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A CONVENIENT SYNTHESIS OF SUBSTITUTED QUINOLINES BY THERMAL OR PHOTOCHEMICAL ELECTROCYCLIC REARRANGEMENT OF o-VINYL IMIDATES UNDER NON-ACIDIC CONDITIONS.

Lin Guo Qiang and Neil H. Baine*
Synthetic Chemistry Department
SmithKline and French Laboratories, L-810
King of Prussia, PA 19406-2799

Abstract: Imidates **4a-e**, Table 1, were prepared by treatment of amides **3a-e** with $Et_3O^+BF_4^-$ in the presence of excess Na_2HPO_4. These underwent smooth rearrangement to quinolines **5a-e** by thermal or photochemical activation.

We recently reported[1] that 2,3 and 2,4-disubstituted quinolines could be readily prepared from the thermal electrocyclic rearrangement of o-vinylic anil derivatives under nonacidic conditions, thereby avoiding the formation of unwanted oxazine by-products **6**. Although this method is convenient and generally useful for the introduction of aryl substituents at the 2-position of the quinoline, it could not be used for the introduction of primary aliphatic groups at this site. In such cases the required anil underwent rapid isomerization under the cyclization conditions to an enamine, which would not react further.

We would like to report a simple two step alternative for the preparation of 2,3 and 2,4-disubstituted quinolines in high yields from o-vinylic anilines[1], which is based upon the thermal or photochemical electrocyclic rearrangement of imidates **4a-e**. Amides **3a-e** were readily prepared in excellent yields from their corresponding o-vinylic anilines and an acid chloride according to standard procedures. Treatment of amides **3a-d** with an excess of $Et_3O^+BF_4^-$ in methylene chloride afforded the corresponding oxazines **6a-d** in about 60% yields, along with the desired imidates **4a-d** in about 15% yields. Oxazines **6** are believed to arise from fluoroboric acid catalyzed cyclization of the amide. Buffered conditions were therefore developed which allowed for the preparation of imidates **4a-e** in good yields. It was possible to significantly reduce the amount of oxazine to 0-5% by the use of excess $Et_3O^+BF_4^-$ in the presence of Na_2HPO_4. Although these reaction were somewhat slow (1-3 days), good yields of the desired imidates **4a-e** could be obtained readily after chromatography. In most cases (**4b-d**) the alkylation stopped and would not proceed further, even after treatment with additional $Et_3O^+BF_4^-$. In these cases the product imidates were separated from the unreacted starting material by flash chromatography[2].

Subjection of imidates **4a-e** to thermolysis in diphenyl ether at reflux or photolysis[3] in cyclohexane at room temperature afforded quinolines **5a-e** in excellent yields. The cyclizations were particularly clean and efficient,

and no oxazine by-products were observed. UV irradiation of imidate **4e** in cyclohexane gave rise to 15% of dihydroquinoline derivative **7** as a by-product, but the efficiency of this cyclization was improved when acetonitrile was used as the solvent (see Table 1). It is interesting to note that UV irradiation[4] of amide **3b** failed to afford any of the desired quinoline **5b**, but gave rather cleanly oxazine **6b** in 90% yield, presumably via a photoenolization process[5]. All thermal cyclizations proceeded in high yields, with the exception of **4e**, which decomposed upon prolonged heating

This method offers several advantages over our previous method[1], which depended upon air oxidation of an initially formed dihydroquinoline to provide the desired final product. Since the starting imidate has the correct oxidation state to directly afford the product quinoline, fewer side products are observed. The desired quinolines are formed in generally high yields under non-acidic conditions, with little or no by-products. Finally, this method is suitable for the introduction of primary substituents at the 2-position of the quinoline.

