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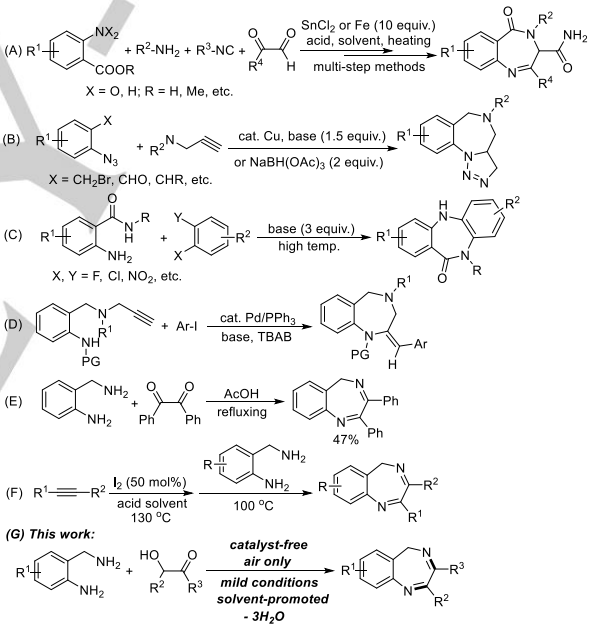
Efficient construction of 5*H*-1,4-benzodiazepine derivatives by a catalyst-free direct aerobic oxidative annulation strategy

Qi Wang,[a] Xiaolan Zhang,[a] Feng Han,[b] Jianping Liu,[b] and Qing Xu*[a,b]

Abstract: A catalyst-free direct aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones can efficiently afford the versatile 5*H*-1,4-benzodiazepine derivatives by employing air as the economic and green oxidant under mild conditions. Interestingly, solvent was found to be crucial to the reaction, so that by using acetic acid as the best solvent, an efficient and practical method can be achieved, requiring no catalysts or additives at all. This method tolerates a wide range of 2-aminobenzylic amines and *α*-hydroxyl ketones, can be scaled up to multigram synthesis and directly applied in one-step synthesis of the pharmaceutically-active *N*-desmethylmedazepam derivatives, revealing the potential of this new method in the synthesis of 5*H*-1,4-benzodiazepine skeleton-based pharmaceuticals and chemicals.

Benzene-fused seven-numbered benzodiazepine heterocycles are significant building blocks in various fields such as the organic chemistry, natural product synthesis, biochemistry, pharmaceutical synthesis, and organic optoelectronic materials.[1-3] Regarding the 1,4-benzodiazepine derivatives, for having good biological and pharmacological activities such as the antianxiety, antidepressant, anticonvulsant, sedative, analgesic, and even anticancer properties,[1,2] various methods have been developed for their construction. For example, multi-step reductive annulation of 2-nitrobenzoic acids (using $SnCl_2$ or Fe as the reducing reagents)[4] or 2-aminobenzoate esters[5] with isonitriles, amines, and 1,2-dicarbonyl compounds or acids could afford 3*H*-benzo[e][1,4]diazepin-5(4*H*)-ones (Scheme 1A); Cu-catalyzed tandem Ullmann C-N coupling of 2-azidobenzylic halides with propargylic amines[6] or reductive coupling [using $NaBH(OAc)_3$ as the reducing reagent] of 2-azidobenzaldehydes/2-azidoacetophenones with propargylic amines[7] followed by intramolecular click reactions of the corresponding intermediates could afford triazolo[1,5-a][1,4]benzodiazepines (Scheme 1B); base-mediated coupling of 2-aminobenzamides with *o*-dihalobenzenes could afford 5*H*-dibenzo[b,e][1,4]diazepin-11(10*H*)-ones (Scheme 1C);[8] Pd/C-catalyzed intramolecular addition and coupling reactions of 2-aminobenzylic propargylamines with aryl iodides could afford methylidene-1,4-benzodiazepines (Scheme 1D).[9] Besides, other intramolecular ring-forming reactions[10] and tedious multi-step reactions[11] could also be employed to prepare the analogous 1,4-benzodiazepine derivatives. In comparison with above methods, known reactions for construction of the analogous 5*H*-1,4-benzodiazepine scaffolds were still limited. Currently known methods mainly include the cyclocondensation of 2-aminobenzylic amines with 1,2-dicarbonyl compounds in refluxing acetic acid (Scheme 1E)[12] and a step-wise reaction of substituted acetylenes with 2-aminobenzylic amines in the presence of iodine (Scheme 1F).[2h] Even though, the above methods (Scheme 1A-F) still have some limitations, such as the tedious multi-step procedures, harsh conditions, using excess amounts of bases, reducing reagents, or additives, generating large amounts of wastes, low atom economy, using transition metal catalysts/ligands and having potential metal residue contaminant in the products, etc. Therefore, developing efficient, practical, atom economic, even transition metal- and waste-free methods for construction of the benzodiazepine derivatives is still a highly desirable research in the field.



