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Efficient synthesis of nebularine and vidarabine *via* dehydrazination of (hetero)aromatics catalyzed by $CuSO_4$ in water†

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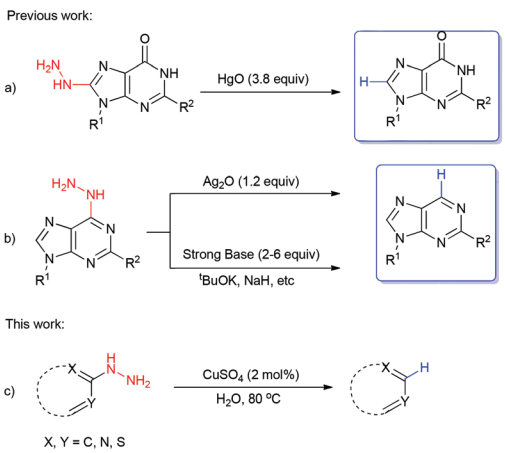
A simple dehydrazination reaction has been achieved in the presence of a catalytic amount of $CuSO_4$ for the first time. With $CuSO_4$ (2 mol%) as a catalyst and water as a solvent, the dehydrazination products were obtained in good yields (66–95%). Moreover, the drugs nebularine and vidarabine were afforded successfully, and vidarabine could be produced on a 0.923 kg scale, which shows good potential for industrial applications.

Hydrazine chemistry is an important area in organic synthesis,[1] and great endeavor has been devoted to the synthesis of substituted hydrazine compounds (R–NHNH$_2$) starting from amines (R–NH$_2$), haloalkanes (R–X) and others.[2a–l] In comparison, dehydrazination reactions have been less studied.[2m,n] The advantages exhibited by the dehydrazination strategy are as follows: (a) the desired dehydrazination products (R–H) can be afforded directly, which is important for synthetic chemistry applications; (b) the deuterated derivatives (R–D) can be effectively synthesized; (c) the deamination and dehalogenation of amines and haloalkanes can occur indirectly; and (d) the product (R–H) can be further functionalized *via* C–H activation strategies.[3] In 1978, Chattopadhyaya and Reese reported the dehydrazination of 8-hydrazinopurine derivatives catalyzed by an excess amount of HgO (3.8 equiv.) (Scheme 1a).[4] Recently, Česnek *et al.* realized the dehydrazination of 6-hydrazinopurine derivatives promoted by Ag_2O (1.2 equiv.) (Scheme 1b).[5] Later, Espinosa *et al.* introduced a strong base (2–6 equiv.) for the dehydrazination of *N*-heteroarylhydrazines (Scheme 1b).[6] Obviously, the high toxicity of HgO and the excess amount of catalyst are not suitable for green and sustainable development. Meanwhile, some functional groups are not tolerant of strong base conditions. Therefore, a green method for dehydrazination with lower catalyst loading, mild reaction conditions and a broad substrate scope is highly desirable.



Scheme 1 Different methods for dehydrazination.

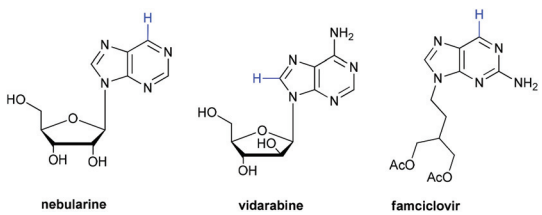


Fig. 1 Examples of purine nucleosides possessing antiviral activities.

Purine nucleosides and their analogues are an integral component of RNA and DNA, and play a significant role in the pharmaceutical industry.[7] As shown in Fig. 1, nebularine is a naturally occurring nucleoside that inhibits growth of the mouse tumour Sarcoma 180 and mycobacteria, and can act as a universal base to bind with all four of the nucleosides of DNA.[8] Vidarabine is an antiviral drug which is active against

