Pergamon

Tetrahedron Letters 41 (2000) 7079–7083

TETRAHEDRON LETTERS

Alkylindan synthesis via an intermolecular [3+2] cycloaddition between unactivated alkenes and in situ generated *p*-quinomethanes

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Received 14 June 2000; revised 10 July 2000; accepted 14 July 2000

Abstract

Alkylindans were synthesized by the intermolecular [3+2] cycloaddition of in situ generated *p*-quinomethanes and aliphatic alkenes. In a highly concentrated lithium perchlorate in nitromethane, *p*-quinomethanes were generated by DDQ oxidation of corresponding alkylphenols, and the desired cycloaddition reaction was completed efficiently to give various indans.

Keywords: addition reactions; cyclization; indanes/hydrindane; phenols.

Quinomethanes have been of much interest as reaction intermediates for varied polycyclic compounds, including biologically active natural products.[1] *o*-Quinomethanes are well-known intermediates of biogenetic hetero-Diels–Alder reactions.[2] *p*-Quinomethanes have also been isolated from natural resources, and their intermolecular [3+2] cycloaddition with aliphatic alkenes was suggested to form natural indans.[3] Furthermore, the reactivity of *p*-quinomethanes has been extensively investigated concerning their remarkable activity in the alkylation of DNA.[4] To date, various methods have been reported for the generation and reaction of *p*-quinomethane intermediates.[5] Although the potential of the reactivity of *p*-quinomethanes has been highlighted, the application for the intermolecular carbon–carbon bond formation of *p*-quinomethanes is limited to highly electron-rich, activated alkenes or intramolecular cyclizations.[6] We anticipate that the intermolecular cycloaddition of in situ generated *p*-quinomethanes and aliphatic alkenes of choice provides varied alkylindans, which have been difficult to synthesize in short steps.

We recently accomplished some cycloaddition reactions by using an electrooxidative reaction system composed of lithium perchlorate/nitromethane solution.[7] We first found that the media showed marked acceleration properties for some Diels–Alder reactions. The media have also been found to promote the oxidative fission of carbon–sulfur bonds followed by an intermolecular

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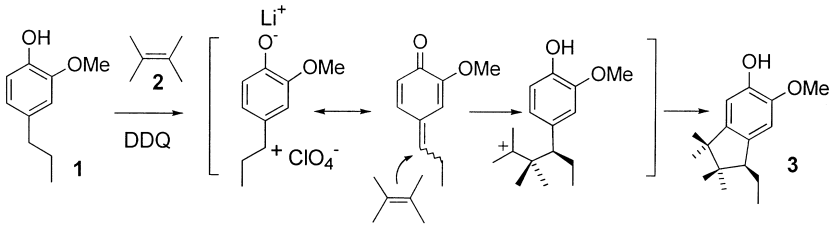
0040-4039/00/$ - see front matter
PII: S0040-4039(00)01216-8

cycloaddition between alkenes and electrogenerated *o*-quinomethanes.[8] Furthermore, an intermolecular [3+2] cycloaddition of electrogenerated phenoxonium cation and alkenes has been completed to form dihydrobenzufurans.[9] It is presumed that the polar ionic solvent system stabilized and promoted intermolecular cycloaddition with unactivated alkenes. It is therefore envisioned that *p*-quinomethane could also be obtained in reaction media which markedly accelerate intermolecular cycloaddition, and that it should give corresponding cycloadducts with unactivated aliphatic alkenes to form indans with varied alkyl substituents. We herein report a new method for the alkylindan synthesis via the [3+2] intermolecular cycloaddition of aliphatic alkenes with in situ generated *p*-quinomethanes.

