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RESEARCH ARTICLE

Synthesis of N-1 Fused Heterocyclic Derivatives Using Potassium Carbonate and PEG-400 as Green Catalyst

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ABSTRACT

Indole, benzimidazole and its substituted derivatives continue to capture the attention due to its synthetic utility and broad range of pharmacological activities. The N-1-substituted fused heterocyclic compounds are usually biologically active and may be applied as potential therapeutic alternatives to antitumor drugs. The molality of catalyst affects the yield of reaction. The catalyst like anhydrous K_2CO_3 for its N-1 alkylation or arylation of indole-3-carboxaldehyde and 2-acetylbenzimidazole in the presence and absence of phase transfer catalyst such as PEG-400 and TEBAC was observed. The molar ratio 1:4 of anhydrous K_2CO_3 with PEG-400 gives, mild reaction conditions with excellent yields. The ease of synthetic method provides an attractive route to the synthesis of N-1-substituted fused heterocyclic derivatives which may act as biological alternatives.

KEYWORDS

2-acetyl –Benzimidazole, Indole-3-Carboxaldehyde, Green Synthesis, PTC

INTRODUCTION

The fused heterocyclic compounds such as indole, benzimidazole and its substituted derivatives continue to capture the attention due to its synthetic utility and broad range of pharmacological activities.[1-2] The N-substituted fused heterocyclic compounds are usually biologically active and may be used as potential therapeutic alternatives to antitumor drugs. Now a day's 2-acetylbenzimidazole molecule and indole-3-carboxaldehyde are associated with a wide range of biological activities such as anticancer, anti-inflammatory, analgesic and anthelmintic etc[3-4]. However, these syntheses were generally promoted by hard bases and high temperature, which would lead to environmentally hazardous residues and low yield of products. Though the replacement of these conditions with the environmentally mild methodologies is one of the central attraction of green chemistry. The anhydrous potassium carbonate (K_2CO_3) has been widely used as mild base catalyst in many organic synthesis such as N-alkylation/arylation and mono-methylation.[5] The various literature reported that reactions of $K_2CO_3$is showing its essentiality for a particular reaction due to its characteristics like solubility in water, mild base character, easy availability, eco-friendly and nontoxic in nature. Thus potassium carbonate provides a mild basic medium for organic reactions to occur and get removed by water.[6,7]

The subject area deals with the effect of the ratio

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of catalyst used anhydrous K_2CO_3 for its N-1 alkylation or arylation of indole-3-carboxaldehyde and 2-acetylbenzimidazole in the presence and absence of phase transfer catalyst such as PEG-400and TEBAC. Hence, it was our goal to optimise the reaction of N-1 substituted on Indole-3-carboxaldehyde and 2-acetylbenzimidazole in reasonably good output.

MATERIAL AND METHODS

All the laboratory chemicals required for the study were procured from S. D. Fine Chemicals Ltd., Mumbai, India. Melting points of all the synthesized compounds were taken in open glass capillaries on EXPO-HiTech melting point apparatus and were uncorrected. All reactions of indole-3-carboxaldehyde and 2-acetyl-benzimidazole derivatives were monitored by using thin layer chromatography (TLC) using aluminium plates coated with silica gel (Merck) using Chloroform: hexane: ethylacetate (4:4:2) as mobile phase.

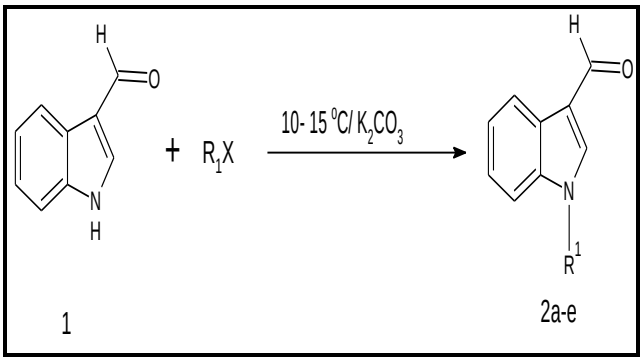
The structures of all the synthesized compounds were characterized from their IR spectra and confirmed from their ^{1}H-NMR spectra. The IR spectra were recorded on Shimadzu FT-IR spectrometer using a KBr pellet method in the range of 4000–650 cm^{-1}. The ^{1}H-NMR spectra were recorded on Varian 400 MHz spectrometer, using TMS as an internal standard and $CDCl_3$ as the solvent.

