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Oxidative cross-dehydrogenative [2 + 3] annulation of α-amino ketones with α-keto esters: concise synthesis of clausenamide analogues†

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A one-pot oxidative cross-dehydrogenative [2 + 3] annulation of α-amino ketones with α-keto esters at room temperature is reported. The protocol features copper/organo cooperative catalysis and provides densely functionalized pyrrolones in high yields. Subsequent reduction furnished multi-substituted pyrrolidinones which represent the core-structure of the natural product clausenamide, a lead molecule for the treatment of Alzheimer's disease.

Pyrrolidinones represent an important nitrogen heterocyclic motif broadly found in various natural products and pharmaceutical agents with diverse biological activities (Fig. 1).[1] They also serve as valuable building blocks to fabricate different molecular frameworks and have found applications in materials sciences.[2] Despite these positive attributes, modular synthetic routes to access pyrrolidinones are limited. While the three component coupling strategy continues to be most favored,[3] the situation becomes more daunting when multi-substituted pyrrolidinones, for instance clausenamide, a lead compound for the treatment of Alzheimer's disease, are concerned.[4] In fact, syntheses of clausenamide and its analogues primarily involve multistep processes.[4] Thus, synthetic endeavors toward densely functionalized pyrrolidinones *en route* to the rapid production of clausenamide derivatives are highly desirable.

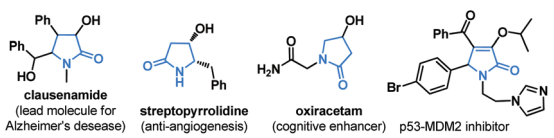

Fig. 1 Natural products and pharmaceutical molecules containing the pyrrolidinone motif.

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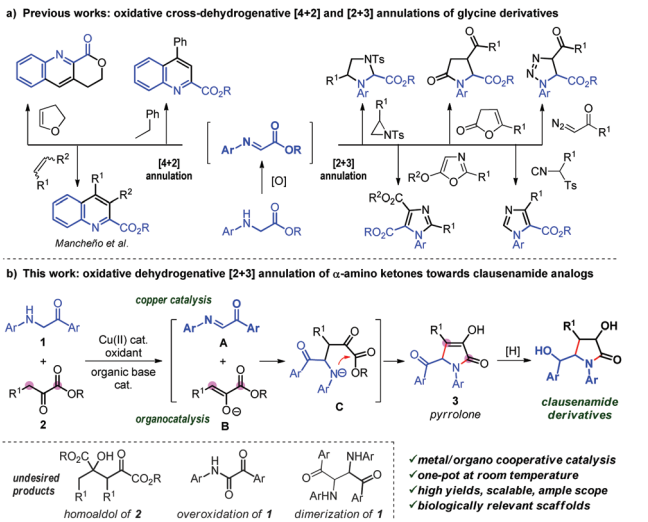
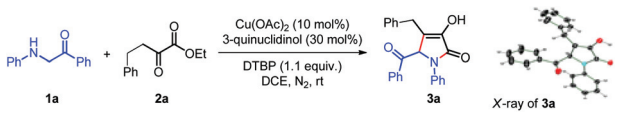
Catalytic cross-dehydrogenative coupling of two C–H bonds under oxidative conditions has emerged as a powerful tool for increasing molecular complexity from simple starting materials in an atom economical and environmentally benign manner.[5] In 2011, Mancheño advanced this strategy in the annulation reaction to prepare quinolines from *N*-arylglycine derivatives and alkenes (Scheme 1a, left).[6] Since then, various oxidative cross-dehydrogenative [4 + 2] and [2 + 3]-cyclization cascades have been established to access six- and five-membered heterocycles at elevated temperature (Scheme 1a).[7,8]

We envisioned that pyrrolidinones would be within reach by cross-dehydrogenative annulation using α-amino ketones **1** and α-keto esters **2**. In the presence of a suitable oxidant, the imine **A** thus generated *in situ* from **1** will react with pronucleophile **2** under the influence of a base catalyst to furnish **C**. The intermediate **C** will then undergo cyclization to give high-value synthon pyrrolone **3**, which on subsequent reduction would deliver the desired clausenamide derivatives (Scheme 1b).