First, the media effect for the generation and the [3+2] cycloaddition of *p*-quinomethanes with alkenes was investigated. Under the usual combination of Lewis acids and solvent conditions, the benzylic oxidation of 2-methoxy-4-propylphenol **1** by dichlorodicyano-*p*-benzoquinone (DDQ) in the presence of 2,3-dimethyl-2-butene **2** gave corresponding cycloadducts **3** in modest yields with messy products. In contrast, DDQ treatment in nitromethane gave the desired cycloadducts **3** in 19% yield, even in the absence of the usual Lewis acid. Furthermore, the addition of lithium perchlorate in the reaction solution (finally 3 M in nitromethane) dramatically increased the yield to 99% in high regioselectivity.[10] The reaction is proposed to proceed by the initial intermolecular carbon–carbon bond formation between the benzyl carbon and alkene followed by Friedel–Crafts alkylation by the in situ generated *tertiary* carbocation. The final cyclization should be completed at the less hindered, electron-rich position of the benzene ring in high regioselectivity. Lithium perchlorate did not work well in other usual solvents (Scheme 1, Table 1). Neither silver oxide (Ag_2O) nor CAN oxidation of **1** in the presence of **2** gave the desired product, even when treated in a solution of 3 M lithium perchlorate/nitromethane. Accordingly, it was revealed that the oxidative reaction medium composed of DDQ and 3 M lithium perchlorate in nitromethane showed a remarkable property in the targeted intermolecular [3+2] cycloaddition reaction. Fig. 1 shows the result of alkylindan synthesis by the oxidation of *p*-alkylphenol derivatives with DDQ followed by the cyclization reaction with alkenes of choice. Alkyl-substituted indan skeletons were easily synthesized at ambient temperature in good yields. Reaction with methylene cyclohexane **11** gave unique spiroindans without isomerization of the alkene. *p*-Ethylphenol **17**, which possesses no additional electron-donating group, showed lower reactivity in the formation of indan rings, but desired indans were also obtained with an increased concentration of lithium perchlorate (6 M) at 60°C. The stereochemistry of the products was established by NOE, chemical shifts, and coupling constants study in ^{1}H NMR.[6,11,12]



Scheme 1.

In the present media, lithium perchlorate is expected to stabilize the in situ generated zwitterion, which is an equivalent of *p*-quinomethane. Furthermore, it is expected to assist in the nucleophilic

Table 1
Media effect on the alkylindan synthesis by the [3+2] cycloaddition of unactivated alkene **2** and *p*-quinomethane generated from *p*-alkylphenol **1**[a]

Solvent	Additive	Yield(%)[b]
CH_3NO_2	$LiClO_4$ (3 M)	> 99
CH_3NO_2	——	19
CH_3CN	$LiClO_4$ (sat.)	5
CH_3CN	$Sc(OTf)_3$ (0.2 eq.)	4
DMF	$LiClO_4$ (1 M)	trace
CH_2Cl_2	$ZnCl_2$ (2 eq.)	4
CH_2Cl_2	$LiClO_4$ (sat.)	trace

a) Reaction was performed at ambient temperature for 1 h.

b) Determined by GLC.

