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1,6-Conjugate Addition to o-Vinylphenyloxazolines. Syntheses of Chuangxinol and 3-n-Butylphthalide

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Abstract: Phtalhides are prepared from o-vinylphenyloxazolines in one pot reaction by 1,6-conjugate addition of alkyllithium and trapping of the benzylic anion with MoOPH, followed by hydrolysis with aqueous oxalic acid. This method was applied to the syntheses of two natural products: chuangxinol and 3-n-butylphthalide. © 1997 Elsevier Science Ltd.

The oxazoline group has proved to be a useful group for organic synthesis, not only as a masking group for carboxylic acid functionality, but as well as an auxiliary group for the functionalization of organic molecules. In recent years special attention has been dedicated to the chemistry of 2-aryloxazolines, mainly because of the nucleophilic displacement of methoxy groups ortho to the oxazoline ring (in the benzene nucleus).[1] Recently,[2] we discovered that o-vinylphenyloxazolines experience 1,6-conjugate addition of carbon nucleophiles; the trapping of benzylic anion was done either with methanol or with methyl iodide.

Following our studies on the reactivity of o-vinylphenyloxazolines, and its application to the synthesis of substances with biological activity, we tried another electrophile suitable to introduce an heteroatom in the benzylic position. Introduction of an oxygen atom would allow us to prepare 1(3H)-isobenzofuranones (phthalides), which may possess a wide range of medicinal properties. (-)-Chuangxinol and (-)-3-n-butylphthalide are two examples of 3-n-alkylphthalides taken from natural sources. The former has been isolated from Ligusticum wallichii and Ligusticum chuanxing,[3] the later is a constituent of celery seed oil, is used for seasoning and flavouring purposes, and is claimed to show antiasthmatic, anti-convulsant, anti-tumour, and anaesthesia prolongation properties.[4] Posible uses for this kind of compound are hair growth and shower bath preparations.[5]

As a first trial for this general approach to 3-n-alkylphthalides we used n-BuLi as a nucleophile. 2-(3-Methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline (**1**), prepared as previously described,[6] was dissolved in THF, cooled to -55°C and commercial n-butyllithium (1.6M in hexane) was added dropwise. After 2 h, MoO_5.Py.HMPA (MoOPH)[7] was added with a Schlenk tube, to afford imino lactone **4a**, as a product of intramolecular ring opening of the oxazoline ring by the hydroxyl group introduced by the MoOPH (**3**).[8] Then, the C=N bond was cleaved by acidic hydrolysis with aqueous oxalic acid, in one pot reaction, affording 3-n-pentyl-4-methoxyphthalide (**6a**) in moderate overall yield (34%).

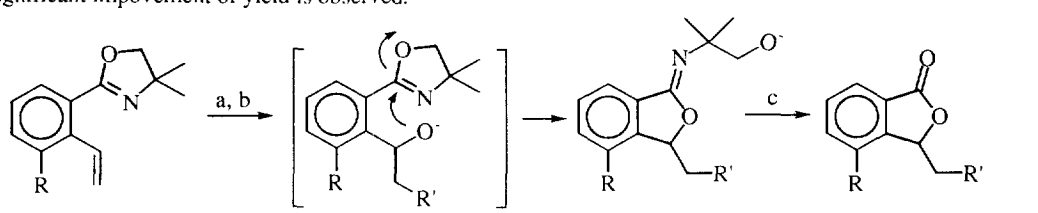
In order to apply this result to the synthesis of the natural phthalide chuangxinol (**8**), we attempted this reaction using n-propyllithium, synthesized from 1-bromopropane and lithium.[9] So, oxazoline **1** was

transformed to **6b**, but now in a good overall yield (75%). Demethylation of **6b** with NaSEt in DMF[10] led to chuangxinol[3] (**8**) in 78% yield.

Due to the unexplained difference of the reactivity between n-BuLi and n-PrLi, we made **6a** using freshly prepared n-BuLi;[9] and we observed an improved yield (71%). This different behaviour is probably because of the presence of lithium bromide in the solution. In fact when lithium bromide was added to the oxazoline prior to the addition of commercial n-BuLi the yield (67%) was similar to the one obtained with freshly prepared n-BuLi.

The same reaction was tried with the oxazoline **2**, without methoxy group in position 3, and commercial n-BuLi giving **7a**, in 35%. In this case, yield increased only to 42% when the reaction was done with freshly prepared n-BuLi. Similar results were obtained when we prepared 3-n-butylphthalide (**7b**) from **2** using n-PrLi as nucleophile (38% overall yield).

