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Chloroformate Free, Scalable Approach for the Synthesis of Organic Carbamates and Their Alkylation

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Abstract: A convenient method for the synthesis of organic carbamates of 2-aminopyridine without using hazardous chloroformate reagent is developed. This alternate approach for the synthesis of organic carbamates and their alkylation to 2-alkylaminopyridines is more practical and economical to be used on large scale. The amazing behavior of 2-aminopyridine helps in forming organic carbamates unlike 3-aminopyridine and 4-aminopyridine.

Keywords: Alkylation, alkyl aminopyridine, 2-aminopyridine, Boc anhydride, carbamates.

INTRODUCTION

Organic carbamates are an important class of compounds having wide applications in pharmaceuticals and agrochemical industry. They are generally used for the protection of amino groups to form structurally diverse intermediates of biological importance. The recent past of carbamates has seen keen interest from pharmaceutical industry for the development of drugs and prodrugs. This interest regarding carbamates has led to the development of recent molecules like discodermolide [1], geldanamycin [2], cephalosporins [3], phytostigmine [4], novobiocin [5], sphingomyelin [6], vancomycin [7], rifampicin [8], rhazinilam [9], maytansine [10], calcheamycin [11], cyclosporine [12], linezolid [13], telithromycin [14] etc. Besides the above mentioned molecules, carbamates have also been reported in improving the activity profile of the parent molecules making them more potent.

The classical methods for the preparation of carbamates include the Hoffmann rearrangement, Curtius rearrangement and Lossen rearrangement reactions. There are several other methods to synthesize carbamates like with the help of phosgene, by reductive carbonylation of aromatic nitro compounds, by the oxidative carbonylation of amines, by using metal/non-metal carbonates/bicarbonates and by using carbon dioxide [15]. Although, there are several reported methods for the synthesis of the carbamates, still there is scope to improve the existing procedures. The existing procedures are hindered due to limitations like long duration of reaction, insignificant yield, and handling of toxic and hazardous chemicals, requirement of special type of reactors and skilled persons to handle these reactions. Due to our interest and in house use to develop efficient, safe and economical method on commercial scale we herein report the synthesis of 2-alkylamino pyridines from the carbamates.

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RESULT AND DISCUSSION

The past decade has seen use of 2-alkylamino pyridines in a wide class of biologically active compounds. The alkyl amino pyridines are used for treating diseases and pathological conditions involving inflammation [16]. The alkyl amino pyridines are involved in the reduction of prochiral ketones [17, 18]. The literature reveals a number of methods for alkylation of amine [19-22], using different methods like by direct alkylation, or by protection of amine followed by alkylation and hydrolysis or by amination of cuprates with N-alkyl hydroxyl amine [23]. All of them could synthesize the alkyl amino pyridines, but they are associated with difficulty of handling of reagents, unwanted side reactions and tedious purification procedures hampering its use for large scale synthesis. The direct alkylation is mostly associated with additional alkylation as the secondary amine formed by first alkylation is more reactive than the primary amine, reducing the yield of mono alkylated product. Unreacted starting material and dialkylated amine as side product are the major impurities of such process which are always difficult to remove. The other method for alkylation is the protection and de-protection; it is time consuming requiring use of hazardous reagents and extra procedure for purification.

Synthesis of carbamates and carbonates is well reported in the literature [15-25]. Although synthesis of carbamates is listed widely in the literature, an organic chemist always gets attracted to invent more and more convenient method for the synthesis. For this various catalysts, solvents, bases were successfully tested. In the recent past, Lowary T. L. and group [24] reported the most convenient synthesis of alkylaminopyridines. It involved alkylation of *N*-formyl 2-aminopyridine followed by hydrolysis, but it required a difficult distillation of *N*-formyl derivative. Alternative method involved the protection of the amine with Boc anhydride in *tert*-butanol [25], then alkylating it in the presence of sodium hydride followed by deprotection of Boc group. According to the reported method, the method was claimed as conven-

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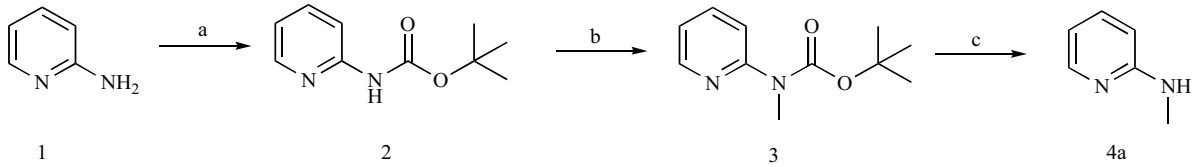
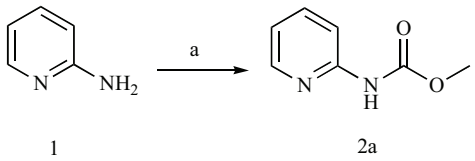


Scheme 1. (a) Boc anhydride, *t*-butanol (b) MeI, NaH, THF (c) H^+.

ient and most suitable for the synthesis of alkylamino pyridine. The reported method is illustrated in Scheme **1**.

