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Cobalt-Catalyzed Regioselective Synthesis of Pyrrolidinone Derivatives by Reductive Coupling of Nitriles and Acrylamides

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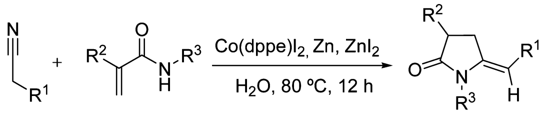
Transition-metal-catalyzed regioselective reductive coupling (RRC) of two organic π components into various new products has emerged as a powerful method for organic synthesis.[1] Alkyne/alkyne,[2a] alkyne/alkene,[2b−l] alkyne/carbonyl,[2m−r] alkyne/imine,[2s] alkene/imine,[2t] alkene/alkene,[2a] alkene/carbonyl,[2b] and diene/carbonyl[2q] RRC reactions catalyzed by ruthenium, rhodium, nickel, and palladium complexes have been reported. The reactions are generally highly atom- and step-economical.[3]

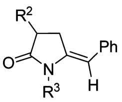
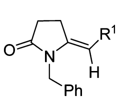
Cobalt complexes have also been employed as catalysts in RRC reactions. In this context, Druliner and Blackstone reported a stoichiometric cobalt-promoted tail-to-tail coupling of acrylonitrile to give adiponitrile.[4] We also found a series of cobalt-catalyzed reductive coupling reactions of alkynes and activated alkenes,[5a,b] reductive dimerization of conjugated alkenes and head-to-tail dimerization of vinyl arenes,[5c] and intermolecular reductive [3 + 2] cycloaddition of allenes and enones.[5d] In 2007, Hilt and Treutwein described an intermolecular cobalt-catalyzed Alder−ene reaction of alkynes with alkenes to form highly substituted 1,4-dienes.[6] To date, the most commonly employed π components include alkynes, alkenes, dienes, allenes, aldehydes, imines, and allylic halides. Our continued interest in metal-catalyzed RRC of two π components[7] prompted us to explore the coupling reaction of nitriles with acrylamides. Herein we report a cobalt-catalyzed regioselective synthesis of pyrrolidinones from intermolecular reductive coupling of nitriles and acrylamides in one pot. It is interesting to note that the pyrrolidinone group is an important core in various natural products and biologically active compounds.[8]

We have previously reported the cobalt-catalyzed RRC reaction of two π components by employing zinc as a reducing agent and water as a proton source.[5] During the course of our investigation of RRC reactions, we noticed that nitrile and acrylamide readily formed pyrrolidinone derivatives. Thus, treatment of 2-phenylacetonitrile (**1a**) with *N*-benzylacrylamide (**2a**) in the presence of Co(dppe)I_2, Zn, ZnI_2, and water at 80 °C for 12 h gave pyrrolidinone derivative **3a** in 91% isolated yield with excellent regioselectivity (Table 1, entry 1). Product **3a** was characterized by its ^1H and ^{13}C NMR and mass spectroscopic data. The *E* stereochemistry of product **3a** was further confirmed by nuclear Overhauser effect (NOE) experiments. To the best of our knowledge, no catalytic reaction using either nitrile or acrylamide as a π component for reductive coupling has been reported previously. It is noteworthy that an intramolecular reductive coupling of nitriles with alkenes using Cp_2ZrCl_2/*n*-BuLi as the reducing agent to give cyclic ketones has been reported by Mori et al.[9]

Table 1. Results of Cobalt-Catalyzed Reductive Coupling of Nitriles and Acrylamides[a]



1a-i **2a-j** **3a-r**

entry	1	2		product	yield,(%)[b]
1	**1a**	**2a**		**3a**: R^2 = H, R^3 = CH_2Ph	91
2	**1a**	**2b**		**3b**: R^2 = H, R^3 = $(CH_2)_2(3\text{-MeO})C_6H_4$	84
3	**1a**	**2c**		**3c**: R^2 = H, R^3 = $CH_2CH(CH_3)Ph$	80
4	**1a**	**2d**		**3d**: R^2 = H, R^3 = CH_2(2-thienyl)	64
5	**1a**	**2e**		**3e**: R^2 = H, R^3 = Ph	58
6	**1a**	**2f**		**3f**: R^2 = H, R^3 = $(CH_2)_3CH_3$	69
7	**1a**	**2g**		**3g**: R^2 = H, R^3 = $CH(CH_3)_2$	73
8	**1a**	**2h**		**3h**: R^2 = H, R^3 = cyclohexyl	78
9	**1a**	**2i**		**3i**: R^2 = Me, R^3 = CH_2Ph	66
10	**1a**	**2j**		**3j**: R^2 = $(CH_2)_2CH_3$, R^3 = CH_2Ph	59
11	**1b**	**2a**		**3k**: R^1 = 4-MeOC_6H_4	78
12	**1c**	**2a**		**3l**: R^1 = 4-ClC_6H_4	71
13	**1d**	**2a**		**3m**: R^1 = 4-FC_6H_4	83
14	**1e**	**2a**		**3n**: R^1 = 1-naphthyl	81
15	**1f**	**2a**		**3o**: R^1 = 2-thienyl	79
16	**1g**	**2a**		**3p**: R^1 = 3-thienyl	61
17	**1h**	**2a**		**3q**: R^1 = methyl	78
18	**1i**	**2a**		**3r**: R^1 = ethyl	83

[a] Unless otherwise mentioned, all reactions were carried out using nitrile **1** (5.0 mmol), acrylamide **2** (1.0 mmol), Co(dppe)I_2 (0.100 mmol), Zn (1.50 mmol), ZnI_2 (0.200 mmol), and H_2O (1.0 mmol) at 80 °C for 12 h. [b] Isolated yields.

