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Redox-Annulation of Cyclic Amines and β-Ketoaldehydes

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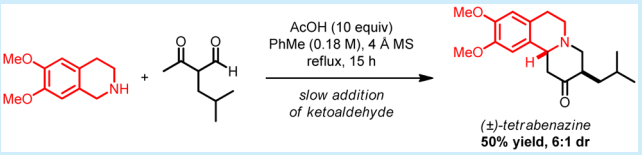
Supporting Information

ABSTRACT: Benzo[*a*]quinolizine-2-one derivatives are readily assembled from 1,2,3,4-tetrahydroisoquinoline and β-ketoaldehydes by means of a new intramolecular redox-Mannich process. These reactions are promoted by simple acetic acid and are thought to involve azomethine ylides as reactive intermediates.



Benzo[*a*]quinolizine derivatives featuring a fused tricyclic ring system are ubiquitous substructures of natural products and unnatural compounds possessing valuable biological activities (Figure 1).[1] Significant efforts have been extended to develop methods for the construction of these structural motifs,[1] in particular benzo[*a*]quinolizine-2-ones, often in the context of natural product synthesis.[2] Here we report a rapid approach to the synthesis of benzo[*a*]-quinolizine-2-one derivatives via a new intramolecular redox-Mannich reaction utilizing cyclic amines such as 1,2,3,4-tetrahydroisoquinoline (THIQ) or tryptoline and readily available β-ketoaldehydes.

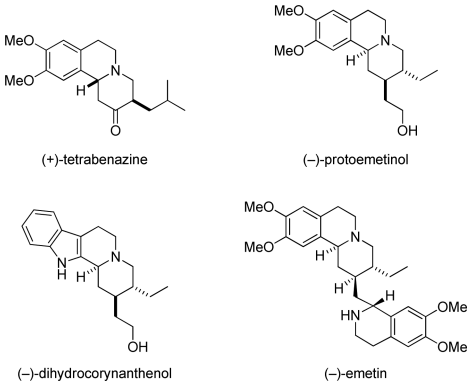
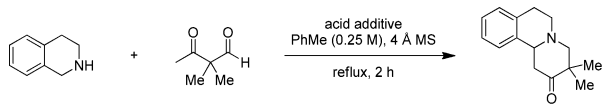


Figure 1. Selected bioactive compounds containing the benzo[*a*]-quinolizine and related structural motifs.

As part of a program aimed at developing new and efficient methods for the C–H functionalization of amines that provide alternatives to commonly employed oxidative approaches,[3−7] our group has recently reported three-component redox-Mannich reactions where ring-substituted β-amino ketones were obtained in a single step from cyclic amines (e.g., pyrrolidine and THIQ), aromatic aldehydes, and ketones such as acetophenone.[5f,8] Furthermore, we developed a strategy for the rapid formation of fused tricyclic ring systems via redox-neutral annulations of cyclic amines with *ortho*-malonate benzaldehydes and 4-nitrobutyraldehydes.[5i,j] These previous successes prompted us to consider the opportunity to develop an intramolecular redox-Mannich reaction involving cyclic amines and readily available β-ketoaldehydes. Such an approach would allow for the facile construction of benzo[*a*]quinolizine-2-one structures.

In order to test the feasibility of the proposed intramolecular redox-Mannich process, THIQ and readily available, non-enolizable 2,2-dimethyl-3-oxobutyraldehyde were selected as test substrates.[9] Representative examples of the initial survey are summarized in Table 1. Conditions previously developed for the three-component intermolecular redox-Mannich reaction provided poor results; only complex product mixtures were obtained (entry 1). A reaction performed under reflux in toluene in the presence of 1 equiv of acetic acid resulted in complete consumption of the ketoaldehyde starting material within 2 h. The desired product **1a** could be isolated in 12% yield (entry 2). Upon increasing the amount of acetic acid to 10 equiv, the optimal amount in the redox-annulation of cyclic

Table 1. Reaction Development[a]



entry	acid additive (equiv)	yield (%)
1[b]	PhCOOH (0.2)	complex
2	AcOH (1)	12
3	AcOH (10)	71
4	AcOH (20)	70
5	PhCOOH (10)	65
6	2-EHA (10)	38

[a]Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields of purified products. 2-EHA: 2-ethylhexanoic acid. [b]Reaction was performed at 50 °C for 12 h.

