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Synthesis of Polycyclic Imidazolidinones via Amine Redox-Annulation

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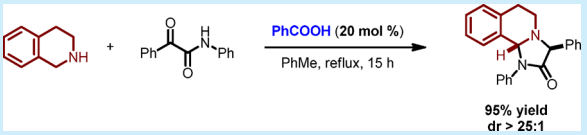
Supporting Information

ABSTRACT: α-Ketoamides undergo redox-annulations with cyclic secondary amines, such as 1,2,3,4-tetrahydroisoquinoline, pyrrolidine, piperidine, and morpholine. Catalytic amounts of benzoic acid significantly accelerate these transformations. This approach provides polycyclic imidazolidinone derivatives in typically good yields.



Imidazolidinones are frequently encountered as substructures of natural products and synthetic, biologically active compounds (Figure 1).[1−3] Among the most common methods

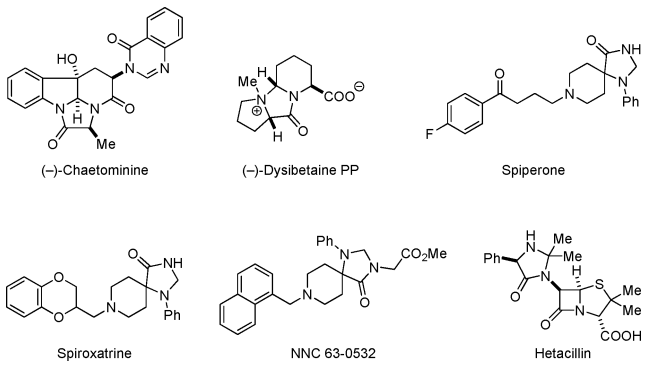
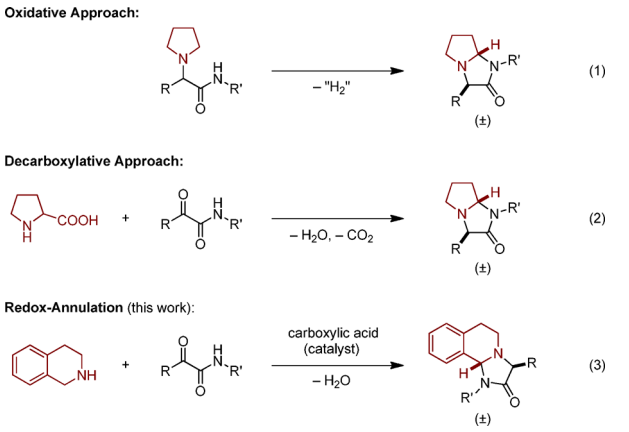


Figure 1. Selected 4-imidazolidinones.

used to build the imidazolidinone motif are condensations of α-aminoacetamide derivatives with aldehydes or ketones, various cycloadditions, ring expansions, and others.[1] Methods have also emerged that are particularly suitable for the preparation of ring-fused imidazolidinones (Scheme 1). One such approach involves an oxidative intramolecular coupling of α-amino-acetamide derivatives (eq 1).[4] A decarboxylative strategy involving the condensation of proline with α-ketoamides to build bicyclic imidazolidinones containing a pyrrolidine ring has also been established (eq 2).[5,6] Here we report a redox-neutral annulation approach to polycyclic imidazolidinones (eq 3).

We[7] and others[8] have developed a range of redox-neutral annulation reactions that proceed via the condensation of a secondary amine with an aldehyde/ketone possessing a pendent (pro)nucleophile. These annulations feature concurrent *N*-alkylation and the functionalization of an amine α-C−H bond.[9,10] The majority of these transformations proceed through azomethine ylide intermediates, utilize carboxylic acids

Scheme 1. Selected Routes to Polycyclic 4-Imidazolidinones



as catalysts or promoters, and result in the formation of a new six-membered ring.[11] Although there are examples of redox-neutral amine α-C−H bond functionalizations of secondary amines that give rise to the formation of new five-membered rings, typically via (3 + 2) cycloaddition of azomethine ylide intermediates[12] or 1,5-electrocyclic ring-closure of conjugated azomethine ylides,[13,14] this chemistry remains underdeveloped and has rarely been applied to C−N bond formation.[13c,i] We reasoned that such an annulation could be applied to the synthesis of bi- or polycyclic imidazolidinones via the condensation of cyclic amines with α-ketoamides (Scheme 1, eq 3).[15]

1,2,3,4-Tetrahydroisoquinoline (THIQ) and 2-oxo-*N*,2-diphenylacetamide (**1a**) were selected as model substrates in order to evaluate the proposed annulation process (Table 1). A 2:1 mixture of THIQ and **1a**, upon heating under reflux in toluene for 2 days, resulted in an incomplete reaction and the

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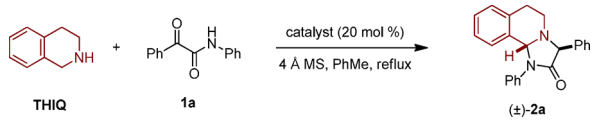
Table 1. Evaluation of Reaction Conditions[a]



entry	THIQ (equiv)	catalyst	time (h)	yield (%)
1	2		48	50
2	2	PhCOOH	7	95
3	2	AcOH	23	92
4	2	2-EHA	21	91
5[b]	2	PhCOOH	44	56
6	1.5	PhCOOH	12	93
7	1.2	PhCOOH	12	88
8[c]	1.5	PhCOOH	15	95

[a]Reactions were performed on a 0.2 mmol scale. All yields correspond to isolated yields. dr >25:1 in all cases. [b]Reaction was run at 50 °C and remained incomplete. [c]Without 4 Å MS.

