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Rhodium-Catalyzed Reaction of *N*-Acylpiperazines with CO and Ethylene. Carbonylation at a C-H Bond Directed by an Amido Group

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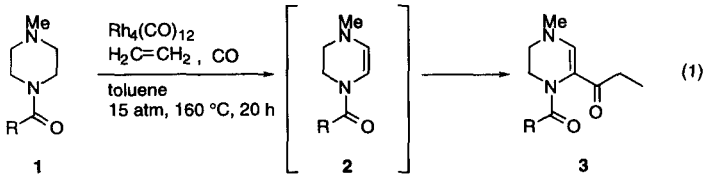
Abstract: The reaction of *N*-acylpiperazines with CO (15 atm) and ethylene at 160 °C in the presence of $Rh_4(CO)_{12}$ results in dehydrogenation and carbonylation at a C-H bond. This reaction represents the first example of carbonylation at a C-H bond promoted by an oxygen functional group.

We recently reported a carbonylation at a C-H bond[1] in the benzene ring in the $Ru_3(CO)_{12}$-catalyzed reaction of pyridylbenzenes with CO and ethylene.[2,3] The carbonylation was observed to take place selectively at an *ortho* C-H bond in the benzene ring and it was also observed that the pyridine ring is a necessary directing group in promoting this reaction. In addition, we also reported that the reaction of *N*-pyridylpiperazines with CO and ethylene in the presence of $Rh_4(CO)_{12}$ results in new type of carbonylation reaction, which involves successive cleavages of first sp^3 C-H bond and then second sp^2 C-H bond.[4] This reaction is proposed to proceed via dehydrogenation, followed by carbonylation at the C-H bond thus formed. In both cases, the presence of a pyridine ring as in, for example, pyridylbenzenes and *N*-pyridylpiperazines, appears to be essential for the reaction to proceed. Although the pyridyl group works well, it is not a particularly useful substituent in terms of synthetic organic chemistry. We have examined various other functional groups[5-8] regarding their ability to promote the cleavage of a C-H bond and for the ease of removal,[9] and recently found that an *N*-acyl group effectively promotes the reaction of piperazines. This reaction is significant, since it represents the first example of carbonylation at a C-H bond which is directed by a functional group other than a C=N moiety.[1-4] In this paper, we wish to report an amido-directed carbonylation at a C-H bond, which is outlined in eq 1.



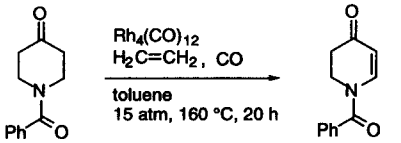
(1)

1 2 3

a: R = Me	71%
b: R = Ph	89%
c: R = 4-$Me_2NC_6H_4$	80%
d: R = 2-pyridyl	88%
e: R = CF_3	0%
f: R = OBu^t	trace (**2f** 11%)

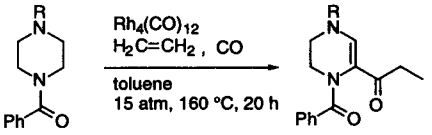
When 1-acetyl-4-methylpiperazine (**1a**, 1 mmol) was reacted with CO (15 atm at 25 °C in a 50-mL stainless steel autoclave) and ethylene (10 atm) in the presence of $Rh_4(CO)_{12}$ (0.04 mmol) in toluene at 160 °C, carbonylation took place smoothly to give 1-(1-acetyl-4-methyl-1,4,5,6-tetrahydro-2-pyrazyl)-1-propanone (**3a**) in 71% isolated yield (eq 1).[10] Benzoyl and picolinoyl substrates, **1b-d**, worked well, but trifluoroacetyl **1e** did not. Carbamate **1f** did not undergo carbonylation, and, instead, a dehydrogenation product **2f** was obtained in low yield. Attempts to react **1a** (1 mmol) with CO (15 atm) and olefins (10 mmol), such as hexene and tert-butylethylene, at 160 °C failed to proceed. We believe that the reaction proceeds via an initial dehydrogenation leading to **2** and then carbonylation at the C-H bond in the resulting enamide **2**, in a manner similar to the previously reported *N*-pyridylpiperazines.[4] Among the transition metal carbonyl complexes we have examined thus far, $Rh_4(CO)_{12}$ is the only active catalyst for this transformation.

