An expedient and rapid green chemical synthesis of N-chloroacetanilides and amides using acid chlorides under metal-free neutral conditions

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ABSTRACT
We are reporting for the first time, rapid N-chloroacetylation of anilines and amines in phosphate buffer within 20 min. Primary and secondary amino derivatives (amines, anilines) were efficiently condensed with various acid chlorides (containing aliphatic, aromatic, cyclic and heteroaromatic units). We have also shown that the modification of the electrophilic nature of the substituents on the acid chloride did not affect the product formation and the required amides are formed in high yields. The major advantage of this process is highlighted by the ease of product isolation (simple filtration/precipitation). This process represents the first example of a metal-free, green chemical synthesis under neutral conditions to provide an eco-friendly, easily scalable and robust process for the preparation of amides that expands the scope, utility and applicability of acid chlorides.

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1. Introduction
Amide bonds (1–5) are one of the most common linkages that are abundantly present both in natural (proteins) and in synthetic compounds (polymers). The difficulty in the controlled synthesis of amides (6–8) and their applications in different fields like polymers (9), engineering materials, detergents and lubricants led to the development of many synthetic methods (10–13), and hydration of nitriles to amides in aqueous medium (14). The physical and chemical properties of amides, such as high polarity, stability, conformational diversity and conversion of them to many other functional groups have been extensively exploited by researchers in various fields. Moreover, the amide bond formation reaction is identified as one of the top reactions presently used in the pharmaceutical industry (7, 15–17). In addition to this role, the formation of amides plays an important part in mass spectrometry (18, 19) or in cell biology (20, 21).

Acid chlorides and anhydrides are the most commonly used reagents for the acetylation of amines. Many simple acid chlorides are inexpensive; hence they are used in many industrial processes. However, these acylating reagents are highly reactive, leading to poor selectivity when other equally reactive functional groups are present. Moreover, acid chlorides and anhydrides have the tendency to react rapidly with water and alcohols, leading to the formation of the corresponding acids and esters, respectively. Thus, the yield and purity of the resulting amides are reduced. In addition, cumbersome removal of impurities from the required products makes these methods less attractive. N-acetylation reactions of amines using other acylating reagents are sensitive to water (22). We have developed bioconjugation reactions, (23) and also utilized amide bond formation reactions (24, 25) in our synthetic strategy.

Chloroacetyl chloride (CAC) (26) is an important two carbon bifunctional unit widely used in synthetic chemistry (27). It is used as a protecting group (28) for alcohols and amines. The acid chloride part is used in many acylation reactions with alcohols, amines, (29–32) alkynes (33) and also in Friedel–Crafts reactions (34, 35). Similarly the
α-chlorine can be replaced by many nucleophiles (OH−, NH2−, SH− etc.) through Sn2 displacement (36–39). Many chloroacetamides are used as herbicides such as alachlor [15972-60-8], metolachlor [51218-45-2].

Acetyl chloride and chloroacetyl chloride can be efficiently used for acylation reactions. The major advantage of chloroacetyl derivatives lies in their ability to be used for further functional modifications. However, the reactivity profiles of chloroacetyl chloride are less explored compared to acetyl chloride. Thus, improving the N-acylation of amino derivatives, without compromising the high reactivity of the acid chlorides to give amides, is a challenging task worth exploring.

Organic synthesis in aqueous media is rapidly gaining importance in view of the fact that the use of many toxic and volatile organic solvents, particularly chlorinated hydrocarbons, contributes to pollution. The Innovative Medicines Initiative (IMI)-CHEM21 solvent guide had identified water as the most preferred green solvent, with a safety, health and environmental score of 1 (40). Furthermore, reactions conducted in aqueous media minimize protection-deprotection sequences (41) that are commonly used in synthetic chemistry. In order to develop a green chemical route to chloroacetamides, we were attracted by two principles (42) of the green chemistry approaches, namely (i) amide formation avoiding poor atom economy reagents, and (ii) replacements for dipolar aprotic solvents.

