Solvent and Catalyst Free Acylation of Anilines with Acetic Acid

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Abstract:

Quantitative yields are produced in a short amount of time by an effective and environmentally friendly microwave-assisted approach that produces amide from amine via acylation without the need for a catalyst. Aniline and glacial acetic acid were directly combined during the synthesis of acetanilide under microwave irradiation, without the use of any catalytic agents. The reaction occurred in the frequency band of 160 MHz in 40 to 50 minutes with almost quantitative yields. We don't employ any harmful or toxic components by using the green synthesis technique.

Keywords: Green synthesis, acylation, microwave irradiation, amide, amine, aniline, acetanilide.

1. Introduction

A new area of chemistry known as "Green chemistry" combines many tools, methods, and technologies. Creating more eco-friendly and effective products are helpful to chemists and chemical engineers in research, development, and manufacturing. These products may also have considerable financial advantages. It will soon be a necessary instrument in the study of synthetic chemistry. [3] The advent of green chemistry has altered what a solvent is used for. The mass transfer is facilitated but not dissolved by the ideal solvent. An ideal green solvent should also be cheap, easily accessible, natural, nontoxic, and have the added advantages of promoting reaction, separation, or catalyst recycling. The most crucial of the many green chemistry principles, which measures the effectiveness of chemical transformation, is maximising the atom economy. [3]

Amide compounds have drawn a lot of interest due to their wide range of applications in the pharmaceutical sector. They have typically been utilized as synthetic route protection routes. Many bioactive substances or medications have an amide functional group, and amide modifications are a crucial approach of optimization for novel chemical entities in medicinal chemistry. The foundation of proteins is made up of peptide bonds, a specific type of Amide bond found in the life sciences. Many significant materials in the chemical industry involve the structure of amides. [2]

Amide bonds are commonly formed in the following ways: the classic synthetic procedures of the acetamido group compounds are carried out by primary amino compounds under various conditions with acyl halides, acid anhydrides, esters, or acids. The acyl halides and acid anhydrides were hygroscopic, and many active acylation agents would be exothermic and produce unwanted acid during the reaction process, so they should be treated carefully, under well-cooled, anhydrous conditions in the presence of acid-tricing agents [2]. If the acylation agents used are esters and acids, the reaction may take longer and lead to lower yields due to their low chemical activity. To ensure the reactions are safe for both the environment and human health, certain chemicals that are more active, such as N, N'-dicyclohexylcarbodiimide (DCC) and N-(3-dimethylaminopropyl)-N-ethylcarbodiimide (EDC), should be added as catalysts. [2]

According to a recent study, amide bond forms account for 65% of all initial screening reactions in industrial medicinal chemistry laboratories, making them one of the most significant transformations in pharmaceutical synthesis. Amides are another significant group of intermediates that are frequently used in the production of fine chemicals, cosmetics, and food additives. However, the majority of the procedures used today to create Amides use stoichiometrically activated, harmful, and caustic substances like acid anhydrides or acyl chlorides, which have a poor atom economy and produce a lot of waste. The reaction is watersensitive, and efficient water removal is a key component in the systems, therefore an excess of these reagents is typically required to get the best amide yields.[1]

To minimize the negative effects of amide formations on the environment, cleaner syntheses must be developed. The most appealing strategy in this regard continues to be the direct interaction of Amines with carboxylic acids. Where possible, it is best to carry out these types of reactions without catalysis; nonetheless, harsh reaction conditions must still be present in order to achieve direct amide production.[1]

One of the most widely utilized transformations in organic synthesis is the acylation of amines because it offers an effective and affordable way to safeguard amino and hydroxyl groups during a multistep synthesis process. Acetyl chloride and acetic anhydride are typically utilized for the amide production in the presence of an acidic or basic catalyst. Both of these reagents, nevertheless, are caustic and not often recommended for usage. Additionally, in the Lewis acid acylation of amines, the acidic environment causes the breakage of delicate functional groups like acetals and TBDMS ethers. Acylation of amines with acetic anhydride was reported for Sc(OTf)3, TMSOTf, and clays such K-10, KSF. The acylation of amines with esters also uses tetrabutylammonium salt, cyanide anion, and Cp2Sm(thf)2. One of the most essential and often employed processes in the synthesis of organic compounds is the protection of amino groups by the creation of amides, particularly acetamides.[5]

