SYNTHESIS OF HIGHLY FUNCTIONALIZED NITROGEN HETEROCYCLE FROM 2-HYDROXYCYCLOBUTANONES AND AROMATIC AMINES

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Abstract. *The development of novel methods for the selective functionalization and transformation of cyclobutanes is of great utility and has received significant attention in organic synthesis. Cyclobutanes play a significant role as building units because they can be easily transformed into a variety of interesting compounds by ring-expansion, -contraction and ring-opening reactions. In this account, we summarize our latest results on the use of 2-hydroxycyclobutanones as starting material of new tandem reactions leading to synthetically relevant nitrogen heterocycles.*

Contents

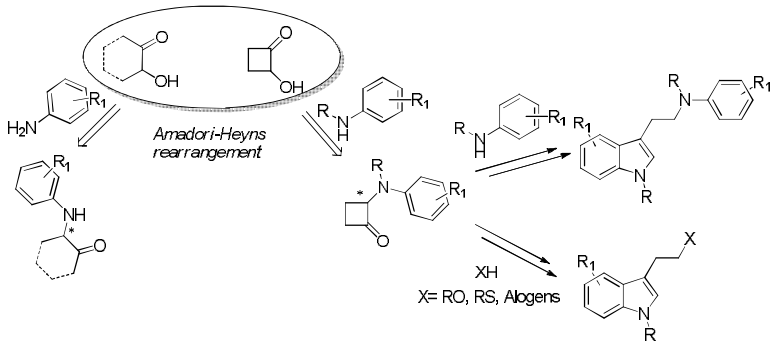
1. Introduction

2-Hydroxycyclobutanones are interesting and useful reagents in organic synthesis. The reactivity of these compounds is connected with the presence of two adjacent functional groups on a strained four-membered ring.[1] As a result, the multifunctional nature of these compounds opens up a range of synthetic possibilities and approaches to unique compounds that cannot be observed in other cyclobutane derivatives.[2] Here we survey our recent advances in the chemistry of 2-hydroxycyclobutanones applied to the synthesis of a number of synthetically useful highly functionalized nitrogen heterocycles.

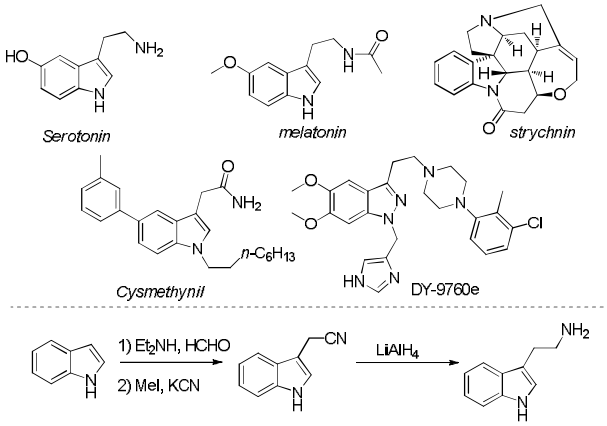
During the last ten years, we have been working on intramolecular rearrangement reactions and synthetic methods based on the transformation of functionalised cyclobutanes as a new reaction mode to facilitate complex heterocycle synthesis in a tandem fashion under mild conditions. In 2013, we reported the first enantioselective organocatalytic synthesis of optically active α-arylamino ketones starting from simple α-hydroxyketones and primary arylamines by an Amadori-Heyns like rearrangement catalysed by Cinchona alkaloids.[3] Then, as a logical extension of the work, the same concept was applied to the formation of intrinsically intriguing optically active 2-arylaminocyclobutanones.[4] We consequently sought to study the potential of 2-arylaminocyclobutanones as synthetic precursors of more complex molecules. We were interested in testing if our developed condensation reaction between α-hydroxycyclobutanone and aromatic amines could be further diversified to include the synthesis of challenging nitrogen heteroaromatic scaffolds such as tryptamines or other high functionalized indoles through both two-step and one-pot procedures (Scheme 1).

2. Synthesis of tryptamines

Tryptamines are attractive, as they are important biologically active compounds widely used in medicine and medicinal chemistry (Scheme 2).[5] The conventional method for the synthesis of tryptamines requires a multistep procedure starting with the Mannich reaction of indole followed by quaternalization of the amine, nucleophilic substitution with cyanide, and final reduction.[6] Recently, Koenigs and co-workers discovered a novel reactivity of iron porphyrin catalyst which enabled the C-H functionalization reaction of indoles with diazoacetonitrile.[7]



Scheme 1. Our previous synthetic studies involving α-hydroxyketones as starting materials and further developments in the field of heterocyclic chemistry.



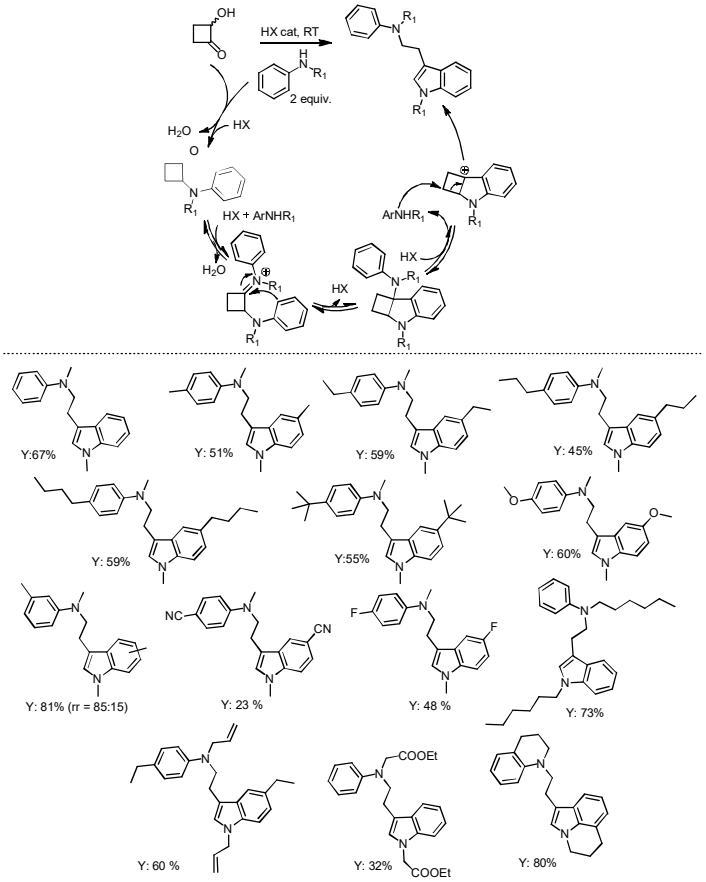
Scheme 2. Occurrence of tryptamines in natural products and biologically active compounds (top). Representative classic multistep procedure for the syntheses of tryptamines (bottom).