Scheme 1. Methods for construction of 1,4-benzodiazepine skeletons.

With a long-term interest in the construction of heterocycle skeletons[13] and the alcohol chemistry,[14] in recent years we have developed some alcohol-based methods for facile synthesis of the versatile heterocycle compounds.[15] As 1,2-dicarbonyl compounds were usually obtained by oxidation of *α*-hydroxyl ketones using excess amounts of oxidants[16] and the known method for 5*H*-1,4-benzodiazepine construction from 1,2-dicarbonyl compounds gave only low yields of the products at high temperatures (Scheme 1E),[12] developing a new method using the readily available *α*-hydroxyl ketones for direct construction of 5*H*-1,4-benzodiazepine scaffolds should be a meaningful work in both the synthetic and pharmaceutical chemistry, because preparation of 1,2-dicarbonyl compounds and generation of wastes in this process,[16] harsh reaction conditions,[12] and the multi-step processes can all be avoided by this new protocol. Herein we report that 5*H*-1,4-benzodiazepine derivatives can be efficiently constructed by a catalyst-free and

[a] Miss Q. Wang, Miss X. Zhang, Prof. Dr. Q. Xu
School of Chemistry and Chemical Engineering, Yangzhou University
Yangzhou, Jiangsu 225002, China
E-mail: xuqing@yzu.edu.cn
[b] Mr. F. Han, Prof. Dr. J. Liu, Prof. Dr. Q. Xu
College of Chemistry and Materials Engineering, Wenzhou University
Wenzhou, Zhejiang 325035, China
E-mail: qing-xu@wzu.edu.cn

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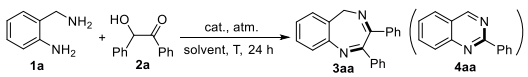
green direct aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones (Scheme 1G). This new method requires no external catalysts, additives, or stoichiometric amounts of oxidants, but can effectively employ air as the economic and safe oxidant and acetic acid (AcOH) the solvent under mild conditions. This reaction produces water as the byproduct and thus is a potentially green and advantageous method for 1,4-benzodiazepine derivative synthesis.

Table 1. Condition screening and optimization.[a]



1a 2a 3aa 4aa

entry	cat. (mol%)	atm.	solv. (mL), temp.	**3aa**%[b]
1	CsOH (20)	air balloon	DMSO (2), 30~80 °C	Trace[c]
2	TEMPO (50) TBN (50)	air balloon	AcOH (1), 80 °C	13
3	TBN (50)	air balloon	AcOH (1), 80 °C	26
4	TEMPO (50)	air balloon	AcOH (1), 80 °C	46
5	-	air balloon	AcOH (1), 80 °C	57
6	-	air balloon	AcOH (0.5), 80 °C	68
7	-	O_2 balloon	AcOH (0.5), 80 °C	75
8[d]	-	O_2 balloon	AcOH (0.5), 80 °C	87
9[d]	-	O_2 balloon	AcOH (0.25), 80 °C	94
10[d]	-	O_2 balloon	AcOH (0.1), 80 °C	91
11[d]	**-**	***air balloon***	***AcOH (0.25), 80 °C***	***95***
12[d]	-	air	AcOH (0.25), 80 °C	74

[a] Unless otherwise noted, the mixture of **1a** (0.5 mmol) and **2a** (0.6 mmol, 1.2 equiv.) in a solvent was sealed in a 100 mL Schlenk tube equipped with an air or O_2 balloon and then heated for 24 h. [b] Unless otherwise noted, isolated yields were based on **1a**. [c] **4aa**: 23~36%. [d] **1a** (0.75 mmol, 1.5 equiv.), **2a** (0.5 mmol). The corresponding isolated yields were based on **2a**.