In our current research involving bioconjugation reactions, we were interested in using CAC as a bifunctional linker, in order to conjugate many water-soluble amino compounds under neutral or near neutral conditions. Almost all of the Schotten-Baumann conditions employed for chloroacetylation of amines uses strong bases. In general, aliphatic acid chlorides hydrolyze much more rapidly than aromatic types; thus, using the Schotten-Baumann technique with aliphatic acid chlorides affords substituted amides contaminated with acids. We were surprised to see that there are only very few reports utilizing near neutral conditions with water as the solvent for chloroacetylation (43, 44) even though CAC is used for functionalization of amines (45). One of the methods utilizes a large excess of CAC (4 eq.), and the reaction requires longer times (12–16 h) to complete (43). An aqueous method developed recently for ranolazine (44) synthesis uses a stoichiometric amount of water (5 eq.) for chloroacetylation using chloroacetic anhydride. The main problem associated with acetylation reactions in water is the intrinsic nature of the acid chlorides to undergo hydrolysis. It is reported that CAC undergoes very slow hydrolysis in water to the corresponding acid (46–48). We presumed, if the chloroacetylation can be carried out faster than the hydrolysis, then it will be possible to carry out the reaction in water.

Few recent reports use acid chlorides for the formation of amides (49, 50). One of them uses expensive silver salts and the other one use highly reactive Dibal-H. The later cannot be used when sensitive functional groups are present. There is no report available for carrying out acylation under neutral conditions using chloroacetyl chloride. So, we wanted to expand the scope and utility of chloroacetyl chloride. The major challenge posed was to develop a method having high selectivity without reducing the high reactivity of acid chlorides.

2. Results and discussion

We have recently developed a chemoselective N-chloroacetylation of aminoalcohols using chloroacetyl chloride in phosphate buffer (communicated) in the presence of neutral HCl scavenger (propylene oxide). The marked difference in the reactivity of amines and alcohols can be attributed to the difference in the basicity/nucleophilicity between amines and alcohols. Since chemoselectivity in synthetic chemistry is always a challenge, we were interested in developing methods for preferential modification of anilino moiety in the presence of amines in our current project. It will be highly beneficial, if anilines (weaker bases) can be selectively functionalized in the presence of aliphatic amines (relatively stronger bases). Unlike amines and alcohols, anilines and amines do not differ vastly in their pKa values. The major challenge we faced was to tweak the reactivity of acid chlorides under certain reaction conditions to give anilides in preference to amides.

2.1. Study of N-chloroacetylation of amines and anilines

Initially, we attempted N-chloroacetylation of various amino compounds in phosphate buffer. The results obtained are summarized in Table 1. All compounds consistently underwent clean reactions to give high to excellent yield of the product within 20 min. Negative ninhydrin test was used for confirmation of product formation in all the cases. In the case of aliphatic amines (Table 1, entries 1–3) and benzylamine (Table 1, entry 4), the isolated yields were around 70–78%. For anilines, the yields were slightly higher (Table 1, entries 5–7).

In order to understand the selectivity and the reactivity of this protocol further, we subjected p-aminophenol (Table 1, entry 9) to N-chloroacetylation. As usual, the
reaction was over within 15 min, and we did not observe any decreases in the rate of product formation. NMR analysis proved the selective acetylation of amine group in the presence of phenolic OH. Selective and rapid $N\text{-}$chloroacetylation of p-aminophenol is used in the derivative preparation of antipyretic drug paracetamol. However, both $N\text{-}$ and $O\text{-}$chloroacetylation took place when p-aminophenol was allowed to react with CAC and pyridine/TEA in CH$_2$Cl$_2$.

To investigate the effect of the electron-withdrawing carboxylic acids on the reaction, we subjected amino-benzoic acid (Table 1, entries 10) to chloroacetylation. We obtained $N\text{-}$chloroacetylation products in very good yields and confirmed that electron-withdrawing carboxylic acids have not played any deleterious role in the reaction. Further, to understand the role of other electron-withdrawing groups on the reaction, we subjected p-cyanoaniline and p-nitroaniline (Table 1, entries 11 and 12), to $N\text{-}$chloroacetylation. In the case of p-nitroaniline, the reaction did not go to completion. The isolated yield was 75% (89% based on recovery of the starting material). This suggests that strong electron-withdrawing groups may decrease the reactivity, but not the yield, in this protocol. Even heteroaromatic, phenolicamine and aromatic secondary amines (Table 1, entry 13–15) gave the corresponding product in 72–83% (Figure 1).