Because of their quick reaction times and high yields, microwave irradiations have been a popular method for conducting chemical syntheses in recent years. Its use in N-acylation amides was also developed, but anhydrides were required to produce the amide bonds under anhydrous circumstances, and the variety of amines were insufficient to reveal the reaction's key driving force. [1] Due to its ability to expedite a number of synthetic transformations while using less time and energy, microwave irradiation of organic processes has grown in popularity quickly. Because of their quick reaction times, selectivity, solvent-free methods, and wider reaction range, microwave irradiation, acetic acid can function by itself as an acetylating agent, although this technique only works with primary amines. [1,2]

For the production of amides, a variety of greener catalytic techniques have been reported. These include using arylboronic or boronic acid derivatives, microwave irradiation, solid supported reagents (such as polymer-bound acylating agents), and N-acylation of amines with organic acids. There have been reports of several different catalysts for the acylation of amines, including solid acid catalysts, immobilized ionic liquids on mesoporous materials, and transition metal salts.[1]

Several reactions involving various catalysts have been described. Using starbon acid as a catalyst and acetic acid as the acetylating agent, one of the processes of amides by N-acylation of primary and secondary amines under microwave irradiation were reported. By introducing 2mmol of aniline, 2mmol acetic acid, and 0.1g of catalyst to a tube and microwave irradiating it at 300 watts for 1–10 minutes at 120–130°C, the conventional N-acylation of amine was carried out in this procedure. Even though the reaction was run longer and more frequently than with any other acid catalyst, the yield was quantitative (>98%) with the starbon acid catalyst.[1,3]



Another article discusses the creation of an amide bond under microwave radiation using acid as the sole solvent. An N-acetylated molecule was produced in this reaction by first mixing benzyl amine and acetic acid in a microwave reaction chamber. Acetic acid served as both a catalyst and a solvent in this process. This method was mild and practical compared to the conventional amide synthesis process, taking only a few minutes as opposed to several hours, and producing excellent yields (greater than 90%). Between 90 and 95% of the main amines react with acetic acid and produce higher yields. Benzoic acid was utilized as an acylation reagent in place of acetic acid, and it produced yields that were just as high. In this process, 800 mg of benzoic acid or acetic acid was combined with 200 mg of aniline, and the mixture was microwave-irradiated at 200 watts, 50°C, for 6 to 8 minutes. The reaction mixture was added to a 1:50 solution of acetic ether and cyclohexane, then refrigerated for a while. The white crystal was obtained and dried after washing, 98% of the yield was achieved. [2]

+ R¹COOH microwave RNH_2

LaY and HY have been reported to act as catalysts in the acylation of amines with acetic acid. Recent studies have shown that Gd(OTf)3 and other elements including iodine, ZnO, bromodimethyl-sulfonium bromide, lanthanide, tosylates, CoCl2.6H2O, and ZrOCl2.8H2O can help amines be acylated with acetic anhydride or acetyl chloride. There have been reports of acetic anhydride-only acylation as well. Because chemicals used in chemical synthesis may either be integrated into the finished product or produced as trash, using acetic acid instead of acetic anhydride or acetyl chloride is both economically and environmentally favourable. Zeolites, an acid catalyst, were also used to carry out the acylation process of amines. In this process, 2 mmol of aniline and 2 ml of acetic acid were combined, along with 200 mg of zeolite catalyst, and microwave irradiation at 600 watts for 30 to 40 minutes at 117 °C was utilized as the catalyst and 73% of the yield was achieved.[5]

 $\begin{array}{c} \hline & zeolite \\ \text{R-NH}_2 + \text{CH}_3\text{COOH} & \xrightarrow{\text{microwave irradiation}} & \text{R-NHCOCH}_3 \end{array}$

Amine acylation is also accomplished using Zn dust as a catalyst. In this reaction, 10ml of acetic acid and 3.3g of aniline were combined with 0.16g of catalyst. The yield was 70-80% after the reaction was cooked on a burner for 45 minutes. Zn, a harmful metal to humans and the environment, is used as a catalyst in this reaction. [3]

 $R-NH_2 + CH_3CHOOH \xrightarrow{Zn \ dust} R-NHCOCH_3$

Although there are many techniques that can be used for this purpose, acetylation of amines is typically done in the presence of base catalysts using acetic anhydride or acetyl chloride. Tertiary amines like triethylamine or pyridine are frequently present during the process. There have also been reports of the use of catalysts such LiCl, I2, montmorillonite-K-10 or KSF, KF-Al2O3, and AlPO4. The acylation of amines with ethyl acetate has also been accomplished using the pyridine (tetrahydroborate) zinc complex. The zinc complex of 0.697g was combined with 0.093g of aniline in THF and ethyl acetate, and the reaction was refluxed for 2.5 hours; the yield was 97%.[4]

