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Newer Green Chemistry Methods for the Synthesis of Different Acetanilide Derivatives from Anilines and Their Comparative Analysis

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ABSTRACT: Green chemistry improves upon all chemical products and processes by reducing negative impacts on human health and environment relative to competing chemistry. Green chemistry is a new and rapidly emerging field in chemical sciences. Its significance is in utilization of techniques and resources in such a way that, there is negligible or minimum production of chemical waste. Now a day many of the principles of green chemistry are not new but more research work is expected from researchers. Uses of green techniques in a coherent approach and the degree to which they are being applied have resulted in an intensified attention on this topic among the academia, industries and regulatory communities. Four acetanilide derivatives (I-IV) were synthesized by conventional method and by three different green chemistry methods. Drawbacks of conventional method were use of hazardous chemical acetic anhydride and by products formation. By using newer green synthesis methods, we have overcome these drawbacks. Atom economy was determined on the basis of mol. weight of desired product and it was found to be excellent in green methods and this signifies the importance of green synthesis methods. This research primarily lays emphasis on the improvement of synthetic techniques, product yields and greener approach.

KEYWORDS: Green synthesis, green chemistry, comparative analysis, acetanilide derivatives, atom economy, greener approach.

I. INTRODUCTION

Green chemistry demonstrates its key principles with reduced negative impact on human health and environment. These principles need to be applied simultaneously for better outcome. It involves pulling together tools, techniques and technologies.¹ In energy-efficient processes to prevent the formation of wastes, provide economy of matter and energy, use safer solvents and renewable chemicals and yield less-hazard materials with low toxicity, as well as to carry out a smart catalysis with reduced number of side products or derivatives under degradable process design.² The development of Green Chemistry redefines the role of a solvent; an ideal solvent facilitates the mass transfer but does not dissolve. Again green solvent should be natural, nontoxic, cheap and readily available with additional benefits of aiding the reaction, separation or catalyst recycling. To minimize risks for the environment, in the different steps of a chemical process in materials fabrication, several methods of control can be applied. Evaluation of the efficiency of chemical transformation will result in maximizing Atom Economy which and is calculated as:³

% atom utilization = Molecular weight of desired product X 100

Molecular weight of (Desired product + waste product)

Here in this study four acetanilide derivatives (I-IV) are synthesized by conventional method and by three different green chemistry methods. The synthesized compounds are purified by column chromatography and are characterized by their physical constants and FTIR. Use of acetic anhydride and formation of by products can be avoided by applying these newer green synthesis methods. All the methods gives the desired products but the atom economy is found excellent with green chemistry methods which indicates the complete use of chemicals. If we synthesized products and materials without using hazardous substances, then much waste, hazards and cost can be evaded. This may leads to generation of ecofriendly synthetic chemistry.

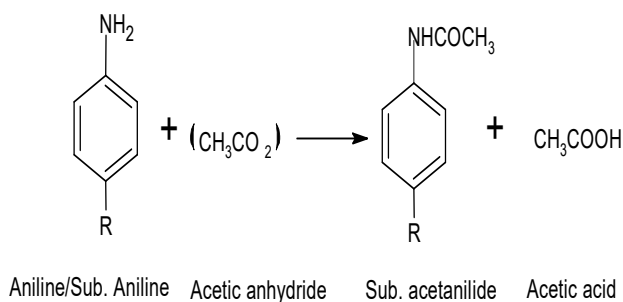
II. MATERIALS AND METHODS:

Apparatus: Round bottom flask, Reflux condenser, Thiel's tube, capillary tube and the melting points were analysed by open capillary method and are uncorrected. Infrared spectra were recorded on FTIR 8400s Shimadzu using KBr.

Chemicals and Reagents: Aniline, p-toluidine, p-chloroaniline, acetic anhydride, p-nitroaniline, conc. HCl, sodium acetate, glacial acetic acid, zinc dust, sulphuric acid, acetyl chloride, triethyl amine, methylene chloride and methylated spirit are taken from Loba Chem Pvt. Limited, Mumbai. All solvents were distilled before use and dried whenever required. All the synthesized products are recrystallized and purified and then promoted for melting point and IR determination.

III. SYNTHESIS OF (I-IV) COMPOUNDS BY TRADITIONAL METHOD:

Procedure- Weigh accurately about 5.1 g of aniline / substituted anilines, 125 ml of water, .6 ml of conc. HCl and transfer into a 250 ml beaker. Stirred until all the anilines mixed completely into mixture. To this beaker 6.9 g (6.4 ml) of redistilled acetic anhydride was added and stirred until it was dissolved. Poured immediately in a solution of 3.8 g of crystalline sodium acetate in 25 ml of water. Stirred the solution vigorously and cooled in ice. Filtered the acetanilide/substituted acetanilide with suction pump, washed with 10 ml water, drained well and dried upon filter paper. The crude products were recrystallized from boiling water and methylated spirit. ^(4, 5)
Non green component: Acetic anhydride leaves one molecule of acetic acid unused.

