C−C versus C−N Annulation Reactions of 2-Alkyl-2-oxazolines and 2-Alkyl-2-thiazolines: A Simple Synthesis of Novel 3-Aminoindene, Phthalimidine, Pyrrolidine, and Piperidine Derivatives

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Dedicated to Professor José Barluenga on the occasion of his 60th birthday

Keywords: Annulation / Synthetic methods / Oxygen heterocycles / Nitrogen heterocycles / Pyrrolidines

The effect of various aromatic and aliphatic dielectrophiles on the lithium azaenolates of 2-alkyl-2-oxazolines and 2-alkyl-2-thiazolines has been examined. This effect varies greatly, depending on the nature of the dielectrophile used. 3-Aminoindene (**3**) and 3-alkylidenephthalimidine (**4**–**5**) derivatives were formed as a result of the reactions with dielectrophiles derived from *ortho*-substituted benzonitriles. Similarly, 2-alkylidenepyrrolidine (**7**) and 2-alkylidenepiperidine (**8**) derivatives were obtained in high yields from 2-alkyl-2-oxazolines or 2-alkyl-2-thiazolines and aliphatic dielectrophiles derived from ω-haloalkyldiphenylacetonitrile. C–C versus C–N annulation reactions are discussed.

Introduction

The use of heterocycles as useful tools in organic synthesis has been known for several decades. Metalated Δ^2-thiazolines were reported some twenty-five years ago,[1] and metalation of other heterocycles (thiazoles, oxadithiazoles, etc.), leading to other heterocyclic products, has also been described.[2] Furthermore, Δ^2-thiazolines, Δ^2-imidazolines, and, most notably, Δ^2-oxazolines have shown great synthetic potential both as protecting groups for carboxylic acids and as chiral auxiliaries in asymmetric reactions.[3] These versatile heterocycles have not only been used successfully as chiral ligands in metal-catalyzed asymmetric synthesis[3d] and lithiation/substitution sequences,[3b] but they have also been transformed into nitrogen-containing heterocycles[3e,3f] and other functional groups.[3b] We have extended the versatility of 2-alkyl-2-oxazolines and 2-alkyl-2-thiazolines by devising a practical route to masked β-dehydroamino acids.[4] These new derivatives have recently been used in the development of a simple, two-step strategy for obtaining β-amino acids through chemoselective reduction of the enamino moiety and deprotection of the carboxylic function,[5] thus underscoring their usefulness. Indeed, while this manuscript was under preparation, a first report regarding their application as chiral ligands for asymmetric catalysis was published.[6]

Phthalimidines are another important class of compounds that have been used as starting materials for the preparation of heterocyclic systems and pharmaceuticals.[7] Although several methods for the synthesis of this class of derivatives have been developed,[8] one of the most common strategies for constructing the isoindolone ring system[9] is the use of the annulation reaction of *ortho*-substituted aryllithium reagents to imines.[9,10] One limitation of this methodology, which has also been applied to the synthesis of 3-aminoindene derivatives,[9b,11] is its tendency to produce poor yields. Two improved, milder procedures have been described recently, making use either of a Lewis acid (e.g. BF_3/diethyl ether) to promote the final annulation reaction,[9b] or of intramolecular cyclization of *N*-acyl-2-lithiobenzamides.[12] In a similar manner, 3-aminoindene derivatives have been obtained in two- or three-step sequences, starting from 2-halogen-substituted aryl nitriles or 2-(cyanoaryl)arylacetonitriles.[9b,11,13] These interesting systems are key intermediates in the synthesis of 1-amino-3-aryl indanes, which show potential antipsychotic activity.[13b]

The final compounds discussed here — namely pyrrolidine and piperidine derivatives — belong to an important group of substances, most of which have pharmacological properties. In fact, their framework is incorporated in the structure of a significant number of natural products. Nitrogen-bearing heterocyclic compounds such as lactam or thiolactam derivatives and cyclic imines have been the most frequently used starting materials for synthesizing these systems.[14] In this area, Rapoport has developed a new strategy to obtain bicyclic α-amino acids from 2-alkylidenepyrrolidines, prepared by treatment of pyroglutamic acid derivatives with α-haloesters.[15] As well as this, 4-halobutanoni-

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triles and related compounds have proved, when treated with zinc or magnesium enolates, to be suitable starting materials for the synthesis of pyrrolidinylidene acetates.[16] Other alternative methodologies starting from cyclic imines and activated carbonic acid derivatives have been reported very recently.[17]

In this report, we describe the behavior of the azaenolates of 2-alkyl-2-oxazolines and 2-alkyl-2-thiazolines **1** (Figure 1) in addition-cyclization reactions with dielectrophiles derived from *ortho*-substituted benzonitriles **2** (**2a**: Y = CH_2Br; **2b**: Y = CN; **2c**: Y = CO_2Me) as a synthetic approach to 3-aminoindene (**3**) and 3-alkylidenephthalimidine (**4**; Z = NH, and **5**: Z = O) derivatives (*Routes a* and *b*, Scheme 1). We have compared this reactivity with that of aliphatic dielectrophiles derived from ω-haloalkyldiphenylacetonitrile **6**, as this process provides expeditious synthetic routes to new 2-alkylidenepyrrolidine (**7**; $n = 1$) and 2-alkylidenepiperidine (**8**; $n = 2$) derivatives (*Route c*, Scheme 1). Since the structure of the final products is strongly affected by the nature of the starting dielectrophile, the behavior of these systems has been evaluated separately.

