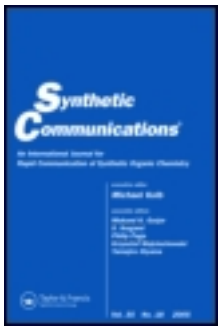

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Choline chloride/Urea Ionic Liquid Catalyzed a Convenient One-Pot Synthesis of Indole-3-Propanamide Derivatives

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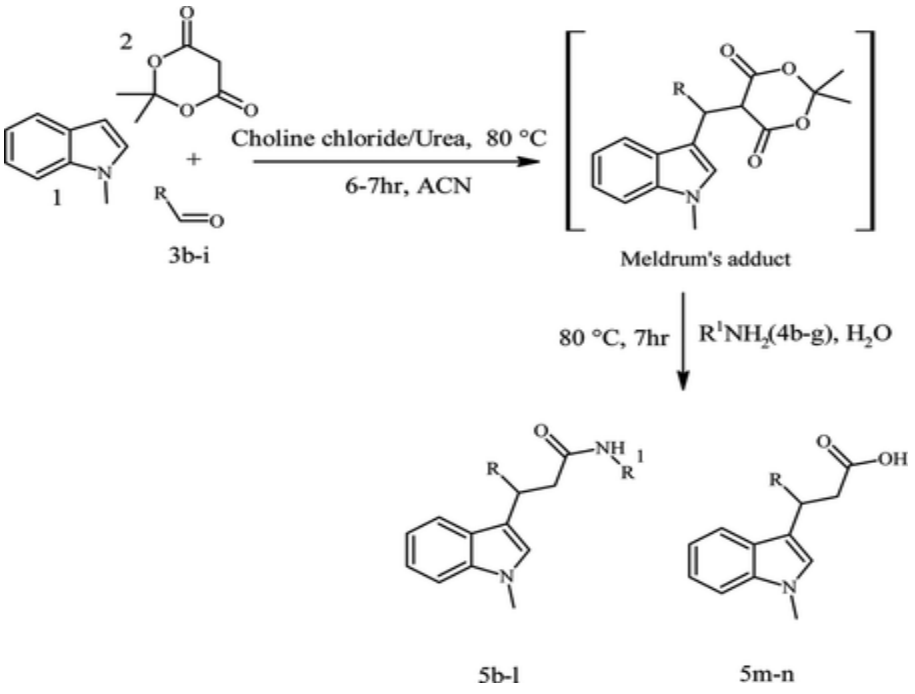
Abstract

A sequential three-component reaction of aromatic aldehydes with Meldrum's acid and *N*-methyl indole in presence of choline chloride/urea ionic liquid as green catalyst has been described. In this one-pot multicomponent reaction, a series of indole-3-propanamide derivatives were synthesized with good to excellent yields. This methodology shows several advantages including fast reaction, easy isolation and operational simplicity makes it a useful and attractive option for the library generation of indole-3-propanamides **(5a-l)** for drug discovery.

[Supplementary materials are available for this article. Go to the publisher's online edition of *Synthetic Communications*® for the following free supplemental resource(s): Full experimental and spectral details.]



KEYWORDS: choline chloride/urea, indole-3-propanamides, multicomponent reaction, Meldrum's acid.

INTRODUCTION

Indole-3-propanamide has been served as precursor to obtain several biologically active molecules, especially for the treatment of brain disorder,[1a] tyrosine kinase inhibitors and in specifically inhibitors of epidermal growth factor (EGF) receptor.[1b] *N*-aryl-3-(indol-3-yl)propanamide shows promising immunosuppressive activity.[2a] The fact that some indolylcarboxamides also act as anti-allergic activity.[2b] Further,indole-3-propanamide have been tested as potential systemic and topical inflammation inhibitors.[3] Thus indole-3-propanamides have become an important precursor for the various pharmaceutical ingredients. Therefore there is demand for better synthetic route for the preparation of indolylcarboxamides. Over the past decade multicomponent reactions have undoubtedly

become a versatile tool for its rapidity, diversity, efficiency and environmental amiability. Keeping above points in mind we have chosen the multicomponent reactions between indole, Meldrum's acid and aldehydes to prepare the beta substituted indole-3-propanamides.[4,5]

