A Convenient Synthesis of 3-Aryl-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-ones

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Regioselective 1,3-dipolar cycloaddition of nitrile oxides **5a-c** to ethyl *o*-hydroxycinnamate (**3**) gave the corresponding ethyl *trans*-3-aryl-4,5-dihydro-5-(2-hydroxyphenyl)-4-isoxazolecarboxylates **6a-c**. Their structure was confirmed by reductive cleavage to **1** and compounds **9a-c**. Compounds **6a-c** afforded upon heating in the presence of pyridine the 3-aryl-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-ones **11a-c**. Compound **10c** was also isolated from **6c** and transformed thermally into **11c**.

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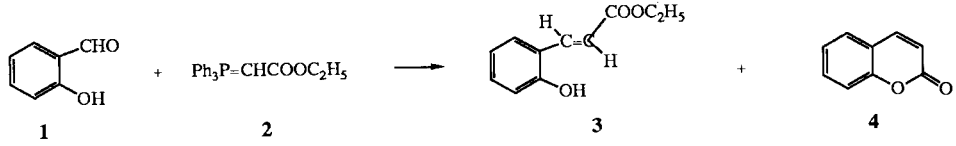
The biological importance of coumapyran has led to a considerable amount of synthetic work in the field of coumarins with 3,4-carbocyclic and 3,4-heterocyclic fused ring systems [1]. 1,3-Dipolar cycloadditions of diphenylnitrilimine [2] and *N*-iminopyridinium ylide [3] to coumarin, followed by dehydrogenation of the heterocyclic rings thus formed, were recently used in the preparation of the corresponding 3,4-fused pyrazole derivatives. In contrast to the above cycloadditions and to the well known preparation of isoxazolines and isoxazoles from alkenes and nitrile oxides [4], the reported [5,6] reactions of coumarin with a number of benzonitrile oxides resulted in the formation of the corresponding 3-benzhydroximoylcoumarins and not in that of fused coumarin 3,4-isoxazolines. The previously mentioned synthesis of some 4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-ones by reaction of 4-chloro-3-formylcoumarins [1,7] or 3-acyl-4-hydroxycoumarins [1,8,9] with hydroxylamine was recently put in doubt and even proved erroneous by Gelin *et al.* [10]. They prepared some of the compounds in question by treating ethyl 2-alkyl-(or aryl)-substituted 3-chromonecarboxylates with hydroxylamine, *via* the intermediate ethyl 3-alkyl(or aryl)-5-(2-hydroxyphenyl)-4-isoxazolecarboxylates of type **10** (Scheme 4). The formation of an analogous ethyl 2-pyrrolecarboxylate intermediate was recently [11] suggested in the preparation of the corresponding [1]benzopyrano[3,4-*b*]pyrrol-4-one. The also recently reported transformation of diethyl 3-(2-hydroxyphenyl)-4,5-dihydro-4,5-isothiazoledicarboxylate to ethyl 4-oxo-4*H*-[1]benzopyrano[4,3-*c*]isothiazole-3-carboxylate was suggested to proceed through a prior lactonization, followed by dehydrogenation of the isothiazoline ring rather, than *via* a prior dehydrogenation to the corresponding isothiazole intermediate [12].

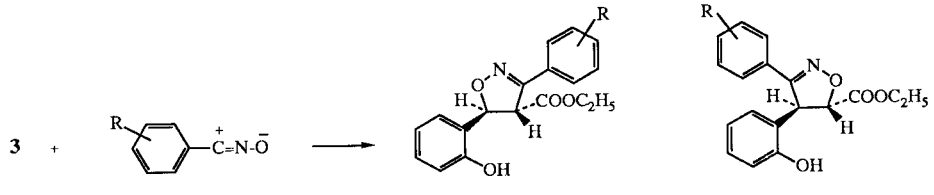
We now wish to report that the title [1]benzopyrano-[3,4-*d*]isoxazol-4-ones **11a-c** are easily prepared by heating in a xylene-pyridine solution the corresponding isoxazo-

Scheme 1



1 **2** **3** **4**

Scheme 2



5a-c **6a-c** **7a-c**

5, 6, 7 R

a H
b 4-CH_3
c 2,4,6-$(CH_3)_3$

lines **6a-c**, obtained through 1,3-dipolar cycloaddition of nitrile oxides **5a-c** to ethyl *o*-hydroxycinnamate **3**.

