TRIPHENYL PHOSPHINE-N-BROMOSUCCINAMIDE(TPP-NBS) MEDIATED RAPID ONE-POT DIRECT SYNTHESIS OF N-ACYLALKYLENAMINES FROM CARBOXYLIC ACID UNDER MILD CONDITION

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ABSTRACT

A series of N-acylalkyleneamines were obtained by the reaction of carboxylic acid and triphenyl phosphine under mild condition. Short reaction time, excellent product yield and mild reaction conditions are important features of the present methodology.

Keywords: *one-pot strategy, carboxylic acid, N-acylalkyleneamines , TPP-NBS reagent.*

INTRODUCTION

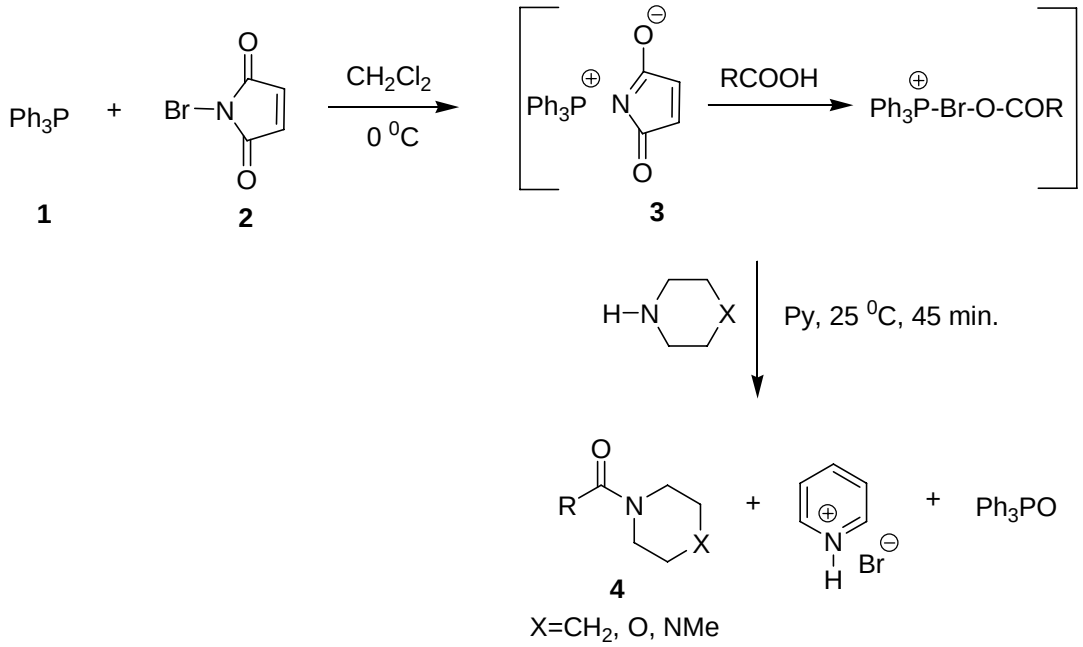
The amide functionality is one of the most widely occurring functionality in many important natural products and man made compounds.[1,2] The formation of amides can be accomplished by using coupling reagents from carboxylic acid and amines.[3] In case of substrates having steric hindrance or low reactivity, amidation can carried out using coupling reagent.[4] But use of coupling reagents caused epimerization.[3,5] Many methods have been used for the synthesis of amides from acid chlorides and amines.[6] In addition, the introduction of morpholine and piperazine moety into aromatic compound is particularly importance in the field of medicinal chemistry[7] including analgesic[8] and antihistaminic.[9]

The method involving the conversion of ester to amide is somewhat limited because it requires either drastic conditions[10] or use of some special reagents.[11-13] Which may interfere with other functional groups present in the molecules. Milder catalysts such as 2-pyridone[14] and boron trifluoride have been used; hitherto, generality of these reactions has not been satisfactorily examined. Another methods using activated amines such as a tin[15], titanium[16] and aluminium[17] has been addressed. However no practical technique is available for the synthesis of tertiary amides.

Due to the expensive and sufficiently selective reagents for the functional group transformation under mild conditions are valuable in organic synthesis since they permit operations that are ether impossible or depend on cumbersome and time consuming protection and deprotection procedures. Therefore, the present methodology is predicted for the direct and rapid synthesis of tertiary amides.

EXPERIMENTAL

All chemicals were of analytical grade. The melting points were determined on the open capillary tube and were uncorrected. The IR spectra were recorded on Bomen FT-IR MB-104 Spectrophotometer with zinc selenide optics ^{1}NMR were recorded on Brucker AC-300 MHz in $CDCl_3$ using TMS as an internal standard.



Scheme-1:Synthesis of N-acylalkyenemines from Carboxylic acid with TPP-NBS reagent.