Ionic liquids are the versatile solvents and reagents for the synthesis of many organic molecules because they are neither volatile nor flammable, and non toxic, can be recovered for reuse.[6] Thus choline chloride/urea ionic liquid has been used successfully in Knoevenagel condensation and other organic reactions.[7,8]

The indole-3-propanamides have been prepared by various methods.[1,3][11–13] All the existing methods suffered from some technical constraints like poor yield, use of pyridine as solvent which is toxic, sometimes formation of bisindoles was observed and sometimes only Knoevenagel products were being observed.[6] Keeping all these in mind and inspired by our earlier use of choline chloride/urea ionic liquid as catalyst,[9,10] and development of new methods for the synthesis of various heterocyclic compounds,[14–25] here we have described a more conventional, but shorter and more economical approach i.e. one pot condensation between *N*-methyl indole, aldehydes and Meldrum's acid in choline chloride/urea ionic liquid catalytic system to get Meldrum's adduct as intermediates (Scheme 2) followed by cleavage of the intermediate Meldrum's adduct by various amines to furnish medicinally important indole-3-propanamide derivatives **(5a-l)** in good to excellent yields.

RESULTS AND DISCUSSION

The synthetic route to target (**5a)** has been outlined in the Scheme 1. It started with mixing three component coupling of *N*-methyl indole, Meldrum's acid with the phenyl acetaldehyde in presence of choline chloride/urea ionic liquid (20 mol%) in acetonitrile solvent to get intermediate Meldrum's adduct under 6 hr stirring at 80^{o} C**.** Later the isolated Meldrum's adduct in the reaction mass was treated with 3-chloro aniline **(4a)** under reflux condition gave *N*-(3-chlorophenyl)-3-(1-methyl-1*H*-indol-3-yl)-4-phenylbutanamide **(5a)**. Here the intermediate Meldrum's adduct formation was confirmed by spectral data with the standard.[10] Alternatively, when Meldrum's adduct was treated with the same amine **(4a)** without isolation, we found that the conversion was neat to give product **(5a)** in good yield. Thus we adopted this methodology for the preparation of remaining indole-3-propanamides **(5b-l)** as given in Scheme 2.

Before choosing the choline chloride/urea ionic liquid, we examined tertiary bases like triethyl amine (TEA) and diisopropyl ethyl amine (DIPEA). Here we found that the reaction was sluggish, and we didn't observe any improvement even at reflux condition. Further, we also did notice that no product formation in the absence of bases both in ethanol and acetonitrile solvent. Based on these results as given in Table 1**,** we have chosen choline chloride/urea (IL) as basic ionic liquid in acetonitrile which could give us better yields of indole-3-propanamides in which the choline chloride/urea catalyst found to expedite the multicomponent condensation between *N*-methyl indole, aldehydes and Meldrum's acid to give compounds (**5a-n)** at reflux condition.

In order to further improve reaction condition we tried various concentration of the ionic liquid at both room temperature and reflux temperature. Irrespective of the concentration of IL we found the reaction did not proceed at room temperature except in the case of (**5a)** where we found 50% conversion after 15 h (IL 20 mol%). Further, we have seen that the reaction mass was charred when we use IL as solvent as well as catalyst. Accordingly, when the reaction was carried out at 50 mol% of IL in acetonitrile solvent, we observe that the yield was significantly increased. So after several efforts we found, 20 mol% of IL in acetonitrile was optimal to obtain good to excellent yields of indole-3-propanamide derivatives. The details are mentioned in Table 2.

Thus, the Meldrum's adducts formed were treated with various amine nucleophiles (**4a-h)** to afford various indole-3-propanamide (**5a-l)**. In the case of amino alcohol **4b** we found only amine is reacted with Meldrum's adduct over alcohol. Similarly, when Meldrum's adduct was treated with water we found exclusively corresponding acid products (**5m & 5n**). This is probably due to the presence of ionic liquid which makes water a strong nucleophile by generating more hydroxyl anions.