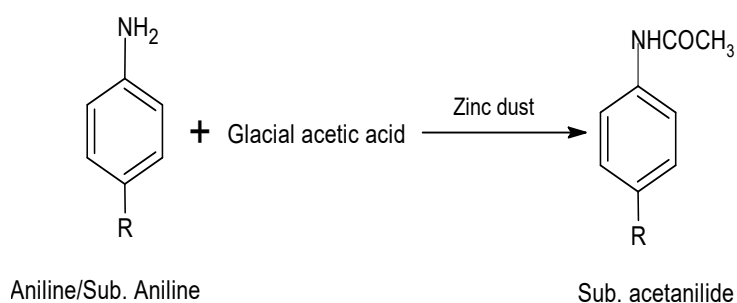


Mechanism- Acetanilide is synthesized from aniline by acetylating it with acetic anhydride in the presence of glacial acetic acid. Aniline is a primary amine and basic in nature. Acetic anhydride is an anhydride of acetic acid, act as a source of acyl group. Aniline reacts with acetic anhydride to form acetanilide by nucleophilic substitution reaction and the reaction is called acetylation. In this reaction, aniline act as the nucleophile and acyl (CH₃CO-) group from acetic anhydride act as the electrophile. Here, the hydrogen atom of -NH₂ group is replaced by the acyl group.

IV. SYNTHESIS OF (I-IV) COMPOUNDS BY GREEN CHEMISTRY METHOD 1:

Procedure- In a 100 ml round bottom flask a mixture of aniline / substituted anilines (3.3g) and zinc dust (0.16g) in acetic acid (10ml) was taken and heated over a gentle flame using water reflux condenser. Mixture was heated for about 45 min and then reaction mixture was carefully poured in cold water (33ml) in 250ml beaker with vigorous stirring. The shining crystals of product were separated slowly. After 15 min, crystals were collected by filtration. The solid crystals were washed over the Buchner funnel with water and product was dried and crystallized in boiling water.⁽⁶⁾

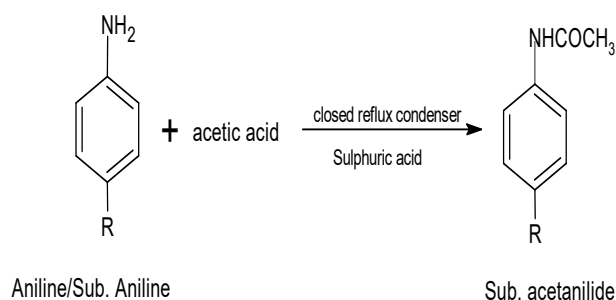
Green component: Minimized waste by-products, avoided use of acetic anhydride.



Mechanism- In green chemistry Acetanilide is prepared from aniline when it reacts with glacial acetic acid instead of acetic anhydride in presence of zinc dust. Zinc dust is used to prevent the oxidation during the chemical reaction.

V. SYNTHESIS OF (I-IV) COMPOUNDS BY GREEN CHEMISTRY METHOD 2:

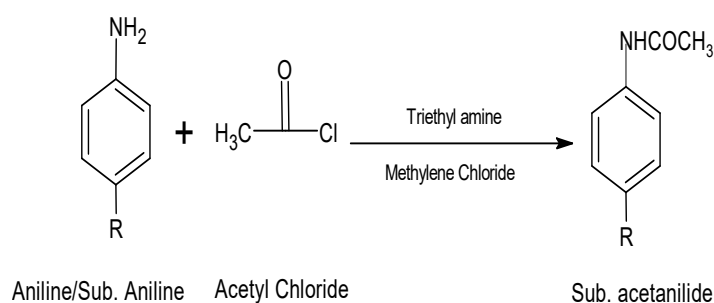
Procedure- Aniline / substituted aniline (40gm), acetic acid (8.4ml), sulphuric acid (0.4ml) (as a catalyst) were mixed to prepare homogeneous slurry by maintaining the room temperature while addition of drop by drop sulfuric acid into the acetic acid and aniline/substituted aniline with continuous stirring. Reflux the mixture over gentle flame using water condenser. Heating was continued for about 1hr., the reaction mixture was then carefully poured in cold water (33ml) in 250ml beaker with vigorous stirring. The shining crystals of product were separated slowly. After 15min, crystals are collected by filtration. The solid crystals were washed over the Buchner funnel with water and product was dried and recrystallized in boiling water.⁽⁷⁾



Mechanism- Sulphuric acid was employed as a heterogeneous catalyst for the acetylation of amines under solvent free condition at room Temperature. Deactivated substrates also acetylated rapidly, and the method showed the preferential selectivity for acetylation of amino group in the presence of hydroxyl group in which no C-acylation was observed.

