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## Graphical Abstract

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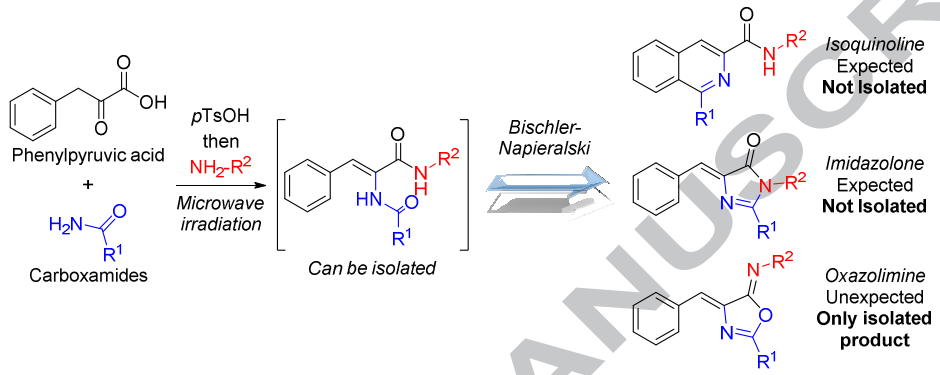

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# Synthesis of 4-benzylidene-oxazol-5(4*H*)-imines, structural analogs of PK11195, under Bischler-Napieralski conditions

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ABSTRACT

A simple and convenient one-pot procedure to prepare 4-benzylidene-2-aryl-1,3-oxazol-5(4*H*)-imines from phenyl pyruvic acid and a series of arylamides, under classical Bischler-Napieralski (B-N) conditions and microwave heating (MW) has been developed. The structures of the prepared compounds were unambiguously assigned through single crystal X-ray diffraction studies. The compounds thus prepared can be used to synthesize bioactive compounds with different molecular architectures.



## 1. Introduction

PK-11195 (**1**, **Figure 1**) is a non-benzodiazepine peripheral benzodiazepine receptor (PBR) antagonist comprised of an isoquinoline ring with an appended aromatic group at C-1 and a carboxamide functionality at C-3. Several methods have been devised to construct this molecule[1] relying on the preparation of the parent acid PK11209 (**2**), and from there the amide is formed via the corresponding acid chloride.

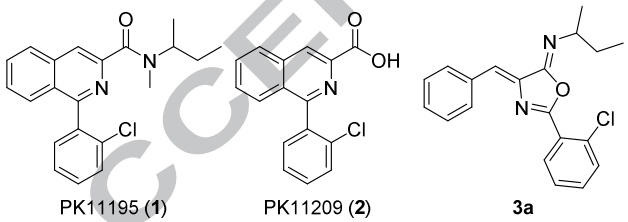
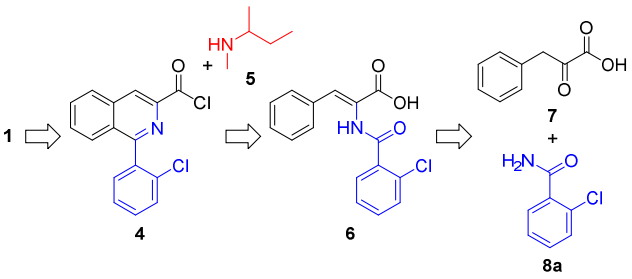



