Available online at www.derpharmachemica.com

Scholars Research Library

Der Pharma Chemica, 2014, 6(3):228-233
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

Synthesis of 3,4-dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo [1,2-*b*]pthalazine-1,6,11(13*H*)-triones using tungstated zirconia (WO_3/ZrO_2)

Srinivasa Reddy Konda[1,2]*, Buchi Reddy Reguri[3] and Mukkanti Kagga[2]

[1]*Brundavan Laboratories Pvt Ltd, No. 305, Yellareddyguda Road, Hyderabad*
[2]*Centre for Pharmaceutical Sciences, JNT University, Kukatpally, Hyderabad, India*
[3]*IPCA Laboratories Ltd, 142 AB, Kandivli Industrial Estate, Mumbai, India*

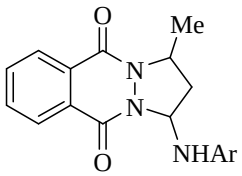
ABSTRACT

A New, robust and fasile route for the three-component synthesis of 2H-indazolo [2,1-b]phthalazine-triones in the presence of a catalytic amount of Tungstated Zirconia (WO_3/ZrO_2) Lewis acid has been developed. Short reaction time, simple operation, and high yields are the advantages of this protocol

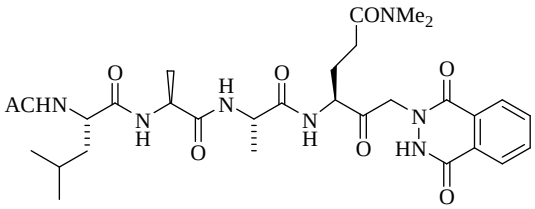
Keywords: 3,4-Dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo [1,2-*b*] pthalazine-1,6,11(13*H*)-triones, Ant hypoxic agent, Antipyretic agent, Tungstated Zirconia, high yields conditions.

INTRODUCTION

Hepatitis virus (HIV) is a causative agent of an acute form of infection hepatitis [1] and belongs to the picorna virus family that contains more than 200 known members, including other pathogens such as human rhinovirus (HRV), foot and mouth disease virus, poliovirus (PV), and encephalomyocarditis virus (EMCV). Picornaviruses pocess a small positive single-stranded RNA genome whose translation in the host cells produces a single ~250 KDa polyprotien, proteolyses processing of which is a core feature of the viral replication strategy. In hepatitis A virus, the 3C cysteine proteinase is the key enzyme necessary for the cleavage of the primary polyprotein [2]. Hence, potent and selective inhibitors of 3C proteinase could serve as attractive targets for the development of new antiviral therapeutic agents (**1**, **Figure 1**).



Antihypoxic and antipyretic agent



HAV 3C inhibitor

Figure 1

The development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment (antihypoxic and antipyretic agent HAV 3C inhibitor (**1**, **Figure 1**)) is an interesting challenge because they show some pharmacological and biological activites [3-5]. Phthalazine derivatives were reported to possess anticonvulsant [6], cardiotonic [7] and vasorelaxant [8] activities. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives [9-15]. In recent years, the development of more economical and environmental friendly conversion process is gaining interest in the chemical community.

MATERIALS AND METHODS

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 and $CDCl_3$ as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up.

***Typical procedure for the synthesis of 2H-indazolo [1,2-b]phthalazine-triones*:** A mixture of benzaldehyde (100 mg, 1 equiv), dimedone (125 mg, 1 equiv), phthalazide (150 mg, 1 equiv) and 5% WO_3/ZrO_2 (100 mg, 0.5 equiv) was stirred in acetonitrile (5 mL) and refluxed at 80 ^{0}C for 5 h. The reaction was monitored by TLC. After completion of the reaction, chloroform was added, catalyst was removed by filtration. The filtrate was washed with water dried over anhydrous Na_2SO_4.The solvent was removed under 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 yellow powder.

