Phenethylamines via Heck Arylation of a New Vinylamine Equivalent

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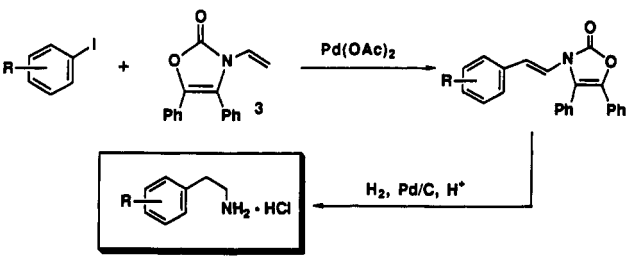
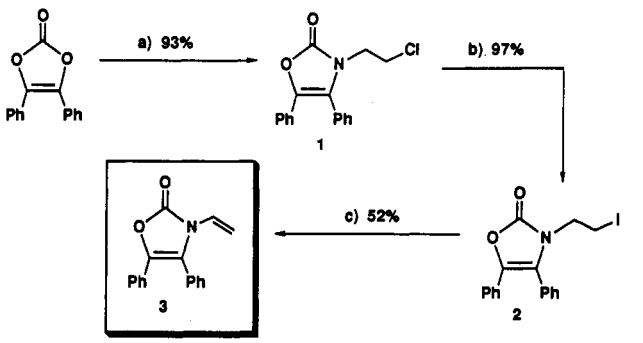
A new vinylamine equivalent, *N*-vinyloxazolone **3**, has been prepared in three steps and shown to undergo Heck arylation with a variety of substrates. The Heck adducts thus obtained are then converted in one step and high yield to phenethylamine hydrochlorides. As a general synthetic method for preparation of substituted phenethylamines, use of this new reagent is shown to be superior to *N*-vinylphthalimide in number of steps, regiospecificity, and chemical yield.

Phenethylamines are an important compound class with members affecting serotonin,[1] dopamine,[2] and norepinephrine[3] receptors. As a partial structure, phenethylamines are common in alkaloidal natural products[4] including the isoquinolines, isopavines, opiates, and berberines. In the course of SAR development in an unrelated heterocyclic system, we desired a convenient method for introduction of an ethylamine moiety to an aromatic ring. Heck arylation of *N*-vinylphthalimide[5] (**4**) has been used in this capacity, yet we were forced to reject this method due to the instability of our system toward the strongly basic conditions (hydrazinolysis) required for the second step of the phthalimide deprotection. In addition, classical methods require reduction of nitroolefins with LAH, which proved unsuitable as well due to the presence of substituents labile toward hydride reducing agents. We have thus developed a new vinylamine equivalent, *N*-vinyloxazolone **3**, which undergoes palladium-catalyzed arylation with a variety of aryl halides. These intermediates are then converted in one step under mildly *acidic* conditions to phenethylamine HCl salts in high yield (Scheme I).

Scheme I



Scheme II[a]



[a] Key: (a) chloroethylamine HCl, DMF, TFA; (b) NaI, NMP; (c) t-BuOK/PhMe.

Results and Discussion

Sheehan[6] has previously developed the diphenyloxazolone unit as an amino protecting group for amino acids in peptide synthesis. We have utilized this method for the three-step synthesis of olefin **3** from commercially available diphenyldioxolone as shown in Scheme II. Condensation of 2-chloroethylamine HCl with the above dioxolone led to chloride **1**, and Finkelstein exchange provided iodide **2**. Elimination was then effected *via* t-BuOK/PhMe to give olefin **3** as an air-stable crystalline solid.

To fully evaluate the reactivity of **3**, Heck arylations with a variety of aryl iodides were performed (Table I). Iodides **5–12** were chosen to adequately address the effect of electron-donating and electron-withdrawing groups, as well as substituents ortho to the iodide, on the course of the reaction. Two different arylation protocols[7] were examined for each iodide (methods A and B), and a third method (C) was examined in two cases. In all three methods, 4 mol % of $Pd(OAc)_2$ was used, iodide concentration was 0.5 M, and a maximum 48 h total reaction time was observed. Method A ($NaHCO_3$, $(n\text{-}Bu)_4NCl$, DMF) was found to be the most general, providing superior yields in most cases. Electron-poor aryl iodides (entries 2–4) gave the highest yields, no doubt reflecting accelerated rates of oxidative addition.[8] We were encouraged to find, however, that electron-rich arenes (entries 5–7) also reacted in respectable yields (58–69%). The lone exception to this observation was *p*-iodophenol, entry 8. Here, a dismal yield (9%) of Heck adduct **20** was obtained *via* method

(1) Review: (a) Nichols, D. E.; Oberlender, R.; McKenna, D. J. *Biochem. Physiol. Subst. Abuse*; CRC: Boca Raton, 1991; Vol. 3, p 1. (b) Nichols, D. E.; Snyder, S. E.; Oberlender, R.; Johnson, M. P.; Huang, X. *J. Med. Chem.* **1991**, *34*(1), 276. (c) Glennon, R. A; Darmani, N. A.; Martin, B. R. *Life Sci.* **1991**, *48*, 2493.

(2) Claudi, F.; Cardellini, M.; Cingolani, G. M.; Piergentilli, A.; Guidubaldo, P.; Balduini, W. *J. Med. Chem.* **1990**, *33*(9), 2408.

(3) Bradford, H. F. *Chemical Neurobiology*; W. H. Freeman: New York, 1986; p 186–7.

(4) Review: Bentley, K. W. *Nat. Prod. Rep.* **1990**, *7*(3), 245.

(5) (a) Francis, J. E.; Webb, R. L.; Ghai, G. R.; Hutchison, A. J.; Moskal, M. A.; deJesus, R.; Yokoyama, R.; Rovinski, S. L.; Contardo, N.; Dotson, R.; Barclay, B.; Stone, G. A.; Jarvis, M. F. *J. Med. Chem.* **1991**, *34*(8), 2570. (b) Hegedus, L. S.; Harrington, P. J. *J. Org. Chem.* **1984**, *49*(15), 2657. (c) Johnson, P. Y ; Wen, J. Q. *J. Org. Chem.* **1981**, *46*(13), 2767. (d) Heck, R. F.; Ziegler, C. B., Jr. *J. Org. Chem.* **1978**, *43*(15), 2649.