As shown in Table 1, employing the base catalysis strategy that were successful in our previous works on heterocycle construction,[15a-c] the model reaction of 2-aminobenzyl amine (**1a**) and benzoin (**2a**) was initially investigated using CsOH as the catalyst under the air atmosphere (entry 1). However, only a trace yield of the target product **3aa** was observed, with considerable yields of **4aa** isolated as the major product. Formation of **4aa** should be due to the easy decomposition of **2a** under the basic conditions. Thus, to avoid the decomposition of **2a** and formation of the unwanted **4aa**, the reaction was further investigated employing neutral or acidic aerobic oxidation strategies. After screening a variety of catalysts and conditions, we found using TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) and TBN (di-*t*-butyl nitrate) as the catalyst and acetic acid (AcOH) as the solvent[15d] could led to successful production of the target 5*H*-1,4-benzodiazepine **3aa** in a low yield (entry 2). To our surprise, using TBN or TEMPO alone could result in higher yields of **3aa** (entries 3-4). Inspired by this interesting finding, the reaction was investigated without adding both TBN and TEMPO. To our delight, the blank reactions could afford 24~57 yields of **3aa** from room temperature to 120 °C, with 80 °C being the best reaction temperature and giving the highest 57% yield of **3aa** (entry 5). This meant that the present reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones is very possibly a catalyst-free reaction in AcOH. As expected, **3aa** could be obtained in higher yields by reducing the solvent dosage (entry 6) and/or by using pure O_2 as the oxidant (entry 7). Since considerable amounts of **2a** or its oxidation product was observed remained unreacted in the reactions (vide infra),[17,18] reversed substrate loadings were adopted to ensure more complete conversion of **2a**. Thus, the yields of **3aa** could be enhanced to 87% by using 1.5 equiv. of **1a** (entry 8). Various neutral and acidic solvents such as toluene, CF_3COOH, and C_2H_5COOH were also tested in the reaction, but the results showed that AcOH is still the best one. Then, reduced solvent dosage was found able to afford even higher yields of the product (entries 9-10, 91-94%). Adopting so-far-the-best conditions (entry 9), the reaction was again re-investigated under the air atmosphere. Satisfactorily, this reaction afforded **3aa** in the highest yield of 95% (entry 11), clearly indicating that, as the oxidant, air is as effective as pure O_2 in this reaction (vide infra).[18] Finally, without adopting the air balloon but with the reaction vessel just sealed with air, the yield of the product decreased dramatically due to insufficient amount of O_2 (entry 12). This means an air balloon is necessary for the reaction by providing an adequate amount of the oxidant.

The above optimized conditions (Table 1, entry 11) were then applied to other substituted 2-aminobenzylic amines and *α*-hydroxyl ketones to extend the scope of the method. As shown in Table 2, similar to the standard reaction (entry 1), for electron-rich *α*-hydroxyl ketones, both *p*- and *m*-methyl-, and even the more bulky *t*-Bu-substituted benzoins afforded good to high yields of the products (entries 2-3, 5). In contrast, the corresponding *o*-methyl-substituted benzoin gave only a low yield of the product (entry 4). Similarly, *p*- and *m*-methoxyl-substituted benzoins also afforded high yields of the products under the standard conditions (entries 6-7), but the *o*-substituted one was low in product yield (entry 8). Low product yields of the *o*-substituted benzoins are most likely due to the steric hindrance derived from the two *o*-methyl or *o*-methoxyl groups on the phenyl rings. The steric effect of the *o*-methyl or *o*-methoxyl groups seemed to be rather strong, so that modified conditions such as higher or lower temperatures, prolonged reaction time, using additives, and/or more loading of **1a** were all not effective to improve the product yields. Moreover, another slightly bulky electron-rich *α*-hydroxyl ketone **2i** also afforded a satisfactory yield of product **3ai** under the standard conditions (entry 9).

