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Redox-Annulations of Cyclic Amines with 2-(2-Oxoethyl)Malonates

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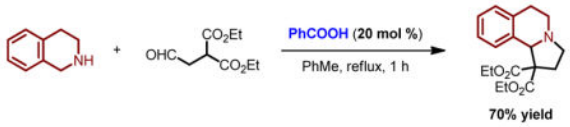
Abstract

Amines such as 1,2,3,4-tetrahydroisoquinoline undergo redox-neutral annulations with 2-(2-oxoethyl)malonates in the presence of catalytic amounts of benzoic acid. These reactions install a fully saturated 5-membered ring and provide access to structures closely related to the natural products crispine A and harmicine.

Graphical abstract



Redox-neutral amine annulation reactions, also referred to as redox-annulations, merge an oxidative α-C–H bond functionalization of an amine with the reductive amination of an aldehyde possessing a pendent (pro)nucleophilic site (Scheme 1, eq 1).[1–7] These reactions are ideally suited to install a fused ring onto a cyclic amine in a simple one-step procedure. In the majority of cases, a new six-membered ring is formed. Redox-annulations with formation of a 5-membered ring have been reported,[8] an example of which is provided in eq 2.[8e,9] Invariably, these reactions install a partially unsaturated 5-membered ring and involve a pericyclic reaction step (e.g., a 1,5-electrocyclization). A possible exception is the recently reported annulation of amines such as 1,2,3,4-tetrahydroisoquinoline (THIQ) with α-ketoamides (eq 3),[3k,4e] although a pericyclic process may also intervene in the formation of the corresponding ring-fused aminal products. Here we report redox-annulations of cyclic amines with 2-(2-oxoethyl)malonates that lead to the installation of a fully saturated 5-membered ring, a structural motif found in the natural products crispine A and harmicine (eq 4).[10]

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Supporting Information

Experimental procedures and characterization data, including the X-ray crystal structure of product **2l** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The title reaction was evaluated under a range of conditions, using THIQ and malonate-aldehyde **1a** as model substrates (Table 1). Under the optimized conditions (Table 1, entry 1), **1a** undergoes a reaction with two equiv of THIQ in the presence of benzoic acid (20 mol %) and 4 Å molecular sieves in toluene under reflux to provide product **2a** in 72% yield following a relatively brief reaction time (1.5 h). Other reaction conditions led to inferior results. For instance, in the absence of a carboxylic acid catalyst, only 38% of **2a** was formed within a 24 h period with the reaction remaining incomplete (entry 2). Increasing the amount of benzoic acid to 50 mol % led to a slightly faster reaction, but no increase in yield (entry 3). Replacement of benzoic acid for acetic acid or 2-ethylhexanoic acid (2-EHA), led to an increase in reaction time and a slight reduction in yield (entries 4 and 5). An increase or reduction in reactant concentration provided unfavorable results (entries 6 and 7), as did a reduction or an increase in the equiv of THIQ (entries 8 and 9).

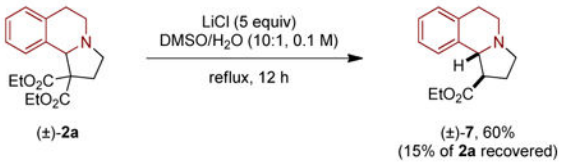
The scope of the amine annulation with 2-(2-oxoethyl)malonates is outlined in Scheme 2. Aldehydes derived from diethyl-, dimethyl-, diisopropyl-, and ditertbutyl malonate provided the corresponding products **2a**–**2d** in moderate to good yields. A trend in the yields of these products was observed, with more sterically demanding ester substituents resulting in lower yields. Substitution of the α-position of the aldehyde was tolerated, albeit with varying reaction outcomes. The corresponding reaction products **2e**–**2h** were isolated as mixtures of diastereomers. Substitution of the THIQ core was well tolerated, including substitution of the non-benzylic α-position of the amine nitrogen atom (products **2i**–**2n**). In addition, amines other than THIQ underwent reactions with **1a** (products **2o** and **2p**). Ketomalonates and aldehydes with two α-substituents did not participate in annulations with THIQ. 1-Phenyl-THIQ and amines with attenuated reactivities such as pyrrolidine and piperidine also did not undergo the title reaction. At least in the case of the latter two substrates, this is likely due to the higher energy barriers of the C–H functionalization step, which under the current conditions appears to be incompatible with the enolizable nature of the aldehyde substrate.[11c, 11e]