**Figure 1**. Structures of PK11195 (**1**), PK11209 (**2**) and 4-benzylidene-oxazol-5(4*H*)-imine (**3a**).

During our research aimed to prepare some analogs of PK11195, we decided to investigate an alternative procedure to obtain this compound in a simple manner. In 2001, Chen[2] reported the formation of 3,4-dihydroisoquinoline derivatives using *N*-acetyl phenylalanine methyl ester analogs under classical Bischler-Napieralski[3] (B-N) conditions ($POCl_3$, benzene, reflux). With this precedent, we devised a strategy consisting of the condensation between pyruvic acid (**7**) and 2-chlorobenzamide (**8a**) catalyzed by *p*TsOH to provide the dehydroaminoacid **6**. Treatment of **6** with $POCl_3$ would allow the construction of the isoquinoline moiety via a B-N reaction. Furthermore, under the reaction conditions we expected the formation of the corresponding acid chloride (**4**), which after quenching the reaction with *N*-methyl *sec*-butyl amine (**5**) or *sec*-butyl amine–followed by methylation–would afford PK11195 (**Scheme 1**). To our surprise, when *sec*-butyl amine was used to quench the reaction mixture, 4-benzylidene-oxazol-5(4*H*)-imine (**3a**, **Figure 1**) was isolated in a reproducible manner.




**Scheme 1**. Original synthetic strategy for PK11195 (**1**).

Despite the apparent simplicity of the structure of (*Z*)-4-benzylidene-oxazol-5(4*H*)-imines, reported procedures for their preparation are scarce, compared with those for their constitutional isomers (*Z*)-4-benzylidene-1*H*-imidazol-5(4*H*)-ones[4-6] or the structurally related (*Z*)-4-benzylidene-oxazol-5(4*H*)-ones. It is worth to mention that the close structural relation between the above compounds hampers an unambiguous characterization, particularly with incomplete spectroscopic information.

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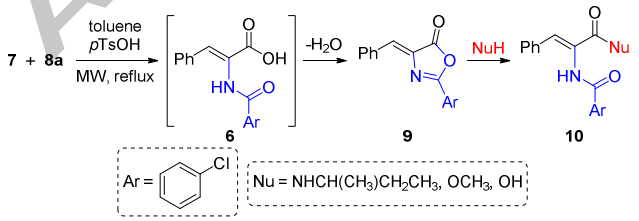
Only a few publications in the literature report the synthesis of 4-benzylidene-oxazol-5(4*H*)imines. In 1972, Boyd[7] reported the reaction of unsaturated azlactones with amines to provide the corresponding amides, which upon treatment with acetic acid and perchloric acid gave a high yield of the benzylidene *N*-monosubstituted iminium perchlorates derivatives. Treatment of the latter compounds with cold aqueous sodium carbonate provided the free base. Sun et al.[8] reported the synthesis of 4-benzylidene-oxazol-5(4*H*)imines through the condensation of benzamidoacetonitriles with aldehydes under acidic conditions. However, ring opening of azlactones with $NH_3$ in EtOH, followed by catalytic hydrogenation, provided the corresponding amide without imine formation. Rudrapal[9] reported the condensation of oxazolones with phenylhydrazine in $EtOH/H_2SO_4$ under reflux conditions, to afford 4-benzylidene-2-methyloxazol-5(4*H*)-ylidene)-2-phenylhydrazones. Hydrazones containing an azomethine group (–NHN=CH–) represent a major class of compounds which possess a broad range of biological activities.[9,10] On the other hand, Esmaeili reported[11] that heating a mixture of *Z*-*α*-benzoyl amino-acrylic acid alkyl esters and cyclohexyl isonitrile under solvent-free conditions, produced 5-imino oxazolines in a diastereoselective manner. The structure and stereochemistry of the imino oxazolines were unambiguously established from X-ray studies.

4-benzylidene-oxazol-5(4*H*)-imines are interesting synthetic compounds that can be used to prepare structurally related derivatives with a variety of potential applications in several disciplines.[7-9,11,12] Herein, we would like to disclose our findings on the synthesis of 4-benzylidene-oxazol-5(4*H*)-imines, along with X-ray diffraction analysis that supports the structural assignment and a mechanistic proposal that explains their formation.