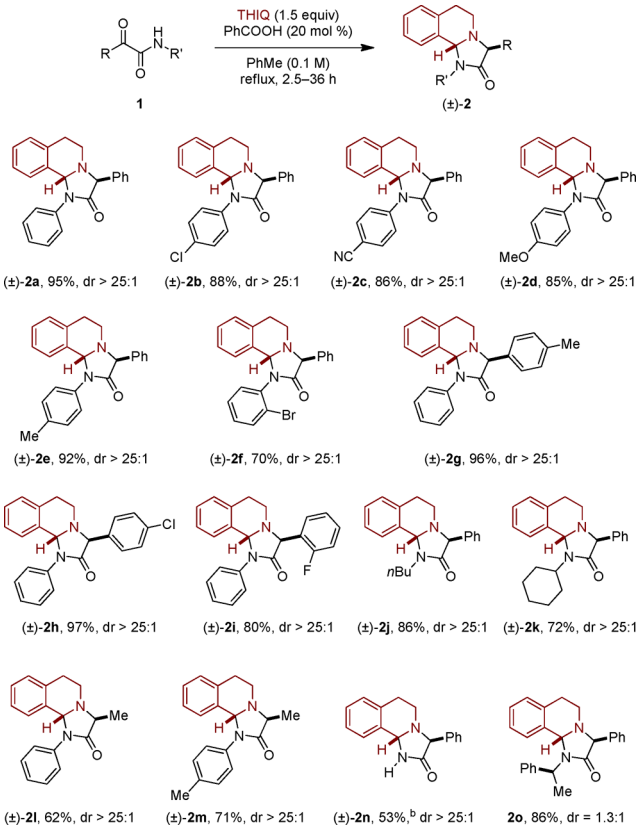
isolation of desired product **2a** as a single diastereomer in 50% yield (entry 1). Utilization of catalytic amounts of benzoic acid (20 mol %) resulted in a significant improvement (entry 2). Complete consumption of **1a** was observed within 7 h, and **2a** was obtained in 95% yield. Replacement of benzoic acid with either acetic acid or 2-ethylhexanoic acid (2-EHA) facilitated the formation of **2a** in similar yields but required prolonged reaction times (entries 3 and 4). A reaction that was performed at 50 °C remained incomplete after 44 h and led to product in moderate yield (entry 5). A reduction of the amount of THIQ to 1.5 equiv was well tolerated (entry 6), whereas further reduction to 1.2 equiv led to a slight drop in yield (entry 7). Notably, the reaction performed equally well in the absence of molecular sieves (entry 8).

The scope of the redox-annulation was explored under the optimized conditions of Table 1 (entry 8). A range of α-ketoamides with different substitution patterns were investigated (Scheme 2). The corresponding 4-imidazolidinone products **2** were isolated in good to excellent yields. Both aromatic and aliphatic substituents on the amide nitrogen were tolerated. Likewise, nonenolizable and enolizable α-ketoamides participated in the annulation reaction. In the case of the primary amide-derived product **2n**, which was obtained in 53% yield, a competing pathway was identified. Specifically, the corresponding transamidation product was obtained in 38% yield.[16] An enantiomerically pure α-ketoamide, derived from (*S*)-1-phenylethan-1-amine, provided product **2o** in 86% yield as a 1.3:1 mixture of diastereomers.

The scope of the amine component is summarized in Scheme 3. Benzylic amines other than THIQ, including the sterically hindered 1-phenyl-THIQ, readily formed annulation products upon reaction with α-ketoamide **1a**. Amines with attenuated reactivities, such as pyrrolidine and azepane, provided 4-imidazolidinone products in good yields. Particularly challenging substrates such as piperidine, morpholine, and thiomorpholine underwent the title reaction at elevated temperatures.