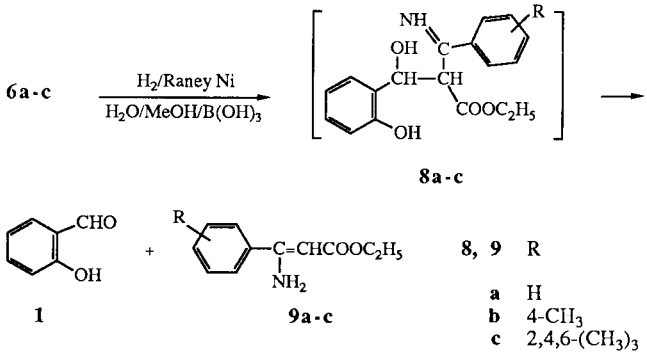
The known starting compound **3** was prepared in 91% yield, along with coumarin (**4**) (4%), through a Wittig reaction of salicylaldehyde (**1**) with ethyl (triphenylphosphoranylidene)acetate (**2**), in refluxing toluene, in analogy to literature [13].

When treating a solution of **3** in dichloromethane with benzonitrile oxide (**5a**), prepared *in situ* from equimolar amounts of benzhydroximoyl chloride and triethylamine and subjecting the reaction mixture to column chromatography, a sole cycloaddition product in 46% yield was isolated and assigned as ethyl *trans*-3-phenyl-4,5-dihydro-5-(2-hydroxyphenyl)-4-isoxazolecarboxylate (**6a**). In a similar way, treatment of **3** with 4-methylbenzonitrile oxide (**5b**) and mesitonitrile oxide (**5c**), and subjection of the reaction mixtures to column chromatography, afforded only the regio-cycloproducts **6b** and **6c** in 51% and 63% yield respectively. All efforts to isolate the regio-isomers **7a-c** from the corresponding reaction mixtures remained unsuccessful, although it was previously reported [14] that reaction of **5a,c** with methyl cinnamate results in both the corresponding 3,5-diphenyl and 3,4-diphenylisoxazoline derivatives, in a ratio of 70:30 and 64:36 and a total yield of 89% and 93% respectively.

The *trans*-configuration of compounds **6a-c** is proposed on the base of the (*E*)-configuration of **3** and on the strictly stereospecific *cis*-addition occuring in 1,3-dipolar cycloadditions of nitrile oxides to olefinic double bonds [4]. The proposed structures for the compounds in question were further supported by the fact that the recorded chemical shifts and coupling constants for their 4-H and 5-H in the ^{1}H nmr spectra are very similar to those reported for analogous isoxazolines [14], and were unequivocally confirmed by their reductive cleavage, as depicted in Scheme 3. Catalytic hydrogenation of compounds **6a-c** in aqueous methanol over Raney Ni, in the presence of boric acid at room temperature, gave salicylaldehyde (**1**) and ethyl β-aminocinnamates **9a** [15], **9b** [16], **9c**, possibly *via* the intermediates **8a-c**, a fact that supports beyond any doubt the suggested regio-form **6a-c** for the compounds in question.

Furthermore, we tried the transformation of compound **6a** to the corresponding isoxazole **10a**, under conditions that were previously applied for the dehydrogenation of

Scheme 3



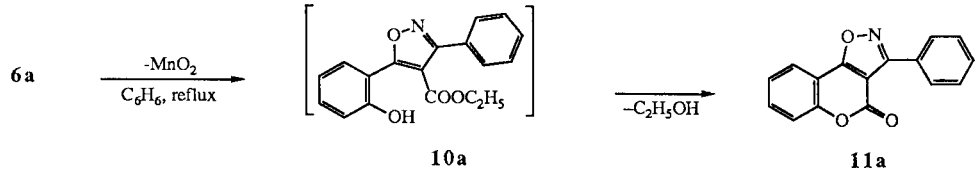
isoxazolines [17]. When a solution of **6a** in benzene was heated under reflux for 16 hours, in the presence of γ-manganese dioxide, the known [10] 3-phenyl-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-one (**11a**) was obtained in 36% yield, possibly by further lactonization of the expected intermediate **10a** (Scheme 4), along with the starting isoxazoline (11%).