Further, the meldrum's adducts were synthesized using various aldehydes such as aliphatic (phenyl acetaldehyde), aromatic (various benzaldehydes) and heterocyclic (quinoline-3-carbaldehyde). In each case the formation of adduct was excellent. The substituents like electron donating (2-ethoxy benzaldehyde) and electron withdrawing (4-nitro benzaldehyde) groups in the benzene ring did not deter the adduct formation as well as their yield (table 1). Altogether, this emphasizes the generality of this new procedure.

In addition, the reaction of various amines with Meldrum's adduct to give corresponding indole-3-propanamides (**5a-l**) was found to be concentration dependent. Thus, when we used 1 equivalent of amines **(4a-h)** to cleave Meldrum's adduct by refluxing at 80^{o}C for 6hr. Along with products **(5a-l)** we found unreacted Meldrum's adduct in the reaction mixture. But at the same time when increase in the amine concentration to 4 to 5 equivalent, the Meldrum's adduct was completely disappeared to give corresponding indole-3-propanamides (**5a-l**) including side products. After several trials, we found that 1.5-2 equivalence of amines were optimum for the complete conversion with minimum impurities. The details of the yields have been given in the Table 3.

Thus, successfully we adopted this trimolecular condensation between *N*-methyl indole, Meldrum's acid and aldehydes using choline chloride/urea (IL) ionic liquid as catalyst for the preparation of indole-3-propanamides. This method proved to be a versatile and general method for the preparation of various indole-3-propanamides, considering the tolerance to diverse aldehydes and the limitations observed in reported methods.

CONCLUSION

In conclusion we have developed a versatile and general method using choline chloride/urea (IL) as catalyst for the three component coupling of *N*-methyl indole, Meldrum's acid and aldehydes to get Meldrum's adduct followed by reaction of amines with this Meldrum's adduct to get indole-3-propanamides. This is an environmentally benign method which offers several advantages such as ease of the reaction, cheaper

catalyst and less hazardous. As well as it sustains diverse aldehydes in synthesizing variety of indole-3-propanamides in good yields.

EXPERIMENTAL

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz and 100 MHz Bruker Spectrometer using $CDCl_3$ or DMSO-d_6 solvents and *TMS* as internal standard. Mass spectra were recorded on Agilent 1200 series single quadrapole mass analyzer.The elemental analysis was recorded in VarioMICRO CHNS elemental analyser. Melting points were recorded (uncorrected) in Buchi Melting Point B-545 instrument. The purity of the compounds was checked by TLC and was further purified by column chromatography**.**

Preparation Of Ionic Liquid (IL)

The ionic liquid choline chloride/urea was prepared according to the procedures reported in literature [26] by heating a mixture of choline chloride and urea with a molar ratio of 1:2 at 80 ^{o}C until a homogeneous liquid was formed.

Typical Procedure For The Preparation Of B-Substituted Indole-3-Propanamide Derivatives

_N_-(3-chlorophenyl)-3-(1-methyl-1_H_-indol-3-yl)-4-phenylbutanamide (5a):

To the solution of *N*-methyl indole (200 mg, 1.52 mmol), Meldrum's acid (220 mg, 1.52 mmol), phenyl acetaldehyde (180 mg, 1.52 mmol) in acetonitrile (2 mL), choline chloride-urea ionic liquid (20 mol%) was added. The resultant mixture was stirred at 80

^{o}C. After 6hr, 3-chloro aniline (291 mg, 2.28 mmol) was added and continued the heating. After 7hr, reaction completion was monitored by TLC which shows absence of starting material. The reaction mixture was cooled to ambient temperature and diluted with water (2 mL). The contents were extracted into ethyl acetate (6 x 3 mL). The organic layer was washed with brine solution (3 mL), dried over anhydrous Na_2SO_4 and concentrated to residue. The residue was further purified by column chromatography (Pet ether and ethyl acetate system). The product collected in the gradient of 30-40% v/v to get pure compound (450mg, 74%). Similar procedure was followed to prepare other analogues.