This transformation provided access to indole-3-acetonitriles that could be reduced to the corresponding tryptamine derivatives in high yield.[8] By comparison with published synthetic reports in this field, our methodology provided an alternative direct access to this family of substrates in a single operation without metal pollutants, whit potential utilization of products in the pharmaceuticals and biology. The working hypothesis for the development of our methodology derives from the results of a previous study, which showed that the cyclobutanone ring, acting as an intramolecular alkylating reagent, activated for nucleophilic addition by release of ring strain, could easily undergo a cascade ring closure-ring fission in the presence of TsOH.[9] Accordingly, this behaviour could be even enhanced if a cyclobutyliminium species was involved.[10] Based on these findings and intrigued by the potential of this unusual chemical reactivity, we envisaged the possibility that by reaction with two equivalent of a secondary aryl amine, α-hydroxy cyclobutanone would provide access to a variety of multisubstituted tryptamines through a new Brønsted acid catalysed cascade reaction (Scheme 3).

Under solvent free conditions and in the presence of 20 mol% of TsOH at room temperature, the initially-formed*, via* Amadori-Heyns rearrangement, 2-aminocyclobutanone reacted further with the second aniline equivalent in a tandem process to form tryptamine derivatives by an acid-induced depart-and-return rearrangement process.[11] Pleasingly, the method gave access to a number of densely functionalized tryptamines with various ring-substituent patterns.

It was found also that *N*-methyl aryl amines containing electron-donating group at the *para*-position were compatible with the reaction conditions as well as halogens. Furthermore, *meta*-substituted anilines

were tolerated and gave good yield of the corresponding tryptamines as inseparable mixtures of the two possible regioisomers of cyclization. On the other hand, when a representative aniline bearing an electron-withdrawing group such as *para*-CN was used as a starting material, the corresponding tryptamine was formed with low chemical yield. Under the optimized conditions, the substituents on the nitrogen atom of the aryl amine showed good tolerance providing moderate to good yields of the expected products. A major limitation of this technology is that it works well for the preparation of "homo-assembled tryptamines", but it is inefficient for the preparation of tryptamines derived from two different anilines, by using one equivalent of each of these amines sequentially in the one-pot procedure. The expected product, with the first aniline incorporated as the indole core, was obtained as the minor product associated with the corresponding isomeric tryptamine and the two "homo-assembled tryptamines".

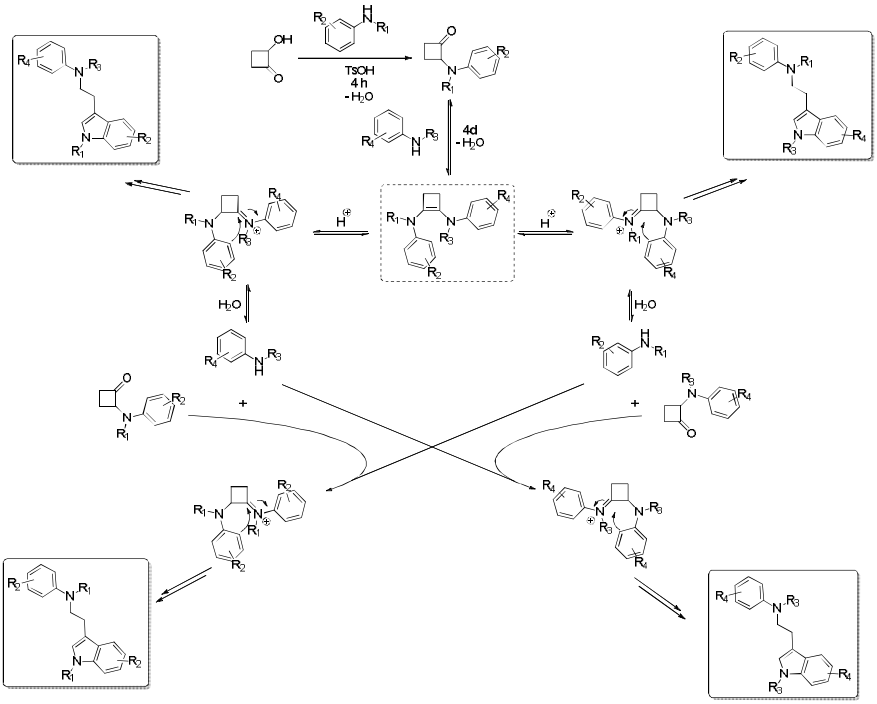


Scheme 3. Proposed reactivity concept relating the synthesis of tryptamines (top). Representative substrate scope of the reaction (bottom).

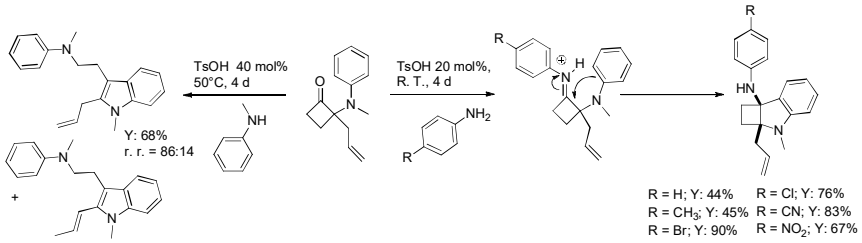
This may be attributable to the acid-catalysed equilibration between the initially formed α-aminocyclobutanone in the presence of the second added aniline that make possible all the combinations between the species in the reaction mixture (Scheme 4).

In any case, the potential versatility of this methodology was also demonstrated through the synthesis of a 2-allyl tryptamine derivative and some valuable cyclobuta-2,3-fused indolines starting from a preformed quaternary α-alkyl-α-amino cyclobutanone (Scheme 5).[12] Although a big effort has been made in these last years for the development of new synthetic protocols to gain access to cyclopropan-, cyclopentan- and

cyclohexan-indolinic C2, C3-fused systems, the analogous term containing a cyclobutanic ring has not received the same attention. Indeed, the first synthetic protocol, based on the gold-catalyzed cyclization reaction [2+2] between an indole and an allenamide, was published only in 2015 by Bandini et al.[13]



Scheme 4. Synthesis of tryptamines derived from two different anilines through a sequential one pot procedure.