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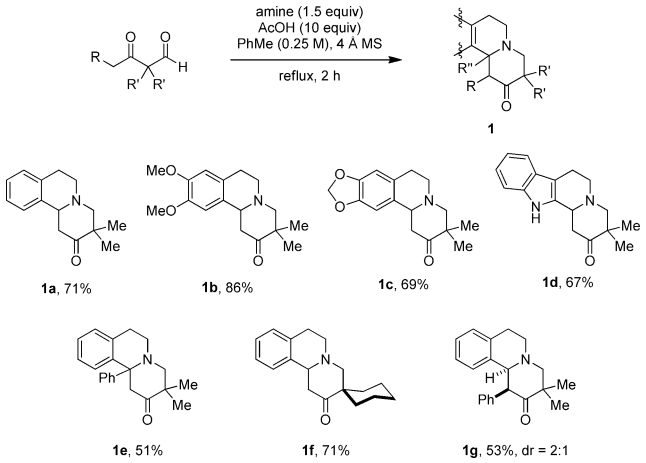
amines with 4-nitrobutyraldehydes,[5j] the yield improved dramatically to 71% (entry 3). A nearly identical result was obtained with 20 equiv of acetic acid (entry 4). Carboxylic acids other than acetic acid were viable promoters of the title reaction but provided inferior results. For instance, **1a** was obtained in 65% yield in the presence of benzoic acid (entry 5). 2-Ethylhexanoic acid (2-EHA), an excellent catalyst in other redox-isomerization processes, provided product **1a** in only 38% yield (entry 6).

With the optimal reaction conditions in hand, the scope of the title reaction was evaluated with a number of nonenolizable β-ketoaldehydes (Scheme 1). Tetrahydroisoquinolines and tryptoline provided good yields of redox-annulation products upon reaction with 2,2-dimethyl-3-oxobutyraldehyde or 1-acetylcyclohexanecarbaldehyde. Substitution of THIQ in the 1-position was well tolerated. A reaction with 1-phenyl-THIQ gave rise to the desired product **1e** in 51% yield.[10] A reaction of THIQ with 2,2-dimethyl-3-oxophenylbutyraldehyde provided product **1g** as a 2:1 mixture of diastereomers in a combined yield of 53%.

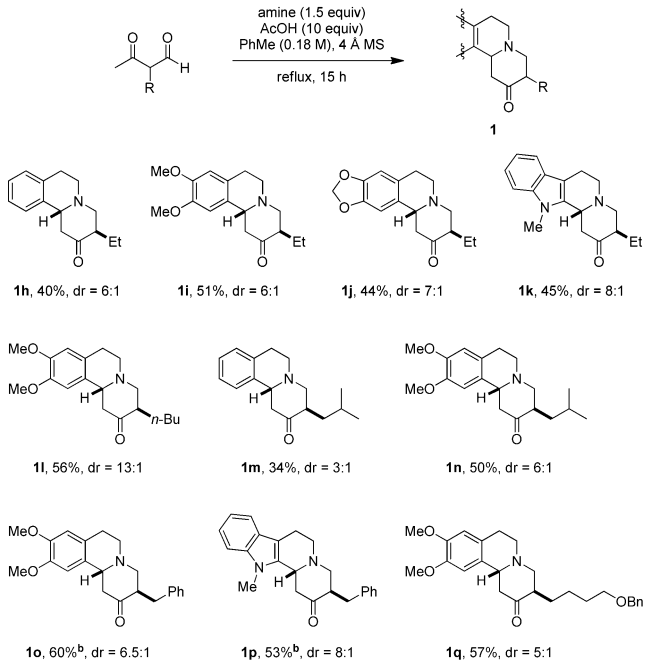
Scheme 1. Scope of the Intramolecular Redox-Mannich Reaction with Non-enolizable β-Ketoaldehydes[a]



[a]Reactions were performed on a 0.5 mmol scale. All yields correspond to isolated yields of purified products.

