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Silver acetate-assisted formation of amides from acyl chlorides

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ABSTRACT

A mild method for the aminolysis of carboxylic acid chlorides to give amides is disclosed. Reactions are carried out in the presence of silver acetate in non-aqueous environments under heterogeneous phase conditions. Amides are easily recovered in very good to excellent yields and without racemization. The approach is successful in forming peptide bonds starting from *N*-(4-nitrobenzenesulfonyl)-amino acid chlorides and allows the formation of dipeptides also when *N*-methylated amino acid derivatives are used.

The amide group plays a relevant role in biological and pharmaceutical compounds, and is commonly present in a large number of synthetic or natural molecules, bioconjugates, bioactive macrocyclic drugs, multifunctional nanostructures, and well-ordered supramolecular architectures.[1–7] As a consequence, the amide bond formation is a crucial process in organic synthesis.[8,9] The direct condensation of an amine with a carboxylic acid to give an amide proceeds only at high temperature, conditions which are incompatible with the presence of other labile functionalities. Therefore, activation of the acyl carbon of the acid or installation of a good leaving group is necessary. A plethora of synthetic strategies for making amides from various carboxylic acid derivatives have been developed.[10,11] Mild reagents are generally employed to prepare the acylating agents by transforming the carboxy components into the corresponding chlorides, mixed anhydrides, active esters, or isocyanates.[12–18] These reagents are then subjected to aminolysis. In all cases, it is necessary to find the optimal working conditions for the method. Steric hindrance of the reaction partners, racemization, optimization of yields, minimizing of by-products, facile final isolation, and exploitation of economical reagents are all aspects that should be evaluated in designing new strategies for amide preparation. Commercially available coupling reagents are used to create amide groups.[19,20] However, they are moisture sensitive and expensive, the procedures are wasteful and the recovery of the final compounds is often complicated by the need for chromatography. The coupling of amines with acid chlorides assisted by DIBAL provides secondary and tertiary amides, although the stability and over-activation of the hydride reagent limit the application of this method.[21] Enzymatic catalysis is troublesome due to the costs and somewhat limited substrate families.[22] Amides are easily prepared by aminolysis of acyl chlorides in many cases. This procedure requires the addition of non-nucleophilic tertiary amines which can induce racemization, hydrolysis, deprotection, and many other unwanted side-reactions. To overcome these drawbacks, non-metal organocatalysts, ionic liquids, and boron reagents have been proposed.[23,24] Today, metal-catalyzed methods based on the use of Zn, Sm, In, Fe, and Cu species are possible solutions in the synthesis of amides from acyl chlorides.[25–29] These approaches are atom-economical, low cost, environmentally friendly, and avoid the use of tertiary amines as bases.

The need for a highly efficient, robust, and helpful method for the rapid and clean realization of the amide bond is still attractive. We decided to investigate the use of weak bases acting in the presence of metal species for the aminolysis of isolable activated carboxylic acid derivative, namely acyl chlorides. From the data reported in the literature, it is evident that the use of organic bases such as tertiary amines should be avoided in the formation of the amide bond. In fact, this kind of bases does not preserve the configurations of chiral atoms of substrates, and racemization takes place through the base-assisted formation of ketene intermediates.[30] On the other hand, the use of inorganic bases in water environments is causative of incomplete reactions, hydrolysis of reagents, and products. Weak inorganic bases have been used to reduce the

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formation of side-products in the acylation of primary amines with carboxylic acid chlorides operating under heterogeneous phase conditions.[31] Nevertheless, in many cases the conversion of starting materials requires long reaction times, limiting the efficiency of the process.

We argued that the use of a weak base containing Lewis species should be striking in assisting the acylation of amines.

Thus, the effectiveness of silver acetate in the reaction of primary and secondary amines with available or easily affordable acyl chlorides was investigated. The silver cation enhances the reactivity of the carbonyl group in acyl chlorides, especially in electrophilic aromatic substitutions.[32,33] Moreover, this metal species generates silver chloride which precipitates in the most currently used solvents, allowing the complete and rapid removal of silver particles at the end of the reaction. Finally, the acetate anion shows a basic strength similar to those of many tertiary amines used as bases and it can efficiently be quenched by forming acetic acid in the reaction environment.

