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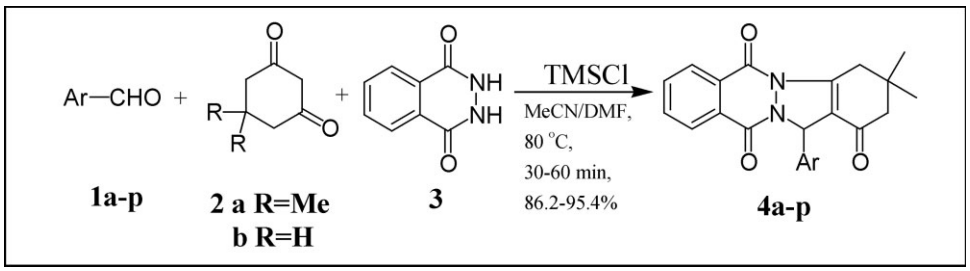

A simple, efficient, and cost-effective method for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives by a one-pot, three-component condensation reaction of phthalazide, dimedone, or 1,3-cyclohexanedione and aromatic aldehydes under CH_3CN/DMF (8:2) media at 80°C for 30–60 min in the presence of trimethylsilyl chloride (TMSCl) is described.

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INTRODUCTION

One-pot multicomponent reactions (MCRs) by virtue of their convergence, productivity, facile execution, and high yield have attracted considerable attention in recent years [1]. There have been tremendous developments in three- or four-component reaction specially the Biginelli [2], Passerini [3], Ugi [4], and Mannich [5] reactions, which have further led to renaissance of MCRs. Nevertheless, great efforts have been and still are being made to find and develop new MCRs.

The development of new synthetic methods for the efficient preparation of heterocycles containing phthalazine ring fragment (antihypoxic and antipyretic agent **I** and HAV 3C inhibitor **II**) is an interesting challenge because they show some pharmacological and biological activities [6–8]. Phthalazine derivatives were reported to possess anticonvulsant [8], cardiotonic [9], and vasorelaxant [10] activities. Therefore, a number of methods have been reported for the synthesis of phthalazine derivatives [11–19]. In recent years, the development of more economical and environmental friendly conversion processes is gaining interest in the chemical community (Figure 1).

In continuation of our work on the use of silica-supported reagents [20], TMSCl has attracted our interest. Among the various silicon-based acidic reagents, TMSCl has received considerable attention as an inexpensive and readily available reagent for various organic transformations [21]. Advantages such as its compatibility with many synthetically valuable nucleophiles (*e.g.*, organometalic reagents and cuprates) and its non-aggregation nature substantially simplify the analysis of the reaction mechanism. Because of this, it has been extensively used as a protecting group for various functional groups such as hydroxy and amino group [20(a),22] and as a promoter for cycloaddition and conjugate addition reactions [21(a)] under mild and convenient conditions to offer the products in excellent yield with high selectivity and one-pot cyclocondensation of dimedone, aldehydes, with/without urea or thiourea to form octahydroquinazolones and 1,8-dioxo-octahydro xanthenes in excellent yields [23]. However, to the best of our knowledge, there is no report on the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-triones using TMSCl as a reagent. In this communication, we report a TMSCl-mediated simple, efficient, and environmentally benign three-component condensation reaction of aromatic aldehydes **1a-p,** 5,5-dimethyl-1,3-cyclohexanedione **2a** or 1,3-cyclohexanedione **2b** and phthalhydrazide **3** in the preparation of 13-aryl-2,3,4,13-tetrahydroindazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione or 3,4-dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione derivatives **4a-p** (Scheme 1).

RESULTS AND DISCUSSION

During the course of our studies directed towards the development of practical, and eco-friendly procedures [24], we developed the applicability of TMSCl for efficient, convenient, and facile synthesis of 13-aryl-

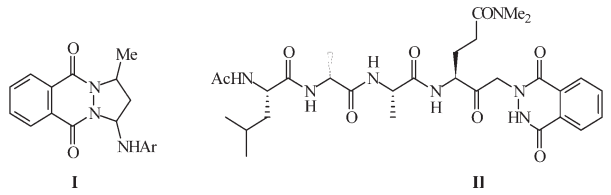


Figure 1. Antihypoxic and antipyretic agent **I** & HAV 3C inhibitor **II**.

