

ENVIRONMENTALLY BENIGN GREEN SYNTHESIS OF INTERMEDIATES AND THEIR DERIVATIVES OF 2-CYCLOHEXYLCARBONYL-4-OXO-1,2,3,6,7,11 B-HEXAHYDRO-4H-PYRAZINO[2,1-A] ISOQUINOLINE VIA N-ALKYLATION/ACYLATION

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ABSTRACT

The active pharmaceutical ingredient, 2-Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11 b- hexahydro-4H-pyrazino[2,1-a] isoquinoline has been achieved in a deep eutectic solvent (DES) which is an efficient, green and novel route of synthesis. The synthesis involves three N-alkylation/acylation reactions. The corresponding reactions using inexpensive raw materials proceed efficiently in a deep eutectic solvent (DES) with an improved yield that makes synthesis cost effective. The present reaction offers excellent selectivity which lacks a product of N, N-dialkylation. Ease of recovery and reusability of DES makes this process efficient and environment-friendly.

Keywords: Isoquinolines, schistosomiasis, Deep eutectic solvents, N-alkylation, Green process.

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INTRODUCTION

Schistosomiasis or bilharzia is an endemic parasitic disease caused by worms.¹ It is commonly associated with poor sanitation. It is also called as a disease of poverty. When people come into contact with fresh water contaminated with larval forms of parasitic blood flukes called schistosomes, it results in infection called Schistosomiasis.

The 2-Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11 b- hexahydro-4H-pyrazino[2,1-a] isoquinoline is the only active ingredient with which all forms of schistosomiasis can be treated successfully. WHO (World Health Organisation) declared it as an essential drug, WHO approach on the use of this drug now makes it feasible to manage the spread of schistosomiasis in poor countries.

There are various synthetic methodologies reported in the literature to prepare intermediates of 2-Cyclohexylcarbonyl-4-oxo-1, 2, 3, 6,7,11 b- hexahydro-4H-pyrazino[2,1-a] isoquinoline.²⁻⁶ These methods however suffer from one or another drawback such as use of strongly acidic and basic reactions conditions, expensive raw materials, unwanted side reactions like dialkylation, moisture sensitive reactions, use of volatile organic solvents and bases, difficulty in recovery of solvent used, higher reaction temperature etc. which makes them environmental damaging and highly expensive. Since volatile reagents and solvents widely and intensively used in chemical industries, and its use has increased for several decades, which inevitably leads to environmental damage, risk to human health and to resource depletion. Thus there is a need to generate and apply less hazardous material and more environment-friendly approaches. We have reported a novel green route for the synthesis of intermediates of Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11 b- hexahydro-4H-pyrazino[2,1-a] isoquinoline using ionic liquid especially Deep Eutectic solvent (DES) .

In recent days green methods such as the use and implementation of Deep eutectic solvent (DES) have fascinated significant interest because of their exclusive properties. DES's are analogous to regular ionic

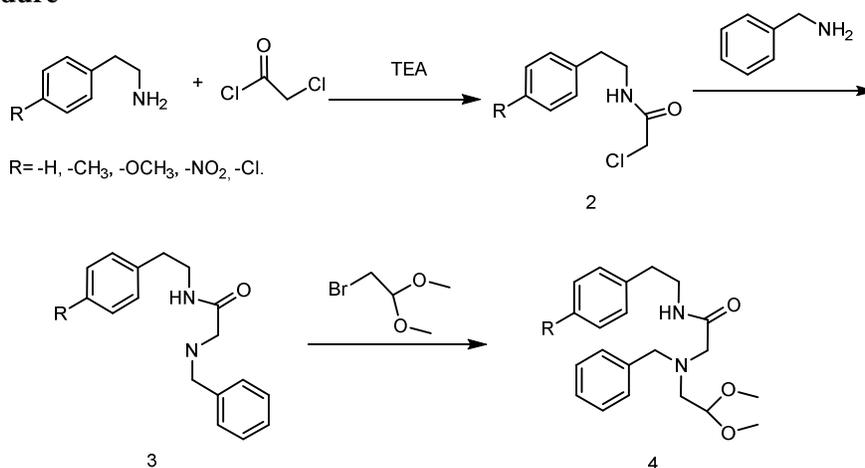
liquids in terms of low vapor pressure and low flammability. The DES used in present research is biodegradable, non-hazardous and economical.⁷⁻⁸ Preparation of DES-associated with simple and feasible technique producing a stoichiometric amount of resultant DES.