For electron-deficient benzoins, *p*-fluoro, *p*- and *m*-chloro-, *p*-trifluoromethyl-, even the more reactive *p*-bromo-, *p*-iodo-, and *p*-cyano-substituted benzoins, all afforded good to high yields of the target products under the standard conditions (entries 10-13, 15-18). Mono-*p*-chloro-substituted benzoin **2m** reacted with **1a** and afforded a mixture of isolable isomers **3am** and **3am'** in a good combined yield of 86% and 59/41 ratio (entry 13).[18] For bearing the reactive halogen and cyano groups, these products may have further synthetic applications in organic and pharmaceutical synthesis. Similarly to the preceding *o*-substituted benzoins (Table 2, entries 4 and 8), the product yield of *o*-chloro-substituted benzoin was lower under the standard conditions, but it could be improved to an acceptable yield of 56% at a higher temperature in a prolonged reaction time (entry 14). For *p*-hydroxyl- and *p*-nitro-substituted benzoins, complex

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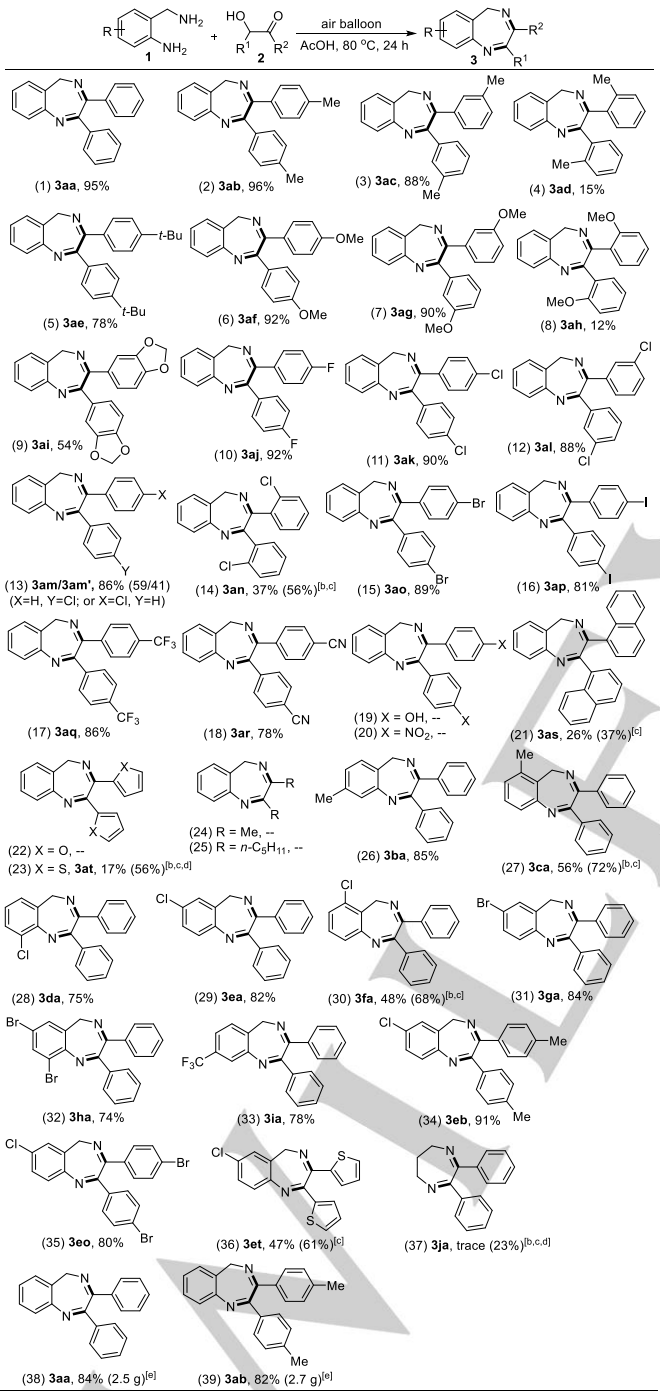
reactions occurred and no target products could be obtained under standard and several modified conditions (entries 19-20). This may be due to the possible side reactions of the active hydroxyl and nitro groups under the acidic conditions. For di(*α*-naphthyl)-substituted *α*-hydroxyl ketone, most likely due to the sterical bulkiness of the *α*-naphthyl group, the yield of product **3as** was not good (entry 21). After attempting a series of modified conditions, the product yield was somewhat improved by prolonged reaction time (entry 21).

