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Preparation of 1,5-diaryl-3-(arylamino)-1H-pyrrol-2(5H)-one derivatives using 1-methylpiperidinium hydrogen sulfate as an efficient catalyst

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A highly efficient and environmentally friendly synthesis of various 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-ones catalyzed by 1-methylpiperidinium hydrogen sulfate via one-pot cyclo-condensation reaction of aldehydes, amines and ethyl 2-oxopropanoate under ambient conditions has been explored. The present methodology offers several advantages such as good yields, simple procedure, shorter reaction times and milder conditions and the products were purified without resorting to chromatography.

Keywords: 1,5-diaryl-3-(arylamino)-1H-pyrrol-2(5H)-one; γ-lactam; ionic liquid; 1-methylpiperidinium hydrogen sulfate

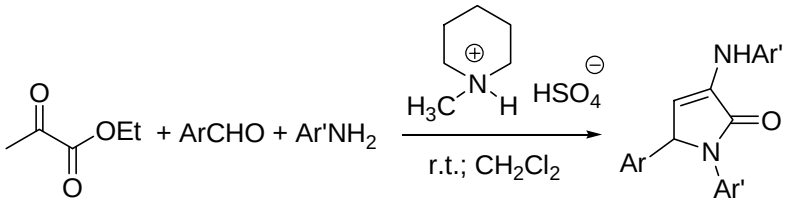
1. INTRODUCTION

The challenges are to carry out a multi-component reaction in such a way that the collection of pre-equilibrated reactions conduit into the main product and do not capitulate side products [1-3]. Multi-component reactions (MCRs) are convergent reactions in which three or more starting materials react to form a product, thus making possible the speedy synthesis of molecular libraries [1-3]. The development of well-organized procedures to access nitrogen heterocyclic compounds especially lactams has instigated continuing interest, as such compounds have been used widely in the construction of natural products and pharmaceutical compounds [4-9]. A large class of lactams is pyrrolidinone and their derivatives. They are also being used increasingly as valuable intermediates in organic synthesis and offer major synthetic opportunities in the synthesis of biological and pharmaceutical compounds [4-9].

Inspired by elegant achievements for the synthesis of mentioned compounds, we envisaged that an exceptional group of these compounds might be developed by employing a reaction of aldehydes and amines with α-oxo esters. Our synthetic efforts lead us to the construction of 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-one derivatives. Previously routes to 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-ones involve two-component condensation of amines with pyrrolidine-2,3-diones [10] and β,γ-unsaturated α-oxo esters [11] or tri-component reaction of amines, aldehyde and pyruvate by the using of acidic catalysts such as H_2SO_4 [12], thiourea and phosphoric acid analogues [13] and triethylammonium hydrogen Sulfate [14]. Despite to this fact that homogeneous liquid acid catalysts suffers from several disadvantages such as high toxicity and also difficulty in separation and recovery, thus replacement of these conventional acids by non-toxic Brønsted acidic ionic liquids is desirable to achieve decrease waste production.

The overall aim of this project is to develop and validate an efficient protocol for synthesis and easy purification of 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-ones from the cyclo-condensation

reaction of aldehydes, aryl amines and ethyl pyruvate in the presence of 1-methylpiperidinium hydrogen sulfate as an efficient acidic ionic liquid [15-16].



Scheme 1. Preparation of 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-one derivatives

2. EXPERIMENTAL

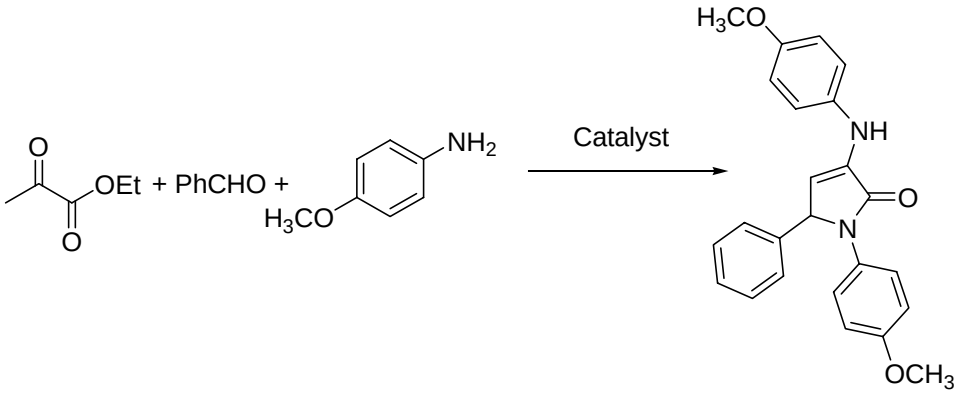
All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a Perkine Elmer 781 spectrophotometer. Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus. TLC was performed on silica gel polygram SIL G/UV 254 plates.

