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Gold-catalyzed amide synthesis from aldehydes and amines in aqueous medium†

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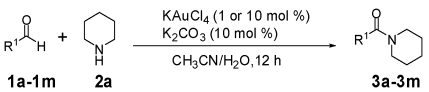
An efficient gold-catalyzed amide synthesis from aldehydes and amines in aqueous medium under mild reaction conditions has been developed.

The amide functionality is commonly found in natural products, proteins, and therapeutic drugs and has significant importance in organic and biological chemistry.[1] The conventional approach for amide synthesis involves coupling of activated carboxylic acids and amines that may require extra functional group interconversions and lead to poor atom and step economy. New developments include Staudinger ligation,[2a] hydrative amide synthesis from terminal alkynes and sulfonyl azides,[2b] and iodonium-promoted nitroalkane–amine coupling reaction.[2c] In 2006, we reported manganese porphyrin-catalyzed oxidative amide synthesis from alkynes and amines.[3] Transition metal-catalyzed amide formation from the reaction of aldehydes,[4] alcohols,[5] and esters[6] with amines has also been reported. However, high reaction temperature, inert atmosphere, and/or anhydrous organic solvents are generally required. In particular, synthesis of tertiary amides from secondary amines remains a challenging task.[7] Thus, the development of new methods for amide synthesis in aqueous medium under mild reaction conditions would be of great interest.

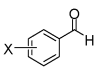
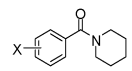
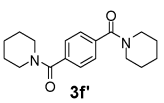
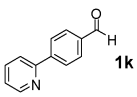
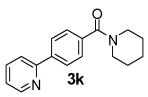
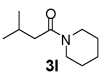
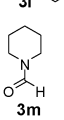
Gold catalysis has emerged as a frontier research area in organic chemistry, owing to its excellent reactivity, compatibility with aqueous medium and mild reaction conditions.[8] Recently, a number of heterogeneous gold catalysts have been used for amide synthesis from alcohols and amines under aerobic conditions.[9] Along with our ongoing research to develop gold catalysis for organic synthesis,[10] we recently found an efficient gold-catalyzed amide synthesis from aldehydes and amines in aqueous medium under mild reaction conditions.

The coupling reaction of *p*-nitrobenzaldehyde **1a** (1 equiv.) and piperidine **2a** (2 equiv.) in the presence of $KAuCl_4$ (1 mol%) and K_2CO_3 (10 mol%) in CH_3CN/H_2O (1 : 1) at 60 °C for 12 h was conducted (Table 1, entry 1, see also Table S1 in ESI†). It was found that amide **3a** was obtained in 61% isolated yield while no amide product was detected without $KAuCl_4$. Without H_2O, only a trace amount of aldehyde conversion was found. In addition, we conducted a detailed study on reaction parameters including catalyst loading, reaction temperature, various metal catalysts, solvent systems and bases toward the reaction of **1a** and **2a**, and amide **3a** was obtained in up to 85% isolated yield (Tables S1–S3 in ESI†).

Table 1 $KAuCl_4$-catalyzed amide synthesis from aldehydes **1a–1m** and piperidine **2a**[a]



1a-1m **2a** **3a-3m**

Entry	Aldehyde	Product	Yield[b] (%)
			
1	X = *p*-NO_2 **1a**	**3a**	61 (A), 85 (B)
2	X = *m*-NO_2 **1b**	**3b**	64 (A), 74 (B)
3	X = *p*-Cl **1c**	**3c**	55 (A), 70 (B)
4	X = *o*-Cl **1d**	**3d**	67 (B)
5	X = *p*-Br **1e**	**3e**	40 (B)
6	X = *p*-CHO **1f**	**3f**	55 (A), 44 (B)
		 **3f'**	6 (A), 15 (B)
7	X = *m*-CHO **1g**	**3g**	67 (A), 42 (B)
8	X = *o*-CHO **1h**	**3h**	40 (B)
9	X = H **1i**	**3i**	50 (B)
10	X = *o*-OH **1j**	**3j**	15 (B)
11	 **1k**	 **3k**	24 (B)
12	 **1l**	 **3l**	52 (A), 50 (B)
13	 **1m**	 **3m**	98 (A), 99 (B)

[a] Conditions A: the reactions were carried out with **1a–1m** (1.0 mmol), **2a** (2.0 mmol, 2 equiv.), $KAuCl_4$ (1 mol%), K_2CO_3 (10 mol%) in CH_3CN/H_2O (1 : 1, 2 mL) at 60 °C for 12 h. Conditions B: the reactions were carried out with **1a–1m** (0.2 mmol), **2a** (0.4 mmol, 2 equiv.), $KAuCl_4$ (10 mol%), K_2CO_3 (10 mol%) in CH_3CN/H_2O (1 : 1, 1 mL) at 40 °C for 12 h. [b] Isolated yield.