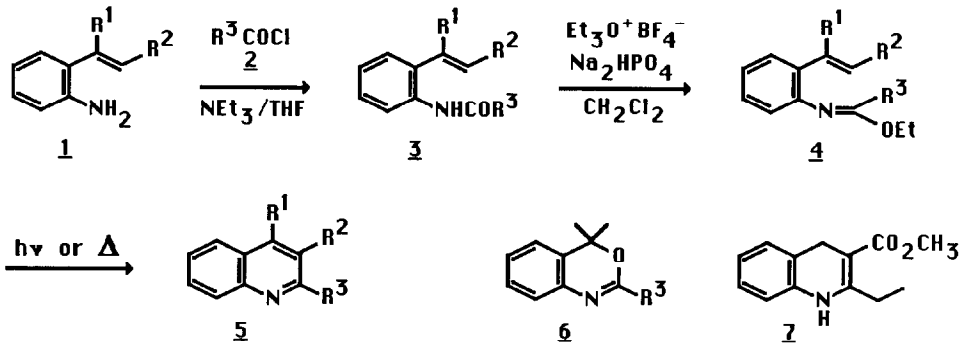
General Procedure for Preparation of Amides **3a-e**: A solution of o-vinylic aniline **1** (3 mmol) and triethylamine (12 ml) in tetrahydrofuran (100 ml) was cooled to 0°C and treated with acid chloride **2** (3.3 mmol). The solution was stirred for 3 hours, quenched into 20 ml brine and extracted with diethyl ether. The combined ethereal extracts were dried over magnesium sulfate and concentrated in vacuo. Purification by vacuum distillation or flash chromatography (5% ethyl acetate/hexane) afforded pure amide **3**.

General Procedure for Preparation of Imidates **4a-e**: A suspension of amide **3** (3 mmol) and disodium hydrogen phosphate (3 g) in methylene chloride (30 ml) was cooled to 0°C and treated with $Et_3O^+BF_4^-$ (15 mmol, 15 ml of 1.0M solution in methylene chloride). The ice bath was removed and stirring was continued at room temperature until the reaction was complete, as determined by TLC or GC (1-3 d). The solution was then quenched into 10% aqueous sodium bicarbonate, and was extracted with diethyl ether. The combined ethereal extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. Purification by flash chromatography (5% ethyl acetate/hexane) afforded pure imidate **4**[6], along with a small amount of oxazine **6** and any unreacted amide.

General Procedure for Thermal Preparation of Quinolines **5a-e**: A solution of **4** (0.46 mmol) in diphenyl ether (10 ml) was heated at reflux under a nitrogen atmosphere for 3-4 hours until the reaction was complete, as determined by TLC or GC analysis. The quinolines **5a-e**[6] were purified by flash chromatography (hexane, then 5% ethyl acetate/hexane).

General Procedure for Photochemical Preparation of Quinolines **5a-e**: A solution of **4** (1.65 mmol) in cyclohexane (100 ml) was degassed under a flow of argon for 2 hours. The solution was then irradiated (Hanovia medium pressure mercury lamp no. 679A-360 (Ace Glass 7825-34) using a quartz liner) until the reaction was complete, as determined by TLC or GC analysis (7h - 3d). The solution was concentrated in vacuo and the quinoline **5**[6] was isolated by bulb to bulb vacuum distillation or flash chromatography.

TABLE 1



	R^1	R^2	R^3	% Yield 3	% Yield 4 (3)[i]	% Yield 5 Thermal	% Yield 5 Phot.	Irradiation Time (hrs.)
a)	CH_3	H	C_2H_5	93	83	91	91	10
b)	CH_3	H	C_5H_{11}	96	71 (10)	82	92	7
c)	CH_3	H	Ph	94	80 (7)	92	92	43
d)	CH_3	H		97	45 (45)	84	71	72
e)	H	CO_2CH_3	C_2H_5	82	91	0[ii]	38[iii] 56[iv]	24 21

[i] % of recovered 3.

[ii] Decomposition.

[iii] Plus 15% of 7.

[iv] Acetonitrile solvent; plus 4% of 7.

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References and Notes

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3 deJong J.; Boyer, J.H. *J. Chem. Soc., Chem. Commun.*, **1971**, 961.