General procedure for the synthesis of N-acylalyeneamines at 25^{0}C:

A mixture of caroboxylic acid(5 mmole) and triphenyl phosphine(5mmole) in dichloromethane(10ml) was cooled 0-5 ^{0}C. NBS(5mmole) was added in fou lots and the reaction mixture was stirred for 30 mins. Reaction was all to warm to room temperature. A mixture of amine(**Table 1**) and pyridine(5 mmoles)was added to reaction mixture. After completion of reaction(TLC), the solvent was removed under reduced pressure. The product was extracted with n-pentane(2X10ml) and washed with water(20ml). The resultant TPP oxide is insoluble in n-pentane and can be separated by simple filtration furnished corresponding N-acylalkylenamine in good to excellent yield after removal of solvent under reduced pressure.

N-(4-nitrobenzoyl)-morpholine(4a) Yield= 92% IR (KBr disc): 3101.8, 2971, 1629.8, 1517, 1156.2 cm^{-1} ; ^{1}HNMR ($CDCl_3$, 300MHz) δ = 3.3-4.2(m, 8H), 7.7(d,2H), 8.3(d,2H).

N,N-Dethylbenzamide(4k) IR(KBr disc) 3031, 2950, 1647, 1447, 1230, 805 cm-1; ^{1}HNMR ($CDCl_3$, 300 MHz) δ= 7.34-7.39(m, 5H), 3.6(br s, 1H), 3.43(s, 2H), 1.20(s, 3H),1.9(s, 3H).

N-Benzoylglycine ester(4n) Yield= 70%; IR(KBr disc) 3239, 3190, 2958, 1757, 1670, 1544, 1248 cm-1; ^{1}HNMR ($CDCl_3$, 300 MHz) δ= 7.82-7.60(m, 5H), 5.9(br s, 1H), 4.48(q, 2H), 4.33(d, 2H),1.25(t, 3H)

Morpholino-3-phenylprop-2-en-1-one(4p) Yield= 91% IR (KBr disc) :2952.5, 2849.2, 1018.5, 1717 cm^{-1} ; 1HNMR ($CDCl_3$, 300MHz) δ = 3.5-3.9(m, 8H), 7.2-7.4(m, 5H), 6.8(d,1H, J= 16Hz), 7.6(d, 1H, J= 16 Hz).

RESULT AND DISCUSSION

The applications of triphenyl phosphine(TPP) with N-bromosuccinamides(NBS) in organic synthesis is well documented in leterature[18]. In this communication, we have reported the use TPP in combination with NBS for the rapid synthesis of amides directly from carboxylic acid. In this process carboxylic acid was first activated with TPP and NBS furnish intermediate **3**, which was further reacted with morpholine or piperidine to afford N-acylalkylenamines under mild reaction condition. Results were summarized in the **Table 1.1.**

The purity of the product was checked by IR and ^{1}HNMR spectroscopical technique. In IR (KBr disc) spectrum of N-cinnamoylmorpholine (**4p**) the band at 3400-3500 due to –OH(acidic) is not observed. Compound shows characteristic signals at 2952.5 and 2849.2 cm^{-1} for C-H stretching, 1752 cm^{-1} for carbonyl group of amide. The ^{1}HNMR ($CDCl_3$, 300MHz) of the same compound show δ= 6.8 doublet and 7.6 doublet with J= 16Hz for trans protons.δ = 3.5-3.9 multiplet for eight protons due to $–N-(CH_2)_2$ and $–O-(CH_2)_2$. Encouraged by these results, we have tried the same methodology for the alcohols, thiols and phenols (**entry 4l, 4o, 4q, 4r and 4s**); ester and thiolester isolated phenols, thiols respectively was very low(**10-25%**). However alcohol did not undergo amidation teaction even after 48hrs. Therefore the present methodology was found to be supperior for amidation of alihatic as well as aromatic amines. In addition, aliphatic diamine afforded diamidation products(**entry 4m**).

In comparison with to other methods our method is superior because the carboxylic acid group can be converted to amide moiety in one pot strategy at room temperature without converting to an acyl bromide , mixed anhydrides, ethyl methyl esters.

CONCLUSION

In conclusion, we have optimized the reaction conditions used in the literature and first time developed a new methodology for synthesis of amides directly from acid activation by situ generated TPP-NBS reagent. The methodology is found to be general and high yielding over reported methods.

ACKNOWLEDGEMENT

The authors are thankful to BCUD, Pune University, Principal of Padmashri Vikhe Patil College, Pravaranagar (M.S.) for providing laboratory facilities and Dr. J. N. Nigal for constant encouragement.

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Table-1:Direct one-pot synthesis of N-acylalkyenemines from Carboxylic acid under mild condition.