General Procedure

N-substituted indole-3-carbaldehyde derivatives (Scheme IA)

The equimole of indole-3-carboxaldehyde and the appropriate alkylating reagent in presence of various catalytic ratio of anhydrous K_2CO_3 (as shown in Table 1) along with and without PTC such as TEBAC and PEG-400 in presence of dimethylformamide were stirred at room temperature.

The reaction was monitored by TLC. After completion, the reaction mixture was cooled, to room temperature and poured onto water. The solid obtained was filtered off, washed with water, dried and recrystallized from ethanol.



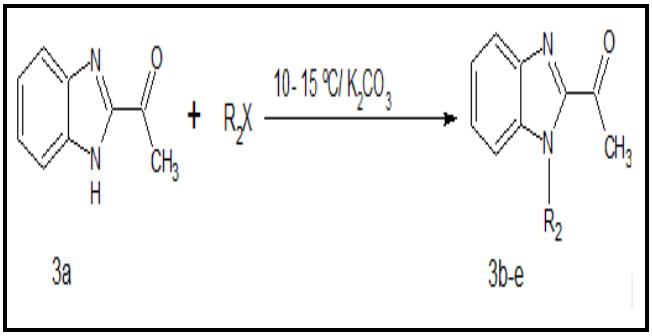
Scheme IA: Synthesis of N1- Derivatives of Indole-3-carbaldehyde

Table 1: Name of alkylating agents

Sr. No.	Substituent (R_1X)
1	Bromo Ethyl
2	Chloro Benzyl
3	2-Cl Benzyl chloride
4	Allyl chloride
5	Dimethyl sulphate
6	1-Bromo-2-methyl-propane

Synthesis of N1-Derivatives of 2-acetyl-benzimidazole (Scheme IB)

The 2- acetyl-benzimidazole was treated with alkylating reagents with different ratio of anhydrous K_2CO_3 and with and without PTC such as PEG-400 and TEBAC to produce N1 derivatives of 2-acetylbenzimidazoleas shown in Scheme IB**.**



Scheme IB: Synthesis of N1- Derivatives of 2-acetyl-benzimidazole

Table 2: Name of alkylating agents

Sr. No.	Substituent (R_2X)
1	Bromo Ethyl
2	Chloro Benzyl
3	2-Cl Benzyl chloride
4	Allyl chloride
5	Dimethyl sulphate
6	1-Bromo-2-methyl-propane

RESULTS AND DISCUSSION

The synthesis of N-1 alkylation and arylation of Indole-3-carboxaldehyde and 2-acetyl-benzimidazole of fused heterocyclic rings by using various alkylating/ arylating agents as shown in (Table 1 & 2) was performed at 10-15ºC in the absence of PTC or by using different PTC such as TEBAC and PEG-400 and different ratio of anhydrous K_2CO_3 (as shown in Scheme IA and IB).Our goal was to synthesis and explore the catalystmole ratio of anhydrous K_2CO_3 by using TEBAC and PEG-400 as a phase transfer catalyst in fused heterocyclic ring. For these, we have selected different ratios of anhydrous K_2CO_3i.e. 1:2, 1:3 and1:4 in presence and absence of Phase transfer catalyst TEBAC and similarly these ratio ofanhydrousK_2CO_3along with PEG-400 and without PEG-400 (as shown in Table 3 and 4).

Optimization of % Yield

The mole ratio of anhydrous K_2CO_3 catalyst increases the percentage yield of N-1 alkyl and aryl derivatives of fused heterocyclic ring.

The graphical representation shows the effects in presence and absence of PEG-400 and TEBAC as phase transfer catalyst on the percentage yield was observed in N-1 substitution of indole-3-carboxaldehyde and N-1 substitution on 2-acetyl-benzimidazole as shown in Figure 1 and Figure 2 respectively. The graphs shows that as ratio of anhydrous $K_2CO_3$is increased the yield of the product also increases.