4 For irradiation of an analogous thioamide see deMayo, P.; Sydness L.K.; Wenska, G. *J. Chem. Soc., Chem. Commun.*, **1979**, 499.

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[6] The spectral and physical data for **4a-e, 5a-e, 6b** and **7** are:

4a: IR (thin film) 3080, 3020, 1660, 1600, 1570, 1480, 1440, 1300, 1220, 1085, 1030, 895, 760; ^{1}H NMR ($CDCl_3$) d 7.19-7.14 (2H, m), 7.00-6.97 (1H, t, J=7.9), 6.66-6.64 (1H, d, J=7.7), 5.05 (1H, s), 4.92 (1H, s), 4.25-4.20 (2H, q, J=7.2), 2.07-2.02 (5H, m), 1.35-1.31 (3H, t, J=7.0), 1.03-0.99 (3H, t, J=7.7); MS (EI) m/e 217, 188, 172, 132, 57; Anal. Calc. for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45, Found: C 77.49, H 8.90, N 6.33.

4b: IR (thin film) 3060, 3020, 1660, 1570, 1480, 1365, 1245, 1220, 1180, 1100, 890, 765; ^{1}H NMR ($CDCl_3$) d 7.18-7.14 (2H, m), 7.00-6.96 (1H, td, J=8.5, 1.2), 6.65-6.63 (1H, d, J=7.5), 5.05-5.04 (1H, t, J=1.6), 4.93-4.92 (1H, d, J=1.4), 4.25-4.19 (2H, q, J=7.0), 2.03-2.00 (5H, m), 1.51-1.44 (2H, m), 1.34-1.31 (3H, t, J=7.0), 1.25-1.11 (4H, m), 0.84-0.80 (3H, t, J=6.9); MS (EI) m/e 259, 230, 175, 160, 132, 43; Anal. Calc. for $C_{17}H_{25}NO$: C 78.72, H 9.71, N 5.40, Found: C 78.89, H 9.40, N 5.42.

4c: IR (thin film) 3060, 3020, 1650, 1590, 1490, 1480, 1435, 1390, 1370, 1260, 1180, 1160, 1105, 1085, 1030, 900, 765, 695; ^{1}H NMR ($CDCl_3$) d 7.29-7.25 (3H, m), 7.20-7.16 (2H, m), 7.15-7.13 (1H, dd, J=7.6, 1.5), 7.05-7.00 (1H, td, J=7.5, 1.5), 6.95-6.90 (1H, td, J=7.5, 1.3), 6.55-6.52 (1H, dd, J=7.8, 0.7), 5.05-5.04 (1H, t, J=1.8), 4.87-4.86 (1H, d, J=0.8), 4.43-4.38 (2H, q, J=7.1), 2.02 (3H, s), 1.45-1.41 (3H, t, J=7.2); MS (EI) m/e 265, 236, 105, 77, 51; Anal. Calc. for $C_{18}H_{19}NO$: C 81.47, H 7.22, N 5.28, Found: C 81.69, H 6.95, N 5.23.

4d: IR (thin film) 3040, 1650, 1595, 1570, 1480, 1450, 1365, 1280, 1220, 1120, 1070, 890, 750; ^{1}H NMR ($CDCl_3$) d 7.33-7.32 (1H, d, J=1.8), 7.26-7.17 (2H, m), 7.06-7.02 (1H, td, J=7.5, 1.3), 6.73-6.71 (1H, dd, J=7.6, 0.7), 6.23-6.22 (1H, dd, J=3.5, 1.6), 5.89-5.88 (1H, d, J=3.4), 4.98-4.97 (1H, q, J=1.6), 4.77-4.76 (1H, d, J=0.9), 4.45-4.39 (2H, q, J=7.0), 1.99 (3H, s), 1.47-1.44 (3H, t, J=7.0); MS (EI) m/e 255, 226, 196, 180, 130, 95.