Scheme 1 Oxidative cross-dehydrogenative annulation towards N-heterocycles.

Table 1 Optimization of oxidative cross-dehydrogenative [2 + 3] annulation conditions[a]



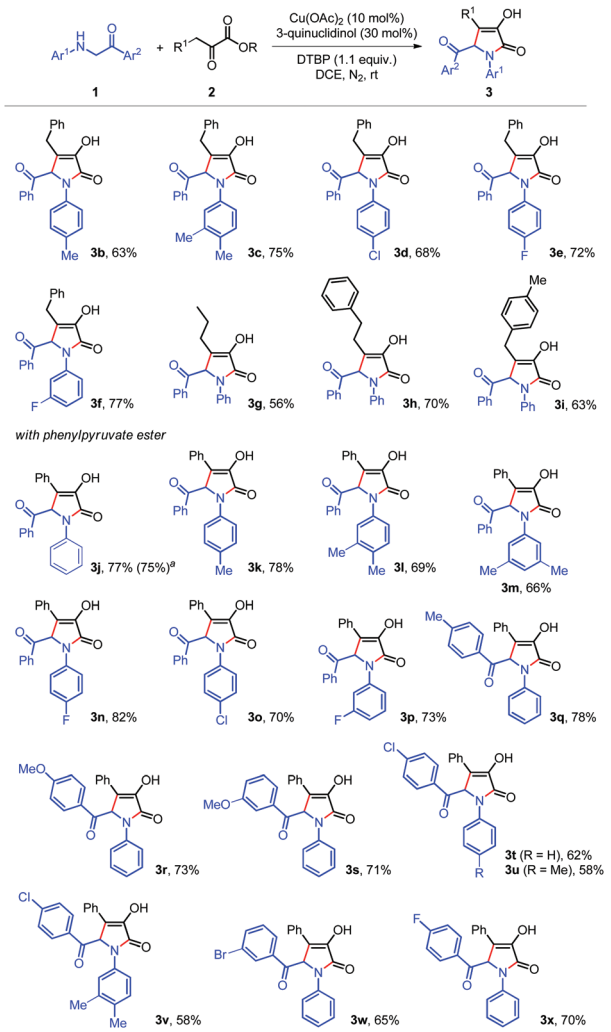
Entry	Deviation from optimal conditions	Yield[b] (%)
1	**None**	**74**
2	$CuCl/CuBr/CuCl_2/CuO/Cu(OAc)_2{\cdot}H_2O$ instead of $Cu(OAc)_2$	Trace/trace/trace/trace/40
3	TBHP/NMO/TEMPO instead of DTBP	49/trace/trace
4	Under O_2 instead of a N_2 atmosphere	Mixture[c]
5	Quinidine/quinine/DABCO/DBU instead of 3-quinuclidinol	48/52/38/33
6	THF/toluene/CH_3CN/MeOH instead of DCE	35/30/56/trace
7	Without $Cu(OAc)_2$	0
8	Without DTBP	12
9	Without 3-quinuclidinol	16
10	With a $K_2CO_3/Cs_2CO_3/K_3PO_4$ base instead of 3-quinuclidinol	<15[d]

[a] Reaction conditions: **1** (0.22 mmol), **2** (0.2 mmol), copper catalyst (0.02 mmol), oxidant (2.2 mmol), base catalyst (0.03 mmol), solvent (4 mL), under a nitrogen atmosphere, rt, and 14 h. [b] Isolated yields. [c] Complex mixture of uncharacterized compounds. [d] Conversions were determined by ^1H NMR of the crude reaction mixture. TBHP = *t*BuOOH; DTBP = *t*BuO*t*Bu; NMO: 4-methylmorpholine *N*-oxide; TEMPO: (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; DABCO: 1,4-diazabicyclo[2.2.2]octane; DBU: 1,8-diazabicyclo[5.4.0]undecane-7-ene.