Table 2. Scope of the substrates.[a]



[a] Unless otherwise noted, see entry 11 of Table 1 for detailed conditions. Isolated yields based on **2**. [b] 120 °C. [c] 48 h. [d] 2.0 equiv. **1**. [e] 10 mmol scale reactions with the reaction vessel equipped with an O_2 balloon to ensure adequate amounts of oxidant O_2 for the reactions.

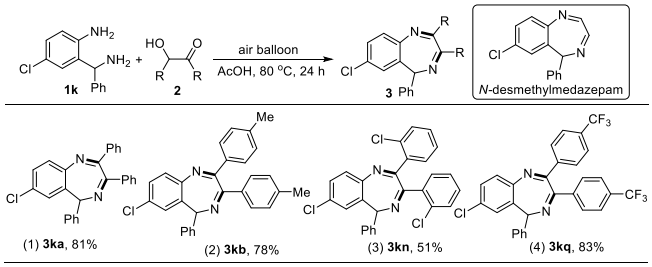
For heteroaryl-substituted *α*-hydroxyl ketones, no product could be obtained with the 2-furyl substituted one (entry 22); while a low yield of the product **3at** was obtained from the 2-thienyl substituted *α*-hydroxyl ketone, which could be further improved a lot by running the reaction with a higher loading of **1a**, at a higher temperature, and in a prolonged reaction time (entry 23). Besides, alkyl-substituted *α*-hydroxyl ketones were also investigated in the method, but no products were obtained at present (entries 24-25), which may be due to the much lower reactivity of the alkyl-substituted *α*-hydroxyl ketones under the present conditions.

For substituted 2-aminobenzylic amines, the reaction of 2-amino-4-methylbenzyl amine afforded a good yield of the product under the standard conditions (entry 26). While, the more steric 2-amino-6-methylbenzyl amine bearing an *o*-methyl group gave only a moderated yield of the product under the same conditions, which could then be improved by running the reaction at a higher temperature in a prolonged reaction time (entry 27). Similarly, 3-chloro-, 5-chloro-, 5-bromo-, 3,5-dibromo-, and 4-trifluoromethyl-2-aminobenzyl amines also afforded good yields of the products under the standard conditions (entries 28-29, 31-33), and the moderate product yield of 2-amino-6-chlorobenzyl amine could also be improved at a higher temperature in a prolonged reaction time (entry 30). Similar to **1a**, 2-amino-5-chlorobenzyl amine (**1e**) reacted with several *α*-hydroxyl ketones to afforded good to high yields of the products (entries 34-35). Its reaction with 2-thienyl substituted *α*-hydroxyl ketone was even better than that of **1a**, giving a moderate yield and a higher yield of **3et** under the standard and modified conditions (entry 36). Finally, an aliphatic 1,3-propanediamine was also tested in the method. Although only trace product was observed under the standard conditions, a considerable yield of the product could be obtained at a higher temperature in a prolonged reaction time (entry 37).

To test both the scalability and practicability of this new method, multigram synthesis of the products was then investigated. As shown in Table 2 (entries 38-39), 10 mmol scale reactions of **1a** with **2a** and **2b** efficiently afforded the target **3aa** and **3ab** in over 80% isolated yields under the standard conditions (80 °C, 24 h),[18] revealing that the method is still very effective in larger scale synthesis.

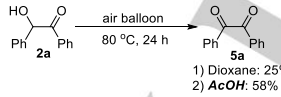
We also considered applying this newly-developed 1,4-benzodiazepine construction method in one-step synthesis of the pharmaceutically active molecules. Literature survey revealed that *N*-desmethylmedazepam and its derivatives (Table 3) have many physiological activities such as anti-anxiety, anti-convulsant, anti-epileptic, sedative, and hypnotic effects, and are therefore widely employed in medical anesthesiological treatment.[1i-1l] Thus, 2-amino-5-chlorobenzhydrylamine **1k**[19] was employed to react with *α*-hydroxyl ketones **2** to obtain the *N*-desmethylmedazepam derivatives. As shown in Table 3, although bearing a benzylic phenyl group and being sterically more bulky than the model substrates, **1k** still reacted efficiently with several electron-rich and –deficient *α*-hydroxyl ketones **2** to afford moderate to good yields of the target products under the standard conditions (entries 1-4). These results are in comparison much better than the multi-step methods reported in the literature,[1m-1n] implying not only the broad scope of this new method but also that this new reaction can be a potentially efficient and practical choice for the synthesis of pharmaceutically-active molecules.

