Synthesis of Isomeric Series of Aryltetrahydrobenzisoxazoles and Arylcyclopentisoxazoles

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Four series of potential PAF-antagonists in which the isoxazole nucleus is condensed with a polyhydrogenated five- or six-carbon ring were prepared. The synthesis of the compounds 3-aryl-4,5,6,7-tetrahydrobenz[*c*]isoxazoles **1**, 3-arylcyclopent[*c*]isoxazoles **2**, 3-aryl-4,5,6,7-tetrahydrobenz[*d*]isoxazoles **3**, and 3-arylcyclopent[*d*]isoxazoles **4**, required an extensive optimization and comparison of the methods available in the literature.

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As a part of a work directed to find new PAF (platelet activating factor) antagonists [1], we became interested in four series of isoxazole-containing compounds, namely the structures of 3-aryl-4,5,6,7-tetrahydrobenz[*c*]isoxazoles **1**, 3-arylcyclopent[*c*]isoxazoles **2**, 3-aryl-4,5,6,7-tetrahydrobenz[*d*]isoxazoles **3**, and 3-arylcyclopent[*d*]isoxazoles **4** (Figure 1). In spite of the synthetic interest of this class of structures, we could not find in the literature general methods for the preparation of isoxazoles condensed to a saturated carbocycle.

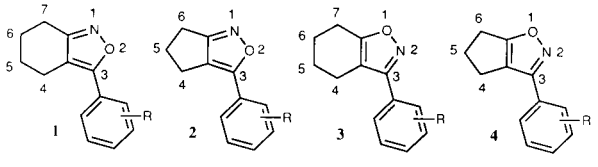


Figure 1

Condensation of 1,4-dianions of cyclopentanone and cyclohexanone oximes with benzoic acid esters [2-4] or benzamides [5] (method A) has been used for the preparation of structures **1** or **2**, although in a low number of examples.

Alternatively, the tetrahydrobenzo[*c*]isoxazoles **1** or cyclopent[*c*]isoxazoles **2** have been obtained from 2-benzoylcycloalkanones, by reaction of these 1,3-dicarbonyl systems with hydroxylamine and subsequent cyclization (method B) [6,7]. In principle, this procedure could lead to a mixture of the isomeric isoxazole systems **1** and **3** or **2** and **4**, depending on the initial attack of the hydroxylamine nitrogen atom upon the cycloalkanone or the benzoyl group, respectively. However, Bianchi [6] and Jacquier [7] described the formation of a single isomer **1** or **2** in some of these reactions, and attributed the observed regioselectivity to the greater reactivity of the unconjugated ketone group, as compared to the aryl-conjugated one.

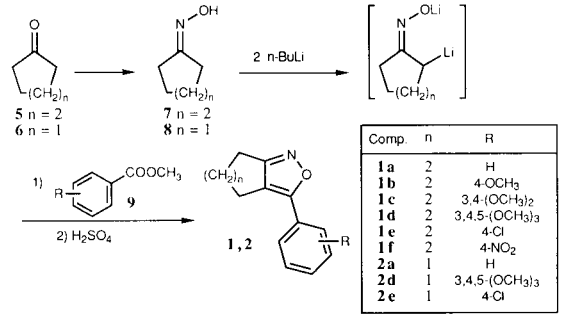
Finally, some members of the isomeric tetrahydrobenz[*d*]isoxazole and cyclopent[*d*]isoxazole series **3** and **4** have been synthesized *via* a 1,3-dipolar cycloaddition between the appropriate benzonitrile oxides and the C=C double bond of cyclic enamines [8-10] or enol ethers [11], followed by acid-catalyzed or Hofmann elimination to give the aromatic isoxazole ring (method C).

We have evaluated and describe here the general applicability of the above methods A-C for the synthesis of the series of isoxazoles **1-4**. This work was directed to extend these methods to new examples, to define the limitations of each procedure, and to verify the isomeric purity of the obtained isoxazoles.