EXPERIMENTAL

Material and Methods

The NMR spectrometer (Varian) of capacity 300MHz was used to record ¹H-NMR spectra using TMS as an internal standard. The chemical shifts are expressed in δ ppm. FT-IR spectra were obtained by using Nicolet-iS5 spectrometer. Mass spectrometry was performed using Shimadzu (QP2010 plus). The progress of the reaction was checked by Thin-Layer chromatography (TLC) and plates were visualized under UV light. All the solvents used in the whole process were procured from Loba Chemicals Ltd (India) and were used as such without purification.

General Procedure



Scheme-1

Synthesis of Deep Eutectic Solvent

Preparation of DES was carried out by combining choline chloride : urea in (1:2) proportion as per the process mentioned in the literature.⁸

Preparation of 2-Chloro-N-phenylacetamide (2)

Charged differently substituted 2-Phenylethylamine (0.41 mol) to round bottom flask containing DES (150 cm³) and Triethylamine (0.53 mol), cooled to 5°C-10°C, and chloroacetyl chloride (0.48 mol) was added at 5°C-10°C in 45 min, stirred at 25°C-30°C for 1.5 h, after completion of reaction 250 cm³ water was added slowly at 10°C-15°C. The pH of reaction mass made neutral by adding dilute HCl, stirred it for 1 hr at the same temperature to ensure complete precipitation. Filtered, followed by water washing. Dried under vacuum at 55°C-60°C, affording white solid with yield 92%.

Preparation of 2-Benzylamino-N-phenethylacetamide (3)

Charged (0.21 mol) of compound (2), 100 cm³ of DES-choline chloride +urea round bottom flask, benzyl amine (0.44 mol) was added slowly in 15 min and stirred at 45°C -50°C. After completion of reaction on TLC, cooled to RT, 250 cm³ water was added, extracted with 2 × 100 cm³ of toluene. Dried it by using sodium sulphate, pH was made ~2- 3 by adding IPA-HCl slowly at 5°C -10°C and stirred for 1 hr at the same temperature. Filtered, washed with 50 cm³ of toluene and was dried under vacuum to give a white solid with yield 85%.

Preparation of 2-[(2, 2-dimethoxyethyl) benzyl amino]-N-phenethylacetamide (4)

Charged (0.16 mol) of compound (3), 150 cm³ ionic liquid preferably choline chloride –urea DES and potassium carbonate (0.28 mol) to flask, bromoacetaldehydedimethyl acetal (0.16 mol) was charged,

temperature of reaction mass was raised to 90°C-95°C and stirred for 8 hr, TLC was checked, after completion of reaction, cooled to 25°C-30°C and 150 cm³ water added and extracted with 2 × 100 cm³ of toluene, organic layer separated and concentrated under vacuum at 50°C-55°C. It is purified by using a conventional method to give yellowish oil with a yield 62%.

Detection Method

Proton NMR (300 MHz) (Varian) spectrometer, FT-IR spectrometer (Nicolet-iS5 spectrometer) , Mass spectrometer (Shimadzu QP2010 plus) and Thin Layer chromatography (TLC) .