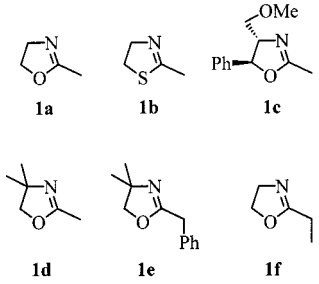
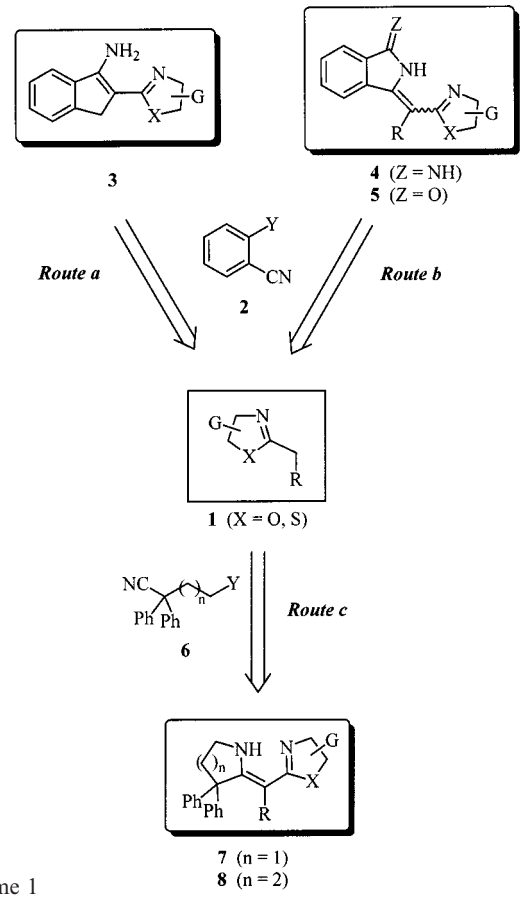
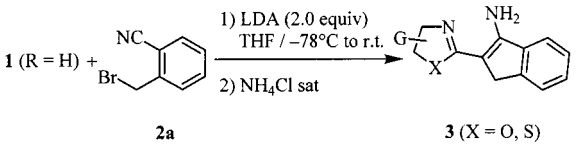


Figure 1. 2-Alkyl-2-oxazolines and 2-alkyl-2-thiazolines **1** used as starting materials to generate the azaenolates



Scheme 1



Scheme 2

Results and Discussion

Synthesis of 3-Aminoindene and Phthalamidine Derivatives

The reactivity of α-metalated heterocycles **1** with 2-cyano-benzyl bromide **(2a)** was studied first (Scheme 2). Treatment of a THF solution of 2-methyl-2-oxa(thia)zolines **1** (R = H) with 2.0 equiv. of LDA at −78 °C and subsequent addition of 1.0 equiv. of nitrile **2a** afforded spectroscopically pure 3-aminoindene derivatives **3** in overall yields of 65−77%, after 6−10 h at room temperature.[18] The results are summarized in Table 1 (entries 1, 4, and 7).

The structures of compounds **3** were deduced from their NMR spectroscopic data. For example, the most characteristic features of the ^1H NMR spectrum of **3a** were two singlets at δ = 3.57 (s, 2 H) and 5.88 (br s, 2 H), which correspond to the methylene group in the indene ring and the amino group, respectively, and also a lack of signals in the region of vinylic protons (*C*−*N* alkylation, vide infra). The formation of compounds **3** can be explained by assuming an initial addition of the lithium azaenolate of **1** to nitrile **2a**, followed by intramolecular *C*−*C* alkylation (Figure 2, Y = CH_2Br); an alternative explanation involves the initial α-alkylation reaction of **1** followed by a Thorpe−Ziegler-type cyclization to give compounds **3**.

Table 1. 3-Aminoindene (**3**), 3-alkylidenephthalimidine (**4**−**5**) and benzonitrile derivatives (**9**) from 2-alkyl-2-oxa(thia)zolines (**1**) and nitriles (**2**)

Entry	1[a]	2[b]	Product	Yield [%][c]
1	**a**	**a**	**3a**	65
2	**a**	**b**	**4a** (*Z*)	73
3	**a**	**c**	**5a** (*Z*) + **9a**	87[d]
4	**b**	**a**	**3b**	70
5	**b**	**b**	**4b** (*Z*)	60
6	**b**	**c**	**9b**	83
7	**c**	**a**	**3c**	77
8	**c**	**c**	**9c**	65
9	**d**	**b**	**4c** (*Z*)	70
10	**e**	**b**	**4d** (*Z*)	81

[a] See Figure 1. − [b] **2a**: Y = CH_2Br; **2b**: Y = CN; **2c**: Y = CO_2Me. − [c] Isolated yield after purification. − [d] Overall yield for **5a** (*Z*) + **9a**.

We next explored the behavior of systems **1** toward benzonitriles with electron-withdrawing groups in the *ortho*-

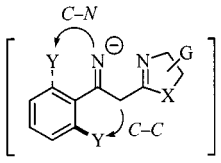
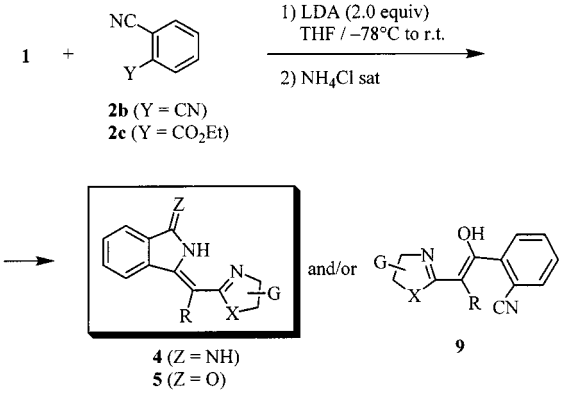


Figure 2. Proposed intermediate and competitive pathways (C−C vs. C−N bond formation); G = oxa(thia)zoline substitution pattern



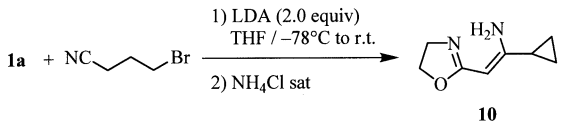
Scheme 3

position, as is the case for **2b** and **2c** (Scheme 3). The reaction conditions were identical to those described above for **2a**, but a different outcome was obtained depending on the structure of nitrile **2**. Thus, when phthalonitrile **2b** was used, the 3-alkylidenephthalimidines **4** were synthesized as their (*Z*) isomers in high yields, as shown in Scheme 3 and Table 1 (entries 2, 5, 9, and 10). A *tandem* addition/*C*−*N* heteroannulation reaction (Figure 2, Y = CN) easily accounts for the formation of compounds **4**. In this case, then, *C*−*C* cyclization did not occur.