## 2. Results and discussion

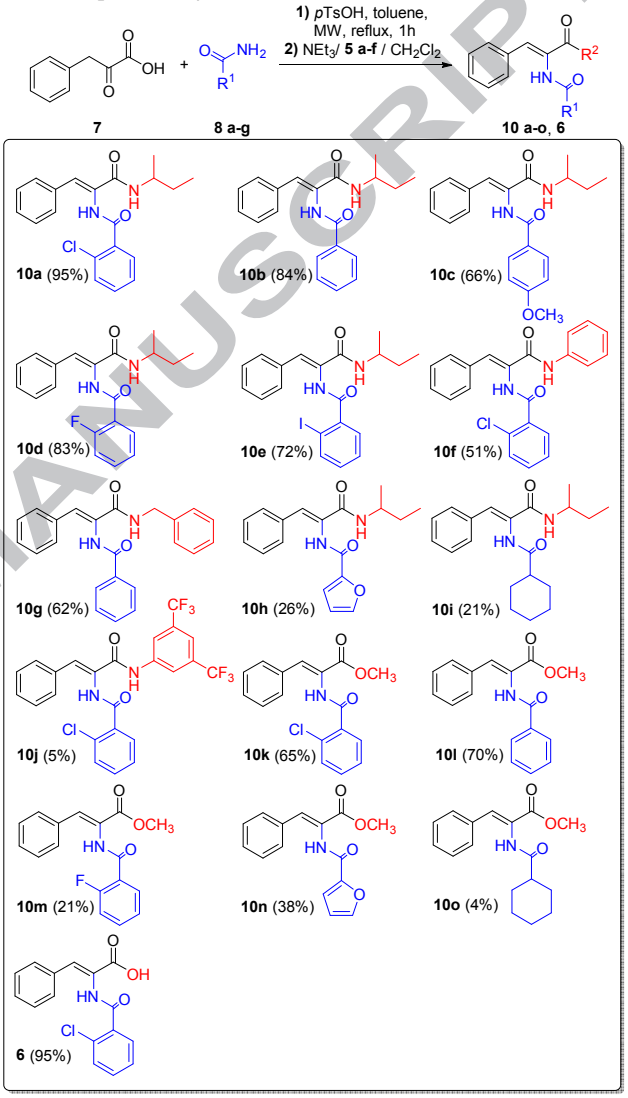
A key step in the devised strategy was the condensation between the keto group of phenyl pyruvic acid and a primary amide. Thus, in our initial experiments when a mixture of 1.5 equiv of pyruvic acid (**7**), 1 equiv of 2-chlorobenzamide (**8a**) and 1 equiv of *p*TsOH was refluxed in toluene under microwave heating (150 W) using a Dean–Stark trap for 1 h, (*Z*)-4-benzylidene-oxazol-5(4*H*)-one **9** was obtained in 85% yield after cooling the reaction mixture to ambient temperature. However, when a mixture of 1.5 equiv of phenyl pyruvic acid (**7**), 1 equiv of 2-chlorobenzamide (**8a**) and 0.2 equiv of *p*TsOH was refluxed (Dean–Stark trap, MW, 150 W) for only 30 min, dehydroamino acid **6** was obtained in 95% yield. Presumably, exposing **6** to the reaction conditions for longer reaction times favors the cyclodehydration reaction producing oxazolone **9**. The formation of **9** can be advantageous since it can be ring-opened with different nucleophiles as illustrated in **Scheme 2**.[13] For instance, reaction of **9** with *sec*-butylamine, MeOH and $H_3O^+$ afforded the corresponding amide **10a**, ester[14] **10k** and acid **6** respectively.