Table 3. Synthesis of pharmaceutically-active *N*-desmethylmedazepam derivatives.[a]

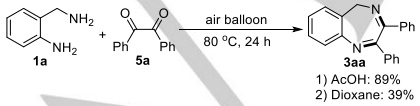


[a] See entry 11 of Table 1 for detailed conditions. Isolated yields based on **2**.

Control reactions[18] were then investigated to explore the possible mechanism of this interesting catalyst-free direct aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones. Firstly, except the diacetylation of **1a** generating an acetamide byproduct, no other possible reaction intermediates were observed when lone **1a** was heated in AcOH under the standard conditions.[17,18] Then, using a neutral solvent like dioxane, the lone reaction of **2a** afforded only a low yield of benzil **5a** (Scheme 2, entry 1). In contrast, in AcOH, the same reaction afforded a much higher 58% yield of **5a** (Scheme 2, entry 2). These results not only showed that 1,2-dicarbonyl compounds like benzil **5a** may be the first generated intermediate in the reaction, but also revealed clearly that solvent AcOH has a great facilitating effect in the aerobic oxidation of *α*-hydroxyl ketones **2** to 1,2-dicarbonyl compounds **5**. The observed easy oxidation of **2** by air especially in AcOH is also consistent with the finding that air has already been a very effective oxidant for the reaction, so that the use pure O_2 is not necessary (Table 1). Furthermore, the reaction of **1a** and **5a** afforded 89% yield of **3aa** under the standard conditions (Scheme 3, entry 1), which is slightly lower than that of the standard reaction using **2a** as the substrate (Table 1, entry 11), but much higher than the literature method using 1,2-dicarbonyl compound **5** (47% yield).[12] This result not only confirmed again that **5** is the reactive intermediate in the reaction, but also suggested that *α*-hydroxyl ketones **2** can be better substrates for 5*H*-1,4-benzodiazepine skeleton construction than 1,2-dicarbonyl compounds **5**.

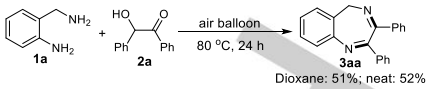


Scheme 2. Catalyst-free aerobic oxidation of benzoin **2a**.



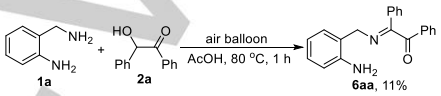
Scheme 3. Annulation of **1a** with dicarbonyl compound **5a**.

On the other hand, the same reaction of **1a** and **5a** in dioxane afforded only 39% yield of **3aa** (Scheme 3, entry 2). Similarly, without using AcOH, the reaction of **1a** and **2a** in dioxane or a neat reaction of them afforded only 51~52% yields of **3aa** (Scheme 4). These yields are all much lower than the yield obtained from the standard reaction using AcOH as the solvent (Table 1, entry 11), clearly demonstrating that AcOH can also greatly facilitate the cyclocondensation step of the whole reaction.[20]



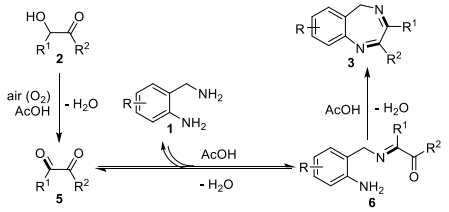
Scheme 4. AcOH-free reaction of **1a** with **2a**.

Next, to probe which amino group of **1** reacts first with **2** or **5**, the reaction of **1a** and **2a** was interrupted at 1 h. A considerable yield of a new product was observed in the reaction, which was isolated and determined to be imine **6aa** as confirmed by NMR analysis (Scheme 5).[18] This result is consistent with the common view that the benzylic amino group is more nucleophilic than the aromatic amino group and thus should react first with **2** or **5** to give the imine intermediate **6**. Like most imines, it was also observed that **6aa** was instable and, after being isolated, can easily hydrolyze to give **1a** and **5a** at room temperature.[18]



Scheme 5. Interrupted reaction of **1a** with **2a** at 1 h for imine intermediate determination.