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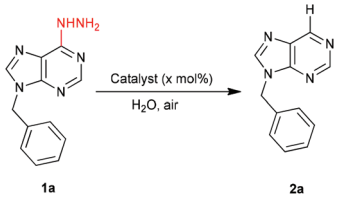
herpes simplex and varicella zoster viruses.[9] Famciclovir has been approved by the FDA for the treatment of herpes zoster (commonly known as shingles) and acute recurrent genital herpes.[10] The industrial production of purine analogues is usually through a dehydrazination reaction promoted by HgO (Scheme 1a). As mentioned earlier, toxic mercury residue presents a health risk to workers and can cause serious environmental pollution. To date, no better alternative suitable for industrial application has been developed. Thus, we wish to develop a green dehydrazination process that avoids the use of toxic HgO. Following on from our previous work on the modification of purine analogues,[11,12] herein we carried out the dehydrazination reaction using a catalytic amount of environmentally friendly and cheap $CuSO_4$ for the first time, with water as a solvent (Scheme 1c).

Initially, we started our study by using 9-benzyl-6-hydrazinopurine (**1a**) as a model substrate to optimize the reaction conditions (Table 1). When $AgNO_3$ or $Mn(OAc)_3$ were used as catalysts, only a trace amount of product **2a** was observed (entries 1 and 2). Other metal salts were then tested, and $FeSO_4$ and $K_3Fe(CN)_6$ could afford the dehydrazination product **2a** with 34% and 62% yield respectively (entries 3 and 4). We were happy to observe that a 94% yield was obtained when $CuSO_4$ (10 mol%) was used as a catalyst (entry 5). Remarkably, the catalytic efficiency was also satisfactory with a lower catalyst loading of 2 mol% (entry 6). The reaction time could be shortened to 6 h and the yield was maintained (entry 7). When the catalyst loading was further lowered to 1 mol%, the product **2a** could still be obtained with a slightly decreased yield (entry 8). Other copper salts including $CuCl_2$ and CuCl were also tested, but a decreased yield was observed (entries 9 and 10). In addition, the reaction temperature was examined and the results showed that 80 °C was the best choice (entries 7 *vs.* 11 and 12). A blank experiment carried out without a metal salt showed that the catalyst was essential for the reaction to occur (entry 13). Meanwhile, when the dehydrazination reaction was performed under N_2, only a trace amount of dehydrazination product **2a** was observed, which indicated that air was crucial for the dehydrazination reaction to occur (entry 14). Therefore, the optimal reaction conditions were $CuSO_4$ (2 mol%) in water under air at 80 °C for 6 h.

To evaluate the generality of the reaction, a number of 6-hydrazinopurine derivatives with different substituents at N9 were examined. As shown in Scheme 2, the corresponding dehydrazination 6-*H* purine derivatives were obtained in good to excellent yields (71–95%). The purine rings bearing different N9-substitutions such as benzyl, alkyl, allyl, ribosyl, deoxyribosyl and arabinofuranosyl groups all furnished the target dehydrazination 6-*H* purine products in good yields (**2a–2h**). In general, the benzyl, alkyl and allyl-substituted substrates gave higher yields compared to the sugar-ring substituted ones (**2a–2c** *vs.* **2d–2h**). When a H atom was substituted

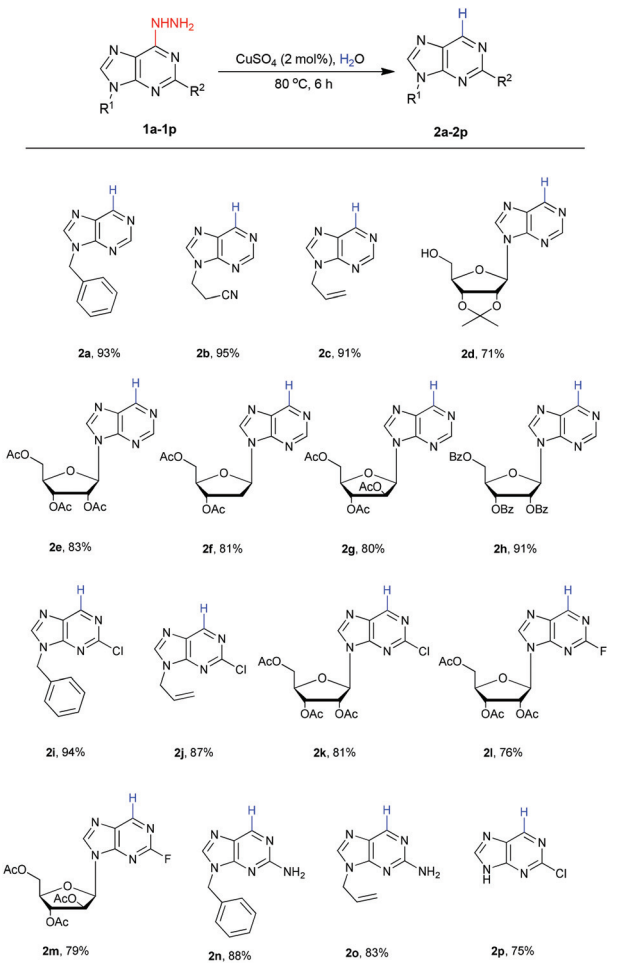
Table 1 Optimization of the reaction conditions[a]