**Scheme 2**. Condensation between phenyl pyruvic acid (**7**) and 2-chlorobenzamide (**8a**).

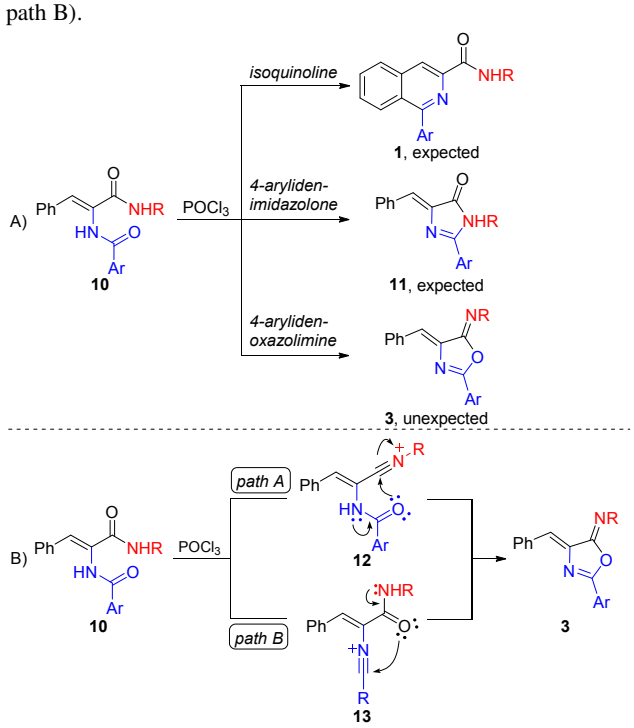
The above procedure can be modified to get amide **10** in a *one-pot* fashion. After the formation of oxazolone **9** was completed (TLC), the addition of 2 equiv of *sec*$BuNH_2$ and $Et_3N$ (4 equiv) afforded **10a** in 95% yield if 1 equiv of *p*TsOH is used, and 65% yield with 0.2 equiv. The scope of this procedure was explored using the amides and nucleophiles shown in **Table 1**. According to the results, when aromatic amides (including furyl amide) are used, the isolated yields of the corresponding products are from modest to excellent. However, when cyclohexanecarboxamide was used, the corresponding product was obtained in low yield.

**Table 1**. Condensation between phenyl pyruvic acid and primary amides to produce *α*,*β*-unsaturated amino acid derivatives.



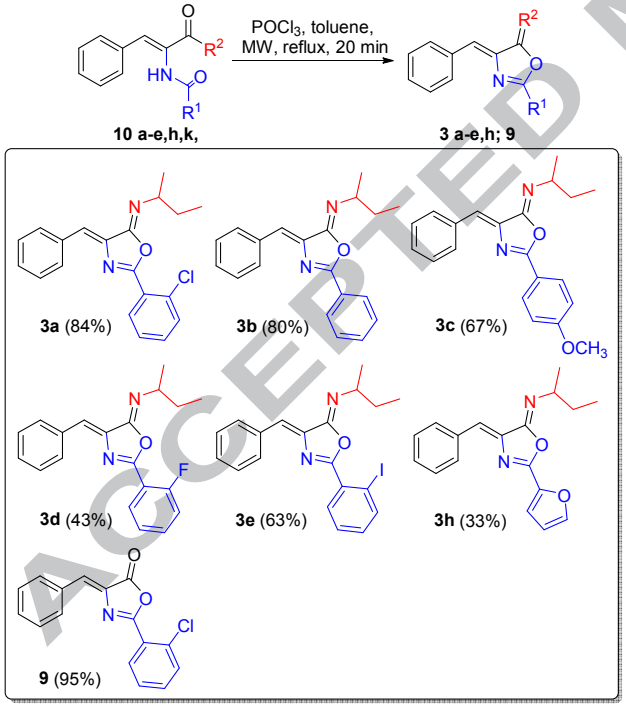

With amide **10a** in hand, we conducted experiments to obtain isoquinoline **1**, according to our original strategy, under B-N conditions. In this manner, when a mixture of **10a** and 5 equiv of $POCl_3$ in toluene was refluxed for 20 min (MW heating, 90 W), 4-benzylidene-oxazol-5(4*H*)-imine **3a** was obtained in 84% yield. Although we anticipated the formation of imidazolone[15] **11** (**Scheme 3A**) we were only able to isolate compound **3**. The possible outcomes for this reaction are depicted in **Scheme 3A**, along with a mechanistic proposal that explains the formation of **3**. Two pathways to convert **10** into 4-benzylidene-oxazol-5(4*H*)imine **3** can be envisioned. Dehydration of the aliphatic amide in **10** would produce intermediate **12** which undergoes a favored 5-*exo*-dig cyclization process[16] (**Scheme 3B**, path A). Likewise, dehydration of the aromatic amide present in **10**,

