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Synthesis of new 1,2-diaryl[2]benzopyrano[3,4-*d*]imidazol-5(1*H*)-one derivatives mediated by ceric ammonium nitrate

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Introduction

From the synthetic point of view the construction of 1*H*-2-benzopyran-1-ones (**1**) (isochromen-1-ones or isocoumarins) framework has been a challenge to the synthetic and medicinal chemists. To this end different synthetic strategies have been developed (Scheme 1).[1–10]

The isocoumarin nucleus is of special interest because of its wide bioactive spectrum; some derivatives have been screening as herbicidal, insecticidal and fungicidal,[2b] DNA-Dependent Protein Kinase inhibitors,[6] anti HIV-1,[11] anti-allergic,[12] anticoagulants,[13] among others.

Some years ago, Opatz and Ferenc developed a strategy for the synthesis of new diaminoisocoumarin derivatives (Scheme 2).[14] This reaction is a combination between the Strecker and Ugi reactions, in fact the diaminoisocoumarin derivatives which are obtained by a Strecker procedure are actually a stable intermediates in the Ugi reaction.[3] Following this strategy, Marcaccini et al. have obtained others diaminoisocoumarin derivatives by using isocyanide derivatives instead of an inorganic cyanide.

Despite the reports found in the literature concerning to the instability of compounds **1** under different reaction conditions[3,15,16] they have attracted our attention since they could be used as starting substrate in the synthesis of new heterocyclic compounds which in turn could be explored for their biological activity.

On the other hand, Ceric Ammonium Nitrate (CAN) has proved to be very useful in organic synthesis for over 45 years and it plays an important role as mediator in different chemical transformations in the field of heterocyclic chemistry.[17] Recently, it has been used in the synthesis or modification of: (a). Substituted phenanthrenes and dihyroquinoline derivatives by a carbon-carbon bond formation,[18a–c] (b). Disubstituted-1,3,4-oxadiazoles, 4,5-dihydrofuran and pterin derivatives by a carbon-oxygen bond formation,[18d–f] (c). Dihydropyrimidine-coumarin analogues by a carbon nitrogen bond formation,[18g] (d). 1,3-Dicarbonyl compounds by a carbon-sulfur bond formation[18h] and (e). Spiro indeno[1,2-*b*]quinolin] derivatives by a combination of carbon-carbon and carbon-nitrogen bond formation,[18i] among others. The reasons for its wide use is due to it has two special chemical characteristics, in the first place it can act as a Lewis acid catalyst and, in the second place it can act as an oxidizing agent since it accepts an electron.

In this paper we present the use of CAN as key mediator in the synthesis of new 1,2-diaryl[2]benzopyrano[3,4-*d*]imidazol-5(1*H*)-one derivatives under mild reaction conditions.

Results and discussions

Our route to prepare compounds **6a–j** starts with the synthesis of 3,4-diaminocoumarin derivatives **1a–d** which are obtained in good yield (Table 1) by the strategy developed by Opatz and Ferenc (Scheme 2).[14] Then, compounds **1a** and **4a** were used as a model to set up the reaction conditions. Therefore, they were reacted together under diverse reaction conditions affording the results shown in Scheme 3.

Initially, we used acetic acid (entry 1), which resulted in the formation of the Schiff base **5a** in high yield (82%); then, molecular iodine was used as catalyst in a non-protic solvent like ethyl acetate, and under these conditions the ring opening-closure, like the Dimroth rearrangement took place to afford compound **7** also in high yield (88%). This result is in agreement with a previous report.[15] In contrast, the use of *p*-toluensulfonic acid as catalyst (entries 3 and 4) with different solvents and temperatures did not afford the desired compound **6a**, instead a mixture consisting mainly of compounds **5a** and **7** was obtained in low yields. Furthermore, the use of a strong Lewis acid as boron trifluoride etherate (entries 5 and 6) afforded a more complex mixture even.

Because of our one-step methodology of cyclocondensation did not work (Scheme 3) and taking into account the instability of compound **1a** (and its analogues **1b–d**) under the explored reaction conditions (Scheme 3), we decided to develop a two-step sequence, firstly isolating compound **5a**, and afterwards inducing it to the corresponding cyclization to yield compound **6a**. Scheme 4 shows the different reaction conditions explored to this end. So, when *p*-toluensulfonic acid was used (in ethyl acetate, entries 1 and 2) as a catalyst either at room temperature or under reflux compound **5a** demonstrated to be stable (in contrast to the starting compounds **1a–d**) but did not form the desired compound **6a**.

