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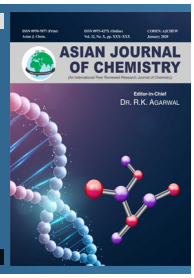

One Pot, Four Component Synthesis of Phthalazine-1,4-diones Derivatives in [BMIM][OH] Medium

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[BMIM][OH] mediated, green and efficient synthesis of phthalazines (**5**) have been developed by condensing diethyl phthalate (**1**), ethyl cyanohydrazide (**2**), substituted benzaldehyde (**3**) and malononitrile (**4**) in the presence of Meldrum's acid at 60-65 °C and at room temperature for 60-90 min. The importance of this method includes shorter reaction time and high yield.

Keywords: Diethyl phthalate, benzaldehydes, Ethyl cyanohydrazide, Meldrum's acid, Ionic liquids.

INTRODUCTION

Now a days, ionic liquids are using widely as reaction medium in modern organic chemistry [1]. Ionic liquids have non-volatile nature at room temperature and the main driving force for motivating chemists to develop green chemistry methods of synthesis of organic and heterocyclic compounds [2-4]. Multi-component reactions are one-pot reactions, which contains three to more components in single reaction vessel to give a final desired product containing substantial components of all the reactants [5-7]. One of great challenges in modern medicinal chemistry is design and discovery of pharmaceutical active molecules.

Heterocyclic products have nitrogen atom extend out over a wide area in the world and their act of applying to pharmaceutical active compounds and agrochemicals are becoming larger degree important [8,9]. Heterocyclic compounds with phthalazine moiety have great considerable priority attention among a large veriety of nitrogen containing compounds because of their biological active properties and clinical applications [10]. Phthalazine compounds possess anticonvulsant [11], cardiotonic [12,13] and vasorelaxant [14] activities. That's why so many preparation methods are reporting for synthesis of phthalazine compounds [15-19]. Nevertheless the development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment is an interesting challenge.

Therefore, it has been well thought-out to prepare phthalazine moiety which containg pyrans. Here, we report one-pot four component reaction for tiltle compounds in weakly basic [BMIM][OH] medium.

EXPERIMENTAL

Melting points are uncorrected and identified in sulfuric acid bath by open capillary tubes. Thin layer chromatography wrere moved on silica gel-G and visualizations were done by UV. ^{1}H NMR spectra were recorded in DMSO-d_6 using TMS as internal standard at 400 MHz operating frequency.

One-pot synthesis of compounds (5a-f): Diethyl phthalate (**1**) (1 mmol) and ethyl cyanohydrazide (**2**) (1 mmol) were heated at 60-65 °C for 0.5 h in [BMIM][OH] (1 mmol) for 0.5 h. To this reaction mass added benzaldehyde (**3**) and malononitrile (**4**) compounds and heated at 60-65 °C for 0.5 h. Reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, water (20 mL) was pored into reaction mass and filtered separated solid by filtration flask. The product was recrystallized from ethanol solvent to obtain compound **5**.

2-(7-Amino-2,2-dimethyl-4-oxo-5-phenyl-4,5-dihydropyrano[2,3-*d*][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione (5a): m.p.: 160–162 °C; IR (KBr, ν_{max}, cm^{-1}): 3146-3434 (br, m, -NH-), 1793 (s, s, -CO-), 1740 (s, s, -CO-), 1693 (s, s, -CONH-); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.3

(s, 3H, -C**H**$_3$), 1.5 (s, 3H, -C**H**$_3$), 5.3 (s, 1H, -C**H**), 7.0-7.9 (m, 9H, Ar-**H**), 8.2 (s, 2H, –N**H**$_2$), 11.3 (s, 1H, **-NH**); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.5, 22.1, 43.7, 72.9, 74.9,78.2, 99.7, 118.5, 123.6, 125.4, 127.3, 127.6, 128.1, 129.2, 135.2, 142.9, 155.2, 158.9, 165.0; HRMS calcd for $C_{24}H_{19}N_3O_7$ [M+H]$^+$: 462.0467. Found: 462.0426.

2-(7-Amino-2,2-dimethyl-4-oxo-5-(*p*-tolyl)-4,5-dihydropyrano[2,3-*d*][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione (5b): m.p.: 168–170 °C; IR (KBr, ν_{max}, cm^{-1}): 3140-3438 (br, m, -NH-), 1790 (s, s, -CO-), 1750 (s, s, -CO-), 1696 (s, s, -CONH-); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -C**H**$_3$), 1.6 (s, 3H, -C**H**$_3$), 2.2 (s, 1H, -C**H**$_3$), 5.4 (s, 1H, -C**H**), 7.1-7.9 (m, 8H, Ar-**H**), 8.1 (s, 2H, –N**H**$_2$), 11.4 (s, 1H, **-NH**); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.4, 21.2, 42.6, 72.8, 73.9,77.1, 99.6, 117.4, 123.5, 124.3, 127.3, 127.6, 128.2, 128.5, 135.2, 142.9, 155.1, 157.8, 165.1; HRMS calcd for $C_{25}H_{21}N_3O_7$ [M+H]$^+$: 476.1433. Found: 476.1482.

