One-pot synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines using supported gold and base as catalysts

Kegnæs, Søren; Mielby, Jerrik Jørgen; Mentzel, Uffe Vie; Jensen, Thomas; Fristrup, Peter; Riisager, Anders

Published in:
Chemical Communications

Link to article, DOI:
10.1039/c2cc16768a

Publication date:
2012

Document Version
Publisher's PDF, also known as Version of record

Citation (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
One-pot synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines using supported gold and base as catalysts†

Søren Kegnæs, Jerrik Mielby, Uffe V. Mentzel, Thomas Jensen, Peter Fristrup and Anders Riisager*

Received 1st November 2011, Accepted 10th January 2012
DOI: 10.1039/c2cc16768a

Synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines via intermediate formation of methyl esters is highly efficient and selective when using a catalytic system comprised of supported gold nanoparticles and added base in methanol.

Selective oxidation of alcohols is one of the most important reactions in organic chemistry and finds use in the manufacture of many bulk commodities, high-value fine chemicals, agrochemicals, and pharmaceuticals. Traditionally, oxidations of alcohols are performed with stoichiometric amounts of high-valent inorganic oxidants such as chromate or permanganate, which inevitably leads to the generation of large amounts of metal waste. In the search for a more sustainable chemical production, researchers have put considerable effort into the development of catalytic oxidations using air or molecular dioxygen as the stoichiometric oxidant.1,2 From the standpoint of green chemistry these aerobic oxidations are attractive, because dioxygen is a cheap and abundant oxidant that produces water as the only by-product.

Since the first fundamental studies by Bond et al.,3 Hutchings,4 Haruta et al.,5 and Prati and Rossi6 supported gold nanoparticles have been recognised as surprisingly active and selective catalysts for a number of aerobic oxidations.7 For instance, supported gold nanoparticles have been used for oxidation of alcohols to aldehydes,8 carboxylic acids9 and esters.10,11 Furthermore, interesting results have been reported for the oxidation of amines and oxidative coupling of alcohols with amines. In particular, supported gold nanoparticles have been used in the synthesis of azo-compounds,12 imines,13 secondary amines,14 and amides.15

Although the increasing number of reports on oxidations with nitrogen-containing compounds represents an interesting development, the field still needs further improvement in terms of catalytic efficiency and practical applicability. For instance, under mild reaction conditions the oxidation of alcohols often requires a strongly alkaline solution and in some systems this represents a strong limitation as various side reactions may decrease the selectivity.2

Scheme 1 Synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines using supported gold nanoparticles and base as catalysts.

Here, we show that the combination of supported gold nanoparticles and base forms an efficient and highly selective catalytic system for the one-pot, two-step synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines, see Scheme 1.

In the first step of the reaction, the gold-catalysed oxidation of the alcohol or aldehyde in methanol yields a methyl ester.16 In the second step, amine is added and the ester is converted into the desired amide by base-catalysed aminolysis. As the same base is promoting both steps of the reaction, the synthesis can be performed in a convenient one-pot procedure without cumbersome isolation or purification of the intermediate. The employed oxidant is pure dioxygen and the reaction can be performed under mild reaction conditions (25–65 °C, atmospheric pressure).

Initially, we used benzyl alcohol as a model compound to study the gold-catalysed oxidative esterification in methanol. The results from these experiments showed that methyl benzoate could be obtained in 92% yield at full conversion after 24 hours employing KOMe as a base and Au/TiO2 as a heterogeneous catalyst. Under the same reaction conditions, we found that addition of hexylamine to methyl benzoate resulted in the formation of N-hexylbenzamide (see ESI†).

The two base-promoted reactions were combined in a novel one-pot reaction procedure and tested for the oxidative coupling of a number of substrates, including different alcohols, aldehydes and amines. All reactions were performed under identical reaction conditions and no optimisation was attempted for the individual substrates.

Table 1 compiles the results from the oxidative coupling of different alcohols and aldehydes with N-hexylamine to form the corresponding N-hexylamides. All examined alcohols, i.e. benzyl alcohol, cinnamyl alcohol, and 1-heptanol, were oxidised with high selectivity to form the corresponding methyl ester. While the oxidation of the aromatic alcohols achieved full conversion in 24 hours, 1-heptanol only achieved 34% conversion at room temperature (Table 1, entry 5). Higher yields of aliphatic
methyl esters have previously been reported at high temperatures and increased pressure of oxygen.\textsuperscript{11} As expected, both aromatic aldehydes, \textit{i.e.} benzaldehyde and furfural, were oxidised to the corresponding methyl esters in high yields (Table 1, entries 2 and 6).

