

Baker's yeast as a biocatalyst for efficient and substrate-selective N-acetylation of anilines

Qasim Ullah ^{*1}, Samreen Kausar ¹, Abida Murtaza ²
and Aarifa Maryam ³

¹Chemistry Section, School of Sciences, Maulana Azad National Urdu University, Gachibowli, Hyderabad-TS. India- 500032.

²Polytechnic, Maulana Azad National Urdu University, Gachibowli, Hyderabad-TS. India- 500032

³Department of Biosciences, Jamia Millia Islamia, Jamia Nagar, New Delhi-110025, India

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Abstract: In the present study, we have developed an efficient N-acetylation method of anilines under green and eco-friendly conditions, where Baker's Yeast (BY) was used as biocatalyst. The results of this study clearly demonstrate towards the N-acetylation of only anilines to form acetanilides (**3a-i**) with acetic anhydride in good to excellent yield. Interestingly, acetylation of phenol/thiophenol, aliphatic amines/heterocyclic amines and amino acids failed under the same conditions. This N-acetylation reaction with substrate-selective follows simple procedure and requires simple work up. Thus, we can conclude that the present method is a simple, efficient, substrate selective and eco-friendly.

Keywords: Anilines; acetylation; acetanilide; acetic anhydride; Baker's yeast; biocatalyst. © 2025 ACG Publications. All rights reserved.

1. Introduction

In 21st century, enzymes catalyzed organic transformations, commonly known as bio-catalysis reaction, has emerged as a very important protocol in organic synthesis and industry. The bio-catalyzed reactions are characterized by their high activity and excellent chemo, stereo and regio-selectivity. A well-known example of biocatalysts is baker yeast (BY).¹

The earliest historical use of yeast dates back to before 6000 BCE when the Sumerians and Babylonians unknowingly utilized this microorganism in beer production. The use of yeast for leavening bread through carbon dioxide production, however, was developed much later, around 4000 BCE in ancient Egypt². BY is found in different forms such as in bricks, discs, granules, creams, fast-rising, instant deactivated or active dry forms.³ BY is used in whole cell form as biocatalyst in various organic transformations due to some inherent features such as easily available, cost effective, easy to handle, easy to manipulate, non-toxic and non-pathogenic. BY can be used in various organic reactions either in water or in organic solvents,⁴ for examples., C-C bond forming reactions, dechlorination, reduction of nitro group, lactonization and hydrolysis of esters.⁵

BY is used in whole cell form as biocatalyst in various organic transformations because, it is widely available, easy to handle, economically viable, easy to manipulate BY, non-toxic and non-pathogenic etc. BY can be used both in dry and pressed form and it catalyzes various organic reactions either in water or in organic medium, for examples. C-C bond forming reactions, hydrolysis of esters, dechlorination, lactonization, reduction of nitro group etc.⁶⁻¹⁰ In recent years, the industry and academia

* Corresponding author: E-Mail: drqasimullah@manuu.edu.in

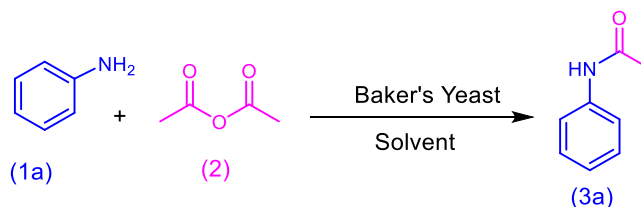
Selective N-acetylation of anilines

has put immense interest to employ **BY** as biocatalyst in the synthesis of various organic compounds.¹¹⁻¹³

Recently, **BY** as a biocatalyst is used in oxidation, hydrogenation or reduction, condensation, hydrolysis and cyclization,¹⁴ reduction of carbonyl compounds.¹⁵⁻⁵⁷ The complex organic molecules are synthesized through synthesis reaction and depend on the functional group of each compound.⁵⁸

