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Eco-friendly synthesis of 6-aryl-4-phenyl-2H-5,6,7-trihydroindazol-3-ones, using benzyltriethylammoniumtetrathiomolybdate-Fe(III) chloride as catalyst.

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Abstract: *Having ascertained that the catalyst benzyltriethy lammoniumtetrathio-molybdate-Fe(III) chloride (coded as MFTT) catalyzes the Mannich-type reaction on imines and brings about a cascade sequence of reactions, involving rearrangement of aminophenyl group, it was of interest to understand the substrate dependence of the catalyst. The synthesis of the tetrahydroindazolones was accomplished in a highly proficient way in three steps: viz. MFTT catalyzed synthesis of substituted Mannich adducts (ii) base catalyzed annulations of these products and (iii) Bi(III) nitrate catalyzed condensation of the esters with hydrazine hydrate discusses the synthesis of 6-aryl-4-phenyl-2H-5,6,7-trihydroindazol-3-ones.*

Keywords: *benzyltriethylammoniumtetrathio-molybdate-Fe(III) chloride, indizolones, pyrazolidone, antipyretic, analgesic, anti-inflammatory.*

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I. INTRODUCTION

The indazolones contain pyrazolidone moiety fused to a benzene ring. This makes them pharmacologically important compounds because most of the pyrazolidinone compounds display analgesic, anti-inflammatory and antipyretic properties. Several pyrazolidones are clinically recommended and marketed. A few examples of the analgesic, antipyretic and anti-inflammatory drugs are morazone,[1] piperylone,[2] propyphenazone,[3] antipyrine [4] and ampyrone.[5] Aminopyrine[6] serves as a diagnostic aid for hepatic function. Muzolimine[7] is believed to be diuretic and antihypertensive in nature. 1-Phenyl-3-pyrazolidinone [8] is useful as a photographic developer. The presence of pyrazolidone pharmaco-chromophore in indazolones and their partially saturated derivatives makes these products equally important antipyretic and anti-inflammatory drugs.[9] These compounds are, therefore, potential candidates for the treatment of tumors.

II. RESULTS AND DISCUSSION

The synthesis of tetrahydroindazolones was achieved in three steps. Initially the reaction between aldehydes, analine and acetophenone was carried out using benzyltriethylammoniumtetrathiomolybdate-Fe(III) chloride (coded as MFTT) catalyst mixture to give a Mannich-type product by the addition of acetophenone to C=N bond. These compounds in their ^{1}H NMR spectra displayed a resonance signal near δ 3.44 (ddd. J = 10.5, 7.1, 3.5 Hz, 2H) attributable to methylene protons adjacent to a carbonyl group. A single proton resonance signal near δ 4.94 (dd, J = 7.1, 3.5 Hz) was attributable to a methine proton. A broad resonance signal (exch. D_2O) integrating for 1H clearly indicated the presence of a secondary amino proton. The compounds **1a-1g** were thus characterized as 1,3-diaryl-3-(phenylamino)propane-1-ones.

In the second step the compounds **1a-1g** and ethylacetoacetate were made to react in presence of benzyltriethylammoniumtetrathiomolybdate-Fe(III) chloride both at room temperature as well as at refluxing temperature in different solvent systems, to give substituted cyclohexanones **2a-2g**. The structures of these compounds were established by spectral analysis.

The compounds **2a-2g** were treated with hydrazine hydrate in presence of $Bi(NO_3)_3$ as catalyst. The reaction proceeded at ambient temperatures and afforded the indazolones in substantial yield. Compounds were purified by simple crystallization and only one tautomeric form was obtained under the reaction conditions. The spectral analysis led to the identification of **3a-3g** as 6-aryl-4-phenyl-2H-5,6,7-trihydro-indazol-3-ones.