3,3-Dimethyl-13-phenyl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione (**4a**): M.p.205 ^{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, AB system J =22 Hz CH_aH_bCO), 6.39 (s, 1H, CHN) 7.20-8.48 (m, 9H, Ar-H). MS-ESI, m/z=373(M+H).

13-(4-Chloro-phenyl)-3,3-dimethyl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione (**4b**): M.p. 263 ^{0}C; IR(KBr) ν_{max} 2957.75, 1656.45, 1622.1, 1369.49 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.23 (s, 6H, $2CH_3$), 2.15 (s, 2H, CH_2CO), 3.12-3.44 (q, 2H, AB system J =20 Hz CH_aH_bCO), 6.31 (s, 1H, CHN) 7.24-8.37 (m, 8H, Ar-H). MS-ESI, m/z=407(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**): M.p. 205 ^{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 (**4d**): M.p.207 ^{0}C; IR(KBr) ν_{max} 2954.86, 1661.13, 1362.11, 1127.17 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.23 (s, 6H, $2CH_3$), 2.41 (s, 2H, CH_2CO), 3.12-3.50 (q, 2H, AB system J =19 Hz CH_aH_bCO), 3.71-3.92 (m, 9H, $3xOCH_3$), 6.43 (s, 1H, CHN), 6.60-8.42(m, 6H, Ar-H). MS-ESI, m/z=463(M+H).

3,3-Dimethyl-13-(4-nitro-phenyl)-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine trione (**4e**): M.p. 208 ^{0}C; IR(KBr) ν_{max} 2897.34, 1659.47, 1525.06, 1348.16 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.13 (s, 6H, $2CH_3$), 2.25 (s, 2H, CH_2CO), 3.12-3.47 (q, 2H, AB system J =19 Hz CH_aH_bCO), 6.43 (s, 1H, CHN), 7.53-8.38 (m, 8H, Ar-H). MS-ESI, m/z=418(M+H).

3,3-Dimethyl-13-(3,4,5-trimethoxy-phenyl)-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-trione (**4f**): M.p. 207 ^{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).

13-(2-Chloro-phenyl)-3,3-dimethyl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione (**4g**): M.p. 254 ^{0}C; IR(KBr): ν_{max} 3638.17,2956.02, 1663.03, 1358.0, 1266.45,705.07 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 1.22 (s, 6H, 2xCH_3), 2.29 (s, 2H, CH_2CO), 3.13-3.42 (q, 2H, AB system J =21 Hz CH_aH_bCO), 6.62 (s, 1H, CHN) 7.23-8.46 (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. 268 ^{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, AB system J =18 Hz CH_aH_bCO), 6.62 (s, 1H, CHN), 7.42-8.46 (m, 11H, Ar-H). MS-ESI, m/z=423(M+H).

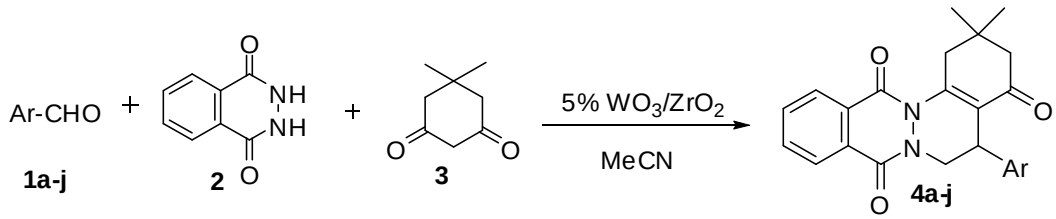
13-(3-Hydroxy phenyl)-3,3-dimethyl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione (**4i**): M.p. 241 ^{0}C; IR(KBr) ν_{max} 2957.75, 1656.45, 1622.81, 1364.49 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.08 (s, 6H, 2CH_3), 2.32 (s, 2H, CH_2CO), 3.32-3.43 (q, 2H, AB system J =19 Hz CH_aH_bCO), 6.31 (s, 1H, CHN) 7.24-8.37 (m, 8H, Ar-H). MS-ESI, m/z=389(M+H).