In contrast, when **2c** was treated with the azaenolate of 2-methyl-2-oxazoline **(1a)**, a 2:3 mixture of the (*Z*) isomer of isoindol-1-one **(5a)** and compound **9a** was obtained in an overall yield of 87% (see Table 1, entry 3 and Scheme 3). The two compounds were easily separated by flash chromatography and identified by means of spectroscopic methods (IR, NMR, and MS). However, when heterocycles **1b** and **1c** were used as starting materials, the reaction did not yield isoindolones **5**, but rather benzonitrile derivatives **9** as the only products (Table 1, entries 6 and 8). These results can be accounted for in terms of a competitive reaction between the azaenolate of **1** and the two electrophilic groups in nitrile **2c**. Lastly, the (*Z*) configuration assigned to compounds **4** and **5** was corroborated by NOE experiments, which showed peak enhancements of the 4-H aromatic hydrogens by the vinylic hydrogens (6.0% for **4a** and 6.6% for **5a**).

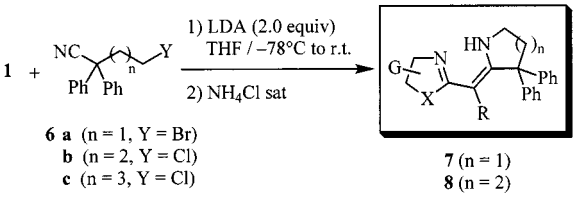
Synthesis of Pyrrolidine and Piperidine Derivatives

Next we examined the reactivity of metalated 2-alkyl-2-oxa(thia)zolines towards aliphatic nitriles bearing a second electrophilic center in the molecule. In an initial experiment, 4-bromobutyronitrile was allowed to react with the lithiated oxa(thia)zoline derivatives under the conditions previously described. Only complex mixtures of products were obtained, however, with **10**[4c] being the main compound produced when starting from **1a** (Scheme 4). Compound **10** is formed by an acid-base reaction between the azaenolate anion and the α-hydrogen of the nitrile, followed by an intramolecular cyclization that generates cyclopropanenitrile, which is the true electrophilic species participating in the reaction.[19]



Scheme 4

This result prompted us to employ ω-halo-α,α-dialkylated nitriles in order to avoid the α-deprotonation that leads to the cyclization of the nitriles. Thus, treatment of 2-alkyl-Δ^2-oxa(thia)zoline azaenolates with nitriles **6** under the conditions previously reported resulted in the formation of derivatives of 2-alkylidenepyrrolidine **7** (*n* = 1) or 2-alkylidenepiperidine **8** (*n* = 2) (Scheme 5).



Scheme 5

Compounds **7** and **8** were prepared in excellent yields, as reported in Table 2. As expected, the reactions took place more rapidly when the dielectrophile bore a Br atom instead of a Cl atom as a leaving group. The formation of five-membered rings did not depend on the nature of the starting azaenolate, as the corresponding pyrrolidine **7** could be synthesized starting from either oxazoline or thiazoline azaenolates, even when R ≠ H. In contrast, to form the six-membered rings **8**, the oxazoline-derived azaenolates had to be heated to reflux in THF in the presence of the nitrile **6b** for several hours (15−17 h) to make the reaction go to completion, while use of thiazoline azaenolates produced no reaction (Table 2, entry 6). The preparation of seven-

Table 2. Synthesis of 2-alkylidene-pyrrolidine (**7**) and 2-alkylidene-piperidine (**8**) derivatives

Entry	**1**	X	R	**6**	Product	Yield [%][a]
1	**a**	O	H	**a**	**7a**	75
2	**b**	S	H	**a**	**7b**	85
3	**c**	O	H	**a**	**7c**	85
4	**f**	O	Me	**a**	**7d**	72
5	**a**	O	H	**b**	**8a**	94
6	**b**	S	H	**b**	–	–
7	**c**	O	H	**b**	**8b**	91
8	**a**	O	H	**c**	–	–

[a] Isolated yield after purification.

membered rings (n = 3, azepines) could not be achieved, even when starting from oxazoline-derived azaenolates and heating the reaction mixture for more than 48 h (Table 2, entry 8).

Flash chromatography and/or crystallization were used to purify compounds **7−8**; their structures were then determined by means of ^{1}H and ^{13}C NMR spectroscopy and HRMS. In the case of compound **7b**, X-ray analysis was used to confirm its structure (Table 2, entry 2).[20] A perspective ORTEP plot of **7b** is given in Figure 3. The X-ray data point to a strong intramolecular hydrogen bond between N(8) and H(100) (N8−H100, 2.11 Å), which indicates the formation of a six-membered ring.[21] In addition, the dihedral angles C5−C6−C7−N8 and N1−C5−C6−C7 (−1.2° and −1.5°, respectively) indicate that both oxazoline and pyrrolidine rings are in the same plane, which suggests the existence of a π-delocalized system that includes the N(8)−H(100) bond.