General procedure: To a mixture of aldehyde (1 mmol), aromatic amine (2 mmol) and *ethyl* pyruvate (1.5 mmol) in n-hexane (5 mL), 1-methylpiperidinium hydrogen sulfate (1 mmol) as catalyst was added and the mixture was stirred for appropriate time at ambient condition. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture displaced to a filter paper and washed with diethyl ether to afford the pure product (Table 3, products **a-s**).

Selected data: 3-(4-chlorophenylamino)-5-(4-tert-butylphenyl)-1-(4-chlorophenyl)-1H-pyrrol-2(5H)-one (product **p**): m.p.: 235-237 °C, ^{1}H NMR (400 MHz, $CDCl_3$): 1.30 (s, 9H), 5.65 (d, J = 2.4 Hz, 1H), 6.06 (d, J = 2.4 Hz, 1H), 6.70 (s, 1H), 7.01 (d, J = 8.8, 2H), 7.13 (d, J = 8.4, 2H), 7.25-7.27 (m, 4H), 7.33 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.8, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 34.6, 63.8, 108.9, 117.9, 122.4, 126.1, 126.2, 126.3, 129.0, 129.3, 130.1, 131.6, 133.6, 135.9, 139.8, 151.5, 167.1 ppm; IR (KBr): 3320, 3065, 2965, 2927, 2867, 1670, 1650, 1599, 1541, 1495, 1419, 1393, 1318, 1297, 1268, 1164, 1092, 1015, 919, 870, 833, 819, 796, 778 cm^{-1}; Found: C, 69.25; H, 5.41; N, 6.27 $C_{26}H_{24}Cl_2N_2O$; requires: C, 69.18; H, 5.36; N, 6.21%].

3. RESULTS AND DISCUSSION

As a preliminary test reaction, catalytic conversion of three-component condensation of benzaldehye, 4-methoxyaniline and ethyl pyruvate to 3-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrol-2(5*H*)-one was examined (Scheme 2, product **a**) in the presence of a number of Lewis and Brønsted acids including SiO_2-H_2SO_4 [17], SiO_2-$FeCl_3$ [18], $Al(H_2PO_4)_3$ [19], $NiCl_2$, $BaCl_2$, $FeSO_4$, SiO_2-$MgCl_2$, SiO_2-$CaCl_2$, $MgCl_2$, $CaCl_2$, SiO_2-$HClO_4$ [20], SiO_2-H_3PO_4, 1-methylpiperidinium hydrogen chloride, 1-methylpiperidinium trifluoroacetate, 1-methylpiperidinium methanesulfonate and 1-methylpiperidinium hydrogen sulfate (Scheme 2; Table 1). Among various catalysts examined, 1-methylpiperidinium hydrogen sulfate exhibited the best catalytic activity (Table 1, Entry 15). Other ionic liquids also gave the desired product in moderate yield (Table 1, Entries 12-14), while, Lewis or Brønsted acids were not as effective as ionic liquids for the present transformation (Table 1, Entries 1-11). Under the standard conditions, no reaction was observed in the absence of catalyst. This shows that the catalyst is essential for the product formation. These investigations into the impact of the countering showed 1-methylpiperidinium hydrogen sulfate to be the most efficient promoter for these conversions among the tested acidic catalysts. The results are summarized in Table 1.



Scheme 2. Preparation of 3-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrol-2(5H)-one

Table 1. Catalyst screening**.**

Entry	Catalyst	Yield (%) [a]
1	SiO_2-H_2SO_4 (0.05 g)	25
2	SiO_2-$FeCl_3$ (0.05 g)	-
3	$Al(H_2PO_4)_3$ (0.05 g)	10
4	$NiCl_2$ (0.1 mmol)	5
5	$BaCl_2$ (0.1 mmol)	-
6	$FeSO_4$(0.1 mmol)	-
	SiO_2-$MgCl_2$ (0.05 g)	-
7	SiO_2-$CaCl_2$ (0.05)	-
8	$MgCl_2$ (0.1 mmol)	-
9	$CaCl_2$ (0.1 mmol)	-
10	SiO_2-$HClO_4$ (0.05 g)	15
11	SiO_2-H_3PO_4 (0.05 g)	17
12	1-methylpiperidinium hydrogen chloride (1 mmol)	20
13	1-methylpiperidinium trifluoroacetate (1 mmol)	29
14	1-methylpiperidinium methanesulfonate (1 mmol)	40
15	1-methylpiperidinium hydrogen sulfate (1 mmol)	41
16	-	-