produces intermediate **13**[17] which after a favored 5-*endo*-dig cyclization process affords 4-arylidenoxazolimine **3** (**Scheme 3B**, path B).




**Scheme 3**. A) Possible outcomes for the reaction between **10** and $POCl_3$. B) Mechanistic proposal that explains the formation of **3**.

**Table 2**. Reaction of **10** with $POCl_3$ to afford **3** and **9**.




Besides $POCl_3$, different dehydrating reagents (DR's) were examined for the *one-pot* synthesis of **3a**, namely: Eaton's reagent,[18] $P_2O_5/POCl_3$ mixtures[19] and propylphosphonic anhydride solution (T3P®).[20] However, the best conditions were the use of $POCl_3$ as DR under microwave irradiation, with a considerable decrease in reaction time, and a reaction yield of 55% for **3a** (with T3P® **3a** was obtained in 14% yield). The use of $POCl_3$ as dehydrating agent allows the preparation of desired product in a *one-pot* fashion. However, we experienced some reproducibility problems depending on the aging time of $POCl_3$. In some experiments, the oxazolone was observed along with the oxazolimine–small amounts of HCl favor the formation of the oxazolone–and in other cases, several side products accompanied the formation of oxazolimine (presumably Von Brown and retro-Ritter products). Nevertheless, when T3P® was used, we observed a cleaner reaction, albeit in low yield.

Formation of oxazolimines **3a-e**,**h** was accomplished using the procedure previously described starting from compounds **10a-e**, **h**. The results are summarized in **Table 2**. Treating **10a** with $POCl_3$ (5 equiv) in toluene for 20 min (MW, reflux) afforded **3a** in 84% yield. When the same transformation was performed using T3P® (10 equiv) and 90 min of microwave heating, **3a** was obtained in 39% yield. The use of 15 equiv of T3P®, or the use of conventional heating had no significant effect on the reaction yield. Good results were obtained for **3b-e** with yields from 43 to 80%. Under the same conditions, **3h** was obtained in 33% yield.

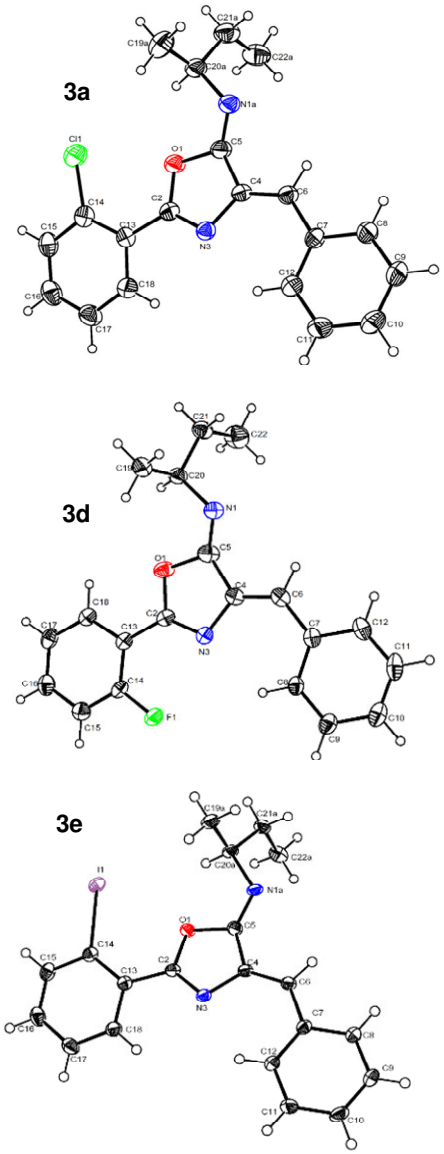



**Figure 2**. ORTEP diagram for the structure of compounds **3a**, **3d** and **3e** derived from SXRD. Thermal ellipsoids are drawn at 50% probability.

