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Graphical Abstract`

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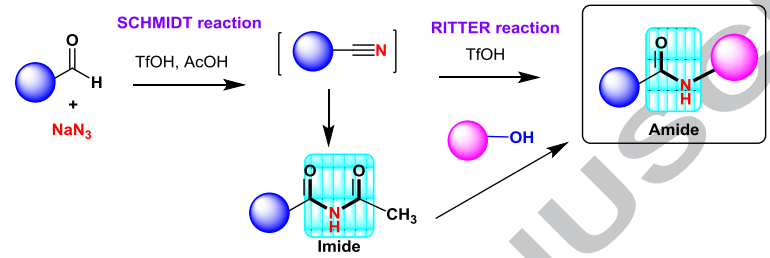

- One-Pot Schmidt-Ritter reaction
- First report of N-acylimides from Schmidt reaction
- Ritter reaction through imide intermediate
- Chromatogarphy free
- Excellent to quantitative Yields
- Large substrate Scope

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TfOH Catalyzed One-Pot Schmidt-Ritter Reaction for the Synthesis of Amides through *N*-acylimides

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ABSTRACT

A one-pot tandem Schmidt-Ritter process for the synthesis of amides has been developed using the super acid as catalyst. The in situ generated aryl /aliphatic nitriles from the reaction of aldehydes and sodium azide in presence of TfOH and AcOH (Schmidt reaction) react with suitable alcohol (Ritter reaction) to give the amides. For the first time we observed that during the Schmidt process N-acylimides were generated along with nitriles, interestingly these *N*-acylimides also participated in the Ritter reaction.

Amide bond is ubiquitous in nature and hence is well studied in organic chemistry.[1-6] Many of the biological active molecules,[2] natural products,[3] pharmaceuticals,[4] agrochemicals[5] and synthetic polymers materials[6] are made up of amide bond. In addition the amide bond is the basis for the key chemical connections of the proteins and peptides.[7] It is present in more than 25% of the marketed drugs, which emphasize the importance of amide bond in the medicinal and pharmaceutical industries.[8] Owing to the importance of the amide bond, several protocols and reagents have been developed.[9] Generally, amides can be obtained from the treatment of amines with acid or acid derivative under suitable conditions (using variety of coupling reagents). Though several other approaches are available for the formation of amide bond, Ritter reaction is the one which uses a completely different protocol.[10,14a] The alcohols which can generate a stable carbocation could react with nitriles to generate the amide bonds (Figure 1, eqn-a). Due to the generality of the Ritter reaction with various alcohols and nitriles several catalytic conditions have been developed to improve the reaction conditions.[10] Later on a cascade Prins-Ritter[11] reaction has been developed which involves a three component synthesis of alcohol, nitrile and aldehyde to access the Pyran containing amide molecules (Figure 1, eqn-b). A Sakurai-Prins-Ritter[12] cascade is also developed which uses the in situ generated alcohol (from aldehyde and allyltrimethyl silane) to react with nitriles to furnish the Pyran containing amides (Figure 1, eqn-c). Very recently Bhaishya Bhaishya and co-workers reported a sequential Schmidt-Ritter[13] reaction for the synthesis of amides from a three component reaction of aldehydes, sodium azide and alcohols (Figure 1, eqn-d). In this reaction in situ generated nitrile is reacted with alcohols to furnish the amides. To the best of our knowledge this is the only report available for the synthesis of amides using a Schmidt-Ritter sequence reaction.[13] Nevertheless the reaction could not bear the more choice of alcohols and aliphatic aldehydes. Previously, we have developed a microwave assisted Ca (II) catalyzed green synthesis of amides through Ritter reaction,[14a] in continuation of our research aimed towards the synthesis of biologically active small molecules[14] through a catalytic process here in we report a TfOH mediated sequential Schmidt-Ritter reaction for the general synthesis of amides and imides.