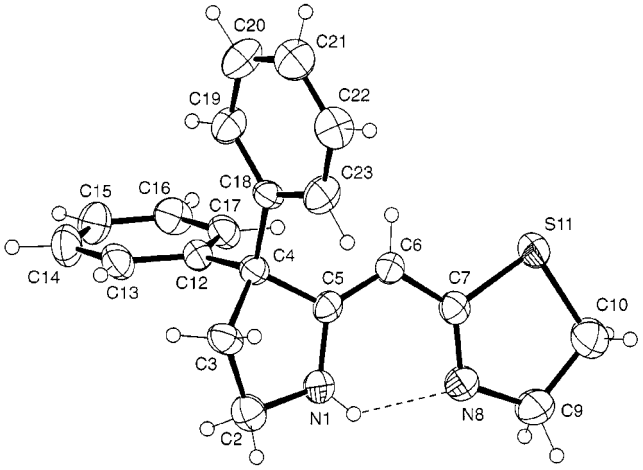
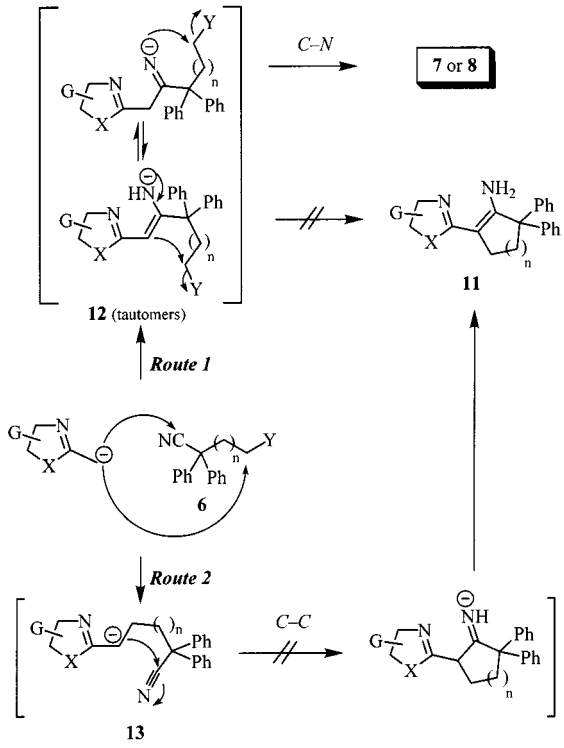


Figure 3. X-ray ORTEP drawing of **7b**, showing the intramolecular N(8)···H interaction; the numbering system is arbitrary

The mechanism proposed to explain the formation of compounds **7** (**8**) rather than the expected **11** is based on the ambivalent character of the dielectrophile.[22] Thus, two possible routes can be considered (Scheme 6). *Route 1* (Scheme 6) involves an initial attack of the azaenolate on the cyano group to form intermediate **12**, which can exist in two tautomeric species and which might go on to give a cyclic β-enaminoester derivative **11** (*C−C* bond formation) or, alternatively, to either 2-alkylidenepyrrolidine **7** or 2-alkylidenepiperidine **8** (*C−N* bond formation). On the other hand, *Route 2* (Scheme 6) involves an initial halogen displacement leading to intermediate **13**, which in the final annulation step can lead only to compound **11**, following a pathway similar to that reported for the synthesis of β-enaminonitriles from diphenylacetonitrile.[23] Taking the above-mentioned results into account, it is clear that the reaction follows *Route 1*, with the formation of a *C−N* bond in the final stage.

Conclusion

In conclusion, we have shown that new 3-aminoindene and 3-alkylidenephthalimidines containing electron-withdrawing groups at the 2-position can be obtained *efficiently* by *C−C* or *C−N* annulation of the appropriate aromatic dielectrophile with 2-alkyl-2-oxa(thia)zolines. Furthermore, 2-alkylidenepiperidine or 2-alkylidene-pyrrolidine derivatives can be prepared in high yields by treating metalated 2-alkyl-2-oxa(thia)zolines with aliphatic dielectrophiles derived from ω-haloalkyldiphenylacetonitrile.



Scheme 6

Experimental Section

General Remarks: THF was distilled under argon from sodium/benzophenone ketyl as a drying agent. Diisopropylamine, used to generate LDA, was refluxed over KOH, distilled, and stored under argon at 4 °C. Solvents used in extractions and in chromatographic columns were distilled prior to use. Oxa(thia)zolines **1** and nitriles **2** and **6a** were commercially available and were used without further purification. Nitriles **6b** and **6c** were prepared from diphenylacetonitrile and 1-bromo-3-chloropropane and 1-bromo-4-chlorobutane, respectively, following methods described in the literature.[24] Complete descriptions of the equipment and analytical methods used for the synthesis and characterization of the described compounds have been reported previously.[4b,4c]

General Procedure for the Synthesis of 3-Aminoindene Derivatives 3: *n*-Butyllithium (7.0 mmol, 2.5 M in hexane) was added dropwise to a solution of diisopropylamine (7.0 mmol) in dry THF (20 mL) at −20 °C. After being stirred for 30 min, the reaction mixture was cooled to −78 °C and a solution of compound **1a−c** (3.5 mmol) in dry THF (20 mL) was added dropwise. The reaction mixture was kept at −78 °C for 45 min to 1 h. A solution of *ortho*-(bromomethyl)benzonitrile (**2a**) (0.71 g, 3.6 mmol) in dry THF (20 mL) was then added at that temperature and the reaction was stirred until it reached room temperature. TLC was then used to monitor the reaction until completion (about 4 h). An aqueous, saturated

NH_4Cl solution was then added, and the mixture was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed several times with saturated brine (20 mL each time) and dried (Na_2SO_4). Solvents were evaporated under reduced pressure to yield solid residues that were rinsed with hexane/ethanol mixtures, filtered, and then recrystallized from a hexane/chloroform mixture. Purification was carried out as indicated in each case.