RESULTS AND DISCUSSION

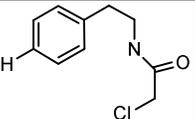
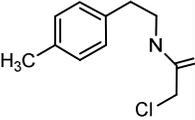
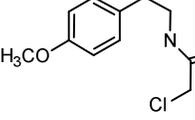
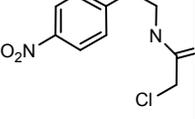
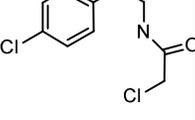
To develop a novel process for the synthesis of intermediates of Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11 b-hexahydro-4H-pyrazino[2,1-a] isoquinoline and to optimize reaction conditions in previously reported methods recyclable Deep Eutectic Solvent (DES) is employed as a solvent in corresponding reactions to get better yield and purity.

Step 1-Preparation of 2-Chloro-N-phenethylacetamide (2)

Reaction of 2-Phenyl ethyl amine and its derivatives with chloroacetylchloride in presence of organic base in DES as solvent gives compound (2) that is corresponding 2-Chloro-N-phenethylacetamide and its derivatives with yield 92%, where DES as a solvent offers many advantages compared to the existing process, like it avoids use of chlorinated solvent or organic solvent as reaction media and for extraction and isolation. It enhances the rate of reaction, reduces the formation of N,N-dialkylated impurities consequently leads to an increase in yield. The DES used is recovered and recycled for three consecutive cycles.

Study of Physical Parameters

Table-1:Physical Properties of 2-Chloro-N-phenethylacetamide (2)

S.No.	Compound	Yield %	Appearance	Melting point	¹ H-NMR	IR cm ⁻¹
1		92	White solid	70°C	7.3-7.8 (6H), 3.5 (1H), 1.8- 2.1 (4H), 0.6 (2H)	3125, 3250, 1545, 1670, 2820, 1250, 760
2		79	White solid	66°C	7.5-8.2 (6H), 3.1 (1H), 1.5-1.9 (4H), 0.8-0.5 (5H)	3100, 3360, 1475, 1600, 2800, 2725, 1165, 780
3		84	White solid	81°C	7.3-8.5 (6H), 7.0 (2H), 3.8-4.3 (4H), 1.7-2.3 (4H), 1.3 (2H)	2980, 3280, 1400, 1680, 2760, 1090, 820
4		55	White solid	132°C	7.6-6.1(6H), 3.5 (1H), 1.1-1.9 (4H), 0.5-0.7 (2H)	3130, 3310, 1525, 1630, 2785, 1100, 755
5		63	White solid	108°C	6.8-7.3 (6H), 4.2 (1H), 1.1-1.6(4H), 0.8- 0.9(2H)	3055, 3378, 1200, 1645, 2900, 1050, 740, 765

Optimization of Reaction Parameters

The given reaction was studied to check the effect of a change in solvent and temperature on yield and rate of reaction.

Table-2: Optimization of Reaction Parameters

S.No.	Reaction Media	Time in hr	Temp (°C)	Yield(%)
1	Toluene	8	25-30°C	66
2	Dichloromethane	2	25-30°C	90
3	Dichloroethane	2	25-30°C	71
4	DES(choline chloride+urea)	1	25-30°C	92
5	Methylisobutyl ketone	11	25-30°C	44
6	Acetonitrile	6	25-30°C	58
7	Tetrahydrofuran	15	25-30°C	42
8	Glycerol	9	25-30°C	38
Temperature Study				
9	DES(Choline chloride + Urea)	1	25-30	92
10	DES(Choline chloride+Urea)	0.5	35-40	81
11	DES(choline chloride+urea)	2.5	20-25	86

(Reaction condition: 2-Phenylethylamine (0.41 mol), reaction media and Triethylamine (0.53 mol) and chloroacetyl chloride (0.48 mol) was added slowly at 5°C-10°C.)

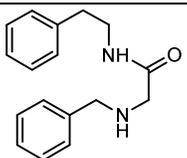
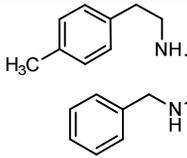
According to Table-2, it is very clear that the given reaction shows best results in DES at 25-30°C in terms of yield, and purity.