Method A. Isoxazoles **1** or **2** from α,*O*-Dilithiooximes.

The procedure first described by Beam and coworkers [2,3], consisting in the condensation of the dilithio derivatives of cyclopentanone or cyclohexanone oximes **7** and **8** with an aromatic ester **9**, was applied to the synthesis of the tetrahydrobenz[*c*]isoxazoles **1a-f** and the cyclopent[*c*]isoxazoles **2a,d** (Scheme I).

Scheme I



Comp.	n	R
1a	2	H
1b	2	4-OCH_3
1c	2	3,4-$(OCH_3)_2$
1d	2	3,4,5-$(OCH_3)_3$
1e	2	4-Cl
1f	2	4-NO_2
2a	1	H
2d	1	3,4,5-$(OCH_3)_3$
2e	1	4-Cl

After the initial condensation step, aromatisation of the isoxazole nucleus was performed by acidic treatment. Although method A led to the tetrahydrobenz[*c*]isoxazoles **1a-e** in moderate yields (24 to 37%), this procedure completely failed to give the *para*-nitrophenyl analog **1f**. Thus, only complex mixtures were obtained after treatment of methyl *p*-nitrobenzoate with dilithiocyclohexanone oxime. In the case of the 3-arylcyclopent[*c*]isoxazole structures **2**, only the unsubstituted compound **2a** was obtained in 27% yield, and we were unable to extend this method to the preparation of the methoxy-substituted analog **2d** or the *p*-chloro derivative **2e**.

The use of an amide instead of the ester **9** in the above condensation reaction has been described to give higher yields of the corresponding isoxazoles [5]. However, in our hands the reaction of dilithiocyclohexanone oxime with *N*,*N*-dimethylbenzamide, followed by acid cyclization, gave only a 14% yield of the isoxazole **1a**.

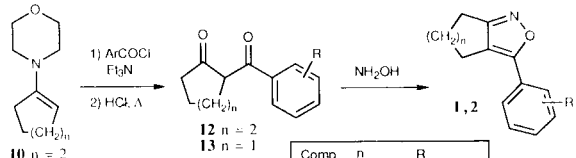
In all cases, the isoxazoles **1** and **2** were obtained as single isomers, as shown by gas-liquid chromatography, tlc and ^{1}H-nmr. The two heterocyclic systems were unambiguously identified in the 300 MHz spectra: the tetrahydrobenz[*c*]isoxazoles **1** showed a multiplet at 1.80 ppm for the C-5 and C-6 methylene groups and a second multiplet centered at 2.70 ppm corresponding to the C-4 and C-7 methylene groups. In the ^{1}H-nmr spectra of the cyclopent-[*c*]isoxazole **2a**, two multiplet signals were again observed, one for two protons at 2.55 ppm, assigned to the C-5 methylene, and the other for 4 protons at 2.80 ppm, due to the C-4 and C-6 methylene groups.

Method B. Isoxazoles **1** or **2** from β-Diketones.

The required 2-benzoylcyclohexanones **12** and cyclopentanones **13** were prepared by the method of Hünig and Lendle [12]. The ^{1}H-nmr spectroscopy showed that most of these compounds in deuteriochloroform solution were mixtures of the enol and β-diketone forms (ratios are reported in the experimental).

When the appropriate β-diketone **12** was made to react with hydroxylamine hydrochloride in pyridine-ethanol solution, the corresponding 3-aryl-4,5,6,7-tetrahydrobenz-[*c*]isoxazole **1a**, **1b**, **1d** or **1f** was obtained in good yields (Scheme II).

Scheme II



Comp.	n	R
1a	2	H
1b	2	4-OCH_3
1d	2	3,4,5-$(OCH_3)_3$
1f	2	4-NO_2
2a	1	H
2b	1	4-OCH_3
2c	1	3,4-$(OCH_3)_2$
2d	1	3,4,5-$(OCH_3)_3$
2f	1	4-NO_2

In all cases the yields were higher than those obtained in method A, and method B could be applied also to the synthesis of the *p*-nitro derivative **1f**, which was isolated in 56% yield from the corresponding diketone.

