Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2018, 10(7): 201-206
(http://www.derpharmachemica.com/archive.html)

Environmentally Benign Green Synthesis of Intermediates and their Derivatives Involving N-Alkylation of 2-Cyclohexylcarbonyl-4-Oxo-1,2,3,6,7,11 B- Hexahydro-4h-Pyrazino[2,1-A] Isoquinoline

Pranaya P Dhawle, Anita Goswami Giri*

Department of Chemistry, B. N. Bandodkar College of Science, Jnanadweepa, Chendani Bunder Road, Thane West, Maharashtra, India 400601

ABSTRACT

Active pharmaceutical ingredient, 2-Cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11 b- hexahydro-4H-pyrazino[2,1-a] isoquinoline has been achieved by deep eutectic solvent (DES) which is an efficient, green and novel route of synthesis. This drug is used in treatment of Schistosomiasis. The N-alkylation reactions with inexpensive raw materials proceed efficiently with improved yield that makes synthesis cost effective. The present reaction offers excellent selectivity which lacks 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-alkylatation, Green process.

INTRODUCTION

Schistosomiasis or bilharzia is endemic parasitic disease caused by worms [1]. It is commonly associated with poor sanitation. It is also called as disease of poverty. When people come into contact with fresh water contaminated with larval forms of parasitic blood flukes called schistosomes, it results into 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 use of this drug now makes it feasible to manage spread of schistosomiasis in poor countries.

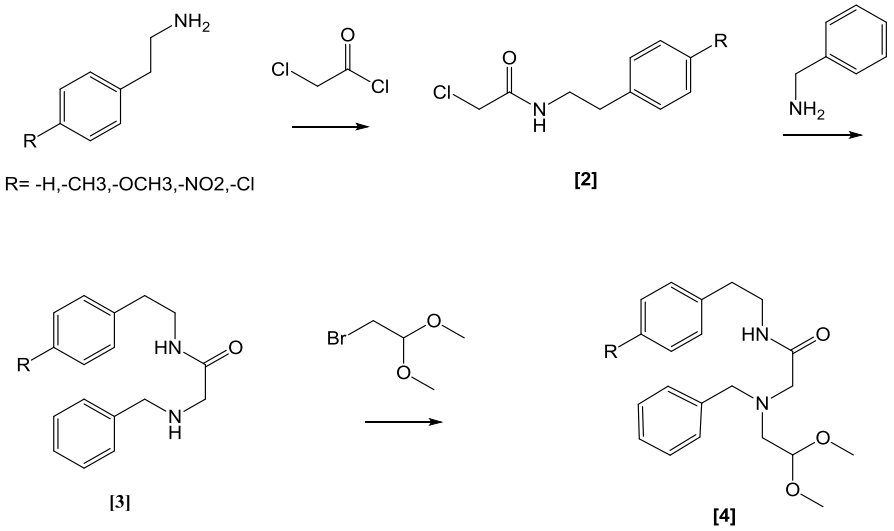
There are various synthetic methodologies reported in literature to prepare intermediates of 2-Cyclohexylcarbonyl-4-oxo-1, 2, 3, 6,7,11 b-hexahydro-4H-pyrazino[2,1-a] isoquinoline [2-6]. These methods however suffer from one or another drawback such as use of strongly acidic and basic reactions conditions, 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 need to generate and apply less hazardous material and more environment friendly approaches. We have reported novel green route for 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) .

Green methods such as use of ionic liquid have recently attracted considerable attention due to their exclusive properties. Deep Eutectic solvent (DES) are similar to conventional ionic liquids in terms of low vapour pressure and low flammability. In addition, DES is biodegradable, non-toxic and inexpensive [7,8]. Preparation of DES is easy and economically viable as it shows 100% atom economy.

MATERIALS AND METHODS

Proton NMR spectra were recorded on 300 MHz (Varian) spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. FT-IR spectra were recorded on Nicolet-iS5 spectrometer. Mass spectral data were obtained using Shimadzu (QP2010 plus). The reactions were monitored by Thin Layer chromatography (TLC) using 0.25 mm Merck silica gel 60 F_{254} precoated plates and visualized under UV light. All the solvents were purchased from Loba Chemicals (India) and were used without further purification.