It is noteworthy that only in case of the presence of the methoxy group (compound **1**) the addition of LiBr to the oxazoline improves the yield. We believe that this influence only affects the step of addition of the electrophile, since in our previous work[2] we obtained a 84% yield of addition of n-BuLi followed by quenching with MeOH against 34% in the present work with MoOPH as electrophile. We already knew[2] of the influence of 3-methoxy group in the step of nucleophile addition (PhLi added to exocyclic double bond of compound **1**, but no to that of molecule **2**[11]). In the present case, we think that it is the methoxy group which now coordinates to LiBr and not the nitrogen or the oxygen of the oxazoline ring because in absence of 3-methoxy group no significant impovement of yield is observed.



1 R=OMe
2 R=H

3

4a R= OMe, R'= n-Bu
4b R= OMe, R'= n-Pr
5a R= H, R'= n-Bu
5b R= H, R'= n-Pr

6a R= OMe, R'= n-Bu
6b R= OMe, R'= n-Pr
7a R= H, R'= n-Bu
7b R= H, R'= Pr
8 R= OH, R'= Pr

a) R'Li, -55°C, THF, b) MoOPH, -55°C to r.t., c) HO_2CCO_2H, H_2O, THF, reflux, d) EtSH, NaH, DMF, reflux

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EXPERIMENTAL

General. Melting points were determined using a Gallenkamp apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AC-300 operating at 300 MHz and 75 MHz (^{13}C) with $CDCl_3$ as the solvent and TMS as the internal standard. Low-resolution electron-impact mass spectra were recorded on a Hewlett-Packard HP-59970MS Chem Station mass spectrometer with direct sample insertion. Infrared spectra were measured on a Mattson FT-IR Galaxy 2020 instrument (cm^{-1}). Flash chromatography was performed using silica gel. Ether and THF were distilled from sodium and benzophenone. DMF was distilled from calcium hydride. Methanol was distilled from magnesium methoxide. 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline (**1**) and 4,4-dimethyl-2-(2-vinylphenyl)-2-oxazoline (**2**) were prepared as in the procedure described by Meyers.[6] n-BuLi and n-PrLi were prepared following the procedure described in ref. 9.

General Procedure. 4-methoxy-3-pentyl-1(3H)-isobenzofuranone (6a): 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline (**1**) (258 mg, 1.12 mmol) in 10 ml of dry THF was cooled to -55°C under an argon atmosphere and freshly prepared n-BuLi[9] (4.82 ml 0.51M in ether, 2.46 mmol) was added dropwise. The resulting dark red solution was stirred for 2 h at -55°C. The reaction was quenched by solid MoOPH (886 mg, 2.02 mmol) added with a Schlenk tube and the reaction mixture was allowed to warm to room temperature. The crude reaction was treatment with an saturated aqueous solution of oxalic acid (20 ml) and refluxed for 8 h. Then, the reaction was extracted with dichloromethane (3 x 30 ml), the organic layer was washed with aqueous saturated sodium hydrogen carbonate, dried (sodium sulphate) and the solvent removed to give a syrup which was purified by flash column (ethyl acetate:hexane, 3:7) to afford 4-methoxy-3-pentyl-1(3H)-isobenzofuranone (**6a**) (187 mg, 71%) as a white solid. m.p. 51-53°C (hexane). υ_{max} (film): 1767 (C=O) cm^{-1}. ^1H RMN ∂ 0.83-0.92 (m, 3H, $C\underline{H}_3CH_2$); 1.25-1.56 (m, 6H, $3XCH_2$); 1.63-1.76 (m,1H, CH_2); 2.20-2.31 (m, 1H, CH_2); 3.91 (s, 3H, OMe); 5.29-5.51 (m, 1H, benzylic hydrogen); 7.05-7.11 (m, 1H, ArH); 7.42-7.48 (br s, 2H, ArH). ^{13}C RMN ∂ 14.3 ($\underline{C}H_3CH_2$); 22.8 (CH_2); 24.9 (CH_2); 31.8 (CH_2); 33.1 (CH_2); 55.98 (OMe); 81.2 (benzylic carbon); 115.2, 117.6, 128.1, 131.1, 138 and 155 (Ar); 202.5 (C=O). m/z (%): 235 (M^++1, 3.6), 234 (M^+, 21), 206 (0.6), 178 (0.5), 163 (100), 135 (16). (Found C, 72.16; H, 8.23. $C_{14}H_{18}O_3$ requires C, 71.775; H, 7.74%).

