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# Formulation of Alternatives to Interchanged amines using a water based compounds

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***Abstract -*** ***The solvents used in chemistry are a fundamental element of the environmental performance of processes in corporate and academic laboratories. Their influence on costs, health safety, and nature cannot be neglected. Quantitatively, solvents are the most abundant constituents of chemical transformations; therefore, acting on solvents and replacing standard solvents with safer products can have a great ecological impact. However, not all green solvents are suitable for the wide scope of organic chemistry reactions. With this inspiration in our mind, in the present paper we developed a sustainable catalytic system using water as catalyst towards the synthesis of substituted aromatic aminals. The present methodology is fast, easy and eco friendly thereby following the sustainable principles of green chemistry. In this paper we developed sustainable method for eco-friendly synthesis of diverse substituted aminals in the absence of catalyst/reagents/additives/inert atmosphere under solvent free conditions. The present protocol is beneficial because of proficient synthetic layout, wide substrate scope with good to excellent yields, good E-factor of 0.20 and high reaction mass efficiency of 83%.***

***Keywords -*** ***Organic Chemistry Reactions , Environmental Performance , Substituted Aromatic Aminals , Catalyst/reagents/additives/inert atmosphere***

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## INTRODUCTION

Synthetically important moieties such as iminium salts (pyridinium salts), α -amino phosphonates, geometric analogues of α-amino acids, functionalized amines via the Barbier and Reformatsky-type reaction, dihydrocoumarins, monoacylaminals, α -aryl glycine derivatives, etc. are all derived from amines. A number of apes and monkeys, for example, have been found to inhibit prostate cancer and prevent the spread of microorganisms by mimicking biocide prototypes. Figure 1.1 shows how aminals can be used as a synthon to precisely create various structurally significant moieties.

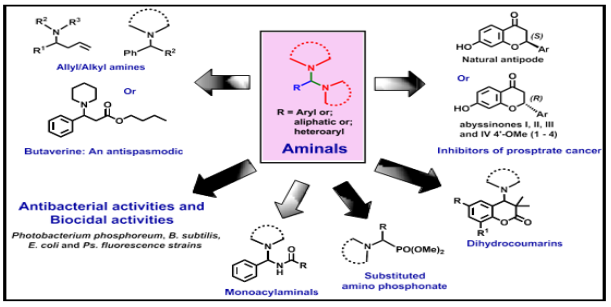
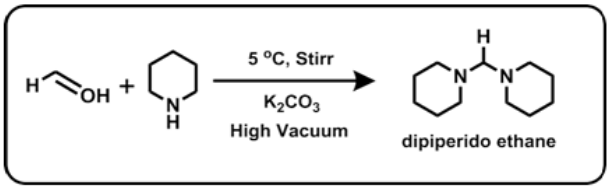



**Figure 1: Schematic representation, applications of aminals in organic synthesis.**

Due to its increased and various usages, such as dimethylaminomethylation in enolates, enolsilylethers, and acidic ketones, aminals have recently been reported as a synthon for the synthesis of eschenmoser and other iminium salts. Furthermore, -amino phosphonates, structural counterparts of the corresponding α -amino acids, are another important class of chemicals displaying a broad spectrum of biological activity. Dihydrocoumarins, a favoured scaffold with therapeutic biological properties including aldose reductase, antioxidant, immunomodulatory, and

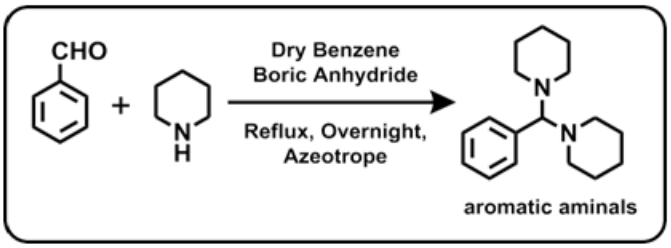
antitrypanosomal activity, etc., may be synthesised using aminols as a synthon.