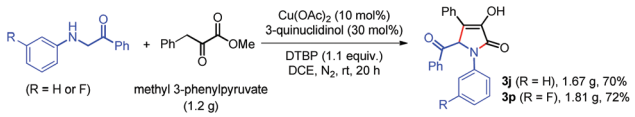
While this approach is highly alluring, judicious reaction conditions are necessary to mitigate undesired homoaldol reaction of α-keto carbonyls.[9] Furthermore, in contrast to glycine derivatives, a very mild oxidant is crucial to evade overoxidation of α-amino ketones **1** to α-keto amides and self-dimerization pitfall.[10] Herein we report the development of this approach for the concise synthesis of densely substituted pyrrolidinones having a clausenamide core. Notably, this cross-dehydrogenative coupling features a metal/organo cooperative catalysis[11] at room temperature.

At the outset, the reaction of α-amino ketone **1a** with α-keto ester **2a** was examined to probe the feasibility of our approach (Table 1). Gratifyingly, when the reaction was performed with 10 mol% of $Cu(OAc)_2$ and 30 mol% of 3-quinuclidinol using DTBP (1.1 equiv.) as an oxidant in 1,2-dichloroethane (DCE) solvent at room temperature under a nitrogen atmosphere, the desired pyrrolone **3a** was formed in 74% isolated yield (entry 1). The product **3a** was crystallized and the structure was unambiguously confirmed through X-ray analysis.[12] Replacement of $Cu(OAc)_2$ with other copper salts such as CuCl, CuBr, $CuCl_2$, CuO, or $Cu(OAc)_2{\cdot}H_2O$ had a deleterious effect (entry 2). While the employment of the TBHP oxidant delivered 49% yield of **3a**, the reaction was unfruitful with NMO and TEMPO (entry 3). The reaction was also very sluggish under an oxygen atmosphere and a complex mixture of unidentified compounds was obtained upon prolonging the reaction time (entry 4). The screening of other bases, for example quinidine, quinine, DABCO, and DBU, gave inferior results (entry 5). Except for DCE, other tested solvents showed decrease in yields (entry 6). Control experiments confirmed that the presence of all the components, $Cu(OAc)_2$ catalyst, 3-quinuclidinol base, and DTBP oxidant, is pivotal for efficient product formation. The reaction completely shuts down in the absence of the copper catalyst and the yields also dropped dramatically in the absence of the oxidant and 3-quinuclidinol catalyst (entries 7–9). Notably, consideration of inorganic bases, for instance K_2CO_3, Cs_2CO_3 or K_3PO_4, turned out to be detrimental, bolstering our hypothesis on metal/organo cooperative catalysis (entry 10).

With the optimized conditions in hand, the scope of the oxidative cross-dehydrogenative [2 + 3] annulation was explored (Scheme 2). The reaction is quite general. A series of α-amino ketones **1** having electron donating alkyl functionality and electron withdrawing halogen substitutions at the *meta*-



Scheme 2 Scope of the oxidative cross-dehydrogenative [2 + 3] annulation reaction. Reaction conditions: **1** (0.22 mmol), **2** (0.2 mmol), $Cu(OAc)_2$ (0.02 mmol), DTBP (2.2 mmol), 3-quinuclidinol (0.03 mmol), solvent (4 mL), under nitrogen atmosphere, rt, and 14 h. Yields of isolated products are given. [a] The reaction was performed with ethyl 3-phenylpyruvate.



