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Synthesis of α- Aminocyclopropyl ketones and 2-Substituted benzoimidazoles from 2-Hydroxycyclobutanones and Aryl Amines

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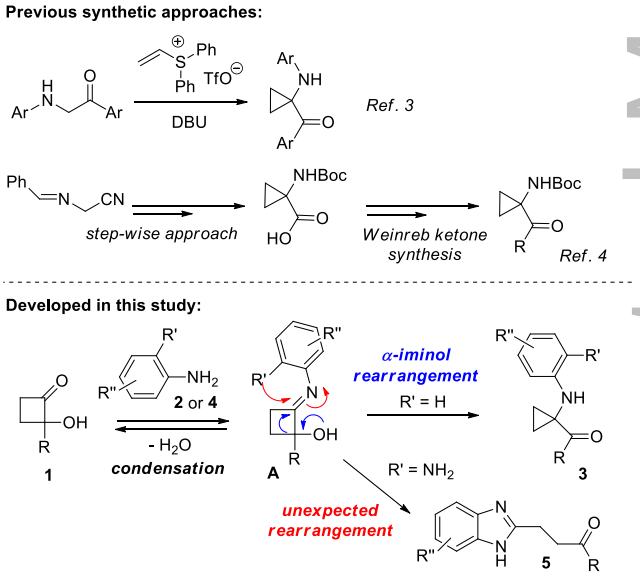
Abstract. We have developed one-step protocols for the preparation of a large selection of α-aminocyclopropyl ketones or benzo[d]imidazoles, by reacting 2-substituted-2-hydroxycyclobutanones with aryl amines or *o*-phenylenediamines, respectively. In most case the reactions proceed at room temperature and are catalyst-free. The formation of benzo[d]imidazoles is rationalized in terms of an unusual ring-closure/ring-fission process followed by aromatization.

Keywords: carbocycles; nitrogen heterocycles; ketones; rearrangement reactions; synthetic methods

Cyclopropylamines are a very important class of organic molecules and a large number of synthetic methods have been proposed for their synthesis.[1,2] Within this family, α-aminocyclopropyl ketones are much less developed. One recent method for the construction of such compounds involves the reaction of α-arylamino ketones and vinyl sulfonium salts in the presence of DBU,[3] while more traditional approaches require multistep procedures[4] (Scheme 1). In the pursuit of our investigations of the reactions of 2-hydroxycyclobutanone with amines,[5,6] we envisaged that the condensation of a 2-substituted-2-hydroxycyclobutanone **1** with an aniline might provide an attractive route to α-aminocyclopropyl ketones **3**, taking advantage of the α-iminol rearrangement[7] of a transient 2-substituted-2-hydroxycyclobutyl imine **A** (Scheme 1). Herein we describe the successful development of this procedure and also disclose the discovery that the use of an *o*-phenylenediamine **4** as the aryl amine partner provides an unexpected new synthetic entry to benzo[d]imidazoles **5**.



Scheme 1. Literature methods for the synthesis of α aminocyclopropyl ketones (top). The new approach developed in this work for the synthesis of these compounds **3** and of benzo[d]imidazoles **5** (bottom).

We began our studies with the benchmark reaction between equimolar amounts of 2-ethyl-2-hydroxycyclobutanone **1a** and aniline **2a**, which gratifyingly afforded α- aminocyclopropyl ketone **3a** in 81% yield after 2 days at room temperature in toluene (Scheme 2). We retained these mild