**ALTERNATIVE AMINALS: GENERAL INFORMATION**



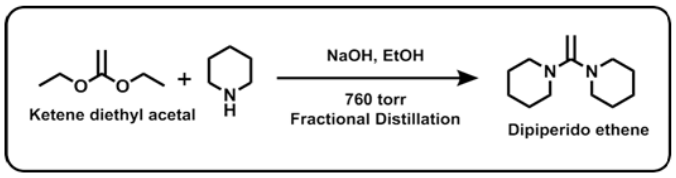

**Scheme 1.1 : Synthesis of aminals**

Subsequently in 1955, Stewart. et. al. reported the synthesis of aromatic aminals under azeotropical water removal with 83-98% yield or by utilising a dehydrating agent such boric anhydride with an isolated yield of 64-92%. (Scheme 1.2).



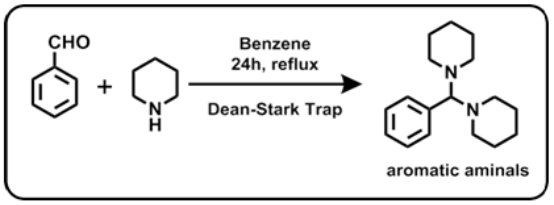

**Scheme 1.2: Synthesis of aminals**

After that, in 1960, Bohme et al. published the synthesis of aminals from the aliphatic aldehydes under basic conditions using fractional distillation as illustrated in Scheme 1.3.




**Scheme 1.3: Synthesis of aminals**

Another synthesis technique for the preparation of aminals was validated by Xu et al. in 2000. They refluxed benzaldehyde and piperidine in benzene for 24 hours using a Dean-Stark trap, and the yield was 72%. (Scheme 1.4).




**Scheme 1.4: Preparation of aminals**

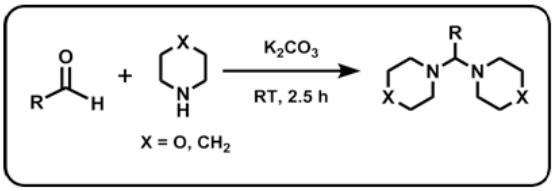
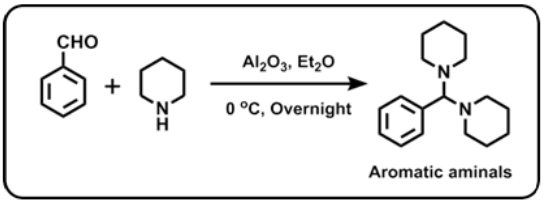
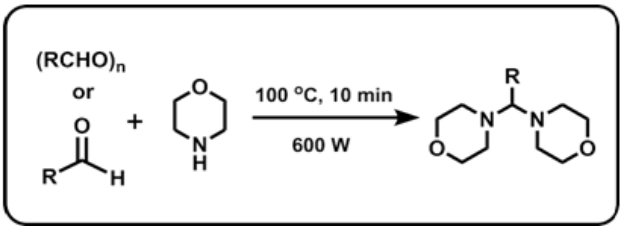



**Figure 2: Synthesis of aminals**

As an alternative method, Hatano et al. (2008) showed that by using a suspension of aldehyde, dried chromatographic alumina in ether, and secondary amine, and then stirring the reaction mixture overnight while maintaining a low temperature, they were able to produce respective aminals in moderate yields (Scheme 1.5).




**Scheme 1.5: Preparation of animals**




**Scheme 1.6: Microwave assisted synthesis of aminals**

However, the reported catalytic systems have significant drawbacks that prevent their widespread use in industrial settings, including the creation of surplus waste, the need for additional additives, the use of toxic organic solvents, increased temperature and reaction time, and the implementation of microwaves. Table 1.1 compares the generic synthetic route maps for the synthesis of substituted aminals, providing a convenient overview of the synthesis of aminals as a whole.

**Table 1.1: Comparative study for the synthesis of aminals**

| S.No. | Reaction condition(s) | Additives | Solvent | Yield of 4aa (%) | Year[ref] |
|---|---|---|---|---|---|
| 1 | Reflux, 12 h | *Ptsa* | Toluene | 64 | *J. Organomet Chem.* **2004**[24] |
| 2 | Microwave, 50 °C, 20 mins | 4A Activated MS | - | ~95 | *Tetrahedron* **2014**[14] *ACS Med. Chem. Lett.* **2010**,[5] |
| 3 | 120 °C, 23h | - | Benzene | ~98 | *Tetrahedron Lett.* **2010**[2] |
| 4 | 12 h, RT, only in case of dialdehydes | - | - | 85-95 | *Chem. Ber.* **1963**[25] |
| 5 | 50 °C, 2 h | Boric anhydride | Benzene | 84 | *Europeon Patent* **1988**[26] |
| 6 | 0 °C, 4h | - | Chloroform | 45-55 | *J. Org. Chem.* **1989**[3] |
| 7 | 0 °C | DMF | EtOH | | *Synth. Commun.* **1995**[27] |
| 8 | 600 W Microwave, 100 °C, 10 min | - | - | 65-98 | *Green Chem.* **2010**[5] |
| 9 | **30 mins, 37µL water** | - | - | **>95** | **Present case** |