The literatures [15, 26-28] revealed use of *t*- butanol and chloroformate for the synthesis of carbamates and sodium hydride for their alkylation. In our efforts to develop a safe and robust method for the synthesis of carbamates on a large scale, we needed to avoid these reagents as each one of them has its own limitation. The use of *t*-butanol as a solvent at low temperature is always troublesome and has limited applications as a solvent due to its lower freezing point (~25°C). The chloroformates are widely used for the protection of amine in the form of carbamates. But being toxic and difficult to handle the use of chloroformates always remained the second choice for the organic chemist. Sodium hydride as we all know requires special techniques to handle, slightest of mishandling might led to a major accident. These factors propelled us to synthesize the reaction in other solvent and use of Boc anhydride for protection of amine Scheme **2**.

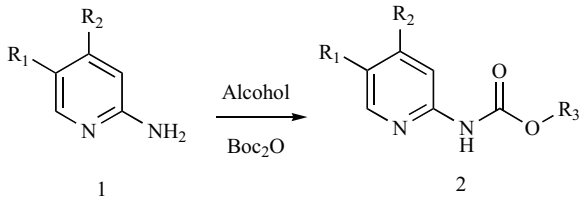


(a) Boc anhydride, MeOH, 99%

Scheme 2. Formation of carbamates using methanol as solvent.

The reaction was first carried out using 2-aminopyridine, Boc anhydride and methanol as a solvent and corresponding Boc derivative was being expecting. But to our surprise we obtained methyl carbamate (Scheme **2**, comp 2a) in 99% yield which was quite high as compared to Boc derivatives reported in literature [15] (70% yield). The formation of methyl carbamate is obviously because of transesterification. As we confirmed the formation of methyl carbamate using methanol and Boc anhydride, we assumed this to be more convenient and high yield approach to make such carbamates without need to handle toxic reagents. To evaluate the robustness of this method we employed solvents like methanol, ethanol and propanol, butanol (Scheme **3**) results of which confirmed the formation of corresponding carbamates in very good yield. The process was found to be operationally very simple as with only partial concentration of the solvent, product precipitated out which was collected by simple filtration in high yield and purity.

Similarly to prepare more organic carbamates we decided to use 4-aminopyridine and 3-aminopyridine instead of using 2-aminopyridine as starting material. The isolated products from the reaction of 4-aminopyridine and 3-aminopyridine with Boc anhydride in methanol were corresponding *tert*-



2a R_1=R_2=H; R_3 = Me
2b R_1=R_2=H; R_3 = Et
2c R_1=R_2=H; R_3 = *i*-Pr
2d R_1=R_2=H; R_3 = n-Bu
2e R_1=R_2=H; R_3 = n-Pr
2f R_1=R_2=H; R_3 = *i*-Bu
2g R_1=Br; R_2=H; R_3 = Me
2h R_1=H; R_2=Me; R_3 = Me

Scheme 3. Formation of carbamates by using various alcohols.

butyl carbamates rather than methyl carbamates. The possible reason for the formation of such product could be attributed to the position of the amine group. In the case of 2-aminopyridine the position of amino group in 2nd place plays a key role, the formation of an intermediate **5** (Fig. **1**) is easily possible which could open with the abundantly available solvents to form corresponding carbamate.

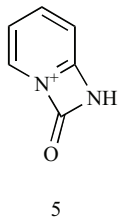
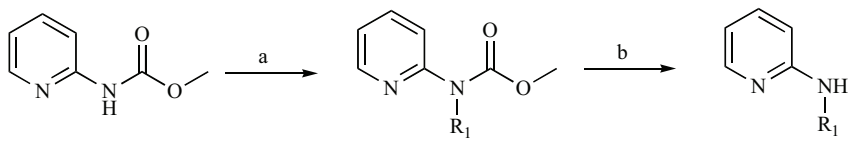


Fig. (1). Cyclic intermediate of 2-aminopyridine.