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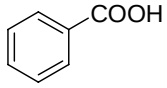
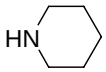
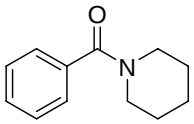
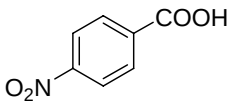
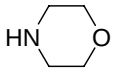
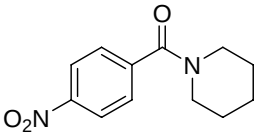
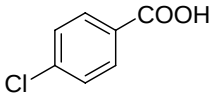
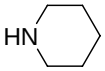
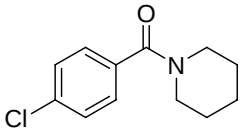
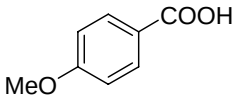
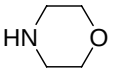
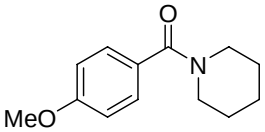
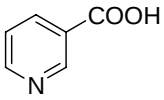
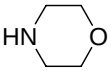
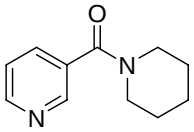
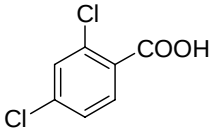
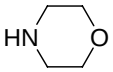
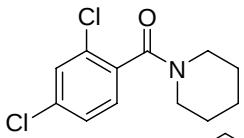
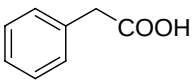
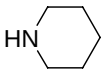
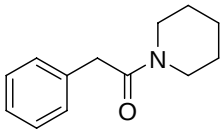
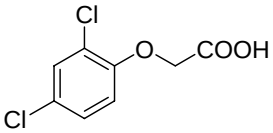
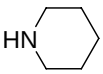
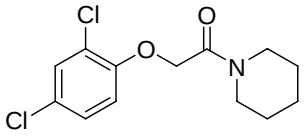
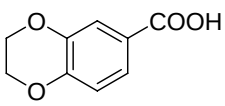
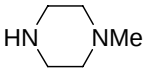
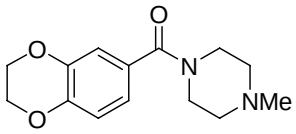
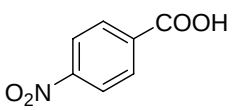
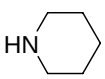
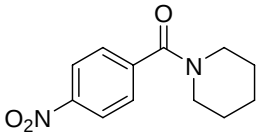
4a				87
4b				92
4c				79
4d				88
4e				86
4f				84
4g				62
4h				90
4i				89
4j				75

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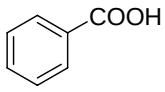
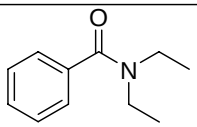
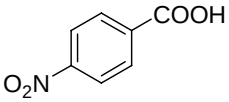
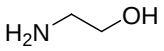
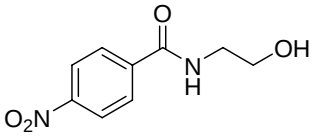
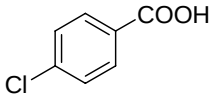
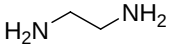
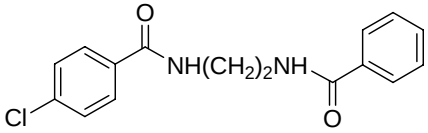
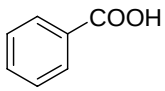
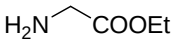
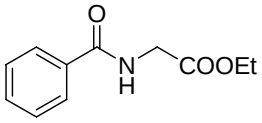
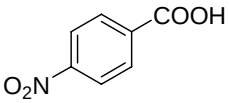
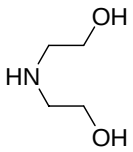
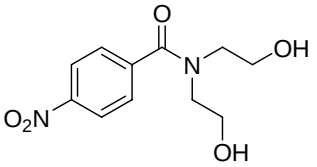
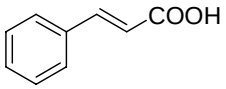
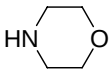
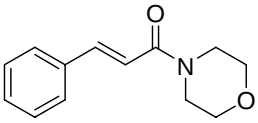
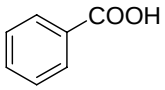
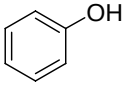
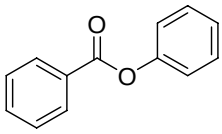
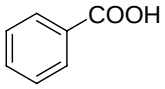
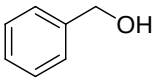
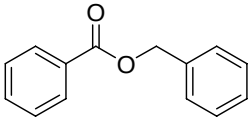
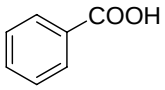
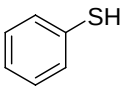
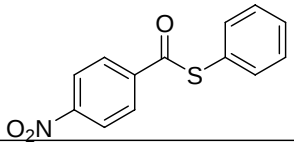
4k				66
4l				98
4m				70
4n				76
4o				80
4p				91
4q				Trace
4r				Trace
4s				Trace

[a] Yield of pure isolated products. [b] All products were characterized by IR, ^{1}H NMR and comparison with authentic samples.

(Received: 12 April 2008 Accepted: 25 April 2008 RJC-178)