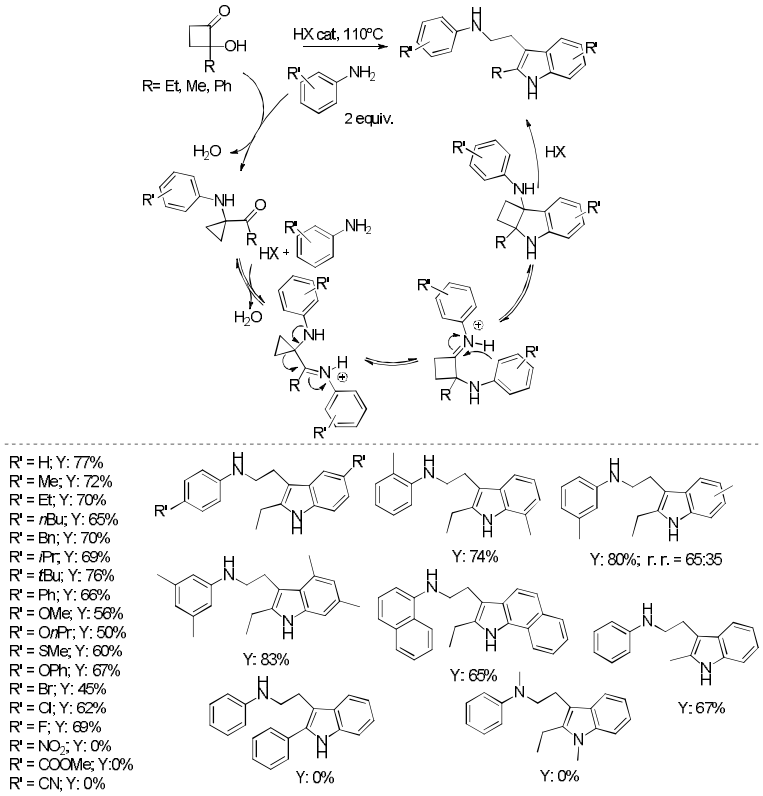


Scheme 5. Preparation of a 2-allyl tryptamine and some tetrahydro-cyclobuta[b]indolyl-amines.

Next, extending our methodology to 2-substituted-2-hydroxycyclobutanones, we discovered a direct route for the preparation of 2-substituted tryptamines. We envisioned that the α-iminol rearrangement of an *in situ* generated 2-substituted-2-hydroxycyclobutyl-imine would efficiently furnish an α-aminocyclopropylketone, which would be converted into a 2-substituted tryptamine derivative, by reaction with a second equivalent of aniline, via an acid catalyzed ring-expansion-ring closure followed by the previously observed depart and return rearrangement process (Scheme 6).[14]

Using TsOH in toluene at 110 °C or diphenyl phosphate (in xylene at 140 °C) as catalyst, the scope of the reaction was evaluated with respect to the presence of substituents on the aromatic ring of aniline and using five representative 2-substituted-2-hydroxycyclobutanones. Anilines bearing electron-donating groups

on the aromatic ring furnished the corresponding tryptamine in good chemical yield while anilines bearing a strong electron-withdrawing groups at the *para*-position failed to produce a tryptamine derivative and the only compound delivered were the corresponding α-aminocyclopropylketone intermediates.



Scheme 6. Proposed reactivity concept relating the synthesis of 2-substituted tryptamines (top). Representative substrate scope of the reaction (bottom).

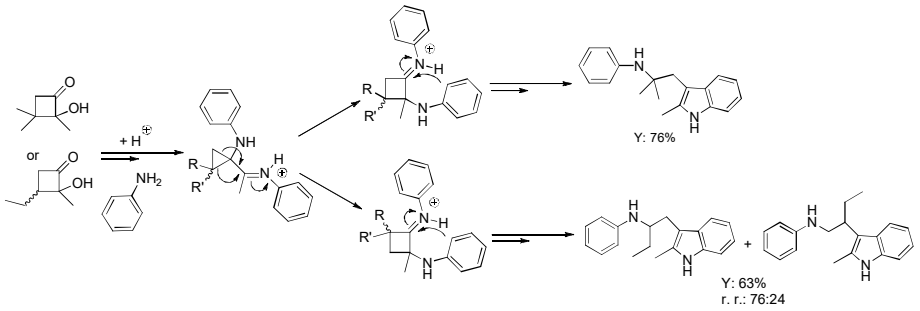
Similarly, 2-phenyl-2-hydroxybutanone, under the same reaction conditions, furnished the corresponding α-aminoketone instead of the corresponding tryptamine. Disappointing results were also obtained using *N*-methyl aniline, used as representative secondary aniline in reaction with 2-ethyl-2-hydroxycyclobutanone. On the other hand, reacting two representative 2,3-disubstituted-2-hydroxycyclobutanones with aniline, the preferential migration of the more substituted cyclopropyl carbon during the ring-expansion step was observed in both cases (Scheme 7).

3. Synthesis of 2-alkoxy-; 2-phenylthio-; 2-phenoxy-; 2-halogen- and 2-trifluoroacetoxy-ethyl-indoles

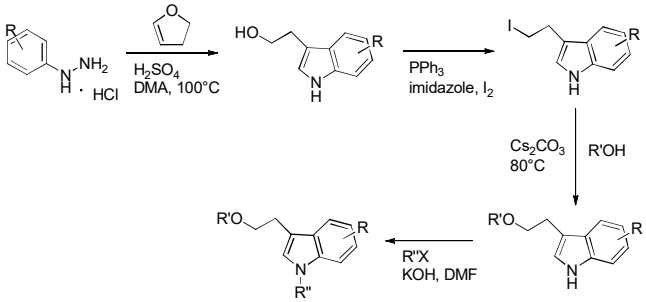
Functionalized indoles constitute an important class of nitrogen heterocycles with widespread application and are found in several natural products possessing diverse biological activities. Moreover, such molecules represent useful building blocks and allow for the synthesis of other nitrogen-heterocycles by post functionalization reactions. In fact, 2-alkoxy-ethyl-indoles are valuable synthons for the generation of interesting indole-fused polycyclic compounds.[15]

Classic method for the syntheses of such derivatives usually require a multistep procedure and harsh conditions (Scheme 8).[16] Having developed a Brønsted acid-catalyzed cascade reaction enabling access to highly substituted tryptamines from 2-hydroxycyclobutanones, we decided to further advance this concept to

include the synthesis of diversely functionalized indoles such as 2-alkoxy-ethyl-indoles starting from a preformed α-arylaminocyclobutanones and alcohols.[17]



Scheme 7. Synthesis of tryptamines derived from 2,3-disubstituted-2-hydroxycyclobutanones.