Based on the above findings, a possible mechanism was proposed for this catalyst-free direct aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones. As shown in Scheme 6, the oxidation of *α*-hydroxyl ketones **2** by air is firstly facilitated by AcOH to give 1,2-dicarbonyl intermediates **5**. Then dehydrative condensation of **5** and **1** occurred at the more nuleophilic benzylic aminio group of **1** to give imine intermediates **6**. In the absence of AcOH, imine **6** is instable and may easily hydrolyze to convert back to **1** and **5**. In the presense of AcOH, intramolecular cyclocondensation of **6** readily occurred to produce the target 5*H*-1,4-benzodiazepines derivatives **3**. In above three consecutive steps, AcOH facilitates both the step of aerobic oxidation of *α*-hydroxylketones and also the following cyclocondensation steps, so that no external catalysts or additives were required at all in this reaction.



Scheme 6. Proposed mechanism for the catalyst-free direct aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones generating 5*H*-1,4-benzodiazepines.

In conclusion, we developed a catalyst-free direct aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones. By using AcOH as the best solvent, the economic and convenient air can be effectively employed as the oxidant for the reaction, leading to a mild, efficient, green, and

practical method for construction of the *5H*-1,4-benzodiazepine skeletons. Interestingly, mechanistic studies revealed that AcOH can not only facilitate the aerobic oxidation of *α*-hydroxyl ketones to 1,2-dicarbonyl compounds, it can also promote the following cyclocondensation step of 1,2-dicarbonyl compounds with 2-aminobenzylic amines. This method tolerates a wide range of both 2-aminobenzylic amines and *α*-hydroxyl ketones, can afford generally good to high yields of the target *5H*-1,4-benzodiazepine derivatives, and also has advantages such as high availability of the substrates, short procedure, simple operation, mild conditions, high atom efficiency, requiring no extra catalysts, additives, and stoichiometric oxidants, and generating no other waste than the water. This method can also be easily scaled up for multigram synthesis of the products and directly applied in one-step synthesis of the pharmaceutically-active *N*-desmethylmedazepam derivatives. Therefore, this new method may have potentially broad applications in organic and pharmaceutical synthesis and other organic optoelectronic materials. Further applications of this catalyst-free aerobic oxidation strategy in the synthesis of more heterocycle compounds are under way in this laboratory.

Experimental Section

Typical Procedure for the catalyst-free aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones: The mixture of 2-aminobenzyl amine **1a** (0.75 mmol, 1.5 equiv.) and 2-hydroxyl-2-phenylacetophenone **2a** (0.5 mmol) in acetic acid (0.25 mL) in a Schlenk tube (100 mL) equipped with an air balloon was stirred at 80 ^{o}C for 24 h. The reaction was then monitored by TLC and/or GC-MS. After completion of the reaction, the reaction mixture was condensed and the residue purified by column chromatography on silica gel using petroleum ether and ethyl acetate (10:1) as the eluent, giving the target product **3aa** in 95% isolated yield.

Acknowledgements

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Keywords: aerobic oxidation • catalyst-free • *α*-hydroxyl ketones • *o*-aminobenzylic amines • 5*H*-1,4-benzodiazepines

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[18] See the Supporting Information section for details.

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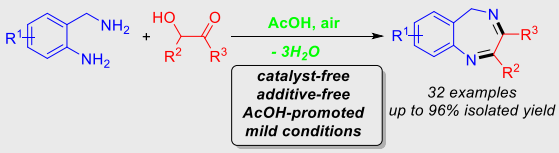

In AcOH and under air atmosphere, catalyst-free aerobic oxidative annulation reaction of 2-aminobenzylic amines and *α*-hydroxyl ketones efficiently afforded 5*H*-1,4-benzodiazepine derivatives under mild conditions. This method tolerates a wide range of substrates, can be scaled up for multigram synthesis and applied in *N*-desmethylmedazepam derivative synthesis, revealing its high potential for the synthesis of 5*H*-1,4-benzodiazepine-based fine chemicals.

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