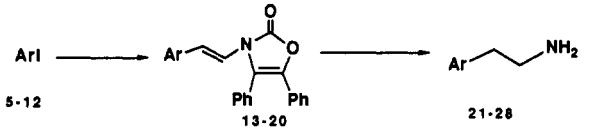
(6) Sheehan, J. C.; Guziec, F. S., Jr. *J. Org. Chem.* **1973**, *38*(17), 3034.

(7) Method A: (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. (b) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*(22), 2667. Method B: Zhuangyu, Z.; Yi, P.; Hongwen, H.; Tsi-Yu, K. *Synth. Commun.* **1990**, *20*(22), 3563. Method C: see ref 5a,d above.

(8) Fauvarque, J.-F.; Pfluger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419.

0022-3263/93/1958-3299$04.00/0

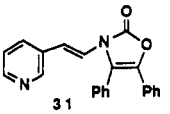
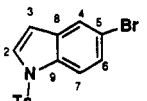
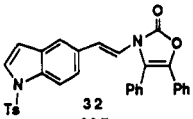
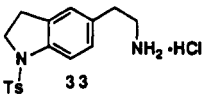
Table I. Arylations of *N*-Vinyloxazolone 3 and Hydrogenation to Phenethylamines



entry	iodide	Heck adduct	method: yield (%)	amine	yield (%)
1	**Ph**	**13**	A: 66 B: 66	**21**	96
2	2-FPh	**14**	A: 73 B: 54	**22**	88
3	3-FPh	**15**	A: 96 B: 75	**23**	80
4	4-ClPh	**16**	A: 87 B: 22	**24**	0%[a]
5	4-MePh	**17**	A: 69 B: 69 C: 74	**25**	87
6	2-OMePh	**18**	A: 59 B: 41	**26**	86
7	4-OMePh	**19**	A: 58 B: 45	**27**	87
8	4-OHPh	**20**	A: 9 B: 42 C: 39	**28**	94

[a] 70% of **21** formed.

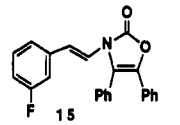
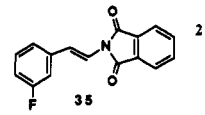
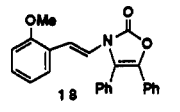
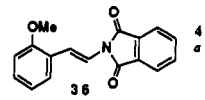
Table II. Heteroarylations of *N*-Vinyloxazolone 3 and Hydrogenation to Amines

bromide	adduct, yield	amine
 **29**	 **31** 89%	Complex mixture obtained
 **30**	 **32** 80%	 **33** 69%

A, while yields of ca. 40% could be obtained with methods B or C. The reasons for this dichotomy are not presently clear. The Heck adducts **13–20** were all found to be chromatographically stable crystalline solids. In addition, no evidence for competing α-arylation[9] was observed in any of the cases studied. Furthermore, the magnitude of the olefinic coupling constants of all the Heck adducts, 14.8 ± 0.7 Hz, clearly indicates only the *E* geometrical isomer was formed. Hydrogenation of these intermediates in EtOH + HOAc with 10% Pd/C furnished only the desired phenethylamines and bisbenzyl. Attempts to deprotect 4-chloro Heck adduct **16** have resulted to date not only in deprotection but reductive dechlorination as well. Two heteroaryl bromides, **29** and **30**, were similarly examined, as shown in Table II. Both bromides reacted more sluggishly under method A (90 °C) than the iodides, as expected, and thus the temperature was increased to 120 °C. In this way high yields of adducts **31** (89%) and **32** (80%) were readily obtained. Hydrogenative deprotection then furnished the indoline **33**, while pyridyl species **31** gave a complex mixture as observed by NMR and TLC and these species were not further addressed.

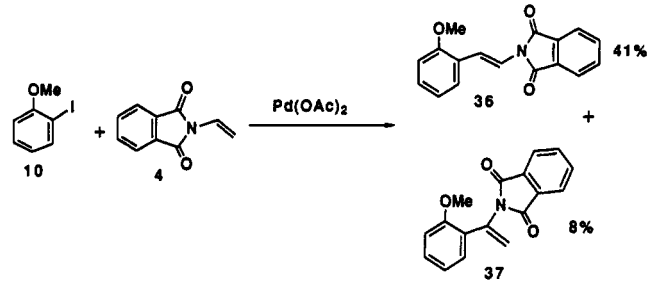
A direct comparison of *N*-vinyloxazolone **3** and *N*-vinylphthalimide[5] (**4**) was performed, and the results are shown in Table III. Conditions chosen for *N*-vinylphthalimide were those previously reported.[5] *N*-Vinyloxazolone **3** was found to be superior in the two representative cases studied. For *N*-vinylphthalimide, unreacted starting materials were generally the principal components observed; however, an intriguing result was found in the reaction of *N*-vinylphthalimide with 2-iodoanisole (Table III and Scheme III). Both β and α arylated products (**36**, **37**) were isolated and rigorously characterized. While control of regioselectivity in Heck olefinations has occasionally proved troublesome,[9] we believe this may represent the first reported example of loss of regiocontrol in arylations involving *N*-vinylphthalimide. The full characterization of this α-arylated product **37** bears comment. ^{13}C NMR/DEPT and heteronuclear correlation (HETCOR) experiments provided unequivocal evidence in making these assignments. Only **37** contains a methylene carbon (δ 117.62 ppm, (t)), and this carbon is clearly coupled to the two 1-proton singlets at δ 5.52 and 5.81 ppm. These singlets are undoubtedly the exomethylene hydrogens.