Acetylation is the most common organic transformation synthetic reaction. Acetylation is frequently used to protect anilines, phenols and thiophenols because it can be moderately deprotected and stable with acidic medium.⁵⁹⁻⁶⁰ Generally, acetic anhydride or acetyl chloride combined with triethyl amine and pyridine act as catalyst are for acetylation reaction.⁶¹⁻⁶³ It was also found that the acetylation reactions can also be catalyzed by 4-(Dimethylamino) pyridine (DMAP),⁶⁴ Silica gel supported sulphuric acid,⁶⁵⁻⁶⁶ Ammonium acetate in acetic acid,⁶⁷ Zinc dust,⁶⁸ ZnCl₂,⁶⁹ CoCl₂,⁷⁰ Sc(OTf)₃,⁷¹ TaCl₅,⁷² Montmorillonite K-10,⁷³ HY-Zeolite,⁷⁴ In(OTf)₃,⁷⁵ Cu(OTf)₂,⁷⁶ YttriaZirconia based Lewis acid,⁷⁷ InCl₃/Mont.K-10,⁷⁸ Manganese (III) bis(2-hydroxyanil)acetylacetonato complex,⁷⁹ Silica sulfate,⁸⁰ p-MeC₆H₄SO₂NBr₂,⁸¹ DBDMH or TCCA,⁸² H₆P₂W₁₈O₆₂·24H₂O,⁸³ La(NO₃)₃·6H₂O,⁸⁴ Ionic liquid based on morpholine,⁸⁵ Borated zirconia,⁸⁶ 2,4,6-Triacyloxy-1,3,5-triazine (TAT),⁸⁷ Sodium dodecyl sulfate (SDS),⁸⁸ and DMAP-Saccharin.⁸⁹ On the other hand the selective acylation of amino group was done by acylsilanes,⁹⁰ micro-reaction system of ambient water (μ-onH₂O) and subcritical water (μ-subH₂O),⁹¹ N-acylimidazoles and either DBU or pyridinium ion⁹² and N-acetylation of anilines/amines at room temperature by utilizing acetonitrile as a surrogate of the acetyl group in presence of basic medium is reported.⁹³ All reported protocols for the acetylation reaction have one or more disadvantages such as high cost of the catalyst, drastic reaction condition, toxicity of the reagent, less yields, instability and hygroscopic nature of the reagent, tedious work-up procedures. Therefore, there is an immense need a simple, selective and efficient method for the protection of anilines.

To overcome the above said limitation and in continuation of our earlier work⁹⁴⁻⁹⁶ and ongoing project on the bio-catalyzed organic transformations, we decide to use the **BY** as biocatalyst for the efficient N-Acetylation of anilines. (Scheme 1) The literature survey shows that **BY**'s was not reported in the N-acetylation of anilines.



Scheme 1. N-acetylation of aniline (**1a**) catalyzed by Baker's yeast

2. Experimental

2.1. Chemical Material and Apparatus

Melting points were determined in open capillaries in a sulphuric acid bath and are uncorrected. All chemicals and solvents were of analytical grade and were used without further purification as received from the suppliers. ¹H-NMR spectra were recorded on Bruker Avance 500MHz spectrometer. The samples were made in CDCl₃/DMSO-d₆ and TMS was used as the internal standard with values chemical shift given in δ scale. The progress of the reaction was monitored by TLC on pre-coated silica gel 60-GF 254 (0.5mm) TLC plates. The HRMS mass spectra were recorded on ESI mass spectrometer. All the compounds are known compounds. Spectral data for the selected compounds are given as supporting information.

2.2. Chemistry

2.2.1. General Procedure for the Synthesis of Acetanilides (**3a-i**) via N-acetylation of Anilines Catalyzed by Baker's Yeast (BY):

Aromatic anilines (**1a-i**) (1 mmol) and acetic anhydride (**2**) (1 mmol) are taken in 10 mL of ethanol. To this, reaction mixture, 500 mg of BY was added. The reaction mixtures were kept on stirring on shaker for 36 h. After completion of the reaction as indicated by TLC (ethyl acetate: hexane 30%), the reaction mixture was filtered through the celite to remove the BY. Thus, obtained residue was washed with ethanol. Thus, filtrate obtained were added water (20 mL) and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were collected, and sodium sulphate was added to remove the moisture. The combined organic layers were evaporated to get the pure crude product. Thus, obtained product was recrystallized with ethanol to get the pure acetanilides (**3a-i**) in good to excellent yield. All the compounds are known compounds, and they are characterized by their melting points, ¹H NMR and Mass spectral data. (See supporting information).

3. Results and Discussion

The commercially available cheap BY was purchased from the local market. It is noteworthy to state that our findings clearly exhibit that BY efficiently catalyzed the selective N-acetylation of aniline under green and mild conditions.