This indicates the importance of position of amino group while forming trans esterification products (**2a-2h**). The position of amino group in 4-amino pyridine and 3-aminopyridine is far away for the formation of this cyclic intermediate, hence they tend to form the normal Boc derivatives.

The last aim of our synthesis was to develop an alternative to sodium hydride which has handling issues. For this purpose we firstly investigated the use of potassium carbonate as a base for alkylation, the isolated product was found to be of moderate yield (50%). Alternatively we used potassium tert-butoxide as base for alkylation of **2a** in tetrahydrofuran. The potassium *tert*-butoxide was found to be effective as product was obtained in more than 97% yield. The obtained product was then hydrolyzed in 10% NaOH and the crude was purified either by distillation or recrystallization. Scheme **4**.



2a 3a 4a

3a; R_1= CH_3 4a; R_1= CH_3

3b; R_1= Et 4b; R_1= Et

3c; R_1= Bn 4c; R_1= Bn

(a) Alkyl halides, Potassium-.*tert*-butoxide, THF (**b)** 10% NaOH, MeOH.

Scheme 4. Alkylation of carbamates.

CONCLUSION

To summarize we hereby report the astonishing behavior of 2-aminopyridine unlike 3-aminopyridine and 4-aminopyridine. Taking this advantage we developed an efficient, economical and scalable route for the synthesis of 2-alkylamino pyridines (**4**) through carbamates (**2**) without using chloroformates, *t*-butanol and sodium hydride. The process is scalable, operationally simple; the use of hazardous reagents is avoided. Water workup and further purification of carbamates are not required making it ideal to explore it on large scale as well as environment friendly by reducing the effluent.

EXPERIMENTAL SECTION

General: Tetrahydrofuran used for alkylation was dried over sodium and the reactions were carried out under nitrogen. For rest of the reactions, commercial grade solvents were used. All reactions were monitored by TLC (silica-coated plates) and visualized under UV light. TLC was performed on Merck 60 F-254 silica gel plates. Yields refer to isolated yields. High-resolution mass spectra were obtained by using QTOF mass spectrometer (QTOF Premier, Waters, USA), using ESI method. ^{1}H NMR spectra were recorded on a 300 MHz Bruker spectrometer and are ^{13}C NMR spectra were recorded on a 50 MHz Bruker spectrometer are reported as parts per million (ppm) downfield from a tetramethylsilane as internal standard. Chemical shifts are reported relative to TMS as an internal standard.

Materials. 2-aminopyridine, Methyl iodide, Ethyl iodide, Benzyl bromide, Boc anhydride, potassium *tert*-butoxide, were commercially available and used without any further purification.

General Procedure for Preparation of Carbamates (2): All the reactions were carried out on 10mmol scale. 2-Aminopyridine was dissolved in appropriate alcohol (3 times) and cooled to 0^{o}C. To this solution Boc anhydride (1.2Eq) was added and reaction mixture was allowed to cool to room temperature. Reaction mixture was stirred at the same temperature for 4hr. Half volume of the alcohol was removed on rotavapor. Solid separated was collected by filtration.

Methyl pyridin-2-ylcarbamate (2a). white solid, mp 129-131^{o}C, 98% yield, ^{1}H NMR ($CDCl_3$) δ= 3.82 (s, 3 H), 6.99-7.01 (m, 1 H), 7.67-7.72 (m, 1 H,), 7.99-8.02 (d, 1 H, *J* = 8.43 Hz), 8.29-8.31 (d, 1 H, *J* = 3.96 Hz), 8.87 (br, s, 1H); ^{13}C NMR ($CDCl_3$) 52.18, 112.53, 118.31, 138.58, 147.45, 152.68, 154.23.

Ethyl pyridin-2-ylcarbamate (2b). white solid, mp 101-103^{o}C, 99% yield, ^{1}H NMR ($CDCl_3$) δ= 1.32-1.37 (t, 3 H, *J* =7.08), 4.23-4.20 (q, 2 H, *J* =7.08), 6.99-7.01 (m, 1 H), 7.67-7.72 (m, 1 H,), 7.99-8.02 (d, 1 H, *J* = 8.43 Hz), 8.29-8.31 (d, 1 H, *J* = 3.96 Hz), 9 (br, s, 1H); ^{13}C NMR ($CDCl_3$) 14.62, 61.20, 112.65, 118.29, 138.41, 138.52, 147.49, 152.75, 153.85.

