Green Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c4gc01515k

Received 6th August 2014,
Accepted 26th September 2014

DOI: 10.1039/c4gc01515k

www.rsc.org/greenchem

Efficient 4,5-dihydro-1*H*-imidazol-5-one formation from amidines and ketones under transition-metal free conditions†

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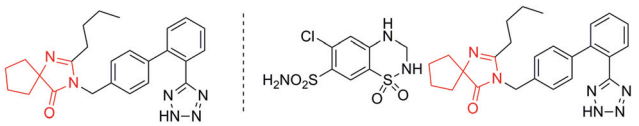
An efficient procedure for 4,5-dihydro-1*H*-imidazol-5-one preparation from aryl amidines and ketones under transition-metal free conditions is described. When cyclic ketones were employed, various spiro-fused 4,5-dihydro-1*H*-imidazol-5-ones were formed in high yields *via* rearrangement reaction.

Nitrogen-containing heterocycles are frequently found in natural alkaloids, functional materials, agrochemicals and pharmaceutical drugs.[1] Therefore, development of efficient methods for the synthesis of heterocycles with multi-nitrogen atoms is of great importance for drug development.[2] Traditionally, imidazole and pyrimidine derivatives were prepared by the condensation of 1,3-dicarbonyl compounds and 1,3-diamines such as ureas, thioureas, amidines and guanidines under acidic or basic conditions.[3] In recent years, transition-metal catalyzed cross-coupling reactions were successfully employed for the construction of nitrogen-containing heterocycles.[4]

Spirans which contain at least two rings and share one spirocarbon atom widely exist in natural products and pharmaceutical drugs.[5] For example, natural and synthetic compounds such as acorenone B,[6] β-vetivone,[7] isocomene,[8] triangulanes[9] and coronane[10] all contain spirocarbon atoms. Due to their unique structural features, the synthesis of spirocycles has attracted much attention from organic chemists and great progress has been made in the past few decades.[11] Compared to the extensively investigated preparation of spirocarbocycles, methods for the synthesis of nitrogen-containing spiroheterocycles were much less developed. A number of substituted 4,5-dihydro-1*H*-imidazol-5-ones which contain a highly strained spiro structure belong to selective and non-toxic herbicides.[12] For example, Avapro and Avalide (both contain a spiro structure produced by Bristol-Myers Squibb) are angiotensin II receptor blockers used to treat hypertension (Scheme 1).[13] The limited methods for spiro-fused 4,5-dihydro-1*H*-imidazol-5-ones are mainly based on the cyclization reaction of the five-membered rings, such as the acylation of amide or nitrile of 1-aminocyclopentancarboxylic acid with pentanoic acid chloride followed by ring closure reaction,[14] the condensation of ethyl 1-aminocyclopentancarboxylate with ethyl pentanimidate,[15] and the reaction of 1-aminocyclopentanecarboxamide with trimethyl orthopentanoate.[16] Dehydrogenation of the corresponding saturated spiro-heterocycles can afford an alternative route for the preparation of 4,5-dihydro-1*H*-imidazol-5-ones.[17] Oxidative rearrangement of tetrahydrobenzimidazoles with dimethyldioxirane can provide spiro-fused 5-imidazolones with good selectivity.[18] However, these methods require highly functionalized five-membered heterocycles usually prepared by several steps which severely limit the reaction scope and their further application. Due to the importance of 4,5-dihydro-1*H*-imidazol-5-ones in pharmaceuticals, it is highly desirable to develop efficient methods to prepare them using readily available raw materials. Herein, we describe a strategy for the preparation of 4,5-dihydro-1*H*-imidazol-5-ones from commercially available amidines and ketones *via* a rearrangement reaction strategy under transition-metal free conditions (Scheme 2).



Avapro (2008 Sales 0.41 billion) **Avalide** (2008 Sales $ 0.36 billion)

Scheme 1 Selected important drugs containing the spiro structure.

To obtain the optimized reaction conditions, the reaction of benzamidine hydrochloride hydrate (**1a**) with cyclohexanone (**2a**) was chosen as the model reaction in the absence of the metal catalyst under an oxygen atmosphere (for details, see Table S1 in ESI†). The desired product **3a** was observed in 5%

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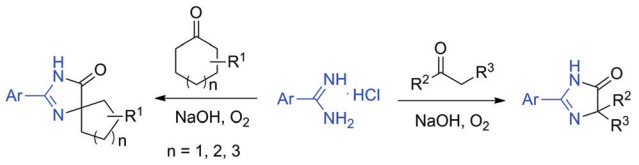
†Electronic supplementary information (ESI) available. CCDC 1017138. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4gc01515k



Scheme 2 New strategy for the synthesis of 4,5-dihydro-1*H*-imidazol-5-ones.