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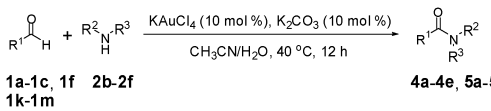
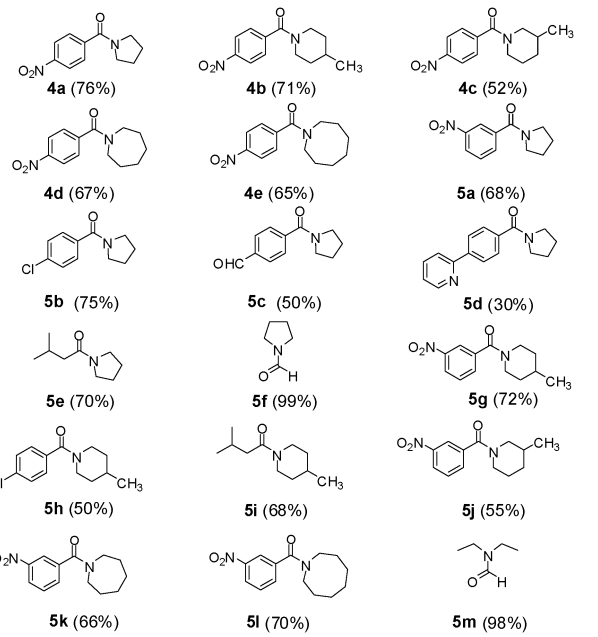
The scope of the amide synthesis reaction was examined by using a variety of aldehydes. Treatment of a series of aldehydes **1a–1m** with piperidine **2a** furnished the corresponding amide products **3a–3m** (Table 1). In general, the amide synthesis reactions were conducted in the presence of 1 mol% $KAuCl_4$ at 60 °C (conditions A), and/or 10 mol% $KAuCl_4$ at 40 °C (conditions B). Benzaldehydes **1a–1e** bearing electron-withdrawing groups ($-NO_2$, $-Cl$, and $-Br$) afforded the corresponding amides **3a–3e** in good isolated yields (40–85%) (entries 1–5). For *para*-dialdehyde **1f**, mono-amide **3f** (55% (A)) and diamide **3f′** (6% (A)) were obtained (entry 6). The observation of the corresponding formylbenzoic acids as byproducts may account for the slightly reduced yields obtained (entries 6–8). Lower yields were obtained for benzaldehyde **1i** (50%) and *ortho*-hydroxyl benzaldehyde **1j** with an electron-donating hydroxyl group (15%) (entries 9 and 10). These results suggested that the electronic effect of aromatic aldehydes would have influence on the amide synthesis reaction. The use of 4-(2-pyridinyl)-benzaldehyde **1k** afforded the corresponding amide **3k** with the pyridine ring remaining intact (entry 11). Furthermore, the present amide synthesis reaction worked for aliphatic aldehyde **1l** and formaldehyde **1m** (entries 12 and 13).

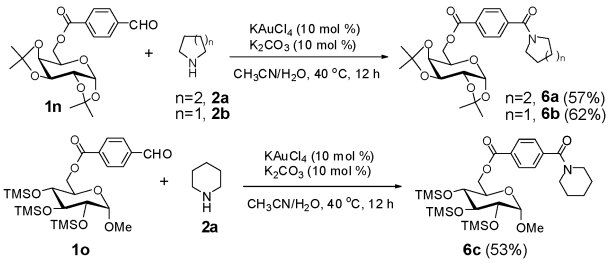
We further examined the scope of this reaction by employing various amines (Table 2). Pyrrolidine **2b**, 4-methylpiperidine **2c**, 3-methylpiperidine **2d**, hexamethyleneimine **2e**, and heptamethyleneimine **2f** provided the desired amides **4a–4e** in good isolated yields (52–76%). When primary amines including benzylamine and aniline were used as the substrates, only the corresponding imines were obtained. To demonstrate the generality of the present amide synthesis reaction, a diversity of aromatic and aliphatic aldehydes were coupled with various secondary amines to afford the corresponding amides **5a–5m** in up to 99% isolated yield.

Table 2 $KAuCl_4$-catalyzed amide synthesis from aldehydes **1a–1c**, **1f**, **1k–1m** and secondary amines **2b–2f**[a,b]





[a] All reactions were carried out with **1a–1c**, **1f** and **1k–1m** (0.2 mmol), **2b–2f** (0.4 mmol, 2 equiv.), $KAuCl_4$ (10 mol%), K_2CO_3 (10 mol%) in CH_3CN/H_2O (1 : 1, 1 mL) at 40 °C for 12 h. [b] Isolated yield.