2,3,4,13-tetrahydroindazolo[1,2-*b*]phthalazine-1,6,11(13*H*)-trione or 3,4-dihydro-3,3-dimethyl-13-aryl-2*H*-indazolo-[1,2-*b*]phthalazine-1,6,11(13*H*)-trione derivatives by a one-pot three-component condensation reaction of aromatic aldehydes **1a-p**, 5,5-dimethyl-1,3-cyclohexanedione **2a** or 1,3-cyclohexanedione **2b** and phthalhydrazide **3** in CH_3CN/DMF (8:2) at 80°C (Scheme 1).

Initially, a pilot reaction was attempted using benzaldehyde **1**, 5,5-dimethyl-1,3-cyclohexanedione **2a** and phthalhydrazide **3** in the presence of TMSCl (0.5 equiv) without any solvent. After 3 h, only 27% of 3,3-dimethyl-13-phenyl-2,3,4,13-tetrahydroindazolo[2,1-*b*]phthalazine-1,6,11-trione product **4a** was isolated. Increasing the amount of TMSCl (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 as well as yield of the products. In protic solvents such as MeOH or EtOH, 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/DMF (8:2) came out as the solvent of choice, which not only afforded the products in good yield, but also with higher reaction rates (95% yield in 0.5 h). The formation of compound **4a** was evident from the appearance of $[M+H]^+$ peak at *m*/*z* 373 in mass spectrum (ESI), —C=O stretching at 1667 cm^{-1} in IR and the appearance of methine proton as singlet at δ 6.34 in ^1H NMR

To extend the scope of this catalytic transformation, the general applicability of this method was verified by reacting a number of substituted benzaldehydes with 5,5-dimethyl-1,3-cyclohexanedione **2a** or 1,3-cyclohexanedione **2b**. No observable substituent effect was noted for the various aromatic aldehydes.

Aromatic aldehydes **1a-p**, 1,3-cyclohexanedione **2a-b** with phthalhydrazide **3** in the presence of TMSCl undergo a fast 1:1:1 addition reaction at 80°C in CH_3CN/DMF for 30–60 min to produce 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives **4a-p** (Scheme 1). The results were excellent in terms of yields and product purity in the presence of TMSCl instead of *p*-TSA24, compounds **4a-p** are stable solids whose structures are fully supported by IR, ^1H, and ^{13}C NMR spectroscopy's, mass spectrometry and elemental analysis.

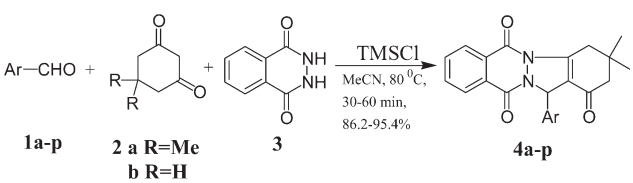
A feasible pathway (Scheme 2) might involve the role of TMSCl as a Lewis acid, which activated the aromatic aldehydes **1** by coordinating to the carbonyl group followed by the removal of TMSOH and HCl with enol form of 1,3-cyclohexanedione **2** to form a heterodienes **5**. Then, the subsequent Michael-type addition of the phthalhydrazide **3** followed by cyclization affords the corresponding products **4**.

In conclusion, we have successfully demonstrated a novel catalytic application of TMSCl for the efficient synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives. This simple procedure is efficient and can be applied to a wide variety of aromatic aldehydes. Shorter reaction times and excellent product yields make this catalytic system an alternative method for the synthesis of 2*H*-indazolo[2,1-*b*]phthalazine-1,6,11(13*H*)-trione derivatives. Further application to explore this simple catalytic system is under progress.