2-(7-Amino-5-(4-methoxyphenyl)-2,2-dimethyl-4-oxo-4,5-dihydropyrano[2,3-*d*][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione (5c): m.p.: 156–159 °C; IR (KBr, ν_{max}, cm^{-1}): 3142-3444 (br, m, -NH-), 1780 (s, s, -CO-), 1754 (s, s, -CO-), 1690 (s, s, -CONH-); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -C**H**$_3$), 1.6 (s, 3H, -C**H**$_3$), 3.9 (s, 1H, -C**H**$_3$), 5.3 (s, 1H, -C**H**), 7.1-7.9 (m, 8H, Ar-**H**), 8.2 (s, 2H, -N**H**$_2$), 11.2 (s, 1H, **-NH**); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.4, 22.3, 42.4, 72.8, 74.6,76.2, 98.5, 118.3, 122.4, 125.4, 127.4, 127.5, 128.2, 129.1, 134.2, 142.8, 154.2, 158.5, 164.5; HRMS calcd for $C_{25}H_{21}N_3O_8$ [M+H]$^+$: 492.1365. Found: 492.1313.

2-(7-Amino-2,2-dimethyl-5-(4-nitrophenyl)-4-oxo-4,5-dihydropyrano[2,3-*d*][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione (5d): m.p.: 172–174 °C; IR (KBr, ν_{max}, cm^{-1}): 3130-3446 (br, m, -NH-), 1785 (s, s, -CO-), 1759 (s, s, -CO-), 1696 (s, s, -CONH-); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.4 (s, 3H, -C**H**$_3$), 1.7 (s, 3H, -C**H**$_3$), 5.4 (s, 1H, -C**H**), 7.1-7.9 (m, 8H, Ar-**H**), 8.4 (s, 2H, –N**H**$_2$), 11.3 (s, 1H, **-NH**); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.1, 22.1, 43.3, 72.5, 74.7,78.3, 99.4, 118.2, 123.3, 125.5, 127.3, 127.6, 128.6, 129.2, 135.3, 142.5, 155.1, 158.6, 165.7; HRMS calcd for $C_{24}H_{18}N_4O_9$ [M+H]$^+$: 507.2431. Found: 507.2484.

2-(7-Amino-2,2-dimethyl-4-oxo-5-(*o*-tolyl)-4,5-dihydropyrano[2,3-d][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione (5e): m.p.: 165–167 °C; IR (KBr, ν_{max}, cm^{-1}): 3143-3435 (br, m, -NH-), 1793 (s, s, -CO-), 1754 (s, s, -CO-), 1690 (s, s, -CO-); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -C**H**$_3$), 1.6 (s, 3H, -C**H**$_3$), 2.3 (s, 1H, -C**H**$_3$), 5.3 (s, 1H, -C**H**), 7.1-7.9 (m, 8H, Ar-**H**), 8.1 (s, 2H, –N**H**$_2$), 11.3 (s, 1H, **-NH**); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 21.3, 22.3, 43.5, 72.7, 74.8,78.2, 99.7, 118.3, 123.5, 125.3, 127.3, 127.4, 128.2, 129.3, 135.3, 142.8, 155.4, 158.6, 165.2; HRMS calcd for $C_{25}H_{21}N_3O_7$ [M+H]$^+$: 476.1433. Found: 476.1479.

2-(7-Amino-5-(4-chlorophenyl)-2,2-dimethyl-4-oxo-4,5-dihydropyrano[2,3-d][1,3]dioxine-6-carbonyl)-2,3-dihydrophthalazine-1,4-dione (5f): m.p.: 152–154 °C; IR (KBr, ν_{max}, cm^{-1}): 3120-3396 (br, m, -NH-), 1770 (s, s, -CO-), 1769 (s, s, -CO-), 1670 (s, s, -CO-); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.3 (s, 3H, -C**H**$_3$), 1.8 (s, 3H, -C**H**$_3$), 5.1 (s, 1H, -C**H**), 7.1-7.9 (m, 8H, Ar-**H**), 8.1 (s, 2H, –N**H**$_2$), 11.3 (s, 1H, **-NH**); ^{13}C NMR (DMSO-d_6, 100 MHz): δ 20.4, 21.5, 43.2, 71.4, 73.6,77.4, 96.3, 116.1, 122.1, 125.4, 127.1, 127.4, 128.5, 129.1, 135.3, 142.5, 154.2, 158.4, 164.4; HRMS calcd for $C_{24}H_{18}ClN_3O_7$ [M+H]$^+$: 496.5234. Found: 496.5291.