All these isoxazole derivatives were obtained as single isomers, identical to the corresponding compounds arising from method A. Thus, we can conclude that the reactivity of the two ketone functions is different enough to make the initial oxime formation completely regioselective, regardless of the electronic donating or withdrawing effect of the substituents on the aromatic ring.

Attempts to extend the above procedure to the synthesis of 3-phenylcyclopent[*c*]isoxazole (**2a**) proved to be unsuccessful. Nevertheless, compound **2a** precipitated in moderate yield from the reaction mixture when the experimental conditions were modified by replacing the pyridine-ethanol solvent for a mixture of sodium acetate, methanol and water. Similar results were obtained for the 3,4-dimethoxyphenyl-substituted compound **2c**, which also was insoluble in this reaction medium. However, other cyclopent[*c*]isoxazoles such as **2b**, **2d** and **2f** could not be synthesized or were obtained in very low yields under these conditions. Proton nmr spectra of crude reaction mixtures arising from the corresponding diketones **13b**, **13d** and **13f** indicated the presence of complex stereoisomeric mixtures of mono- and dioximes, as well as the absence of significative amounts of the corresponding cyclization products **2**. The failure in the synthesis of several cyclopent[*c*]isoxazoles **2** by the use of method B can be interpreted on the basis of two different factors. First of all, in some cases the very extensive enolization of the cyclopentanone carbonyl group in 2-benzoylcyclopentanones may reverse the regioselectivity of the initial attack of hydroxylamine. Indeed, the two cyclopentanones **13d** and **13f** in deuteriochloroform solution showed keto-enol ratios of 0:100 and 13:87 respectively, whereas the values found for **13a** and **13c** in the same conditions were 43:57 and 80:20 respectively.

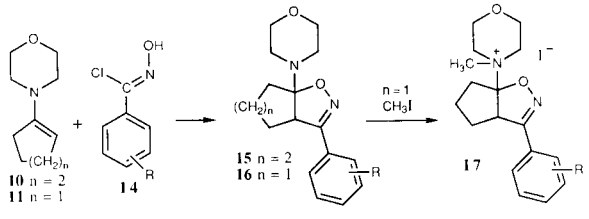
However, the extent of enolization cannot be the only factor responsible for the different reaction course observed in the formation of **2b**, as compared to the case of **2a** and **2c**, since the cyclopentanone **13b** was found by nmr to contain nearly a 40% of dicarbonyl tautomer in deuteriochloroform solution. In this case the higher solubility of the isoxazole **2b** in the methanol-water medium prevents its precipitation under the reaction conditions. Since the cyclization step is reversible and the ring strain of the fused five-membered system difficults the final dehydration, the main product expected in this reaction is a mixture of mono- and dioximes of the diketone system. On the other hand, the low solubility of isoxazoles **2a** and **2c** allows their precipitation, thus shifting the equilibria towards the cyclic form. The presence of the monooximes in the crude reaction mixture from 4-methoxy diketone **13b** could be demonstrated by nmr and also by treatment of this mixture with acetyl chloride, which promoted cyclization and dehydration of the monooximes to a mixture of the isomeric isoxazoles **2b** and **4b**, in low yields (<5%).

The isoxazoles **1** or **2** synthesized following method B were in all cases isomerically pure and showed the same ^{1}H-nmr pattern which was found for the isomers obtained through method A (two multiplets for the cycloaliphatic moiety, see above).

Method C. Isoxazoles **3** or **4** from Nitrile Oxides and Enamines.

The 3-aryl-4,5,6,7-tetrahydrobenz[*d*]isoxazoles **3a-c**, **3e** and **3f**, and their five-membered analogs **4a** and **4c** were prepared as described by Kuehne and coworkers [8], by reaction of the appropriate benzohydroximinoyl chlorides **14** with an excess of the cyclohexanone or cyclopentanone enamines **10** and **11**. Under these basic conditions, the benzohydroximinoyl chloride is converted into the corresponding nitrile oxide, which undergoes a 1,3-dipolar cycloaddition upon the enamine double bond to give a dihydroisoxazole **15** or **16** (Scheme III).

