Mechanistic investigation of the one-pot formation of amides by oxidative coupling of alcohols with amines in methanol

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ABSTRACT

The one-pot formation of amides by oxidative coupling of alcohols and amines via intermediate formation of methyl ester using supported gold and base as catalysts was studied using the Hammett methodology. Determining the relative reactivity of four different para-substituted benzyl alcohol derivatives showed that the first step of the reaction generates a partial positive charge in the benzylic position (i.e. by hydride abstraction), while the second step of the reaction builds up negative charge in the rate determining step. The aminolysis of the methyl ester intermediate was further investigated by means of DFT/B3LYP. The transition state structures and energies were determined for both a concerted and a neutral two-step reaction mechanism. As expected, the base-promoted two-step mechanism was found to be the most energetically favourable and this reaction mechanism was used to construct a theoretical Hammett plot that was in good agreement with the one obtained experimentally.

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1. Introduction

Formation of amides is a fundamental reaction in chemical synthesis and is used in the production of a broad range of bulk commodities, high-value fine chemicals, agrochemicals, and pharmaceuticals [1]. Amides are usually prepared by coupling of carboxylic acids and amines using a coupling reagent or by activation of the carboxylic acid. Alternative procedures include the Staudinger ligation [2], aminocarbonylation of aryl halides [3], and oxidative amidation of aldehydes [4]. Unfortunately, all these methods require the use of stoichiometric amounts of reagents, making them generally expensive and wasteful reactions [5]. In the search for a more sustainable chemical production, great efforts have been put into replacing the stoichiometric reagents with catalytic processes. This approach is not only cheaper and more environmentally friendly but also facilitates the possibility of starting from substrates other than carboxylic acids, thus paving the way for previously unavailable synthetic routes to amides [5].

In 2007 Milstein and co-workers [6] reported the first direct acylation of amines by alcohols under liberation of molecular hydrogen using a homogeneous ruthenium catalyst. Although this simple and highly atom-efficient reaction have inspired several other research groups to further develop this reaction [7,8], the special handling of expensive metal complexes and ligands remains a limitation that may prevent general application. In contrast, the handling of a heterogeneous catalyst is usually more straightforward [9].

Since the first fundamental studies by Bond et al. [10], Hutchings [11], Haruta et al. [12], and Prati and Rossi [13], supported gold nanoparticles have been recognised as surprisingly active and selective heterogeneous catalysts for a number of aerobic oxidations using molecular oxygen (or even air) as the terminal oxidant [14,15]. From the standpoint of green and sustainable chemistry these oxidations are attractive, because oxygen is a cheap and abundant oxidant that produces water as the only by-product.

Recently, we reported that the combination of supported gold nanoparticles and base forms an efficient and highly selective catalytic system for the one-pot synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines in methanol [16] (see Scheme 1).

In the first step of this reaction, a methyl ester is obtained by the gold-catalysed aerobic oxidation of the alcohol or aldehyde in methanol [17,18]. It is notable that in this step the methanol serves as both solvent and reactant. In the second step of the reaction, addition of amine affords the amide by base-catalysed aminolysis of the methyl ester. As the same base promotes both steps of the reaction, the oxidative coupling can be performed in a convenient one-pot procedure under mild reaction conditions (25–65 °C, atmospheric pressure). It is important to mention that this approach is conceptually different from the gold-catalysed reactions previously reported by Wang et al. [19] and Soulé et al. [20], which are

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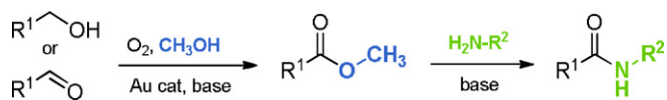
Scheme 1. Synthesis of amides by aerobic oxidative coupling of alcohols or aldehydes with amines using supported gold and base as catalysts.

proposed to involve the formation and subsequent oxidation of a hemiaminal intermediate to the desired amide.

To study the structure-reactivity relationship we employed the well-known Hammett methodology [21] and focused our attention on a range of *para*-substituted benzyl alcohol derivatives (see Scheme 2).

In line with previous work [22,23], the results were obtained by performing competition experiments rather than establishing absolute kinetics. There were several reasons to choose this approach. First of all, a competition experiment is more robust towards small variations in the reaction conditions and allows the reaction to be followed to relatively high conversion without deviation from linearity. Secondly, a competition experiment can be designed to investigate a different step than the overall rate-determining step. In this study, we were interested in the elementary steps of the reaction that are directly involved in the activation of the substrates. It was therefore desirable to disregard any effects from steps involving, *e.g.* activation of dioxygen.