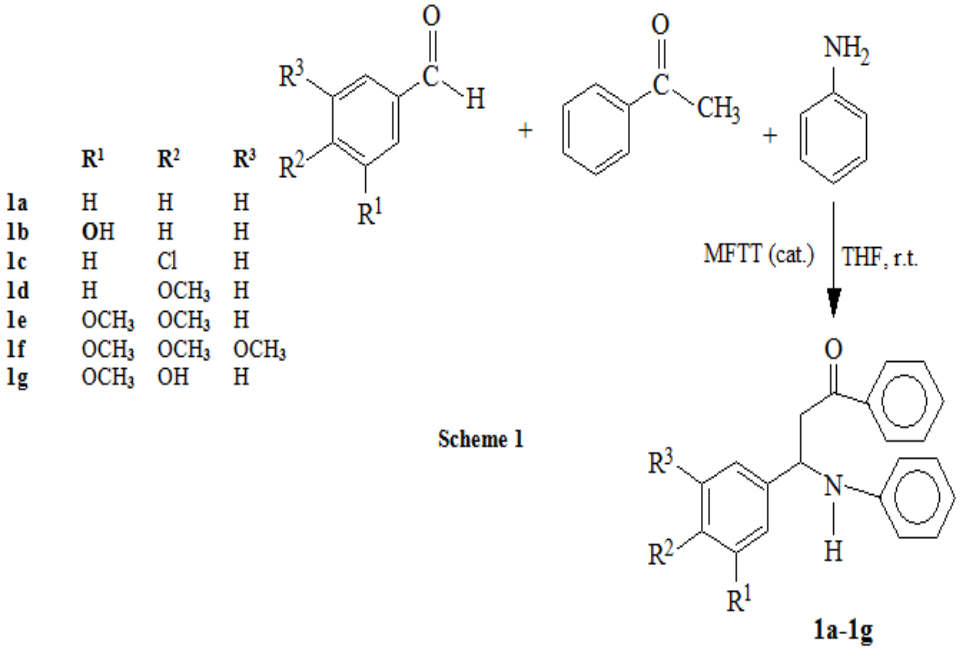
III. CONCLUSION

An efficient and environmentally friendly three step process for the preparation of novel 6-aryl-4-phenyl-2H-5,6,7-trihydro-indazol-3-ones has been developed.

IV. EXPERIMENTAL

Step-I: General method for preparation of 1,3-diaryl-3(phenyl amino) propane-1-one

The appropriate aromatic aldehyde, aniline and acetophenone (1:1:1 mol) were dissolved in THF (10-15 mL) and benzyltriethylammoniumtetrathio- molybdate-Fe(III) chloride catalyst mixture, taken in proportion by the weight of aldehydes, so that the concentration of the catalyst did not exceed 20 mole percent, was added to the reaction mixture (Scheme 1). The reaction mixture was stirred at room temperature and monitored by tlc. On completion of the reaction (40-45 hrs), the product mixture was filtered. The organic solution was diluted with water and extracted with ethylacetate. After usual work up and concentration the products **1a-1g** separated out as crystalline materials in 70-80% yield (Table-1).



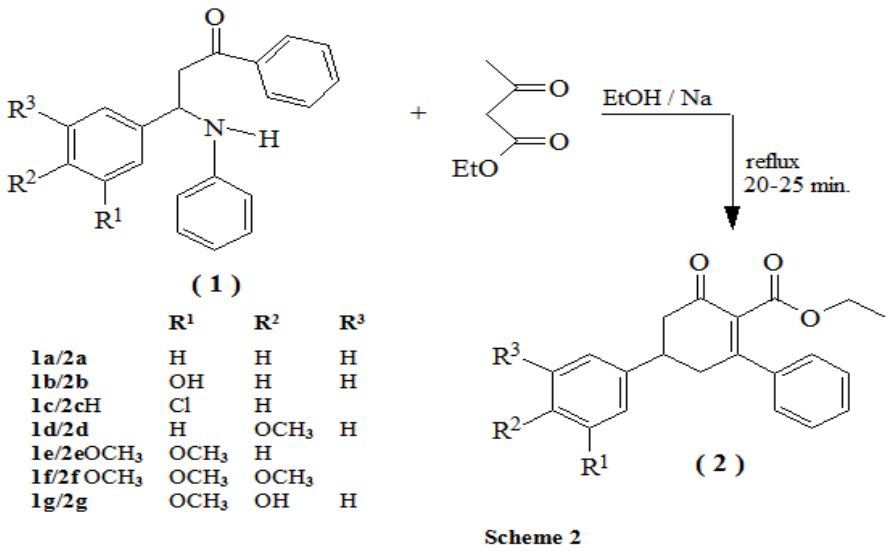
Scheme 1

Table-1: Percentage yield of 1a-1g

Compound	Percent yield	Compound	Percent Yield
1a	80	**1e**	75
1b	78	**1f**	70
1c	75	**1g**	76
1d	70		

Step-II: General method for preparation of ethyl 6-oxo-2,4-diarylcyclohex-1-ene carboxylate

Initially 100-150 mg of sodium metal was added in piece meals to dry alcohol at ice-bath temperature. The mixture was stirred for 15-20 minutes, till all of the sodium metal reacted. To this solution was added of 1,3-diaryl-3(phenylamino)propan-1-one (**1a-1g**) (1 x 10^{-3} mole) and ethylaceto- acetate (1 x 10^{-3} moles). The reaction mixture was refluxed for (20-25 minutes) on water bath under anhydrous conditions. On completion of reaction the product mixture was cooled and poured in water and extracted with chloroform. After usual work up products **2a-2g** separated out as crystalline material in 50-60% yield (Table-II). The compounds were recrystallised from ethylacetate (Scheme 2).