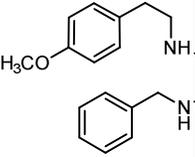
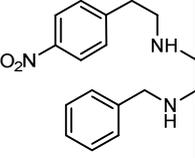
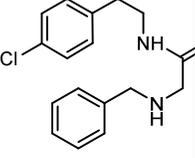
Step 2-Preparation of 2-Benzylamino-N-phenethylacetamide (3)

The compound (2) on further reaction with benzyl amine in DES as a reaction media gives compound (3), 2-Benzylamino-N-phenethylacetamide and with yield 85%, the same reaction tried in different solvent using same equivalents of reagents and bases, but in solvents other than DES, reaction leads to formation of dimer impurity (N, N-dialkylated product) which ultimately leads to decrease in yield, also time required for completion of reaction in DES is less compared to other solvents.

Study of Physical Parameters

Table-3: Physical Properties of 2-Benzylamino-N-phenethylacetamide (3)

S.No.	Compound	Yield %	Appearance	Melting point	¹ H-NMR	IR cm ⁻¹
1		85	White solid	80°C	7.3-8.1 (12H), 3.1-3.6 (2H), 1.2-1.7(8H)	3115, 3430, 3630, 1350, 1670, 1225, 2780
2		68	White solid	92°C	7.1-7.6(9H), 3.7-4.1(2H), 1.0-1.4 (8H), 0.6-1.1(3H)	3085, 3250, 3310, 1275, 1695, 1100, 2925

3		60	Off white solid	88°C	7.5-8.1 (9H), 3.4-3.9 (5H), 1.2-2.7 (8H)	3000, 3300, 3490, 1105, 1675, 1210, 2880
4		52	Light yellow solid	112°C	6.8-7.2 (9H), 3.6-4.1(2H), 1.4-1.8(8H)	3135, 3295, 3310, 1080, 1700, 1165
5		39	White solid	106°C	7.9-8.3(9H), 3.2-3.8(2H), 1.2-1.6(4H), 0.9(2H)	3075, 3500, 3620, 1100, 1705, 1085

Optimization of Reaction Parameters of Synthesis of 2-Benzylamino-N-phenethylacetamide (3)

The effect of a change in solvent, temperature and reagent on the corresponding reaction was studied by evaluating variation in yield and purity of said product (Table-4).

Table-4: Effect of Reaction Media and Temperature on the Reaction of 2-chloro-N-phenethylacetamide and its Derivatives with Benzyl Amine

Entry	Reaction media	Time in h	Temp °C	Yield %	Conclusion
1	Toluene	28	75°C-80°C	45	Use of DES as a solvent avoids N, N-Dialkylation, it also increases yield and reduces reaction time.
2	Water	25	75°C-80°C	60	
3	Dichloroethane	22	75°C-80°C	55	
4	DES (choline chloride+urea)	5	75°C-80°C	66	
5	Methyl isobutyl ketone	26	75°C-80°C	55	
6	Acetonitrile	18	75°C-80°C	40	
7	Tetrahydrofuran	35	75°C-80°C	42	
8	Glycerol	14	75°C-80°C	60	
9	Hexane	35	75°C-80°C	18	
10	Carbon tetrachloride	35	75°C-80°C	32	
Temperature Study					
1	DES (choline chloride+urea)	1	75°C-80°C	66	The reaction gives maximum yield and quality product at a range of temp 45°C -50°C
2	DES (choline chloride+urea)	1.5	65°C-70°C	72	
3	DES (choline chloride+urea)	3	55°C-60°C	80	
4	DES (choline chloride+urea)	4	45°C-50°C	85	
5	DES (choline chloride+urea)	6	35°C-30°C	82	

(Reaction condition: Compound (2) (0.21 mol), reaction media and benzyl amine (0.44 mol) was added slowly in 15 min and stirred at 45°C -50°C.)

The reaction produces maximum yield and quality product in DES -choline chloride +urea as a reaction media at 45°C -50°C.