4e: IR (thin film) 3060, 1700, 1660, 1620, 1500, 1320, 1250, 1230, 1190, 1170, 1080, 990, 875, 765; ^{1}H NMR ($CDCl_3$) d 7.83-7.79 (1H, d, J=16.1), 7.60-7.55 (1H, d, J=7.8), 7.32-7.28 (1H, t, J=7.6), 7.08-7.04 (1H, t, J=7.5), 6.74-6.72 (1H, d, J=7.6), 6.42-6.37 (1H, d, J=16.2), 4.35-4.30 (2H, q, J=6.9), 3.78 (3H, s), 2.11-2.06 (2H, q, J=7.3), 1.41-1.38 (3H, t, J=7.0), 1.05-1.01 (3H, t, J=7.5); MS (EI) m/e 261, 202, 176, 172, 158, 156, 146, 128, 118, 89, 57; Anal. Calc. for $C_{15}H_{19}NO_3$: C 68.94, H 7.33, N 5.36, Found: C 68.94, H 7.01, N 5.46.

5a: IR (thin film) 3060, 3020, 1600, 1560, 1500, 1450, 1405, 920, 860, 760; ^{1}H NMR ($CDCl_3$) d 7.99-7.97 (1H, d, J=8.5), 7.86-7.84 (1H, d, J=8.3), 7.60-7.57 (1H, td, J=8.2,0.9), 7.43-7.40 (1H, td, J=8.2, 1.1), 7.07 (1H, s), 2.91-2.85 (2H, q, J=7.5), 1.32-1.28 (3H, t, J=7.7); MS (EI) m/e 171, 170, 154, 143, 128, 115, 77, 51; HRMS Calc. for $C_{12}H_{13}N$: 171.1048, Found: 171.1043.

5b: IR (thin film) 3060, 3020, 1600, 1560, 1500, 1450, 1410, 875, 860, 760; ^{1}H NMR ($CDCl_3$) d 8.08-8.06 (1H, d, J=8.4), 7.95-7.93 (1H, d, J=8.3), 7.69-7.65 (1H, t, J=8.0), 7.51-7.47 (1H, t, J=7.9), 7.14 (1H, s), 2.94-2.90 (2H, t, J=7.8), 2.67 (3H, s), 1.84-1.78 (2H, m), 1.43-1.35 (4H, m), 0.92-0.88 (3H, t, J=7.0); MS (EI) m/e 213, 184, 170, 157, 142, 128, 115; Anal. Calc. for $C_{15}H_{19}N$: C 84.46, H 8.98, N 6.57, Found: C 84.19, H 8.72, N 6.82.

5c: IR (thin film) 3060, 3030, 1600, 1550, 1510, 1500, 1490, 1450, 1225, 1080, 1040, 900, 875, 790, 770, 760, 690; ^{1}H NMR ($CDCl_3$) d 8.19-8.17 (1H, d, J=8.4), 8.14-8.12 (2H, m), 7.95-7.93 (1H, t, J=8.3), 7.71-7.66 (2H, m), 7.52-7.41 (4H, m), 2.70 (3H, s); MS (EI) m/e 219, 204, 189, 176, 140, 108; Anal. Calc. for $C_{16}H_{18}N$: C 87.64, H 5.98, N 6.39, Found: C 87.80, H 5.98, N 6.34.

5d: IR (thin film) 3100, 3060, 1600, 1550, 1500, 1480, 1450, 1410, 1320, 1220, 1160, 1085, 900, 880, 815, 755, 740; ^{1}H NMR ($CDCl_3$) d 8.14-8.11 (1H, d, J=8.4), 7.93-7.91 (1H, d, J=8.3), 7.70-7.66 (1H, td, J=8.6, 1.3), 7.64-7.61 (2H, dd, J=12.7, 1.8), 7.51-7.47 (1H, td, J=8.1, 1.0), 7.19-7.18 (1H, d, J=3.4), 6.57-6.56 (1H, dd, J=3.3, 1.6), 2.70 (1H, s); ^{13}C NMR ($CDCl_3$) d 153.5 (C_q), 148.3 (C_q), 147.6 (C_q), 144.3 (C_q), 143.5 (CH), 129.5 (CH), 129.0 (CH), 126.9 (C_q), 125.5 (CH), 123.3 (CH), 117.5 (CH), 111.8 (CH), 109.5 (CH), 18.3 (CH_3); MS (EI) m/e 209, 180, 152, 115, 104, 89, 77, 63.