	R^1	R^2	R^3
1a/2a	H	H	H
1b/2b	OH	H	H
1c/2cH	Cl	H	
1d/2d	H	OCH_3	H
1e/2eOCH_3	OCH_3	H	
1f/2fOCH_3	OCH_3	OCH_3	
1g/2g	OCH_3	OH	H

Scheme 2

Table-II Percentage yield of 2a-2g

Compound	Percent yield	Compound	Percent Yield
2a	50	**2e**	52
2b	53	**2f**	55
2c	57	**2g**	56
2d	60		

Step-III:General method for preparation of 6-aryl-4-phenyl-2H-5,6,7-trihydroindazol-3-ones

Compounds **2a-2g** (1 x 10^{-3} moles), hydrazine hydrate (1 x 10^{-3} moles), and $Bi(NO_3)_3$ (5 mol%) in CH_2Cl_2 (15-20 mL) were stirred at room temperature. The reaction was monitored on tlc and after 40-46 hrs, CH_2Cl_2 was removed by evaporation. The residue was added to water (25 mL) and extracted twice with 30 mL portions of ethylacetate. The combined ethylacetate extract was washed with 30 mL water, dried over anhydrous sodium sulphate and evaporated to dryness to a thick brown mass. Crystallization of brown mass from ethylacetate-pet.ether furnished crystals of compounds **3a-3g** in 60-70% yield (Table-III).

Table-III. Percentage yield of 3a-3g

Compound	Percent yield	Compound	Percent Yield
3a	62	**3e**	61
3b	65	**3f**	70
3c	64	**3g**	68
3d	67		

All the solvents were of LR and were obtained from merck. The elemental analysis of these compounds was performed on CHN elementary (Analysen system Gm6H, Germany). The elemental analysis (C,H,N) of these compounds were found within a limit of ± 0.5% theoretical value of 0.5 mm thickness. The TLC plates were prepared from silica gel G merck. Iodine chamber was used for visualization of TLC spots. The FT-IR spectrum was recorded in KBr pellets on Perkin Elmer FT-IR spectrometer. The m.pts were determined on Yorko m.pt apparatus and thermometer was incorrect. ^{1}H NMR spectrum was recorded in $CDCl_3$ with TMS as internal standard on Brucker NMR spectrophotometer operating as 200 MHz chemical shifts and are expressed in δ-values in (PPm) relative to TMS as internal standard.

V. SPECTRA DATA OF THE COMPOUNDS

(3a) 4,6-Diphenyl-2H-5,6,7-trihydroindazol-3-one

Colorless crystals m.p. 152 °C. IR: υ_{max}cm^{-1} 3429, 3058, 1680 ($CONH_2$), 1657 (-C=O), 1573, 1496, 1446, 1372, 1262, 1205, 1038, 882, 747. ^{1}H-NMR: δ 1.68 (dd, J = 14.0, 6.4 Hz, 2H), 1.96 (dd, J = 14.0, 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 1H), 7.02 (s br, 1H, NH), 7.12-7.25 (m, 10H, H-Ar). ^{13}C-NMR: δ_C 32.7 (C-6), 43.1 (C-7), 43.9 (C-

5), 119.2 (C-3), 126.9 (C-4′), 127.0 (2C, C-2′, C-6′), 128.2 (C-3′, C-5′), 129.4 (2C, C-8′, C-12′), 130.5 (C-10′), 135.5 (C-7′), 148.7 (C-1), 156.6 (C-7a), 159.0 (C-4), 168.9 (C-3). MS: *m/z* (rel. int). 288.3515 (100)(M^+) (Calcd. for $C_{19}H_{16}N_2O$, 288.3507), 260 (40), 77 (41), 129 (65), 157 (58), 79 (42), 80 (60). Anal. CHN(%): Found: C, 79.16; H, 5.62; N, 9.78. Calcd. for $C_{19}H_{16}N_2O$; C, 79.14; H, 5.59; N,9.71.