Table III. Comparison of Two Vinylamine Equivalents on Heck Arylations

iodide	adduct, yield	adduct, yield
 **7**	 **15** 96%	 **35** 29%
 **10**	 **18** 59%	 **36** 41%[a]

[a] 8% of α-arylated material **37** also obtained (see Scheme III, Experimental Section.

Scheme III



In summary, a new vinylamine equivalent has been prepared in three steps and found to readily undergo Heck arylation with a variety of different substrates. The reactions are operationally simple and regiospecific, yields exceed those observed with *N*-vinylphthalimide, and a mildly acidic one-step deprotection provides the amine hydrochlorides directly. This two-step synthesis of phenethylamines from aryl iodides and bromides is not only facile but necessary in cases where the subsequent use of strong bases or hydrides preclude access to these important compounds *via* more classical methods.

Experimental Section

General. Compounds were used as received. Aryl iodides were purchased from Lancaster and Aldrich Chemical Co.'s, 4,5-diphenyldioxolone was obtained from Fluka, and all phenethylamines were purchased from Aldrich Chemical Co.

3-(2-Chloroethyl)-4,5-diphenyl-2(3*H*)oxazolone (1). To 470 mL of DMF at rt was added 43.8 g of 2-chloroethylamine

(9) Cabri, W.; Candiani, I.; Bedeschia, A. *J. Org. Chem.* **1992**, *57*(13), 3558.

hydrochloride (378 mmol, 2 equiv), 31.8 g of $NaHCO_3$ (378 mmol, 2 equiv), and 45.0 g of dioxolone **2** (189 mmol, 1 equiv) in the order given. After 18 h, the mixture was added to 800 mL of EtOAc, washed with 0.5 N HCl (2 × 500 mL), H_2O (2 × 500 mL), and saturated NaCl (1 × 500 mL), and dried (Na_2SO_4), and the solvent were removed *in vacuo*. The residue was immediately dissolved in 225 mL of CF_3CO_2H (2.9 mol, 15 eq.,), allowed to stand for 2 h, and again evaporated to dryness. The residual oil was azeotroped with PhMe (2 × 500 mL) and swirled with warm hexane to cause rapid crystallization of the product. Recrystallization of this solid (hexane/EtOAc) gave 42.95 g of **1**, and recrystallization of the mother liquors gave a further 9.66 g for a combined total of 52.61 g of 1, 93% yield, as a colorless crystalline solid, mp 101–102.5 °C. ^1H NMR ($CDCl_3$) δ: 7.58–7.54 (m 3H), 7.48–7.44 (m, 2H), 7.28–7.20 (m, 5H), 3.81 (t, J = 6.7 Hz, 2H), 3.64 (t, J = 6.2 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 154.19 (s), 134.67 (s), 130.57 (d), 130.29 (d), 129.57 (d), 128.38 (d), 127.73 (d), 127.45 (s), 126.57 (s), 124.27 (d), 123.07 (s), 43.23 (t), 40.16 (t). IR (KBr) cm^{-1}: 1766, 1601, 1445, 1432, 1386, 1359, 1325. MS (CH_4 CI) m/e: 300 (MH^+, 1 Cl), 299 (M^+, 1 Cl), 264 (MH^+ – Cl), 195, 105. UV (95% EtOH): λ_1 214 nm, ϵ_1 = 10 400; λ_2 287 nm, ϵ_2 = 8400. Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 68.11; H, 4.66; N, 4.60.

3-(2-Iodoethyl)-4,5-diphenyl-2(3*H*)oxazolone (2). To a suspension of 201.8 g (1.319 mol, 7 eq.) of sodium iodide in 250 mL of NMP at 90 °C was added 56.5 g (0.189 mol, 1 eq.) of chloride 1 over 10 min. After 3 h at 90 °C, the reaction mixture was cooled to 0 °C, diluted with 100 mL of H_2O, and poured into 800 mL of cold H_2O. After 20 min the slurry was filtered and the solid dried to give 71.5 g (97%) of iodide **2** as a colorless crystalline solid, mp 112–114 °C. ^1H NMR ($CDCl_3$) δ: 7.57–7.52 (m, 3H), 7.45–7.41 (m, 2H), 7.26–7.19 (m, 5H), 3.82 (t, J = 7.5 Hz, 2H), 3.17 (t, J = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ: 154.40 (s), 135.02 (s), 130.80 (d), 130.13 (d), 128.86 (d), 128.22 (d), 127.85 (s), 126.94 (s), 124.71 (d), 123.01 (s), 44.29 (t), 0.00 (t). IR (KBr) cm^{-1}: 1758, 1438, 1385, 1344, 1174. MS (CH_4 CI) m/e: 392 (MH^+), 391 (M^+), 299, 264 (M^+ – I), 128, 105. UV (95% EtOH): λ_1 215 nm, ϵ_1 = 15 800; λ_2 287 nm, ϵ_2 = 14 300. Anal. Calcd for $C_{17}H_{14}INO_2$: C, 52.19; H, 3.61; N, 3.58. Found: C, 52.07; H, 3.45; N, 3.54.

3-Ethenyl-4,5-diphenyl-2(3*H*)oxazolone (3). A solution of 71.0 g of iodide **2** (0.182 mol, 1 eq.) in 1 L of PhMe at 75 °C was treated with 31.1 g of t-BuOK (0.247 mol, 1.36 eq.) in two portions at 15 min intervals. The suspension was heated under N_2 for 1.5 h, cooled to rt, and added to 1 L of H_2O in a separatory funnel. The organic phase was washed with H_2O (2 × 1 L), 0.1 N HCl (1 × 1 L), and saturated NaCl (1 × 1 L) and dried (Na_2SO_4), and the solvents were removed *in vacuo* to give 52 g of a yellow oil. The oil was dissolved in 90 mL of MeOH, clouded with 10 mL of H_2O, and scratched to cause rapid crystallization of 24.7 g (52%, first crop only) of pure *N*-vinyloxazolone **3** as a colorless crystalline solid, mp 95–97 °C. ^1H NMR ($CDCl_3$) δ: 7.58–7.47 (m, 3H), 7.45–7.30 (m, 2H), 7.28–7.20 (m, 5H), 6.22 (dd, J = 16.2, 9.5 Hz, 1H), 5.64 (d, J = 15.8 Hz, 1H), 4.83 (d, J = 8.8 Hz, 1H). ^{13}C NMR ($CDCl_3$ δ: 151.97 (s), 134.40 (s), 130.69 (d), 130.20 (d), 129.51 (d), 128.39 (d), 127.99 (d), 127.18 (s), 126.42 (s), 125.77 (d), 124.56 (d), 121.73 (s), 103.68 (t). IR (KBr) cm^{-1}: 1764, 1632, 1600, 1501, 1446. MS (CH_4 CI) m/e: 264 (MH^+), 263 (M^+), 220, 165, 130, 104. UV (95% EtOH): λ_1 219 nm, ϵ_1 = 15 300; λ_2 289 nm, ϵ_2 = 15 600. Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.24; H, 4.78; N, 5.29.