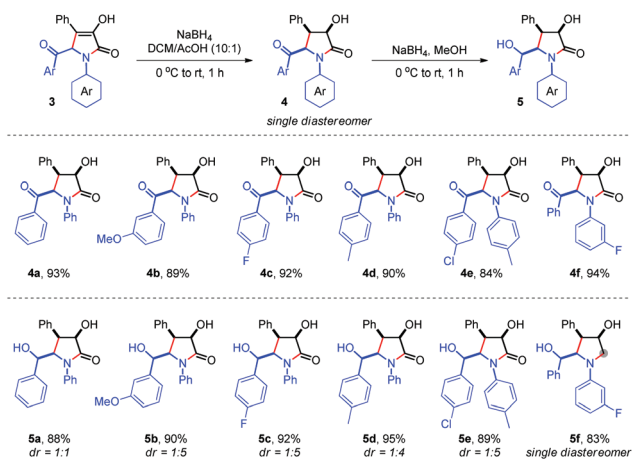
Scheme 3 Gram scale reaction.

and *para*-positions on the *N*-aryl ring reacted smoothly with α-keto ester **2a** to furnish highly substituted pyrrolones **3b–f** in high yields (63–77%). The substituted α-keto ester **2** encompassing long chain alkyl (**3g**) as well as their analogues with aryl groups (**3h–i**) also effectively participated in this reaction, producing desired products in good yields (56–70%).

Interestingly, more hindered methyl 3-phenylpyruvate showed good reactivity to afford **3j** in 77% yield. The corresponding ethyl ester was also equally effective, giving **3j** in comparable yield. The cross-dehydrogenative [2 + 3] efficacy of phenylpyruvate ester was intently exploited further as these products exhibit the desired substitution pattern necessary for the production of clausenamide derivatives. To our delight, reactions of diverse α-amino ketones **1** with substitutions in the *N*-aryl (**3k–p**) and carbonyl-aryl rings (**3q–x**) uniformly delivered expected pyrrolones in good yields (58–82%).

Notably, the reaction efficiency of the small scale reaction was comparable upon scale-up. Gram scale reactions of methyl 3-phenylpyruvate with α-amino ketones rendered **3j** and **3p** in 70% and 72% yields, respectively (Scheme 3).

Next, we focused our attention on utilizing the pyrrolone products **3** in the synthesis of various analogues of the clausenamide natural product.[4] While direct reduction of pyrrolone **3** with $NaBH_4$ was cumbersome and resulted in a complex mixture of diastereoisomers, a two-step reduction strategy turned out to be very effective to mitigate the diastereoselectivity issue (Scheme 4). Firstly, pyrrolones **3** were exposed to $NaBH_4$ in a dichloromethane/acetic acid mixture (10 : 1), furnishing 2-pyrrolidinones **4** as a single diastereomer in excellent yields. Subsequent treatment of **4** with $NaBH_4$ in MeOH gave clausenamide analogues **5** in high yields. In this case,



Scheme 4 Synthesis of clausenamide analogues.

two diastereomers were formed, which were separable *via* silica gel column chromatography. Very surprisingly and unlike other 2-pyrrolidinones **4a–e**, the reduction of amide functionality in **4f** was also observed under $NaBH_4$/MeOH conditions, affording tetra-substituted pyrrolidine **5f** as a single diastereomer with 83% isolated yield.

In conclusion, we have disclosed an unprecedented [2 + 3] annulation reaction of α-amino ketones with α-keto esters based on the oxidative cross-dehydrogenative strategy that features metal/organo cooperative catalysis. The catalytic reaction is operationally simple, scalable, and provides versatile *N*-aryl pyrrolones in high yields at room temperature. The pyrrolone products were judiciously utilized in a sequential reduction process with $NaBH_4$, offering a concise synthetic route to analogues of clausenamide, an anti-dementia drug candidate with increasing demand. Further applications of this strategy in the synthesis of other heterocyclic frameworks are currently being pursued in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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12 CCDC 1867654† contains the supplementary crystallographic data for compound **3a**.