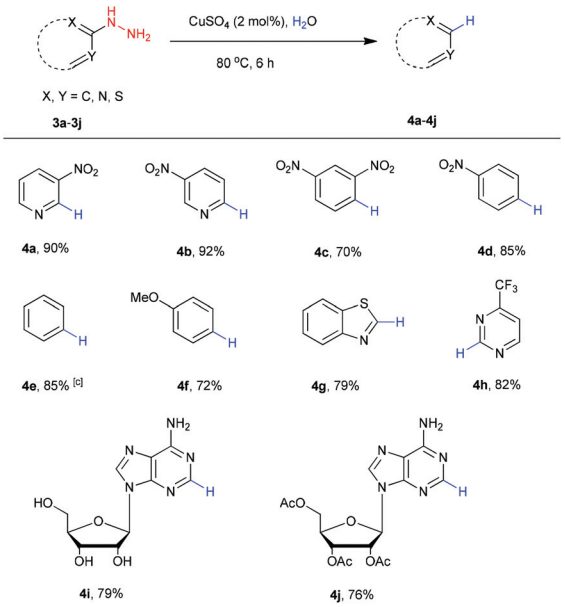
1a 2a

Entry	Catalyst	*x* [mol%]	Temp. [°C]	*T* [h]	Yield[b] [%]
1	$AgNO_3$	10	80	10	Trace
2	$Mn(OAc)_3$	10	80	10	Trace
3	$FeSO_4$	10	80	10	43
4	$K_3Fe(CN)_6$	10	80	10	62
5	$CuSO_4$	10	80	10	94
6	$CuSO_4$	2	80	10	93
7	$CuSO_4$	2	80	6	93
8	$CuSO_4$	1	80	20	87
9	$CuCl_2$	2	80	6	76
10	CuCl	2	80	6	16
11	$CuSO_4$	2	100	6	90
12	$CuSO_4$	2	60	6	63
13	None		80	6	0
14[c]	$CuSO_4$	2	80	6	Trace

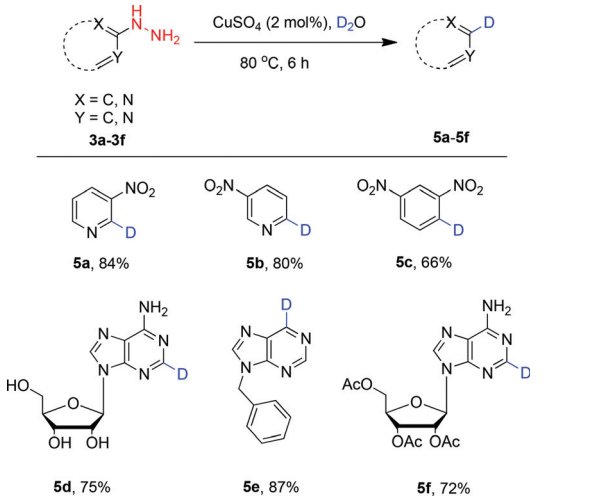
[a] Reaction conditions: **1a** (0.25 mmol), H_2O (3.0 mL), under air. [b] Isolated yield based on **1a**. [c] Under N_2.