To obtain the optimize reaction conditions; we studied the various solvents as shown in Table 1. We started our experiments with the reactions of aniline (**1a**), and acetic anhydride (Ac₂O) in the presence of BY (Biocatalyst) using various solvents as listed in Table 1 (Scheme 1).

When we preformed the reactions by using THF/BY/RT/12 hr, we did not get any product as the reaction did not proceed (Entry-1, Table-1). Similar results were seen, when we used DCM/BY/RT/12 h, benzene/BY/RT/12 h, Toluene/BY/RT/12 h, EtOAc/BY/RT/12 h and AcCN/BY/RT/12 h and no reaction is proceeded. (Entries-2-6, Table-1) Interestingly, when we used the protic solvent ethanol or methanol, we found that the reaction was taking place and the product formation started. Thus, when the reaction was done by using ethanol or methanol/BY/ RT/12 h, we observed the formation of the product (**3a**) in 10% yield (Entry-7, Table-1). Encourage by the formation of the product, we moved to see the effect of the reaction time i.e., we did the reaction by enhancing the reaction time. It was observed that when the reaction was done by using ethanol or methanol/BY/RT/24hr, the yield increased to 25% (Entry-8, Table-1). When the reaction time is increased up to 48 hr, under the same reaction condition i.e., ethanol or methanol/BY/RT/48 h, the product formation reached to 50% (Entry-9, Table1). Finally, when the reaction was carried out by using ethanol or methanol/BY/ RT/36 h, under the same condition, we obtained the acetanilide (**3a**) as the product in 90% yield (Entry-10, Table 1).

After successfully getting the optimized conditions, we want to identify the essentiality of BY as a catalyst, we carried out the reaction without the use of BY, the results showed that even up to 36 hr, no product formation was observed (Entries-11-13, Table1). Thus, the reaction is highly solvent dependent as it is proceeding in the protic solvents such as ethanol and methanol. It is clearly documented in the literature that the protic solvents are generally considered suitable for acetylation reactions, as they can help stabilizing the transition state during the reaction due to their ability to form hydrogen bonds with the reactants. Although, the reaction is equally going smoothly, when both methanol and ethanol were used as solvent, but we decided to use ethanol as solvent of choice because ethanol is more preferable green solvent as compared to methanol. Finally, we carried out the reaction by using ethanol/BY/RT/36 h and 90% of acetanilide (**3a**) is obtained as the product (Entry-14, Table 1).

After getting the optimized conditions and the essentiality of the BY, as biocatalyst in this reaction, we focused towards to determine the quantity of the BY i.e. how much BY is required to accomplish the N-acetylation of aniline. We carried out the reaction by taking different amount of BY. The results are presented in the Table 2. The results indicate that when 50 mg of the BY was used; only 10% of conversion is observed even after 36 h (Entry-1, Table-2). But, when we increased the quantity of the BY from 50 mg to 100 mg, the product formation increased to 20% (Entry-2, Table-2). Further,

Selective N-acetylation of anilines

when we increased the amount of BY 200 mg, 300 mg and 400 mg, we got the yields 40%, 60% and 75% respectively (Entries-3-5, Table 2). Moreover, when 500 mg of BY was used, we obtained 90% of the product (Entry-6, Table 2). To further check the effect of the BY, we increased the quantity of the BY from 500 mg to 600 mg, 750 mg and 1000 mg surprisingly, we found that there was no further increase in the product formation (Entries-7-7, Table 2). Thus, we finally came to a conclusion that 500 mg of the BY is sufficient to catalyze the reaction. Therefore, with all the above optimizations and variable conditions, we finally decided that the ethanol/BY (500mg)/RT/36 h is the best reaction condition for the N-acetylation of aniline (**1a**) to obtain the acetanilide (**3a**).

Table 1. Solvent effect on Baker's yeast (BY) catalyzed N-acetylation of aniline with acetic anhydride (Ac₂O)

S. No	Solvent	Reaction conditions	Yield % of 3a
1	THF	BY/ RT/12 h	NR
2	DCM	BY/ RT/12 h	NR
3	Benzene	BY/ RT/12 h	NR
4	Toluene	BY/ RT/12 h	NR
5	EtOAc	BY/ RT/12 h	NR
6	AcCN	BY/ RT/12 h	NR
7	Ethanol or Methanol	BY/ RT/12 h	10
8	Ethanol or Methanol	BY/ RT/24 h	25
9	Ethanol or Methanol	BY/ RT/48 h	50
10	Ethanol or Methanol	BY/ RT/36 h	90
11	Ethanol or Methanol	Without BY/ RT/12 h	NR
12	Ethanol or Methanol	Without BY/ RT/24 h	NR
13	Ethanol or Methanol	Without BY/ RT/36 h	NR
14	Ethanol*	BY/ RT/36 h	90