Reaction scheme



Experimental

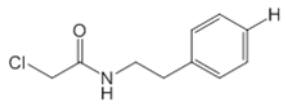
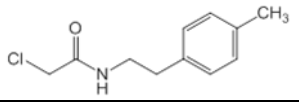
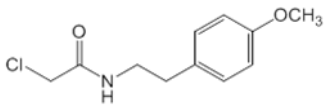
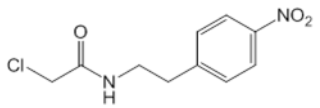
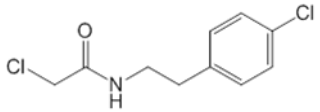
Synthesis of deep eutectic solvent

The DES was prepared by combining choline chloride with urea according to the procedure reported in the literature [8].

Procedure

Preparation of 2-Chloro-N-phenethylacetamide (2) (Table 1): Charged differently substituted 2-Phenylethylamine (0.41 mol) to round bottom flask containing DES (150 ml) 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 0°C-10°C for 1.5 h, after completion of reaction 250 ml water was added slowly. The $_p$H of reaction mass made neutral by adding dilute HCl, stirred it for 1 h at 10°C-15°C to ensure complete precipitation. Filtered, washed with water and dried under vacuum at 55°C-60°C, affording white solid with yield 82%.

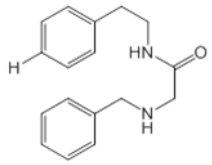
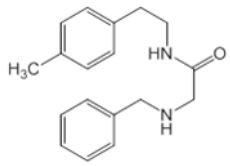
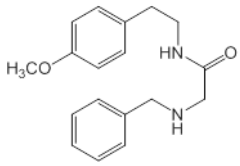
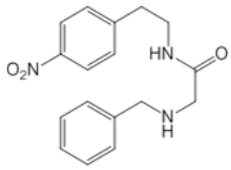
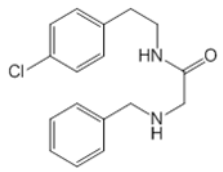
Table 1: Preparation of 2-Chloro-N-phenethylacetamide (2)

S. No.	Compound	Yield%	Appearance	Melting point	^{1}H-NMR	IR
1		82	White solid	70^{o}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		66	White solid	66^{o}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		73	White solid	81^{o}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		48	White solid	132^{o}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		54	White solid	108^{o}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

Preparation of 2-Benzylamino-N-phenethylacetamide (3) (Table 2): Charged (0.21 mol) of compound (2), 100 ml 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 (it takes ~1-h),cooled to RT, 250 ml water was added, extracted with 2 × 100 ml of toluene. Dried it by using sodium sulphate, pH was made ~2-3 by adding IPA-HCl slowly at 5°C -10°C, stirred at the same temperature for 1 h. Filtered, washed with 50 ml of toluene and was dried under

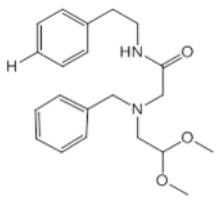
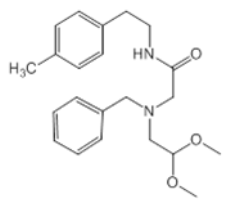
vacuum to give white solid with yield 85%.

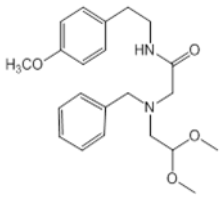
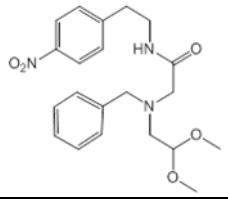
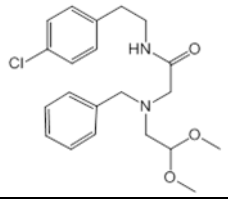
Table 2: Preparation of 2-Benzylamino-N-phenethylacetamide (3)

S. No.	Compound	Yield%	Appearance	Melting point	^{1}H-NMR ∂ ppm	IR Cm^{-1}
1		85	White solid	80^{o}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^{o}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^{o}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^{o}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^{o}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

Preparation of 2-[(2, 2-dimethoxyethyl) benzyl amino]-N-phenethylacetamide (4) (Table 3): Charged (0.16 mol) of compound (3), 150 ml ionic liquid preferably choline chloride –urea DES and potassium carbonate (0.28 mol) to flask, bromoacetaldehydedimethyl acetal (0.16 mol) was added and reaction mass was heated to 90°C-100°C for 8 h, TLC was checked, after completion of reaction, cooled to 25°C-30°C and 150 ml water added and extracted with 2 × 100 ml of toluene, organic layer separated and concentrated under vacuum at 50°C-55°C. It is purified by using conventional method to give yellowish oil with yield 52%.

