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Glycerol-promoted catalyst-free one-pot three component synthesis of 1*H*-pyrazolo[1,2-b]phthalazinediones

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ABSTRACT

Glycerol-promoted catalyst-free one-pot three component synthesis of 1H-pyrazolo[1,2-b]phthalazinediones has been achieved. Use of greener solvent glycerol, catalyst-free reaction condition, high yields, one pot reaction and simple product isolation method without use of column chromatography are the noteworthy aspects of the synthetic route. Mechanistic route of the reaction proves the promoting nature of the glycerol. Indeed, we accentuated the direct utilization of glycerol as solvent to research community which is indispensable in economical and environmental viewpoint.

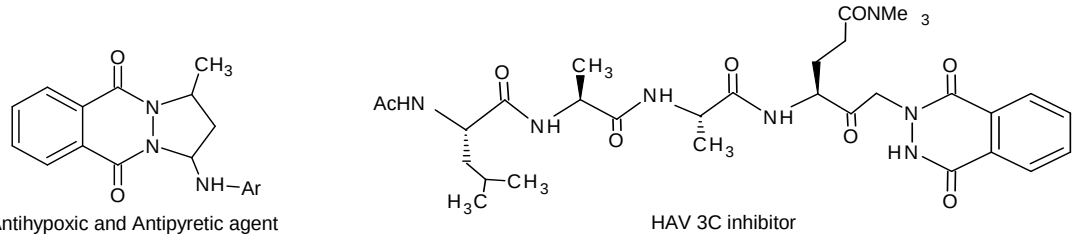
Keywords: Glycerol, Uncatalyzed, 1H-pyrazolo[1,2-b]phthalazinediones, promoting medium.

INTRODUCTION

Multicomponent reactions (MCRs) which built the skeletons found in natural products, drug like molecules and materials in single step has fascinated research community in recent days.[1] MCRs play an important role to pursue wide array of molecular diversity and complexity within single step in cost- and time- effective manner .[2,3]

Organic chemist must remain capable of furnishing products of high molecular complexity without jeopardizing the ecological system. Use of multicomponent reactions to generate diverse molecules along with environmentally friendly aspects such as catalyst-free condition, use of greener solvent perfectly answer these constrains. Relevantly, glycerol proved to be a very handy and vital greener solvent by promoting organic transformations such as Pd-catalyzed Heck C-C coupling and Suzuki reaction in glycerol.[4] Some organic transformations such as aza-michael addition of amines, anilines and indole, ring opening of styrene oxide with p-anisidine and acid catalyzed dehydrative dimerization of tertiary alcohol were eventuated in presence of glycerol.[5]

Heterocycles containing bridgehead hydrazine are endowed with pharmacological properties and clinical applications.[6-14] For example, pyrazolo[1,2-b]phthalazinedione derivatives are very important structural motif as they were reported as anti-inflammatory, analgesic, antihypoxic and antipyretic agent (Fig. 1).[15] Beside these, phthalazine derivatives were reported to possess anticonvulsant[16], cardiotonic[17] and vasorelaxant activities[18].



Antihypoxic and Antipyretic agent HAV 3C inhibitor

Fig. 1

Inspite of their wide utility range, very few methods have been developed for the synthesis of pyrazolo[1,2-b]phthalazine derivatives.[19-21] Apparently, these methods suffer from drawbacks such as relative toxic catalyst, harsh reaction conditions etc.

Fascinating properties of glycerol, vital utility range of phthalazinediones and in continuation of our work in heterocyclic chemistry[22-25] enthused us to design a simple, proficient and candid synthetic route for the synthesis of 1H-pyrazolo[1,2-b]phthalazinediones using glycerol. Thus, we have demonstrated a very convenient synthesis of phthalazinedione derivatives by catalyst-free one-pot three component reaction of phthalhydrazide, malononitrile and aryl aldehydes promoted by glycerol.

MATERIALS AND METHODS

General:

All chemicals used were of research grade and obtained from Aldrich. The reactions were carried out in glass tube of diameter 2.5cm at 80^0C. Progress of reaction was monitored by TLC (Silica gel 60 F_{254}). ^{1}H and ^{13}C spectra of isolated compounds were reported by using DMSO solvent on Brucker 300 MHz spectrometer with TMS as an internal standard.

Typical Procedure for Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione derivatives:

The mixture of aryl aldehydes (1mmol), malononitrile (1mmol) and phthalhydrazide (1mmol) in 5ml glycerol was stirred at 80^0C in an oil bath and progress of reaction was monitored by TLC. After the completion of the reaction, dilution of reaction mixture with water followed by simple filtration afforded product, which was dried, recrystallized from ethanol and advanced for analysis.