Scheme 8. Representative classic multistep procedure for the syntheses of 3-(2-alkoxyethyl)-indoles.

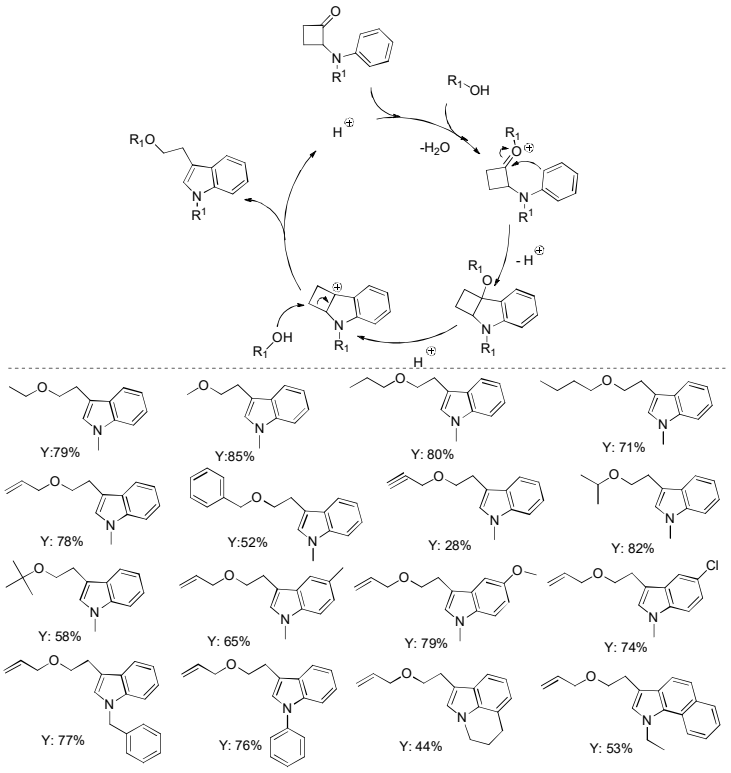
To meet such a challenge, we developed a novel synthetic approach that would proceed through a Brønsted acid-catalyzed condensation of an α-arylaminocyclobutanone with an alcohol to give an oxonium ion which is then converted into the corresponding tricyclic intermediate followed by an acid-induced "depart-and-return" process (Scheme 9). The versatility of this reaction protocol was explored using different alcohols and a number of α-arylaminocyclobutanones. Indeed, under the standard conditions (toluene, TsOH 20 mol%, 80 °C, 48 h), direct access into all the structural 3-(2-alkoxyethyl)-1-methyl-1*H*-indole combinations reported in Scheme 9 was possible.

Notably, this new development provides a viable access to NH indoles in only two (usually high-yielding) steps. In fact, prompted by the demonstration (in Scheme 9) that our reaction methodology could be used to react *N*-benzyl-*N*-phenyl-α-aminocyclobutanone and allyl alcohol to provide *N*-benzyl-3-(2-allyloxyethyl)indole in 77% yield, we extended the application to react the same derivative with a panel of other alcohols to provide four new *N*-benzyl-3-(2-alkoxyethyl)indoles in 75-82% yields (Scheme 10). Each of the five *N*-benzyl-3-(2-allyloxyethyl)indoles was then subjected to Birch reduction conditions, which cleanly provided the requisite NH indoles. In four cases, the yields were good to excellent (75-90%); only the allyl derivative was obtained in a more moderate yield (50%) due to a competitive deallylation reaction.

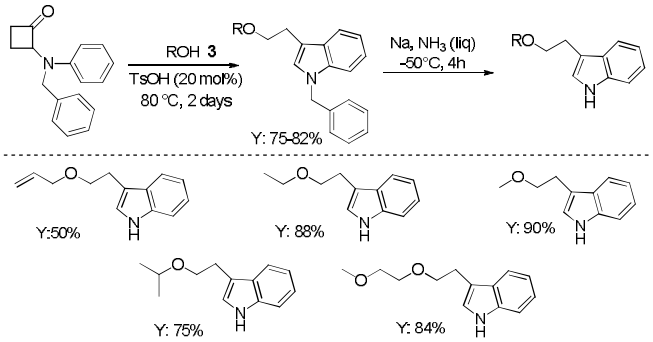
Furthermore, this protocol allowed the construction of 2-phenylthio-; 2-phenoxy-; 2-halogen- and 2-trifluoroacetoxy-ethyl-indoles through an expanded scope of substrates simply using slightly modified reaction conditions (Scheme 11). The new method offered significant flexibility to access these important heteroaromatic frameworks with challenging substitution patterns.

To demonstrate the synthetic utility of the above protocol, 3-(2-iodoethyl)-1-methyl-1*H*-indole obtained from 2-(methyl(phenyl)amino)cyclobutanone as crude reaction product, in the presence of

p-methoxy aniline was further elaborated and easily converted to the corresponding tryptamine in good yield (69%) over two steps.



Scheme 9. Proposed reactivity concept relating the synthesis of 3-(2-alkoxyethyl)-1-methyl-1*H*-indoles (top). Representative substrate scope of the reaction (bottom).

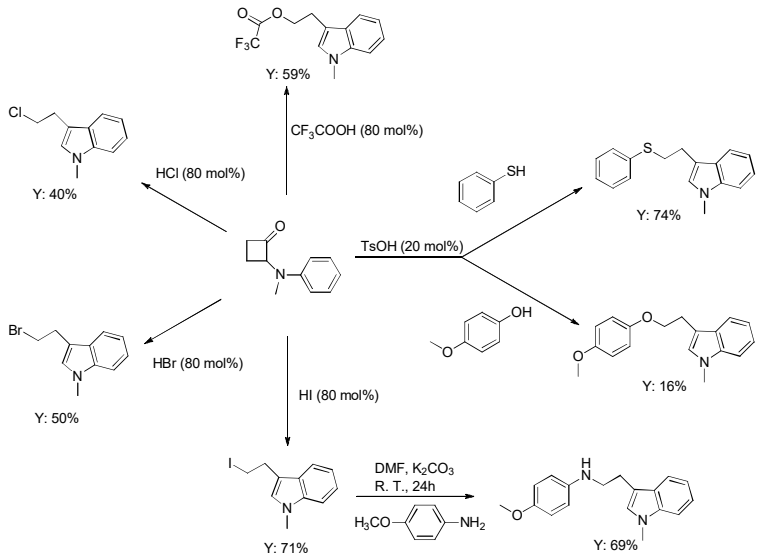


Scheme 10. Two-step reaction sequence for the synthesis of NH indoles

4. Synthesis of 2,2-bis(2-pyridylamino)cyclobutanols and 5-(pyridine-2-ylamino)dihydrofuran-2(3*H*)-ones

Dihydrofuran-2(3*H*)-ones are important scaffolds due to their presence in several biologically active compounds and as valuable building blocks in organic synthesis.[18] Although the preparation of these