3-butyl-4-methoxy-1(3H)-isobenzofuranone (6b). 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline (**1**) (321 mg, 1.39 mmol) in dry THF (20 ml) was treated with n-PrLi[9] (5.56 ml 0.55M in ether, 3.06 mmol) for 2 h at -55°C. Addition of MoOPH (1.1 g, 2.5 mmol) and treatment with oxalic acid (48 ml) as in the General Procedure, afforded after work up and purification of the residue by flash chromatography (ethyl acetate: hexane, 3:7) 3-butyl-4-methoxy-1(3H)-isobenzofuranone (**6b**) (230 mg, 75%) as a white solid. m.p. 46°C (hexane). υ_{max} (film): 1768 (C=O) cm^{-1}. ^1H NMR ∂ 0.79 (t, 3H, J=6.8 Hz, $C\underline{H}_3CH_2$); 1.19-1.28 (m, 4H, $2xCH_2$); 1.63 (m, 1H, $CH(O)C\underline{H}_2$); 2.19 (m, 1H, $CH(O)C\underline{H}_2$); 3.84 (s, 3H, OMe); 5.38 (dd, 1H, J= 2.8 Hz, J= 8.0 Hz, benzylic hydrogen); 7.02 (dd, 1H, J= 1.2Hz and J= 7.6 Hz, ArH); 7.35 (m, 2H, ArH). ^{13}C NMR ∂ 14.09 ($\underline{C}H_3CH_2$); 22.31 (CH_2); 26.84 (CH_2); 32.41 (CH_2); 55.56 (OMe); 80.66 (benzylic carbon); 114.93, 116.85, 127.77, 130,73, 137.69 and 154.26 (Ar); 170.65 (C=O). m/z, (%): 221(M^++1, 1.4), 220 (M^+, 9), 163 (100), 135 (19). (Found C, 70.70; H, 7.362. $C_{13}H_{16}O_3$ requires C, 70.89; H, 7.32%).

3-pentyl-1(3H)-isobenzofuranone (7a): 4,4-dimethyl-2-(2-vinylphenyl)-2-oxazoline (**2**) (134 mg, 0.67 mmol) was treated with freshly prepared n-BuLi[9] (2.88 ml 0.51M in ether, 1.47 mmol) for 5 h at -55°C. Addition of MoOPH (530 mg, 1.26 mmol) and treatment with oxalic acid (12 ml) as in the General Procedure, gave after work up and purification of the residue by flash chromatography (ethyl acetate: hexane, 2:8) 3-pentyl-1(3H)-isobenzofuranone (**7a**) (57 mg, 42%) as a pale yellow syrup. υ_{max} (film): 1762 (C=O) cm^{-1}. ^1H NMR ∂ 0.89 (br s, 3H, $C\underline{H}_3CH_2$); 1.32-1.52 (m, 6H, $3xCH_2$); 1.69-1.82 (m, 1H, $ArCH(O)C\underline{H}_2$); 2.00-2.09 (m, 1H, $ArCH(O)C\underline{H}_2$), 5.48 (dd, 1H, J=4.0 Hz, J=7.6Hz, benzylic hydrogen); 7.43 (d, 1H, J=7.63Hz, ArH); 7.52 (t, 1H, J=7.4 Hz, ArH), 7.67 (t, 1H, J=6.8 Hz, ArH); 7.91 (d, 1H, J=7.6 Hz, ArH). ^{13}C NMR ∂ 13.9 ($\underline{C}H_3CH_2$); 22.4 (CH_2); 24.4 (CH_2); 31.8 (CH_2); 34.7 (CH_2); 81.5 (benzylic carbon); 121.7, 125.6, 126.1, 129.0, 133.9 and 150.1 (Ar); 170.7 (C=O). m/z (%): 204 (M^+, 8), 176 (3), 148 (4), 133 (100). (Found C, 75.96; H, 8.129. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.895%).