Scheme III



Comp.	n	R
3a	2	H
3b	2	4-OCH_3
3c	2	3,4-$(OCH_3)_2$
3e	2	4-Cl
3f	2	4-NO_2
4a	1	H
4c	1	3,4-$(OCH_3)_2$

In the tetrahydrobenz[*d*]isoxazole series **3**, the final deamination step takes place in concentrated hydrochloric acid, through protonation of the morpholine nitrogen atom and elimination, leading to the aromatic heterocycles **3** in 36-51% yield, after purification.

Again, the high ring strain in the five-membered cyclopent[*d*]isoxazoles **4** made very difficult the final dehydration step and, consequently, the intermediates **16a,c** remained unreacted, even after prolonged acidic treatment. Their aromatisation was performed *via* Hofmann reaction, after conversion of **16a,c** in the corresponding methylammonium salts **17a,c** by treatment with methyl iodide. The amine elimination took place when the compound was heated at 200° in the presence of an excess of silver oxide, separating the formed isoxazoles **4a,c** by simultaneous sublimation.

Chromatographic and ^{1}H-nmr spectroscopic analysis of the isoxazole derivatives **3** and **4** obtained through method C always showed that these compounds were single isomers and that they were different from compounds **1** and **2**, arising from methods A and B. Thus, in the 300 MHz nmr spectra of tetrahydrobenz[*d*]isoxazoles **3** the four cycloaliphatic methylene groups gave separate signals (two multiplets near 1.75 and 1.85 ppm, and two triplets near 2.55 and 2.70 ppm), in contrast to the two multiplets present in the spectra of isomers **1**. Finally, the cyclopent[*d*]isoxazoles **4** gave only one cycloaliphatic signal, a multiplet centered around 2.7 ppm, whereas the C-5 methylene and the C-4 + C-6 methylene groups were clearly differentiated in the isomeric cyclopent[*c*]isoxazoles **2**.

EXPERIMENTAL

Melting points were taken in a Büchi apparatus and are uncorrected. The proton nuclear magnetic resonance (^{1}H-nmr) spectra were obtained using a Varian Gemini 300 MHz spectrometer, in deuteriochloroform as a solvent. Tetrahydrofuran was distilled from sodium (benzofenone). *n*-Butyllithium was purchased from Fluka and was periodically titrated. Methyl benzoates were either purchased or prepared through a standard procedure [13]. All the acid chlorides were commercially available. 1-Morpholinocyclopentene and 1-morpholinocyclohexene were purchased from Fluka. The cyclopentanone and cyclohexanone oximes were prepared by a standard procedure [14]. Benzaldoximes and benzohydroximinoylchloride were prepared according to the literature [15].

General Procedure for the Preparation of β-Diketones **12** and **13**.

A solution of 50 mmoles of the appropriate enamine **10** or **11** and 50 mmoles of triethylamine in 30 ml of chloroform was cooled to -10°, and a solution of 50 mmoles of the corresponding benzoyl chloride in 15 ml of chloroform was added dropwise. The mixture was stirred at room temperature overnight. Then, 15 ml of 4*N* hydrochloric acid were added and the solution was refluxed for 5 hours. The organic layer was separated and washed with water (to *p*H 5). The aqueous layer was neutralized and extracted with chloroform. The combined organic extracts were dried and concentrated.

2-Benzoylcyclohexanone (**12a**).

This compound was obtained as a white-ivory solid (dichloromethane:petroleum ether), mp 76-78°; ir (chloroform): ν 1712 (CO cyclohexanone), 1660 (CO benzoyl) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.30 (dd, 2-H), β-diketone:enol ratio 93:7.

2-(4-Methoxybenzoyl)cyclohexanone (**12b**).