VI. SYNTHESIS OF (I-IV) COMPOUNDS BY GREEN CHEMISTRY METHOD 3:

Procedure- Weigh accurately about aniline(3.23ml), acetyl chloride(3.26ml), triethyl amine(3.31ml), methylene chloride(59ml) and mixed all reagents in 250 ml beaker at 0-5 °C. Stir the mixture for sufficient time and then maintain reaction at room temperature for 2-4hrs using magnetic stirrer. Crystals are obtained after 4hrs. The shining crystals of product were separated slowly. After 15 min, crystals were collected by filtration. The solid crystals were washed over the Buchner funnel with water and product was dried and crystallized in boiling water.⁽⁸⁾



Mechanism- The nucleophilic substitution of aromatic amines with acid chloride results in the formation of N-substituted amides. The reaction of aniline with acetyl chloride is carried out in alkaline medium. This reaction is popularly called Schotten-Baumann reaction. Mechanism includes attack of aniline on carbonyl carbon of acetyl chloride then loss of proton and finally removal of HCL that leads to formation of acetanilide.

VII. RESULTS AND DISCUSSION

Four acetanilide derivatives (I-IV) were synthesized by conventional method and by three different green chemistry methods. The synthesized products were recrystallized and melting point was taken which are compatible with the reported melting points. The percent yield obtained by green chemistry methods was found to be more than that of conventional method. All the compounds were characterized by FTIR which confirmed the formation of respective compounds and this shows the presence of aromatic ring (3055-3122 cm⁻¹), amine group (3275-3481 cm⁻¹), amide (1631-1676 cm⁻¹). The atom economy was calculated on basis of the molecular weight of desired product and the molecular weight of all the products. From this calculation, it was seen that the atom economy is more in case of green chemistry methods than by the conventional method of synthesis. The found values signify the utility of green synthesis methods in which atom economy was obtained in an excellent amount. Green chemistry method 1 is found to be somewhat superior form Green chemistry methods 2 and 3 w.r.t. percentage yield of product and atom economy. The detail results are tabulated as shown.

Comp No.	Compound	R	Conventional Method		Green Chemistry Methods						
			% yield	M.P. (°C)	Method 1		Method 2		Method 3		FTIR (cm ⁻¹)
					% yield	M.P. (°C)	% yield	M.P. (°C)	% yield	M.P. (°C)	
I	Acetanilide	-H	55.66	114-116	79.78	112-114	70.77	111-113	71.42	112-114	Aromatic-3053 NH-3270 Amide-1679 Methyl-1452
II	4-acetamido toluene	-CH ₃	76.67	148-149	82.22	145-147	80.04	146-148	79.09	145-147	Aromatic-3128 NH-3294 Amide-1665 Methyl-1453 Methyl-1401
III	P-Nitro acetanilide	-NO ₂	64.76	215-216	72.09	210-212	66.70	216	64.01	210-212	Aromatic-3052 NH-3477 Amide-1628 Methyl-1442 Nitro-1395
IV	P-chloro acetanilide	-Cl	59.67	179-181	76.00	182-183	59.71	180	61.72	182-183	Aromatic-3061 NH-3305 Amide-1666 Methyl-1370 Chloro-706

Comp No.	Compound	Atom Economy (In %)			
		Conventional Method	Green Chemistry Methods		
			Method 1	Method 2	Method 3
I	Acetanilide	42.74	69.92	63.17	66.52
II	4-acetamido toluene	44.36	71.29	66.34	70.34
III	P-Nitro acetanilide	45.87	75.00	70.32	71.25
IV	P-chloro acetanilide	47.29	73.34	71.43	70.65

VIII. CONCLUSION

The aim of this research is to focus on green synthesis methods by the design of highly effective, environment friendly synthetic practices / procedures to provide lifesaving medicines and to quicken lead optimization processes in drug discovery while minimizing environmental degradation. Here the attempt is made for optimizing synthetic techniques and increasing product yield along with atom economy. Green chemistry is growing at a very fast pace and can be useful to the eco-friendly advantages of the synthetic alternatives based on unconventional methods like microwave or ultrasound irradiation or the usage of eco-friendly solvents like water, etc., are becoming progressively popular. Thus there is a need to modify the conventional procedures into green chemistry methods and these processes are to be taught to the chemistry students at their undergraduate levels. By learning these principles, students will develop the potential to assess the reaction conditions of a conventional reaction by focusing on solvents and reagents first, Identify harmful materials or inefficient procedures, modify the process and evaluate the efficacy of the new procedure. Moreover, experiments setup according to green chemistry protocol can be easily conducted on laboratory level i.e. it will reduce reliance on fume hoods and will improve the student's perception towards synthetic chemistry.

IX. ACKNOWLEDGEMENT:

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X. CONFLICTS OF INTEREST:

The authors declare that there is no conflict of interest.

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