2-(4,5-Dihydro-1,3-oxazol-2-yl)-1*H*-3-indenamine (3a): Recrystallization (*n*-hexane/$CHCl_3$ 4:1) gave a white solid (0.45 g, 65%). − m.p. 130−132 °C. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.57 (s, 2 H), 4.00 (t, *J* = 8.5 Hz, 2 H), 4.27 (t, *J* = 8.5 Hz, 2 H), 5.88 (br s, 2 H), 7.30−7.50 (m, 4 H). − ^{13}C NMR ($CHCl_3$, TMS, 62.8 MHz): δ = 35.1 (t), 54.5 (t), 66.4 (t), 96.5 (s), 118.4 (d), 124.6 (d), 126.4 (d), 127.6 (d), 139.0 (s), 143.8 (s), 151.4 (s), 164.9 (s). − HRMS (EI) for $C_{12}H_{12}N_2O$: calcd. 200.0949; found 200.0955.

2-(4,5-Dihydro-1,3-thiazol-2-yl)-1*H*-3-indenamine (3b): Recrystallization (*n*-hexane/$CHCl_3$ 4:1) gave a light brown solid (0.53 g, 70%). − m.p. 126−128 °C. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 7.42−7.30 (m, 4 H), 6.20 (br s, 2 H), 4.37 (t, *J* = 8.0 Hz, 2 H), 3.55 (s, 2 H), 3.24 (t, *J* = 8.0 Hz, 2 H). − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 165.9 (s), 149.7 (s), 143.9 (s), 139.2 (s), 127.5 (d), 126.5 (d), 124.5 (d), 118.6 (d), 103.1 (s), 64.6 (t), 36.8 (t), 33.0 (t). − HRMS (EI) for $C_{12}H_{12}N_2S$: calcd. 216.0721; found 216.0725.

2-[(4*S*,5*S*)-(4,5-Dihydro-1,3-oxazol-2-yl)-4-methoxymethyl-5-phenyl]-1*H*-3-indenamine (3c): Recrystallization (*n*-hexane/$CHCl_3$ 6:1) gave a white solid (0.86 g, 77%). − m.p. 51−53 °C. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.46 (s, 3H), 3.50−3.80 (m, 4 H), 4.31 (m, 1 H), 5.37 (d, *J* = 6.6 Hz, 1 H), 5.91 (br s, 2 H), 7.30−7.50 (m, 9 H). − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 33.5 (t), 58.7 (q), 73.9 (d), 74.7 (t), 81.7 (d), 96.3 (s), 117.8 (d), 123.9 (d), 125.0 (d), 125.7 (d), 127.0 (d), 127.3 (d), 128.1 (d), 128.7 (s), 138.5 (s), 141.1 (s), 144.0 (s), 164.5 (s). − $[\alpha]_D^{25}$ = +32.6 (*c* = 0.34, CH_2Cl_2). − HRMS (EI) for $C_{20}H_{20}N_2O_2$: calcd. 320.1524; found 320.1521. − $C_{20}H_{20}N_2O_2$ (320.4): C 75.00, H 6.25, N 8.75; found C 74.81, H 6.12, N 8.58.

Phthalimidine (4), Isoindolone (5), and Benzonitrile (9) Derivatives. − General Procedure: These compounds were prepared by a procedure similar to that described above for compounds **3,** but using either 1,2-dicyanobenzene **2b** (0.46 g, 3.6 mmol) or methyl 2-cyanobenzoate **2c** (0.58 g, 3.6 mmol) as dielectrophiles. After aqueous workup and evaporation of the solvents, solid residues were purified by recrystallization, while oils were purified by flash chromatography.

3-[(*Z*)-1-(4,5-Dihydro-1,3-oxazol-2-yl)methylidene]-2,3-dihydro-1*H*-isoindol-1-imine (4a). Recrystallization (*n*-hexane/$CHCl_3$ 3:1) gave a dark brown solid (0.55 g, 73%). − m.p. 131−133 °C. − IR (KBr) $\tilde{\nu}$ = 3404, 3233, 1641, 1604 cm^{-1}. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.94 (t, *J* = 8.0 Hz, 2 H), 4.24 (t, *J* = 8.0 Hz, 2 H), 5.55 (s, 1 H), 7.46−7.70 (m, 4 H). − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 54.5 (t), 66.8 (t), 84.1 (d), 120.7 (d), 121.9 (d), 130.2 (d), 131.2 (d), 136.0 (s), 146.3 (s), 161.6 (s), 164.7 (s); the signal corresponding to one C(s) around δ = 130 was not observed, probably due to overlap with other signals. − HRMS (EI) for $C_{12}H_{11}N_3O$: calcd. 213.0902; found 213.0898.

3-[(*Z*)-1-(4,5-Dihydro-1,3-thiazol-2-yl)methylidene]-2,3-dihydro-1*H*-isoindol-1-imine (4b): Flash chromatography (*n*-hexane/EtOAc 4:1) on silica gel gave a brown oil (0.48 g, 60%). − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.24 (t, *J* = 8.3 Hz, 2 H), 4.30 (t, *J* = 8.3 Hz, 2 H), 5.74 (s, 1 H), 7.20−7.90 (m, 4 H), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 33.4 (t), 64.5 (t), 99.9 (d), 120.6 (d), 121.9 (d), 130.0 (d), 131.0 (s), 131.1 (d), 136.3 (s), 145.0 (s), 162.9 (s), 165.4 (s). − HRMS (EI) for $C_{12}H_{11}N_3S$: calcd. 229.0673; found 229.0628.

3-[(*Z*)-1-(4,5-Dihydro-4,4-dimethyl-1,3-oxazol-2-yl)methylidene]-2,3-dihydro-1*H*-isoindol-1-imine (4c): Flash chromatography (*n*-hexane/EtOAc 4:1) on silica gel gave a brown oil (0.59 g, 70%). − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 1.22 (s, 6 H), 3.86 (s, 2 H), 5.45 (s, 1 H), 7.30−7.60 (m, 4 H). − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 28.4 (q), 67.0 (s), 76.5 (t), 84.2 (d), 120.3 (d), 121.5 (d), 129.8 (d), 130.8 (d), 135.7 (s), 146.1 (s), 161.6 (s), 161.9 (s); the signal corresponding to one C(s) around δ = 130 was not observed, probably due to overlap with other signals. − HRMS (EI) for $C_{14}H_{15}N_3O$: calcd. 241.1215; found 241.1214.