 $RR'NH \xrightarrow{(Py)Zn(BH4)2} RR'NCOCH_3$

There is also a mention of a catalytic activity using zinc acetate. Aniline and glacial acetic acid were combined in this synthesis, and zinc acetate was used as a catalyst. Under clean conditions, zinc acetate can likewise operate as a N-acetylating agent in equimolar quantities, but the yields are lower and the reaction periods are longer.

 $R-NH_2 + CH_3COOH \xrightarrow{Zn \ acetate} RNHCOCH_3$

2. Experimental

Instrument used: Microwave (Ultrasonic Ltd)

Chemicals and Reagents: Aniline, glacial acetic acid and 50% ethanol. (Merk)

Typical procedures for acylation of aniline:

Without employing a catalyst, aniline was first added in a stoichiometric amount to glacial acetic acid to create acetanilide. Due to its excellent solubility with other organic solvents, acetic acid is used as a solvent in this procedure. 3.235g of aniline and 10ml of glacial acetic acid were combined and microwaved in a glass tube for 5 minutes at 320 MHz. The reaction had a mole ratio of (1:5). After 5 minutes, the reaction mixture was vigorously stirred and carefully poured drop by drop into a beaker with 30 cc of ice cold water. The shining product crystals were slowly separated. When the crystals first formed, they were filtered, collected, and then washed with water over the Buchner funnel. Using 50% ethanol, the product was dried and crystallized again.

Aniline, 3.3 g and 9 ml of glacial acetic acid were combined in a glass tube. The combination was heated for 5 minutes at 480 MHz in a microwave. The reaction's molar ratio was found to be (1:3). After 5 minutes, the reaction was carefully added drop by drop while being vigorously stirred into a beaker holding 30ml of ice cold water. The Buchner funnel was used to separate and filter the shining acetanilide crystals. After being cleaned with water, the crystals were dried over a sodium lamp. Later, using 50% ethanol, the dry product was recrystallized.

2.3g of aniline and 9ml of glacial acetic acid were combined in a glass tube. The combination was put inside a microwave chamber and exposed to 480 MHz radiation for 7 minutes. The reaction's molar ratio was determined to be (1:3). After 7 minutes, the reaction was vigorously stirred and gently emptied drop by drop into a beaker with 30 cc of ice water. It was possible to view the product's shining crystal as it passed through the Buchner funnel. The crystals were dried after being cleaned with water. Using 50% ethanol, the dry product was recrystallized.

3.23g of aniline and 10ml of glacial acetic acid were combined in a glass tube. The combination was put inside a microwave chamber and subjected to 480 MHz radiation for 7 minutes. The reaction's molar ratio was determined to be (1:5). After 7 minutes, the reaction was vigorously stirred and gently emptied drop by drop into a beaker with 30 cc of ice water. The product's shining crystals were visible after being filtered via the Buchner funnel. Water was used for the washings, and a sodium lamp was used to dry the product. Using 50% ethanol, the dry product was recrystallized.

Aniline (2.3g) and glacial acetic acid (9ml) were combined in a glass tube. The combination was positioned in a microwave chamber and subjected to 480 MHz radiation for 5 minutes. The reaction taken had a molar ratio of (1:3). After 5 minutes, the reaction was carefully added drop by drop while being vigorously stirred into a beaker holding 30ml of ice cold water. The product's brilliant crystals were obtained after being filtered using the Buchner funnel. Water was used for the washings, and the product was dried. The product was recrystallized using 50% ethanol after drying.

1.32g of aniline and 8ml of glacial acetic acid were combined in a glass tube. The combination was positioned in a microwave chamber and exposed to 480 MHz radiation for 5 minutes. The reaction taken had a molar ratio of (1:10). After 5 minutes, the reaction was vigorously stirred and gently emptied out drop by drop into a beaker with 30 cc of ice water. The shining crystals of the product were obtained which was filtered over the Buchner funnel. The crystals underwent a water wash before being dried with a sodium lamp. Later, using 50% ethanol, the product was recrystallized.