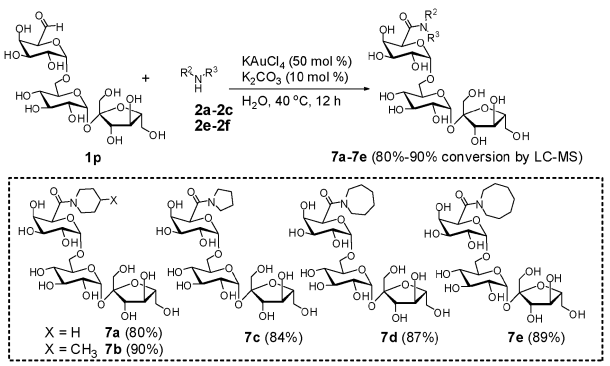


Scheme 1 $KAuCl_4$-catalyzed amide synthesis from aldehydes **1n** and **1o** and amines **2a** and **2b**.

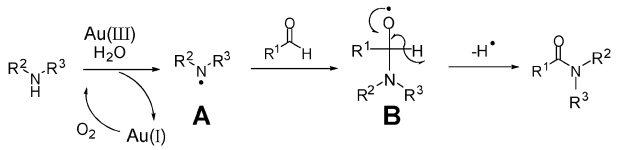
In addition, we further examined the functional group compatibility of the $KAuCl_4$-catalyzed amide synthesis reaction (Scheme 1). The reactions of monosaccharides **1n** and **1o** with secondary amines **2a** and **2b** in the presence of $KAuCl_4$ (10 mol%) and K_2CO_3 (10 mol%) in CH_3CN/H_2O (1 : 1) at 40 °C for 12 h were conducted. The corresponding amide products **6a–6c** with the ketal and trimethylsilyl ether groups remaining intact were obtained in 53–62% isolated yields. It should be noted that the ester moieties were also tolerated in the present amide synthesis reaction, whereas ester–amide exchange reaction was reported using ruthenium catalyst.[6]

Oligosaccharides are involved in a wide range of biological processes and thus important targets for bioconjugation.[11] Given the high functional group tolerance and mild aqueous reaction conditions of the present $KAuCl_4$-catalyzed amide synthesis reaction, we proceeded to investigate the modification of an oligosaccharide-based aldehyde bearing polyhydroxyl groups (Scheme 2). We were pleased to find that the reaction of unprotected D-raffinose aldehyde **1p** (10 mM in H_2O) with amines **2a–2c** and **2e** and **2f** (5 equiv.) in the presence of $KAuCl_4$ (50 mol%) and K_2CO_3 (10 mol%) in H_2O at 40 °C for 12 h gave **7a–7e** with the hydroxyl groups remaining intact with up to 90% aldehyde conversion as shown by LC-MS analysis.[12]

A reaction mechanism for the gold-catalyzed amide synthesis from aldehydes and amines in aqueous medium is proposed (Scheme 3). An aminyl radical (**A**) is generated from the reaction



Scheme 2 $KAuCl_4$-catalyzed modification of D-raffinose aldehyde **1p** and secondary amines **2**.



Scheme 3 Proposed reaction mechanism.

between an amine and an Au(III) ion in aqueous medium. The reaction of **A** with an aldehyde gives an alkoxy radical (**B**) which affords an amide as the product *via* loss of a hydrogen radical. Oxygen acts as the oxidant for the re-oxidation of the Au(I) to the Au(III) ion to complete the catalytic cycle.

Mechanistic studies have been conducted to support the above reaction mechanism. Addition of TEMPO and diyldibenzene (radical scavengers) significantly suppressed the coupling reaction of **1a** or **1i** with **2a** (Schemes S1a and S1b in ESI†), suggesting the involvement of radical species. Generation of amine radicals through the reaction of amines with gold ions[13] and in gold(III)/gold(I) redox processes in aqueous medium has been reported.[8a,14] Thus, an aminyl radical (**A**) generated from the reaction between an amine and an Au(III) ion in aqueous medium is proposed.

The reaction of **1i** (34% ^{18}O-incorporation) and **2a** was conducted in $H_2{}^{18}O$ (Scheme S1d, ESI†) to give the product amide **3i** with 30% ^{18}O-incorporation as confirmed by ESI-MS analysis, indicating that the amide carbonyl oxygen atom originated from the aldehyde. No TEMPO adduct formation with **1i** as observed by ^{1}H NMR and chromatography analysis suggests that an acyl radical would not be generated under the reaction conditions (Scheme S1h, ESI†).[15] Thus, an alkoxy radical (**B**) generated from the reaction of an aminyl radical (**A**) and an aldehyde is suggested.

The reaction between **1i** and **2a** in air gave **3i** in 50% isolated yield (Scheme S1i, ESI†). When the reaction was carried out under a N_2 atmosphere, **3i** was found in 5% isolated yield, indicating that oxygen in air is important. Under an oxygen atmosphere (balloon), no amide product was detected. This would be attributed to the oxidation of aminyl radical species by oxygen.[16] In this regard, oxygen acting as an oxidant for the oxidation of Au(I) to Au(III) is suggested.[17]

In conclusion, we have developed an efficient gold-catalyzed amide synthesis from aldehydes and amines with high functional group tolerance in aqueous medium under mild reaction conditions. This method allows an easy access to amides from the reaction of aromatic, aliphatic and polyhydroxyl oligosaccharide-based aldehydes with secondary amines.

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