13-Phenyl-2,3,4,13-tetrahydro-indazolo[1,2-b] phthalazine-1,6,11-trione (**4j**): M.p. 183-185 ^{0}C; IR(KBr) ν_{max} 2928.63, 1656.46, 1362.87,1174.99 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO-d_6): δ 2.13-2.50 (s, 4H, 2xCH_3), 3.22-3.62 (m, 2H, CH_2CO), 6.35 (s, 1H, CHN) 7.14-8.40 (m, 9H, Ar-H). MS-ESI, m/z=345(M+H).

RESULTS AND DISCUSSION

As a part of the ongoing research program on synthesis of 3,4-Dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo [1,2-*b*] pthalazine-1,6,11(13*H*)-triones, we wish to report herein a new and fasile synthesis using Tungstated Zirconia (5% WO_3/ZrO_2). Lewis Acid catalysts have gained considerable interest over the years due to economic and environmental considerations.

One such Lewis acid catalyst is Tungstated Zirconia (5% WO_3/ZrO_2). This catalyst is generally inexpensive, easily available and convenient to handle. Recently, this catalyst has emerged as remarkable Lewis acid imparting high chemo-, regio- and diastereo selectivity in various organic transformations. Multicomponent reactions of dimedone(5,5-dimethyl-1,3-cyclohexanedione or 1,3-cyclohexanedione), an aldehyde and N-nucleophilic hetero cycles have recently attracted the interest of the synthetic community because the formation of different condensation products can be expected depending on the specific condition and structure of the building blocks. Pthalhydrazide(2,3-dihydro-1,4-pthalazinedione) containing two NH-nucleophilic groups is a very interesting heterocyclic compound . In the present work, we took advantage of NH groups in a three-component condensation reaction of dimedone (**3**), pthalhydrazide (**2**) and aromatic aldehydes (**1a-j)** in the preparation of 3,4-dihydro-3,3-dimetrhyl-13-aryl-2*H*-indizalo[1,2-*b*]pthalazine-1,6,11(13H) trione. The synthetic route was outlined in (**Scheme 1**).



Scheme 1. Synthesis of 3,4-Dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo [1,2-*b*] pthalazine-1,6,11(13*H*)-triones using Tungstated Zirconia (5% WO_3/ZrO_2)

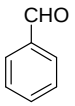
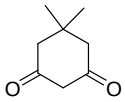
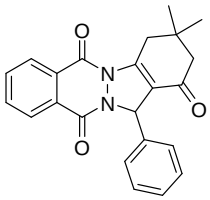
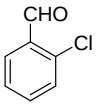
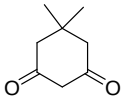
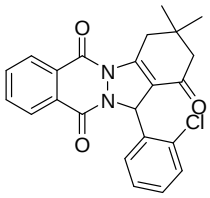
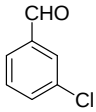
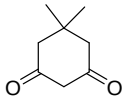
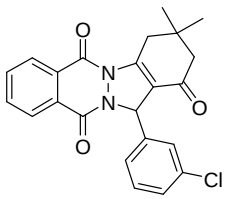
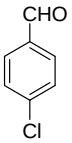
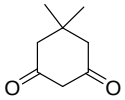
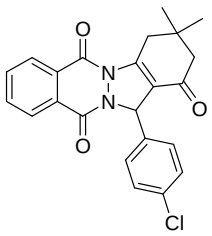
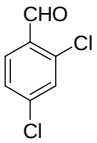
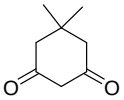
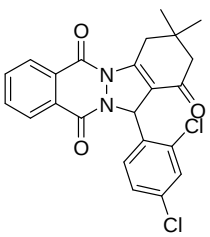
Hence, we targeted to synthesize the Initially, a pilot reaction was attempted using benzaldehyde **1a**, phthalhydrazide (**2**), 5,5-dimethyl-1,3-cyclohexanedione (**3**) in the presence of 5% WO_3/ZrO2 (0.5 eq) without any solvent. After 3 hours only 20% of 3,3-Dimethyl-13-phenyl-2,3,4,13-tetrahydro-indizalo[1,2-b]phthalazine-1,6,11-trione product was isolated.