Therefore, it is still difficult for chemists to create a simple catalytic system for the synthesis of aromatic aminals despite the importance of this synthon.

## CURRENT INVESTIGATION

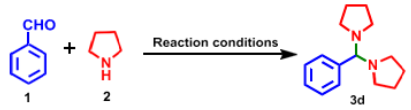
Keeping this motivation in mind, we have devised a sustainable catalytic system for the synthesis of substituted aromatic aminals using water as the catalyst in the current chapter. Following the sustainable principles of green chemistry, the current approach is quick, simple, and environmentally beneficial.

## DISCUSSION AND RESULTS

### Substituted amino acid synthesis in the presence of water

At first, copper triflate and copper oxide nanoparticles (CuO NPs) were used to catalyse a room-temperature, water-based model reaction between benzaldehyde (1) and pyrrolidine (2), as shown in table 1.2 (Entries 1 – 2). In 30 minutes, a 100% conversion to the target aminal (3d) was seen (Entries 1 – 2, Table 1.2). It was intriguing to learn that pure CuO NPs allow for a 100% conversion to product 3d at room temperature (Entry 3, Table 1.2). Surprisingly, in only 30 minutes, under catalyst-free conditions and using water as a solvent, product 3d was formed at room temperature with 95% conversion (entry 4, Table 1.2). This finding suggests that water may be catalysing this process; we conducted control experiments to verify this hypothesis. Catalytic amounts of CuO NPs (5mg) and $H_2O$ (37L for 1 mmol scale) were used in the reaction, and 100% conversion was achieved (entry 5, Table 1.2).

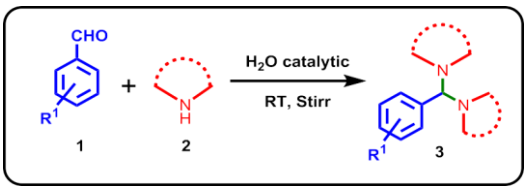
**Table 1.2: Optimization study for the synthesis of substituted aminals (3d)[a]**



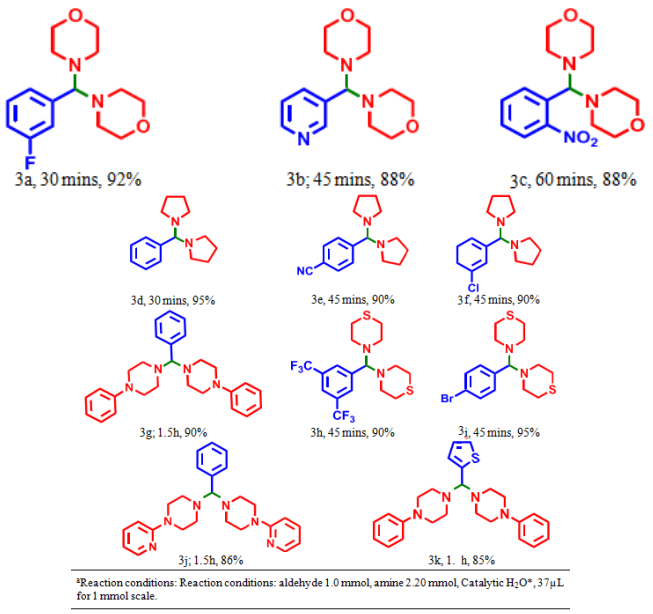

| Entry | Catalyst (mg) | Solvent | Temp(°C) | Time(mins) | Conversion of3d(%)[b] |
|---|---|---|---|---|---|
| 1 | Copper triflate (5.0) | $H_2O$ | RT | 30 | 100 |
| 2 | CuO NPs (5.0) | $H_2O$ | RT | 30 | 100 |
| 3 | CuO NPs (5.0) | Neat | RT | 30 | 100 |
| 4 | No catalyst | $H_2O$ | RT | 30 | 95 |
| 5 | CuO NPs (5mg), $H_2O^b$ | - | RT | 30 | 100 |
| **6** | **$H_2O^b$** | - | **RT** | **30** | **95** |