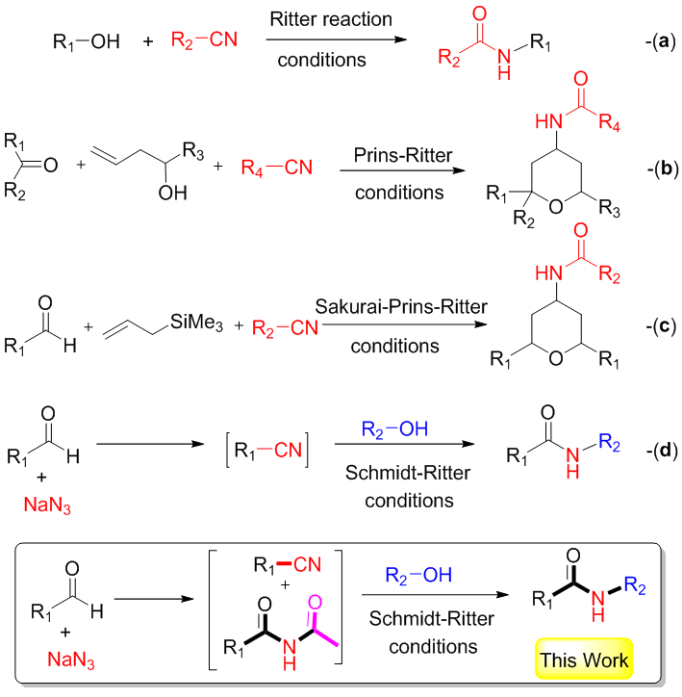

Figure 1 Ritter & Sequential Ritter reactions

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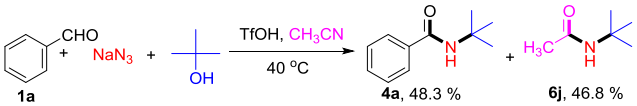
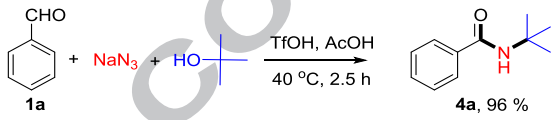
Recently Rokade *et al.*[15] reported Schmidt reaction of aryl aldehydes with NaN_3 in presence of TfOH in acetonitrile to access the nitriles instantly in high yields. Nevertheless for a sequential Schmidt-Ritter reaction acetonitrile cannot be a suitable solvent due to the probability of the competitive Ritter reaction of alcohols with acetonitrile (solvent) and the aryl nitrile which is in situ generated. This was practically experienced when the reaction was performed with benzaldehyde (**1a**) & NaN_3 with TfOH in acetonitrile, it furnished the amide **4a** (with Schmidt nitrile) & **6j** (with acetonitrile) in 48.3% & 46.8% respectively. Hence the modification for the Schmidt reaction conditions is required to avoid the competitive Ritter reaction.



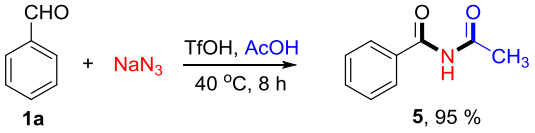
Scheme 1. Competitive Schmidt-Ritter reaction

Initiation of our exploration to modify Schmidt conditions commenced by subjecting benzaldehyde (**1a,** 1 mmol**),** NaN_3 (**2,** 1.5 mmol) in AcOH (0.2 mL, as solvent)[13] catalyzed by TfOH (3 mmol) at rt and the reaction was completed in 12 h. To minimize the reaction time, the reaction was performed at 40 °C and we were glad to note the formation of benzonitrile (85%) within 1.2 h alongwith the N-acylimide (**5**) in 12%. Interestingly when the same reaction was left for 8 h, we observed the complete formation of N-acylimide (**5**, 95%). We further decided to minimize the catalyst loading to 2 mmol and found no change in the reaction time and yield. When 1 mmol of the catalyst was used the reaction completed in 2.5 h. In the absence of solvent (AcOH) the reaction could furnish the traces of the nitrile. We also tried to replace the TfOH by other Bronsted acid (PTSA) and a metal catalyst ($Ca(OTf)_2$) and found that they could not promote the reaction. So, we concluded that for the Schmidt reaction the use of 2 mmol TfOH in AcOH is the ideal condition and decided to extend this for the sequential Schmidt-Ritter reaction. *t*-BuOH (2 mmol) was added to the above set conditions and found that after 6 h the reaction yielded 96% of N-^{t}Butyl benzamide (**4a**). To accelarate the rate of Ritter reaction, we added additional 1 mmol of TfOH along with *t*-BuOH (2 mmol) in the second step and observed the formation of amide **4a** in 3 h (96%). Looking at the advantage of using TfOH in the second step, we felt this as the optimum condition for the One-Pot sequential Schmidt-Ritter reaction[16] (Scheme 2).