Unexpectedly, we later observed that compound **11a** is obtained in higher yield (66%) by refluxing for 100 hours a solution of **6a** in xylene containing pyridine. Similarly, compound **6b** was thermally converted, in presence of pyridine, to the fused derivative **11b**, in 25% yield (Scheme 5). By a similar treatment of compound **6c** for 100 hours 3-(2,4,6-trimethylphenyl)-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-one (**11c**) and ethyl 3-(2,4,6-trimethylphenyl)-5-(2-hydroxyphenyl)-4-isoxazolecarboxylate (**10c**) were obtained in 56% and 7% yield respectively (Scheme 5). When the reaction time was shortened to only 40 hours compounds **11c** and **10c** were obtained again in 11% and 42% yield respectively, along with non-reacting starting compound **6c** (29%). Although the described thermal transformations of compounds **6a-c** were monitored by tlc and the reaction mixtures were systematically separated by chromatographic methods, isoxazoles **10a,b** were not detected or isolated. It should also be noticed that compounds **6a-c** were recovered unchanged after prolonged reflux in xylene solutions in absence of pyridine.

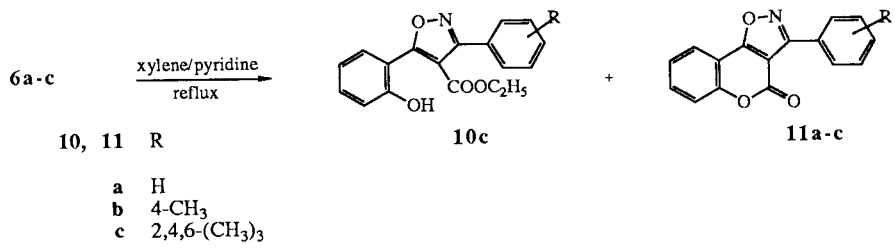
When a solution of compound **10c** in xylene was heated at reflux for 100 hours compound **11c** was obtained in 46% yield.

Of special interest is furthermore the fragmentation pattern observed in the mass spectra of compounds **6a-c**, ob-

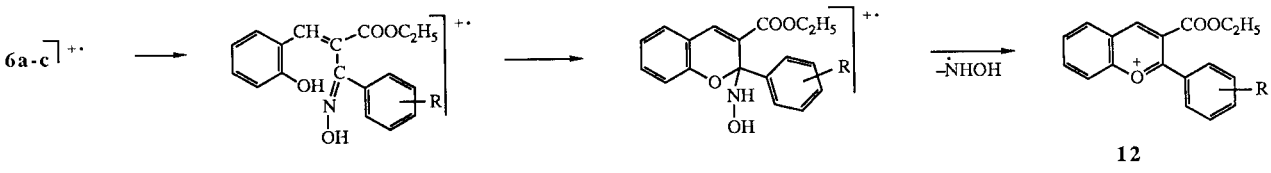
Scheme 4



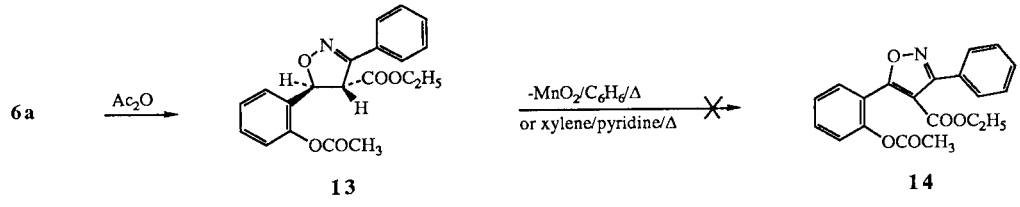
Scheme 5



Scheme 6



Scheme 7



tained at 160-220°. The fragments corresponding to M-2 were not recorded, and the ions M-46 appeared in very low abundance, while the base peak in the case of compounds **6a,b** was the fragment M-32, corresponding to direct NHOH elimination from the molecular ion. A similar fragment of 24% relative intensity was also recorded in the spectrum of compound **6c**. To this unexpected main fragment can be assigned the structure of a pyrylium ion **12**, formed by opening of the isoxazoline ring and further transformations as suggested in Scheme 6. The spectrum of compound **10c** showed as base peak the fragment M-46.