Table 1 also shows that all the investigated methyl esters reacted with $N$-hexylamine to form the corresponding amide in good yields. It is notable that the second step of the reaction occurred with excellent selectivity when using $N$-hexylamine ($>99\%$) independent of the structure of the ester.

Table 2 summarises the results from the oxidative coupling of benzyl alcohol with different amines to form the corresponding amides. The reaction proceeded smoothly when employing benzylamine, while the more sterically demanding amines aniline and pentan-3-amine were unable to react under the applied reaction conditions. Furthermore, the oxidative coupling of benzyl alcohol with ammonia resulted in formation of benzamide.

To investigate the observed structure-reactivity relationship for the aminolysis of methyl benzoate in Table 2 we performed a computational study. The exchange reaction is expected to take place via formation of an anionic, tetrahedral intermediate, which forms the basis for the computational study.

The calculated energetic profiles of the aminolysis for the five different amines are shown in Fig. 1. The three successful examples ($\text{NH}_3$, Et$\text{NH}_2$ and Bn$\text{NH}_2$) all have relatively low energies for both the tetrahedral intermediate and the amide product. In contrast, the amide formed from pentan-3-amine is also thermodynamically favoured by 7 kJ mol$^{-1}$ (similar to ethylamine), but the tetrahedral intermediate is disfavoured by 12 kJ mol$^{-1}$ relative to the one derived from ethylamine. This illustrates that the more sterically demanding pentan-3-amine cannot form the tetrahedral intermediate as the reaction is kinetically controlled.

With aniline the tetrahedral intermediate is similar in energy to the other mono-substituted amines, however, the amide product is almost 40 kJ mol$^{-1}$ higher in energy than the ester.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Alcohol/ & Product & Ester yield [\%] & Amide yield\textsuperscript{b} [\%] \\
\hline
1 &  &  & 92 & 90 (59) \\
2 &  &  & 93 & 92 (64) \\
3 &  &  & >99 & 46 (34) \\
4 &  &  & 74 & 74 (18) \\
5 &  &  & 34 & 34 (25) \\
6 &  &  & >99 & 99 (84) \\
7 &  &  & 73 & 73 (73) \\
\hline
\end{tabular}
\caption{Yield of ester and amide obtained in the oxidative coupling of alcohols and aldehydes with $N$-hexylamine\textsuperscript{a}}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Entry & Amine & Product & Ester yield [\%] & Amide yield\textsuperscript{b} [\%] \\
\hline
1 &  &  & 92 & 90 (59) \\
2 &  &  & 92 & 54 (15) \\
3 &  &  & 92 & 38 (16) \\
4 &  &  & 92 & — \\
5 &  &  & 92 & — \\
6 &  &  & 92 & 41$^c$ \\
\hline
\end{tabular}
\caption{Yield of ester and amide obtained in the oxidative coupling of benzyl alcohol with amines\textsuperscript{a}}
\end{table}

\textsuperscript{a} $R = (\text{CH}_2)_5\text{CH}_3$. Reaction conditions: alcohol or aldehyde (5 mmol), methanol (50 mmol), anisole (0.5 mmol), KOMe (1.25 mmol), 1 wt\% Au/TiO$_2$ (197 mg). After 24 hours 25 mmol amine was added and the mixture was heated to 65 °C for additional 96 hours. \textsuperscript{b} Number in parenthesis is the yield after 24 hours. \textsuperscript{c} Isolated yield.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme2}
\caption{The reaction pathway from methyl ester to amide via an anionic, tetrahedral intermediate, which forms the basis for the computational study.}
\end{scheme}
GC-FID and GC-MS using a HP-5 column from Agilent Technologies. The reaction mixture was heated to 65 °C for 24 hours. The reaction mixture was dissolved in water and neutralised to pH 7 by addition of 0.1 M HCl. The product benzamide was recovered by extraction with ethyl acetate which was subsequently removed on a rotary evaporator to give 41% in isolated yield.

We gratefully acknowledge the support of the Danish Council for Independent Research, Grant No. 10-093717.

Notes and references

22 Jaguar version 7.8, Schrödinger, LLC, New York, NY, 2011.

This journal is © The Royal Society of Chemistry 2012