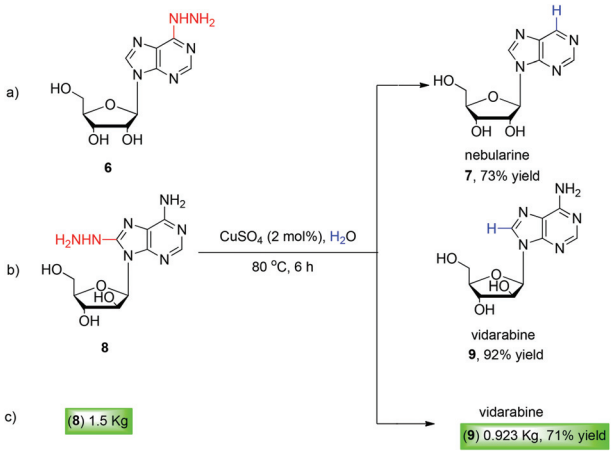
Scheme 2 Dehydrazination reaction of various 6-hydrazinopurine derivatives.[a,b] [a] Reaction conditions: **1a–1p** (0.25 mmol), $CuSO_4$ (0.005 mmol), H_2O (3.0 mL), oil bath, 80 °C, 6 h. [b] Isolated yield based on **1**.



Scheme 3 Dehydrazination of heteroaromatic substrates.[a,b] [a] Reaction conditions: **3a–3j** (0.25 mmol), $CuSO_4$ (0.005 mmol), H_2O (3.0 mL), oil bath, 80 °C, 6 h. [b] Isolated yield based on **3**. [c] 20 h, GC-MS yield, 100% conversion.



Scheme 4 Selective synthesis of deuterium-labelled compounds.[a,b] [a] Reaction conditions: **3a–3f** (0.25 mmol), $CuSO_4$ (0.005 mmol), H_2O (3.0 mL), oil bath, 80 °C, 6 h. [b] Isolated yield based on **3**.



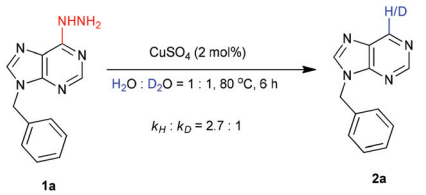
Scheme 5 (a) Synthesis of the drug nebularine; (b) Synthesis of the drug vidarabine; (c) 1.5 kg scale synthesis of the drug vidarabine.

with a Cl or F atom at C2 in the purine derivatives, the yields of the dehydrazination products were almost unchanged (**2a** *vs.* **2i**, **2e** *vs.* **2k**, **2g** *vs.* **2m**). When a H atom at C2 in the purine derivatives was substituted with an amino group, excellent, if slightly reduced, yields could still be observed (**2n** and **2o**). These results indicated that the catalytic system could tolerate different functional groups successfully. Moreover, the free nucleobase could also proceed well through the dehydrazination reaction, giving the corresponding product in a good yield (**2p**).

Next, a variety of hydrazino-substituted purines and other aromatic compounds were examined, and the results are summarized in Scheme 3. 2-Hydrazinopyridine could be converted to the corresponding pyridines in excellent yields (90% and 92%, **4a** and **4b**). It is worth noting that phenylhydrazines bearing electron-withdrawing groups or electron-donating groups could all be dehydrazinated with good yields (70–85%, **4c–4f**). As far as we know, it is the first time that phenylhydrazines have been used as starting materials in the dehydrazination reaction. Other heteroaromatics such as benzothiazole and pyrimidine also displayed good reaction activities (**4g** and **4h**, 79% and 82% product yields). Removal of the hydrazino group on the C2 or C8 position of purine nucleosides also gave rise to the corresponding products in good yields (**4i** and **4j**, 79% and 76%).

Considering the importance of deuterium-labeled compounds in mechanistic investigations, we attempted the synthesis of deuterium-labeled compounds using the method described here. When D_2O was used as a solvent, the desired deuterium-labeled compounds were obtained in good yields (Scheme 4). Therefore, this method provides novel and rapid access to deuterium-labeled heteroaromatic and purine derivatives.

