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H_2O_2-Promoted Reactions of Aliphatic Primary Amines with 1,3-Diketones for the Synthesis of 1*H*-Pyrrol-3(2*H*)-ones at Ambient Temperature in Water

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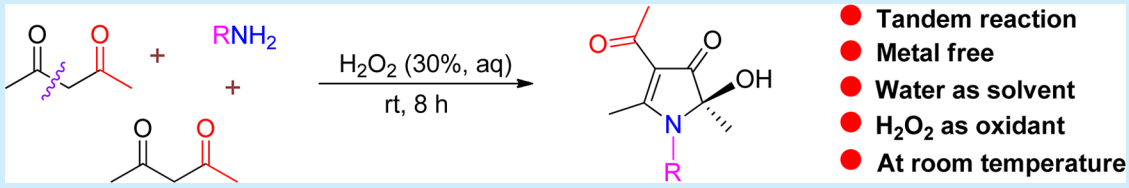
Supporting Information



ABSTRACT: A green organic reaction of aliphatic primary amines with 1,3-diketones promoted by 30% aqueous H_2O_2 has been developed. It provides an inexpensive, regioselective, and efficient approach to 1*H*-pyrrol-3(2*H*)-ones with high yields from the simple and readily available starting materials in one pot via multicomponent tandem cyclization reactions and C−C cleavage under very mild and environmentally friendly reaction conditions.

The 1*H*-pyrrol-3(2*H*)-one ring system is found in many natural products, pharmaceuticals, and biologically active compounds,[1] and yet despite this, only a few established methodologies are available for the synthesis of 1*H*-pyrrol-3(2*H*)-ones.[2] However, the restricted reaction conditions, limited substrate scope, and complex byproducts produced by these methods remain a disadvantage. Therefore, to develop a rapid, mild, green, and efficient method for the direct construction of 1*H*-pyrrol-3(2*H*)-one scaffolds with multiple functional groups is still highly desirable. In this general direction, an elegant synthesis of 1*H*-pyrrol-3(2*H*)-ones was developed recently by Guan using $Cu(TFA)_2$-catalyzed oxidative tandem cyclization of enamino amides.[3]

As inexpensive and available starting materials, 1,3-diketones have been widely used as starting materials in organic synthesis.[4] In 2013, a H_2O_2-mediated oxidative formation of amides was reported from aromatic amines and 1,3-diketones.[5] However, the reactions of 1,3-diketones with aliphatic primary amines could not afford the desired *N*-acylation products.[5] Herein, we describe an efficient one-pot multicomponent tandem cyclization reaction of aliphatic primary amines with 1,3-diketones promoted by 30% aqueous H_2O_2 without any additives, which generates multifunctionalized 1*H*-pyrrol-3(2*H*)-ones in good yields (Scheme 1).

We initiated our investigation with the model substrates of pentane-2,4-dione (**1a**) and benzylamine (**2a**) in the presence of an oxidant, and the results are summarized in Table 1. To our great delight, the model reaction carried out in the presence of neat 30% aqueous H_2O_2 at room temperature proceeded smoothly and only the tandem reaction product, 4-acetyl-1-benzyl-2-hydroxy-2,5-dimethyl-1*H*-pyrrol-3(2*H*)-one (**3a**), was isolated in 81% yield (Table 1, entry 1). It was characterized by ^1H and ^{13}C NMR, HRMS, and further confirmed by X-ray diffraction analysis.[6] Cumene hydroperoxide and TBHP (*tert*-butyl hydroperoxide) as oxidant exhibited relatively lower efficiency (Table 1, entries 2 and 3). Unfortunately, other oxidants, $PhI(OAc)_2$, DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), BQ (1,4-benzoquinone), DTBP (di-*tert*-butyl peroxide), $(NH_4)_2S_2O_8$, and $K_2S_2O_8$ were ineffective, and no desired product was isolated (Table 1, entries 4−9). When the reaction was performed in toluene, dioxane, and THF, 38−52% yields of **3a** were obtained. However, other organic solvents including DMF, DMSO, CH_3CN, and DME stopped the reaction completely, and only starting materials were recovered (Table 1, entries 10−16). With respect to the oxidant loading, 2.0 equiv of 30% aqueous H_2O_2 was found to be optimal. The concentration of H_2O_2 (aq) in the range of 20−30% led to the most efficient reactions. Therefore, the optimized reaction