3-butyl-1(3H)-isobenzofuranone (7b). 4,4-dimethyl-2-(2-vinylphenyl)-2-oxazoline (**2**) (126 mg, 0.627 mmol) in dry THF (10 ml) was treated with n-PrLi (2.51 ml 0.55M in ether, 1.38 mmol) for 5 h at -55°C. Addition of MoOPH (0.497 g, 1.13 mmol) and treatment with oxalic acid (12 ml) as in the General Procedure gave after work up and purification of the residue by flash chromatography (ethyl acetate: hexane, 3:7) 3-butyl-1(3H)-isobenzofuranone (**7b**) (45 mg, 38%) as a colorless syrup. υ_{max} (film): 1764 (C=O) cm^{-1}. ^1H NMR ∂ 0.89 (t, 3H, J=4.0 Hz, $C\underline{H}_3CH_2$); 1.31-1.51 (m, 4H, 2xCH_2);1.71-1.8 (m, 1H, CH(O)$C\underline{H}_2$); 2.04-2.17 (m, 1H, CH(O)$C\underline{H}_2$); 5.47 (dd, 1H, J=4.0 Hz, J=8.0 Hz, benzylic hydrogen); 7.45 (d, 1H, J=7.63Hz, ArH); 7.52 (t, 1H, J=7.6 Hz, ArH); 7.64 (t, 1H, J=7.6 Hz, ArH); 7.87 (d, 1H, J=7.6 Hz, ArH). ^{13}C NMR ∂ 13.5 ($\underline{C}H_3CH_2$); 22.42 (CH_2); 26.86 (CH_2); 34.4 (CH_2); 81.44 (benzylic carbon); 121.74, 125.64, 126.12, 129.0, 133.95 and 150.12 (Ar); 171.1 (C=O). m/z (%): 190 (M^+, 6), 176 (4), 148 (2), 133 (100). (Found C, 75.85; H, 7.70. $C_{12}H_{14}O_2$ requires C, 75.77; H, 7.42%).

(±)-Chuangxinol (3-butyl-4-hydroxy-1(3H)-isobenzofuranone) (**8**). Ethanethiol (0.085 ml, 1.16 mmol) dissolved in dry dimethylformamide (2 ml) was added to a suspension of sodium hydride (63 mg of an 80% oil dispersion, 2.1 mmol) in dry DMF (3 ml) under an atmosphere of argon. The mixture was stirred for 5 min. before a solution of 3-butyl-4-methoxy-1(3H)-isobenzofuranone (**6b**) (154 mg, 0.7 mmol) in dry DMF (5 ml) was added, the solution was then refluxed for 3 h. The cooled mixture was acidified with 10% aqueous hydrochloric acid and extracted with ether. The ether layer was washed with water and extracted with 10% aqueous sodium hydroxide, the alkaline extracts were acidified and reextracted with ether. The ethereal solution was washed with water, dried, evaporated and purified by flash chromatography (ethyl acetate: hexane, 3:7) to give (±)-chuangxinol (**8**) (113 mg, 78%) as a white solid. m.p. 165-6°C (dichloromethane), lit.[3] 188-190°C (benzene). υ_{max}: 1693 (C=O); 3112-3143 (OH) cm^{-1}. ^1H RMN (CD_3OD) ∂ 1.04 (t, 3H, J=4.4 Hz, $C\underline{H}_3CH_2$); 1.4-1.58 (m, 4H, 2xCH_2); 1.82-1.95 (m, 1H, CHOC$\underline{H}_2$); 2.4-2.5 (m, 1H, CHOC$\underline{H}_2$); 5.72 (dd, 1H, J=7.7 Hz, J=3.2 Hz, $CHOCH_2$); 7.23 (d, 1H, J= 7.3 Hz, Ar-H); 7.45 (d, 1H J=7.3 Hz, Ar-H); 7.51 (d, 1H, J=7.3 Hz, Ar-H). ^{13}C RMN (CD_3OD) ∂ 23.69 ($\underline{C}H_3CH_2$); 31.73 (CH_2); 33.38 (CH_2); 35.08 (CH_2); 81.66 ($CHOCH_2$); 115.76, 118, 120.33, 122.42, 130.97 y 133.09 (Ar); 173.4 (C=O). m/z, (%): 206 (M^+, 5), 188 (4), 149 (100), 121 (16). (Found C, 69.64; H, 7.165. $C_{12}H_{14}O_3$ requires C, 69.885; H, 6.84%).

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11. We prepared oxazolines with methoxy group either in position 4, 5 or 6, but none of them shown addition products when treated with PhLi.

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