Preparation of 3-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)-3-oxopropanenitrile (6) *via* step-wise reaction: A mixture of diethyl phthalate (**1**) and ethyl cyanohydrazide (**2**) were heated at 60-65 °C in [BMIM][OH] (1 mmol) for 0.5 h. Reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, water (20 mL) was pored into reacction mass and filtered separated solid by filtration flask. The product was recrystallized from ethanol solvent to obtain compound **6**. Yield = 71 %. m.p. 153-154 °C [lit m.p. 150-152 °C] [21].

Preparation of (*E*)-2-(2-cyano-3-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)-3-oxoprop-1-en-1-yl)benzene-1-ylium (7) from compounds 6 and 3: A mixture of compound **6** (1 mmol), compounds **3a-f** (1 mmol) and [BMIM][OH] (1 mmol) were heated at 60-65 °C for 0.5 h. Reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, water (20 mL) was pored into reacction mass and filtered separated solid by filtration flask. The product was recrystallized from ethanol solvent to obtain **7**. Yield = 89 %.

Compound 7: m.p.: 200–202 °C; IR (KBr, ν_{max}, cm^{-1}): 3267-3518 (br, m, -NH-), 2258 (s, s, -CN-), 1749 (s, s, -CO-), 1683 (s, s, -CO-),1613 (s, s, -CO-); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.6-8.4 (m, 10H, Ar-**H** and NC-C=C**H**), 11.4 **(s, 1H, -OH)**; ^{13}C NMR (DMSO-d_6, 400 MHz): δ 35.5, 81.3, 81.4, 117.2, 122.9, 124.0, 127.2, 128.4, 128.5, 129.0, 129.1, 129.6, 133.0, 136.1, 143.4, 164.4, 164.5, 164.8; HRMS calcd for $C_{18}H_{11}N_3O_3$ [M+H]$^+$: 318.0423. Found: 318.0426.

Preparation of compound 5 from compounds 7 and 4: A mixture of compound **7** (1 mmol), compound **4** (1 mmol) and [BMIM][OH] (1 mmol) were heated at 60-65 °C for 0.5 h. Reaction was monitored by thin-layer chromatography (TLC). After completion of reaction, water (20 mL) was pored into reacction mass and filtered separated solid by filtration flask. The product was recrystallized from ethanol solvent to obtain compound **5**. Yield = 83 %.

RESULTS AND DISCUSSION

Firstly, multi-component reaction of diethyl phthalate (**1**) (1 mmol), ethyl cyanohydrazide (**2**) (1 mmol), benzaldehyde (**3a**) (1 mmol) and malononitrile (**4**) (1 mmol) in different ionic liquid medium (([DBUH][OAc], [BMIM][Br] and [BMIM][OH]) at 60-65 °C to form compound **5a** have been taken as a replica reaction [20]. However, it is established that the one-pot reaction of in the presence of [BMIM][OH] as medium for 60-90 min at 60-65 °C give the highest yield (90 %) for compound **5a** (Table-1, entry 1). Here, intially compound **1** was reacted with cyanohydrazide (**2**) in [BMIM][OH] at 60-65 °C for 30 min to form compound **6** as intermediate (confirmed by TLC that means absence of starting materials). To this reaction, mass added compounds **3a** and **4** and again heated at 60-65 °C for 0.5 h to form compound **5a**. The compound **5a** was obtained in excellent yield (90 %) on simple work-up of reaction mixture. The structure of compound **5a** has been confirmed by ^{1}H NMR, IR and Mass spectroscopy.

TABLE-1
EFFECT OF IONIC LIQUID AND TEMPERATURE ON REACTION OF COMPOUNDS **1**, **2**, **3a** AND **4** TO YIELDING COMPOUND **5a**

Entry	Ionic liquid	Temp. (°C)	Time (min)	Compd. **5a** (%)
1	[BMIM][OH]	60-65	60	90
2	[BMIM][Br]	60-65	120	70
3	[DBU][OAc]	60-65	150	85
4	[BMIM][OH]	RT	300	75
5	[BMIM][OH]	40-45	150	78
6	[BMIM][OH]	80-85	50	80