3-[(*Z*)-1-(4,5-Dihydro-4,4-dimethyl-1,3-oxazol-2-yl)-1-phenylmethylidene]-2,3-dihydro-1*H*-isoindol-1-imine (4d): Recrystallization (*n*-hexane/$CHCl_3$ 5:1) gave a brown solid (0.90 g, 81%). − m.p. 56−58 °C. − IR (KBr) $\tilde{\nu}$ = 3390, 3250, 1625 cm^{-1}. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 1.31 (s, 6 H), 3.82 (s, 2 H), 6.13 (d, *J* = 8.0 Hz, 1 H), 7.07 (t, *J* = 7.8 Hz, 1 H), 7.27−7.39 (m, 6 H), 7.64 (d, *J* = 7.8 Hz, 1 H). − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 28.7 (q), 67.4 (s), 78.2 (t), 102.9 (s), 121.4 (d), 124.5 (d), 128.2 (d), 128.7 (d), 129.4 (d), 130.6 (d), 131.1 (d), 132.1 (s), 135.0 (s), 135.7 (s), 143.9 (s), 162.1 (s), 163.1 (s). − HRMS (EI) for $C_{20}H_{19}N_3O$: calcd. 317.1528; found 317.1527. − $C_{20}H_{19}N_3O$ (317.4): C 75.69, H 6.03, N 13.24; found C 75.80, H 5.93, N 13.01.

3-[(*Z*)-1-(4,5-Dihydro-1,3-oxazol-2-yl)-1-phenylmethylidene]-2,3-dihydro-1*H*-isoindol-1-one (5a): Flash chromatography (*n*-hexane/EtOAc 3:1) on silica gel followed by recrystallization (*n*-hexane/$CHCl_3$ 3:1) gave a white solid (0.24 g, 32%). − m.p. 146−148 °C. − IR (KBr) $\tilde{\nu}$ = 3273, 1718 cm^{-1}. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.94 (t, *J* = 12.5 Hz, 2 H), 4.19 (t, *J* = 12.5 Hz, 2 H), 5.72 (s, 1 H), 7.37−7.68 (m, 4 H), 10.00 (br. s, 1 H, NH), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 54.5 (t), 66.9 (t), 88.9 (d), 120.5 (d), 123.7 (d), 129.8 (s), 130.6 (d), 132.4 (s), 136.4 (s), 143.3 (s), 163.7 (s), 168.0 (s). − HRMS (EI) for $C_{12}H_{10}N_2O_2$: calcd. 214.0742; found 214.0745. − $C_{12}H_{10}N_2O_2$: C 67.28, H 4.70, N 13.08; found C 67.27, H 4.51, N 12.87.

2-[(*Z*)-2-(4,5-Dihydro-1,3-oxazol-2-yl)-1-hydroxy-1-ethenyl]benzonitrile (9a): Flash chromatography (*n*-hexane/EtOAc 3:1) on silica gel followed by recrystallization (*n*-hexane/$CHCl_3$ 4:1) gave a white solid (0.36 g, 48%). − m.p. 115−117 °C. − IR (KBr) $\tilde{\nu}$ = 3267, 2330 cm^{-1}. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.80 (t, *J* = 8.4 Hz, 2 H), 4.50 (t, *J* = 8.4 Hz, 2 H), 5.42 (s, 1 H), 7.30−7.70 (m, 4 H), 9.90 (br. s, 1 H, OH), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 43.0 (t), 67.7 (t), 75.8 (d), 110.4 (s), 119.0 (s), 128.0 (d), 129.8 (d), 132.1 (d), 134.4 (d), 144.3 (s), 170.9 (s), 185.2 (s). − HRMS (EI) for $C_{12}H_{10}N_2O_2$: calcd. 214.0742; found 214.0740.

2-[(*Z*)-2-(4,5-Dihydro-1,3-thiazol-2-yl)-1-hydroxy-1-ethenyl]benzonitrile (9b): Recrystallization (*n*-hexane/$CHCl_3$ 4:1) gave a light brown solid (0.67 g, 83%). − m.p. 89−91 °C. − IR (KBr) $\tilde{\nu}$ = 3199, 2330 cm^{-1}. − ^{1}H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.25 (t, *J* = 7.6 Hz, 2 H), 3.91 (t, *J* = 7.6 Hz, 2 H), 5.75 (s, 1 H), 7.30−7.70 (m, 4 H), 10.64 (br. s, 1 H, OH), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 29.2 (t), 49.8 (t), 88.0 (d), 110.6 (s), 119.3 (s), 128.0 (d), 130.0 (d), 132.1 (d), 134.5 (d), 143.9 (s), 171.3 (s), 183.7 (s). − HRMS (EI) for $C_{12}H_{20}N_2OS$: calcd. 230.0514; found 230.0514. − $C_{12}H_{10}N_2OS$: C 62.59, H 4.38, N 12.16; found C 62.39, H 4.20, N 12.26.