3-[(*E*)-(2-Phenylethenyl)]-4,5-diphenyl-2(3*H*)oxazolone (13). Colorless crystalline solid, mp 178.5–180 °C. ^1H NMR ($CDCl_3$) δ: 7.60–7.48 (m, 5H), 7.34–7.18 (m, 11H), 6.60 (d, J = 14.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 151.93 (s), 135.38 (s), 134.59 (s), 130.73 (d), 130.37 (d), 129.65 (d), 128.57 (d), 128.47 (d), 128.07 (d), 127.37 (d), 127.15 (s), 126.37 (s), 125.84 (d), 124.62 (d), 121.94 (s), 119.98 (d), 119.40 (d). IR (KBr) cm^{-1}: 1765, 1643, 1447, 1377, 1260. MS (CH_4 CI) m/e: 340 (MH^+), 339 (M^+), 293, 164. UV (95% EtOH): λ_1 220 nm, ϵ_1 = 10 400; λ_2 309 nm, ϵ_2 = 14 600. Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.17; H, 4.86; N, 4.07.

3-[(*E*)-[2-(2-Fluorophenyl)ethenyl]]-4,5-diphenyl-2(3*H*)-oxazolone (14). Colorless crystals, mp 158–159 °C. ^1H NMR ($CDCl_3$) δ: 7.58–7.46 (m, 4H), 7.31–7.16 (m, 9H), 7.15–6.93 (m, 2H), 6.80 (d, J = 15.5 Hz, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ: 160.08 (d, $^1J(^{13}C-^{19}F)$ = 250 Hz), 151.97 (s), 134.85 (s), 130.82 (d), 130.45 (d), 129.71 (d), 125.83 (d), 128.46 (d), 128.20 (d), 127.97 (d, ^3J ($^{13}C-^{19}F$) = 3.9 Hz), 127.21 (s), 126.43 (s), 124.76 (d), 124.18 (d, ^3J ($^{13}C-^{19}F$) = 3.9 Hz), 123.37 (d, ^2J ($^{13}C-^{19}F$) = 12.7 Hz), 122.11 (d, ^2J ($^{13}C-^{19}F$) = 9.8 Hz), 115.93 (d), 115.62 (d), 113.56 (d). IR (KBr) cm^{-1}: 1775, 1764, 1645, 1489, 1446, 1381, 1258, 1231. MS (CH_4 CI) m/e: 358 (MH^+), 357 (M^+), 356, 311, 164. UV (95% EtOH): λ_1 221 nm, ϵ_1 = 15 900; λ_2 309 nm, ϵ_2 = 22 800. Anal. Calcd for $C_{23}H_{16}FNO_2$: C, 77.30; H, 4.51; N, 3.92. Found: C, 77.16; H, 4.45; N, 3.88.

3-[(*E*)-[2-(3-Fluorophenyl)ethenyl]]-4,5-diphenyl-2(3*H*)-oxazolone (15). Colorless crystals, mp 144–145 °C (hexane/t-BME). ^1H NMR ($CDCl_3$) δ: 7.63–7.48 (m, 5H), 7.33–7.17 (m, 7H), 6.99–6.86 (m, 3H), 6.65 (d, J = 14.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 162.90 (d, $^1J(^{13}C-^{19}F)$ = 245 Hz), 151.83 (s), 137.72 (s), 134.78 (s), 130.71 (d), 130.49 (d), 130.09 (d), 129.97 (d), 129.73 (d), 128.47 (d), 128.16 (d), 127.00 (s), 126.19 (s), 124.64 (d), 121.82 (s), 120.40 (d), 118.57 (d), 114.09 (d, $^2J(^{13}C-^{19}F)$ = 22 Hz), 112.16 (d, $^2J(^{13}C-^{19}F)$ = 22 Hz). IR (KBr) cm^{-1}: 1761, 1642, 1613, 1585, 1444, 1382, 1265. MS (CH_4 CI) m/e: 358 (MH^+), 357 (M^+), 337, 164, 105. UV (95% EtOH) λ_1 222 nm, ϵ_1 = 21 400; λ_2 311 nm, ϵ_1 = 31 700. Anal. Calcd for $C_{23}H_{16}FNO_2$: C, 77.30; H, 4.51; N, 3.92. Found: C, 77.00; H, 4.39; N, 3.92.