Scheme 1. H_2O_2-Promoted Reactions of Aliphatic Primary Amines with 1,3-Diketones

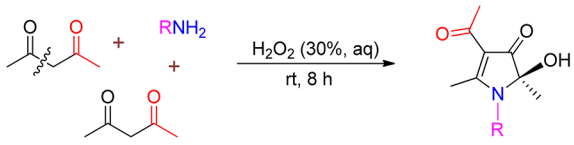


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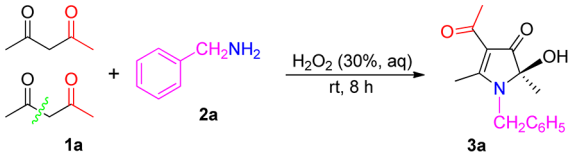
Table 1. Optimization of the Oxidant and Solvent[a]



entry	oxidant	solvent	yield[b] (%)
1	H_2O_2 (30% aq)		81
2	cumene hydroperoxide		35
3	TBHP		41
4	$PhI(OAc)_2$		NR
5	DDQ		trace
6	BQ		trace
7	DTBP		NR
8	$(NH_4)_2S_2O_8$		NR
9	$K_2S_2O_8$		trace
10	H_2O_2 (30% aq)	toluene	52
11	H_2O_2 (30% aq)	dioxane	40
12	H_2O_2 (30% aq)	THF	38
13	H_2O_2 (30% aq)	DMF	NR
14	H_2O_2 (30% aq)	DMSO	NR
15	H_2O_2 (30% aq)	CH_3CN	NR
16	H_2O_2 (30% aq)	DME	NR

[a]Reaction conditions: pentane-2,4-dione (**1a**, 1.20 mmol), benzylamine (**2a**, 0.50 mmol), oxidant (1.0 mmol), solvent (2.0 mL) if needed, rt, air, 8 h. [b]Isolated yield.

conditions used 30% aqueous H_2O_2 (2.0 equiv) at room temperature under air for 8 h.

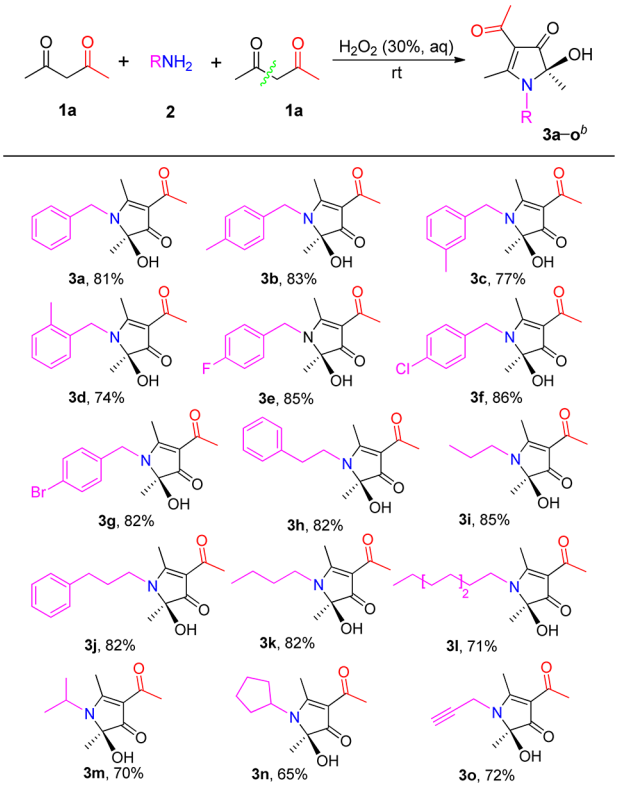
To evaluate the scope of this novel strategy for the synthesis of 1*H*-pyrrol-3(2*H*)-ones, various aliphatic primary amines were reacted with pentane-2,4-dione (**1a**) under the optimized reaction conditions, as shown in Scheme 2. The expected products were obtained in good yield. Notably, electron-donating and electron-withdrawing groups (Me, F, Cl, and Br) on the *para*-, *meta*-, and *ortho*-positions of the benzene rings in benzylamines underwent the tandem multicomponent reactions smoothly and generated the desired products (**3b**–**g**) in 74–86% yield. A slight *ortho*-position effect was found (**3b** vs **3c** vs **3d**). Other aliphatic straight-chain primary amines, such as 2-phenylethanamine, *n*-propylamine, 3-phenylpropan-1-amine, *n*-butylamine, and *n*-octylamine, reacted with **1a**, and **3h**–**l** were obtained in 71–85% yield. It should be noted that *i*-$PrNH_2$ and cyclopentylamine also reacted with **1a** well and afforded the corresponding products **3m** and **3n** in 70% and 65% yield, respectively. It was found that prop-2-yn-1-amine reacted with **1a** to provide the desired product **3o** in 72% yield.