5e: IR (thin film) 3060, 1720, 1615, 1595, 1560, 1485, 1430, 1270, 1230, 1200, 1070, 800, 765; ^{1}H NMR ($CDCl_3$) d 8.60, (1H, s), 7.98-7.96 (1H, d, J=8.4), 7.75-7.73 (1H, d, J=8.1), 7.69-7.65 (1H, td, J=8.4, 1.4), 7.44-7.41 (1H, t, J=7.6), 3.88-3.87 (3H, d, J=1.1), 3.28-3.23 (2H, q, J=7.4), 1.30-1.27 (3H, t, J=7.4); ^{13}C NMR ($CDCl_3$) d 166.8 (C_q), 162.9 (C_q), 148.5 (C_q), 140.0 (CH), 131.5 (CH), 128.5 (CH), 126.4 (CH), 125.5 (C_q), 123.2 (C_q), 52.3 (CH_3), 30.8 (CH_2), 13.9 (CH_3); MS (EI) m/e 215, 200, 184, 156, 128, 77; HRMS Calc. for $C_{13}H_{13}NO_2$: 215.0946, Found: 215.0946.

6c: IR (thin film) 3060, 3020, 1620, 1600, 1570, 1480, 1450, 1380, 1365, 1315, 1260, 1100, 1070, 865, 765, 695; ^{1}H NMR ($CDCl_3$) d 8.17-8.14, (2H, m), 7.51-7.42 (3H, m), 7.34-7.28 (2H, m), 7.21-7.17 (1H, td, J=7.5, 1.8), 7.16-7.13 (1H, dd, J=7.1, 1.3), 1.71 (6H, s); ^{13}C NMR ($CDCl_3$) d 156.8 (C_q), 138.8 (C_q), 132.2 (C_q), 131.4 (C_q), 131.3 (CH), 128.5 (CH), 128.2 (2CH), 128.0 (2CH), 126.6 (CH), 125.1 (CH), 122.2 (CH), 78.3 (C_q), 28.4 ($2CH_3$); MS (EI) m/e 237, 222, 132, 105, 91, 77; Anal. Calc. for $C_{18}H_{19}NO$: C 81.47, H 7.22, N 5.28, Found: C 81.69, H 6.95, N 5.23.

7: IR (thin film) 3400, 3060, 3020, 1730, 1660,1600, 1165, 1020, 740; ^{1}H NMR ($CDCl_3$) d 7.98, (1H, b), 7.55-7.53 (1H, dd, J=6.9, 2.8), 7.26-7.24 (1H, dd, J=6.2, 1.9), 7.14-7.09 (2H, m), 3.70 (2H, s), 3.65 (3H, s), 2.80-2.74 (2H, q, J=7.6), 1.29-1.25 (3H, t, J=7.7); ^{13}C NMR ($CDCl_3$) d 172.6 (CO), 138.4 (C_q), 135.1 (C_q), 128.4 (C_q), 121.2 (CH), 119.5 (CH), 118.1 (CH), 110.4 (CH), 103.5 (C_q), 51.8 (CH), 30.1 (CH_2), 19.4 (CH_2), 13.9 (CH_3); MS (EI) m/e 217, 174, 158, 143, 130; Anal. Calc. for $C_{13}H_{13}NO_2$: C 72.54, H 6.09, N 6.51, Found: C 72.25, H 6.01, N 6.45.

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