General Arylation Method A. 3-[(*E*)-[2-(4-Chlorophenyl)-ethenyl]]-4,5-diphenyl-2(3*H*)oxazolone (16). A mixture of 1.00 g of 1-chloro-4-iodobenzene (4.15 mmol, 1 eq.), 38 mg of $Pd(OAc)_2$ (0.17 mmol, 0.04 eq.), 1.18 g of (n-Bu)$_4$NCl hydrate (4.15 mmol, 1 eq.), 0.87 g of $NaHCO_3$ (10.4 mmol, 2.5 eq.), 2.19 g of *N*-vinyloxazolone **1** (8.30 mmol, 2 eq.), and 20 mL of DMF was heated at 90 °C for 48 h. The reaction mixture was cooled and diluted with 25 mL of H_2O and the solid filtered. This solid was then chromatographed on silica gel (CH_2Cl_2) to give 0.977 g of oxazolone **16** (87%) as a colorless crystalline solid, mp 196.5–197 °C. ^1H NMR ($CDCl_3$) δ: 7.58–7.45 (m, 5H), 7.30–7.07 (m, 10H), 6.59 (d, J = 14.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 151.84 (s), 134.70 (s), 133.89 (s), 132.88 (s), 130.70 (d), 130.42 (d), 129.68 (d), 128.68 (d), 128.44 (d), 128.12 (d), 126.97 (d), 126.22 (s), 124.59 (d), 121.74 (s), 119.77 (d), 118.54 (d). IR (KBr) cm^{-1}: 1758, 1641, 1381, 1058. MS (CH_4 CI) m/e: 374 (MH^+, 1 Cl), 373 (M^+, 1 Cl), 337 (M^+ – Cl), 164. UV (95% EtOH): λ_1 222 nm, ϵ_1 = 12 000; λ_2 313 nm, ϵ_2 = 19 200. Anal. Calcd for $C_{23}H_{16}ClNO_2 \cdot 0.25H_2O$: C, 73.02; H, 4.40; N, 3.70. Found: C, 72.98; H, 4.13; N, 3.68.

3-[(*E*)-[2-(4-Methylphenyl)ethenyl]]-4,5-diphenyl-2(3*H*)-oxazolone (17). Colorless crystalline solid, mp 159–160 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$) δ: 7.58–7.46 (m, 5H), 7.33–7.05 (m, 10H), 6.61 (d, J = 14.7 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 151.99 (s), 137.27 (s), 134.51 (s), 132.45 (s), 130.71 (d), 130.30 (d), 129.60 (d), 129.26 (d), 128.44 (d), 128.00 (d), 127.17 (s), 126.43 (s), 125.75 (d), 124.58 (d), 121.98 (s), 120.17 (d), 118.61 (d), 21.09 (q). IR (KBr) cm^{-1}: 1763, 1643, 1446, 1377, 1257, 1058. MS (CH_4 CI) m/e: 354 (MH^+), 353 (M^+), 164, 104. UV (95% EtOH): λ_1 204 nm, ϵ_1 = 39 300; λ_2 223 nm, ϵ_2 = 20 400; λ_3 297 nm, ϵ_3 = 26 300; λ_4 311 nm, ϵ_4 = 30 000. Anal. Calcd for $C_{24}H_{19}NO_2$: C, 81.56; H, 5.42; N, 3.96. Found: C, 81.51; H, 5.41; N, 3.95.

3-[(*E*)-[2-(2-Methoxyphenyl)ethenyl]]-4,5-diphenyl-2(3*H*)-oxazolone (18). Colorless crystalline solid, mp 181–182 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$) δ: 7.59–7.49 (m, 4H), 7.37–7.16 (m, 9H), 6.90 (d, J = 14.8 Hz, 1H), 6.90–6.81 (m, 2H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$) δ: 156.73 (s), 151.96 (s), 134.43 (s), 130.83 (d), 130.10 (d), 129.48 (d), 128.43 (d), 128.25 (d), 127.94 (d), 127.84 (d), 127.29 (s), 126.67 (s), 124.57 (d), 124.17 (s), 122.17 (s), 120.88 (d), 120.53 (d), 116.48 (d), 110.65 (d), 55.04 (q). IR (KBr) cm^{-1}: 1751, 1637, 1495, 1381, 1258. MS (CH_4 CI) m/e: 370 (MH^+), 369 (M^+), 357, 164. UV (95% EtOH): λ_1 203 nm, ϵ_1 = 43 000; λ_2 216 nm, ϵ_2 = 30 200; λ_3 223 nm, ϵ_3 = 25 800; λ_4 298 nm, ϵ_4 = 26 400; λ_5 312 nm, ϵ_5 = 32 000; λ_6 319 nm, ϵ_6 = 31 000. Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 77.75; H, 5.14; N, 3.76.

General Arylation Method B. 3-[(*E*)-[2-(4-Methoxyphenyl)ethenyl]]-4,5-diphenyl-2(3*H*)oxazolone (19). In a 30-mL stainless steel bomb were placed a flat stir bar, 0.39 g of NaOAc (4.70 mmol, 1.1 eq.), 1.24 g of oxazolone **3** (4.70 mmol, 1.1 eq.), 1.02 g of 4-iodoanisole (4.27 mmol, 1.0 eq.), 39 mg of $Pd(OAc)_2$ (0.17 mmol, 0.04 eq.), 3 mL of DMF, and 1.5 mL of H_2O in the order given. The bomb was sealed and heated in a 110 °C oil

bath behind a blast shield for 48 h. The bomb was cooled to 0 °C, the contents were partitioned between EtOAc and H_2O, and the aqueous fraction was reextracted with EtOAc. The organic layers were washed with H_2O (2×) and saturated NaCl and dried (Na_2SO_4), and the solvents were removed *in vacuo*. The solid thus obtained was chromatographed on silica eluting with 1:1 CH_2Cl_2/Hex to give 0.716 g (45%) of pure **19** as a colorless crystalline solid, mp 171.5–172 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.58–7.46 (m, 5H), 7.32–7.22 (m, 5H), 7.15–7.10 (m, 3H), 6.80 (d, J = 8.7 Hz, 2H), 6.51 (d, J = 14.7 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 159.05 (s), 152.04 (s), 134.46 (s), 130.72 (d), 130.28 (d), 129.59 (d), 128.44 (d), 127.98 (d), 127.87 (s), 127.21 (s), 127.05 (d), 126.49 (s), 124.57 (d), 122.04 (s), 120.08 (s), 117.65 (d), 114.00 (d), 55.16 (q). IR (KBr) cm^{-1}: 1760, 1646, 1605, 1513, 1447, 1381, 1251, 1175, 767. MS (CH_4 CI) *m/e*: 370 (MH^+), 369 (M^+), 324. UV (95% EtOH): λ_1 203 nm, ϵ_1 = 45 700; λ_2 305 nm, ϵ_2 = 35 000; λ_3 314 nm, ϵ_3 = 36 500. Anal. Calcd for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 77.67; H, 5.10; N, 3.78.