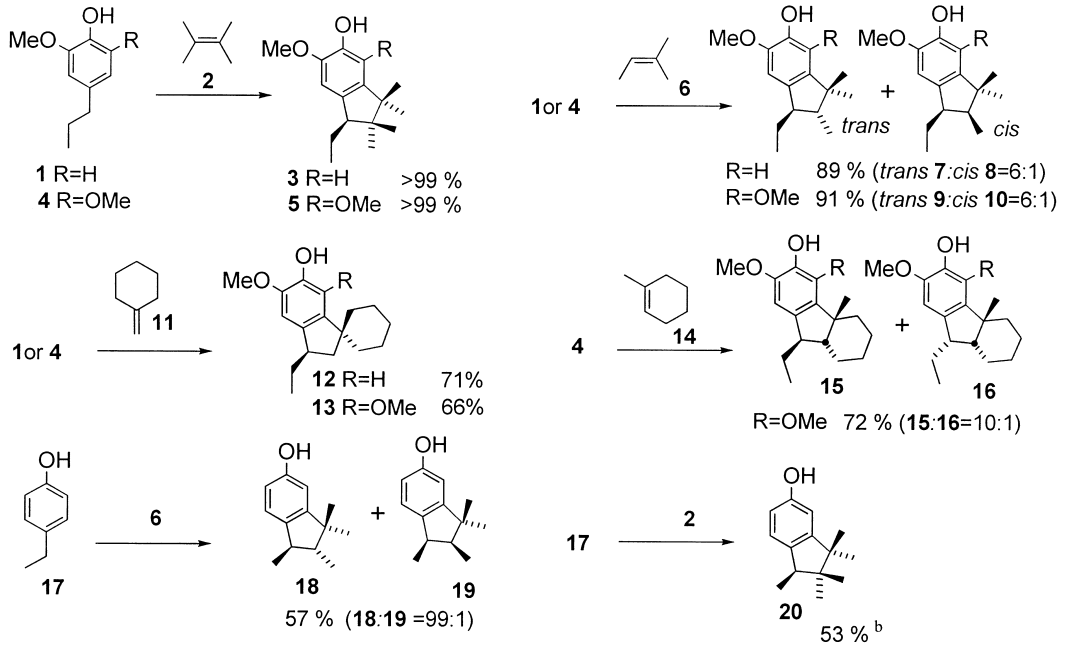


Figure 1. Synthesis of indans in the lithium perchlorate/nitromethane system.[a] (a) Cycloaddition reactions were performed in 3 M lithium perchlorate in nitromethane in the presence of 3 equiv. mol of DDQ at ambient temperature. (b) Reaction was performed in 6 M lithium perchlorate in nitromethane at 60°C in a sealed tube

attack of alkenes by stabilizing carbocation generated in accordance with the nucleophilic attack of the alkenes at the benzyl position of oxidized phenols. It is also suggested that the highly polar ionic media composed of lithium perchlorate and nitromethane afford a large internal pressure of the solvent, which effectively promotes the desired intermolecular reaction.

In conclusion, by using this unique reaction medium, *p*-quinomethane was efficiently generated by the DDQ oxidation of corresponding 4-alkylphenols, and the following cycloaddition

reactions with unactivated alkenes proceeded smoothly to give alkylindan skeletons, which are difficult to obtain in good yields through other methods.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 283, 'Innovative Synthetic Reactions') from the Ministry of Education, Science, Sports and Culture, Japan.

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10. General procedure: DDQ (1.5 mmol, 342 mg) was dispersed in 5 ml of nitromethane, and alkylphenol **1** (0.5 mmol, 83 mg), alkene **2** (1.0 mmol, 84 mg), and lithium perchlorate (160 mg) were dissolved in the solution. The reaction mixture was allowed to stand at ambient temperature for 1 h under Ar atmosphere. After the reaction was completed, products were extracted with *n*-hexane. The *n*-hexane was removed in vacuo after drying on $MgSO_4$, and the residue was then separated by silica-gel column chromatography (*n*-hexane:AcOEt) to give the desired cycloadduct **3**.
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12. NMR data of major products (in $CDCl_3$, TMS as an intl. std). Compound **3**: δ_C 144.6 (2C), 144.0, 136.2, 108.2, 106.1, 56.1, 53.3, 48.7, 47.2, 25.4, 22.5, 22.2, 22.1, 19.0 and 14.7; δ_H 6.72 (1H, s), 6.68 (1H, s), 5.50 (1H, s), 3.86 (3H, s), 2.66 (1H, t, $J=6.76$ Hz), 1.70–1.50 (2H, m), 1.19 (3H, t, $J=7.41$ Hz), 1.09 (3H, s), 1.01 (3H, s), 0.98 (3H, s) and 0.65 (3H, s). Compound **5**: δ_C 145.8, 144.0, 137.0, 136.5, 135.0, 101.7, 60.5, 56.3, 53.6, 48.5, 48.3, 23.9, 22.6, 22.3, 21.7, 18.9 and 14.7; δ_H 6.52 (1H, s), 5.37 (1H, s), 3.88 (3H, s), 3.86 (3H, s), 2.61 (1H, t, $J=6.59$ Hz), 1.71–1.54 (2H, m), 1.27 (3H, s), 1.17 (3H, t, $J=7.41$ Hz), 1.08 (3H, s), 0.97 (3H, s), 0.68 (3H, s). Compound **7**: δ_C 145.6, 145.0, 144.2, 135.6, 108.1, 105.7, 56.1, 49.7, 49.2, 44.4, 27.0, 26.9, 23.7, 12.7 and 10.9; δ_H 6.72 (1H, s), 6.66 (1H, s), 5.50 (1H, s), 3.87 (3H, s), 2.62 (1H, dt, $J=9.89$, 4.94 Hz), 1.86–1.68 (3H, m), 1.22 (3H, s), 1.03 (3H, d, $J=7.25$ Hz), 0.95 (3H, t, $J=7.58$ Hz), 0.90 (3H, s). Compound **9**: δ_C 146.0, 143.2, 136.6, 136.2, 135.2, 100.8, 60.0, 55.9, 49.2, 49.2, 44.9, 26.6, 23.2, 21.4, 11.8 and 10.3; δ_H 6.45(1H, s), 5.37(1H, s), 3.91 (3H, s), 3.86 (3H, s), 2.57 (1H, dt, $J=10.38$, 5.11 Hz), 1.83–1.67 (3H, m), 1.39 (3H, s), 0.99 (3H, d, $J=6.92$ Hz), 0.99 (3H, s) and 0.94 (3H, t, $J=7.58$