[a]Reaction conditions: Reaction conditions: aldehyde (**1**) 1.0 mmol, pyrrolidine (**2**) 2.20 mmol, 3.0 mL water. [b] Catalytic $H_2O$*, 37µL for 1 mmol scale.

After conducting the reaction in the presence of a catalytic amount of $H_2O$ (37 L for 1 mmol scale) solely, we were shocked to find that the linked product 3d was generated in 95% yield, shedding light on the involvement of CuO NPs in the reaction (Entry 6, Table 1.2). In addition, when compared to the methods described in the literature, the proposed catalytic system displayed considerable improvements across a wide range of reaction parameters (Entry 6, Table 1.2 and Entries 1 – 9, Table 1.1). 5,6,14,17-23 Following the identification of optimum reaction processes, a variety of substituted aminals were produced by reacting different substrates such amines (2) and aldehydes (1), as depicted in scheme 4b.3. Subsequently, we tested a variety of aromatic aldehydes and found that electron-withdrawing substituents (4- CN, 3-F, 4-Br, 3,5-CF3, 3-Cl, etc.) were well tolerated, with isolated yields of the desired products ranging from 82% to 95%.




**Scheme 1.7: Water catalyzed synthesis of substituted aminals derivatives**




Herein is laid forth the chemistry profile of 3h. The 1H NMR spectrum (Figure1.2) of compound 3h showed the signature tetrahydric -CH proton as a singlet at 3.89 ppm. Specifically, the protons in thiomorpholine showed as multiplets between δ2.73 and 2.57 ppm. All three protons showed up as singlets at δ 7.80 and δ7.60 ppm, which is in line with the phenyl ring's aromaticity. As can be seen in figure 3.3, 13C analysis also validated the structure of compound 3h. At 27.49 ppm, the tetrasubstituted carbon aliphatic peak in the aminal nucleus was seen. In addition, the aromatic carbons emerged in the range of δ137.91 to 121.88 ppm, whereas the aliphatic peak corresponding to the thiomorpholine nucleus carbons appeared at 88.20 and 51.14 ppm. In addition, the single crystal data and structure of compound 3h are displayed in figures 1.3 and 1.4, respectively, verifying the expected structural arrangement of the synthesised aminoids.

**Figure 3: $^{1}$H NMR spectrum of compound 3h**

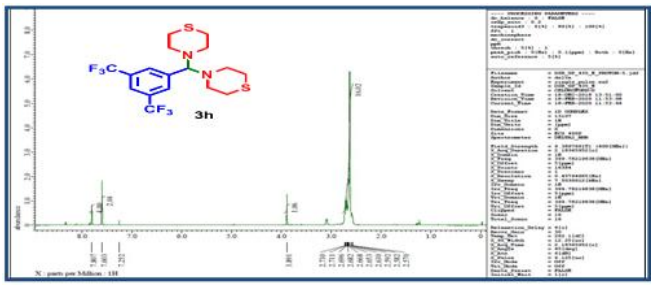



**Figure 4: $^{13}$C NMR spectrum of compound 3h**

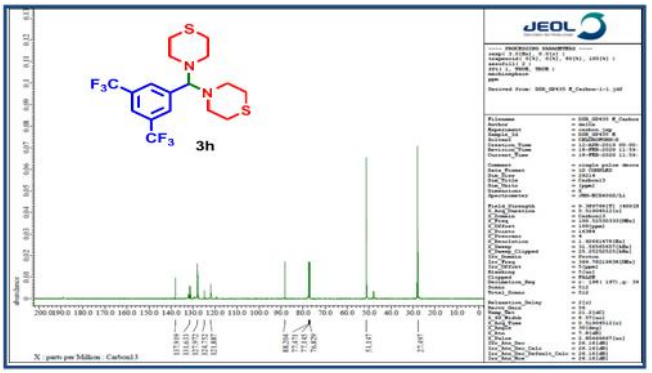



**Figure 5: Single crystal XRD data of compound 3h**

**checkCIF/PLATON report**

Structure factors have been supplied for datablock(s) gpu-35e

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No syntax errors found. CIF dictionary Interpreting this report