Isopropyl pyridin-2-ylcarbamate (2c). white solid, mp 75-77^{o}C, 99% yield, ^{1}H NMR ($CDCl_3$) δ= 1.32-1.34 (d, 6 H, *J* = 6.24 Hz), 5.01-5.09 (m, 1 H), 6.95-6.99 (m, 1 H), 7.65-7.77 (m, 1 H,), 8.00-8.02 (d, 1 H, *J* = 8.46 Hz), 8.31-8.8.33 (d, 1 H, *J* = 5.96 Hz), 8.95 (br, s, 1H); ^{13}C NMR ($CDCl_3$) 22.15, 68.85, 112.52, 118.34, 138.39, 147.63, 152.49, 154.27.

n-butyl pyridin-2-ylcarbamate (2d). white solid, mp 60-63^{o}C, 99% yield, ^{1}H NMR ($CDCl_3$) δ= 0.93-0.98 (t, 3 H, *J* = 7.35 Hz), 1.37-1.49 (m, 2 H), 1.65-1.75 (m, 2 H), 4.19-4.23 (m, 2 H), 6.95-6.98 (m, 1 H), 7.66-7.72 (m, 1 H,), 8.01-8.04 (d, 1 H, *J* = 8.43 Hz), 8.32-8.8.34 (d, 1 H, *J* = 4.08 Hz), 9.4 (br, s, 1H); ^{13}C NMR ($CDCl_3$) 13.67, 19.07, 30.79, 65.01, 112.64, 118.11, 138.46, 147.14, 152.88, 153.95.

n-propyl pyridin-2-ylcarbamate (2e). white solid, mp 72-74^{o}C, 99% yield, ^{1}H NMR ($CDCl_3$) δ= 0.96-1.01 (t, 3 H, *J* = 7.38 Hz), 1.55-1.80 (m, 2 H), 4.15-4.19 (t, 3 H, *J* = 6.79 Hz), 6.96-6.99 (m, 1 H), 7.66-7.72 (m, 1 H,), 8.01-8.04 (d, 1 H, *J* = 8.46 Hz), 8.33-8.8.34 (dd, 1 H, *J* = 4.98 Hz, 1.02 Hz), 9.48 (br, s, 1H); ^{13}C NMR ($CDCl_3$) 10.39, 22.39, 66.83, 112.72, 118.19, 138.53, 147.45, 125.99, 154.03.

***i*-butyl pyridin-2-ylcarbamate (2f).** white solid, mp 67-69^{o}C, 98% yield, ^{1}H NMR ($CDCl_3$) δ= 0.96-0.98 (d, 6 H, *J* = 6.72 Hz), 1.97-2.06 (m, 1 H), 3.98-4.00 (d, 2 H, *J* = 6.72 Hz), 6.96-6.99 (m, 1 H), 7.66-7.72 (m, 1 H,), 8.00-8.03 (d, 1 H, *J* = 8.46 Hz), 8.32-8.8.34 (dd, 1 H, *J* = 4.98 Hz, 1.02 Hz), 9.28 (br, s, 1H); ^{13}C NMR ($CDCl_3$) 19.06, 27.99, 71.30, 112.71, 118.10, 138.44, 147.38, 152.90, 153.96.

Methyl 5-bromopyridin-2-ylcarbamate (2g). white solid, mp 188-191^{o}C, 97% yield, 1H NMR (DMSO-d_6) 3.34 (s, 3 H), 7.80-7.83 (d, 1 H, *J* = 8.94 Hz), 7.96-8.00 (dd, 1 H, *J* = 2.43, 2.47 Hz), 8.37-8.38 (d, 1 H, *J* = 2.16 Hz); ^{13}C

(DMSO-d_6) 52.45, 113.15, 114.34, 141.01, 148.82, 151.71, 154.43.

Methyl 4-methylpyridin-2-ylcarbamate (2h). White solid, mp 131-132°C, 99% yield, ^{1}H NMR ($CDCl_3$) δ= 2.36 (s, 3 H), 3.81 (S, 3 H), 4.76 (br, s, 1 H), 6.81-6.82 (d, 2 H, *J* = 5.01 Hz), 7.86 (S, 3 H), 8.15-8.17 (d, 2 H, *J* = 5.1 Hz), ^{13}C NMR ($CDCl_3$) 21.24, 52.19, 113.01, 119.68, 147.13, 150.01, 152.65, 154.36.