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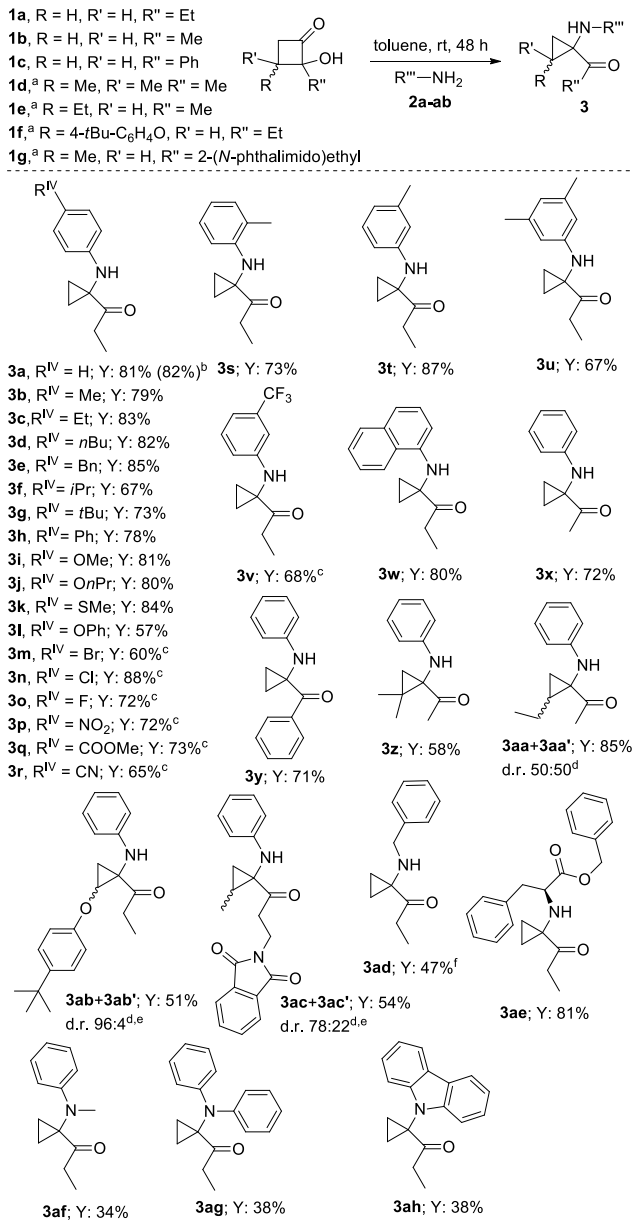
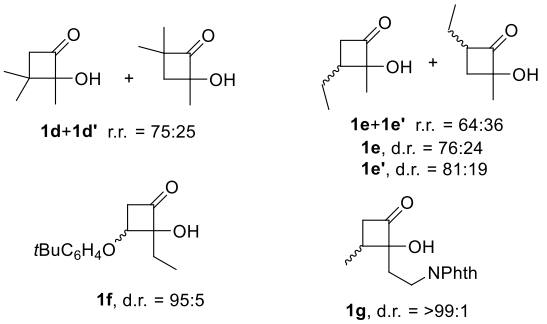
conditions as standard for subsequent investigations of the reaction scope.



Scheme 2. Substrate scope in the synthesis of α-aminocyclopropyl ketones **3**. Reaction conditions: **1** (0.438 mmol), **2** (0.438 mmol), toluene (0.5 mL). Isolated yield are given. [a] See Scheme 3 for substrate composition. [b] Performed using 5 mmol of **1** and **2**. [c] Reactions were performed at 50 °C. [d] The d. r. was determined by ^{1}H NMR analysis of the crude mixture. [e] The relative configurations (*cis*/*trans*) of diastereoisomers could not be unambiguously assigned by NOESY experiments (see ESI). [f] No dimerization by-products were found in the reaction mixture.

A wide selection of *para*-substituted anilines **2b-r** reacted with cyclobutanone **1a** to give the desired products **3b-r** in moderate to high yields. The transformation was successful using anilines bearing electron-releasing functional groups, including alkyl (**2b-g**), phenyl (**2h**), alkoxy (**2i-j**), alkylthio (**2k**) and phenoxy (**2l**), to give the corresponding products **3b-l** (57-85% yield). Reactions with *para*-substituted anilines bearing halogens (**2m-o**) or electron-withdrawing groups, such as nitro (**2p**), methoxycarbonyl (**2q**) and cyano (**2r**), required a higher reaction temperature (50 °C) but otherwise proceeded equally well to give the adducts **3m-r** (60-88% yield). Alkyl substituents in other positions on the aniline (**2s-u**) were well tolerated and provided the derivatives **3s-u** as anticipated (67-87% yield), while the reaction with *m*-(trifluoromethyl)aniline (**2v**) required heating (50 °C) to furnish **3v** (68% yield). The reaction of 1-naphthyl amine (**2w**) also provided the corresponding product **3w** efficiently (80% yield).

We next examined the scope of the reaction using a selection of substituted 2-hydroxycyclobutanones. As we had hoped, both the 2-methyl and 2-phenyl derivatives **1b** and **1c** reacted smoothly with aniline **2a** to deliver the functionalized α- aminocyclopropyl ketones **3x** and **3y** in good yields (71-72%). More highly-substituted 2-hydroxycyclobutanones are not easy substrates to work with since they can exist in solution as an equilibrium mixture of regioisomers;[8] we prepared and studied compound samples **1d/1d'** and **1e/1e'** as shown in Scheme 3. We were pleased to note that the sterically-challenged trimethylated 2-hydroxycyclobutanone mixture **1d/1d'** reacted successfully with aniline **2a** in the standard conditions to provide **3z** as a single compound in 58% yield, while regioisomeric mixture **1e/1e'** gave **3aa**/**3aa'** with no diastereoselectivity but in a satisfying 85% yield. Substrates **1f** and **1g** were also employed successfully to give **3ab**/**3ab'** and **3ac**/**3ac'** in lower chemical yields but with good to excellent diastereoselectivity. To illustrate the usefulness of this protocol, the reaction between **1a** and **2a** was also conducted on a larger scale (5 mmol) to provide **3a** without erosion of the yield (82%; 776 mg).