These results lead to the conclusion that compounds **11a-c** are formed by further thermal lactonization of the initially formed isoxazoles **10a-c**, and furthermore that the dehydrogenation of isoxazolines **6a-c** to isoxazoles **10a-c** proceeds thermally and only in the presence of pyridine. On the other hand a prior lactonization in compounds **6a-c** is not favoured, because of the *trans* arrangement of their 5-(2-hydroxyphenyl)- and 4-ethoxycarbonyl-substituents.

Although the above experiments were successful in what concerns the preparation of the target title compounds, we tried to prepare isoxazole **14** from isoxazoline **13** (Scheme 7) under similar conditions, in an effort to study further this unexpected dehydrogenation of the isoxazoline ring, observed in the case of compounds **6a-c**. The acetyl derivative **13** was prepared in 71% yield by heating a solution of **6a** in acetic anhydride. When a solution of **13** in xylene-pyridine was heated under reflux, no dehydrogenation was observed, even after prolonged time of heating, as tlc examination of the solution indicated and the starting compound was recovered. Compound **13** remained also unchanged when heated in a benzene solution in presence of γ-manganese dioxide, while its mass spectrum exhibited again as base peak the fragment [M-42]-32, in analogy to the spectrum of compound **6a**.

These results prove that under the conditions applied in the above experiments, the dehydrogenation proceeds only in the presence of an *o*-hydroxyl substituent in the 5-phenyl ring, a fact that is probably due to its participation in the reaction sequence. An initial *o*-quinone methide generation *via* elimination of a hydrogen molecule from -OH and 5-H of **6a-c**, followed by tautomerisation to the fully aromatic ring system could possibly account for the formation of compounds **10**, though it is known that the quinone methide formation from the corresponding (hydroxyaryl)methyl derivatives proceeds in the presence of oxidising agents [18].

No efforts to optimize yields were made.

In conclusion, the 1,3-dipolar cycloaddition reactions of

readily obtained nitrile oxides to available *o*-hydroxycinnamates and the further dehydrogenation - lactonization of the isoxazolines obtained, offer an easy route for the preparation of 3-substituted 4*H*-[1]benzopyrano[3,4-*d*]-isoxazol-4-ones.

EXPERIMENTAL

Melting points are uncorrected and were determined with a Kofler hot-stage apparatus. The ir spectra were obtained with a Perkin-Elmer 297 spectrophotometer as Nujol mulls. The ^{1}H nmr spectra were recorded with deuteriochloroform as solvent on a Bruker Model AW 80 (80 MHz) spectrometer, with tetramethylsilane as the internal standard. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6L mass spectrometer. The ionization energy was maintained at 70 eV. Microanalyses were performed on a Perkin-Elmer 240 B CHN analyser.

Ethyl *trans*-3-Phenyl-4,5-dihydro-5-(2-hydroxyphenyl)-4-isoxazolecarboxylate (**6a**).