General Procedure for Alkylation (3). To a suspension of 2 in THF (10 times) and potassium *tert*-butoxide (1.2Eq), alkyl halide was added drop wise at 0°C and reaction mixture was allowed to cool to room temperature. Reaction mixture was then stirred at the same temperature for 12hr. It was cooled to 0°C and quenched by water (5 times). Product was extracted into ethyl acetate. Concentration of organic layer offered the crude product which was used directly for next reaction.

Methyl methylpyridin-2-ylcarbamate (3a). Yellow liquid, 99% yield, ^{1}H NMR ($CDCl_3$) δ= 3.45 (s, 3 H), 3.80 (s, 3 H), 7.01-7.05 (m, 1 H), 7.62-7.71 (m, 2 H), 8.38-8.40 (d, 1 H *J* = 4.17 Hz); ^{13}C NMR ($CDCl_3$) 34.24, 53.01, 118.97, 119.67, 137.17, 147.58, 154.83, 155.91.

Methyl ethylpyridin-2-ylcarbamate (3b). Pale yellow liquid, 99% yield, ^{1}H NMR ($CDCl_3$) δ= 1.19-1.23 (t, 3H, J = 7.02 Hz), 3.78- 4.05 (m, 2 H), 7.02-7.26 (m, 1 H), 7.57-7.68 (m, 2 H), 8.39-8.40 (d, 1 H *J* = 3.78 Hz); ^{13}C NMR ($CDCl_3$) 14.09, 42.21, 52.83, 119.90, 119.92, 137.21, 147.86, 154.17, 155.61

Methyl benzylpyridin-2-ylcarbamate (3c). Pale brown liquid, 99.5% yield, ^{1}H NMR ($CDCl_3$) δ= 3.76 (s, 3 H), 5.24 (s, 2 H), 7.01-7.05 (m, 1 H), 7.20-7.21 (m, 5 H), 7.62-7.63 (m, 2 H), 8.38-8.40 (d, 1 H, *J* = 4.53 Hz); ^{13}C NMR ($CDCl_3$) 50.01, 53.06, 119.80, 120.06, 126.95, 127.45, 128.29, 137.32, 138.62, 147.82, 153.95, 155.82.

General Procedure for Hydrolysis (4). 10% of aq. NaOH (8times), methanol (2times) and (3) were refluxed for 3hr. After cooling to room temperature the product was extracted into ethyl acetate. Concentration of organic layer yielded the crude product which was purified by either distillation or recrystallization.

N-methylpyridin-2-amine (4a). Color less liquid, 97% yield**,** ^{1}H NMR ($CDCl_3$) δ= 2.90-2.92 (d, 3 H, *J* = 5.1 Hz), 4.57 (br, s, 1 H), 6.36-6.39 (d, 1 H, *J* = 8.37 Hz), 6.54-6.58 (m, 1 H), 7.39-7.44 (m, 1H), 8.08-8.09 (d, 1 H, *J* = 3.96 Hz), ^{13}C NMR ($CDCl_3$) 28.89, 106.20, 112.40, 137.29, 147.98, 159.73.

N-ethylpyridin-2-amine (4b). Color less liquid, 96% yield, ^{1}H NMR ($CDCl_3$) δ= 1.23-1.27 (t, 3H, *J* = 7.17 Hz), 3.25- 3.34 (m, 2 H), 4.45 (br, s, 1H), 6.35-6.37 (m, 1 H), 7.38-7.43 (m, 1 H), 8.06-8.08 (d, 1 H, *J* = 3.87 Hz), ^{13}C NMR ($CDCl_3$) 14.81, 36.82, 106.33, 112.54, 137.32, 112.54, 137.32, 148.12, 158.92

N-benzylpyridin-2-amine (4c). White solid, mp 88-90°C (methanol), 98% yield, ^{1}H NMR ($CDCl_3$) δ= 4.49-4.51 (d, 2 H, *J* = 5.52 Hz), 4.88 (br, s, 1 H), 6.35-6.38 (d, 1 H, *J* = 8.31 Hz), 6.56-6.60 (m, 1 H), 7.28-7.41 (m, 6 H), 8.09-8.11 (d, 1 H, *J* = 3.75 Hz); ^{13}C NMR ($CDCl_3$) 46.34, 106.79, 113.14, 127.23, 127.41, 128.68, 137.48, 139.23, 148.21, 158.70.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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