3-Amino-5, 10-dioxo-1-phenyl-5, 10-1H-pyrazolo[1,2-b]phthalazine-2- carbonitrile (4a).

IR (KBr): 3362, 2198, 1660, 1601 cm^{-1}. ^{1}H NMR(DMSO,d_6,300MHz): δ6.21(s,1H,CH), 7.4-7.53(m,5H,Ar-H), 8.03(bs,2H.NH_2), 8.17(t,3H,Ar-H),8.34(q,1H,Ar-H). C^{13} NMR(DMSO,d_6,75MHz): δ 61.87, 63.51,100.02, 116.31, 127.18, 127.24, 127.77, 128.72, 128.93, 129.09, 134.10, 135.04,138.69, 151.09, 154.09, 157.04 ppm. Anal Calcd for $C_{18}H_{12}N_4O_2$: C, 68.35. H, 3.82. N, 17.71%. Found: C, 68.33. H, 3.81. N, 17.70%.

3-Amino-1-(2-chlorophenyl)-4,9–dioxo-3a,4,9a–tetrahydro-1H-cyclopenta[b]naphthalene-2-carbonitrile (4b).

IR (KBr): 3373, 3176, 2210, 1679, 1659 cm^{-1}. ^{1}H NMR(DMSO,d_6,300MHz): δ6.46 (s,1H,CH), 7.28 (bs,2H.NH_2), 7.35(t,2H,Ar-H),7.89(d,2H,Ar-H) 8.05-8.28(m,4H,Ar-H). C^{13} NMR(DMSO,d_6,75 MHz): δ 60.27, 61.41, 115.73, 127.25, 127.87, 127.95, 128.56, 128.83, 130.18, 130.24, 132.03, 134.14, 135.06, 151.50, 153.84, 156.94 ppm. Anal Calcd for $C_{18}H_{11}ClN_4O_2$: C, 61.64. H, 3.16. N, 15.97%. Found: C, 61.67. H, 3.15. N, 15.95%.

3-Amino-1-(4-chlorophenyl)-4,9–dioxo-3a,4,9a–tetrahydro-1H-cyclopenta[b]naphthalene-2-carbonitrile (4d).

IR (KBr): 3363, 2361, 2196, 1660 cm^{-1}. ^{1}H NMR(DMSO,d_6,300MHz): δ6.16 (s,1H,CH), 7.42-7.55(m,4H,Ar-H) 7.97 (bs,2H.NH_2), 8.00-8.29(m,4H,Ar-H). C^{13} NMR (DMSO,d_6,75MHz): δ 61.61, 62.87, 100.08, 116.93, 126.99, 128.25, 129.51, 133.53, 135.29, 138.06, 151.38, 154.40, 157.42 ppm. Anal Calcd for $C_{18}H_{11}ClN_4O_2$: C, 61.64. H, 3.16. N, 15.97%. Found: C, 61.62. H, 3.18. N, 15.93%.

3-Amino-1-(3-nitrophenyl)-4,9–dioxo-3a,4,9a–tetrahydro-1H-cyclopenta[b]naphthalene-2-carbonitrile (4f).

IR (KBr): 3433, 3323, 2198, 1658, 1602 cm^{-1}. ^{1}H NMR(DMSO,d_6,300MHz): δ6.33 (s,1H,CH), 7.94 (bs,2H.NH_2), 7.9-8.38(m,8H,Ar-H). C^{13} NMR(DMSO,d_6, 75MHz): δ 60.67, 62.73, 100.04, 116.10, 122.50, 123.76, 127.21, 127.77, 128.91, 129.35, 130.41, 134.12, 134.17, 140.84, 148.46, 151.56, 154.37, 157.15 ppm. Anal Calcd for $C_{18}H_{11}N_5O_4$: C, 59.84. H, 3.07. N, 19.38%. Found: C, 59.81. H, 3.09. N, 19.35%.

3-Amino-1-(3-hydroxyphenyl)-4,9–dioxo-3a,4,9a–tetrahydro-1H-cyclopenta[b]naphthalene-2-carbonitrile (4i).

IR (KBr): 3372, 3268, 2192, 1660, 1578 cm^{-1}. ^{1}H NMR(DMSO,d_6,300MHz): δ 1.28(bs, 1H,OH), 6.00 (s,1H,CH), 6.69-7.13 (m,4H,Ar-H), 7.87(d,2H,Ar-H),8.00(bs,2H,NH_2) 8.10-8.25(dd,2H,Ar-H). C^{13} NMR(DMSO,d_6,75MHz): δ 61.92, 63.36, 113.81, 115.88, 116.01, 117.58, 127.16, 127.70, 128.73, 128.91, 129.74, 133.78, 134.79, 150.86,

153.78, 156.76, 157.89 ppm. Anal Calcd for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.64; N, 16.86%. Found: C, 65.08; H, 3.63; N, 16.85%.