Similar to the previously reported *N*-pyridyl system,[4] the presence of a second nitrogen atom in the six-membered ring is important for the carbonylation to proceed. No reaction was observed, when substrates having no additional nitrogen atom, such as *N*-benzoylmorpholine and *N*-benzoylpiperidine, were examined. The reaction of **4** with CO and ethylene resulted in dehydrogenation to give **5** in 30% yield, along with 69% of unreacted **4** (eq 2), although no reaction had been observed in the case of the corresponding pyridyl system.[4]



4 **5** 30% (2)

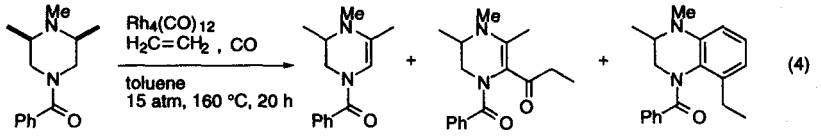
The replacement of an *N*-Me group by an *N*-Ph group, as in **6a**, failed to afford the corresponding carbonylation product and the starting material was recovered (eq 3). In contrast, the reaction of the *o*-methoxyphenyl compound **6b** gave ketone **7b**, albeit in low yield, along with 58% of recovered **6b**. The reaction of benzyl isomer **6c** gave the corresponding carbonylation product **7c** in a good yield, similar to the methyl isomer **1b**, as shown in eq 1.



6 **7** (3)

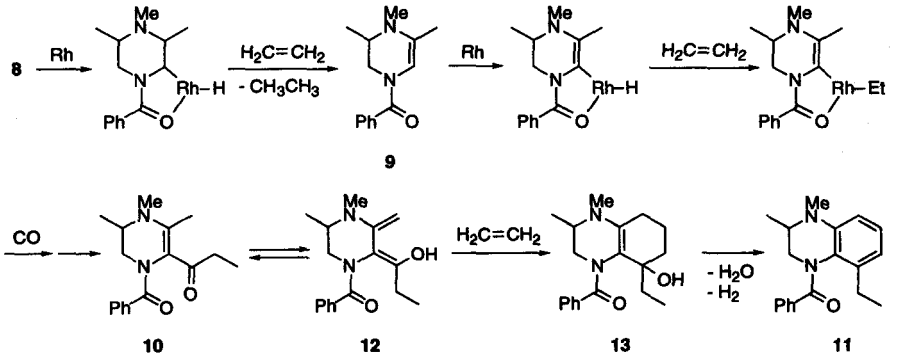
a: R = Ph	0%
b: R = 2-$MeOC_6H_4$	35%
c: R = $PhCH_2$	79%

An interesting observation was made for the reaction of a substrate having Me groups in the ring. The reaction of *cis*-1-benzoyl-3,4,5-trimethylpiperazine (**8**) did not give the expected carbonylation product **10** and instead, gave a mixture of the dehydrogenation product **9** and 1-benzoyl-3,4-dimethyl-8-ethyl-1,2,3,4-tetrahydroquinoxaline (**11**) into which two molecules of ethylene and one molecule of CO were incorporated (eq 4).



8 **9** 43% **10** 0% **11** 34%

A possible mechanism for the formation of **10** and **11** is shown in Scheme 1. A primary product **9** is formed by hydrogen transfer from **8** to ethylene.[11] The product, **9**, is converted to the expected product **10** via carbonylation at a C-H bond. The Diels-Alder reaction of an enol form **12**[12] with ethylene under the reaction condition, as shown in eq 4, gives an adduct **13**, which undergoes dehydration and aromatization to form a quinoxaline ring. Alternatively, these conversion can proceed as the reactions in the ligand **12**, coordinated to the rhodium. The pathway leading from **8** to **10** contains two types cleavages of C-H bonds, first an sp^3 C-H bond and then an sp^2 C-H bond. The formation of **3** and **7** can be accounted for by assuming a similar scenario.



Scheme 1

In summary, an amide functionality can serve as directing group for carbonylation at a C-H bond. The reacion involves cleavages of C-H bonds, first an sp^3 C-H bond and then an sp^2 C-H bond, in succession. A search for other functional groups, which are able to promote carbonylation at a C-H bond is now underway.

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