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

S. No.	Compound	Yield%	Appearance	Boiling point	^{1}H-NMR ∂ ppm	IR Cm^{-1}
1		52	Yellow oil	More than 250^{o}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		40	yellow oil	More than 250^{o}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		46	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		38	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		33	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

RESULTS AND DISCUSSION

To develop novel process for 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.

Effect of DES as a reaction media on reactions

Step 1-Preparation of 2-Chloro-N-phenethylacetamide [2]: Reaction of 2-Phenyl ethyl amine and its derivatives with choloroacetylchloride in presence of organic base in DES as solvent gives compound (2) that is corresponding 2-Chloro-N-phenethylacetamide and its derivatives with yield 82%, where DES as a solvent offers many advantages compared to existing process, like it avoids use of chlorinated solvent or organic solvent as reaction media and for extraction and isolation.

Step 2-Preparation of 2-Benzylamino-N-phenethylacetamide (3) (Table 4): The compound (2) on further reaction with benzyl amine in DES as a reaction media gives [3], 2-Benzylamino-N-phenethylacetamide and with yield 85%, 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.

Table 4: Effect of reaction media and temperature on 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	Methylisobutyl 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	Reaction gives maximum yield and quality product at 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: 21 mmol of compound (2), 10 ml of solvent, benzyl amine (44 mmol) was added slowly in 15 min and stirred at given temp for mentioned time).

Step 3-Preparation of 2-[(2, 2-dimethoxyethyl) benzyl amino]-N-phenethylacetamide (4) (Table 5)

In next step, condensation of 2-Benzylamino-N-phenethylacetamide and its derivatives with Bromoacetaldehyde dimethyl acetal is carried out in different solvent but reaction requires higher temperature and prolong time for completion but DES as a reaction media gives better results and yield 52% to obtain 2[(2,2-Dimethoxyethyl)benzylamino]-N-phenethylacetamide.

Table 5: Effect of reaction media and temperature on reaction of 2-Benzylamino-N-phenethylacetamide with Bromoacetaldehydedimethyl acetal

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	Methylisobutyl 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	Reaction gives maximum yield and quality product at range of temp 45-50°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	
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 increase in yield of said product.
2	N,N-Dimethylacetamamide	7	130°C-135°C	25	
3	Hexamethylphosphoramide	7	130°C-135°C	30	
4	N-Methyl-2-pyrrolidone	7	130°C-135°C	28	
5	DES (choline chloride+urea)	7	130°C-135°C	40	
Temperature Study					
1	DES (choline chloride+urea)	7	130-135	40	Increase in temperature leads to degradation of product formed.
2	DES (choline chloride+urea)	7	120-125	43	
3	DES (choline chloride+urea)	8	110-115	47	
4	DES (Choline chloride+urea)	9	90-95	52	
5	DES (Choline chloride+urea)	12	140-145	30	

(Reaction condition: 16 mmol of compound (3), 10 ml solvent, 28 mmol K_2CO_3 and 16 mmol of Bromoacetaldehyde dimethylacetal and reaction mass heated to corresponding temperature for mentioned time).

Recyclability Studies

The DES is soluble in water which comes in filtrate or water layer depending on mode of work up, which can be easily recovered from water by evaporating the water under vacuum at 70°C-75°C. The recycled DES was used as a solvent for next batch of same reaction, which can be used up to three times for corresponding reaction without loss of activity.

CONCLUSION

Herein we report the novel efficient, convenient and green process for preparation of intermediates with different substituents, of 2-cyclohexylcarbonyl-4-oxo-1,2,3,6,7,11b-hexahydro-4H-pyrazino [2,1-a] isoquinoline. It offers distinct improvements in terms of good yield, low impurity profile, decreased reaction time, use of environmentally benign solvents etc. The recyclability and biodegradability of deep eutectic solvent (DES) which is used as a solvent makes the process environment friendly and economically more viable.

ACKNOWLEDGMENT

Authors are thankful to Department of Chemistry, B.N. Bandodkar College of science for recording FT-IR, SAIF IIT-Bombay for recording 1H-NMR spectra and mass spectra.

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