Subsequently, we attempted to investigate the scope with various 1,3-diketones, and the results are listed in Scheme 3.

When 1-phenylbutane-1,3-dione (**1b**), 1-(4-chlorophenyl)-butane-1,3-dione (**1c**), and 1-(4-methoxyphenylbutane-1,3-dione (**1d**) were reacted with benzylamine, 3-phenylpropan-1-amine, 2-phenylethanamine, *n*-$PrNH_2$, *n*-octylamine, *n*-decylamine, and allylamine under the present reaction conditions, the corresponding products **3p**–**x** were obtained in 51–75% yield with high regioselectivity.

It is important to note that hexane-2,4-dione (**1e**) and 6-methylheptane-2,4-dione (**1f**) reacted with *n*-$PrNH_2$ under the present reaction conditions to generate the product **3y** in 85% yield and **3z** in 81% yield (Scheme 4). The reactions show high regiocontrol, which originates from steric hindrance around the carbonyl group in these *β*-diketones. However, when other 1,3-diketones, such as 1,3-diphenylpropane-1,3-dione, heptane-3,5-dione, 2,6-dimethylheptane-3,5-dione, and 2,2,6,6-tetramethylheptane-3,5-dione were used to react with benzylamine, no desired product was observed owing to steric hindrance.

Scheme 2. Reactions of Pentane-2,4-dione (1a) with Various Primary Aliphatic Amines[a]



[a]Reaction conditions: pentane-2,4-dione (**1a**, 1.20 mmol), primary aliphatic amine (**2**, 0.50 mmol), H_2O_2 (30% aq, 1.0 mmol), rt, air, 8 h. [b]Isolated yield.

To investigate the reaction mechanism, the control experiments were performed and the results are presented in Scheme 5. The condensation of pentane-2,4-dione (**1a**) with benzylamine (**2a**) generated product **4a** with 85% yield in water at room temperature.[7] When **4a** reacted with **1a** in 1:1 molar ratio in the presence of H_2O_2 (30% aq), **3a** was obtained in 86% yield. On the other hand, when the reaction of **4a** was mediated by 30% aqueous H_2O_2 in the absence of **1a**, no product was observed, and **4a** was recovered in 95% yield. No reaction also occurred when **1a**, **2a** and 30% aqueous H_2O_2 were kept in darkness or in the presence of TFA (2.0 equiv) without H_2O_2.[2c,3] Moreover, the addition of a radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) suppressed the reaction significantly, further indicating that the radical process is most likely in this reaction.