Spectral Data

***N*-(3-Chlorophenyl)-3-(1-Methyl-1*H*-Indol-3-Yl)-4-Phenylbutanamide (5a)**

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.70 (d, J = 7.28 Hz, 2H), 2.95 (dd, J = 6.88, 13.4 Hz, 1H), 3.05 (dd, J = 7.64, 13.48 Hz, 1H), 3.67 (s, 3H), 3.73-3.79 (m, 1H), 6.97-7.05 (m, 2H), 7.09-7.12 (m, 5H), 7.18-7.21 (m, 2H), 7.25 (t, J = 8.08 Hz, 1H), 7.32-7.36 (m, 2H), 7.63 (d, J = 8.00 Hz, 1H), 7.73 (s, 1H), 10.05 (s, 1H). ppm; ^{13}C NMR (100 MHz, DMSO-d_6): 32.75, 35.09, 41.76, 42.70, 110.09, 116.72, 117.88, 118.74, 119.04, 119.45, 121.43, 123.13, 126.26, 126.89, 127.17, 128.45, 129.48, 130.74, 133.39, 137.20, 140.79, 141.04, 171.0 ppm. LCMS: m/z=403.2 (M+1). Anal. Calcd. for $C_{25}H_{23}ClN_2O_2$: C, 74.52; H, 5.75; N, 6.95; Found: C, 74.20; H, 5.521; N, 6.62.

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SUPPORTING INFORMATION:

Full experimental detail, ^{1}H and ^{13}C NMR spectra, LCMS and Elemental Analysis data can be found via the ‘‘Supplementary Content’’ section of this article’s webpage.’’

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Table 1. Optimization of basic condition for the synthesis of indole-3-propanmides at 80^{o} C

Solvents	Catalyst	Result
CAN	--	NR
EtOH	--	NR
CAN	TEA	<20%
CAN	DIPEA	<20%
EtOH	IL	<50%
CAN	IL	75%

Note:- IL: Choline chloride /urea, NR: No reaction.

TEA: triethyl amine.

DIPEA: Diisopropyl ethyl amine.

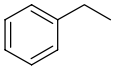
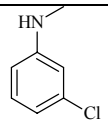
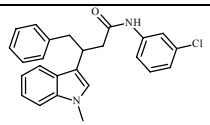
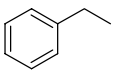
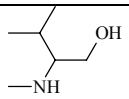
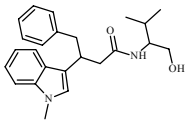
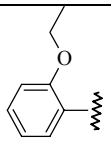
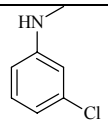
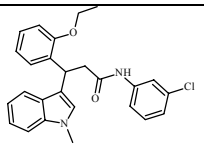
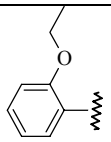
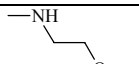
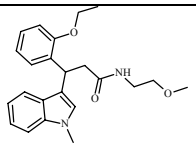
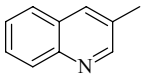
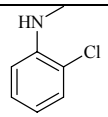
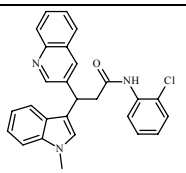
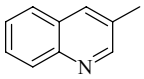
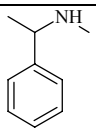
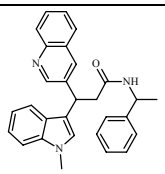
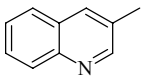
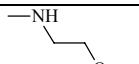
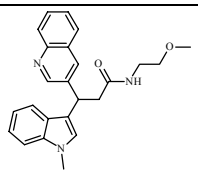
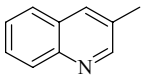
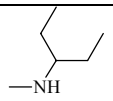
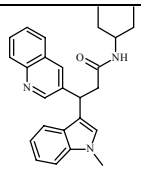
Table 2. Optimization of reaction condition for the synthesis of indole-3 propanamides in different concentrations of ionic liquid [a]