4-[2(*E*)-(4,5-Diphenyl-2-oxo-4-oxazolin-3-yl)ethenyl]phenol (20). ^1H NMR (300 MHz, DMSO-d_6) δ: 9.54 (s, 1H), 7.59–7.54 (m, 5H), 7.32–7.17 (m, 5H), 7.01 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 14.7 Hz, 1H), 6.66 (d, J = 8.5 Hz, 2H), 6.42 (d, J = 14.7 Hz, 1H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 157.60 (s), 151.67 (s), 133.73 (s), 131.10 (d), 130.75 (d), 129.91 (d), 129.03 (d), 128.37 (d), 127.41 (d), 126.52 (s), 125.89 (s), 124.45 (d), 122.90 (s), 121.35 (d), 117.22 (d), 115.97 (d). IR (KBr) cm^{-1}: 3376, 1730, 1384, 1174. MS (CH_4 CI) *m/e*: 356 (MH^+), 355 (M^+), 310, 263, 105, 91. UV (95% EtOH): λ_1 214 nm, ϵ_1 = 2710; λ_2 306 nm, ϵ_2 = 28 600; λ_3 314 nm, ϵ_3 = 29 000. Anal. Calcd for $C_{23}H_{17}NO_3 \cdot {}^1/_8H_2O$: C, 77.24; H, 4.86; N, 3.92. Found: C, 77.10; H, 4.76; N, 3.87.

General Deprotection. 2-(*p*-Tolyl)ethylamine·HCl (25). Oxazolone **17** (0.500 g, 1.41 mmol) was suspended in 20 mL of 95% EtOH + 4 mL of HOAc, and 150 mg of 10% Pd/C was added. The mixture was hydrogenated at 50 psi and 50 °C for 3 h, 50 mg of additional 10% Pd/C was added, and the mixture was hydrogenated for 1 h further. TLC indicated only the presence of bisbenzyl and 2-(*p*-tolyl)ethylamine. The mixture was filtered through Solka-floc, and the solvents were removed *in vacuo*. The residue was azeotroped with PhMe (2 × 25 mL), dissolved in 10 mL of EtOH, and acidified with ethanolic HCl. Excess EtOH was removed *in vacuo* and the residual solid suspended in 2 mL of EtOH and diluted with 25 mL of Et_2O. The resultant white solid was filtered under a stream of N_2 and dried to constant weight in a 70 °C vaccum oven to give 210 mg of pure 2-(*p*-tolyl)ethylamine·HCl **25**, 87% yield, as a white solid. This material was identical (^1H NMR, ^{13}C NMR, IR, mp) with that obtained *via* addition of ethereal HCl to Aldrich 2-(*p*-tolyl)-ethylamine base.

5-Bromo-1-tosylindole (30). NaH (0.312 g, 13 mmol, 1.3 eq.) was added in portions to 60 mL of dry DMSO at 25 °C under N_2. The reaction was cooled to 0 °C, 1.96 g of 5-bromoindole (10.0 mmol, 1 eq.) was added, and the mixture was again warmed to 25 °C. Et_2O (20 mL) was added and the resulting mixture stirred for 1.5 h. Upon cooling to 0 °C, 2.29 g of TsCl (12 mmol, 1.2 eq.) was added and the reaction then allowed to stir for 3 h at 25 °C. The reaction was then added to ice/H_2O, extracted wtih Et_2O, and dried (Na_2SO_4), and solvents were removed *in vacuo* to yield 3.3 g of a white solid. Recrystallization from Hex/EtOAc furnished 2.15 g, 61%, first crop only, of pure **30** as a colorless crystalline solid, mp 133-134 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.87 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 1.8 Hz, 1H), 7.56 (d, J = 3.7 Hz, 1H), 7.40 (dd, J = 8.8, 1.7 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 6.59 (d, J = 3.6 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 145.18 (s, C13), 134.79 (s, C10), 133.38 (s, C9), 132.35 (s, C8), 129.88 (d, C12 + C15), 127.45 (d, C2), 127.32 (d, C6), 126.67 (d, C11 + C16), 123.93 (d, C4), 116.65 (s, C5), 114.82 (d, C7), 108.19 (d, C3), 21.48 (q, C14). IR (KBr) cm^{-1}: 1440, 1371, 1169, 1121, 706, 575. MS (CH_4 CI) m/e: 350 (MH^+, 1 Br), 349 (M^+, 1 Br), 299, 271, 196, 155, 117. UV (95% EtOH): λ_1 218 nm, ϵ_1 = 35 900; λ_2 252 nm, ϵ_2 = 18 900. Anal. Calcd for $C_{15}H_{12}BrNO_2S$: C, 51.44; H, 3.45; N, 4.00. Found: C, 51.41; H, 3.29; N, 3.94.