To a stirred and ice-cooled solution of ethyl *o*-hydroxycinnamate (**3**) (1.54 g, 8 mmoles) and benzhydroximoyl chloride (1.55 g, 10 mmoles) in dry methylene chloride (20 ml) was added dropwise a solution of dry triethylamine (1.4 ml, 10 mmoles) in dry methylene chloride (5 ml) over 30 minutes. The reaction mixture was stirred at 0° for further 10 minutes and at room temperature for 24 hours and ether was then added to it. The precipitated triethylamine hydrochloride was filtered off, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with methylene chloride as eluant to give colourless crystals of compound **6a** (1.14 g, 46%), mp 136-138° (methylene chloride/hexane); ir (Nujol): 3360, 3070, 1706, 1600 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15 (t, J = 7.5 Hz, 3 H), 4.20 (q, J = 7.5 Hz, 2 H), 4.52 (d, J = 7.2 Hz, 1 H, 4-H), 6.20 (d, J = 7.2 Hz, 1 H, 5-H), 6.78-7.17 (m, 2 H), 7.25-7.55 (m, 5 H), 7.65-7.80 (m, 2 H); ms: m/z (%) 311 (M$^+$, 22), 294 (2), 280 (20), 279 (100), 265 (2), 220 (15), 207 (10), 204 (14), 162 (15), 146 (25), 144 (17), 121 (29), 120 (15), 119 (22), 118 (29).

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.64; H, 5.41; N, 4.48.

Ethyl *trans*-3-(4-Methylphenyl)-4,5-dihydro-5-(2-hydroxyphenyl)-4-isoxazolecarboxylate (**6b**).

To a stirred and ice-cooled solution of compound **3** (1 g, 5.2 mmoles) and 4-methylbenzhydroximoyl chloride (1.7 g, 10 mmoles) in dry methylene chloride (15 ml) was added dropwise a solution of dry triethylamine (1.4 ml, 10 mmoles) in dry methylene chloride (5 ml), over 30 minutes. The reaction mixture was then worked up as described above, to give colourless crystals of compound **6b** (0.86 g, 51%), mp 104-106° (methylene chloride/hexane); ir (Nujol): 3360, 3070, 1707, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.15 (t, J = 7 Hz, 3 H), 2.28 (s, 3 H), 4.16 (q, J = 7 Hz, 2 H), 4.48 (d, J = 7.5 Hz, 1 H, 4-H), 6.16 (d, J = 7.5 Hz, 1 H, 5-H), 6.75-7.36 (m, 6 H), 7.51 (d, J = 7 Hz, 2 H); ms: m/z (%) 325 (M$^+$, 24), 308 (2), 294 (24), 293 (100), 279 (1), 265 (6), 234 (8), 221 (6), 133 (16), 121 (20), 119 (12), 118 (20).

Anal. Calcd. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.15; H, 5.65; N, 4.34.

Ethyl *trans*-3-(2,4,6-Trimethylphenyl)-4,5-dihydro-5-(2-hydroxyphenyl)-4-isoxazolecarboxylate (**6c**).

A solution of compound **3** (0.96 g, 5 mmoles) and 2,4,6-trimethylbenzonitrile oxide (**5c**) (1.61 g, 10 mmoles) in dry methylene chloride (20 ml) was heated under reflux for 48 hours. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel with methylene chloride as eluant, to give colourless crystals of compound **6c** (1.16 g, 63%), mp 175-177° (methylene chloride); ir (Nujol): 3265, 1738, 1640, 1610 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 0.90 (t, J = 7 Hz, 3 H), 2.21 (s, 6 H), 2.26 (s, 3 H), 3.80-4.15 (m, 2 H), 4.50 (d, J = 10.7 Hz, 1 H, 4-H), 6.21 (d, J = 10.7 Hz, 1 H, 5-H), 6.80-7.07 (m, 3 H), 7.11-7.43 (m, 3 H); ms: m/z (%) 353 (M$^+$, 100), 352 (5), 336 (8), 335 (12), 322 (7), 321 (24), 307 (3), 292 (10), 290 (12), 289 (14), 262 (29), 232 (17), 231 (53), 202 (15), 186 (61), 162 (17), 159 (44), 158 (34), 146 (25), 121 (34).

Anal. Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.36; H, 6.25; N, 4.33.

General Procedure for Reduction of Compounds **6a-c**.

