzo[*b*]furan-5-ols **10**[10e,20] in excellent yields. In contrast to the realized [4+2] cycloaddition reactions, these formal [3+2] cycloadditions were more sensitive to the changes in solvents: the yields of *trans*-2,3-dihydrobenzo[*b*]furan-5-ols **10** were more than that were in MeCN, moreover, reaction time and volume of solvent were reduced considerably, using 10 mol % $BF_3{\cdot}OEt_2$ as Lewis acid catalyst (Table 1).

In conclusion, this Letter describes a simple and convenient process for the synthesis of new 2,4-diaryl-1,2,3,4-tetrahydroquinolines, 2-aryl-2,3-dihydrobenzo[*b*]furan-5-ols under green conditions through catalyzed cycloaddition reactions using the same starting rich alkenes, *trans*-isoeugenol, and *trans*-anethole, which are important components of the essential oil of various tropical plants. The notable features of this procedure are mild and green reaction conditions, simplicity in operation, good yields and reaction rates, and cleaner reaction profiles. This method could be a useful and attractive process for the diversity-oriented synthesis of biologically important molecules. At present, further investigations are in progress to find additional synthetic applications of catalyzed cycloaddition process under PEG-400 conditions.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.049.

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17. *Selected spectral data for* **9a–c**: *cis-4-(4-Hydroxy-3-methoxy-phenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline* (**9a**): white solid, mp 173–174 °C. IR (KBr): 3462, 1607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si), δ (ppm): 0.56 (3H, d, $J = 6.5$ Hz, 3-Me), 2.17 (1H, m, 3-H), 3.70 (1H, d, $J = 10.9$ Hz, 4-H), 3.80 (3H, s, OMe), 4.06 (1H, br s, NH), 4.14 (1H, d, $J = 9.9$ Hz, 2-H), 5.55 (1H, br s, OH), 6.49 (1H, d, $J = 7.9$ Hz, 5-H), 6.54 (1H, d, $J = 7.2$ Hz, 7-H), 6.59 (1H, d, $J = 7.3$ Hz, 8-H), 6.97 (1H, 't', $J = 7.2$ Hz, 6-H), 6.67 (1H, d, $J = 1.2$ Hz, 2-HAr), 6.73 (1H, dd, $J = 8.0$, 1.6 Hz, 6-HAr), 6.86 (1H, d, $J = 8.0$, 1.6 Hz, 5-HAr) 7.30 (1H, d, $J = 7.1$ Hz, 4-HPh), 7.35 (2H, 't', $J = 7.0$ Hz, 3-HPh y 5-HPh), 7.42 (2H, d, $J = 7.2$ Hz, 2-HPh y 6-HPh); ^{13}C NMR (100 Hz, $CDCl_3$, Me_4Si), δ (ppm): 158.4, 146.8, 145.0, 144.2, 142.8, 136.2, 130.0, 128.6, 127.2, 127.0, 125.6, 122.8, 117.6, 114.0, 113.4, 111.2, 64.0, 56.0, 52.2, 41.6, 16.6. GC–MS (EI) ($t_R = 33.44$ min), m/z: 345 (63, M^+), 316 (25), 254 (29), 206 (100). Anal. Calcd for $C_{23}H_{23}NO$: C, 79. 97; H, 6.71; N, 4.05. Found: C, 79.65; H, 6.94; N, 4.23. *cis-8-Ciano-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline* (**9b**): Beige solid, mp 219–220 °C. IR (KBr): 3398, 3513, 2962, 2210, 1268 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, Me_4Si), δ (ppm): 0.50 (3H, d, $J = 5.9$ Hz, 3-Me), 2.20 (1H, m, 3-H), 3.66–3.70 (4H, m, 4-H y OMe), 4.20 (1H, d, $J = 10.0$ Hz, 2-H), 6.66 (1H, s, OH), 6.50 (1H, 't', $J = 7.4$ Hz, 6-H), 6.52–6.65 (1H, m, 7-H y 6-HAr), 6.72 (1H, br s, 2-HAr), 6.78 (1H, d, $J = 8.0$ Hz, 5-HAr), 7.33 (1H, d, $J = 6.9$ Hz, 4-HPh), 7.38 (2H, d, $J = 7.4$ Hz, 2-HPh and 6-HPh), 7.44 (2H, 't', $J = 7.3$ Hz, 3-HPh and 5-HPh), 8.85 (1H, s, NH); ^{13}C NMR (100 Hz, DMSO-d_6, Me_4Si), δ (ppm): 147.7, 147.5, 145.1, 142.4, 133.5, 133.2, 130.5, 128.2, 127.8, 127.6, 127.1, 121.6, 118.0, 116.0, 115.4, 112.5, 93.6, 62.5, 55.6, 50.0, 16.0. GC–MS (EI) ($t_R = 68.04$ min), m/z; 370 (20, M^+), 231 (100), 151 (5), 91 (5). Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C. 77.65; H, 6.17; N, 7.43. *cis-8-Nitro-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline* (**9c**): Red solid, mp 241–242 °C. IR (KBr): 3448, 2927, 1514, 1282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, Me_4Si), δ (ppm): 0.62 (3H, d, $J = 6.5$ Hz, 3-Me), 2.40 (1H, m, 3-H), 3.72 (1H, d, $J = 11.5$ Hz, 4-H), 3.85 (3H, s, OMe), 4.32 (1H, d, $J = 10.1$ Hz, 2-H), 5.58 (1H, br s, OH), 6.45 (1H, 't', $J = 7.4$ Hz, 6-H), 6.60 (1H, d, $J = 1.9$ Hz, 2-HAr), 6.72 (1H, dd, $J = 8.0$, 1.9 Hz, 6-HAr), 6.78 (1H, br d, $J = 8.6$ Hz, 5-H), 6.91 (1H, d, $J = 8.0$ Hz, 5-HAr), 7.27–7.45 (5H, m, all HPh), 8.01 (1H, dd, $J = 8.6$, 1.0 Hz, 7-H), 8.47 (1H, s, NH); ^{13}C NMR (100 Hz, $CDCl_3$, Me_4Si), δ (ppm): 147.0, 144.6, 143.0, 141.1, 136.1, 134.1, 130.9, 129.5, 128.9, 128.5, 127.6, 124.8, 122.6, 121.5, 114.7, 110.6, 110.7, 63.4, 56.0, 51.8, 39.1, 16.4. GC–MS (EI) ($t_R = 38.56$ min), m/z: 390 (30, M^+), 251 (100), 105 (10), 77 (10). Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.17. Found: C, 70.59; H, 5.84; N, 7.02. All the products **9d–f** were characterized by comparing their physical and spectral data with those of reported compounds (see, Ref. 15).
18. From ^1H NMR analysis we were unable to find the small constants of $J_{2e,3a}$ and the large constants of $J_{3a,4a}$ Hz for the minor diastereoisomers **9a–f**. However, all chemical literature fonts for minor component of imino Diels–Alder reactions indicate at an equatorial–axial (cis) relationship for the protons H_2, and H_3 and an axial–axial (trans) relationship for the protons H_3 and H_4, see: (a) Fadel, F.; Titouni, S. L.; Soufioui, M.; Ajamay, H.; Mazzah, A. *Tetrahedron Lett.* **2004**, *45*, 5905; (b) Zhang, W.; Guo, Y.; Liu, Z.; Jin, X.; Yang, L.; Liu, Z.-L. *Tetrahedron* **2005**, *61*, 1325.
19. *General experimental procedure for the synthesis of tetrahydroquinoline derivatives*: A mixture of aniline (4.30 mmol) and benzaldehyde (4.73 mmol) in PEG-400 (5 mL) was stirred at room temperature for 20 min. One equivalent of $BF_3{\cdot}OEt_2$ was added into the mixture. Finally, *trans*-isoeugenol (or *trans*-anethole) was added dropwise to the reaction mixture. The temperature was kept to 70 °C under inert atmosphere (nitrogen) for 10 h. After complete conversion, as indicated by TLC, the crude product was purified by column chromatography without previous extraction to obtain tetrahydroquinolines **9a–f**.
20. *General experimental procedure for the synthesis of benzo[b]furan-5-ol derivatives*: To a mixture of 1,4-benzoquinone (4.62 mmol) and natural product (*trans*-isoeugenol or *trans*-anethole, 4.62 mmol) in PEG-400 (7 mL), $BF_3{\cdot}OEt_2$ (10 mol %) was added at 0 °C. The reaction mixture was taken slowly to room temperature and continuous stirring done kept, and after complete conversion, as indicated by TLC, the reaction mixture was treated with a saturated solution of Na_2CO_3, and extracted with ethyl acetate (2×30 mL), the organic layers were dried over Na_2SO_4. The crude product was purified by column chromatography to obtain benzo[*b*]furan-5-ols **10a** and **b**. When CH_2Cl_2 was employed, the same procedure was used as described above.