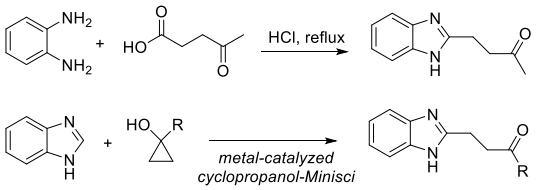


Scheme 3. Highly-substituted 2-hydroxycyclobutanones **1d/1d'-1g** used in this work.

Returning to **1a** as the representative 2-hydroxycyclobutanone, we further explored the reaction scope using other amine partners. The aliphatic amines benzylamine (**2x**) and phenylalanine benzyl ester (**2y**) both reacted smoothly with **1a** in standard conditions, to provide the corresponding α-

aminocyclopropyl ketones **3ad** and **3ae** with moderate (47%) and good (81%) chemical yields, respectively. The reactions of **1a** with the secondary aryl amines *N*-methylaniline (**2z**), diphenylamine (**2aa**) and carbazole (**2ab**) were more sluggish; nevertheless these substrates were converted into the corresponding α- aminocyclopropyl ketones **3af**-**ah** in acceptable yields (34-38%).

It was during the course of these studies with alternative amine partners that we made an important discovery. The reaction of **1a** with *o*-phenylenediamine **4a** in standard conditions did not produce an α- aminocyclopropyl ketone; instead, 2-(3-oxopentyl)benzo[d]imidazole **5a** was obtained in 77% yield. Benzo[d]imidazoles are an important family of heterocycles and a number of synthetic routes thereto have been developed.[9] However, there are very few reports of direct and efficient syntheses of 2-(oxoalkyl)benzo[d]imidazoles (Scheme 4). The most straightforward method, condensation of *o*-phenylenediamine with 4-oxopentanoic acid, requires strong acid conditions and high temperature.[10] More recent approaches employ an elegant metal catalyzed cyclopropanol-Minisci reaction of the parent heterocycle.[11] Since our standard conditions are mild and catalyst-free, we decided to apply them to develop a new synthesis of these compounds.



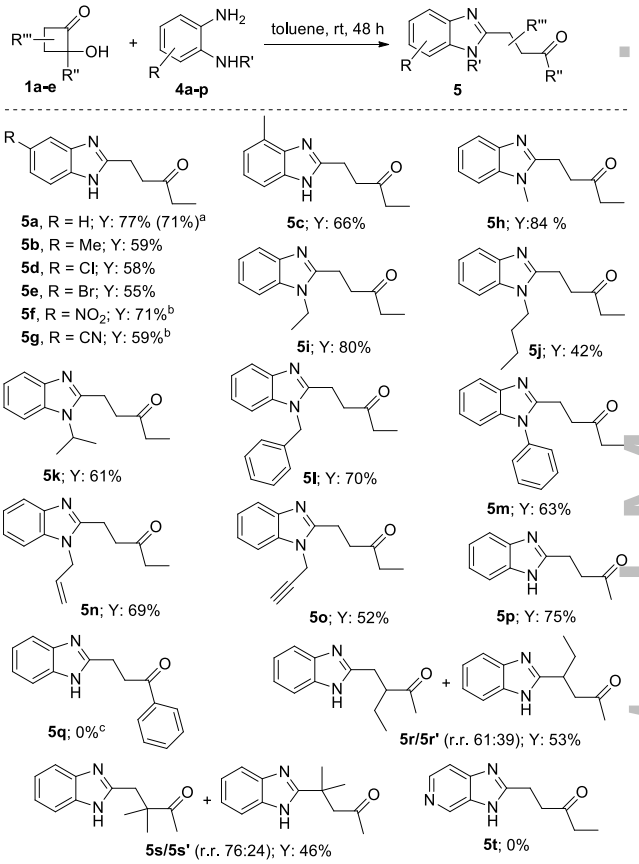
Scheme 4. Literature methods for the synthesis of 2-(oxoalkyl)benzo[d]imidazoles.

In the event, a wide variety of substituted *o*-phenylenediamines **4** reacted with equimolar amounts of cyclobutanone **1a** to give the desired products (Scheme 5). Six ring-substituted *o*-phenylenediamines **4b-g** were examined. The 4-methyl (**4b**), 3-methyl (**4c**), 4-chloro (**4d**) and 4-bromo (**4e**) derivatives provided the corresponding benzo[d]imidazoles **5b-e** in decent yields (55-66%). For substrates bearing strong electron withdrawing groups, 4-nitro (**4f**) or 4-cyano (**4g**), the presence of an acid catalyst (TsOH, 20 mol%) was required to achieve good conversions and provide the requisite benzo[d]imidazoles **5f**-**g** (59-71% yields). A panel of eight *N*-substituted *o*-phenylenediamines **4h-o**, bearing primary, secondary, unsaturated alkyl or aryl *N*-substituents, were all compatible with the protocol and reacted with **1a** in standard conditions to furnish the corresponding 1,2-disubstituted benzo[d]imidazoles **5h-o** in moderate to high yields (42-84%).