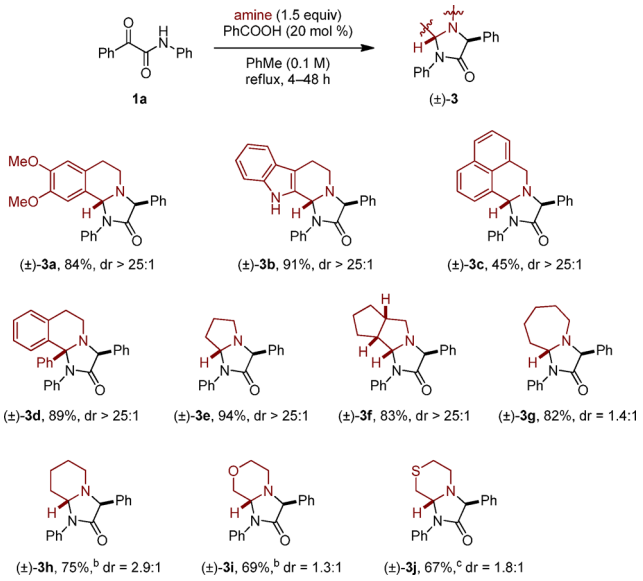
As shown in Schemes 2 and 3, reactions involving THIQ, related benzylic amines, and pyrrolidine underwent redox-annulations with α-ketoamides in highly diastereoselective fashion. In contrast, reactions with azepane, piperidine, morpholine, and thiomorpholine were poorly diastereoselective. We suspected that the aminal stereogenic center might be configurationally unstable under the reaction conditions. Thus, product ratios may reflect the different thermodynamic stabilities of the two diastereomers. To test this hypothesis,

Scheme 2. Ketoamide Scope[a]



[a]Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields. [b]Transamidation product (1-(3,4-dihydroisoquinolin-2(1*H*)-yl)-2-phenylethane-1,2-dione) was obtained in 38% yield.

Scheme 3. Amine Scope[a]



[a]Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields. [b]Reaction was performed in PhMe (0.25 M) under microwave irradiation for 30 min at 220 °C. [c]Reaction was performed in PhMe (0.25 M) under microwave irradiation for 1 h at 220 °C.

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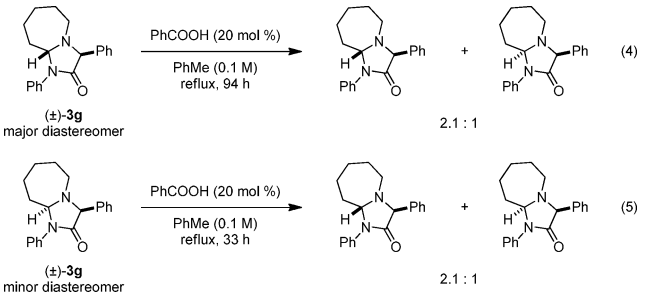
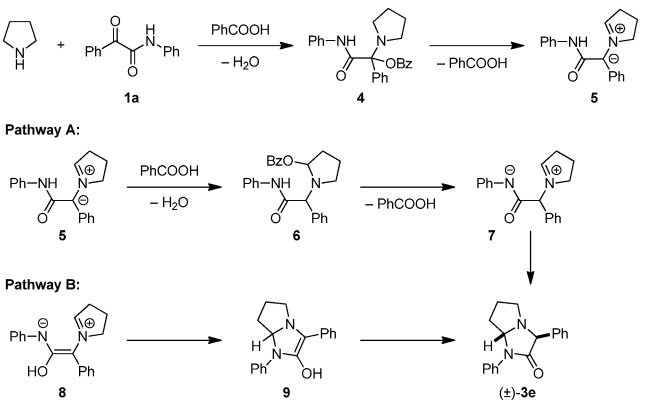
the readily available pure diastereomers of product **3g** were exposed to the reaction conditions (eqs 4 and 5). Upon



extended heating, both mixtures converged to a final 2.1:1 ratio of diastereomers. These experiments establish that product isomerization can indeed occur under the reaction conditions.

Two plausible mechanistic scenarios are shown in Scheme 4, depicting pyrrolidine and α-ketoamide **1a** as prototypical

Scheme 4. Mechanistic Considerations



examples. Based on previous investigations, the initial formation of *N*,*O*-acetal **4** appears highly likely. Again based on precedent, **4** could lose benzoic acid to form azomethine ylide **5**. Following the general mechanism of other redox-annulations,[11] **5** could reengage benzoic acid to form *N*,*O*-acetal **6**. The latter ultimately undergoes ring closure to final product **3e** with loss of benzoic acid, possibly via the zwitterionic intermediate **7** (pathway A). In an alternate scenario, conjugated azomethine ylide **8**, which represents a tautomer of azomethine ylide **5**, undergoes ring closure in what is formally a 1,5-electrocyclization.[14g] The resulting intermediate **9** then undergoes tautomerization to product **3e** (pathway B).[17]

In conclusion, we have achieved high-yielding syntheses of polycyclic imidazolidinones via redox-annulations of cyclic amines with a range of α-ketoamides. These reactions are efficiently catalyzed by benzoic acid and are rare examples of redox-neutral transformations in which an amine α-C–H bond is replaced by a C–N bond in the context of five-membered ring formation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03309.

Experimental procedures and characterization data, including X-ray crystal structures of products **2a** and **3d** (PDF)

X-ray data for compound **2a** (CIF)

X-ray data for compound **3d** (CIF)

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Notes

The authors declare no competing financial interest.

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