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POLYANILINE SULFATE SALT CATALYZED ONE-POT THREE-COMPONENT SYNTHESIS OF 2*H*-INDAZOLO[2,1-b]PHTHALAZINE-TRIONES

K. R. VIJAYAPAL REDDY and T. V. D. PRASAD RAO*

Department of Chemistry,Osmania University, Hyderabad-500 007, TS, India.
Corres. Author E-mail: thyp123@gmail.com

ABSTRACT

An alternative route has been developed for the synthesis of 2H indazolo[2,1-b]pthalazine-trione derivativesby one pot three component condensation reaction of benzaldehydes (**1a-n**)pthalhydrazide(**2**) and 5,5 dimethyl –1,3–cyclohexanedione (**3**) along with acetonitrile and DMF solvent systemusing polyaniline sulfate salt (PASS) as a catalystin good to excellent yields.

Keywords: Polyanilinesulfate salt, multicomponent condensation, 2*H*-indazolo[2,1-*b*]phthalazine-triones.

INTRODUCTION

The new synthetic methods were developed for the efficient synthesis of heterocycles containing phthalazine ring fragment (antihypoxic and antipyretic agent **I** & **HAV** 3C inhibitor **II**) (Fig. 1) is an important challenge, because they show some pharmacological and biological activites[iii-v]. Phthalazinederivatives were reported to possess anticonvulsant[xi], cardiotonic[vii] and vasorelaxant[viii] activities. A number ofmethodshave been reported for the synthesis of phthalazinederivatives[ix-xv].It is a challenge to develop the newsyntheticmethods for the efficient preparation of heterocycleshavingphthalazine ring fragment, despite theavailable methods.

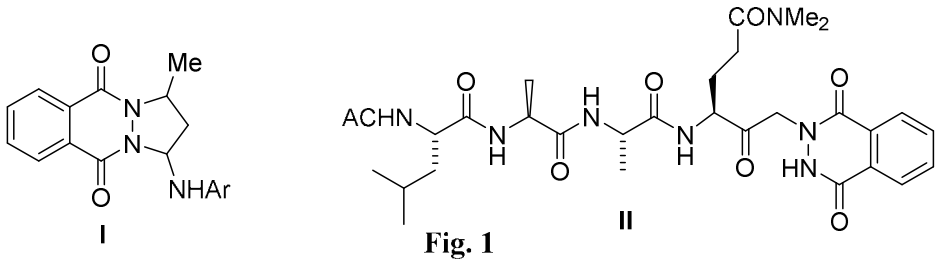


Fig. 1

In view of economic and environmental factors, Lewis Acid catalysts have gained importance over the years. One such Lewis acid catalyst is Polyaniline-sulfate salt.

This catalyst is generally inexpensive, easy to prepare and convenient to handle. Several organic transformationsprepared using polyaniline salts as polymer based solid acid catalyst (Fig.2) in organic solvents wererecently reported[xvi].

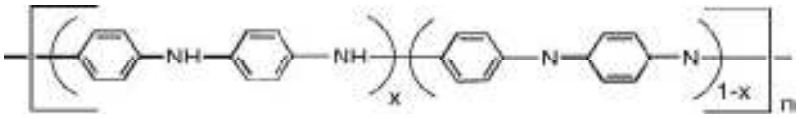


Fig. 2

The formation of different condensationproducts can be expecteddepending on specific conditionsand the building blockstructures[xvii-xxi]from the multicomponent reactions of dimedone (5,5-dimethylcyclohexane-1,3-dione), an aldehyde, and *N*-nucleophilicheterocyclesattracted the interest of synthetic community. The heterobicyclic compound,Phthalhydrazide (2,3-dihydro-1,4-phthalazinedione) containing two NH-nucleophilicgroupsis very interesting compound.In the present work, we took the advantage of –NH groups in three-component condensation reaction of dimedone(**3)**, pthalhydrazide(**2)** and aromatic aldehydes (**1a-n)** in the preparation of 3,4-dihydro-3,3-dimetrhyl-13-aryl-2*H*-indizalo[1,2-*b*]pthalazine-1,6,11(13*H*)trione (Scheme1).