(3b) 6-(3-Hydroxyphenyl)-4-phenyl-2H-5,6,7-trihydroindazol-3-one

Colorless crystals m.p. 161 °C. IR: $\upsilon_{max}cm^{-1}$ 3490 (br, OH), 2480, 1682, 1601, 1510, 1430, 1375, 1353, 1349, 1311, 1258, 1255, 1110, 1037, 940, 830. ^{1}H-NMR: δ 1.68 (dd, *J* = 14.0, 6.4 Hz, 2H), 19.6 (dd, *J* = 14.0, 6.9 Hz, 2H), 3.01 (t, *J* = 6.9 Hz, 1H), 6.82 (s, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 7.02 (s br, 1H, NH), 7.12 (d, *J* = 8.1 Hz, 2H), 7.26-7.35 (m, 5H). ^{13}C-NMR: δ_C 33.1 (C-6), 43.2 (C-7), 129.1 (C-5), 119.3 (C-3), 120.4 (C-2′), 121.6 (C-4′), 126.8 (2C, C-8′,C-12′), 127.5 (C-5′), 128.6 (3C, C-6′, C-3′, C-9′), 129.1 (C-11′), 130.2 (C-10′), 130.8 (C-1′), 135.5 (C-7′), 156.5 (C-7a), 159.1 (C-4), 168.2 (C-3). MS : *m/z* (rel. int.) 304.3512(100) (M^+) (Calcd. for $C_{19}H_{16}N_2O_2$, 304.3504), 276 (42), 157 (59), 94 (45), 129 (70), 80 (65). Anal. CHN(%): Found: C, 74.95; H, 5.30; N, 9.27. Calcd. for $C_{19}H_{16}N_2O_2$; C, 74.98; H, 5.29; N, 9.20.

(3c) 6-(4-Chlorophenyl)-4-phenyl-2H-5,6,7-trihydroindazol-3-one

Colorless crystals, m.p. 181 °C. IR: $\upsilon_{max}cm^{-1}$ 3433, 2973, 1684 ($CONH_2$), 1604, 1573, 1493, 145, 1414, 1394, 1261, 1241, 1207, 1194, 1090, 1037, 825. ^{1}H-NMR: δ 1.68 (dd, *J* =14.0, 6.4 Hz, 2H), 1.98 (dd, *J* = 14.0, 6.9 Hz, 2H), 3.01 (t, *J* = 6.9 Hz, 1H), 6.56 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.02 (s br, 1H, NH), 7.26-7.35 (m, 5H). ^{13}C-NMR: δ_C 33.8 (C-6), 43.2 (C-7), 44.1 (C-5), 119.3 (C-3), 120.4 (C-2′), 126.9 (2C, C-8′, C-12′), 128.6 (2C, C-3′, C-9′), 129.0 (C-2′), 130.1 (C-2′, C-6′), 130.3 (C-10′), 130.8 (C-1′), 133.1 (C-4′), 135.5 (C-7′), 156.5 (C-7a), 159.1 (C-4), 168.1 (C-3). MS: *m/z* (rel. int.) 322.7966 (100) (M^+) (Calcd. for $C_{19}H_{15}ClN_2O$, 322.7958), 294 (42), 157 (60), 112.5 (46), 80 (62), 129 (71). Anal. CHN(%):Found: C, 70.72; H, 6.70; N, 8.65. Calcd. for $C_{19}H_{15}ClN_2O$: C, 70.69; H, 6.68; N, 8.67.

(3d) 6-(4-Methoxyphenyl)-4-phenyl-2H-5,6,7-trihydroindazol-3-one

Colorless crystals, m.p. 178 °C. IR: $\upsilon_{max}cm^{-1}$ 3431, 2973, 2920, 1682 ($CONH_2$), 1600, 1512, 1443, 1384, 1345, 1306, 1253, 1111, 1037, 943, 883, 837. ^{1}H-NMR: δ 1.68 (dd, *J* = 14.0, 6.4 Hz, 2H), 1.98 (dd, *J* = 14.0, 6.9 Hz, 2H), 3.00 (t, *J* = 6.9 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.02 (sbr, 1H, NH), 7.24 (d, *J* = 8.5 Hz, 2H), 7.28-7.35 (m, 5H). ^{13}C-NMR: δ_C 33.2 (C-6), 43.3 (C-7), 44.7 (C-5), 56.8 (OCH_3), 116.1 (C-3′, C-5′), 119.1 (C-3), 126.8 (2C, C-8′, C-12), 128.6 (C-9′, C-11′), 129.1 (2C, C-2′, C-6′), 129.3 (C-10′), 130.5 (C-7′), 132.4 (C-1′), 156.5 (C-7a), 159.2 (C-4), 168.2 (C-3). MS : *m/z* (rel. int.) 318.3782 (100) (M^+) (Calcd. for $C_{20}H_{18}N_2O_2$, 318.3774), 290 (43), 157 (58), 108 (44), 157 (57), 80 (63), 129 (69). Anal. CHN(%):Found: C, 75.48; H, 5.72; N, 8.75.
Calcd. for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.69; N, 8.79.