Aniline 1ml and of glacial acetic acid 1ml were combined in a glass tube. The combination was positioned in a microwave chamber and exposed to 160 MHz radiation for 10 minutes. The reaction taken had a molar ratio of (1:5). After 10 minutes, the reaction was vigorously stirred and gently emptied drop by drop into a beaker with 30 cc of ice water. The product's shining crystals were created after being filtered via a Buchner funnel. After being cleaned with water, the crystals were dried with a sodium lamp. 50% ethanol was used to recrystallize the product.

A mixture of 2.04g of aniline and 3.75ml of glacial acetic acid was placed in a glass tube. The combination was heated for 20 minutes at 160 MHz using a microwave. The reaction's molar ratio was determined to be (1:3). After 20 minutes, the reaction was carefully taken out of the microwave and vigorously stirred before being gently poured drop by drop into a beaker with 30 cc of ice water. The product's shining crystals were obtained after being filtered using the Buchner funnel. The crystals were dried after being cleaned with water. Using 50% ethanol, the dry product was recrystallized.

A mixture of 2.04g of aniline and 3.75ml of glacial acetic acid was placed in a glass tube. The reaction was positioned in a microwave chamber and subjected to 160 MHz radiation for 30 minutes. The reaction's molar ratio was determined to be (1:3). After 30 minutes, the reaction mixture was carefully taken out of the microwave and vigorously stirred before being gently poured drop by drop into a beaker with 30 cc of ice water. The product's shining crystals were separated, and it was then filtered using a Buchner funnel. The crystals were totally dried after being cleaned with water. Later, using 50% ethanol, the dry product was recrystallized.

A mixture of 2.04g of aniline and 3.75 ml of glacial acetic acid was placed in a glass tube. A microwave chamber was used to irradiate the process for 40 minutes at 160 MHz. The reaction's molar ratio was determined to be (1:3). After 40 minutes, the reaction mixture was carefully taken out of the microwave and vigorously stirred before being gently poured drop by drop into a beaker with 30 cc of ice water. The product's brilliant crystals were separated, and it was then filtered using a Buchner funnel. The crystals were totally dried after being cleaned with water. Later, using 50% ethanol, the dry product was recrystallized.

2.04 grams of aniline and 3.75 milliliters of glacial acetic acid were combined in a glass tube. A microwave chamber was used to irradiate the process for 40–50 minutes at 160 MHz. The

reaction's molar ratio was determined to be (1:3). After 40-50 minutes, the reaction mixture was carefully taken out of the microwave and vigorously stirred before being gently poured drop by drop into a beaker with 30 cc of ice water. The product's brilliant crystals were separated, and it was then filtered using a Buchner funnel. The crystals were totally dried after being cleaned with water. Later, using 50% ethanol, the dry product was recrystallized.

With water as a solvent:

2.04 g of aniline, 3.75 ml of glacial acetic acid, and 1 ml of water were combined in a glass tube. A microwave chamber was used to irradiate the process for 50 minutes at a frequency of 160 MHz. The reaction's molar ratio was determined to be (1:3). After 50 minutes, the reaction mixture was carefully taken out of the microwave and vigorously stirred before being gently poured drop by drop into a beaker with 30 cc of ice water. The product's brilliant crystals were separated, and it was then filtered using a Buchner funnel. The crystals were completely dried after being cleaned with water. Later, using 50% ethanol, the dried product was recrystallized.

These were the standard processes carried out with water and acetic acid as the solvent. The product is produced when aniline and acetic acid combine. Every technique involved altering the stoichiometric ratio of the reaction, influencing how much acetic acid and aniline were produced. The amount of acetic acid used in conventional methods is considerably higher than the amount of aniline utilized. To prevent any wastage, if a process is referred to as "green synthesis," then the number of chemicals used must be reduced and in an equal amount. This assignment involves reducing the amount of acetic acid and carrying out the processes. Aniline and glacial acetic acid were employed in this experiment in a ratio of 1:3. The production of acetic acid is reduced in this way.