3-amino-1-(3,4-dimethoxyphenyl)-5,10-dioxo-5,10-dihydro-1H-pyrazolo[1,2-b]phthalazine-2-carbonitrile (4j).
IR (KBr): 3005, 2905, 2222, 1659, 1271 cm^{-1}. ^1H NMR(DMSO,d_6,300MHz): δ 3.8 (s,3H,OCH_3), 3.89 (s,3H,OCH_3), 7.1 (s,1H,CH), 7.57(t,2H,Ar-H), 7.8(d,2H,Ar-H), 8.05(d,2H,Ar-H), 8.26(s,1H,Ar-H), 11.44 (bs,2H.NH_2), C^{13} NMR(DMSO,d_6,75MHz): δ 55.97, 56.32, 111.36, 111.41, 113.81, 114.60, 124.35, 125.56, 127.71, 128.20, 132.42, 149.29, 154.81, 155.79, 160 ppm. Anal Calcd for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89%. Found: C, 63.85; H, 4.25; N, 14.88%.

RESULTS AND DISCUSSION

Considering the promoting nature of glycerol,[4,5] we carried out a blank reaction of phthalhydrazide, benzaldehyde and malononitrile using glycerol at ambient temperature but very low yield was obtained. Thus, we decided to optimize the temperature condition and carried out the same reaction at various temperatures ranging from 50 to 100^0C. It was found that increase in temperature gradually increased the yield and at 80^oC reaction afforded optimized yield of 92% within 50 min (table I, entry 1)(Scheme I).

Since the reaction marches under catalyst-free condition we decided to study the effect of solvents on the reaction and worked the same reaction in various solvents like DMF, DMSO, toluene, methanol, ethylene glycol etc (table I, entries2-6) which is found to be captious attributing low or no yield. When water was checked as solvent, moderate yield (40%) was obtained might be due to hydrophobicity of phthalhydrazide (table I, entry 7).

Scheme I: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-dione in Glycerol, Crude Glycerol or Water at 80^0C.

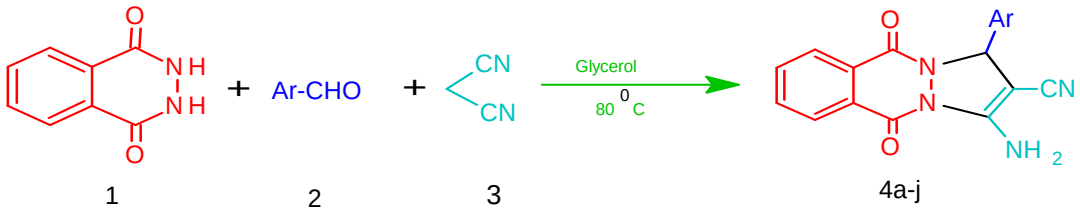


Table I: Synthesis of 1H-pyrazolo[1,2-b]phthalazine-dione in various solvents under catalyst-free conditions. [a]

Entry	Solvent	Yield (%)[b]	Time	Temperature
1	Glycerol	92	50 min	80^0C
2	Ethylene Glycol	40	4 h	80^0C
3	Methanol	<5	5 h	Reflux
4	Toluene	0	6 h	100^0C
5	DMF	0	6 h	100^0C
6	DMSO	0	6 h	100^0C
7	Water	40	4 h	100^0C

[a] *Reaction using 1 mmol of each component i.e. phthalhydrazide, malononitrile, and benzaldehyde, solvent: 5ml.*
[b] *Isolated yield.*

Efficacy of glycerol over solvent like ethylene glycol which also has almost similar properties can be explained on the basis of viscosity and strength of hydrogen bonding network created by glycerol. In comparison with ethylene glycol, glycerol has high degree of viscosity as well as more number of –OH atoms which increase the strength of hydrogen bonding with substrates. Our sincere effort to circumvent the concerns of mechanism of reaction (Scheme II) depict, in first step glycerol formulate electrophilic activation of aldehyde to increase rate of formation of knoevenagel product supported using a report by Fei *et al*.[26] In second step, it accelerates the rate of aza-michael addition of one of the nitrogen of phthalhydrazide on knoevenagel product and cyclization as shown in scheme 2 supported using report by Yang long Gu *et al* on aza-michael addition reaction.[5]

Enthused with these results to investigate the substrate scope of protocol we reacted structurally diverse aryl aldehydes in the reaction. It was found that almost all aldehydes participated well in the reaction attributing the satisfactory yields indicated in table II (Scheme I).