To a solution of compound **6** (0.5 mmole) in a mixture of 8:2:5 methanol/water/ethyl acetate (7.5 ml) boric acid (70 mg, 1.1 mmoles) and a spatula tip (estimated 10 mg) of W-2 Raney Nickel (Fluka AG) were added. The mixture was placed under hydrogen by repeated (5 times) evacuation and flushing with hydrogen gas, by means of a balloon attached to a three-way stopcock. The mixture was stirred vigorously for 24 hours and then filtered through Celite into a separating funnel, containing water/methylene chloride (1:1) (40 ml). After separation the aqueous layer was extracted with methylene chloride three more times (3 × 20 ml) and the combined organic layers were washed with brine (2 × 15 ml), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was chromatographed on silica gel with hexane/ethyl acetate (1:1) as eluant to give in order of elution, first salicylaldehyde (**1**) (in 54%, 38% and 23% yield from compounds **6a**, **6b**, **6c** respectively) and then compound **9**.

Ethyl β-Aminocinnamate (**9a**).

This compound was obtained from **6a**, yield 66%, oil with ir, ^{1}H nmr spectral data identical to those reported previously [15].

Ethyl 4-Methyl-β-aminocinnamate (**9b**).

This compound was obtained from **6b**, yield 47%, oil; ir (film): 3430, 3320, 1664, 1615 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.24 (t, J = 6.4 Hz, 3 H), 2.33 (s, 3 H), 4.14 (q, J = 6.4 Hz, 2 H), 4.93 (s, 1 H), 7.16 (d, J = 8 Hz, 2 H), 7.40 (d, J = 8 Hz, 2 H); ms: m/z (%) 205 (M$^+$, 53), 177 (4), 176 (4), 161 (10), 160 (67), 134 (12), 133 (100), 119 (46), 118 (48), 117 (30).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.55; H, 7.65; N, 6.39.

Ethyl 2,4,6-Trimethyl-β-aminocinnamate (**9c**).

This compound was obtained from **6c**, yield 38%, oil; ir (film): 3435, 3325, 1665, 1620 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.27 (t, J = 7 Hz, 3 H), 2.28 (s, 9 H), 4.15 (q, J = 7 Hz, 2 H), 4.51 (s, 1 H), 6.86 (s, 2 H); ms: m/z (%) 233 (M$^+$, 95), 218 (10), 205 (16), 204 (100), 189 (10), 188 (56), 186 (29), 160 (30), 159 (32), 158 (44), 146 (87), 145 (52), 144 (62), 130 (48).

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.20; H, 8.08; N, 5.80.

3-Phenyl-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-one (**11a**).

Procedure A.

To a solution of compound **6a** (0.233 g, 0.75 mmole) in dry

benzene (25 ml), γ-manganese dioxide (0.329 g, 3.75 mmoles) was added and the mixture was heated under reflux for 16 hours. The inorganic precipitates were filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with ethyl acetate/hexane (2:3) as eluant, to give compound **11a** (71 mg, 36%), mp 196-198° (ethyl acetate/hexane) (lit [10], mp 198-200°); ir (chloroform): 3050, 1740, 1632, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.33-7.93 (m, 6 H), 8.05-8.47 (m, 3 H); ms: m/z (%) 264 (20), 263 (M^+, 100), 235 (5), 144 (8), 143 (62), 120 (88), 119 (15).

Anal. Calcd. for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.32. Found: C, 73.18; H, 3.57; N, 5.31.

The fraction eluted next gave the starting compound **6a** (26 mg, 11%).

Procedure B.

A solution of compound **6a** (0.218 g, 0.7 mmole) and dry pyridine (0.5 ml) in dry xylene (10 ml) was heated under reflux for 100 hours. The solvent was removed under reduced pressure and the residue was triturated with ethyl acetate to give compound **11a** (0.121 g, 66%).

3-(4-Methylphenyl)-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-one (**11b**).

A solution of compound **6b** (0.26 g, 0.8 mmole) and dry pyridine (1 ml) in dry xylene (10 ml) was heated under reflux for 100 hours. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel with methylene chloride as eluant, to give compound **11b** (55 mg, 25%), mp 200-201° (methylene chloride/hexane); ir (Nujol): 3040, 1750, 1628, 1595 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3 H), 6.90-7.80 (m, 5 H), 7.90-8.40 (m, 3 H); ms: m/z (%) 277 (M^+, 100), 249 (2), 158 (21), 157 (98), 156 (16), 120 (33).

Anal. Calcd. for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.63; H, 4.15; N, 5.04.