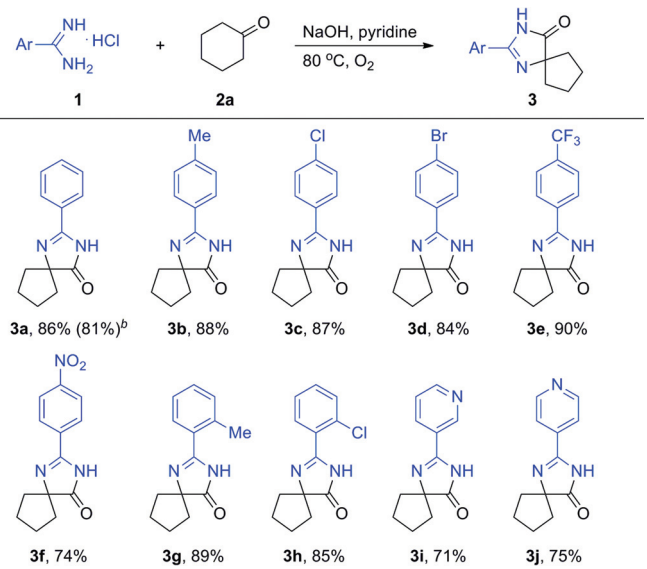
yield when the reaction was carried out in pyridine (entry 2). Basic conditions are favorable to this kind of reaction, and the reaction yield could be improved to 33% when NaOH was used as the base (entry 4). The amount of base is very important to the reaction yield, and the desired product was obtained in 93% GC yield when 4.5 equiv. of NaOH was used (entry 8). Besides pyridine, another nitrogen-containing solvent quinoline was also proved to be a good reaction medium for this kind of reaction (entry 11). A slightly lower yield was obtained when the reaction was carried out in other organic solvents such as NMP and toluene (entries 10 and 12). Other solvents such as DMSO, DMF, DMA, 1,4-dioxane and 1,2-dichlorobenzene were less effective for this reaction. High yield still could be obtained when the reaction temperature was decreased to 60 °C (entry 14). Oxygen was necessary and a much lower yield was obtained when the reaction was carried out in air (entry 16).

With the optimized reaction conditions established, the substrate scope with respect to amidines was examined, and the results were summarized in Table 1. The isolated yield of **3a** was 86%. When the same reaction was carried out on a 5 mmol scale, **3a** was obtained in 81% isolated yield. The desired product **3b** was obtained in 88% yield when 4-methylbenzimidamide (**1b**) was treated with cyclohexanone (**2a**) under the optimized conditions. Halogen functional groups such as chloro, bromo and trifluoromethyl were well tolerated to give the corresponding spiro-fused heterocycles (**3c–3e**) in high yields. A nitro substituent was also compatible, and the corresponding product **3f** was obtained in 74% yield. The position of the methyl substituent did not show much impact on the reactivity (**3b** and **3g**, **3c** and **3h**). To our delight, nitrogen-containing hetero amidines such as **1i** and **1j** smoothly reacted with **2a** to give the desired products **3i** and **3j** in good yields. Unfortunately, aliphatic amidines were not active under the current optimized reaction conditions.

The scope of the reaction with symmetrical cyclic ketones is outlined in Table 2. Cyclohexanones bearing alkyl substituents at the *para* position were able to smoothly react with **1a** to give the corresponding spiro-fused heterocycles in high yields (entries 1–5). Other cyclic ketones such as cycloheptanone (**2h**) and cyclooctanone (**2i**) also could be used for this kind of reaction, and the corresponding products **3q** and **3r** were obtained in 81% and 89% yields, respectively (entries 7 and 8). In all cases, spiro-fused heterocycles were selectively formed in good to high yields when cyclic ketones were used.

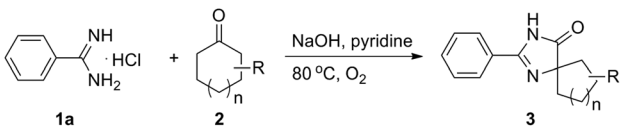
Besides cyclic ketones, linear ketones were also investigated to form non-spiro-fused heterocycles and the results are summarized in Table 3. The reaction showed good selectivity when various methyl–alkyl ketones were reacted with **1a**, and only the longer alkyl group selectively shifted while the methyl

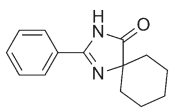
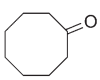
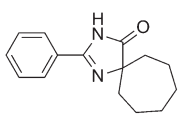
Table 1 Reaction of **2a** with various aryl amidines (**1**)[a]



[a] Conditions: **1** (0.2 mmol), **2a** (0.3 mmol), NaOH (4.5 equiv.), pyridine (0.8 mL), 80 °C, 24 h. Yields refer to isolated products based on **1**. [b] 5 mmol scale reaction yield in parenthesis.