Scheme II: Plausible Mechanism of the route

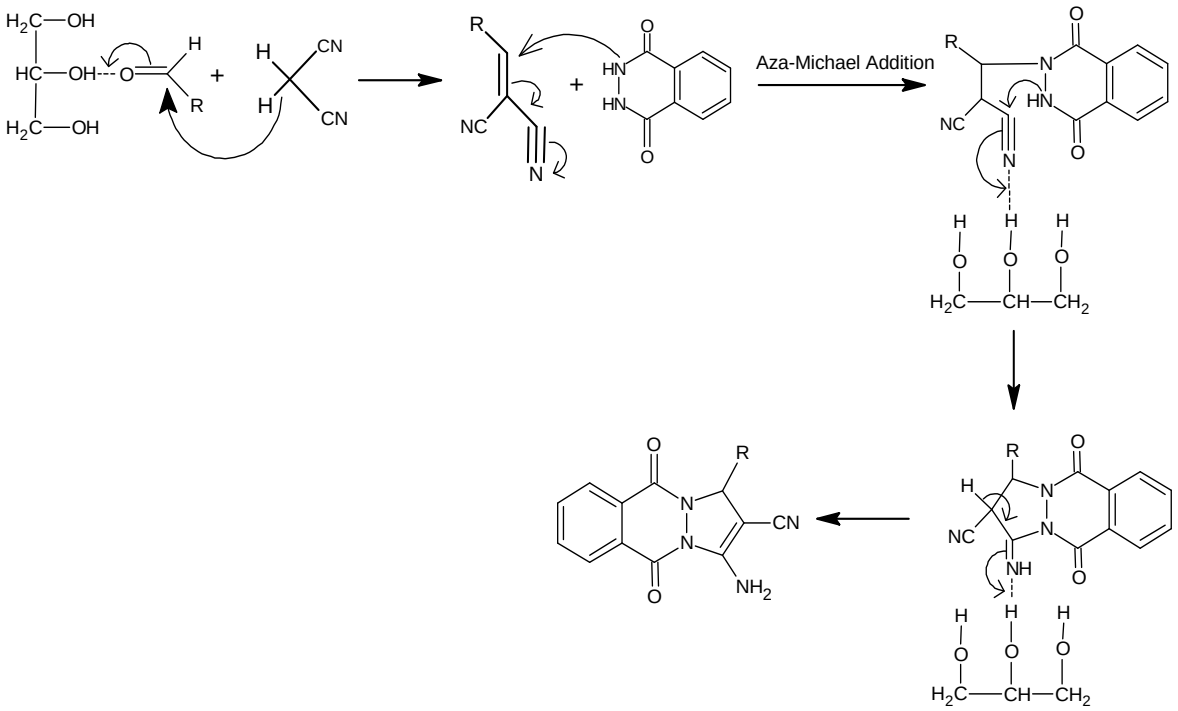
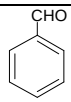
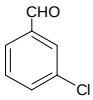
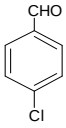
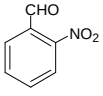
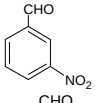
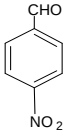
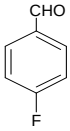
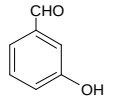
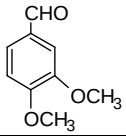


Table II Catalyst-free one-pot Synthesis of 1H-pyrazolo[1,2-b]phthalazine-dione in Glycerol.[a]

Entry	Aldehydes		Time (min)	Yield (%)[b]	Melting Point Reported. m.p. (0C)/Lit. m.p (0C) [Ref]
1		4a	50	92	276 / (276-278) [19]
2		4b	70	90	260-262 /(259-261) [19]
3		4c	65	89	266 / (266-267) [20]
4		4d	50	94	269-270 / (270-272) [19]
5		4e	75	85	265 / (265-266) [20]
6		4f	50	89	268-270 / (269-271) [21]
7		4g	47	89	231 / (230-232) [21]
8		4h	65	86	263-265 / (263-265) [20]

9		4i	45	88	212 The product was prepared for first time
10		4j	45	92	150-152 The product was prepared for first time

[a] *Reaction at 1 mmol of Each component i.e. phthalhydrazide, malononitrile and aryl aldehydes at 80°C.*
[b] *Isolated Yield.*

CONCLUSION

This report will enthuse contemporary organic chemist toward direct utilization of glycerol as promoting medium to generate conspicuous molecules such as 1H-pyrazolo[1,2-b]phthalazinediones. We have designed a simple, efficient and noteworthy synthetic protocol for the synthesis of 1H-pyrazolo[1,2-b]phthalazinediones in glycerol which complies with the stringent criteria of green chemistry. Isolation of high yields without column chromatography, catalyst-free condition, use of greener solvent glycerol are the prominent aspects of the synthetic route.

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