The feasibility of a silver acetate-assisted aminolysis of acyl chlorides (Fig. 1) was preliminarily exploited by reacting benzoyl chloride with *N*,*N*-diethylamine. A set of experiments was conducted for modeling the conditions of the treatment. The aminolysis was performed in diethyl ether at room temperature using almost equimolar amounts of the acyl chloride and secondary amine. In this first experiment, a diethyl ether solution of benzoyl chloride (one equivalent) was added to a stoichiometric amount of *N*,*N*-diethylamine dissolved in the same ethereal medium. After adding silver acetate (three equivalents), reaction went to completion in 15 min. The formation of a black precipitate was indicative of the reduction of silver ions caused by exposure to light, whereas *N*,*N*-diethylbenzamide (**1**) was recovered after hydrolytic work-up of the reaction mixture in however unsatisfying yield (37%). We thus repeated the experiment using glassware protected from exposure to light and maintaining the same reagent stoichiometry used in the previous test. After 15 min, TLC showed the complete consumption of benzoyl chloride. The formation of a white precipitate indicated that silver cation reduction did not occur (no traces of black solid were observed) and the expected amide was isolated in 87% yield. Further optimization studies were carried out using cheaper sodium acetate (two equivalents) together with silver acetate (one equivalent), instead of three equivalents of the more expensive silver salt. This modification did not affect the efficiency of the method, and reaction times and yields remained practically unaltered. We also experienced that the silver-assisted aminolysis of benzoyl chloride was strictly depending on the sequence adopted for reagent adding. In fact, when a mixture of the acylating agent and silver acetate was stirred for five minutes at room temperature before adding amine, a mixture of *N*,*N*-diethylbenzamide (42%) and *N*,*N*-diethylacetamide (53%) was recovered. The interaction between the acetate anion and benzoyl chloride can explain the reaction outcome. A mixed anhydride was generated and this species further reacted with the amine affording the two observed acylated compounds. Oppositely, the benzoyl derivative was exclusively isolated when the amine and silver acetate were added to an ethereal solution of the chloride, according to the detailed procedure here reported.[34]

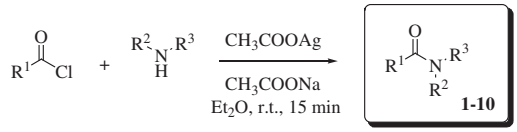


Figure 1. The silver acetate-assisted aminolysis of acyl chlorides.

Benzoylation is a very important task in organic synthesis for the protection of amino groups. Thus, we studied whether the aminolysis of benzoyl chloride can be performed using different primary and secondary amines. According to the optimized conditions, benzoyl chloride (one equivalent) dissolved in diethyl ether was reacted with an equimolar amount of amine, in the presence of a mixture of sodium acetate (two equivalents) and silver acetate (one equivalent) at room temperature (Fig. 1).

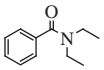
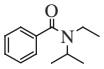
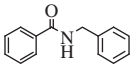
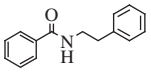
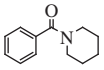
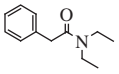
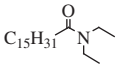
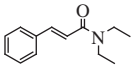
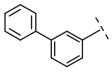
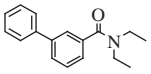
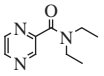
The data summarized in Table 1 indicate that the protocol was found to be highly effective in the direct preparation of structurally different amides under very mild conditions. As expected, benzoyl chloride reacted with different amines to afford the respective amides **1**–**5** in good to excellent yields (Table 1, entries a–e). Lower yields were observed with *N*-ethyl-*N*-isopropyl amine and piperidine (Table 1, entries b and e). In these cases the corresponding amides were obtained in 82% and 81% yields, respectively, most likely due to the steric requirements imposed by the aliphatic cycle of piperidine and the ramified chain of the secondary amine. Other acylating agents different from benzoyl chloride were also investigated. The reaction of *N*,*N*-diethylamine with the commercial chlorides of phenylacetic, palmitic, 3-phenylbenzoic, cinnamic and pyrazine-2-carboxylic acids (Table 1, entries f–j) afforded the respective amides **6**–**10** in good yields confirming the synthetic potential of the protocol. TLC and GC–MS analysis of crude mixtures showed the formation of only one product. It is important to mention that all final products were easily isolated by a simple hydrolytic work-up of the respective reaction mixtures and obtained without need for chromatography. ^{1}H and ^{13}C NMR spectroscopy furnished data which were consistent with the structures assigned to the expected compounds.