Though the exact reaction mechanism is still not clear, a tentative mechanism is proposed in Scheme 6 on the basis of the literature and our observations. First, a free-radical oxidation of pentane-2,4-dione (**1a**) to generate the alkyl radical **I**, and an oxidation of **4** with hydroxyl radical to amino radical **II**, is believed to occur.[5,8] Then, radical cross-coupling of **I** and **II** leads to intermediate **III**, which undergoes an intramolecular cyclization to intermediate **IV** followed by tautomerization and oxidation to intermediate **V**. In the following process, a 1,3-methyl migration of **V** produces a

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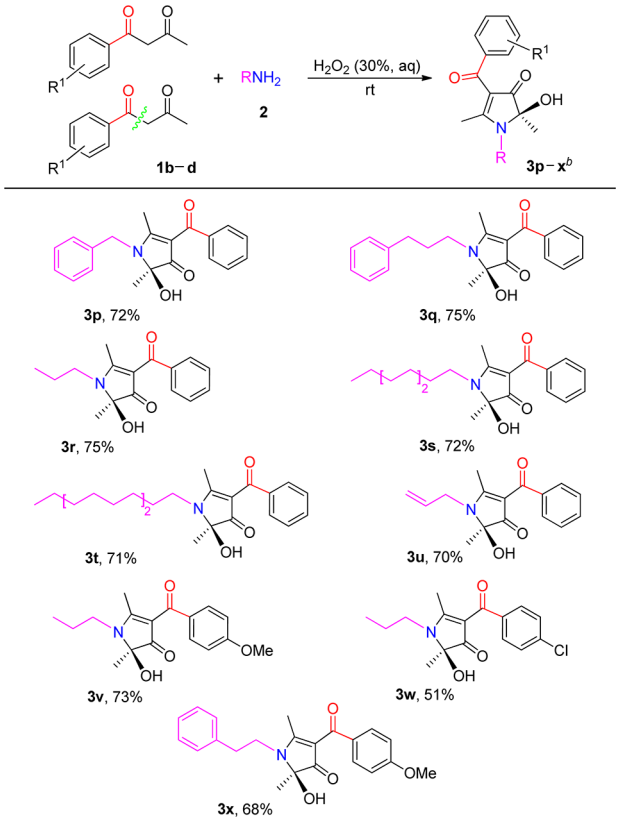
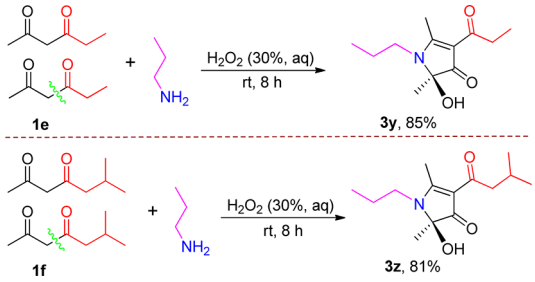
Scheme 3. Reactions of 1-Arylbutane-1,3-diones with Primary Aliphatic Amines[a]

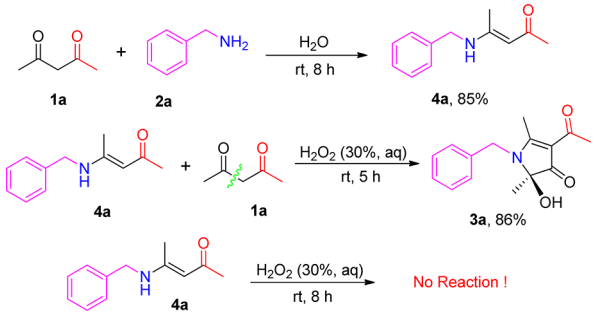


[a]Reaction conditions: 1-arylbutane-1,3-dione (**1**, 1.20 mmol), primary aliphatic amine (**2**, 0.50 mmol), H_2O_2 (30% aq, 1.0 mmol), rt, air, 8 h. [b]Isolated yield.