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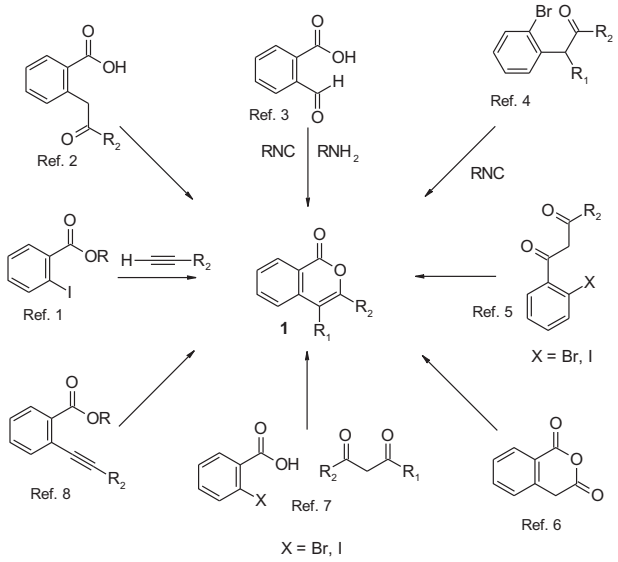
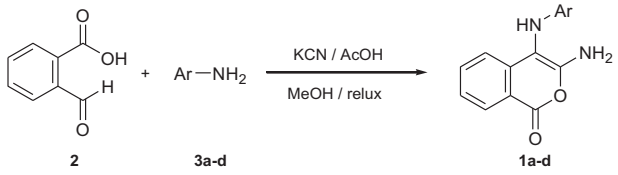


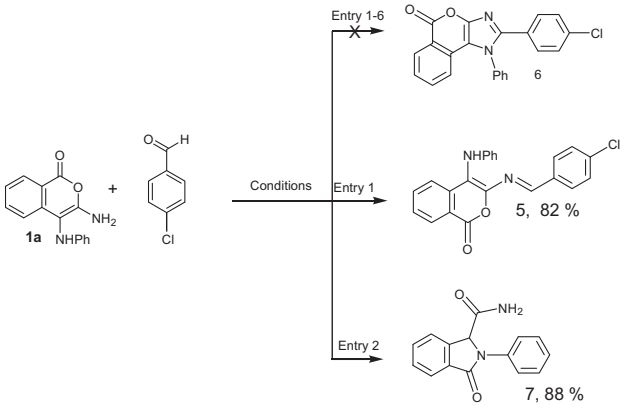
Scheme 1. Synthetic approximations to different isocoumarin derivatives.



Scheme 2. Synthesis of 3,4-diaminoisocoumarin derivatives **1a–d**.

Table 1
Yields for the products **1a–d**.

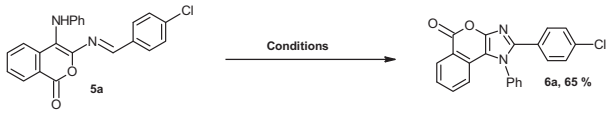
Compound	Ar	Yield
1a	C_6H_5	86
1b	4-MeC_6H_4	81
1c	4-BrC_6H_4	84
1d	4-ClC_6H_4	80



Entry	Solvent	Catalyst	Product(s)
1	**AcOH**[a]	**AcOH**	**5a**
2	AcOEt[b]	I_2	**7**
3	THF[b,c]	*PTSA*	**5a** + **7**
4	AcOEt[a,c]	*PTSA*	**5a** + **7**
5	$ClCH_2CH_2Cl$[b]	$BF_3.OEt_2$	**Complex Mixture**
6	AcOEt[b]	$BF_3.OEt_2$	**Complex Mixture**

a. 50 °C. b. Room temperature. c. Low yield for both compounds

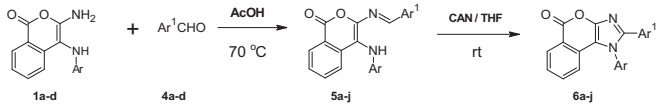
Scheme 3. Different attemps to obtain compound **6a** from **1a** and **4a**.