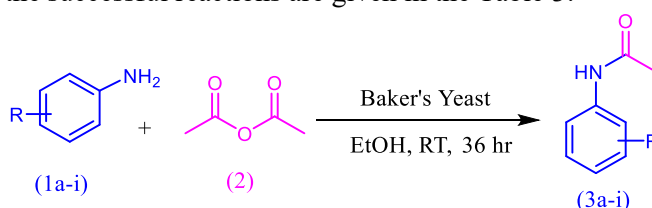
*As ethanol is green solvent, therefore, the ethanol is taken as the solvent of choice for this reaction.

Table2. Effect on Baker's Yeast (BY) on N-acetylation of aniline with acetic anhydride (Ac₂O)

S. No	Quantities of used BY in EtOH, at RT, for 36 h	Conversion to 3a (yield %)
1	50 mg	10
2	100 mg	20
3	200 mg	40
4	300 mg	60
5	400 mg	75
6	500 mg*	90
7	600 mg	90
8	750 mg	90
9	1000 mg	90

*As we used more than 500 mg of BY i.e., 600 mg, 750 mg and 1000 mg, no effect on the yield was observed. Therefore, 500 mg of BY was taken optimal quantity for this reaction.

After getting the optimized condition in hand, we started to check the generality of this reaction by carrying out the reaction with substituted anilines (Scheme 2). Surprisingly, the reaction is found very selective and gave the products (**3a-i**) in good to excellent yields with electron donating and halogen containing anilines (**1a-i**) and the anilines containing electron withdrawing group were failed to give the products. The results of the successful reactions are given in the Table 3.



Scheme 2. Synthesis of acetanilides (**3a-i**) by N-acetylation of anilines (**1a-i**) catalyzed by Baker's Yeast

Table 3. Baker's Yeast catalyzed N-acetylation of anilines with acetic anhydride (Ac₂O)

S. No.	Substrate (2)	Products (3) ^a	Time Yield ^b (min) (%)
1	Aniline (1a)	Acetanilide (3a)	90
2	4-Chloroaniline (1b)	4-Chloroacetanilide (3b)	85
3	4-Fluoroaniline (1c)	4-Fluoroacetanilide (3c)	83
4	4-Methylaniline (1d)	4-Methylacetanilide (3d)	88
5	4-Isopropylaniline (1e)	4-Isopropylacetanilide (3e)	90
6	2,4-Dimethylaniline (1f)	2,4-Dimethylacetanilide (3f)	90
7	2,4,6-Trimethylaniline (1g)	2,4,6-Trimethylacetanilide (3g)	88
8	4-Methyl-3-nitroaniline (1h)	4-Methyl-3-nitroacetanilide (3h)	70
9	2-Methyl-4-nitroaniline (1i)	2-Methyl-4-nitroacetanilide (3i)	68

^aAll the products are known compounds and are characterized by ¹H-NMR, mass spectral data and were compared with authentic samples and literature values. ^bIsolated yields of the purified products.

The results of the N-acetylation reaction of the substituted anilines (**1a-i**) showed that the reactions proceeded well, when the un-substituted aniline reacted (**1a**) and gave the product (**3a**) in high yields. With electron donating groups such as methyl or isopropyl, the yields of the corresponding acetanilides were found between 88-90% (**3d-g**) (Entries-4-7, Table 3). On the other hand, when the halogens were used as substituent, the yields of the acetanilides (**3b-c**) were slightly low ranging from 83-85% (Entries-2-3, Table 3). Surprisingly, when the NO₂ group was introduced into the methyl anilines, the yields dropped to 70 & 68 % for corresponding acetanilide formation (**3h-i**) (Entries-8-9, Table 3).

Furthermore, when we took the 4-nitroaniline as substrate and carried out the reaction in the present reaction condition, the desired corresponding 4-nitroacetanilide was not obtained and starting material 4-nitroaniline is recovered. Similar results were obtained, when 4-aminophenol, 4-aminothiophenol, 2-aminobenzothiazole, 2-aminobenzimidazole, 2-aminopyridine, 2-aminopyridimidine, morpholine, ethylamine, propylamine and butylamine were used as starting material in this reaction condition, as this reaction failed to give the corresponding N-actylated products.