**Datablock: gpu-35e**

Bond precision: C-C = 0.0031 A Wavelength=0.71073

Cell: a=8.6240(6) b=9.3138(7) c=14.0859(9)
alpha=106.613(7) beta=90.903(6) gamma=114.341(7)
Temperature: 293 K

| | Calculated | Reported |
|---|---|---|
| Volume | 976.18(14) | 976.18(14) |
| Space group | P -1 | P -1 |
| Hall group | -P 1 | -P 1 |
| Moiety formula | C17 H20 F6 N2 S2 | C17 H20 F6 N2 S2 |
| Sum formula | C17 H20 F6 N2 S2 | C17 H20 F6 N2 S2 |
| Mr | 430.47 | 430.47 |
| Dx,g cm-3 | 1.464 | 1.465 |
| Z | 2 | 2 |
| Mu (mm-1) | 0.332 | 0.332 |
| F000 | 444.0 | 444.0 |
| F000' | 444.78 | |
| h,k,lmax | 11,12,19 | 11,12,19 |
| Nref | 5401 | 4704 |
| Tmin,Tmax | 0.920,0.951 | 0.938,1.000 |
| Tmin' | 0.920 | |

3h

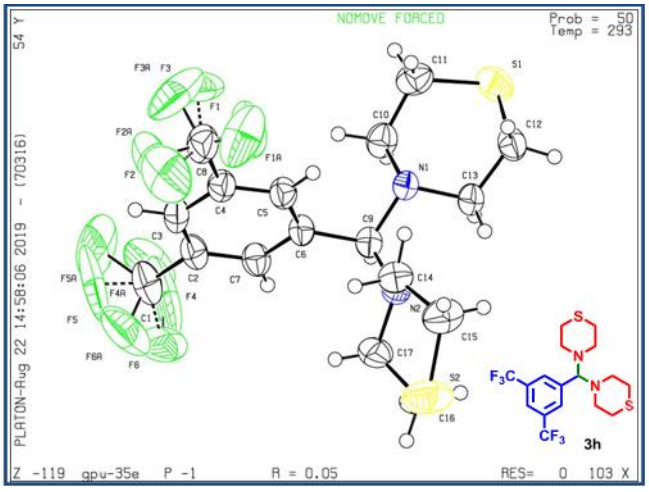
Correction method= # Reported T Limits: Tmin=0.938 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 0.871 Theta(max)= 29.433

R(reflections)= 0.0507( 3367) wR2(reflections)= 0.1122( 4704)

S = 1.032 Npar= 300

**Figure 6: Single crystal XRD structure of compound 3h**




Single crystal X-ray diffraction was then used to identify the structure of compound 3i, as displayed in figures 1.6 and 1.7. The X-ray diffraction intensities

of single crystals of compounds 3h and 3i were measured at 298K with graphite monochromated Mo-Ka radiation (λ = 0.71073Å) using an Oxford CCD diffractometer equipped with the Xcalibur, a sapphire diffraction measurement instrument.

**Figure 7: Single crystal XRD data of compound 3i**

**checkCIF/PLATON report**

Structure factors have been supplied for datablock(s) gp435b

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No syntax errors found. CIF dictionary Interpreting this report

**Datablock: gp435b**

Bond precision: C-C = 0.0054 A Wavelength=0.71073

Cell: a=5.6197(7) b=8.9138(15) c=17.342(3)
alpha=83.545(13) beta=84.578(11) gamma=75.825(13)
Temperature: 293 K

| | Calculated | Reported |
|---|---|---|
| Volume | 834.9(2) | 834.9(2) |
| Space group | P -1 | P -1 |
| Hall group | -P 1 | -P 1 |
| Moiety formula | C15 H21 Br N2 S2 | C15 H21 Br N2 S2 |
| Sum formula | C15 H21 Br N2 S2 | C15 H21 Br N2 S2 |
| Mr | 373.36 | 373.37 |
| Dx,g cm-3 | 1.485 | 1.485 |
| Z | 2 | 2 |
| Mu (mm-1) | 2.704 | 2.704 |
| F000 | 384.0 | 384.0 |
| F000' | 384.02 | |
| h,k,lmax | 7,12,23 | 7,12,23 |
| Nref | 4595 | 3993 |
| Tmin,Tmax | 0.528,0.615 | |
| Tmin' | 0.504 | |