Scheme 4. Tandem Reactions of 1e and 1f with *n*-Propylamine

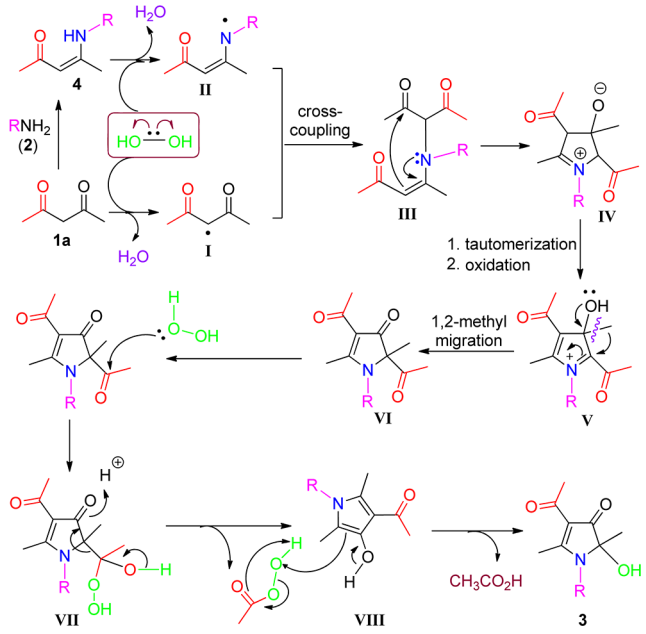


Scheme 5. Control Experiments

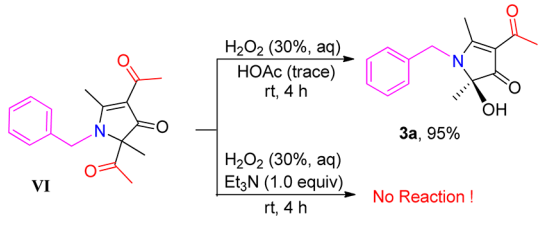


key intermediate **VI**,[2c,3,9] followed by its reaction with H_2O_2 to generate intermediate **VII**. The intermediate **VII** proceeds to afford **VIII** and peroxyacetic acid. Finally, the desired product **3** is formed through the reaction of **VIII** with peroxyacetic acid, along with the formation of acetic acid. To confirm the proposed reaction mechanism, an important intermediate **VI** was prepared according to literature.[10] When the reaction of obtained **VI** was carried out under the aforementioned conditions in the presence of trace amount of HOAc, 1*H*-pyrrol-3(2*H*)-one **3a** was obtained in almost quantitatively yield. However, the reaction of **VI** in the presence of 30% aqueous H_2O_2 and Et_3N, no product **3a** was detected (Scheme 7).

Scheme 6. Proposed Reaction Mechanism



Scheme 7. Transformation of VI to 3a



In conclusion, we have developed a novel one-pot procedure for the synthesis of multifunctionalized 1*H*-pyrrol-3(2*H*)-ones through a H_2O_2-promoted tandem cyclization reaction of aliphatic primary amines with 1,3-diketones under metal-free and additive-free conditions at ambient temperature in water.[11] The reaction is highly efficient and cost-effective and has a broad substrate scope while operating under mild and environmentally friendly conditions.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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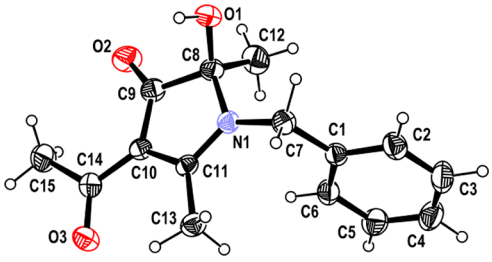
(6) X-ray single crystal structure of **3a**.



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(11) The reaction solution was analyzed by ICP-MS, and the determination data indicated that Cu, Fe, Pd, Ni, Co, Ru, and Rh are less than 0.2 ppm (under detection limit).