2. Experimental study

2.1. Reaction procedure and analysis

A series of competition experiments were performed to investigate the structure-reactivity relationship of the two consecutive steps of the oxidation-aminolysis reaction. In these experiments, anisole (0.5 mmol), potassium methoxide (1.25 mmol), and methanol (50 mmol) were charged to a reaction tube together with benzyl alcohol (2.5 mmol) and either (4-methylphenyl)methanol, (4-methoxyphenyl)methanol, (4-chloro-phenyl)methanol, or (4-(trifluoro-methyl)phenyl)methanol (2.5 mmol). The reaction tubes were connected to a reaction station providing stirring, heating and dioxygen gas for the oxidative esterification (atmospheric pressure). The system was flushed with O_2 before 197 mg 1 wt% Au/TiO$_2$ catalyst (Mintek) was added, corresponding to an Au/substrate molar ratio of 1/500. During the following two days, samples of 0.1 ml were periodically collected, filtered, and analysed by GC-FID and GC–MS using anisol as internal standard. When all reactions had reached full conversion, hexane-1-amine (10 mmol) was added and the temperature was increased to 65 °C (reflux temperature of methanol). During the following two days additional samples were collected and analysed.
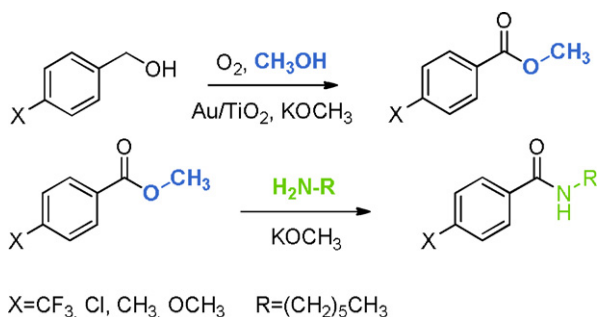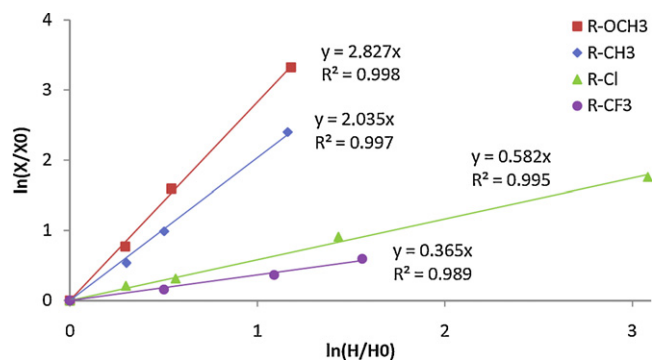

Fig. 1. Kinetic plot for the first step of the reaction showing the relative reactivity of four different *para*-substituted derivatives relative to benzyl alcohol.

2.2. Results and discussion

In the first series of experiments, the conversion of all benzyl alcohols followed first order kinetics, which allowed the construction of the kinetic plots shown in Fig. 1. From these plots the relative reactivity could be determined as the slopes of the lines found by linear regression [24]. The assumption that the oxidation of all methyl esters followed first order kinetics could be justified from the good correlation coefficients ($R^2 > 0.98$).

With the relative reactivity of the four different *para*-substituted methyl esters at hand, the Hammett plot could be constructed using three distinct sets of σ-values from literature [25,26] (Fig. 2).

Fig. 2 shows that the best linear correlation of log(kX/kH) was obtained with the σ$^+$-values ($R^2 = 0.922$), which resulted in a relatively large negative slope ($\rho = -0.680$). A negative slope in the Hammett plot indicates that a positive charge is built up during substrate activation, which suggests that the reaction proceeded through the generation of a partial cation in the benzylic position, *i.e.* by β-hydride elimination.

Fristrup et al. [27] have previously reported a similar result from the gold-catalysed oxidation of benzyl alcohol to benzaldehyde ($\rho = -1.10$). In that study the involvement of the β-hydride abstraction step was further confirmed by a significant kinetic isotope effect (KIE), when benzyl alcohol with deuterium incorporated in the α-position was employed as substrate. Furthermore, Fristrup et al. [28] have investigated the conversion of benzaldehyde to methyl benzoate and found here a positive ρ value ($\rho = 2.51$). These results suggest that the gold-catalysed esterification of alcohols with methanol occurs through the formation of an aldehyde intermediate and that this is the rate-determining step. The formation of an aldehyde intermediate also explains the formation of imines when the oxidation is carried out in presence of both methanol and amine [29].
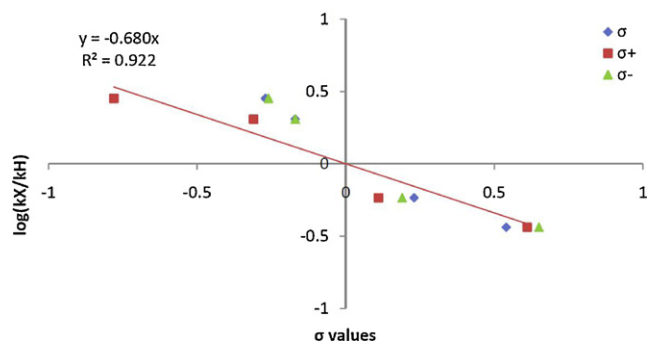

Scheme 2. Overview of the competition experiments carried out to determine the relative reactivity of the various *para*-substituted benzyl methyl esters.

Fig. 2. Hammett plot obtained using the relative reactivity determined during the oxidation of the benzyl alcohols.