[a] Isolated Yield; reaction condition: room temperature, EtOH as solvent (5 ml), reaction time: 150 min

For find optimize the reaction conditions, the reaction was carried out by the using of different solvents (Table 2, Entries 1-7) or solvent-free condition (Table 2, Entry 8). Among the solvent screened, CH_2Cl_2 was found to be the best promoter in terms of reaction times and yields (Table 2, Entry 2).

For find optimized amount of 1-methylpiperidinium hydrogen sulfate, the reaction was carried out by varying amount of the catalyst (Table 2, Entries 9-11). Maximum yield was obtained when 1 mmol of catalyst was used (Table 2, Entry 1). Further increase in the amount of 1-methylpiperidinium hydrogen sulfate in mentioned reaction did not have any significant effect on the product yield. The results are summarized in Table 2.

Table 2. Optimization of the reaction conditions in the synthesis of 3-(4-methoxyphenylamino)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrol-2(5H)-one (Scheme 2).

Entry	Catalyst (mmol)	T (°C)	Solvent (5 mL)	Yield (%)[a]
1	1	r.t.	*n*-Hexane	50
2	1	r.t.	CH_2Cl_2	89
3	1	r.t.	Et_2O	49
4	1	r.t.	EtOAc	58
5	1	r.t.	EtOH	41
6	1	r.t.	MeOH	23
8	1	r.t.	-	51
9	0.5	r.t.	CH_2Cl_2	27
10	0.25	r.t.	CH_2Cl_2	26
11	-	r.t.	CH_2Cl_2	5

[a] Isolated Yields, reaction time: 4 h

Next, the scope and efficiency of this procedure was explored for the synthesis of a wide variety of substituted 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-ones (Scheme 1, Table 3).

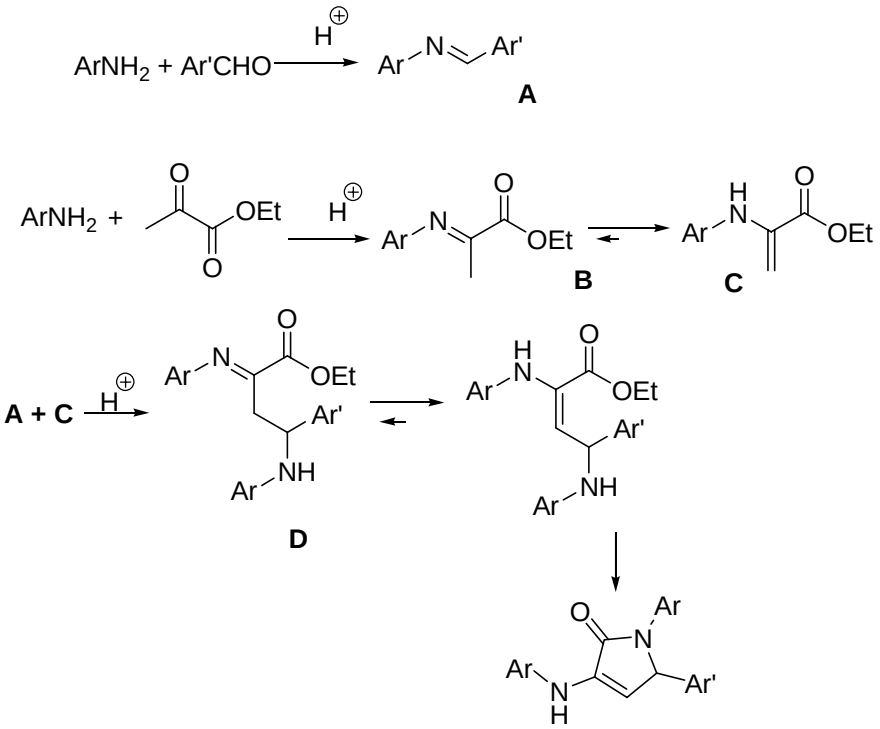
As expected, this reaction proceeded smoothly and the desired products were obtained in good yields. In general, aromatic/aliphatic aldehydes and aromatic amines were well tolerated in this reaction system (Table 3, product **a-s**). Based on the obtained results, the electronic effects and the steric effects of the substituents both in amines and aldehydes played significant role in the yields of products. Aromatic aldehyde systems that possessed substitutions at the *ortho*, *meta* or *para* positions had the yield, however, aromatic aldehydes containing electron-donating groups gave shorter time and higher yields than that with electron-withdrawing groups. When *ortho*-substituted aldehydes (Table 3, product **c**) were used in this process, the corresponding product was obtained in good yields but in longer reaction time. Electron donating group on the amine was able to facilitate the transformation by giving evidently higher yield of products and shorter reaction times than the entries using halogen atom functionalized anilines (Table 3). Furthermore, hetero-aromatic aldehyde also fit in good yields (Table 3, product **n**). Aliphatic aldehyde could join in the system successfully and our results show that aliphatic aldehydes react with 4-methyl aniline, and ethyl pyruvate successfully in good yields (Table 3, product **m**). However, in contrast to the findings of aromatic amines, aliphatic amines did not provide corresponding products under present conditions (Table 3, product **s**).