Our study was then extended to more challenging aldehydes, i.e., enolizable 2-monosubstituted β-ketoaldehydes. These substrates are particularly appealing from a practical point of view, considering that most structurally related natural products and other bioactive compounds possess only one substituent at the corresponding position in the products. Consistent with the more challenging nature of enolizable β-ketoaldehydes, the original conditions which involve direct mixing of all reagents provided the desired products in low yields, likely a result of competing aldol processes. Gratifyingly, yields of the desired redox-annulation products could be improved significantly by delivering the aldehyde slowly via syringe pump to a refluxing mixture of the amine and acetic acid. An addition time of 15 h proved optimal. Tetrahydroisoquinolines and tryptolines readily underwent the title reaction with 2-alkyl β-ketoaldehydes, providing the corresponding tricyclic products in moderate to good yields and synthetically useful levels of diastereoselectivity (Scheme 2). Reactions involving 2-benzyl-3-oxobutyraldehyde did not require slow addition of the aldehyde. Presumably due to the poor solubility of this aldehyde

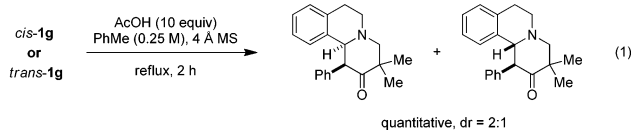
Scheme 2. Scope of the Intramolecular Redox-Mannich Reaction with Enolizable β-Ketoaldehydes[a]



[a]Reactions were performed on a 0.5 mmol scale. A solution of the aldehyde in 0.75 mL of toluene was added slowly over 15 h to a mixture of the amine, acetic acid, and 4 Å MS in 2 mL of toluene. All yields correspond to isolated yields of purified products. [b]All reagents were mixed directly and heated under reflux in toluene (0.25 M) for 20 h.

in toluene, competing reaction pathways were minimized. Notably, THIQs with electron-donating groups on the aryl ring generally produced products in higher yields than parent THIQ. Tryptoline with a free indole *N*H-proton failed to undergo the desired redox annulation with enolizable β-ketoaldehydes.

The interconversion between benzo[*a*]quinolizine-2-one and the corresponding ring-opened isoquinolinium ions under acidic conditions is a well-known process.[11] As a consequence, the diastereomeric ratios of the annulation products likely represent the thermodynamic equilibrium ratios of the two diastereomers. Consistent with this notion, exposure of either diastereomerically pure *cis*-**1g** or *trans*-**1g** to the optimal reaction conditions resulted in the identical 2:1 ratio of both diastereomers, the same ratio that was observed in the initial reaction (eq 1). This experiment further served to establish the stability of the products under the reaction conditions, as the starting material was recovered essentially quantitatively.



In order to explore the reactivity of related carbonyl substrates, a β-diketone was used in place of a β-ketoaldehyde. Interestingly, acetylacetones such as **2** provided no expected product under the standard conditions for enolizable β-ketoaldehydes (eq 2). Instead, *N*-acetyl THIQ was isolated in

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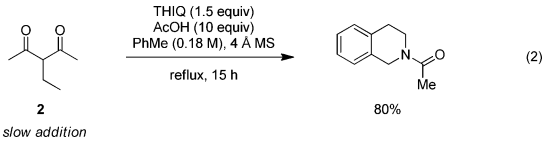
80% yield. The formation of this species is consistent with a retro-Claisen pathway.[12]



(2)

Products of the intramolecular redox-Mannich reaction, in particularly those shown in Scheme 2, are closely related to a number of natural products and other bioactive compounds. For instance, compound **1n** is known as tetrabenazine, a drug used to treat chorea such as Huntington's disease.[13] Enantiomerically pure (+)-**1n** is readily available via the resolution of the racemic mixture by (+)-camphorsulfonic acid.[13b] Compound **1i** has previously been converted to (±)-protoemetinol and (±)-emetin via short synthetic sequences.[1a,2c]

In conclusion, we have developed an intramolecular redox-Mannich reaction between cyclic amines and β-ketoaldehydes as a facile entry to benzo[*a*]quinolizine-2-one derivatives. Challenging enolizable β-ketoaldehydes provided the desired products with useful levels of diastereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00151.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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