2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepane (**3**) did not undergo the expected annulation with malonate-aldehyde **1a** under a range of conditions. Instead, regiodivergent annulation led to the formation of product **4**, resulting from the substitution of a less activated non-benzylic C–H bond (Scheme 3). Under the optimized conditions using microwave irradiation, product **4** was isolated in 54% yield. This type of regiodivergent annulation has been observed previously,[3c,3g,5a] although not to the exclusion of the typically dominant reaction pathway. As was established in analogous redox-annulations of THIQ with 4-nitrobutyraldehydes, the primary site of C–H functionalization is almost certainly the benzylic position. Subsequent isomerization of an intermediate *N*,*O*-acetal via the corresponding azomethine ylide ultimately results in the final product **4**.[3g]

Decarboxylative annulations of proline and pipecolic acid have been shown in some cases to provide products not readily or not efficiently accessible from redox-annulations of pyrrolidine and piperidine.[11–13] Given the failure of pyrrolidine and piperidine in the present case, a decarboxylative variant of the title reaction was also explored (Scheme 4). Gratifyingly, condensation of **1a** with proline in the presence of excess acetic acid under

reflux in mesitylene provided pyrrolizidine **5** in 81% yield. Application of identical conditions to a reaction with pipecolic acid and **1a** furnished indolizidine **6** in 69% yield.

As shown in eq 5, annulation product **2a** was subjected to Krapcho dealkoxycarbonylation conditions,[14] resulting in the formation of a single diastereomer of monoester **7** in 60% yield. Under the indicated conditions, starting material **2a** was recovered in 15% yield. Attempts to increase the conversion led to a reduction in the yield of product **7**.



(5)

In summary, we have achieved redox-annulations of amines with 2-(2-oxoethyl)malonates, reactions that rapidly form the core structures of natural products such as crispine A and harmicine. These reactions likely represent the first examples of redox-annulations leading to five-membered ring formation without intervention of pericyclic processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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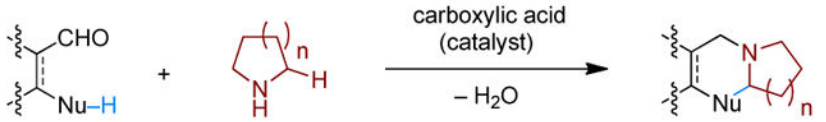
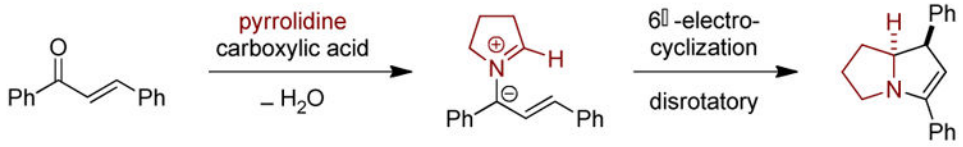
Redox-annulations with formation of a 6-membered ring:



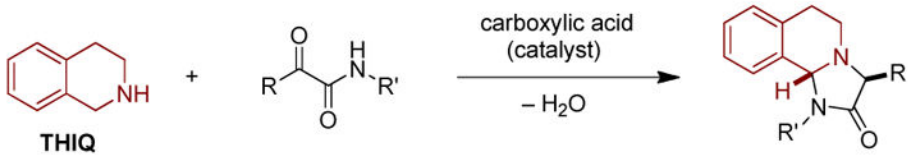
(1)

Pericyclic redox-annulation with formation of a 5-membered ring:



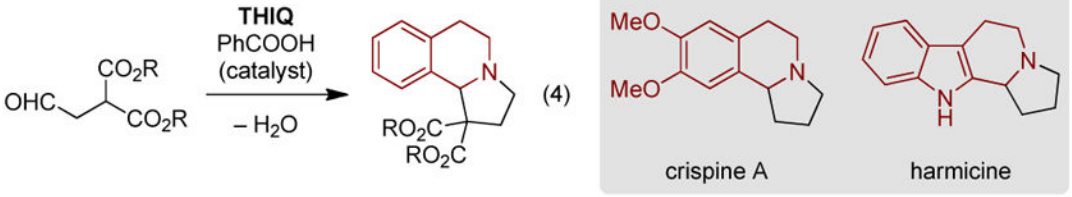
(2)

Redox-annulation with formation of a C–N bond and a 5-membered ring:



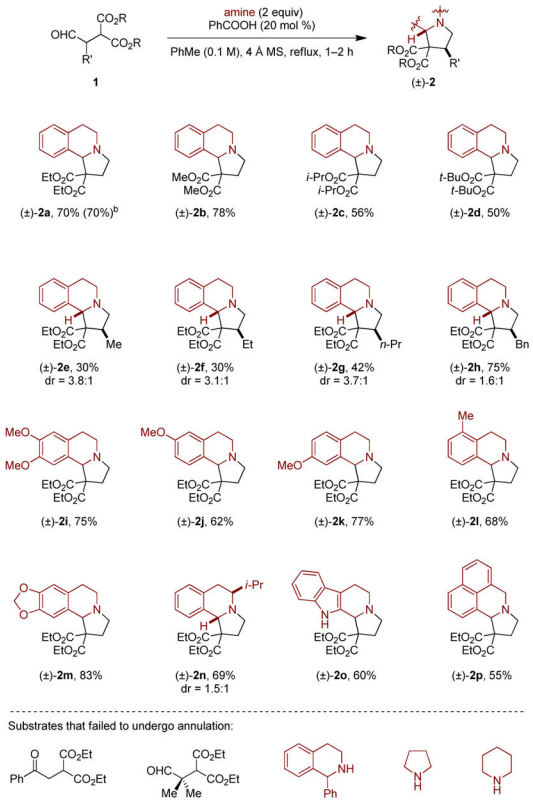
(3)

Redox-annulation with formation of a fully saturated 5-membered ring (this work):



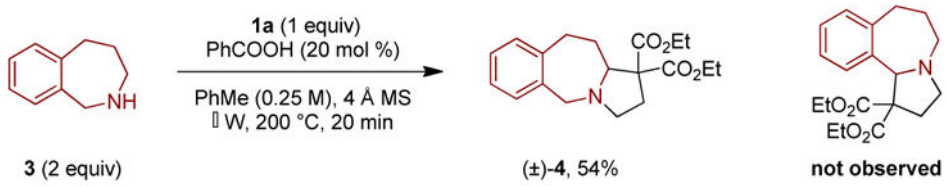
(4)

Scheme 1.
Redox-Annulations of Amines

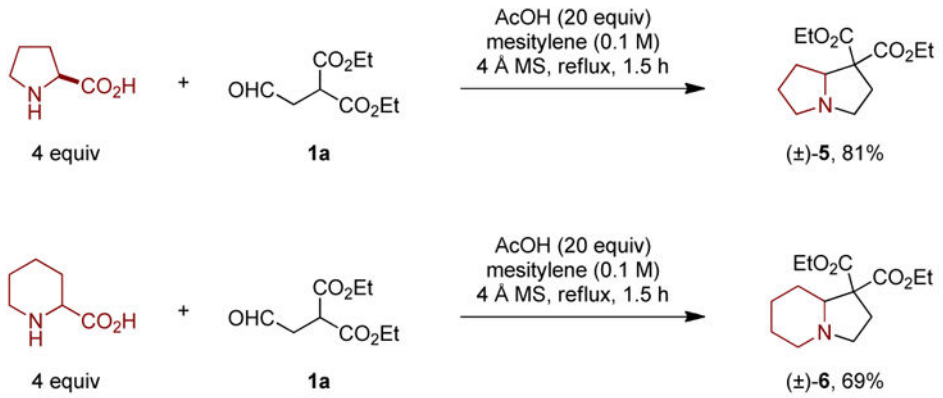


Scheme 2. Scope of the Redox-Annulation[a]

[a]Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields. [b] Value in parentheses corresponds to yield for a reaction conducted on a 2 mmol scale.



Scheme 3.
Redox-Annulation with Divergent Regioselectivity

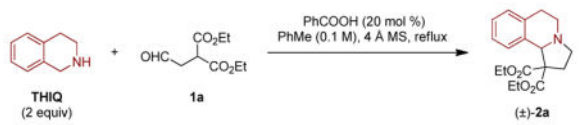


Scheme 4. Decarboxylative Annulations[a]

[a]Reactions were performed on a 0.5 mmol scale. The aldehyde was added slowly over 1 h, followed by an additional 0.5 h reaction time. Yields correspond to isolated yields.

Table 1

Reaction Development[a]



entry	deviation from optimized conditions	time (h)	yield (%)
1	none	1.5	72
2	no PhCOOH	24	38
3	50 mol % of PhCOOH	1	72
4	AcOH instead of PhCOOH	2.5	66
5	2-EHA instead of PhCOOH	2.5	67
6	0.2 M conc	1.5	67
7	0.05 M conc	2.5	69
8	1.5 equiv of THIQ	2	46
9	3 equiv of THIQ	1.5	55

[a]Reactions were performed on a 0.2 mmol scale. All yields correspond to isolated yields.

2-EHA = 2-ethylhexanoic acid