The flexibility of the method and its possible application to other classes of acylating agents were verified by subjecting a series of *N*-(4-nitrobenzenesulfonyl)-α-amino acid chlorides (Table 2), prepared as previously reported,[35] to the treatment with *N*,*N*-diethyl amine (Fig. 2). All acyl chlorides reacted smoothly with the secondary amine under the conditions adopted for the cases reported in Table 1. As desired, the treatment gave the corresponding amides **11**–**17** which were isolated in good to excellent yields by the simple hydrolytic work-up of the respective reaction mixtures and without need for chromatography. Also in these cases all products were pure enough for the spectroscopic, TLC, and GC–MS analysis, and the structures of products were assigned by ^{1}H and ^{13}C NMR.

The reaction of the enantiomeric pair of *N*-protected amino acid chlorides prepared starting from L-Phe and D-Phe allowed us to investigate the effects of the experimental conditions of our protocol on the chiral configuration of the starting materials. The two α-amino acid derivatives reacted with the enantiomerically pure (*S*)-1-methylbenzylamine to afford the corresponding diastereomeric amides **16** and **17** which were recovered in good yields (82% and 86%, respectively) without need for chromatography. The crude products **16** and **17** were subjected to LC–MS analysis and NMR spectroscopy. LC–MS runs showed similar retention times for **16** and **17**, whilst ^{1}H NMR spectra demonstrated that each amide was obtained as a single diastereomer. In fact, the respective spectroscopic analysis did not show residual signals attributable to other diastereomers within the sensitivity limits of the spectroscopic technique, proving that **16** and **17** were formed without racemization.

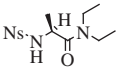
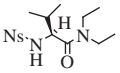
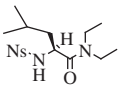
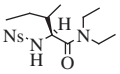
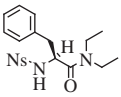
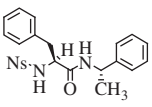
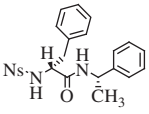
N-(4-Nitrobenzenesulfonyl)-α-amino acid chlorides are largely employed in the synthesis of peptides.[35] Therefore, we thought that the silver acetate-assisted protocol should also be helpful in preparing short peptides. Exemplificative of the preparation of *N*-(4-nitrobenzenesulfonyl)-dipeptides, the coupling of *N*-(4-nitrobenzenesulfonyl)-alanine chloride with isoleucine methyl ester hydrochloride (Fig. 2, R^5 = H) was investigated. The corresponding

Table 1
Amides produced via Figure 1

Entry	R^1	R^2	R^3	Product	Amide	Yield[a] (%)
a	C_6H_5	C_2H_5	C_2H_5	**1**		92
b	C_6H_5	C_2H_5	$CH(CH_3)_2$	**2**		82
c	C_6H_5	H	$C_6H_5CH_2$	**3**		87
d	C_6H_5	H	$C_6H_5(CH_2)_2$	**4**		89
e	C_6H_5	R^2–R^3 = $(CH_2)_4$		**5**		81
f	$C_6H_5CH_2$	C_2H_5	C_2H_5	**6**		93
g	$C_{15}H_{31}$	C_2H_5	C_2H_5	**7**		88
h	$C_6H_5CH=CH$	C_2H_5	C_2H_5	**8**		90
i		C_2H_5	C_2H_5	**9**		79
j		C_2H_5	C_2H_5	**10**		75

[a] Yields referred to the starting amount of the respective acyl chloride.

Table 2
Amides produced from *N*-(4-benzenesulfonyl)-α-amino acid chlorides via Figure 2

Entry	R^1	R^2	R^3	R^4	Product	Structure	Yield[a] (%)
a	CH_3	H	C_2H_5	C_2H_5	**11**		87
b	$CH(CH_3)_2$	H	C_2H_5	C_2H_5	**12**		85
c	$CH_2CH(CH_3)_2$	H	C_2H_5	C_2H_5	**13**		84
d	$CH(CH_3)CH_2CH_3$	H	C_2H_5	C_2H_5	**14**		81
e	$C_6H_5CH_2$	H	C_2H_5	C_2H_5	**15**		92
f	$C_6H_5CH_2$	H	H		**16**		82
g	H	$C_6H_5CH_2$	H		**17**		86

[a] Yields referred to the starting amount of the respective acyl chloride. (Ns = 4-nitrobenzenesulfonyl group).