(3e) 6-(3,4-Dimethoxyphenyl)-4-phenyl-2H-5,6,7-trihydroindazol-3-one

Colorless crystals, m.p. 175 °C. IR: $\upsilon_{max}cm^{-1}$ 3433, 2978, 1685 ($CONH_2$), 1601, 1512, 1443, 1384, 1347, 1308, 1255, 1110, 1037, 943, 883, 837. ^{1}H-NMR: δ 1.67 (dd, J = 14.0, 6.4 Hz, 2H), .97 (dd, J = 14.0, 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 1H), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 6.58 (d, *J* = 8.1 Hz, 1H), 6.78 (d, *J* = 2.0 Hz, 1H), 7.02 (s br, 1H, NH), 7.12 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.27-7.34 (m, 5H). ^{13}C-NMR: δ_C 33.2 (C-6), 43.3 (C-7), 44.5 (C-5), 56.3 (OCH_3), 56.5 (OCH_3), 113.6 (C-5′), 113.8 (C-2′), 119.1 (C-3), 121.1 (C-6′), 126.8 (C-8′, C-12′), 128.6 (C-9′, C-11′), 129.3 (C-10′), 130.5 (C-7′), 141.4 (C-1′), 156.5 (C-7a), 159.2 (C-4), 168.1 (C-3). MS: *m/z* (rel. int.) 348.4046 (100) (M^+) (Calcd. for $C_{21}H_{20}N_2O_3$, 348.4038), 320 (44), 157 (60), 125 (45), 129 (69), 80 (61). Anal. CHN(%):Found: C, 72.39; H, 5.73; N, 8.03. Calcd. for $C_{21}H_{20}N_2O_3$: C, 72.39; H, 5.78; N, 8.04.

(3f) 6-Phenyl-6-(3,4,5-trimethoxyphenyl)-2H-5,6,7-trihydroindazol-3-one

Colorless crystals, m.p. 173 °C. IR: $\upsilon_{max}cm^{-1}$ 3437, 2979, 1686 ($CONH_2$), 1601, 1512, 1443, 1385, 1349, 1308, 1255, 1110, 1037, 943, 835. ^{1}H-NMR: δ 1.68 (dd, J = 14.0, 6.4 Hz, 2H), 1.96 (dd, J = 14.0, 6.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 1H), 3.75 (6H, s, 2 x OCH_3), 3.76 (3H, s, OCH_3), 6.37 (s, 2H), 6.40 (s, 1H), 7.02 (s br, 1H, NH), 7.26-7.30 (m, 5H). ^{13}C-NMR: δ_C 33.0 (C-6), 42.9 (C-7), 44.5 (C-5), 56.8 (s), 56.9 (s), 57.0 (s), 104.3 (C-2′), 105.5 (C-6′), 119.1 (C-3), 126.7 (2C, C-8′, C-12′), 128.6 (2C, C-9′, C-11′), 129.1 (C-10′), 129.4 (C-4′), 130.5 (C-7′), 144.8 (C-1′), 146.8 (C-3′), 147.0 (C-5′), 156.5 (C-7a), 159.2 (C-4), 168.2 (C-3). MS: *m/z* (rel. int.) 378.4310 (100) (M^+) (Calcd. for $C_{22}H_{22}N_2O_4$, 378.4302), 350 (42), 157 (60), 156 (45), 129 (69), 80 (64). Anal. CHN(%): Found: C, 69.84; H, 5.85; N, 7.39. Calcd. for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40.

(3g) 6-(4-Hydroxy-3-methoxyphenyl)-4-phenyl-2H-5,6,7-trihydro-indazol-3-one

Colorless crystals, m.p. 168 °C. IR: $\upsilon_{max}cm^{-1}$ 3540, 3434, 3540, 3231, 2997, 1676 ($CONH_2$), 1605, 1513, 1445, 1382, 1347, 1308, 1255, 1110, 1037, 786. ^{1}H-NMR: δ 1.66 (dd, *J* = 14.0, 6.3 Hz, 2H), 1.96 (dd, *J* = 14.0, 6.9 Hz, 2H), 3.74 (s, 3H), 6.56 (d, *J* = 8.5 Hz, 1H), 6.63 (s, 1H), 7.02 (s br, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.26-7.35 (m, 5H). MS: *m/z* (rel. int.) 334.7376 (100) (M^+) (Calcd. for $C_{20}H_{18}N_2O_3$, 334.3768), 306 (45), 157 (60), 125 (45), 129 (70), 80 (64). Anal. CHN(%):Found: C, 71.88; H, 5.43; N, 8.39. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.42; N, 8.37.

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