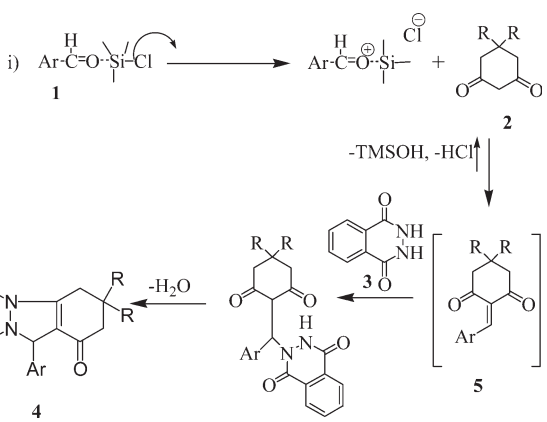
EXPERIMENTAL

Melting points were measured with Fiescher-Johns melting point apparatus. ^1H NMR spectra were recorded with an AVANCE 300 Bruker (at 300 MHz) and Gemini 200 MHz spectrometers in $CDCl_3$. Chemical shifts relative to TMS as internal standard are given as δ values in ppm. ^{13}C NMR was

Scheme 1



Scheme 2



recorded in $CDCl_3$ on a Varian (75 Hz) spectrometer. IR spectra were taken with a Perkin–Elmer 1725A FT-IR spectrophotometer. EI–MS mass spectra were measured at 70 eV (EI).

General procedure. A solution of benzaldehyde **1a** (10 m*M*), dimedone **2a** (10 m*M*) and phthalhydrazide **3** (12 m*M*), and CH_3CN/DMF (8 mL/2 mL) containing TMSCl (10 m*M*) was refluxed (80°C) till the reaction was completed (monitored by TLC). After completion, the reaction mass was poured into ice cold water, stirred, and filtered. The solid product **4a** obtained was filtered through a Buckner funnel, washed with hexane (2 × 5 mL) and dried. Spectral data for new compounds:

13-(2,4-Dichlorophenyl)-3,3-dimethyl-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione (4b). Pale yellow crystalline powder; Yield: 94.8%; mp 208–209°C. IR (KBr): V_{max} 2942, 1657, 1362, 1268, 711 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 1.24 (s, 3H); 1.25 (s, 3H); 2.31 (s, 2H); 3.16–3.41 (dd, *J* = 2.2, 18.8 Hz, 2H); 6.57 (s, 1H); 7.28–7.36 (m, 2H, Ar); 7.46 (d, *J* = 8.3 Hz, 1H, Ar); 7.80–7.89 (m, 2H, Ar); 8.23–8.38 (m, 2H). LC/MS: *m*/*z* = 441 $[M+H]^+$. *Anal*. Calcd for $C_{23}H_{18}Cl_2N_2O_3$: C, 62.60; H, 4.11; N, 6.35%. Found: C, 62.53; H, 4.10, N, 6.35%.

13-(3-Hydroxyphenyl)-3,3-dimethyl-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione (4f). Light yellow crystalline powder, mp 257–258°C. Yield: 89.2%. ^1H NMR (200 MHz, DMSO-d_6): δ = 1.20 (s, 6H); 2.27 (s, 2H); 3.11–3.41 (dd, *J* = 1.4, 18.8, 2H); 6.23 (s, 1H); 6.63–6.82 (m, 3H, Ar); 7.02–7.10 (t, *J* = 8.0, 1H, Ar); 7.84–7.89 (m, 2H, Ar); 8.16–8.32 (m, 2H, Ar); 9.02 (brs, 1H, OH). LC/MS: *m*/*z* = 389 $[M+H]^+$. *Anal*. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21%. Found: C, 71.11; H, 5.17; N, 7.21%.

3,3-Dimethyl-13-naphthalen-1-yl-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione (4g). Pale yellow crystalline powder, Yield: 88.4%. mp 264–265°C. ^1H NMR (200 MHz, DMSO-d_6): δ = 1.19 (s, 3H); 1.23 (s, 3H); 2.25 (s, 2H); 3.20–3.47 (dd, *J* = 2.2, 18.8 Hz, 2H); 7.12 (s, 1H); 7.36–7.59(m, 4H, Ar); 7.75–7.84 (m, 5H, Ar); 8.15–8.36 (m, 2H, Ar). LC/MS: *m*/*z* = 423 $[M+H]^+$. *Anal*. Calcd for $C_{27}H_{22}N_2O_3$; C, 76.76; H, 5.25; N, 6.63%. Found: C, 76.76; H, 5.24; N, 6.63%.