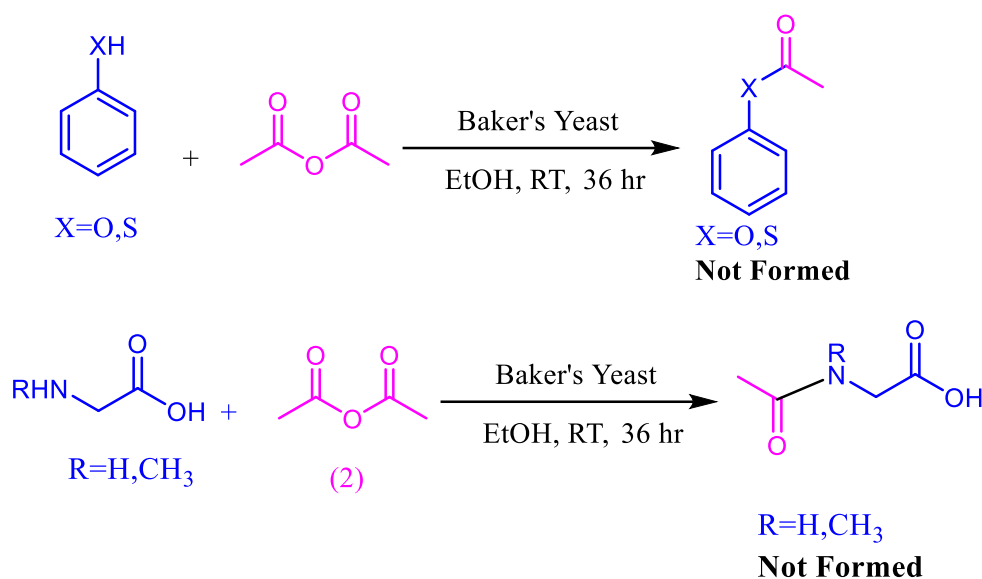
It is to state that in most of these cases, the reactions did not proceed, and the starting materials were recovered. In few cases, lumps of solids were obtained, which were difficult to isolate or separate. Thus, these observations clearly indicate that the reactions are highly specific, as only anilines are taking part in the reaction for the acetylation reaction. The result of this studies clearly advocating that the BY is acting as biocatalyst, which in turn exhibiting both substrate specificity. Therefore, it is reasonable to conclude that, in this case, the BY is acting as a highly specific biocatalyst as it is acetylating only the aromatic amines i.e., anilines as substrate.

The products obtained in these reactions (**3a-i**) are fully characterized by their mass and ¹H NMR spectra. All the acetanilides obtained in this study were known compounds. In the ¹H NMR spectra, the characteristic peaks of methyl protons of the acetyl groups are obtained as a singlet in the range of δ 2.10-2.35 ppm and characteristic NH proton as a broad peak between δ 2.5 to 8.0 ppm. These peaks confirm the formation of acetanilides. In the mass spectra, in most of the cases, the M⁺¹ ion peaks are observed, which confirm acetanilides formation. The spectral data in the form of spectra are being provided in the supplementary information file.

After getting the above said interesting results, we decided to investigate the acetylation of phenol or thiophenol to obtain the phenylacetates as the product. When we carried out the reaction of phenol in the present reaction condition, we observed that reaction did not proceed (Scheme 3). Similar, results were obtained, when 4-chlorophenol, 4-fluorophenol and 4-methylphenol were used and the reactions failed to give the corresponding phenyl acetates. Furthermore, when the amino acids (Glycine and Alanine) were subjected to this reaction, they could not give the corresponding N-acetylated

Selective N-acetylation of anilines

products. It is assumed that as amino acids exist in their zwitterionic form, therefore, they do not participate in the reaction. Furthermore, as mentioned earlier, the aliphatic amines do not involve in this reaction which might be due to highly basic nature of aliphatic amines. Thus, it is anticipated that the highly basic nature of amines is retarding the reactions of N-acetylation.



Scheme 3. Attempts to syntheses of N-acetylation of phenol/thiophenol and aminoacids catalyzed by Baker's Yeast.

Table 4. Comparison of the Baker's Yeast Catalyzed N-acetylation of aniline with acetic anhydride (Ac_2O) to produce the acetanilide with the literature catalytic method.