Scheme 2. Optimum Conditions for One-Pot Sequential Schmidt-Ritter reaction.

As we observed that Schimdt reaction furnished N-acylimide **5** in 95% yield after 8 h (Scheme 3), a literature survey indicated that generally, N-acylimides were synthesised from a nitrile and acetic anhydride in the presence of a suitable catalyst. [17]However, to the best of our knowledge there is no report available for their synthesis starting from aldehydes. Therefore, for the first time we are reporting the N-acyliimide synthesis under Schmidt reaction conditions (Scheme 3).



Scheme 3. Synthesis of N-acylimides in Schmidt reaction

Fortunately, these acylimides also took part in the Ritter reaction to furnish the desired amide as the sole product. To authenticate this, the isolated N-acylimide **5** was treated with different alcohols under the Ritter conditions (Figure 2). Cyclohexanol reacted with **5** to yield the amide **4q** in 96% yield after 3 h. An acyclic 2°-alcohol (sec-butanol) gave the amide **4e** in 93% yield. Tertiary butanol gave the t-butylamide **4a** in 95%. Benzhydrol gave the corresponding amide **4t** in 89% yield after 4 h.

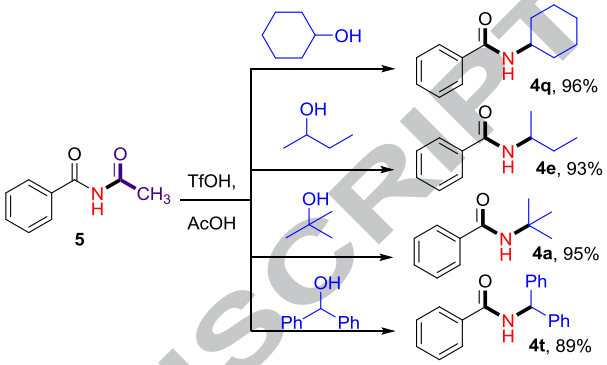
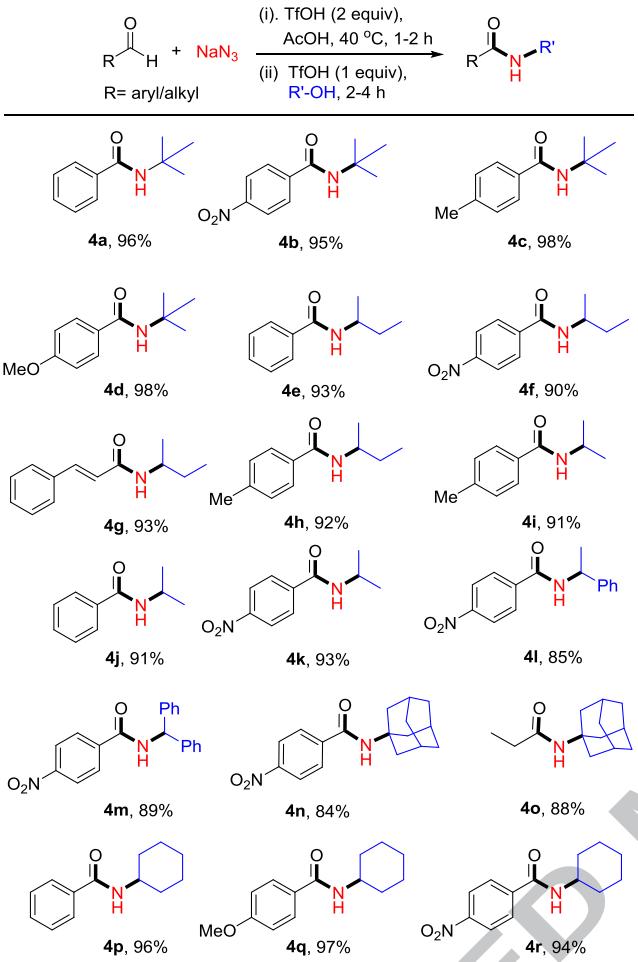


Figure 2. Synthesis of N-alkyl amides from N-acylimides with alcohols. Conditions: for the compounds **4q**, **4e** and **4t** the reaction temperature was 90 °C and 4a was at 40 °C