This new green and efficient dehydrazination reaction was also applied to the synthesis of nebularine and vidarabine due to their significant antiviral activities. To our satisfaction, the reaction proceeded smoothly to afford nebularine (**7**) in a 73% yield (Scheme 5a) and vidarabine (**9**) in a 92% yield (Scheme 5b). As shown in Scheme 5c, the reaction to produce the drug vidarabine (**9**), when carried out on a 1.5 kg scale based on our method, resulted in good amounts of the drug (0.923 kg, 71% yield, Scheme 5c). Compared to the original industrial synthetic method that uses an excess of HgO as the dehydrazination reagent, with Hg produced as a side product and causing serious environmental pollution, this method shows good potential for industrial applications.

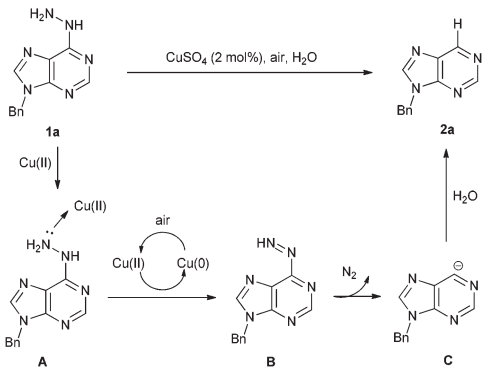


Scheme 6 The isotope effects of H_2O/D_2O.

Finally, some experiments were designed to study the mechanism of the reaction. Firstly, a kinetic isotope effect (KIE) experiment was performed (Scheme 6). The competition experiments between **1a** and H_2O/D_2O showed a primary KIE of 2.7 : 1, which indicates that the formation of C6–H in the purine **1a** is the rate-determining step of the reaction. When the reaction to produce vidarabine (**9**) was performed on a 1.5 kg scale, a large amount of foam was observed (see ESI† for details), and we propose that this foam contained N_2 gas released from the reaction. As air was crucial for the dehydrazination reaction to take place (Table 1, entry 14), the function of air was tested. Under a N_2 atmosphere, when air was replaced by another oxidant such as $K_2S_2O_8$, the reaction still worked well (56% yield, see ESI† for details), which proved that air functions as an oxidant. In addition, a blank experiment was carried out in the absence of H_2O and no product was observed, which showed that the H atom of the C6–H came from H_2O (see ESI† for details). Although the reaction proceeded well in the presence of excess amounts of the radical scavenger TEMPO, the radical process could still not be completely excluded (see ESI† for details).

Based on the above results, a preliminary mechanism for the dehydrazination reaction is proposed in Scheme 7. Firstly, the hydrazine group is activated by the Cu(II) salt (Scheme 7, **A**) and oxidized to the diazene intermediate **B**. Cu(II) is regenerated in the presence of air. The anion intermediate **C** is then generated from diazene[13] with the release of N_2. Finally, the C–H bond is formed between the anion intermediate **C** and H_2O to give the product **2a**.

In summary, we realized the dehydrazination reaction in the presence of a catalytic amount of $CuSO_4$ for the first time. With environmentally friendly and cheap $CuSO_4$ (2 mol%) as a catalyst and water as a solvent, the synthesis of a series of hydrazine-containing compounds proceeded well, affording the dehydrazination products in good to excellent yields. Furthermore, the catalytic system could tolerate different functional groups including –F, –Cl, $–NH_2$, alkyl, allyl, ribosyl, deoxyribosyl and arabinofuranosyl groups. More importantly, the drugs nebularine and vidarabine could be obtained successfully, and vidarabine could even be obtained on a 0.923 kg scale, which shows good potential for industrial applications. In addition, deuterium-labelled compounds could be easily obtained. This new rapid and efficient method, avoiding the use of toxic solvents, represents a promising green route for the dehydrazination reaction. Further studies into the mechanism are currently underway.



Scheme 7 Preliminary proposal for the mechanism.

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