heterocycles has been a topic of great interest in the last few years, the number of 5-nitrogen-substituted γ-lactones reported was relatively scarce.[19] In addition, general synthetic protocols for the synthesis of 5-aza-heteroarylamino γ-lactones have not been reported previously. During our studies on the tandem condensation/keto-enol tautomerization reaction between 2-hydroxycyclobutanone and amines we also found that 2-aminopyridines reacted differently with the respect to anilines and alkyl amines and led to the formation of 1-hydroxy-2-diaminocyclobutane scaffolds, under mild conditions even in the absence of any catalytic agent, that is stabilized likely by intramolecular hydrogen bonding (Scheme 12).[20]



Scheme 11. Synthesis of 2-phenylthio-; 2-phenoxy-; 2-halogen- and 2-trifluoroacetoxy-ethyl-indoles.

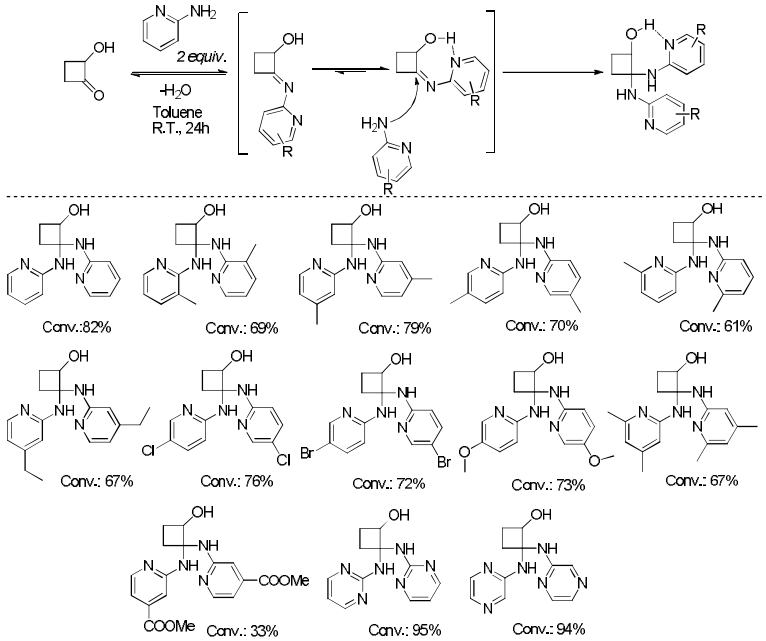
Then, it was apparent that this reaction turned out to be quite general for a selection of substituted 2-aminopyridines as well as 2-aminopyrazine and 2-aminopyrimidine, giving moderate to good yields when 2 equivalents of the 2-aminopyridine were employed in toluene solution at room temperature.

An important aspect of this chemistry was that 2,2-bis(2-pyridylamino)cyclobutanols were easily transformed into the corresponding 5-(pyridine-2-ylamino)dihydrofuran-2(3*H*)-ones, in moderate to good chemical yield, by Dess-Martin periodinane oxidation, through a new rearrangement reaction resulting in a cyclobutyl ring expansion (Scheme 13). 3-Substituted-2-amino pyridines such as 2,2-bis((3-methylpyridin-2-yl)amino)cyclobutanol as well as 2,2-bis(pyrazin-2-ylamino)cyclobutanol represented a limitation of this method.

5. Synthesis of carbonyl-containing alkyl-substituted benzo[d]imidazoles

Continuing our work on the reactivity of 2-hydroxycyclobutanone with amines, we realized also that the related transformation, namely α-iminol rearrangement,[21] involving a 2-substituted-2-hydroxycyclobutanone have received less attention in organic synthesis and for this reason remained virtually unexplored as a general tool for the preparation of important functionalized cyclopropylamines. Therefore, the lack of a report on the use of 2-substituted-2-hydroxycyclobutanones for the synthesis of functionalized α-aminocyclopropylketones prompted us to explore such catalyst-free transformation at room temperature. A number of differently substituted aryl amines, bearing electron-donating or electron-withdrawing substituents, reacted efficiently with various 2-substituted-2-hydroxycyclobutanones to give the desired α-aminocyclopropylketones in good to high yields (Scheme 14). Interestingly, during the course of our study, we found that *o*-phenylenediamines reacted differently with the respect to aryl-amines.[22] In fact, reacting 2-ethyl-2-hydroxycyclobutanone with

o-phenylenediamine, under the same reaction conditions, surprisingly, led to the unexpected formation of 1-(1*H*-benzo[*d*]imidazol-2-yl)pentan-3-one, through most likely, a catalyst-free ring fission process which have not been previously described in the literature.

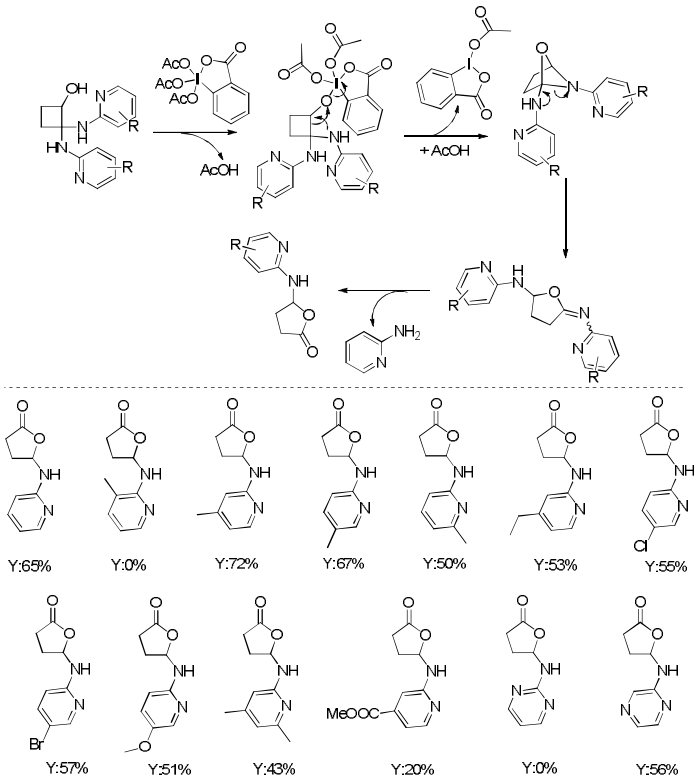


Scheme 12. Mechanistic proposal that explains the formation of 2,2-bis(2-pyridylamino)cyclobutanols (top). Representative substrate scope of the reaction (bottom).