2-{(*Z*)-2-[(4*S*,5*S*)-4,5-Dihydro-4-methoxymethyl-5-phenyl-1,3-oxazol-2-yl]-1-hydroxy-1-ethenyl}benzonitrile (9c): Recrystallization

(*n*-hexane/$CHCl_3$ 4:1) gave a white solid (0.76 g, 65%). − m.p. 139−141 °C. − IR (KBr) $\tilde{\nu}$ = 3424, 2331 cm^{-1}. − ^1H NMR ($CDCl_3$, TMS, 250 MHz): δ = 3.44 (s, 3 H), 3.53 (d, *J* = 5.2 Hz, 2 H), 4.00 (m, 1 H), 5.39 (d, *J* = 6.3 Hz, 1 H), 5.75 (s, 1 H), 7.10−7.90 (m, 9 H), 10.00 (br. s, 1 H, OH). − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 59.4 (q), 62.6 (t), 72.7 (d), 75.3 (d), 83.4 (d), 110.5 (s), 119.0 (s), 125.8 (d), 128.0 (d), 129.0 (d), 129.2 (d), 129.9 (d), 132.1 (d), 134.5 (d), 137.4 (s), 143.9 (s), 169.9 (s), 185.3 (s). − $[\alpha]_D^{25}$ = −14.18 (*c* = 0.67, CH_2Cl_2). − HRMS (EI) for $C_{20}H_{18}N_2O_3$: calcd. 334.1317; found 334.1307. − $C_{20}H_{18}N_2O_3$ (334.4): C 71.84, H 5.43, N 8.38; found C 71.61, H 5.25, N 8.21.

2-Alkylidenepyrrolidine (7) and 2-Alkylidenepiperidine (8) Derivatives. − General Procedure: *n*-Butyllithium (2.5 M in hexane, 3.7 mmol) was added dropwise under argon to a solution of diisopropylamine (3.7 mmol) in 10 mL of dry THF at −20 °C. After being stirred for 30 min, the reaction mixture was cooled to −78 °C and a solution of compound **1** (1.85 mmol) in THF (10 mL) was added. The resulting mixture was stirred at −78 °C for 1 h, and a solution of dielectrophile **6** (1.85 mmol) in THF (10 mL) was slowly added. The solution was allowed to come to room temperature, and the reaction was then monitored until completion (about 4 h) by TLC. To obtain 2-alkylidenepiperidines (**8**) it was necessary to reflux the reaction mixture for 15−17 h. An aqueous, saturated NH_4Cl solution was then added and the mixture was extracted with dichloromethane (3 × 40 mL). The combined organic layers were washed several times with saturated brine (20 mL each time) and dried (Na_2SO_4). Solvents were evaporated under reduced pressure to yield crude product: either **7** or **8**. Purification was carried out as indicated in each case.

2-[(*Z*)-3,3-Diphenyl-2-pyrrolidinylidenemethyl]-4,5-dihydro-1,3-oxazole (7a): Recrystallization (*n*-hexane/$CHCl_3$ 4:1) gave a white solid (0.42 g, 75%). − m.p. 119−121 °C. − ^1H NMR ($CDCl_3$, TMS, 250 MHz): δ = 2.73 (t, *J* = 6.2 Hz, 2 H), 3.40 (t, *J* = 6.2 Hz, 2 H), 3.92 (t, *J* = 8.8 Hz, 2 H), 4.13 (t, *J* = 8.8 Hz, 2 H), 4.18 (s, 1 H), 7.22−7.29 (m, 10 H), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 40.5 (t), 43.9 (t), 54.2 (t), 60.7 (s), 66.0 (t), 82.0 (d), 126.9 (d), 128.2 (d), 128.9 (d), 143.7 (s), 165.9 (s), 167.8 (s). − HRMS (EI) for $C_{20}H_{20}N_2O$: calcd. 304.1575; found 304.1568.

2-[(*Z*)-3,3-Diphenyl-2-pyrrolidinylidenemethyl]-4,5-dihydro-1,3-thiazole (7b): Recrystallization (*n*-hexane/$CHCl_3$ 4:1) gave a white solid (0.50 g, 85%). − m.p. 174−176 °C. − ^1H NMR ($CDCl_3$, TMS, 250 MHz): δ = 2.72 (t, *J* = 6.2 Hz, 2 H), 3.17 (t, *J* = 7.7 Hz, 2 H), 3.39 (t, *J* = 6.2 Hz, 2 H), 4.27 (t, *J* = 7.7 Hz, 2 H), 4.41 (s, 1 H), 7.20−7.30 (m, 10 H), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 33.8 (t), 41.3 (t), 44.6 (t), 61.5 (s), 64.6 (t), 86.0 (d), 127.5 (d), 128.8 (d), 129.5 (d), 144.2 (s), 164.5 (s), 167.7 (s). − HRMS (EI) for $C_{20}H_{20}N_2S$: calcd. 320.1347; found 320.1348. − $C_{20}H_{20}N_2S$ (320.5): C 75.00, H 6.25, N 8.80; found C 75.10, H 6.32, N 8.77.

(4*S*,5*S*)-2-[(*Z*)-3,3-Diphenyl-2-pyrrolidinylidenemethyl]-4-methoxymethyl-5-phenyl-4,5-dihydro-1,3-oxazole (7c): Flash chromatography (*n*-hexane/acetone 5:1) on alumina followed by recrystallization (*n*-hexane/$CHCl_3$ 4:1) gave a white solid (0.67 g, 85%). − m.p. 105−107 °C. − ^1H NMR ($CDCl_3$, TMS, 250 MHz): δ = 2.73−2.76 (m, 2 H), 3.45 (s, 3 H), 3.30−3.50 (m, 2 H), 3.52 (dd, *J* = 7.2 and 4.8 Hz, 1 H), 3.62 (dd, *J* = 7.2 and 4.8 Hz, 1 H), 4.18 (m, 1 H), 4.27 (s, 1 H), 5.13 (d, *J* = 6.6 Hz, 1 H), 7.22−7.37 (m, 15 H), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 40.9 (t), 44.5 (t), 60.0 (q), 61.5 (s), 74.9 (d), 76.4 (t), 77.7 (d), 82.8 (d), 126.3 (d), 127.5 (d), 128.4 (d), 128.8 (d), 129.2 (d), 129.4 (d), 142.2 (s), 144.2 (s), 144.3 (s), 166.7 (s), 167.9 (s). − $[\alpha]_D^{25}$ = +8.26 (*c* = 0.23, CH_2Cl_2). − HRMS (EI) for $C_{28}H_{28}N_2O_2$: calcd. 424.2150, found 424.2147. − $C_{28}H_{28}N_2O_2$: C 79.20, H 6.65, N 6.60; found C 74.79, H 6.37, N 8.64.