N-protected dipeptide methyl ester **18** was isolated in high yields (85%) without need for chromatography. ^1H and ^{13}C NMR spectroscopy confirmed the structure attributed to **18**. For completeness, we investigated the reaction between *N*-(4-nitrobenzenesulfonyl)-alanine and *N*-methyl-isoleucine methyl ester (Fig. 2, $R^5 = CH_3$). The coupling of *N*-methyl amino acid derivatives to obtain *N*-methylated dipeptides is often bothersome.[36] The method was successful in giving the desired *N*-methylated dipeptide derivative **19** which was isolated in very good yields (80%) avoiding further chromatographic purification.

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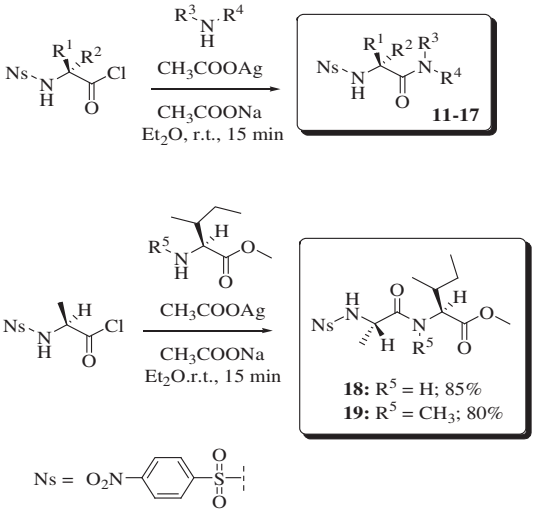

Figure 2. The silver acetate-assisted aminolysis of *N*-(4-nitrobenzenesulfonyl)-α-amino acid chlorides and the peptide bond formation.

In summary, the use of silver acetate was proposed for the high-yielding aminolysis of a variety of acyl chlorides under heterogeneous phase conditions. In all cases, amides are easily recovered and isolated pure in high to excellent yields without need for chromatography. The silver cation assists the amide bond formation, and the acetate anion as well as silver chloride is easily removed at the end of the reaction. The operative conditions circumvent unwanted side-reactions and racemization that are commonly observed when acylating agents are used in the presence of tertiary amines. Similar results have been obtained by using acyl fluorides.[37–39] The aminolysis of *N*-(4-nitrobenzenesulfonyl)-α-amino acid chlorides by α-amino acid methyl esters or their *N*-methylated derivatives is advantageously used to install peptide bonds avoiding the use of expensive coupling reagents. This simple method could be widespread in a variety of applications, opening up previously unavailable synthetic routes to important target molecules.

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Supplementary data

Supplementary data (general experimental details and lists of spectral data for all compounds. GC–MS, ^{1}H and ^{13}C NMR analysis of compound **5**, and NMR and LC–MS analysis of crude compounds **16** and **17**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.067.

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34. The following experimental procedure reported for the silver acetate-assisted synthesis of *N,N*-diethylbenzamide (**1**) is representative for the preparation of amides **2**–**17** and *N*-(4-nitrobenzenesulfonyl)-protected dipeptide methyl esters **18** and **19**. *N,N*-Diethylamine (1 mmol), silver acetate (1 mmol) and sodium acetate (2 mmol) were added to a solution of benzoyl chloride (1 mmol) in diethyl ether (10 mL). The heterogeneous mixture was magnetically stirred at room temperature for 15 minutes, preserving the reaction flask from exposure to light. After this time, a white precipitate was formed and TLC (diethyl ether/P.E. 70:30 v/v) showed the complete conversion of the starting chloride. The mixture was paper filtered, washed with 1 N aqueous HCl (3 × 5 mL), 1 N aqueous NaOH (3 × 5 mL) and once with brine (5 mL). The ethereal layers were dried (Na_2SO_4) and evaporated to dryness under reduced pressure conditions. *N,N*-Diethylbenzamide (**1**) was recovered as a viscous colorless oil without need for chromatography. Yield: 92%; TLC: R_f = 0.77; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31–7.40 (m, 5H, ArH), 3.52 (m, 2H, CH_2), 3.23 (m, 2H, CH_2), 1.25 (m, 3H, CH_3) 1.10 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.3, 137.2, 129.1, 128.4, 126.2, 43.3, 39.2, 14.2, 12.9. MS (EI, 70 eV) *m*/*z* (% rel.): 177 [M^+], 176 (49), 162 (8), 148 (16), 134 (12), 105 (100), 77 (48), 51 (21). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.65; H, 8.51; N, 7.88.
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