Step 3-Preparation of 2-[(2, 2-dimethoxyethyl) benzyl amino]-N-phenethylacetamide (4)

In next step, condensation of 2-Benzylamino-N-phenethylacetamide and its derivatives with Bromoacetaldehyde dimethyl acetal is carried out in the different solvent but reaction requires higher temperature and prolong the time for completion but DES as a reaction media gives better results and yield 62% to obtain 2[(2,2-Dimethoxyethyl)benzylamino]-N-phenethylacetamide.

Study of Physical Parameters

The given compound was characterized by studying different physical parameters (Table-5).

Table-5: Physical properties of 2-[(2, 2-dimethoxyethyl) benzyl amino]-N-phenethylacetamide (4)

S.No	Compound	Yield %	Appearance	Melting point	¹ H-NMR	IR cm ⁻¹
1		62	Yellow oil	More than 250°C	7.4-8.3 (10H), 3.3 (1H), 3.9-4.2 (6H), 1.1-1.6 (10H), 0.8 (1 H)	3108, 3400, 1590, 1200, 1050, 1100
2		57	yellow oil	More than 250°C	7.6-8.5 (9H), 3-3.8 (7H), 1.3-1.9 (10H), 0.5-0.9 (4H)	3060, 3375, 1670, 2880, 1190, 1075
3		55	Yellow oil	More than 250°C	8.0-8.4(9H), 3.2-3.9 (10H), 0.9-1.8 (11H)	3095, 3560, 1700, 2935, 1060, 2920, 1130
4		48	Dark brown oil	More than 250°C	6.7-7.4 (9H), 3.6-4.3 (7H), 1.2-1.5 (11H)	3140, 3470, 1655, 2785, 1125, 1200, 1350
5		36	Brownish yellow oil	More than 250°C	6.9-7.9(9H), 3.3-4.1(7H), 0.8-1.9 (11H)	3130, 3500, 1710, 2850, 1075, 1145, 1280

Optimization of Reaction Parameters

The change in yield and purity of given reaction with respect to change in solvent and reaction temperature was studied and results obtained are framed in Table-6.

Table-6: Optimization of Reaction Parameters.

Entry	Reaction Media	Time in hr	Temp °C	Yield%	Conclusion
1	N,N-Dimethylformamide	7	130°C-135°C	20	DES as a reaction media leads to an increase in yield of said product.
2	N,N-Dimethylacetamide	7	130°C-135°C	25	
3	Hexamethylphosphoramide	7	130°C-135°C	30	
4	N-methyl pyrrolidone	7	130°C-135°C	28	
5	DES (choline chloride+urea)	7	130°C-135°C	49	
Temperature Study					
1	DES (choline chloride+urea)	7	130-135	49	Increase in temperature leads to degradation of product formed.
2	DES (choline chloride+urea)	7	120-125	53	
3	DES (choline chloride+urea)	7.5	110-115	57	
4	DES (Choline chloride+urea)	8	90-95	62	
5	DES (Choline chloride+urea)	12	85-90	58	

(Reaction condition: Compound (3) (0.16 mol), reaction media, potassium carbonate (0.28 mol) and bromoacetaldehydedimethyl acetal (0.16 mol) was added at a given temperature.) DES (choline chloride- urea) as a solvent offers best results at 90-95°C.

Recyclability Studies

The DES is highly soluble in water which goes to either filtrate or water layer based on the type of work up. It can be recovered from aqueous solution by distilling out the water under vacuum at 70°C-75°C. The recycled DES was used as a solvent for the next batch of the same reaction, which can be used up to three times for the corresponding reaction without loss of activity.

CONCLUSION

Herein we report the novel efficient, convenient and green process for preparation of intermediates (carrying different substituents) of 2- cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a] isoquinoline via N-alkylation/acylation reaction. It offers distinct improvements in terms of good yield, low impurity profile, decreased reaction time, use of environmentally benign solvents etc. It avoids unwanted side reactions. Deep eutectic solvent (DES) used is recyclable and biodegradable that makes the process environmentally benign and cost-effective.

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