3-[(*E*)-[2-(3-Pyridyl)ethenyl]]-4,5-diphenyl-2(3*H*)oxazolone (31). Into a 30-mL stainless steel bomb were placed a flat stir bar, 1.48 g of *N*-vinyloxazolone **3** (5.61 mmol, 1.1 eq.), 46 mg of $Pd(OAc)_2$ (0.20 mmol, 0.04 eq.), 1.42 g of (n-Bu)$_4$NCl·H_2O (5.10 mmol, 1.1 eq.), 1.08 g of $NaHCO_3$ (12.8 mmol, 2.5 eq.), 6 mL of DMF, and 0.491 mL of 3-bromopyridine (5.10 mmol, 1 eq.) in the order given. The mixture was stirred for 5 min at 25 °C, and the bomb was sealed and placed in a preequilibrated 120 °C oil bath behind a blast shield. After 24 h at 120 °C, the bomb was cooled to 0 °C and opened, and the contents were partitioned between H_2O and 1:1 CH_2Cl_2/EtOAc. The organic phase was washed with saturated NaCl and dried (Na_2SO_4), and the solvents were removed *in vacuo* to give a yellow solid. Chromatography on silica gel eluting with 1:1 CH_2Cl_2/EtOAc furnished 1.54 g, 89%, of pure 3-pyridyloxazolone as a yellow crystalline solid, mp 175–176 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.41–8.38 (m, 2H), 7.58–7.45 (m, 6H), 7.29-7.13 (m, 7H), 6.64 (d, J = 14.8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 151.75 (s), 148.28 (d), 147.44 (d), 134.82 (s), 132.32 (d), 131.33 (s), 130.70 (d), 130.55 (d), 129.77 (d), 128.47 (d), 128.21 (d), 126.89 (s), 126.04 (s), 124.61 (d), 123.35 (d), 121.63 (s), 120.86 (d), 115.80 (d). IR (KBr) cm^{-1}: 1761, 1640, 1378, 1260, 1060, 761, 744, 701, 694, 665. MS (CH_4 CI) *m/e*: 341 (MH^+), 340 (M^+), 295, 165, 104. Anal. Calcd for $C_{22}H_{16}N_2O_2$: C, 77.63, H, 4.74; N, 8.23. Found: C, 77.26; H, 4.76; N, 8.07.

3-[(*E*)-[2-(1-Tosyl-5-indolyl)ethenyl]]-4,5-diphenyl-2(3*H*)-oxazolone (32). Into a 30-mL stainless steel bomb were placed a flat stir bar, 2.10 g of bromide **30** (6.00 mmol, 1 eq.), 1.74 g of *N*-vinyloxazolone **3** (6.60 mmol, 1.1 eq.), 54 mg of $Pd(OAc)_2$ (0.24 mmol, 0.04 eq.), 1.67 g of (n-Bu)$_4$NCl·H_2O (6.00 mmol, 1 eq.), 1.27 g of $NaHCO_3$ (15.0 mmol, 2.5 eq.), and 7 mL of DMF in the order given. The bomb was stirred for 5 min at 25 °C, sealed, and placed in a preequilibrated 120 °C oil bath. After 24 h, the bomb was cooled to 0 °C and opened, the contents were partitioned between 1/2 saturated NaCl and EtOAc, and the aqueous phase was reextracted with EtOAc. The organic extracts were washed with saturated NaCl and dried (Na_2SO_4) and the volatiles removed *in vacuo* to yield 3.9 g of a yellow solid. This solid was dissolved in 1 L of boiling EtOH, Darco was added, and the mixture was heated for 5 min. The mixture was filtered through solka-floc and the filtrate again evaporated. This solid was recrystallized from EtOAc to yield 2.55 g, 80%, of pure **32** as a yellow crystalline solid, mp 184–186 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.86 (d, J = 8.6 Hz, 1H), 7.73 (d, J = 8.3 Hz, 2H), 7.59–7.19 (m, 15H), 7.14 (dd, J = 8.7, 1.4 Hz, 1H), 6.60 (d, J = 14.9 Hz, 1H), 6.57 (d, J = 4.3 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 152.00 (s), 144.92 (s), 135.02 (s), 134.04 (s), 131.05 (s), 130.79 (s), 130.73 (d), 130.34 (d), 129.78 (d), 129.64 (d), 128.44 (d), 128.05 (d), 127.13 (s), 126.65 (d), 126.43 (s), 124.60 (d), 122.31 (d), 121.94 (s), 120.22 (d), 118.90 (d), 113.60 (d), 108.94 (d), 21.45 (q). IR (KBr) cm^{-1}: 1759, 1372, 1174, 1131, 675, 592, 538. MS (CH_4 CI) *m/e*: 533 (MH^+), 532 (M^+), 378, 333. UV (95% EtOH): λ_1 228 nm, ϵ_1 = 29 900; λ_2 262 nm, ϵ_2 = 18 300; λ_3 311 nm, ϵ_3 = 29 900. Anal. Calcd for $C_{32}H_{24}N_2O_4S \cdot {}^1/_2H_2O$: C, 70.96; H, 4.65; N, 5.17. Found: C, 71.09; H, 4.46; N, 5.19.

1-Tosyl-5-(2-aminoethyl)-2,3-dihydro-1*H*-indole (33). To a suspension of 0.500 g of oxazolone **32** (0.939 mmol) in 20 mL of 95% EtOH and 5 mL of glacial HOAc was added 200 mg of 10% Pd/C and the mixture hydrogenated at 50 psi and 50 °C for 4 h. TLC analysis indicated incomplete reaction; thus, an additional 200 mg of 10% Pd/C was added and hydrogenated as before to a single spot (4 h). The mixture was filtered through solka-floc and the filtrate stripped *in vacuo*. The residue was azeotroped with PhMe, dissolved in 50 mL of EtOH, acidified with ethanolic HCl, and again stripped *in vacuo* to a white solid. This solid was suspended in 5 mL of EtOH, diluted with 200 mL of Et_2O, and filtered. After being dried to constant weight in a 70 °C vacuum oven, the material was recrystallized from EtOH to give 227 mg (69%) of pure indoline **33** as a colorless crystalline solid, mp 165–167 °C. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.04 (s, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.38–7.32 (m, 3H), 7.04–7.01 (m, 2H), 3.83 (t, J = 8.4 Hz, 2H), 3.35–3.31 (m, 2H), 2.87–2.73 (m, 6H), 2.30 (s, 3H). ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 144.58 (s), 140.38 (s), 133.37 (s), 133.18 (s), 132.76 (s), 130.22 (d), 128.12 (d), 127.50 (d), 126.03 (d), 114.34 (d), 50.36 (t), 32.57 (t), 27.48 (t), 21.29 (q). MS (CH_4 CI) *m/e*: 316 (MH^+), 300 ($MH^+ - NH_2$), 299, 286, 132. UV (95% EtOH): λ_1 204 nm, ϵ_1 = 30 000; λ_2 222 nm, ϵ_2 = 12 800; λ_3 237 nm, ϵ_3 = 8000. Anal. Calcd for

$C_{17}H_{20}N_2O_2S\cdot HCl\cdot H_2O$: C, 55.05; H, 6.25; N, 7.55. Found: C, 55.40; H, 5.91; N, 7.46.