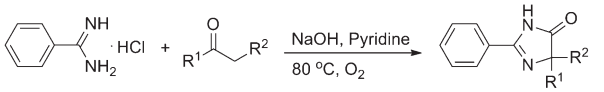
Table 2 Reaction of **1a** with various cyclic ketones (**2**)[a]



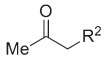
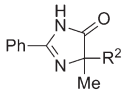
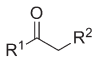
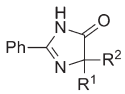
Entry	Substrate		Product	Yield[b] (%)
1	R = Me	**2b**	**3k**	80
2	R = Et	**2c**	**3l**	84
3	R = iso-C_3H_7	**2d**	**3m**	83
4	R = *n*-C_5H_{11}	**2e**	**3n**	85
5	R = *tert*-C_5H_{11}	**2f**	**3o**	71
6	R = Ph	**2g**	**3p**	76
7		**2h**		81
8		**2i**		89

[a] Conditions: **1a** (0.2 mmol), **2** (0.3 mmol), NaOH (4.5 equiv.), pyridine (0.8 mL), 80 °C, 24 h. [b] Isolated yield based on **1a**.

Table 3 Reaction of **1a** with non-cyclic ketones (**2**)[a]



1a **2** **3**

Entry	Substrate		Product	Yield[b] (%)
				
1	$R^2 = C_2H_5$	**2j**	**3s**	68
2	$R^2 = n\text{-}C_3H_7$	**2k**	**3t**	71
3	$R^2 = \text{iso-}C_3H_7$	**2l**	**3u**	61
4	$R^2 = n\text{-}C_4H_9$	**2m**	**3v**	80
5	$R^2 = n\text{-}C_5H_{11}$	**2n**	**3w**	77
6	$R^2 = n\text{-}C_6H_{13}$	**2o**	**3x**	75
7	$R^2 = n\text{-}C_7H_{15}$	**2p**	**3y**	73
				
8	$R^1 = C_2H_5$, $R^2 = CH_3$	**2q**	**3z** (**3s**)	74
9	$R^1 = n\text{-}C_3H_7$, $R^2 = n\text{-}C_2H_5$	**2r**	**3aa**	70
10	$R^1 = n\text{-}C_4H_9$, $R^2 = n\text{-}C_3H_7$	**2s**	**3ab**	81
11	R^1 = Ph, $R^2 = CH_3$	**2t**	**3ac**	85
12	R^1 = Ph, R^2 = Ph	**2u**	**3ad**	86

[a] Conditions: **1a** (0.2 mmol), **2** (0.3 mmol), NaOH (4.5 equiv.), pyridine (0.8 mL), 80 °C, 24 h. [b] Isolated yield based on **1a**.

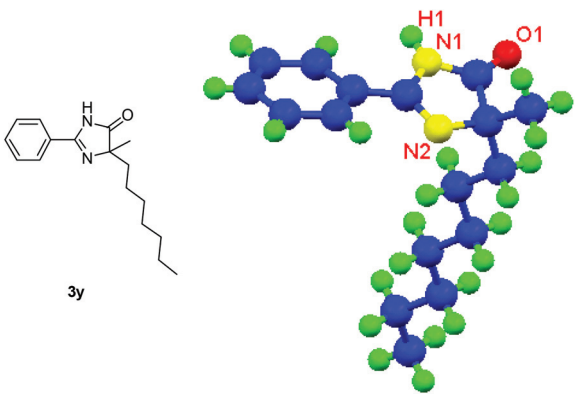
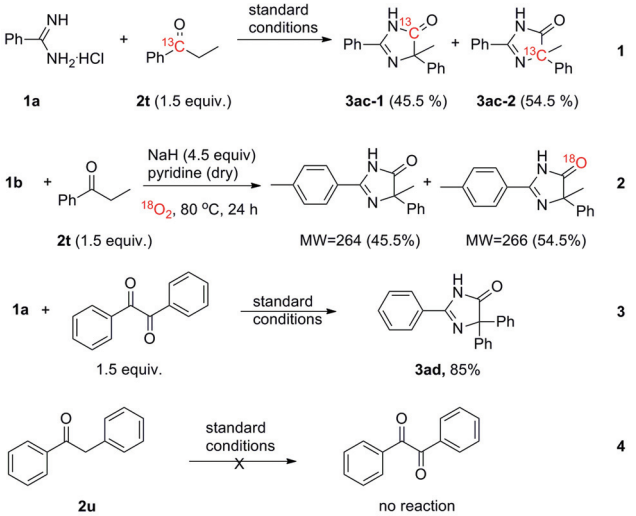