We probed the reaction scope further using more complex 2-hydroxycyclobutanones (Scheme 5). *o*-Phenylenediamine **4a** reacted efficiently with **1b** giving the desired product **5p** in good yield (75%), but the 2-phenyl derivative **1c** gave a complex mixture from which **5q** could not be isolated. Reaction with **1d** and **1e** afforded the corresponding regioisomeric benzo[d]imidazole mixtures **5r**/**5r'** and **5s**/**5s'** with moderate yields (46-53%).

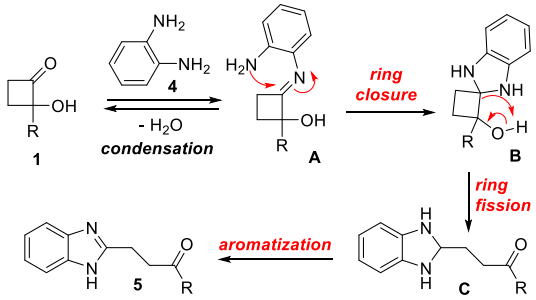
In an effort to access the imidazo[4,5-*c*]pyridine ring system we examined the reaction between **1a** and 3,4-diaminopyridine **4p**. In the standard reaction conditions however, the target compound **5t** was not isolated; only starting materials were recovered from the reaction mixture.

Finally, to illustrate the usefulness of the methodology, the reaction between **1a** and **4a** was conducted on a larger scale (4.7 mmol) to provide adduct **5a** in a slightly lower yield (71%; 671 mg).



Scheme 5. Substrate scope in the synthesis of benzo[d]imidazoles **5**. Reaction conditions: **1** (0.438 mmol), **4** (0.438 mmol), toluene (0.5 mL). Isolated yield are given. [a] Performed using 4.7 mmol of **1a** and **4a**. [b] The reaction was carried out in the presence of TsOH (20 mol%). [c] Complex mixture.

We propose a tandem ring-closure/ring-fission mechanism for the formation of benzo[d]imidazoles **5** (Scheme 6). Condensation of the 2-hydroxycyclobutanone **1** and the *o*-phenylenediamine **4** gives the α-iminol **A** as expected. Attack of the vicinal nitrogen leads to intermediate **B** which evolves by fission and release of ring strain to give **C**; this latter is readily aromatized to give **5**.



Scheme 6. Proposed mechanism for the formation of benzo[d]imidazoles **5** from **1** and **4**.

In conclusion, the results reported here provide generally efficient and wide-scope access to highly functionalized α-cyclopropylamino ketones or 2-substituted benzo[d]imidazoles in very mild conditions, starting from equimolar amounts of a 2-substituted 2-hydroxycyclobutanone and an appropriate amine. The synthetic procedures facilitate expedient access to these molecules which are of wide general interest and are amenable to further derivatization.

Experimental Section

General procedure for the preparation of α-aminocyclopropyl ketones 3a-l, 3s-u, 3w-ah and benzo[d]imidazoles 5a-e, 5h-s.

A solution of **1** (0.438 mmol) and amine **2** or **4** (0.438 mmol) in toluene (0.5 mL) was stirred at room temperature for 48 h. Without any work- up, the crude product mixture was purified directly by flash column chromatography (SiO_2, petroleum ether/ether = 10:1→1:1) to give the designated compounds. Yields refer to chromatographically pure materials.

Procedure for the preparation of α- aminocyclopropyl ketones 3m-3r, 3v.

A solution of **1a** (0.050 g, 0.438 mmol) and amine **2m-r** or **2v** (0.438 mmol) in toluene (0.5 mL) was stirred at 50 °C for 48 h. Without any work- up, the crude product mixture was purified directly by flash column chromatography (SiO_2, petroleum ether/ether = 5:1→1:1) to give the designated compounds. Yields refer to chromatographically pure materials.

Procedure for the preparation of benzo[d]imidazoles 5f and 5g.

A solution of **1a** (0.050 g, 0.438 mmol), amine **4f** or **4g** (0.438 mmol) and TsOH (0.0876 mmol) in toluene (0.5 mL) was stirred at room temperature for 48 h. Without any work- up, the crude product mixture was purified directly by flash column chromatography (SiO_2, petroleum ether/ether = 5:1→1:1) to give the designated compounds. Yields refer to chromatographically pure materials.

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COMMUNICATION

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