This compound was obtained as a white-ivory solid (dichloromethane:petroleum ether), mp 108-112°; ir (chloroform): ν 1730 (CO cyclohexanone), 1660 (CO benzoyl) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.30 (dd, 2-H), β-diketone:enol ratio 75:25.

2-(3,4,5-Trimethoxybenzoyl)cyclohexanone (**12d**).

This compound was obtained as a light yellow solid after silica gel chromatographic purification (eluent dichloromethane:ethyl acetate 9:1), mp 126-128°; ir (chloroform): ν 1700 (CO cyclohexanone), 1635 (CO benzoyl) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.30 (dd, 2-H), β-diketone:enol ratio 100:0.

2-(4-Nitrobenzoyl)cyclohexanone (**12f**).

This compound was obtained as a yellow solid after silica gel chromatography (eluent diethyl ether:petroleum ether), mp 76-78°; ir (chloroform): ν 1700 (CO cyclohexanone), 1670 (CO benzoyl) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.32 (dd, 2-H), β-diketone:enol ratio 30:70.

2-Benzoylcyclopentanone (**13a**).

This compound was obtained as an oil and purified by distillation; ir (chloroform): ν 1730 (CO cyclopentanone), 1660 (CO benzoyl) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.00 (t, 2-H), β-diketone:enol ratio 43:57.

2-(4-Methoxybenzoyl)cyclopentanone (**13b**).

This compound was obtained as an oil after silica gel chromatography (eluent dichloromethane); ^{1}H-nmr (deuteriochloroform): δ 4.12 (t, 2-H), β-diketone:enol ratio 37:63.

2-(3,4-Dimethoxybenzoyl)cyclopentanone (**13c**).

This compound was obtained as an oil and purified by silica gel chromatography (eluent dichloromethane); ir (chloroform): ν 1730 (CO cyclopentanone), 1655 (CO benzoyl) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 4.15 (t, 2-H), β-diketone:enol ratio 80:20.

2-(3,4,5-Trimethoxybenzoyl)cyclopentanone (**13d**).

This compound was obtained as a white-ivory solid and purified by silica gel chromatography (eluent diethyl ether:petroleum ether), mp 83-86°; ^{1}H-nmr (deuteriochloroform): δ 1.95 (quintuplet, 2H, 4-H_2), 2.47 (t, 2H, 3-H_2), 2.87 (t, 2H, 5-H_2), 3.88 (s, 9H, OCH_3), 7.00 (s, 2H, aromatic), β-diketone:enol ratio 0:100.

2-(4-Nitrobenzoyl)cyclopentanone (**13f**).

This compound was obtained as a white solid after silica gel chromatography (eluent diethyl ether:petroleum ether 8:2), mp 86-88°; ^{1}H-nmr (deuteriochloroform): δ 4.25 (t, 2-H), β-diketone:-enol ratio 13:87.

General Procedures for the Preparation of 3-Aryl-4,5,6,7-tetrahydrobenz[*c*]isoxazoles **1** and 3-Arylcyclopent[*c*]isoxazoles **2**.

Method A.

To a stirred solution of 48 mmoles of the oxime **7** or **8** in 160 ml of tetrahydrofuran, cooled to 0° and under a nitrogen atmosphere, 105 mmoles of 1.6 *M* solution of *n*-butyllithium were added. The mixture was stirred for 30-40 minutes at 0° and then for an additional period of 15-45 minutes at 20°. The solution was cooled again to 0° and 24 mmoles of the appropriate ester **9** dissolved in 40 ml of tetrahydrofuran were added. After stirring at 0° for 30-60 minutes and at room temperature for 1-2 hours, the mixture was made acidic by the addition of a solution of 18.3 g of concentrated sulfuric acid in 100 ml of tetrahydrofuran and 25 ml of water. The resulting mixture was heated under reflux for 1 hour, cooled, and the layers were separated. The aqueous layer was neutralized with sodium bicarbonate and extracted with ether. The combined organic extracts were dried over sodium sulfate, filtered, concentrated, and the residue was purified by column chromatography on alumina or silica gel.