2.2. Study of chemoselectivity in $N\text{-}$chloroacetylation of anilines vs. aliphatic amines

Since benzylamine gave a little lower yield compared to aniline, we were wondering can we exploit this to our benefit. We then wanted to study the chemoselectivity

![Figure 1. Products from the reaction of amines and anilines with CAC.](image-url)
of aromatic vs. aliphatic amines using the current method. To our surprise, it was found that aniline reacted in preference to benzylamine (Table 2, entry 1). Use of water also gave the same result (Table 2, entry 2), whereas CH₂Cl₂ gave a higher yield of the amide (Table 2, entry 3). Finally, use of FeCl₃ (20 mol %) completely suppressed the reactivity of benzylamine. This suppression effect was independent of solvent (Table 2, entry 5). To further confirm our findings, aniline was reacted in the presence of other aliphatic amines (Table 2, entries 6–9). The competitive reaction between aniline and an alkyl amine or cyclohexylamine preferentially gave the anilide. From Table 2, it became clear that phosphate ions play an important role in selective reactivity (Table 2, entries 6–8). A detailed computational study to ascertain the role of phosphate ions is currently underway. 4-Aminobenzylamine, having both an aniline moiety and a primary amine moiety on the same substrate (Table 2, entry 9), underwent N-chloroacetylation at both the amino groups. However, use of FeCl₃ (Table 2, entry 10) completely suppressed the reactivity at the benzylamine moiety and only the aniline moiety reacted. This protocol can thus be used to chloroacetyl anilines selectively in the presence of aliphatic amines. It is important to bear in mind that aliphatic amines also undergo acylation efficiently, but when anilines are present, anilides are formed in preference to amides.

2.3. Study of the reaction of various amines and anilines with structurally and electronically diverse acid chlorides

Finally, to expand the scope of this process we prepared various amides/anilides by condensation of amines/anilines with different acid chlorides. The results were reported in Table 3. Many structurally diverse amides were formed with ease using this protocol. Individually aliphatic or aromatic amines can be reacted with aliphatic or aromatic acid chlorides to yield the corresponding amide/anilide derivatives in high yields. We used aliphatic (Table 3, entries 2, 4–6, 12, 15, 17, 21), aromatic (Table 3, entries 1, 7, 9–11, 13, 14), α, β-unsaturated (Table 3, entries 8, 22), cyclic (Table 3, entry 18), and heterocyclic (Table 3, entries 23, 24) acid chlorides. We also varied the electrophilic nature (Table 3, entries 3, 16, 19, 20) of the substituent on the acid chloride. For the amine part

| Table 2. Competitive reaction of amines and aniline. |
|---|---|---|---|---|
| No. | ArNH₂ | R NH₂ | Solvent | Additive | Product* (Anilide: amide) |
| 1 | Aniline | Benzylamine | Buffer | – | 87:13 |
| 2 | Aniline | Benzylamine | Water | – | 88:12 |
| 3 | Aniline | Benzylamine | CH₂Cl₂ | – | 64:36 |
| 4 | Aniline | Benzylamine | Buffer | FeCl₃ | 100:0 |
| 5 | Aniline | Benzylamine | CH₂Cl₂ or MeCN | FeCl₃ | 100:0 |
| 6 | Aniline | Cyclohexylamine | Buffer | – | 98:2 |
| 7 | Aniline | Dicyclohexylamine | Buffer | – | 100:0 |
| 8 | Aniline | Butylamine | Buffer | – | 100:0 |
| 9 | NH₂C₆H₄CH₂NH₂ | Bu | Buffer | – | Disubstituted |
| 10 | NH₂C₆H₄CH₂NH₂ | FeCl₃ | Buffer | – | 100:0 |

Note: Substrate – 0.5 mmol each, CAC – 0.5 mmol, metal salt – 20 wt % of substrate, buffer – Phosphate buffer 20 mmol, 10μL/1 mg of substrate. Bold values signify that very high selectivity that was found for anilines.