Having established reaction conditions, we further explored the substrate scope of our methodology by using various aryl/alkyl aldehyde, alcohols & *t*-BuOAc. 4-nitro benzaldehyde (electron withdrawing substitution) gave the *t*-butylamide **4b** in 95% yield. Other benzaldehydes with electron donating groups (-Me, -OMe) gave the corresponding amides **4c** and **4d** in 98% yields. Probably the reaction was not affected by the electronic factors on the benzene ring. In the similar way, sec-butanol reacted with aryl aldehydes and yielded the amides **4e-4h** in excellent yields (Table 1). Interestingly, cinnamaldehyde also reacted with the same rate to yield the amide **4g** in 93% yield. Another acyclic secondary alcohol, 2-propanol gave the amides **4i, 4j, 4k** in 91, 91 & 93% yields. The benzylic alcohols such as 1-phenylethan-1-ol and diphenylmethanol furnished amides **4l** and **4m** in 85, 89% yields with 4-nitro benzaldehyde (Table 1). In case of adamantyl alcohol 4-nitro benzaldehyde gave the amide **4n** in 84% yield, In addition it also reacted with the aliphatic nitrile generated from the propioanaldehyde yielded the amides **4o, 4p** in 88, 86%. Finally, cyclohexanol was treated with simple benzaldehyde, anisaldehyde (electron donating) and 4-nitro benzaldehyde (electron withdrawing) to furnish the amides **4q, 4r** and **4s** in 96, 97 & 94% yields respectively.

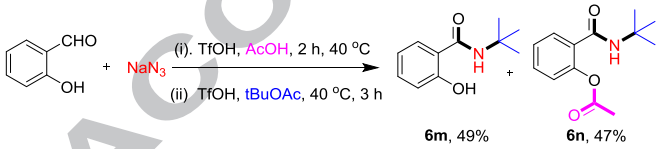
The scope of the various aldehydes in the One-Pot Schmidt-Ritter reaction was also studied with *t*-butyl acetate as the carbocation source (Table 2). Benzaldehydes with both the electron donating groups (methyl, methoxy, N,N-dimethyl) and electron withdawing groups (nitro, methyl ester) on the para position gave the excellent yields with t-BuOAc (Table 2, first row). Para-halogenated benzaldehydes (F, Cl, Br) reacted in the similar way to yield the amides **6c-6e** in excellent yields (second row). Heteroaromatic aldehyde, 2-furfural gave **6f** in 94%. Cinnamaldehyde gave **6g** in 96% yield. 4-ethynylbenzaldehyde gave the amide **6h** with t-BuOAc in 95% yield. An interesting observation was made when isophthalaldehyde was treated with excess of *t*-BuOAc, both the aldehydes were functionalized to the respective bisamide **6i** in 96% yield. Finally, aliphatic aldehydes such as acetaldehyde, propionaldehyde and isovaleraldehyde also gave the respective amides **6j, 6k** and **6l** in good yields.

Table 1. Substrate scope of aldehydes and alcohols in the TfOH catalyzed One-Pot Schmidt-Ritter reaction.



Conditions: for the synthesis of compounds **4a-4d** , the second step (Ritter) was carried out at 40 °C and for the rest of the compounds **4e-4r** it was at 90 °C; Yields after filtration.

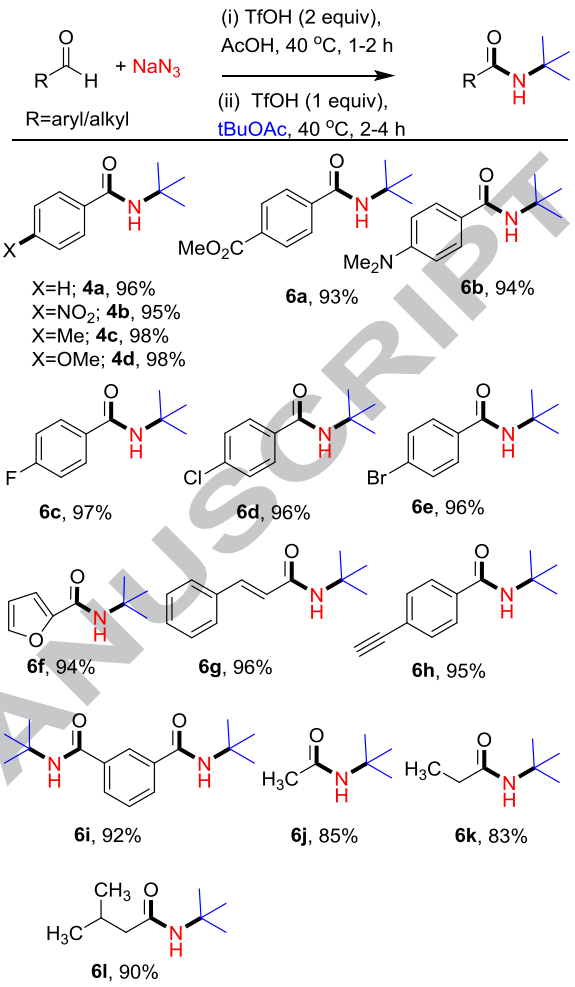
In case of salicylaldehyde with *t*-BuOAc, the reaction resulted into the mixture of amides **6m** and **6n** (O-acyl) in 49% and 47% respectively (isolated yields by column chromatography). Probably the phenolic –OH is being acylated under the reaction conditions through a in situ generated acetic anhydride (Scheme 4).