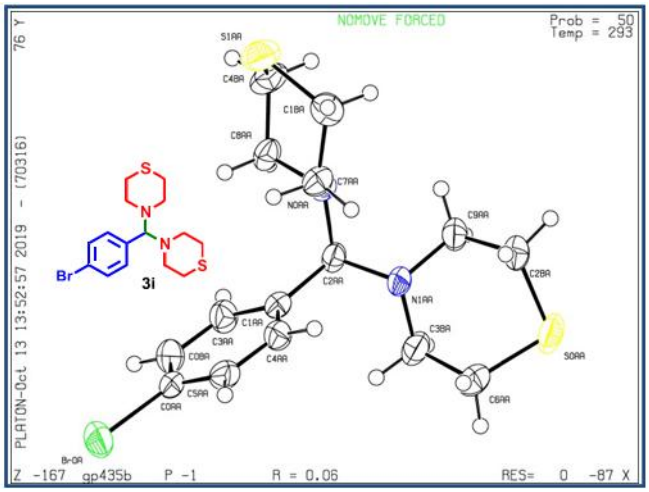

Correction method= Not given

Data completeness= 0.869 Theta(max)= 29.358

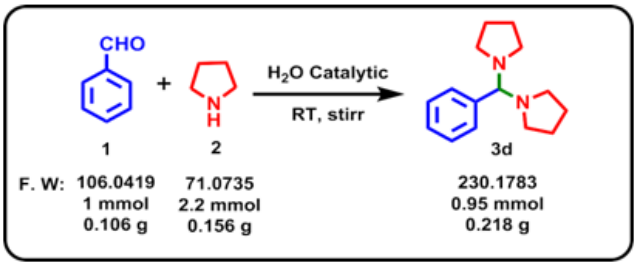
R(reflections)= 0.0635( 2736) wR2(reflections)= 0.1708( 3993)

S = 1.058 Npar= 181

**Figure 8: Single crystal XRD structure of compound 3i**




**Model reaction**




**E factor**

**E-factor = [total mass of raw materials minus the total mass of product] / mass of productE-factor for 3d = [0.106 g (1) + 0.156 g (2) - 0.218 (3d)] / [0.218 (3d)]**

**E-factor = 0.20**

**Process mass intensity (PMI)**

**PMI = ∑(mass of stoichiometric reactants)/[mass of product]**

**= [0.106 g (1) + 0.156 g (2)] / [0.218 g (3d)]**

**Process mass intensity PMI = 1.20**

**Reaction mass efficiency (RME)**

**RME = mass of product /∑(mass of stoichiometric reactants) × 100**

**= [0.218 g (3d)] / [0.106 g (1) + 0.156 g (2)] × 100**

**Reaction mass efficiency RME = 83 %**

**Atom economy (AE)**

AE = [MW of product] ÷ ∑(MW of stoichiometric reactants) × 100

AE of compound 3d = [230.17 (3d)] ÷ [262.04] × 100

**Atom economy AE = 88 %**

**Carbon efficiency (CE)**

$$CE = \frac{\text{Amount of carbon in product}}{\text{Total carbon present in reactants}} \times 100$$

$$= \frac{(\text{No. of moles of product 3d} \times \text{No. of carbons in product 3d})}{(\text{moles of 1} \times \text{carbon in 1}) + (\text{moles of 2} \times \text{carbon in 2})} \times 100$$

$$= \frac{(0.95 \times 15)}{(1 \times 7 + 2.2 \times 4)} \times 100$$

**Carbon efficiency CE = 90 %**

Note: above reaction was performed under catalyst free and solvent free conditions water is used as a catalyst which is green so the mass of water is excluded

## CONCLUSIONS

In conclusion, we devised a solvent-free, environmentally benign approach for the synthesis of a wide variety of substituted amino acids. With its well-thought-out synthetic arrangement, broad substrate scope, good to exceptional yields, good E-factor of 0.20, and high reaction mass efficiency of 83%, the present approach is advantageous.

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