MATERIAL AND METHODS

General methods

Fischer-Johns melting point apparatus has been used to measure the melting pointsand they are uncorrected. IR spectra were recorded as neat liquids or KBr pellets and absorptions are reported in cm^{-1}. Spectrometers of 300 MHz (Bruker) and 500 MHz (Varian) were used to recordNMR spectra and spectrometersof 75MHz and 125 MHz were used to record ^{13}C NMR spectra. Analytically pure reagents and solvents were used without further purification. An analytical thin layer chromatography (TLC) performed on silica gel GF254 pre-coated plates were used to monitorall the experiments.Silica gel finer than 200 mesh was used for column chromatography.

Preparation of Polyaniline-Sulfate Salt by the aqueous-polymerization pathway using sulfuric acid:

Aniline (2.3 mL) and sulfuric acid (9 mL) were dissolved in 90 mL of distilled water containing 5.71 g of ammonium persulfate was added drop wise to the above solution over a period of approximately 20 minutes. The reaction was allowed to proceed for 4 h. The precipitate was separated from the reaction mixture and washed three times with 300 mL water followed by 300 mL of acetone. The powder was dried at 100 ^{o}C till the constant mass was reached[xx].

Typical procedure for the synthesis of 2*H*-indazolo [1,2-*b*]phthalazine-triones:

A mixture of benzaldehyde (100 mg, 1.0equiv), dimedone (125 mg, 1.0equiv), phthalazide (150 mg, 1.0equiv) and 2.4 wt%ofpoly aniline sulfate salt was stirred in acetonitrile (5 mL) and refluxed at 80 ^{o}C for 2 h. The reaction was monitored by TLC. After completion of the reaction,chloroform was added andthe catalyst was removed by filtration. The filtrate was washed with water and dried over anhydrous Na_2SO_4.The solventwas

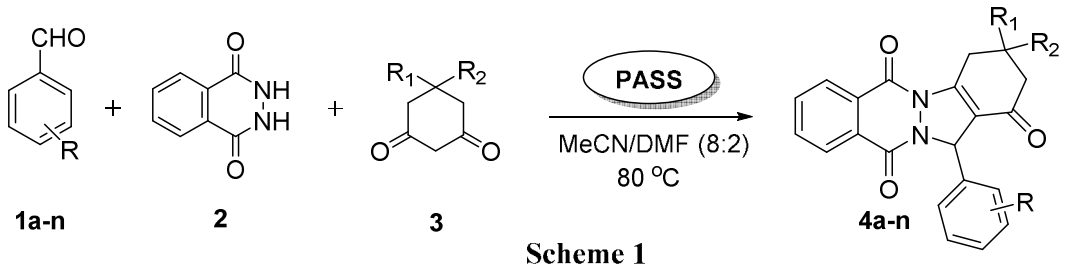
removedunder reduced pressure. The residue is recrystallized from ethyl acetate/n-hexane (1:3) to afford pure product indizalo[1,2-*b*]phthalazine-triones as a fluorescent powder.

Representative Spectral data:

3,3-Dimethyl-13-phenyl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione (**4a**): Yield 80%, m.p.202-204^{0}C (Reported[xxiii]m.p. 204-206^{0}C; IR(KBr): ν_{max} 2952.32, 1661.77, 1619.11, 1362.42 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6):
δ 1.23 (s, 6H, $2CH_3$), 2.30 (s, 2H, CH_2CO), 3.12-3.48 (q, 2H, CH_aH_bCO), 6.39 (s, 1H, CHN) 7.20-8.48 (m, 9H, Ar-H). MS-ESI, m/z=373(M+H).***13-(2,4-Dichloro-phenyl)-3,3-dimethyl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione*** (**4c**): Yield 86%, m.p. 206-207^{0}C (Reported[xxiv]m.p. 208-209^{0}C; IR(KBr) ν_{max} 2957.85, 1664.41, 1359.32, 1267.16 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.22 (s, 6H, $2CH_3$), 2.28 (s, 2H, CH_2CO), 3.12-3.50 (q, 2H, AB system *J* =21 Hz CH_aH_bCO), 6.58 (s, 1H, CHN) 7.21-8.40 (m, 8H, Ar-H). ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6): δ 191.26 (C=O), 155.22, 153.46, 151.40, 134.07, 133.12, 132.77, 131.62, 128.27, 127.78, 127.36, 126.84, 115.56, 62.29, 50.06, 37.22, 33.88, 28.11, 27.57. MS-ESI, m/z=441(M+H).***3,3-Dimethyl-13-(3,4,5-trimethoxy-phenyl)-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-trione*** (**4f**): Yield 82%, m.p. 200-201^{0}C (Reported[xxiv]m.p. 202-203^{0}C; IR(KBr): ν_{max} 2960.01, 1659.51, 1356.09, 1264.18 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.15 (s, 6H, 2xCH_3), 2.30 (s, 2H, CH_2CO), 3.11-3.42 (q, 2H, AB system *J* =20 Hz CH_aH_bCO), 6.32 (s, 1H, CHN), 8.18-8.38 (m, 8H, Ar-H). MS-ESI, m/z=407(M+H).***3,3-Dimethyl-13-naphthalen-1-yl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione*** (**4h**): M.p. 264-266^{0}C; IR(KBr) ν_{max} 2958.87, 1654.94, 1361.84 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.32 (s, 6H, $2CH_3$), 2.42 (s, 2H, CH_2CO), 3.3-3.56 (q, 2H, CH_aH_bCO), 6.62 (s, 1H, CHN), 7.42-8.46 (m, 11H, Ar-H). MS-ESI, m/z=423(M+H).

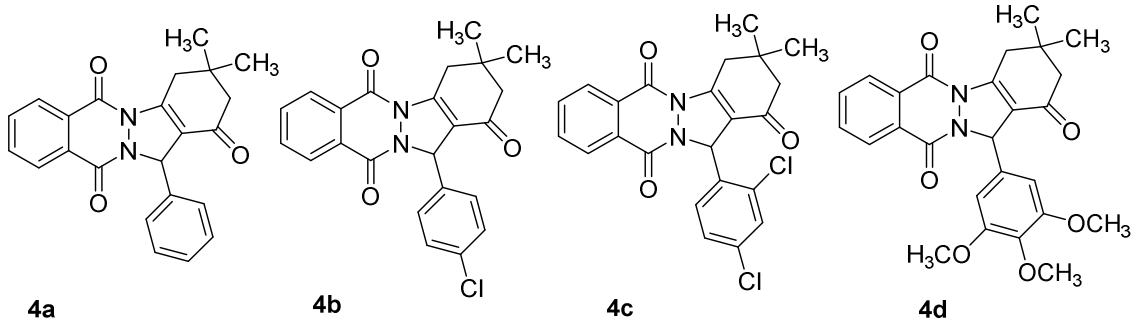
Results and Discussion

Initially, a pilot reaction was attempted using benzaldehyde(**1a**), phthalhydrazide (**2**), 5,5-dimethyl-1,3-cyclohexanedione (**3**) in the presence of polyaniline-sulfate salt along with acetonitrile and DMF solvent system. After 3 hours only 20% of 3,3-dimethyl-13-phenyl-2,3,4,13-tetrahydro-indizalo[1,2-*b*]phthalazine-1,6,11-trione product was isolated. Increasing the amount of polyaniline-sulfate salt (2.4 wt% to 5.0 wt%) did not improve the product yield to a considerable amount. We have also been investigated the effect of different solvents on the rate of reaction and as well as yield of the products. The reaction was very slow and the product yieldis low in presence of solvents such as MeOH or EtOH and also in coordinating solvents such as diethyl ether, THF and dimethyl ether, similar results were obtained. On the other hand, the reactions conducted in chlorinated solvents such as dichloromethane and chloroform, the reaction rates as well as product yields are improved. After carrying out the reaction in different solvents, acetonitrile found to be the solvent of choice, which is not only give the products in good yield, but also with higherrate of reactions (80% yield in 5 h).