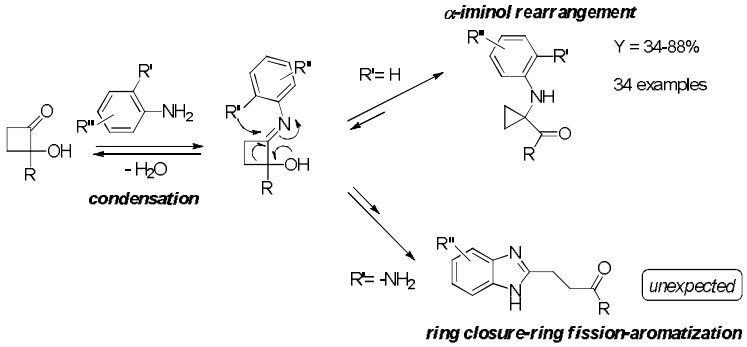
Benzo[*d*]imidazole are common motifs in pharmaceutical research and widely used in organic synthesis.[23] For what concern the synthesis of these compounds,[24] different approaches that involve the condensation reaction of *o*-phenylenediamines with various starting materials such as carboxylic acid derivatives or aldehydes in the presence of strongly acid or oxidative conditions, have been reported (Scheme 15). An alternative method involves treatment of o-phenylenediamines with ketones, β-ketoesters, β-diketones under microwave radiation and high temperatures. However, we noticed that few methods allowed the construction of carbonyl-containing alkyl-substituted benzo[d]imidazoles.

The literature records examples of the classical chemistry, which involve the condensation of 1,2-phenylenediamine with 4-oxopentanoic acid,[25] and the recently reported direct metal catalyzed cyclopropanol Minisci reaction of benzo[d]imidazole itself.[26] Given their inherently important value in synthetic organic chemistry, we decided to investigate this unexpected reaction. A variety of differently substituted *o*-phenylenediamines bearing electron-donating substituents, was allowed to react (toluene, room temperature 48h) efficiently with 2-hydroxy cyclobutanone to give the desired products in moderate to good yields (Scheme 16). In the case of *o*-phenylenediamines bearing strong electron withdrawing groups such as $–NO_2$ or –CN the reaction required the presence of an acid catalyst (TsOH 20 mol%) to achieve good conversions. Unfortunately, the extension of this methodology for the preparation of 3-(1*H*-benzo[*d*]imidazol-2-yl)-1-phenylpropan-1-one was unsuccessful as a complex mixture was obtained when 2-phenyl-2-hydroxycyclobutanone was used as starting material in reaction with *o*-phenylenediamine. *N*-substituted *o*-phenylenediamines were also compatible with this protocol providing the corresponding 1,2-disubstituted benzimidazoles in good to high yields. Based on these results, a plausible mechanism for the formation of benzo[d]imidazoles was proposed. In the first step, 1-hydroxycyclobutanone and *o*-phenylendiamine are condensed to form the corresponding imine intermediate. In the second step, the

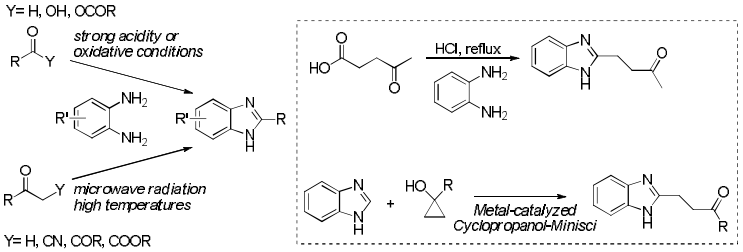
subsequent intramolecular cyclization, instead of a ring contraction, gives a dihydrobenzimidazole intermediate. Finally, this derivative undergoes ring fission to produces a 2,3-dihydro-1*H*-benzo[d]imidazole, which is transformed into the corresponding benzoimidazole by aromatization.



Scheme 13. Mechanistic proposal that explains the formation of 5-(pyridine-2-ylamino)dihydrofuran-2(3*H*)-ones (top). Substrate scope of the reaction (bottom).

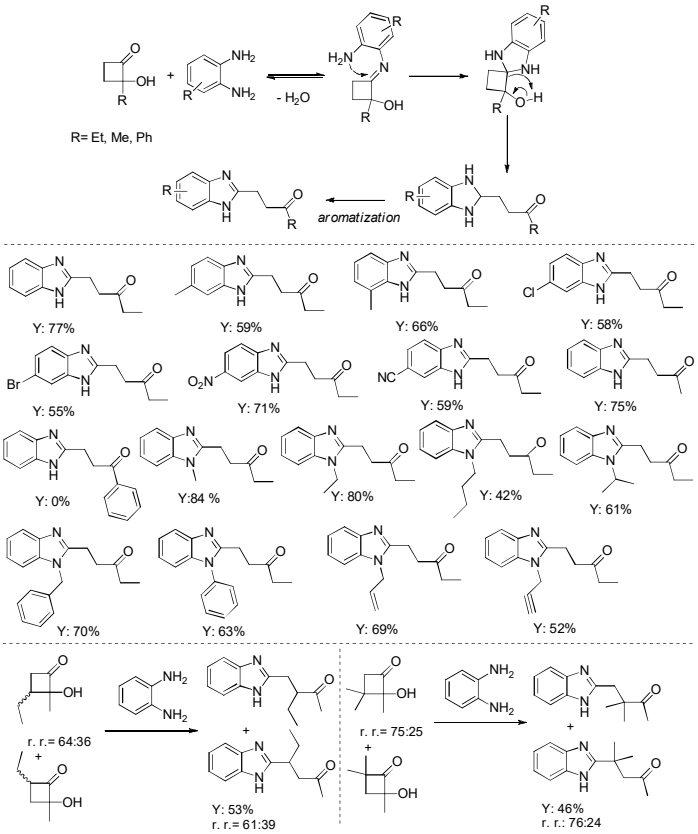


Scheme 14. The new approach developed for the synthesis of α-aminocyclopropylketones and benzo[d]imidazoles.



Scheme 15. Previous works on the synthesis of alkyl-substituted benzo[d]imidazoles.