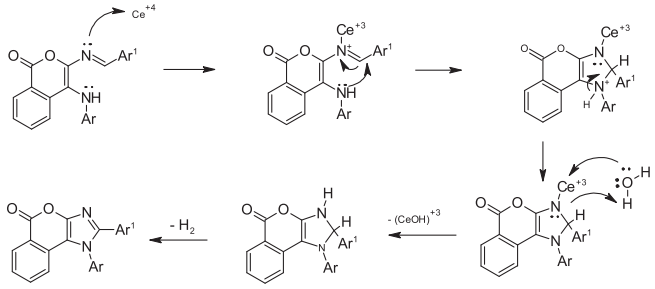
Entry	Solvent	Catalyst	Product(s)
1	AcOEt[a]	*PTSA*	**5a**
2	AcOEt[b]	*PTSA*	**5a**
3	AcOEt[a,b]	*Cu(AcO)₂*	**5a**
4	**THF**[a]	***CAN***	**6a**

Scheme 4. Different attemps to obtain compound **6a** from **5a**. a. Room temperature, b. Heating at 70 °C.

Table 2
Two-step synthesis of 1,2-diaryl[2]benzo-pyrano[3,4-*d*]imidazoles **6a–j** via imines **5a–j**.



Comp.	Ar	Ar^1	**5** (%)	**6** (%)
a	C_6H_5	4-ClC_6H_4	82	65
b	C_6H_5	C_6H_5	85	42
c	C_6H_5	4-$NO_2C_6H_4$	82	67
d	4-MeC_6H_4	4-ClC_6H_4	77	52
e	4-MeC_6H_4	4-$NO_2C_6H_4$	90	71
f	4-MeC_6H_4	4-$MeOC_6H_4$	80	44
g	4-BrC_6H_4	C_6H_5	87	63
h	4-BrC_6H_4	4-ClC_6H_4	84	56
i	4-BrC_6H_4	4-$NO_2C_6H_4$	93	69
j	4-ClC_6H_4	4-$NO_2C_6H_4$	92	74



Scheme 5. An approximation to a plausible mechanism for oxidative cyclization.

Then, we used $Cu(AcO)_2$ as a Lewis catalyst but this strategy did not work either (entry 3). As a last resort CAN was used as a catalyst and tetrahydrofuran as solvent. To our delight, the compound **5a** was transformed into the new desired product **6a** in good yield (entry 4). Then, we tried several reaction conditions in order to optimize the cyclization step mediated by CAN, finding that the best yields were obtained when equimolar quantities of CAN and imine **5a** were used.[19]

Encouraged by these results, we synthesized 10 new imine derivatives **5a–j** which were cyclized to derivatives **6a–j** (Table 2) using the above optimized conditions (entry 1 in Scheme 3, and entry 4 in Scheme 4, respectively) and so, to prove the scope of this procedure with different aryl substituents.

Three facts are noteworthy, firstly the mixture takes an intense orange color due to CAN and, with the progress of the reaction, the color of the solution turns into a light yellow. Secondly, after isolation of compound **6**, the inorganic salt is white which implies a change in the oxidation state of the cerium atom from Ce^{+4} to Ce^{+3} (it is well known that cerium (III) salts are white). Thirdly, the addition of two drops of water reduce the reaction time, as judged by faster change of color of the reaction mixture. With these evidences, we postulate the following plausible mechanism for the formation of compounds **6**.

Conclusion

In summary, we have implemented a simple two-step methodology for obtaining a new series of 1,2-diaryl[2]benzopyrano[3,4-*d*] imidazol-5(1*H*)-one derivatives **6a–j** in acceptable to good yields through a carbon-nitrogen bond-forming reaction by using CAN as key mediator. Which constitutes a simple way to form this interesting tricyclic system that fused isocoumarin and imidazole rings, what is of interest to develop new bioactive derivatives. The role of the CAN is important since it acts as Lewis catalyst, as it was proposed in the mechanism (Scheme 5).

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.02.087.

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19. Details of experimetal procedures and spectroscopy data for all the compounds can be found in the Supplementary material.