2-[(*E*)-[2-(3-Fluorophenyl)ethenyl]]-1*H*-isoindole-1,3(2*H*)-dione (35). For general experimental procedure see **36** below. Compound **35** prepared in 29% yield. Yellow solid, mp 186.5–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93–7.91 (m, 2H), 7.81-7.77 (m, 2H), 7.64 (d, J = 15.1 Hz, 1H), 7.39–7.15 (m, 4H), 6.99–6.96 (m, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 166.15 (s), 163.00 (d, ^1J (^{13}C–^{19}F) = 245 Hz), 138.27 (s), 134.53 (d), 131.43 (s), 130.05 (d), 123.63 (d), 121.94 (d), 118.67 (d, ^3J(^{13}C–^{19}F) = 2.3 Hz), 118.46 (d), 114.25 (d, ^2J(^{13}C–^{19}F) = 21.1 Hz), 112.50 (d, ^2J(^{13}C–^{19}F) = 22.6 Hz). IR (KBr) cm^{-1}: 1715, 1651, 1609, 1582, 1383. MS (CH_4 CI) m/e: 268 (MH^+), 267 (M^+), 248, 148, 120. UV (95% EtOH): λ_1 218 nm, ϵ_1 = 31 200; λ_2 278 nm, ϵ_2 = 28 400; λ_3 284 nm, ϵ_3 = 29 600; λ_4 198 nm, ϵ_4 = 16 100; λ_5 314 nm, ϵ_5 = 10 300. Anal. Calcd for: $C_{16}H_{10}O_2FN\cdot{}^1/_4H_2O$: C, 70.72; H, 3.89; N, 5.15. Found: C, 70.78; H, 3.57; N, 5.09.

2-[(*E*)-[2-(2-Methoxyphenyl)ethenyl]]-1*H*-isoindole-1,3-(2*H*)-dione (36). In a 30-mL stainless steel bomb were placed a flat stir bar, 8.5 mL of MeCN, 1.01 g of 2-iodoanisole (4.23 mmol), 39 mg of $Pd(OAc)_2$ (0.17 mmol, 0.04 eq.), 0.159 g of (o-Tol)$_3$P (0.51 mmol, 0.12 eq.), 0.388 mL of TEA (5.29 mmol, 1.25 eq.), and 0.81 g of *N*-vinylphthalimide (4.65 mmol, 1.1 eq.) in the order given. The contents were stirred for 5 min at 25 °C and sealed, and the bomb was heated for 48 h at 95 °C behind a blast shield. The bomb was then cooled to 0 °C, the contents were partitioned between H_2O and EtOAc, and the aqueous phases were reextracted with EtOAc. The organic phase was washed with satd NaCl (2×) and dried (Na_2SO_4), and the solvents were removed *in vacuo* to yield a brown solid. The material was chromatographed on silica gel eluting with CH_2Cl_2 to give 95 mg of pure α-arylated material **37** (8%) and 769 mg of mixed fractions containing **36** and unreacted *N*-vinylphthalimide. These latter mixed fractions were then rechromatographed on silica gel which was packed with hexane, yet eluted with 1:1 Hex/CH_2Cl_2 to give 0.256 g of *N*-vinylphthalimide (35%), followed by 0.42 g of pure β-arylated material **36** (41%). Data for **36**. Yellow needles, mp 151.5–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91-7.84 (m, 3H), 7.76–7.74 (m, 2H), 7.49–7.42 (m, 2H), 7.26–7.23 (m, 1H), 6.99–6.90 (m, 2H), 3.91 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 166.33 (s), 156.88 (s), 134.28 (d), 131.58 (s), 128.56 (d), 126.99 (d), 124.64 (s), 123.39 (d), 120.58 (d), 118.28 (d), 116.20 (d), 110.68 (d), 55.34 (q). IR (KBr) cm^{-1}: 1714, 1640, 1464, 1383, 1244. MS (CH_4 CI) m/e: 280 (MH^+), 279 (M^+), 131, 119, 105. UV (95% EtOH): λ_1 217 nm, ϵ_1 = 36 800; λ_2 234 nm, ϵ_2 = 16 600; λ_3 272 nm, ϵ_3 = 21 900; λ_4 280 nm, ϵ_4 = 25 600; λ_5 317 nm, ϵ_5 = 15 100. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.85; H, 4.62; N, 4.98.

2-[1-(2-Methoxyphenyl)ethylidene]-1*H*-isoindole-1,3(2*H*)-dione (37). For experimental procedure see **36** above. Data for **37**. White solid, mp 204–204.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90–7.87 (m, 2H), 7.76–7.73 (m, 2H), 7.43 (d, J = 7.4 Hz, 1H), 7.30 (t, J = 7.3 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.81 (s, 1H), 5.52 (s, 1H), 3.56 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 166.88 (s), 156.32 (s), 135.31 (s), 134.01 (d), 131.84 (s), 129.99 (d), 129.76 (d), 124.87 (s), 123.44 (d), 120.73 (d), 117.62 (t), 110.65 (d), 55.46 (q). IR (KBr) cm^{-1}: 1715, 1464, 1378, 1261, 1132. MS (CH_4 CI) m/e: 280 (MH^+), 279 (M^+), 161, 132, 105. UV (95%) EtOH): λ_1 217 nm, ϵ_1 = 36 000; λ_2 231 nm, ϵ_2 = 19 800; λ_3 289 nm, ϵ_3 = 3300. Anal. Calcd for $C_{17}H_{13}NO_3\cdot 0.35H_2O$: C, 71.49; H, 4.83; N, 4.90. Found: C, 71.65; H, 4.61; N, 4.85.