The strain energy release of the cyclobutane ring would be the driving force for this unusual fragmentation. Notably, the tandem condensation-ring closure-ring fission process could also be conducted starting from 2,3-disubstituted-2-hydroxycyclobutanones in the presence of *o*-phenylenediamine (Scheme 16). As the above-mentioned cyclobutanones exist in solution as an equilibrium mixture of two regioisomers, the reaction afforded the corresponding regioisomeric benzo[d]imidazoles with moderate yields.



Scheme 16. Mechanistic proposal that explains the formation of benzo[d]imidazoles (top). Substrate scope of the reaction (bottom).

6. Conclusions

In summary, in this account, we focused on the potentiality of 2-hydroxycyclobutanones in organic chemistry, in order to show how we have used the chemistry of such versatile molecules in the synthesis of highly functionalized nitrogen heterocycles. The proposed protocols offered also the opportunity to gain new insights on the reaction mechanism of α-iminol and mechanistically related rearrangements. The results obtained encourage us to continue searching for ways to improve the synthetic potential of 2-hydroxycyclobutanones and pushes us to provide further contributions in this direction. In fact, additional work needs to be undertaken in order to extend the synthetic applications and to overcome the current limitations of this chemistry.

Acknowledgements

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References

1. For selected reviews on cyclobutanes, see: (a) Namsylo, J. C.; Kaufmann, D, E. *Chem. Rev.* **2003**, *103*, 1485-1537. (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev*. **2003**, *103*, 1449-1484. (c) Fu, N.-Y.; Chan, S.-H. In *The Chemistry of Cyclobutanes*, Rappoport, Z.; Liebman, J. F., Eds.; Wiley: Chichester, **2005**, 357-440; (d) Lee-Ruff, E. in *The Chemistry of Cyclobutanes*, Rappoport, Z.; J. F. Liebman, J. F., Eds.; Wiley: Chichester, **2005**, 281-355. (e) Salaün, J. *Science of Synthesis* **2004**, *26*, 557-606. (f) Secci, F.; Frongia, A.; Piras, P. P. *Molecules* **2013**, *18*, 15541-15572.
2. (a) Cuccu, F.; Serusi, L.; Luridiana, A.; Secci, F.; Caboni, P.; Aitken, D. J.; Frongia, A. *Org. Lett*. **2019**, 21, 7755-7758; (b) Porcu, S.; Luridiana, A.; Martis, A.; Frongia, A.; Sarais, G.; Aitken, D. J.; Boddaert, T.; Guillot, R.; Secci, F. *Chem. Commun*. **2018**, *54*, 13547-13550; (c) Aitken, D. J.; Capitta, F.; Frongia, A.; Ollivier, J.; Piras, P. P.; Secci, F. *Synlett* **2012**, 727-730; (d) Aitken, D. J.; Capitta, F.; Frongia, A.; Gori, D.; Guillot, R.; Ollivier, J.; Piras, P. P.; Secci, F.; Spiga, M. *Synlett* **2011**, *2011*, 712-716.
3. Frongia, A.; Secci, F.; Capitta, F.; Piras, P. P.; Sanna, M. L. *Chem. Commun*. **2013**, *78*, 8812-8814.
4. (a) Aitken, D. J.; Caboni, P.; Eijsberg, H.; Frongia, A.; Guillot, R.; Ollivier, J.; Piras, P. P.; Secci, F. *Adv. Synth. Catal*. **2014**, *356*, 941-945. For the synthesis of fully aliphatic 2-aminocyclobutanones, see: (b) Frongia, A.; Melis, N.; Serra, I.; Secci, F.; Piras, P. P.; Caboni, P. *Asian J. Org. Chem.* **2014**, *3*, 378-381; (c) Melis, N.; Ghisu, L.; Guillot, R.; Caboni, P.; Secci, F.; Aitken, D. J.; Frongia, A. *Eur. J. Org. Chem*., **2015**, *2015*, 4358-4366.
5. (a) Winter-Vann, A. M.; Baron, R. A.; Wong, W.; dela Cruz, J.; York, J. D.; Gooden, D. M.; Bergo, M. O.; Young, S. G.; Toone, E. J.; Casey, P. J. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 4336-4341; (b) Go, M.-L.; Leow, J. L.; Gorla, S. K.; Schüller, A. P.; Wang, M.; Casey, P. J. *J. Med. Chem.* **2010**, *53*, 6838-6850; (c) Fukunaga, K.; Han, F.; Shioda, N.; Moriguchi, S.; Kasahara, J.; Shirasaki, Y. *Cardiovasc. Ther.* **2006**, *24*, 88-100; (d) Liu, X.; Yuan, Z.; Wang, J.; Cui, Y.; Liu, S.; Ma, Y.; Gu, L.; Xu, S. *Biochem. Biophys. Res. Commun.* **2017**, *484*, 40–44.
6. For critical assessments of strategies for indole synthesis, see: (a) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29-41; (b) Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195 7210.
7. (a) Takano, S.; Nishimura, T.; Ogasawawa, K. *Heterocycles* **1977**, *6*, 1167-1171; (b) Pierce, L. T.; Cahill, M. M.; McCarthy, F. O. *Tetrahedron* **2011**, *67*, 4601-4611; (c) Tsotinis, A.; Vlachou, M.; Papahatjis, D. P.; Calogeropoulou, T.; Nikas, S. P.; Garratt, P. J.; Piccio, V.; Vonhoff, S.; Davidson, K.; Teh, M.-T.; Sugden, D. *J. Med. Chem.* **2006**, 49, 3509-3519; (d) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.* **1977**, *42*, 3945-3949.
8. Hock, K. J.; Knorrscheidt, A.; Hommelshein, R.; Ho, J.; Weissenborn, M. J.; Koenigs, R. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 3630-3634.
9. (a) Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P. *Synlett* **2002**, *2002*, 796-798; (b) Bernard, A. M.; Floris, C.; Frongia, A.; Piras, P. P.; Secci, F. *Tetrahedron* **2004**, *60*, 449-457.
10. Capitta, F.; Frongia, A.; Ollivier, J.; Piras, P. P.; Secci, F. *Synlett*, **2011**, *2011*, 89-93.