In accordance with the mechanism delineated by Li *et al.* [13] the first step of this process involves the catalytic condensation of an aldehyde with amine to form the corresponding imine (**A**). The second molecule of amine then undergoes coupling reaction with ethyl pyruvate to form intermediate **B** which is equilibrated with their enamine form (**C**). In continue the formation of intermediate **D** resulting from the condensation of intermediate **A** with intermediate **C** was established. Finally the imine – enamine conversion of intermediate **D** following by loss of ethanol from enamine form results in the synthesis of 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-one derivatives (Scheme 3).

Table 3: Synthesis of 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-one derivatives using 1-methylpiperidinium hydrogen sulfate as catalyst (Scheme 1).

Entry	Aldehyde	Amine	Product	Time (h)	Yield (%)a
1	Benzaldehyde	4-Methoxyaniline	**a**	4	89
2	4-Flourobenzaldehyde	4-Methoxyaniline	**b**	4.5	82
3	2-Chlorobenzaldehyde	4-Methoxyaniline	**c**	6	85
4	4-Nitrobenzaldehyde	4-Methoxyaniline	**d**	9	85
5	3-Nitrobenzaldehyde	4-Methoxyaniline	**e**	9	95
6	2-Methylbenzaldehyde	4-Methoxyaniline	**f**	6	87
7	4-Methoxybenzaldehyde	4-Methoxyaniline	**g**	3.5	93
8	4-Methylbenzaldehyde	4-Methoxyaniline	**h**	3.5	84
9	4-*tert*-Butylbenzaldehyde	4-Methoxyaniline	**i**	4	80
10	4-Chlorobenzaldehyde	4-Methoxyaniline	**g**	5	81
11	Benzaldehyde	4-Methylaniline	**k**	4	73
12	4-Methylbenzaldehyde	4-Methylaniline	**l**	4	65
13	Butyraldehyde	4-Methylaniline	**m**	4	70
14	Furfural	4-Methylaniline	**n**	5	61
15	Benzaldehyde	4-Chloroaniline	**o**	6	61
16	4-*tert*-Butylbenzaldehyde	4-Chloroaniline	**p**	4	74
17	4-Chlorobenzaldehyde	4-Chloroaniline	**q**	7	73
18	4-Flourobenzaldehyde	4-Chloroaniline	**r**	5	67
19	4-Chlorobenzaldehyde	Cyclohexylamine	**s**	10	-

[a]Isolated yields. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples [11-14].



Scheme 3. proposed mechanism for the preparation of 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-ones**.**

The work-up procedure is very clear-cut; that is the products were isolated and purified by simple filtration and washing with diethyl ether. Our protocol has been used from ionic liquids during the reaction process, that making it superior to the reactions that use hazardous liquid acidic catalysts.

4. CONCLUSION

In summary, an efficient protocol for the preparation of 1,5-diaryl-3-(arylamino)-1*H*-pyrrol-2(5*H*)-one derivatives was described. The reactions were carried out under ambient conditions with short reaction times and produce the corresponding products in good yields. The present methodology offers several advantages such as good yields, simple procedure, shorter reaction times and milder conditions and the products were purified *without* resorting to chromatography.

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