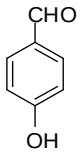
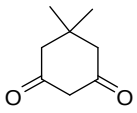
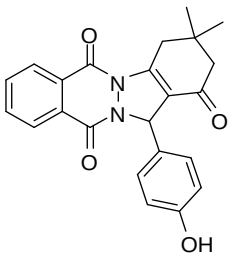
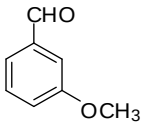
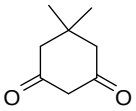
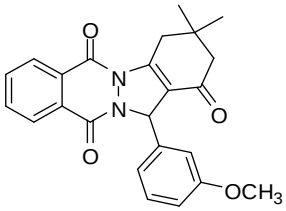
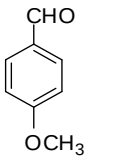
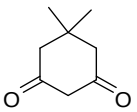
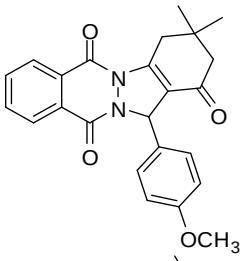
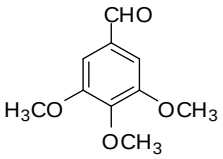
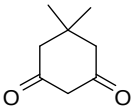
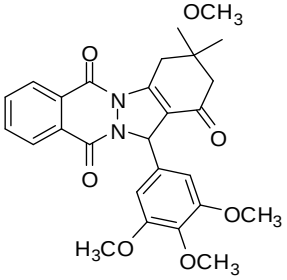
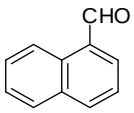
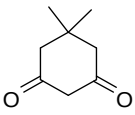
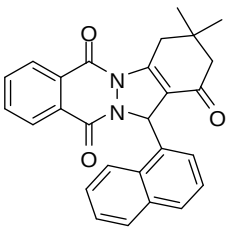
Increasing the amount of 5% WO_3/ZrO_2 (1.0 equiv) did not improve the product yield to a considerable amount. Subsequently, we investigated the effect of different solvents on the reaction rate and as well as yield of the

products. In protic solvents such as Methanol or Ethanol, the reaction was very slow and resulted in lower product yield. Similar results were obtained in coordinating solvents such as THF, diethyl ether and dimethyl ether.

On the other hand, conducting the reactions in chlorinated solvents such as dichloromethane and chloroform improved both the reaction rates as well as product yields. After screening for different solvents, Acetonitrile came out as the solvent of choice, which not only afforded the products in good yield, but also with higher reaction rates (**85% yield in 5 h**).

TABLE-1 Synthesis of 2*H*-indizalo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione derivatives using 5% WO_3/ZrO_2 as a catalyst

S. No.	Aldehyde	Ketone	Product	Time (h)	Yield (%)
a				5.0	87
b				5.0	82
c				5.5	80
d				5.0	85
e				5.5	82

S. No.	Aldehyde	Ketone	Product	Time (h)	Yield (%)
f				5.5	80
g				5.0	84
h				5.0	83
i				6.0	78
j				6.0	76

Aromatic aldehydes (**1a-j)**, phthalhydrazide 2, 5,5-dimethyl-1,3-cyclohexanedione 3a in the presence of 5% WO_3/ZrO_2 undergo a fast 1:1:1addition reaction at 80 ^{0}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 (Table-1).** The results were excellent in terms of yields and product purity in the presence of 5% WO_3/ZrO_2 as TMSCl and *p*-TSA. 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. Compounds (**4a-j)** are stable solids whose structures are fully supported by IR, ^{1}H NMR and mass spectrometry