Encouraged by above optimization results conditions, the one-pot reaction has been carried out at different temparature (room temperature, 40, 60 and 80 °C) in the presence of [BMIM][OH] mediated to get desired compound **5a**. However, it is established that the one-pot reaction of [compound **1** (1 mmol), compound **2** (1 mmol), compound **3a** (1 mmol) and compound **4a** (1 mmol)] in the presence of [BMIM][OH] as medium (1 mmol) for 60-90 min at 60-65 °C give the highest yield (90 %) for compound **5a** (Table-1, entry 1). In order to examine the quantity of [BMIM][OH], the one-pot reaction has been carried out at different quantity (0.5, 1 and 2 mmol) of [BMIM][OH] with respect of diethyl phthalate (**1**). However, it was found that the one-pot reaction of [compound **1** (1 mmol), compound **2** (1 mmol), compound **3a** (1 mmol) and compound **4a** (1 mmol)] in the presence of [BMIM][OH] as medium (1 mmol) for 2 h at 60-65 °C gave the highest yield (90 %) (Table-2, entry 2).

TABLE-2
EFFECT OF AMOUNT OF [BMIM][OH] FOR ONE POT REACTION

Entry	mmol of [BMIM][OH]	Time (h)	Compd. **5a** (%)
1	0.5	4	82
2	1.0	1	90
3	2.0	1	83

Having optimized good reaction conditions, the over simplification of the reaction was identified by conducting the one pot reaction with several others compounds **3b-f** respectively in [BMIM][OH] medium at 60-65 °C for 2 h giving compounds **5b-f** in good yields. It is established that this reaction works with a wide variety of substrates. It is worthy to mention that the reaction of compounds **1**, **2**, **3a-f** and **4** could get higher yield and require shorter reaction time for formation of compounds **5a-f**.

The synthesis of compound **5** could also be achieved in step-wise syntheses. Thus, a mixture of diethyl phthalate (**1**) and ethyl cyanohydrazide (**2**) was heated at 60-65 °C for 0.5 h in [BMIM][OH] medium to form intermediate **6** [21]. Then, compound **6** was reacted with benzaldehyde (**3**) at 60-65 °C for 0.5 h in [BMIM][OH] medium to form intermediate **7** [18] followed by compound **7** was reacted with malononitrile (**4**) at 60-65 °C for 0.25 h in [BMIM][OH] medium to form compound **5** (**Scheme-I**).

Conclusion

In summary, successfully modified a easy multi-component reaction for synthesis of phthalazine-1,4-diones with simple work up procedures in green methods.

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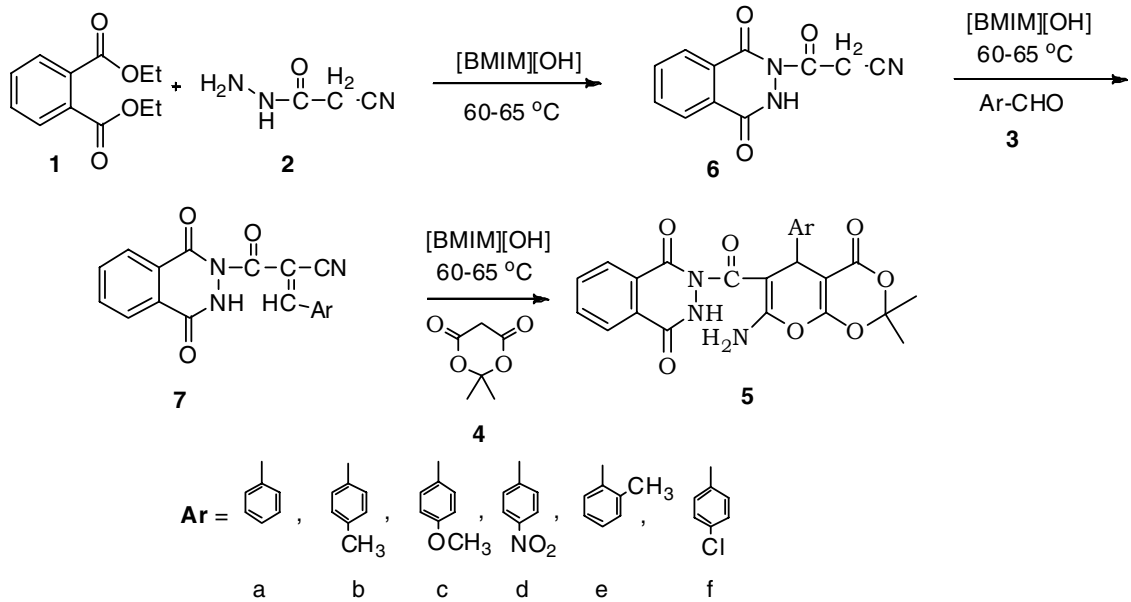
CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.



Scheme-I: Step-wise synthesis of compound **5**

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