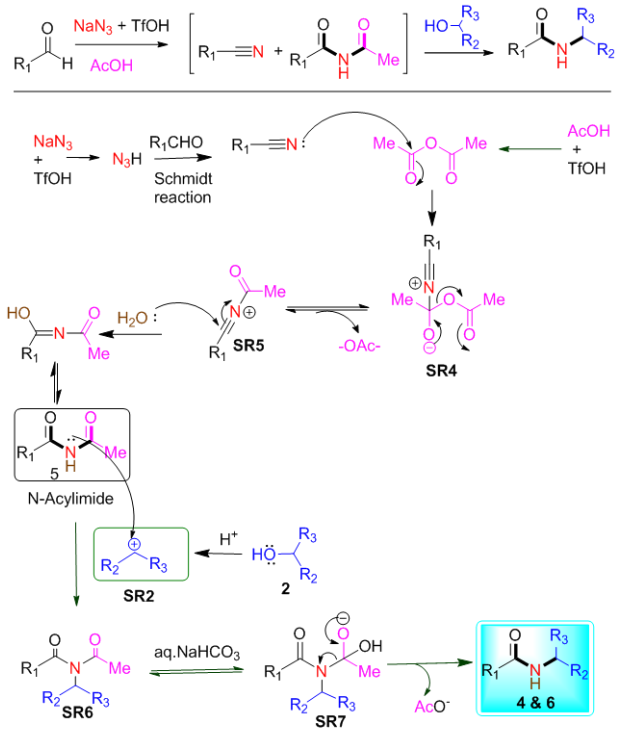
Scheme 4. Schmidt-Ritter reaction of salicylaldehyde

Based on the experiments performed, we outlined a plausible mechanistic pathway for the sequential one-pot Schmidt-Ritter reaction (Scheme 5). Initially, NaN_3 produce hydrazoic acid with TfOH/AcOH which further undergoes Schmidt reaction with aldehydes to form the nitrile (SR1). In the next step alcohol (2) forms a stable carbocation with triflic acid, which further reacts with the in situ generated nitrile to form the amides **4/6** (Ritter reaction). Alternatively, this in situ generated nitrile (SR1) undergo a nucleophilic addition with the acetic anhydride (which formed from AcOH and TfOH) to yield the intermediate **SR5.** Hydrolysis of **SR5** forms the N-acylimide **5.** Further TfOH promotes the N-alkylation of imide **5** with alcohol (2) to give **SR6**. Finally the base hydrolysis of **SR6** leads to the formation of amide **4/6.**

Table 2. Substrate scope of aldehydes with t-BuOAC in the TfOH catalyzed One-Pot Schmidt-Ritter reaction.



Reaction was carried out at 40 °C and the yields are reported after simple filtration.



Scheme 5. Plausible mechanism for the TfOH catalyzed One-Pot Schmidt-Ritter reaction through aldehyde → {nitrile →imide} → amide

In summary, we have developed a facile method for the sequential one-pot Schmidt-Ritter reaction from the easily available aldehydes, sodium azide and alcohols with TfOH. For the first time we developed a new method for the synthesis of N-acylimides through Schmidt reaction and proved that this imides are also the intermediates in the Ritter reaction to form the amides. This method ensures the wide substrate scope with excellent yields and the products were isolated by simple filtration.