Fig. 1 X-ray structure of **3y**.

group remained (entries 1–7). When 2-decanone (**2p**) was used, the desired product **3y** was obtained in 73% yield. The structure of **3y** was confirmed by X-ray crystallography (Fig. 1). Besides methyl–alkyl ketones, several other symmetrical alkyl–alkyl ketones were also employed for this reaction to give the corresponding products in good yields (entries 8–10). To our delight, non-symmetrical aromatic ketones such as propiophenone (**2t**) and 1,2-diphenylethanone (**2u**) also could be used for this reaction and the desired products **3ac** and **3ad** were obtained in 85% and 86% yields (entries 11 and 12).

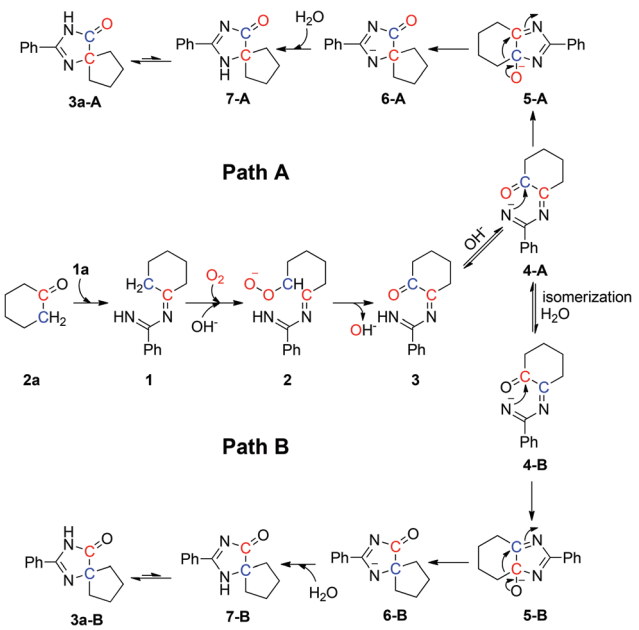
To gain insight into the reaction mechanism, several control experiments were conducted (Scheme 3). The reaction result of **1a** with ^{13}C labeled **2t** showed that the ^{13}C-labeled



Scheme 3 Control experiments.

carbon atom in **2t** appeared at two different sites in the product **3ac** (eqn (1)). The result of ^{18}O labeling reaction showed that part of the carbonyl oxygen atom in the product came from the molecular oxygen (eqn (2)). Benzamidine hydrochloride hydrate (**1a**) could smoothly react with benzil to afford the desired product **3ad** in 85% yield (eqn (3)). However, **2u** could not be converted into benzil in the absence of **1a** (eqn (4)). This means the CH_2 group *ortho* to the carbonyl group in ketone might be oxidized to the carbonyl group and serves as a key intermediate under the standard reaction conditions with the aid of the amidine substrate.

Based on our observations and the literature, a plausible mechanism with two pathways is outlined in Scheme 4. The



Scheme 4 Proposed reaction mechanism.

reaction of **2a** with **1a** generates intermediate **1**, which converts into intermediate **2** under an oxygen atmosphere in the presence of NaOH. Chemical **2** can be converted into carbonyl intermediate **3** [19] and affords **4-A** by protonation. The nitrogen anion of **4-A** attacks the carbon atom of the carbonyl group to form **6-A**,[20] and **6-A** traps a hydrogen ion to yield **7-A** which can be further resonated to give the final product **3a-A** (**path A**). In another pathway, **4-A** is converted into **4-B** by isomerization and hydrolysis reaction. The nitrogen anion of **4-B** attacks the carbon atom of the carbonyl group to form **6-B**,[20] and **6-B** traps a hydrogen ion to yield **7-B** which can be further resonated to give the final product **3a-B** (**path B**).

Conclusions

In summary, we have developed a base-promoted approach for the synthesis of 4,5-dihydro-1*H*-imidazol-5-ones using amidines and ketones under transition-metal free conditions. Various amidines and ketones are suitable substrates for this reaction to give the corresponding products in good yields. When cyclic ketones were employed, various spiro-fused 4,5-dihydro-1*H*-imidazol-5-ones were selectively formed in good to high yields. This method affords an efficient approach especially for spiro-fused 4,5-dihydro-1*H*-imidazol-5-ones using readily available starting materials.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (21172185, 21372187), the New Century Excellent Talents in University from Ministry of Education of China (NCET-11-0974) and the Hunan Provincial Innovative Foundation for Postgraduate (CX2013B269).

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