Substrate	Time (min)	Molar ratio	Yield (%)	Product
NH ₂				NHCOCH3
	5	1:5	22.23	

NH2	5	1:1	10.85	NHCOCH ₃
NH2	7	1:3	30.28	NHCOCH ₃
NH ₂	7	1:5	37.27	NHCOCH ₃
NH2	5	1:3	20.00	NHCOCH3

Table 2:

Substrate	Time (min)	Molar ratio	Yields (%)	Product
NH ₂				NHCOCH3
	5	1:10	No yield	

NH2	10	1:3	50.62	NHCOCH ₃
NH2	20	1:3	70.13	NHCOCH ₃
NH2	30	1:3	72.09	NHCOCH3
NH ₂	40-50	1:3	75-80	NHCOCH ₃

3. Result and Discussion

From an economic and environmental perspective, using acetic acid in the acylation reaction rather than the corrosive acetyl chloride or acetic anhydride has many benefits, and the only by-product is water. The green chemistry approach was used to produce acetanilide. Re-crystallizing the synthesized materials yielded melting points that are consistent with previously reported melting points. It was discovered that the green chemistry process produced a higher yield percentage than the traditional method did.

Stereochemistry of amines:

In contrast to what would be predicted if pure p-orbitals of nitrogen were used to form bonds, the bonds to nitrogen in amines are pyramidal and have bond angles that are closer to the tetrahedral value of 109.5° than to the 90° value expected. We believe that the nitrogen in amines is best constructed with hybrid sp3-type orbitals, of which three are used for σ bond formation and the fourth is home to an electron pair that is not involved in a bond.

Spectroscopy of amines:

NMR: The amine hydrogens are visible at concentrations between 0.5 and 5.0 ppm. The location is determined by the concentration of the sample and the degree of hydrogen bonding. Typically, the hydrogens on carbons that are directly linked to an amine range from 2.3 to 3.0 ppm. All hydrogens on non-carbon atoms will often exchange with deuteriums when D_2O is added, making these resonances dissipate. The existence of -NH can be determined by adding a few drops of D_2O and watching the signal disappear.

IR: The infrared spectrum of aniline;

Stretching vibrations: Compared to O-H absorptions, the N-H stretching absorption is less susceptible to hydrogen bonding. Free N-H absorption is seen in the 3400–3500 per cm range in both the gas phase and diluted CCl₄ solution. N-H absorptions are typically 40 to 70 times more frequent in aromatic amines. A 1600 per cm overtone for aromatic amines is thought to interact with a smaller absorption at about 3200 per cm.

Primary amines typically exhibit bending vibrations, such as strong in-plane NH₂ scissoring absorptions at 1550–1650 per cm and out-of-plane wagging at 650–900 per cm.

A primary amine like aniline was chosen for the acylation of amines because it may react with glacial acetic acid to produce the matching amide without the need for a catalyst. 40 minutes of exposure time and a maximum microwave power output of 480 MHz were chosen as the reaction parameters. Without using a catalyst, quantitative conversion of the starting material was discovered in less than 15 minutes of reaction time. The reaction parameters have to be optimized next. The yield was impacted as expected by a decrease in microwave power and time. The most crucial variables in the process were probably the duration of the microwave irradiation and the volume of solvent acetic acid. When the duration was reduced, less than a 50% yield was obtained for the majority of the reactions. The yield between 70 and 80% was achieved with concomitant increase in the amount of solvent and irradiation time to 40 to 50 minutes.

The reaction between aniline and glacial acetic acid was conducted in the absence of microwave irradiation in the presence of Zn dust as a catalyst in order to compare the efficiency of microwave irradiation with that of traditional heating. The reaction took longer than an hour to finish itself. The yield that was obtained was lower than that of the microwave reaction, which uses no catalyst at all.

Tables 1 and 2 provide comparisons of the various reactions over a range of time scales and molar ratios.

As could be seen, reaction number 10 provides the highest yield, with the reaction's molar ratio being set at 1:3. In this synthesis, 2.04g of aniline and 3.7 ml of acetic acid are utilized. At 160 MHz, the reaction is microwave-irradiated for 40 to 50 minutes. When the reaction is fully converted, the yield is between 70 and 80 percent.

6. Conclusion

In conclusion, a variety of pharmaceutical intermediates, including acetanilide, might be prepared using our effective, atom-economic, and environmentally benign methodology. We have created a process for the microwave-induced acylation of amines that is effective, quick, safe, high-yielding, and environmentally friendly. The current technique works with anilines and primary amines. The benefit of this approach is that no hazardous or corrosive chemicals are required to carry out the reaction. This is remarkable and increases the method's economic value. Acetic acid is used as a solvent in a 1:3 ratio to successfully create amide, and the technique was shown to be independent of the substrate combination and, more crucially, of the effective removal of water, which has been claimed to be essential to achieving high amide yields. Incorporating acetic acid into current techniques can make the facilitated acylation of amines a compelling study topic.

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