3-Phenyl-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1a**).

This compound was obtained in 33% yield by column chromatography on alumina (hexane), as a white-ivory solid, mp 65-66° (lit [2,5] 65-67°, [7] 66°); ^{1}H-nmr (deuteriochloroform): δ 1.80 (m, 4H, 5-H_2 and 6-H_2), 2.72 (m, 4H, 4-H_2 and 7-H_2), 7.40 and 7.70 (m, 5H, aromatic).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.57; N, 7.03. Found: C, 78.52; H, 6.56; N, 6.98.

3-(4-Methoxyphenyl)-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1b**).

This compound was obtained in 24% yield by column chromatography on silica gel (dichloromethane-hexane 1:1), as a white solid, mp 81-82° (lit [3] 78-79.5°); ^{1}H-nmr (deuteriochloroform): δ 1.77 (m, 4H, 5-H_2 and 6-H_2), 2.72 (m, 4H, 4-H_2 and 7-H_2), 3.80 (s, 3H, OCH_3), 6.94 (d, 2H, aromatic), 7.64 (d, 2H, aromatic).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.22; H, 6.60; N, 5.99.

3-(3,4-Dimethoxyphenyl)-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1c**).

This compound was obtained in 31% yield by column chromatography on silica gel (dichloromethane), as a white solid, mp 120-122°; ^{1}H-nmr (deuteriochloroform): δ 1.80 (m, 4H, 5-H_2 and 6-H_2), 2.75 (m, 4H, 4-H_2 and 7-H_2), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.90 (d, 1H, aromatic), 7.25 (m, 2H, aromatic).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.60; N, 5.40. Found: C, 69.32; H, 6.72; N, 5.25.

3-(3,4,5-Trimethoxyphenyl)-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1d**).

This compound was obtained in 37% yield by column chromatography on alumina (dichloromethane), as a white solid, mp 94-96°; ^{1}H-nmr (deuteriochloroform): δ 1.75 (m, 4H, 5-H_2 and 6-H_2), 2.70 (m, 4H, 4-H_2 and 7-H_2), 3.82 (s, 3H, OCH_3), 3.85 (s, 6H, 2 OCH_3), 6.90 (s, 2H, aromatic).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.61; N, 4.84. Found: C, 66.54; H, 6.72; N, 4.83.

3-(4-Chlorophenyl)-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1e**).

This compound was obtained in 31% yield by column chromatography on silica gel (dichloromethane-hexane 2:3), as a white solid, mp 134-135° (lit [3] 135-138°); ^{1}H-nmr (deuteriochloroform): δ 1.80 (m, 4H, 5-H_2 and 6-H_2), 2.75 (m, 4H, 4-H_2 and 7-H_2), 7.40 (d, 2H, aromatic), 7.65 (d, 2H, aromatic).

Anal. Calcd. for $C_{13}H_{12}NOCl$: C, 66.81; H, 5.17; N, 5.99. Found: C, 66.90; H, 5.31; N, 6.01.

3-Phenylcyclopent[*c*]isoxazole (**2a**).

This compound was obtained in 27% yield by column chromatography on silica gel (dichloromethane:hexane 7:3), as a white solid, mp 105-106° (lit [3] 104-106°); ^{1}H-nmr (deuteriochloroform): δ 2.55 (m, 2H, 5-H_2), 2.80 (m, 4H, 4-H_2 and 6-H_2), 7.40 and 7.65 (m, 5H, aromatic).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.98; N, 7.56. Found: C, 78.10; H, 5.75; N, 7.48.

Method B. Procedure B.1.

A solution of 5.15 mmoles of the corresponding β-diketone **12** and 5.15 mmoles of hydroxylamine hydrochloride in 30 ml of an 1:1 mixture of pyridine and ethanol was heated under reflux for 7-20 hours, cooled and concentrated under reduced pressure. The residue was purified by column chromatography over alumina of silica gel.

3-Phenyl-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1a**).