11. Melis, N.; Secci, F.; Boddaert, T.; Aitken, D. J.; Frongia, A. *Chem. Commun*. **2015**, *51*, 15272-15275.
12. Ghisu, L.; Melis, N.; Secci, F.; Caboni, P.; Frongia, A. *Tetrahedron* **2016**, *72*, 8125-8364.
13. Jia, M.; Monari, M.; Yang, Q.-Q.; Bandini, M. *Chem. Commun.* **2015**, *51*, 2320-2323.
14. Serusi, L; Cuccu, F.; Secci, F.; Aitken, D. J.; Frongia, A. *Synthesis* **2020**, accepted manuscript.
15. (a) Ascic, E.; Ohm, R. G.; Petersen, R.; Hansen, M. R.; Hansen, C. L.; Madsen, D.; Tanner, D.; Nielsen, T. E. *Chem. Eur. J.* **2014**, *20*, 3297-3300; (b) Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem. Int. Ed*. **2013**, *52*, 12910-12914; (c) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358-1373; (d) Fu, L.; Davies, H. M. L. *Org. Lett.* **2017**, *19*, 1504-1507.
16. Lombardo, V. M.; Thomas, C. D.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2013**, *52*, 12910-12914.
17. Serusi, L.; Bonnans, M.; Luridiana, A.; Secci, F.; Caboni, P.; Boddaert, T.; Aitken, D. J.; Frongia, A. *Adv. Synth. Catal*. **2019**, *361*, 1908-1912.
18. For selected reviews on γ-lactones and related compounds, see: (a) Alonso, D. M.; Wettstein, S. G.; Dumestic, J. A. *Green Chem.* **2013**, *15*, 584-595; (b) Lorente, A.; Merketegi, J. L.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567-4610; (c). Kitson, R. R. A; Millemaggi, A.; Taylor, R. J. K. *Angew. Chem. Int. Ed*. **2009**, *48*, 9426-9451; (d) Salvador, G.; Margarita, P.; Pablo, R.; Jose, S. *Mini-Rev. Org. Chem.* **2009**, *6*, 345358.
19. (a) Genicot, C.; Gobeaux, B.; Ghosez, L. *Tetrahedron Lett*. **1991**, *32*, 3827-3830; (b) Ghosez, L.; Mahuteau-Betzer, F.; Genicot, C.; Vallribera, A.; Cordier, J.-F. *Chem. Eur. J.* **2002**, *8*, 3411-3422; (c) Gunter, M. *J. Chem. Res. (S)* **1987**, *3*, 66-67; (d) Dong, L.-B.; Wu, Y.-N.; Jiang, S.-Z.; Wu, X.-D.; He, J.; Yang, Y.-R.; Zhao, Q.-S. *Org. Lett*. **2014**, *16*, 2700-2703; (e) Tseng, I.-J.; Shen, S.-Y.; Chen, Y.-T.; Huang, C.-Y.; Lin, C.-T.; Lin, P.-Y. *Chem. Pharm. Bull.* **2012**, *60*, 1453-1457.
20. Ghisu, L.; Melis, N.; Secci, F.; Caboni, P.; Arca, M.; Guillot, R.; Boddaert, T.; Aitken, D. J.; Frongia, A. *Org. Biomol. Chem*. **2017**, *15*, 9779-9784.
21. (a) Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477-567; (b) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. *Org. Lett.* **2008**, *10*, 4009-4012; (c) Zhang, X.; Staples, R. J.; Rheingold, A. L.; Wulff, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 13971-13974; (d) Zhang, X.; Dai, Y.; Wulff, W. D. *Synlett* **2018**, *29*, 2015-2018; (e) Li, G.; Piemontesi, C.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed*. **2019**, *58*, 2870-2874.
22. Serusi, L; Soddu, F.; Cuccu, F.; Peretti, G.; Luridiana, A; Secci, F.; Caboni, P.; Aitken, D. J.; Frongia, A. *Adv. Synth. Catal.* **2020**, 362, 4159-4163.
23. Review on benzo[d]imidazoles: Singla, P.; Luxami, V.; Paul, K. *RSC Adv.* **2014**, *4*, 12422-12440.
24. For the synthesis of benzo[d]imidazoles, see: (a) Murru, S.; Patel, B. K.; Bras, J. L.; Muzart, J. *J. Org. Chem*. **2009**, *74*, 2217-2220; (b) Reddy, P. L.; Arundhathi, R.; Tripathi, M.; Rawat, D. S. *RSC Adv.* **2016**, *6*, 53596-53601; (c) Ravi, O.; Shaikh, A.; Upare, A.; Singarapu, K. K.; Bathula, S. R. *J. Org. Chem*. **2017**, *82*, 4422-4428; (d) Tandon, V. K.; Kumar, M. *Tetrahedron Lett*. **2004**, *45*, 4185-4187; (e) Dudd, L. M.; Venardou, E.; Garcia-Verdugo, E.; Licence, P.; Blake, A. J.; Wilson, C.; Poliakoff, M. *Green Chem.* **2003**, *5*, 187-192; (f) Li, Z.; Dong, J.; Chen, X.; Li, Q.; Zhou, Y.; Yin, S.-F. *J. Org. Chem*. **2015**, *80*, 9392-9400; (g) Aridoss, G.; Laali, K. K. *Eur. J. Org. Chem*. **2011**, *2011*, 2827-2835; (h) Das, K.; Mondal, A.; Srimani, D. *J. Org. Chem*. **2018**, *83*, 9553-9560; (i) Li, Z.; Song, H.; Guo, R.; Zuo, M.; Hou, C.; Sun, S.; He, X.; Sun, Z.; Chu, W. *Green Chem*. **2019**, *21*, 3602-3605; (j) Bose, A.; Sau, S.; Mal, P. *Eur. J. Org. Chem.* **2019**, *2019*, 4105-4109. For the synthesis of benzo[d]imidazoles from phenylendiamines and ketones under oxidant-, metal-, and radiation-free conditions, see: (k) Mayo, M. S.; Yu, X.; Zhou, X.; Feng, X.; Yamamoto, Y.; Bao, M. *Org. Lett.* **2014**, *16*, 764-767; (l) Miao, C.; Hou, Q.; Wen, Y.; Han, F.; Li, Z.; Yang, L.; Xia, C.-G. *ACS Sustainable Chem. Eng*. **2019**, *7*, 12008-12013.
25. Boyle, J.; Fenwick, A. E.; Gethin, D. M.; McCusker C. F. (Pharmacia & Upjohn) *US Patent* US2008/0103130A1.
26. (a) Nikolaev, A.; Legault, C. Y.; Zhang, M.; Orellana, A. *Org. Lett.* **2018**, *20*, 796-799; (b) Lu, S.-C.; Li, H.-S.; Xu, S.; Duan, G.-Y. *Org. Biomol. Chem.* **2017**, *15*, 324-327; (c) Bume, D. D.; Pittis, C. R.; Lectka, T. *Eur. J. Org. Chem.* **2016**, *2016*, 26-30.