The fraction eluted next gave compound **6b** (72 mg, 28%).

Thermal Transformations of Compound **6c**.

A.

A solution of compound **6c** (60 mg, 0.17 mmole) and dry pyridine (0.5 ml) in dry xylene (8 ml) was heated under reflux for 100 hours. The solvent was removed under reduced pressure and the residue was subjected to preparative tlc [silica gel, methylene chloride/hexane (1:1)].

3-(2,4,6-Trimethylphenyl)-4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-one (**11c**).

This compound was obtained from the faster moving band (33 mg, 56%), mp 215-217° (ethanol); ir (Nujol): 3080, 1742, 1630 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.16 (s, 6 H), 2.34 (s, 3 H), 6.98 (s, 2 H), 7.31-7.86 (m, 3 H), 8.02-8.15 (m, 1 H); ms: m/z (%) 306 (25), 305 (M^+, 100), 304 (43), 290 (36), 277 (11), 276 (14), 220 (21), 194 (42), 186 (44), 185 (37), 165 (29), 157 (46), 156 (24), 145 (28), 144 (15), 120 (49), 119 (31).

Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.64; H, 5.05; N, 4.61.

Ethyl 3-(2,4,6-Trimethylphenyl)-5-(2-hydroxyphenyl)-4-isoxazolecarboxylate (**10c**).

This compound was obtained from the next band (4 mg, 7%), mp 111-113° (methylene chloride/hexane); ir (Nujol): 3220, 1724, 1626, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.82 (t, J = 7 Hz, 3 H), 2.08 (s, 6 H), 2.30 (s, 3 H), 4.01 (q, J = 7 Hz, 2 H), 6.86-7.73 (m, 6 H), 8.40 (br s, 1 H); ms: m/z (%) 352 (10), 351 (M^+, 46), 322 (7), 306 (26), 305 (100), 291 (10), 142 (13), 130 (17), 121 (70), 119 (20).

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.63; H, 6.11; N, 3.99.

B.

A solution of compound **6c** (0.205 g, 0.58 mmole) and dry pyridine (1.5 ml) in dry xylene (15 ml) was heated under reflux for 40 hours. The solvent was removed under reduced pressure and the residue was worked up as above to give compounds **11c** (20 mg, 11%) and **10c** (85 mg, 42%). The starting compound **6c** was then obtained from the slower moving band (60 mg, 29%).

Thermal Transformation of Compound **10c** to **11c**.

A solution of compound **10c** (42 mg, 0.12 mmole) in dry xylene (3 ml) was heated under reflux for 100 hours. The solvent was removed under reduced pressure and the residue was chromatographed [preparative tlc, silica gel, methylene chloride/hexane (1:1)] to give compound **11c** (17 mg, 46%).

Ethyl *trans*-3-Phenyl-4,5-dihydro-5-(2-acetoxyphenyl)-4-isoxazolecarboxylate (**13**).

A mixture of compound **6a** (0.13 g, 0.4 mmole), acetic anhydride (1.85 ml, 19.6 mmoles) and concentrated sulfuric acid (6 drops) was stirred at room temperature for 5 hours. The reaction mixture was concentrated under reduced pressure. The residue was chromatographed [preparative tlc, silica gel, ethyl acetate/hexane (5:95)] to give from the faster moving band compound **13** (0.104 g, 71%), mp 86-88° (chloroform/hexane); ir (Nujol): 3060, 1754, 1725 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.13 (t, J = 7.5 Hz, 3 H), 2.24 (s, 3 H), 4.06 (q, J = 7.5 Hz, 2 H), 4.39 (d, J = 7 Hz, 1 H), 6.13 (d, J = 7 Hz, 1 H), 6.98-7.82 (m, 9 H); ms: m/z (%) 354 (10), 353 (M^+, 37), 352 (2), 312 (9), 311 (56), 294 (26), 281 (31), 280 (75), 279 (100), 251 (13), 207 (53), 119 (33).

Anal. Calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96. Found: C, 67.90; H, 5.43; N, 4.21.

Compound **6a** (27 mg, 21%) was obtained from the next band.

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