When the methyl ester **10k** was subjected to the same reaction conditions, oxazolone **9** was obtained in 95% yield (**Table 2**). A similar result was obtained for the reaction between **10k** and T3P®, affording **9** in 81% yield, which is a structural isomer of 4-(3-chlorobenzylidene)-2-phenyl-1,3-oxazol-5(4*H*)-one, a compound with reported antimicrobial activity.[21]

Discriminating between the structures of oxazolimines and imidazolones proved to be spectroscopically challenging, as can also be intuited from literature reports on the synthesis of this kind of compounds. Fortunately, we were able to obtain crystals, and the structure of 4-benzylidene-oxazol-5(4*H*)-imine was unequivocally assigned through single-crystal X-ray diffraction studies.

Single crystals suitable for X-ray diffraction (SXRD) were obtained for compounds **3a**, **3d** and **3e** and solved in the P 21/C, P 21/C and P-1 space groups, respectively. Crystals were obtained from DMSO solutions in a NMR tube (a drop of water was added) of the corresponding products in solvent-free packing. *Sec*-butyl groups were disordered, and were refined and modeled in two contributions using variable site occupational factor, SOF, with a 0.75/0.25 ratio. All compounds feature the oxazol-imine moiety, as can be appreciated in the crystal structures in **Figure 2**.

Interestingly, the π-conjugated system in **3d** presents periodic stacking in the crystalline phase (**Figure 3**). This feature has been considered a desirable property, since it favors carrier mobility in organic electronic devices, such as field-effect transistors, which makes this compound a potentially interesting material for solid state applications.[22]

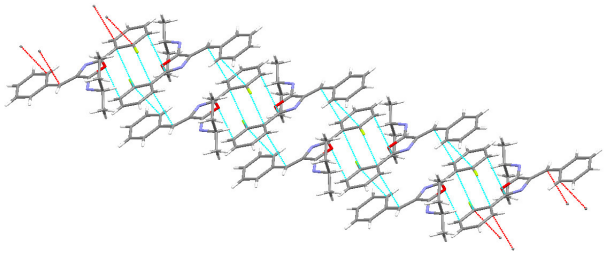


**Figure 3**. Crystal packing for **3d**, illustrating the periodic π - stacking displayed in the solid state.

## 3. Conclusions

We have developed a one-pot synthetic methodology for the easy preparation of 4-benzylidene-2-aryl-1,3-oxazol-5-(4*H*)-imines starting from phenyl pyruvic acid and aryl amides. The same compounds can be obtained from *α,β*-unsaturated acid derivatives, with a significant increase in overall yield. The developed methodology can also be used for the preparation of other *α,β*-unsaturated acid derivatives with moderate to good yields. Both procedures are based on the in situ formation of an oxazolone as intermediate. Even though the structural discrimination between benzylidene-2-aryl-1,3-oxazol-5-(4*H*)-imines and benzylidene-1H-imidazol-5(4*H*)-ones is not straight forward, we were able to unambiguously confirm the structure of the benzylidene-2-aryl-1,3-oxazol-5-(4*H*)-imines obtained in this work using single-crystal X-ray diffraction studies.

Compound **3a** can be considered as a structural analog of PK11195 and might show similar bioactivity. We believe that the proposed methodology can be used to prepare bioactive compounds with different molecular complexities. Additionally, the prepared compounds can find some applications in solid-state organic electronics.

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## Supplementary Material

Supplementary data associated with this article can be found, in the online version, at