S. No.	Different Methods	Reaction Condition	Yield %	Remarks	Reference
1	SiO ₂ -ZnCl ₂ ,	SiO ₂ -ZnCl ₂ , CH ₃ CN, 80 °C, 2.5 h	95	Catalyst preparation required 10 h	69
2	Manganese (III) bis(2-hydroxyanil)acetylacetonato complex,	[Mn(haacac)Cl]/30 °C, 6 h	95	Preparation of catalyst is required 15 h of heating under air condition	79
3	Sodium dodecyl sulfate (SDS),	SDS (1mg/ml H ₂ O), H ₂ O, rt, 5-10 h	80		88
4	Acyloxy silanes,	DCH/Citric acid/THF/H ₂ O (1:1), 50 °C, 24h	83		90
5	N-acylimidazoles and either DBU or pyridinium ion	PPTS, DMF, rt or DABCO, CH ₃ CN, rt	90	Non selective reaction	92
6	Present Method	Ethanol/ BY (500mg)/ rt/36 h	90	Mild and easy work up	-

To prove the superiority of the present method over the earlier reported method, a comparison has been done by taking N-acetylation reaction of aniline to form the acetanilide. For example: the method developed with SiO₂-ZnCl₂ required 10 h for the catalyst preparation. Similarly, the method

reported by using Manganese (III) bis(2-hydroxyanil)acetylacetonato complex, also required 15 hr of heating under air condition for the preparation of catalyst. Whereas the catalysts such as sodium dodecyl sulfate (SDS) and acylsilanes gave 80% and 83% yields respectively. The method developed by using N-acylimidazoles and either DBU or pyridinium ion is not selective reaction as other products are also formed. Thus, the present method with reaction conditions Ethanol/BY (500mg)/rt/36 h is superior, as it follows mild reaction condition and easy work up procedure. The comparisons are summarized in the Table 4.

The fact that this reaction is substrate-selective may be a sign that the reaction is most likely to proceed via an enzyme. Otherwise, phenols and other amine compounds or amino acids would also be expected to be converted into products via simple organocatalysts. Furthermore, it is interesting that while the reaction takes place in ethanol, ethyl alcohol is not o-acetylated. This gives the impression that the reaction is most likely enzymatic. Otherwise, in a reaction that proceeds via a simple organocatalyst, aliphatic amines, amino acids and phenols would also be expected to be acetylated.

4. Conclusion

On the basis of the present study, we can conclude that we have developed an efficient, bio-catalyzed and specific method for N-acetylation of anilines in presence of BY. The results of this study clearly demonstrate the substrate-selectivity towards the N-acetylation of anilines to form acetanilides (**3a-i**) with acetic anhydride in good to excellent yield. The results of this study clearly explain/demonstrate the N-acetylation of anilines to form acetanilides (**3a-i**) with acetic anhydride in good to excellent yield. Interestingly, acetylation of phenol/thiophenol, aliphatic amines/heterocyclic amines and amino acids fails under the same conditions, attributed this method to be highly specific for the formation of acetanilides via N-acetylation of anilines. This N-acetylation reaction follows simple procedure and requires simple work up, which makes this reaction to be worthy in the multi step organic synthesis reactions as well. Thus, we can conclude that the present method is simple, efficient, substrate-selective for anilines and eco-friendly.

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Conflict of interest

All the authors declare that there are no conflicts of interest.

Author's contributions

The author's contributions are as follows: Ms. Samreen Kauser and Ms. Arifa Maryam were involved in optimizing the experimental procedures and characterization and data collections of the product. Dr. Qasim Ullah is a Principal Investigator of this project and involved in the designing of the project, optimization of the reaction conditions, characterization, interpretation of spectral data and manuscript writing etc. Mrs. Abida Murtaza was involved in the interpretations and characterization of the spectral data and drafting of the manuscript.

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Supporting Information

Supporting Information accompanies this paper on <http://www.acgpubs.org/journal/organic-communications>

Selective N-acetylation of anilines

ORCID Qasim Ullah: [0000-0002-6133-7083](https://orcid.org/0000-0002-6133-7083)Samreen Kausar: [0009-0001-2724-5361](https://orcid.org/0009-0001-2724-5361)Abida Murtaza: [0009-0009-7782-6912](https://orcid.org/0009-0009-7782-6912)Aarifa Maryam: [0009-0004-1126-3866](https://orcid.org/0009-0004-1126-3866)

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Selective N-acetylation of anilines

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