The percentage yield of product increases with the use of PEG-400 as a PTC.

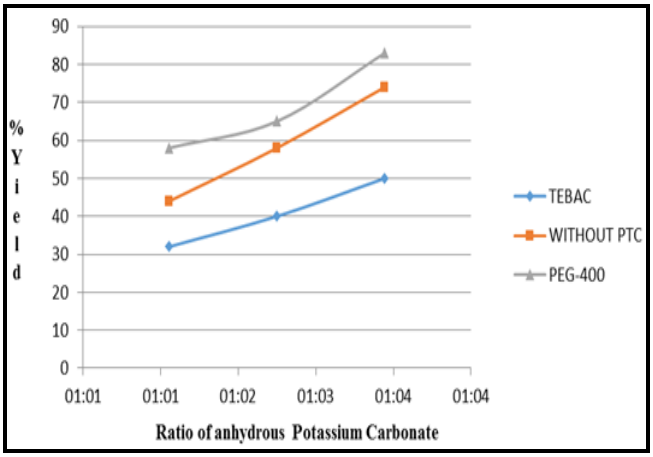


Figure 1: Effect of ratio of K_2CO_3 on % yield of N-1 substituent of Indole-3- carboxaldehyde

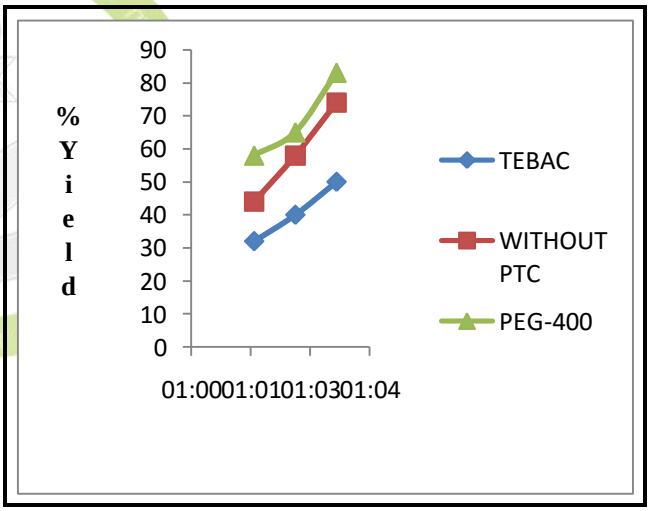


Figure 2: Effect of ratio of K2CO3 on % yield of N-1 substituent of 2-acetyl- benzimidazole

Optimization of Time

The molar ratio of anhydrous K_2CO_3 also have effect on reaction time with and without PTC such as PEG-400 and TEBAC. As the mole ratio of anhydrous K_2CO_3 increases the time required to complete the reaction decreases.

According to graph (Fig.3) less time required to complete the reaction by using mole1:4 ratio of K_2CO_3 along with PEG-400 act as PTC. The result as shown in Table 3 was for indole-3-

carboxaldehyde and Table 4 was for 2- acetyl benzimidazole.

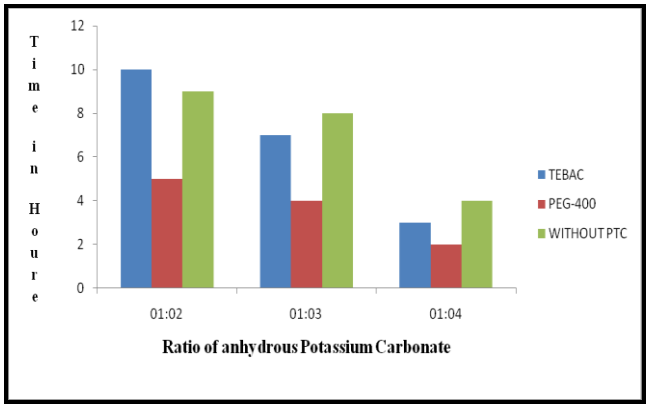


Figure 3: Effect of ratio of K_2CO_3 on reaction time of N-1 substituent of Indole-3-caeboxaldehyde