3,3-Dimethyl-13-(3,4,5-trimethoxyphenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione (4h). Pale yellow crystalline powder, mp 202–203°C; Yield: 86.2%. ^1H NMR (200 MHz, DMSO-d_6): δ = 1.24 (s, 3H); 1.25 (s, 3H); 2.32 (s, 2H); 3.12–3.44 (dd, *J* = 2.2, 18.8, 2H); 3.77 (s, 3H); 3.82 (s, 6H); 6.34 (s, 1H); 6.57 (s, 2H, Ar); 7.82–7.86 (m, 2H, Ar); 8.26–8.34 (m, 2H, Ar).LC/MS: *m*/*z* = 463 $[M+H]^+$. *Anal*. Calcd for $C_{26}H_{26}N_2O_6C$, 67.52; H, 5.67; N, 6.06%. Found: C, 67.49; H, 5.62; N, 6.00%.

13-Phenyl-2,3,4,13-tetrahydroindazolo[2,1-b]phthalazine-1,6,11-trione (4i). Pale yellow crystalline powder, Yield: 93.8%. mp 224–225°C. IR (KBr): V_{max} 3290, 1685, 1512, 1479, 1181, 1125 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 2.18–2.45 (m, 4H); 3.19–3.61 (m, 2H); 6.34 (s, 1H); 7.23–7.41 (m, 5H, Ar); 7.83–7.88 (m, 2H, Ar); 8.09–8.32 (m, 2H, Ar). LC/MS: *m*/*z* = 345 $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{16}N_2O_3$: C, 73.24; H, 4.68; N, 8.13%. Found: C, 73.20; H, 4.64; N, 8.13%.

13-(2,4-Dichlorophenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4j). Pale yellow crystalline powder, Yield: 94.0%; mp 274–275°C. IR (KBr): V_{max} 2943, 1659, 1362, 1265, 701 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 2.15–2.42 (m, 4H); 3.23–3.46 (m, 2H); 6.60 (s, 1H); 7.25–7.48 (m, 2H, Ar); 7.72–7.93 (m, 3H, Ar); 8.03–8.37 (m, 2H, Ar). LC/MS: *m*/*z* = 413 $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{14}Cl_2N_2O_3$: C, 61.03; H, 3.41; N, 6.78%. Found: C, 61.01; H, 3.42; N, 6.77%.

13-(2-Chlorophenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4k). Pale yellow crystalline powder, Yield: 91.1%; mp 250–252°C. IR (KBr): V_{max} 2925, 1660, 1366, 1270, 703 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 2.22–2.58 (m, 4H); 3.31–3.47 (m, 2H); 6.63 (s, 1H); 7.26–7.50 (m, 4H, Ar); 7.90–7.95 (m, 2H, Ar); 8.10–8.19 (m, 1H, Ar), 8.31–8.36 (m, 1H, Ar); LC/MS: *m*/*z* = 379 $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40%. Found: C, 66.58; H, 3.88; N, 7.42%.

13-(4-Chlorophenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4l). Pale yellow crystalline powder, Yield: 92.0%; mp 272–273°C. IR (KBr): V_{max} 3290, 1685, 1512, 1479, 1181, 1125 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 2.23–2.43 (m, 4H); 3.21–3.52 (m, 2H); 6.33 (s, 1H); 7.23–7.43 (m, 4H, Ar); 7.92–7.77 (m, 2H, Ar); 8.17–8.35 (m, 2H, Ar). LC/MS: *m*/*z* = 379 $[M+H]^+$. δ = (75 MHz, $CDCl_3$ + DMSO-d_6) 21.6, 23.8, 30.4, 60.5, 63.7, 117.7, 126.6, 127.8, 129.0, 132.6, 133.4, 134.2, 135.9, 152.7, 153.5, 155.1, 161.8, 167.3, 191.8. *Anal*. Calcd for $C_{21}H_{15}ClN_2O_3$: C, 66.58; H, 3.99; N, 7.40%. Found: C, 66.55; H, 3.99; N, 7.38%.