•Product distribution based on NMR integration.

| Table 3. Reaction of amines or anilines with various acid chlorides. |
|---|---|---|---|
| Entry | Amine/aniline | Acid chloride | Yield (%) |
| 1 | Aniline | Benzoyl chloride | 89 |
| 2 | Aniline | Pivaloyl chloride | 86 |
| 3 | Aniline | Dichloroacetyl chloride | 83 |
| 4 | Aniline | Phenyl acetyl chloride | 81 |
| 5 | Aniline | 3-Chloropropionyl chloride | 77 |
| 6 | p-Toludine | 3-Chloropropionyl chloride | 73 |
| 7 | Cyclohexylamine | p-Toluoyl chloride | 80 |
| 8 | Cyclohexylamine | Cinnamyl chloride | 68 |
| 9 | Aniline | p-Nitrobenzoyl chloride | 82 |
| 10 | p-Toludine | p-Nitrobenzoyl chloride | 79 |
| 11 | p-Nitroaniline | p-Nitrobenzoyl chloride | 80 |
| 12 | Butylamine | Diphenyl acetyl chloride | 74 |
| 13 | Aniline | Isophthaloyl chloride² | 85 |
| 14 | p-Toludine | Isophthaloyl chloride² | 81 |
| 15 | Aniline | Isobutyl chloride | 77 |
| 16 | Aniline | Methyl malonoyl chloride | 74 |
| 17 | Aniline | Methylmalonyl chloride | 74 |
| 18 | Aniline | Cyclopropanecarbonyl chloride | 70 |
| 19 | Cyclohexylamine | Methoxycarbonyl chloride | 69 |
| 20 | p-Toludine | Methoxycarbonyl chloride | 75 |
| 21 | Cyclohexylamine | Acetyl chloride | 72 |
| 22 | Butylamine | Cinnamoyl chloride | 70 |
| 23 | Aniline | 2-Furoyl chloride | 75 |
| 24 | Butylamine | 2-Furoyl chloride | 68 |

Note: Substrate – 0.75 mmol, Acid chloride – (0.83 mmol)² Acid chloride – (0.4 mmol), propyleneoxide (1.6 mmol), solvent – Phosphate buffer, 10μL/1 mg of substrate.
we have used anilines (Table 3 entries 1–6, 9–11, 13–18, 20, 23) and amines (Table 3, entries 7, 8, 12, 19, 21, 22, 24). In all cases, we observed the required amide formation. The isolated yields of the obtained anilides were excellent in most cases. Even the dicarboxyl chloride (Table 3, entries 13, 14) underwent the reaction smoothly. Electron-withdrawing groups on the aniline (Table 3, entry 11) or on the acid chloride (Table 3, entries 3, 9–11, 16) did not affect the product formation. The current protocol of using buffers as a solvent is highly beneficial, because (i) we can avoid the use of toxic organic solvents, (ii) we can isolate the product with ease. Due to the poor solubility of the product in the reaction medium, they can be easily isolated by simple precipitation/filtration. This completely avoids the laborious column chromatography procedure for purification of the products (Figure 2).

3. Conclusions

In conclusion, we have shown for the first time that chloroacetyl chloride can be effectively and efficiently used for chloroacetylation of anilines and amines under neutral, metal-free and green chemical conditions. The generality of the reaction has been studied. It was found that the reaction occurs within 20 min, and the isolated yields are high in the presence of an HCl scavenger. Finally, many acid chlorides were also successfully converted to amides very efficiently. The involvement of phosphate in facilitating the selectivity is currently under investigation by computational methods and the results will be reported elsewhere.

Supporting information summary

Complete experimental details with spectroscopic data, 1H NMR and 13C NMR for select compounds are given in the supporting information.

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Disclosure statement

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