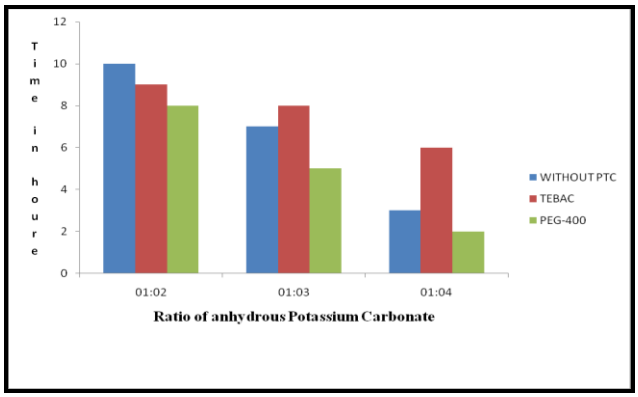


Figure 4: Effect of ratio of K_2CO_3 on reaction time of N-1 substituent of 2-acetyl-benzimidazole

Table 3: Comparisons of the result for the synthesis of N-1-Substituted Indole-3- carboxaldehyde derivatives with various PTC and ratios of anhydrous K_2CO_3

No. Entry for N-1 indole-3-carboxaldehyde	Ratio of Catalyst	Time in hours	A %Yield TEBAC	B % Yield Without PTC	C % Yield With PEG-400
IA	1:2	10	34		
IB	1:2	9		48	
IC	1:2	5			55
IIA	1:3	7	45		
IIB	1:3	8		60	
IIC	1:3	4			68
IIIA	1:4	3	55		
IIIB	1:4	4		70	
IIIC	1:4	2			85

Table 4: Comparisons of the result for the synthesis of N-1-Substituted 2-acetyl- benzimidazole derivatives with various PTC and ratios of anhydrous K_2CO_3

No. Entry for N-1-2-acetyl-benzimidazole	Ratio of Catalyst	Time in hours	A %Yield TEBAC	B %Yield Without PTC	C % Yield With PEG-400
IA	1:2	10	32		
IB	1:2	9		44	
IC	1:2	8			58
IIA	1:3	7	40		
IIB	1:3	8		58	
IIC	1:3	5			65
IIIA	1:4	3	50		
IIIB	1:4	6		74	
IIIC	1:4	2			83

Spectral Data of Compound

1-ethyl-1H-indole-3-carbaldehyde 2a

Yield 83%; m.p.101-103ºC; Rf. 0.36; FTIR: ν_{max} (cm^{-1})3044, 2821, 2362, 1650, 1536, 1458, 1376, 838 cm^{-1}; H^1-NMR ($CDCl_3$): δ 1.51 (t, 3H, CH_3), 3.38 (s, 3H, CH_3), 4.22 (q, 2H, N-CH_2), 7.39–7.25(m, 7H, Ar-H), 8.31(m, 1H, H-4), 9.97 (s, 1H, CHO) ppm.

1-benzyl-1H-indole-3-carbaldehyde 2b

Yield 83%; m.p.101-103ºC; Rf. 0.36; FTIR: ν_{max} (cm^{-1}) 3060, 2834, 2362, 1649, 1519, 1453, 750; H^1-NMR ($CDCl_3$): δ5.33 (d, 2H, N-CH_2), 7.68–7.28 (m, 7H, Ar-H), 8.32 (m, 1H, H-4), 9.97 (s, 1H, CHO) ppm;

1-(2-chlorobenzyl)-1H-indole-3-carbaldehyde 2c

Yield 83%; m.p.105-107ºC; Rf. 0.60; FTIR: ν_{max} (cm^{-1}) 3060, 2834, 2362, 1649, 1519, 1453, 750; H^1-NMR ($CDCl_3$): δ 5.43 (d, 2H, N-CH_2), 7.30–7.14 (m, 7H, Ar-H), 8.34 (m, 1H, H-4), 9.99 (s, 1H, CHO) ppm.