13-(3-Hydroxyphenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4m). Pale yellow crystalline powder, Yield: 89.4%; mp 267–268°C. ^1H NMR (200 MHz, DMSO-d_6): δ = 2.21–2.43 (m, 4H); 3.20–3.61 (m, 2H); 6.24 (s, 1H); 6.66–6.82 (m, 3H, Ar); 7.10 (t, *J* = 8.8 Hz, 1H, Ar); 7.86–7.89 (m, 2H, Ar); 8.21–8.32 (m, 2H, Ar); 9.04 (brs, 1H). LC/MS: *m*/*z* = 361 $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77%. Found: C, 69.98; H, 4.49; N, 7.77%.

13-Naphthalen-1-yl-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4n). Pale yellow crystalline powder, Yield: 88.9%; mp 260–262°C; ^1H NMR (200 MHz, DMSO-d_6): δ = 2.19–2.38 (m, 4H); 3.22–3.62 (m, 2H); 7.10 (s, 1H); 7.34–7.64 (m, 4H, Ar); 7.75–7.89 (m, 4H, Ar); 8.09–8.11 (m, 1H, Ar); 8.29–8.34 (m, 1H, Ar); 8.47 (d, *J* = 8.0 Hz, 1H, Ar). LC/MS: *m*/*z* = 395 $[M+H]^+$. *Anal*. Calcd for $C_{25}H_{18}N_2O_3$: C, 76.13; H, 4.60; N, 7.10%. Found: C, 76.11; H, 4.61; N, 7.11%.

13-(4-Bromo-phenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4o). Pale yellow crystalline powder, Yield: 93.0%; mp 280–281°C. IR (KBr): V_{max} 2942, 1658, 1363, 1265, 703 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 2.21–2.26 (m, 2H); 2.38–2.42 (m, 2H); 3.25–3.31 (dt, *J* = 5.7 Hz, 1H); 3.48–3.54 (dt, *J* = 5.7 Hz, 1H); 6.30 (s, 1H); 7.34 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H, Ar); 7.88 (t, *J* = 4.7 Hz, 2H, Ar); 8.19 (t, *J* = 4.7 Hz, 1H, Ar), 8.31 (t, *J* = 4.7 Hz, 1H, Ar). δ_C (75 MHz, DMSO-d_6) 21.7, 23.9, 36.2, 63.7, 69.2, 117.7, 121.0, 126.6, 127.4, 128.4, 129.0, 129.7, 130.9, 133.7, 134.4, 136.8, 153.1, 155.3, 160.7, 165.7, 192.2. LC/MS: *m*/*z* = 423 $[M+H]^+$. *Anal*. Calcd for $C_{21}H_{15}BrN_2O_3$: C, 59.59; H, 3.57; N, 6.62%. Found: C, 59.59; H, 3.54; N, 6.61%.

13-(3-Methoxyphenyl)-2,3,4,13-tetrahydroindazolo[2,1-b]-phthalazine-1,6,11-trione (4p). Pale yellow crystalline powder, Yield: 88.2%; mp 210–211°C. IR (KBr): V_{max} 2942,

1658, 1366, 1427, 701 cm^{-1}. ^1H NMR (200 MHz, DMSO-d_6): δ = 2.21–2.46 (m, 4H); 3.19–3.65 (m, 2H); 3.79 (s, 3H, OMe); 6.30 (s, 1H); 6.81 (dd, J = 8.0 Hz, 1H, Ar); 6.94–6.96 (m, 2H, Ar); 7.24 (t, J = 8.08 Hz, 1H, Ar); 7.89–7.91 (m, 2H, Ar); 8.17–8.33 (m, 2H, Ar). LC/MS: m/z = 375 $[M+H]^+$. *Anal*. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48%. Found: C, 70.55; H, 4.83; N, 7.48%.

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