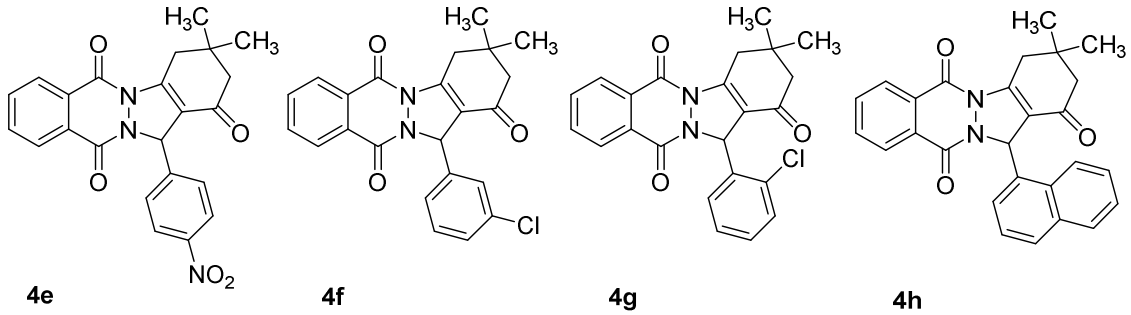


1a-n **2** **3** **4a-n**

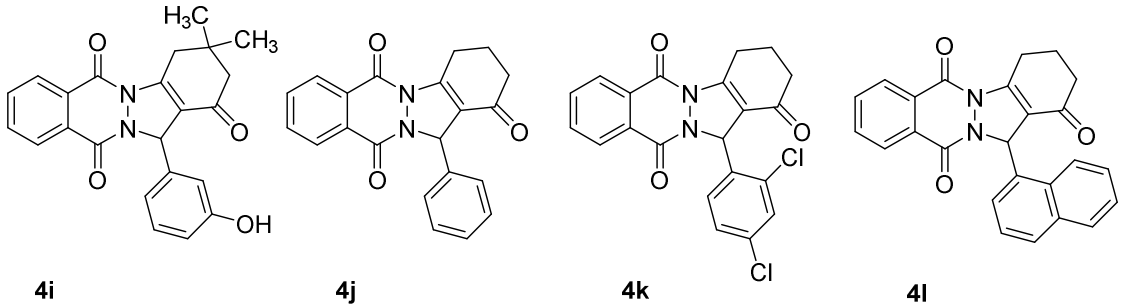
Scheme 1



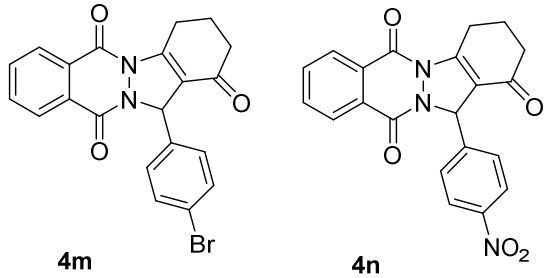
4a **4b** **4c** **4d**



4e **4f** **4g** **4h**



4i **4j** **4k** **4l**



4m **4n**

Aromatic aldehydes (**1a-n)**, phthalhydrazide(**2**), 5,5-dimethyl-1,3-cyclohexanedione (**3a**) in the presence of 2.4 wt%ofpolyaniline-sulfate salt undergo a fast 1:1:1addition reaction at

80^{o}C in CH_3CN for 5 h to produce 2*H*-indizalo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione derivatives **4a-n (Scheme 1).** The results were excellent in terms of yields and product purity in the presence of 2.4 wt% polyaniline-sulfate salt. The nature of these compounds as 1:1:1 adducts, was apparent from their mass spectra, which displayed in each case, the molecular ion peak at appropriate m/z values. The compounds **4a-n** are stable solids whose structures are fully supported by IR, ^{1}H NMR, ^{13}C NMR spectroscopes and mass spectrometry.

Conclusion

In conclusion, we developed an efficient process for one-pot three component synthesis of phthalazinetriones by the condensation of various aldehydes,phthalhydrazide, dimedone in acetonitrile at 80 ^{o}C temperature using 2.4 wt%ofpolyaniline-sulfate salt as a catalyst. This methodology offered very attractive features such as reduced reaction times and high yields. This simple procedure combined with ease of recovery and reuses of the catalyst. This method is economic, benign and waste free chemical process for the synthesis of phthalazinetriones.

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