Hz). Compound **12**: δ_C 145.3 (2C), 144.4, 137.2, 108.3, 105.9, 56.0, 46.8, 43.5, 42.1, 38.9, 37.3, 28.6, 26.1, 23.9, 23.3 and 12.1; δ_H 6.73 (1H, s), 6.67 (1H, s), 5.49 (1H, s), 3.86 (1H, s), 2.96 (1H, ddt, J = 7.81, 4.12, 9.06 Hz), 2.37 (1H, dd, J = 13.18, 7.81 Hz), 1.95 (1H, m), 1.79–1.21 (12H, m) and 1.00 (3H, t, J = 7.08 Hz). Compound **13**: δ_C 144.6, 144.0, 137.3, 137.2, 136.0, 101.4, 60.4, 56.2, 48.6, 43.9, 41.8, 37.5, 34.8, 28.7, 26.0, 23.8, 23.3 and 12.1; δ_H 6.46 (1H, s), 5.38 (1H, s), 3.92 (3H, s), 3.86 (3H, s), 2.91 (1H, dq, J = 8.40, 4.12 Hz), 2.46–2.30 (2H, m), 1.93 (1H, m), 1.83–1.21 (11H, m) and 0.99 (3H, t, J = 7.08 Hz). Compound **15**: δ_C 146.1, 143.5, 137.6, 136.9, 135.6, 102.0, 60.5, 56.4, 50.1, 44.9, 44.7, 35.4, 23.9, 23.8, 23.7, 23.0, 21.6 and 10.9; δ_H 6.51 (1H, s), 5.37 (1H, s), 3.88 (3H, s), 3.87 (3H, s), 2.89 (1H, dt, J = 9.87, 4.94 Hz), 1.84–1.20 (11H, m), 1.48 (3H, s) and 0.94 (3H, t, J = 7.58 Hz). Compound **18**: δ_C 154.6, 154.4, 138.6, 123.5, 112.9, 109.0, 54.4, 44.6, 42.5, 26.3, 23.4, 17.1 and 11.6; δ_H 6.98 (1H, d, J = 8.57 Hz), 6.63 (1H, d, J = 8.57 Hz), 6.62 (1H, s), 4.55 (1H, s), 2.60 (1H, dq, J = 10.22, 7.08 Hz), 1.57 (1H, dq, J = 10.22, 7.08 Hz), 1.25 (3H, d, J = 7.08 Hz), 1.24 (3H, s), 1.04 (3H, d, J = 7.08 Hz) and 0.93 (3H, s). Compound **20**: δ_C 154.2, 153.7, 137.7, 123.2, 112.5, 109.0, 48.6, 47.4, 44.8, 25.6, 21.4, 20.6, 19.0 and 12.1; δ_H 6.92 (1H, d, J = 7.58 Hz), 6.63–6.57 (2H, m), 4.52 (1H, s), 2.91 (1H, q, J = 7.08 Hz), 1.13 (3H, d, J = 7.08 Hz), 1.10 (3H, s), 1.01 (3H, s), 0.99 (3H, s) and 0.60 (3H, s).