4,5-Dihydro-2-[(*Z*)-1-methyl-3,3-diphenyl-2-pyrrolidinylidenemethyl]-1,3-oxazole (7d): Flash chromatography (*n*-hexane/acetone 1:1) on silica gel gave a light brown oil (0.43 g, 72%). − ^1H NMR ($CDCl_3$, TMS, 250 MHz): δ = 1.15 (s, 3 H), 2.78 (t, *J* = 6.6 Hz, 2 H), 3.27 (t, *J* = 6.6 Hz, 2 H), 3.95 (t, *J* = 8.0 Hz, 2 H), 4.18 (t, *J* = 8.0 Hz, 2 H), 7.00−7.50 (m, 10 H), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 12.8 (q), 43.8 (t), 47.1 (t), 54.3 (t), 61.5 (s), 65.5 (t), 83.1 (s), 127.6 (d), 128.1 (d), 128.9 (d), 142.6 (s), 162.0 (s), 169.7 (s), − HRMS (EI) for $C_{21}H_{22}N_2O$: calcd. 318.1736; found 318.1732.

2-[(*Z*)-3,3-Diphenylhexahydro-2-pyridinylidenemethyl]-4,5-dihydro-1,3-oxazole (8a): Flash chromatography (*n*-hexane/EtOAc 5:1) on silica gel followed by recrystallization (*n*-hexane/$CHCl_3$ 5:1) gave a white solid (0.55 g, 94%). − m.p. 123−125 °C. − ^1H NMR ($CDCl_3$, TMS, 250 MHz): δ = 1.70 (m, 2 H), 2.59 (t, *J* = 6.2 Hz, 2 H), 3.30 (t, *J* = 5.5 Hz, 2 H), 3.90−4.10 (m, 5 H), 7.20−7.30 (m, 10 H). − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 19.0 (t), 33.4 (t), 40.3 (t), 53.1 (s), 54.0 (t), 64.9 (t), 82.4 (d), 126.4 (d), 127.8 (d), 128.9 (d), 144.9 (s), 162.7 (s), 167.0 (s). − HRMS (EI) for $C_{21}H_{22}N_2O$: calcd. 318.1732; found 318.1733. − $C_{21}H_{22}N_2O$ (318.4): C 79.20, H 6.96, N 8.80; found C 79.01, H 6.73, N 8.65.

(4*S*,5*S*)-2-[(*Z*)-3,3-Diphenylhexahydro-2-pyridinylidenemethyl]-4,5-dihydro-4-methoxymethyl-5-phenyl-1,3-oxazole (8b): Flash chromatography (*n*-hexane/EtOAc/MeOH 5:1:0.1) on silica gel followed by recrystallization (*n*-hexane/$CHCl_3$ 5:1) gave a white solid (0.74 g, 91%). − m.p. 167−169 °C. − ^1H NMR ($CDCl_3$, TMS, 250 MHz): δ = 1.58 (m, 2 H), 2.50 (t, *J* = 6.0 Hz, 2 H), 3.20 (t, *J* = 6.7 Hz, 2 H), 3.40 (s, 3 H), 3.41 (dd, *J* = 9.6 and 7.5 Hz, 1 H), 3.55 (dd, *J* = 9.6 and 4.7 Hz, 1 H), 3.91 (s, 1 H), 4.12 (m, 1 H), 5.00 (d, *J* = 6.6 Hz, 1 H), 7.10−7.25 (m, 15 H), 9.00 (br. s, 1 H, NH), − ^{13}C NMR ($CDCl_3$, TMS, 62.8 MHz): δ = 19.1 (t), 33.3 (t), 40.3 (t), 53.3 (s), 59.2 (q), 74.2 (d), 75.6 (t), 81.4 (d), 82.2 (d), 125.7 (d), 126.5 (d), 127.7 (d), 127.8 (d), 127.9 (d), 128.5 (d), 129.0 (d), 141.4 (s), 144.8 (s), 145.1 (s), 163.3 (s), 166.8 (s). − $[\alpha]_D^{25}$ = +17.7 (*c* = 0.05, CH_2Cl_2). − HRMS (EI) for $C_{29}H_{30}N_2O_2$: calcd. 438.2307; found 438.2293.

X-ray Crystallographic Study of 2-[(*Z*)-3,3-Diphenyl-2-azolanylidenmethyl]-4,5-dihydro-1,3-thiazole (7b):[20] $C_{20}H_{20}N_2S$, *M* = 320.4, colorless prismatic crystal, orthorhombic, space group *Pcab*, *a* = 11.248(1), *b* = 16.185(1), *c* = 18.214(2) Å, *V* = 3315.8(5) $Å^3$, *Z* = 8, *F*(000) = 1360, Mo-K_α radiation (λ = 0.7107 Å), μ = 1.96 cm^{-1}, D_c = 1.28 g·cm^{-3}, Enraf−Nonius CAD4 diffractometer: 2910 unique reflections, 1604 observed with $I > 2\sigma(I)$ criterion. Solving was by direct methods with the program SIR92,[25] and the non-hydrogen atoms were anisotropically refined with the XRAY76 system.[26] The hydrogen atoms were found in the Fourier difference map and refined with a fixed common thermal parameter; there were 268 refined parameters. In the final stages, an empirical weighting scheme was chosen in order to give no trends in Δ*F* vs. $<wΔ^2F>$ and vs. $<\sin\theta/\lambda>$ using the program PESOS.[27] Final *R* = 0.065 and *R*w = 0.069. Geometrical calculations were performed with PARST.[28]

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[20] Crystallographic data (excluding structure factors) for compound **7b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145492. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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