CONCLUSION

In conclusion, we developed an efficient process for one-pot three component synthesis of phthalazine triones by the condensation of various aldehydes, phthalhydrazide, dimedone in acetonitrile at 80 ^{0}C temperature using 5% WO_3/ZrO_2 as a catalyst. This methodology offered very attractive features such as reduced reaction times, 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 phthalazine triones.

Acknowledgement
The authors thank Brundavan Laboratories Private Limited for the financial support and encouragement.

REFERENCES

[1] F. B. Hollinger, J. R. Ticehurst, D. M. Knipe, P. M. Howley, R. M. Channock, J. L. Melnick, T. P. Monath, B. E. Roizmann, S. E. Starauss, *Eds*., *Lippincot Raven*:Philadelphia, **1996**.
[2] (a) E. M. Bergmann, M. N. G. James, *In proteases as Targets for Therapy*; Vonder Helm, B. Korant, *Eds*; Springer:Heiderlberg, **1999**; (b) A. E. Gorbalenya, E. J. Snijder. *Drug Discov. Des.*, **1996**, *6*, 64; (c) R. R. Rueckert, *In fields Virology*; B. N. Fields; D. M. Knipe; P. M. Howeley; R. M. Channock; J. L. Melnick; T. P. Monath; B. E. Roizmann; S. E. Starauss; Eds., *Lippincott-Raven:Philadelphia*, **1996**.
[3] F. Al-Assar; K. N. Zelenin; E. E. Lesiovskaya; I. P. Bezhan; B. A. Chakchir, *Pham Chem. J*. **2002**, *36*, 598.
[4] R. P. Jain; J. C.Vederas, *Biorg. Med. Chem. Lett*. **2004,** *14*, 3655.
[5] R. W. Carling; K. W. Moore; L. J. Street; D. Wild; C. Isted; P. D. Leeson,; S. Thomas; D. O'Conner; R. M. McKernan; K. Quirik; S. M. Cook; J. R. Atack; K. A. Wafford; S. A. Thompson; G. R. Dawson; P. Ferris; J. L. Castorn, *J. Med. Chem.* **2004**, *47*, 1807.
[6] S. Grasso; G. Desarro; N. Micalw; M. Zappala; G. Puia; M. Baraldi; C. Demicheli, J. *Med. Chem.* **2000**, *43*, 2581.
[7] Y. Nomoto; H. Obase; M. Teranishi; J. Nakamura; K. Kubo, *Chem.Pharm. Bull.* **1990**, *38*, 2179.
[8] N. Watanabe; Y. Kabasawa; Y. Takase; M. Matsukura; K. Miyazaki; H. Ishihara; K. Kodama; H. Adachi, *J. Med. Chem.* **1998**, *41*, 3367.
[9] T. Sheradsky; R. Moshenberg, *J. Org. Chem.* **1986**, 51, 3213.
[10] H. W. Heine; L. M. Baclawski; S. M. Bonser; G. D. Wachod, *J. Org. Chem.* **1976**, *41*, 3229.
[11] Y. K. Ramtohup; M. N. James; J. C. Vederas, *J. Org. Chem.* **2002**, 67, 3169.
[12] L. P. Liu; J. M. Lu; M. Shi, *Org. Lett.* **2007**, *9*, 773.
[13] A. Caampai; K. Kormendy; F. Ruff, *Tetrahedron* **1991**, *47*, 4457.
[14] A. S. Amarasekara; S. Chandrasekara, *Org. Lett.* **2002**, *4*, 773.
[15] J. Hwang; H. S. Choi; Y. D. Gong, *Tetrahedron Lett*. **2005**, *46*, 3107.