1-methyl-1H-indole-3-carbaldehyde 2d

Yield 72%; m.p.63-65ºC; Rf. 0.68; FTIR: ν_{max} (cm^{-1}) 3060, 2834, 2362, 1649, 1519, 1453, 750; H^1-NMR ($CDCl_3$): δ 3.39 (s, 3H, N-CH_3), 7.59–7.28(m, 7H, Ar-H), 8.27(m, 1H, H-4), 9.97 (s, 1H, CHO) ppm.

1-(prop-2-en-1-yl)-1H-indole-3-carbaldehyde 2e

Yield 81%; m.p.67-67ºC; Rf. 0.48; FTIR :ν_{max} (cm^{-1}) 3054, 2843, 2359, 1651, 1531, 1486, 937, 756; H^1-NMR($CDCl_3$): δ 4.73 (m, 1H, =CH_2), 4.75(d, 2H, NCH_2), 5.31 (d, 1H, =CH_2), 5.94 (m, 1H, CH=), 7.68–7.25 (m, 7H, Ar-H), 8.29–8.22 (m, 1H, H-4), 9.96(s, 1H, CHO) ppm.

1-(1H-benzimidazol-2-yl)ethanone 3a

Yield 75%; m.p.195-198ºC; Rf. 0.83; FTIR: ν_{max} (cm^{-1}) 3054, 2843, 2359, 1674; H^1-NMR ($CDCl_3$): δ 3.48(s,3H, CH_3- C=O), 13.27 (s, br, 1H, NH), 7.80-7.33(m, 5H, Ar-)ppm.

1-(1-ethyl-1H-benzimidazol-2-yl)ethanone 3b

Yield 75%; m.p.95-98ºC; Rf. 0.66; FTIR: ν_{max} (cm^{-1}) 3044, 2821, 2362, 1687, 1536, 1458, 1376, 838 NMR ($CDCl_3$): δ 1.45 (t, 3H, CH_3), 2.84 (s, 3H, CH_3-C=O), 4.66 (m, 2H, N-CH_2), 7.50–7.35(m, 5H, Ar-H), ppm.

1-(1-benzyl-1H-benzimidazol-2-yl)ethanone 3c

Yield 73%; m.p.103-105ºC; Rf. 0.48; FTIR: ν_{max} (cm^{-1}) 3060, 2834, 2362, 1686, 1519, 1453, 750; NMR ($CDCl_3$): δ 2.84 (s, 3H, CH_3-C=O)5.85 (d, 2H, N-CH_2), 7.92–7.11 (m, 9H, Ar-H),ppm.

1-[1-(2-chlorobenzyl)-1H-benzimidazol-2-yl]ethanone 3d

Yield 77%; m.p.106-108ºC; Rf. 0.56; FTIR: ν_{max} (cm^{-1}) 3060, 2834, 2362, 1690, 1519, 1453, 750 NMR ($CDCl_3$): δ 2.84 (s, 3H, CH_3-C=O)5.85 (d, 2H, N-CH_2), 7.94–6.33 (m, 8H, Ar-H), ppm.

1-[1-(2-methylpropyl)-1H-benzimidazol-2-yl] ethanone 3e

Yield 79%; m.p.94-96ºC; Rf. 0.62; FTIR: ν_{max} (cm^{-1}) 3054, 2843, 2359, 1651, 1531, 1486, 937, 756 NMR($CDCl_3$): δ ^{1}H-NMR: δ ,0.931(s, 6H, Iso-butyl) 2.84 (s, 3H, CH_3-C=O)2.25 (m, 3H, CH_3), 7.94–6.33 (m, 6H, Ar-H), ppm.

CONCLUSION

We have developed an inexpensive, simple and eco-friendly method for synthesis of N-alkyl derivatives of two fused heterocyclic compound of indole-3-carboxaldehyde and 2-acetylbenzimidazole. The mole ratio 1:4 of anhydrous K_2CO_3 along with PEG-400 gives mild reaction conditions with excellent yields. Further this method is not only simple but also by using green phase transferred catalysts and it also avoids the use of hard base. The ease of synthetic method provides an attractive route to the synthesis of N-1-substituted heterocyclic derivatives which may act as biological alternatives.

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