Under similar reaction conditions, various N-substituted acrylamides reacted smoothly with **1a** to give the corresponding substituted pyrrolidinones. Thus, *N*-3-arylpropyl acrylamides **2b** and **2c** underwent reductive cyclization with **1a** to give **3b** and **3c** in 84 and 80% yield, respectively (entries 2 and 3). Similarly, the coupling of *N*-thienylmethyl acrylamide **2d** with **1a** afforded the corresponding pyrrolidinone **3d** in 64% yield (entry 4). The reductive coupling reaction also works with *N*-phenyl- and *N*-alkyl-substituted acrylamides. Accordingly, the reaction of **2e** with **1a** afforded **3e** in 58% yield (entry 5). Similarly, *N*-alkyl-substituted acrylamides **2f**−**h** reacted well with **1a** to produce substituted pyrrolidinones in good to excellent yields (entries 6−8). Acrylamides **2i** and **2j** having methyl and propyl substitution at the α-carbon also worked smoothly with **1a**, providing **3i** and **3j** in 66 and 59% yield, respectively (entries 9 and 10).

The present cobalt-catalyzed reductive coupling reaction was successfully extended to various substituted phenylacetonitriles **1b**−**e**. Thus, electron-donating 4-methoxyphenylacetonitrile (**1b**) reacted well with **2a** to afford the corresponding cyclized product **3k** in 78% yield (entry 11). In a similar manner, the reaction of 4-chloro- and 4-fluorophenylacetonitriles **1c** and **1d** with **2a** gave pyrrolidinones **3l** and **3m** in 71 and 83% yield, respectively (entries 12 and 13). 2-Naphthylacetonitrile (**1e**) underwent reductive cyclization with **2a** to afford **3n** in 81% yield (entry 14). Similarly, both 2- and 3-thienylacetonitriles **1f** and **1g** reacted smoothly with **2a** to provide the expected pyrrolidinone derivatives **3o** and **3p** in

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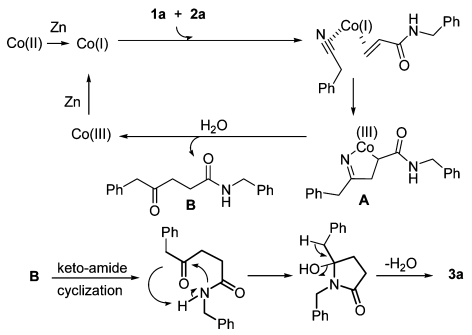
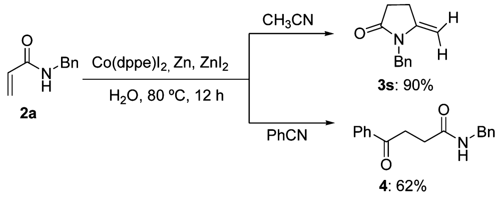
Scheme 1



79 and 61% yield, respectively (entries 15 and 16). Alkyl nitriles also worked well for this reaction. Thus, propionitrile (**1h**) and butyronitrile (**1i**) nicely underwent cyclization with **2a** to give **3q** and **3r** in 78 and 83% yield, respectively (entries 17 and 18).

Under similar reaction conditions, acetonitrile also effectively reacted with **2a** in a highly regioselective manner to provide pyrrolidinone **3s** in 90% yield (eq 1): Very interestingly, reductive



(1)

coupling of benzonitrile with **2a** also proceeded to give linear product **4**, but no further keto−amide cyclization step occurred.[10] Thus, it is necessary for the nitrile to possess α-protons in order for the cyclization and dehydration to proceed.

The mechanism of the present reductive coupling cyclization is intriguing in view of the ability of the catalyst to assemble the two π components (nitrile and acrylamide) in a highly regio- and stereoselective manner (Scheme 1). The catalytic cycle is likely initiated by the reduction of Co(II) to Co(I) by zinc dust. This is followed by the chemoselective cyclometalation of Co(I) with nitrile and acrylamide to form cobaltaazacyclopentene intermediate **A**. Protonation of **A** followed by hydrolysis gives intermediate **B** and a Co(III) species. The Co(III) species is reduced by zinc to regenerate the active Co(I) species for the next cycle.[11] Intermediate **B** further undergoes keto−amide cyclization[10] and elimination of water to give the final pyrrolidinone derivative **3a**. Such a metalloazacyclopentene species has been proposed as a key intermediate in the RRC reactions catalyzed by nickel complexes.[2s,t] The formation of cobaltaazacyclopentene **A** by the assembly of two π components is generally regioselective, with the carbon atom having an electron-withdrawing functionality near the metal center.[5,7] This mechanism explains the regioselectivity of the present reductive coupling product. In the catalytic reaction, ZnI$_2$ probably acts as a Lewis acid to remove a halide from the Co(I) center, assisting the coordination of the nitrile and acrylamide to the metal center. In addition, it can also activate the keto group in **B**, assisting in the cyclization of **B** to give the final product **3**.

In conclusion, we have successfully developed a novel method for the synthesis of pyrrolidinones via cobalt-catalyzed reductive coupling of nitrile and acrylamide followed by keto−amide cyclization and dehydration in one pot. Further detailed investigations of the mechanism, the substrate scope, and the application of this methodology in natural product synthesis are in progress.

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Supporting Information Available: General experimental procedures, characterization details, and crystallographic data (CIF) for **3b** and **3h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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