This compound was isolated in 56% yield and was identical to the compound obtained following Method A.

3-(4-Methoxyphenyl)-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1b**).

This compound was isolated in 85% yield and was identical to the compound obtained following Method A.

3-(3,4,5-Trimethoxyphenyl)-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1d**).

This compound was isolated in 74% yield and was identical to the compound obtained following Method A.

3-(4-Nitrophenyl)-4,5,6,7-tetrahydrobenz[*c*]isoxazole (**1f**).

This compound was obtained in 56% yield by column chromatography on silica gel (dichloromethane), as a white solid, mp 225-226°; ^{1}H-nmr (deuteriochloroform): δ 1.85 (m, 4H, 5-H_2 and 6-H_2), 2.80 (m, 4H, 4-H_2 and 7-H_2), 7.90 (d, 2H, aromatic), 8.30 (d, 2H, aromatic).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.91; N, 11.47. Found: C, 63.65; H, 4.67; N, 11.60.

Method B. Procedure B.2.

A solution of 6.5 mmoles of the appropriate β-diketone **13**, 6.5 mmoles of hydroxylamine hydrochloride and 6.5 mmoles of sodium acetate in 10 ml of methanol:water 4:1 was heated under reflux for 1 hour and cooled. Crystallization occurred and the solid was filtered off and purified by column chromatography.

3-Phenylcyclopent[*c*]isoxazole (**2a**).

This compound was isolated in 29% yield and was identical to the compound obtained following Method A.

3-(3,4-Dimethoxyphenyl)cyclopent[*c*]isoxazole (**2c**).

This compound was obtained in 21% yield by column chromatography on silica gel (dichloromethane), as a white solid, mp 108-109°; ^{1}H-nmr (deuteriochloroform): δ 2.52 (m, 2H, 5-H_2), 2.80 (m, 4H, 4-H_2 and 6-H_2), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.90 (d, 1H, aromatic), 7.20 (m, 2H, aromatic).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.32; H, 5.98; N, 5.87.

General Procedure for Preparation of 3-Aryl-4,5,6,7-tetrahydrobenz[*d*]isoxazoles **3** (Method C, Procedure C.1).

A solution of 25 mmoles of the corresponding benzohydroximinoyl chloride **14** and 75 mmoles of the enamine **10** in 250 ml of dichloromethane was stirred at 20° for 20 hours. The solvent was evaporated, 150 ml of water were added, and the precipitated dihydroisoxazole **15** was filtered.

This compound was dissolved in 50 ml of methanol and 80 ml of concentrated hydrochloric acid and heated under reflux for 1 hour. After cooling and neutralization with aqueous sodium bicarbonate, the precipitated isoxazoles **3** were separated by filtration and purified by crystallization or chromatography.

3-Phenyl-4,5,6,7-tetrahydrobenz[*d*]isoxazole (**3a**).

This compound was obtained in 38% yield as a white solid, after crystallization from ethanol-water, mp 57-58° (lit [8] 53-54°, [11] 52-53°); ^{1}H-nmr (deuteriochloroform): δ 1.76 and 1.87 (two multiplets, 4H, 5-H_2 and 6-H_2), 2.60 and 2.72 (two triplets, 4H, 4-H_2 and 7-H_2), 7.40 and 7.70 (m, 5H, aromatic).

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.57; N, 7.03. Found: C, 78.12; H, 6.24; N, 7.27.

3-(4-Methoxyphenyl)-4,5,6,7-tetrahydrobenz[*d*]isoxazole (**3b**).

This compound was obtained in 41% yield as a white solid, after crystallization from ethanol-water, mp 70-72°; ^{1}H-nmr (deuteriochloroform): δ 1.74 and 1.85 (two multiplets, 4H, 5-H_2 and 6-H_2), 2.55 and 2.70 (two triplets, 4H, 4-H_2 and 7-H_2), 3.80 (s, 3H, OCH_3), 6.90 (d, 2H, aromatic), 7.15 (d, 2H, aromatic).

Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.51; H, 6.81; N, 6.21.

3-(3,4-Dimethoxyphenyl)-4,5,6,7-tetrahydrobenz[*d*]isoxazole (**3c**).

This compound was obtained in 44% yield by column chromatography on silica gel (dichloromethane-hexane 1:1), as a white solid, mp 89-91°; ^{1}H-nmr (deuteriochloroform): δ 1.77 and 1.87 (two multiplets, 4H, 5-H_2 and 6-H_2), 2.58 and 2.72 (two triplets, 4H, 4-H_2 and 7-H_2), 3.90 (s, 6H, OCH_3), 6.90 (d, 1H, aromatic), 7.20 (d, 1H, aromatic), 7.35 (s, 1H, aromatic).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.60; N, 5.40. Found: C, 69.31; H, 6.83; N, 5.61.

3-(4-Chlorophenyl)-4,5,6,7-tetrahydrobenz[*d*]isoxazole (**3e**).

This compound was obtained in 51% yield as a white solid, after crystallization from ethanol-water, mp 92-94°; ^{1}H-nmr (deuteriochloroform): δ 1.72 and 1.82 (two multiplets, 4H, 5-H_2 and 6-H_2), 2.52 and 2.70 (two triplets, 4H, 4-H_2 and 7-H_2), 7.35 (d, 2H, aromatic), 7.60 (d, 2H, aromatic).

Anal. Calcd. for $C_{13}H_{12}NOCl$: C, 66.81; H, 5.17; N, 5.99. Found: C, 66.99; H, 5.31; N, 6.10.

3-(4-Nitrophenyl)-4,5,6,7-tetrahydrobenz[*d*]isoxazole (**3f**).

This compound was obtained in 36% yield as a white-ivory solid, after crystallization from ethanol-dichloromethane, mp 181-184° (lit [9] 180°); ^{1}H-nmr (deuteriochloroform): δ 1.80 and 1.90 (two multiplets, 4H, 5-H_2 and 6-H_2), 2.60 and 2.75 (two triplets, 4H, 4-H_2 and 7-H_2), 7.90 (d, 2H, aromatic), 8.25 (d, 2H, aromatic).

Anal. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.91; N, 11.47. Found: C, 64.12; H, 5.05; N, 11.32.

3-Arylcyclopent[*d*]isoxazoles **4** (Method C, Procedure C.2).

Cycloaddition between the benzohydroximinoyl chloride **14** and the cyclopentanone enamines **11a,c** was performed as indicated above. To a solution of 6.61 mmoles of the obtained aminodihydroisoxazole **16a,c** in 30 ml of acetone were added 5 ml of methyl iodide and the resulting solution was heated under reflux for 4 hours. After 3 days of stirring at room temperature, the solvent was evaporated to dryness and 1.89 g of silver oxide were added to the residue of **17a,c**. The mixture was placed on a sublimator, heated at 200° under reduced pressure (0.5 Torr), and the isoxazole **4a,c** was obtained by sublimation.

3-Phenylcyclopent[*d*]isoxazole (**4a**).

This compound was obtained in 37% yield as a white solid, mp 81-82° (lit [8] 79-80°); ^{1}H-nmr (deuteriochloroform): δ 2.65-2.78 (m, 6H, 4-H_2, 5-H_2 and 6-H_2), 7.35 and 7.70 (m, 5H, aromatic).

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.98; N, 7.56. Found: C, 77.92; H, 6.04; N, 7.35.

3-(3,4-Dimethoxyphenyl)cyclopent[*d*]isoxazole (**4c**).

This compound was obtained in 21% yield as a white solid, mp 93-94°; ^{1}H-nmr (deuteriochloroform): δ 2.65-2.80 (m, 6H, 4-H_2, 5-H_2 and 6-H_2), 3.89 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 6.88 (d, 1H, aromatic), 7.20 (d, 1H, aromatic), 7.40 (s, 1H, aromatic).

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.24; H, 5.99; N, 5.85.

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