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20. *General experimental procedure for the synthesis Amides 4:* To a magnetically stirred solution of benzaldehyde (1 mmol) and NaN_3 (1.5 mmol) in AcOH (0.2 mL), TfOH (2 mmol) was added and the reaction mixture was heated at 40 ^{o}C for 1-2 h. On the complete conversion of aldehyde (monitored by TLC), alcohol (1 mmol) was added along with TfOH (1 mmol). The reaction was continued to heating at 90 ^{o}C (in the case of t-butanol the reaction temperature was 40 ^{o}C) for another 3-5 h. After the completion, the reaction was cooled to 0 ^{o}C and saturated aq. $NaHCO_3$ was added slowly. The precipitate formed was filtered and washed with plenty of cold water and dried to obtain the desired secondary benzamide as white solid in 98% yield. (Compounds obtained were pure hence, no further purification or recrystallisation was required). *N*-(tert-butyl)benzamide (**4a**).[10a,19] White solid; MP: 132-134 ^{o}C; Yield: 96%; IR (KBr): 3334, 2980, 2933, 1634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75-7.74 (d, *J* = 7 Hz, 2H), 7.51-7.48 (m, 1H); 7.45-7.42 (m, 2H), 5.98 (s, 1H), 105 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.9, 135.9, 131.1, 128.4, 126.7, 51.6, 28.8 ppm; HRMS: calcd. for $[M+H]^+$ $C_{11}H_{15}NO$: 177.1153, found: 177.1155. *General procedure for the syntheses of N-(tert-butyl)amides (**6**).* To a magnetically stirred solution of aldehyde (1 mmol) and NaN_3 (1.5 mmol) in AcOH (0.2 mL), TfOH (1 mmol) was added and the reaction mixture was heated at 40 ^{o}C for 1-2 hrs. On the complete conversion of aldehyde (monitored by TLC) tert-butyl acetate was added alongwith TfOH (1 mmol).The reaction was continued to heating at 40 ^{o}C for another 3-5 hrs. After the completion, the reaction was brought to room temperature and ice-cooled aq. sat. $NaHCO_3$ was added to the reaction mixture. The precipitate formed was filtered and washed with plenty of cold water and dried to obtain the desired benzamide as white solid in 96% yield. (Compounds obtained were pure hence, no further purification or recrystallisation was required). *Methyl 4-(tert-butylcarbamoyl)benzoate* (***6a***).[10a,19] Yellow solid; MP: 128-130 ^{o}C; Yield: 93%; IR (KBr): ν 3415, 3051, 2952, 1638, 1564 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.1 (d, *J* = 8.5 Hz, 2H), 7.79 (d, *J* = 8.5 Hz, 2H), 6.01 (s, 1H), 3.96 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3, 166.0, 139.8, 132.5, 129.8, 126.8, 52.4, 51.9, 28.8 ppm; HRMS: calcd. for $[M+H]^+$ $C_{13}H_{17}NO_3$: 235.1208 , found: 235.1210. *General procedure for the syntheses of N-acylimides* **(5):** To a magnetically stirred solution of benzaldehyde (1 mmol), NaN_3 (1.5 mmol) and AcOH (0.2 mL), TfOH (1 mmol) was added and the reaction mixture was heated at 40 ^{o}C for 8-10 hrs. On completion (monitored by TLC) reaction was brought to 0 ^{o}C and sat. solution of $NaHCO_3$ was added to the resultant reaction mixture and the precipitate formed was filtered and dried to obtain desired N-acetylbenzamide in 95% yield. *N-acetylbenzamide* **(5).**[17a] White solid; MP: 110-112 ^{o}C; Yield: 95%; IR

(KBr): ν 3270, 3120, 2991, 1738, 1550, 1240 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.59 (s, 1H), 7.94 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 2.61 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.4, 166.1, 133.2, 132.6, 128.9, 128, 25.8 ppm;IR (KBr): ν 3270, 3120, 2991, 1738, 1550, 1240 cm^{-1}; HRMS: calcd. for $[M+H]^+$ $C_9H_9NO_2$: 163.0633, found: 163.0635.

HIGHLIGHTS

- ✓ TfOH catalyzed sequential Schmidt-Ritter reaction is described from easily available aldehydes, sodium azide and alcohols
- ✓ A new method was discovered for the formation of N-acylimide through Schmidt process
- ✓ First report of Schmidt-Ritter reaction through N-acylimide intermediates
- ✓ Chromatography-free isolation (simple filtration).
- ✓ This synthetic protocol endures the key features like step-economy, large substrate scope & high yields