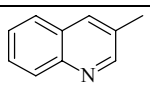
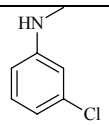
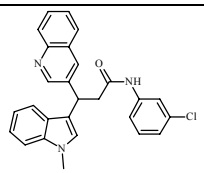
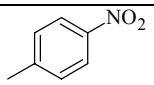
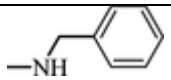
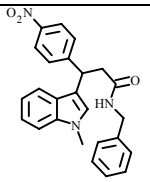
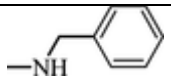
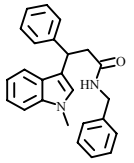
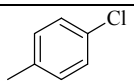
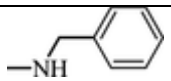
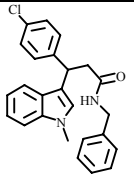
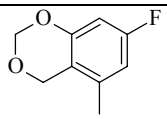
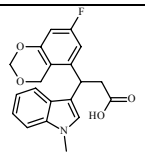
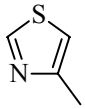
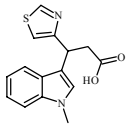
Entry	Aldehydes Mol %	*N*-methyl Indole Mol %	Meldrum's acid Mol %	Ionic Liquid mol	Time (h)	Yield[b] (%)
1	1	1	1	as solvent	1	---
2	1	1	1	50 mol%	4	< 50
3	1	1	1	20 mol%	6	85

[a]All reactions were carried out at reflux temperature.

[b]isolated yields.

Table 3. Physical data of indole-3-propanamide **5a-l** and indole-3-propanoic acid **5m-n** analogues.

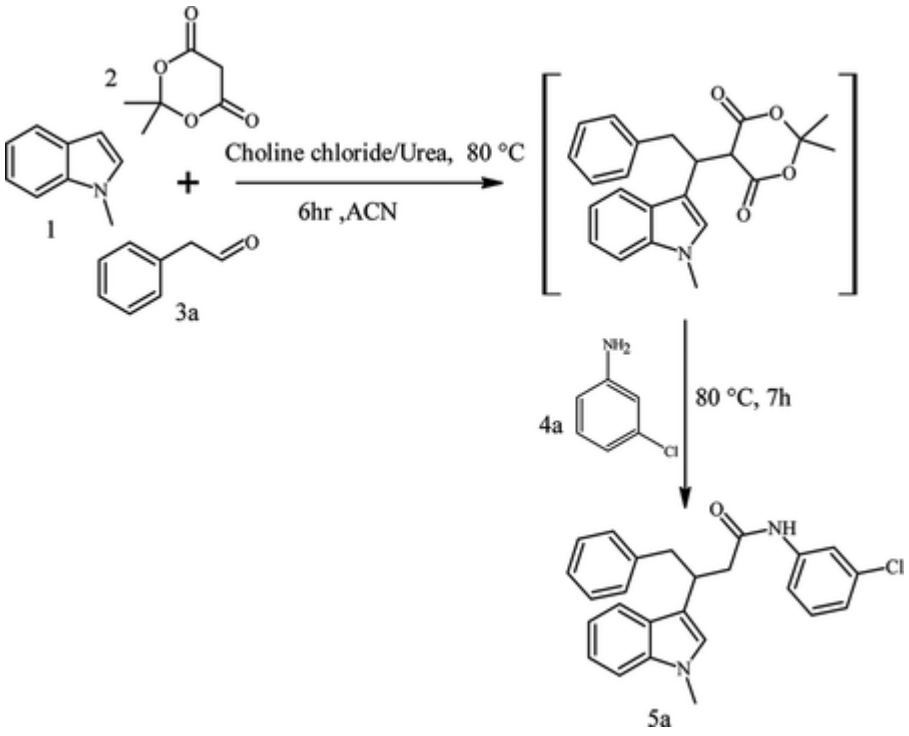
Entry	R	R^1	Products	Yield [b] (%)	M.P/ ^oC
5a				74	154-155
5b				84	203-204
5c				85	147-148
5d				89	123-124
5e				85	193-194
5f				86	205-206
5g				80	185-186
5h				88	169-171

5i				90	200-202
5j				90	215-218
5k				91	200-204
5l				92	210-213
5m		-OH		81	216-217
5n		-OH		84	235-237

[a]All reactions were carried out at reflux temperature

[b]isolated yields.

Scheme 1. Preparation of *N*-(3-chlorophenyl)-3-(1-methyl-1*H*-indol-3-yl)-4-phenylbutanamide **5a**.



Scheme 2. Three component coupling to prepare indole-3-propanamide **5b-l.** and indole-3-propanoic acid analogues **5m-n**.