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Pyridinium *p*-Toluenesulfonate: A Mild and Efficient Catalyst for The Regioselective Tetrahydropyranylation of Indazole Derivatives Under Solvent-Free Conditions

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An efficient and regioselective tetrahydropyranyl (THP) protection on substituted 1*H*-indazoles in solution phase as well as under solvent-free conditions catalyzed by microwave irradiation in the presence of pyridinium *p*-toluenesulfonate (PPTS) as mild catalyst.

Key Words: Substituted 1*H*-indazoles, Regioselective tetrahydropyranyl ether-protection, Pyridinium *p*-toluenesulfonate, Solution phase, Solvent-free conditions.

INTRODUCTION

In several syntheses of biologically active natural products, it is desired to reach the molecules by protection and deprotection of a variety of functional groups. Amines and hydroxyl groups are normal functional groups and their protection as tetrahydropyranyl (THP) is common and widely used transformation in organic synthesis[1]. The tetrahydropyran derivatives are useful for the reason that they are less expensive, easily deprotected and stable under variety of reaction conditions such as strongly basic media, metal hydrides, metal triflates, Grignard reagents, acylating agents, oxidative reagents and alkylating agents[2]. Tetrahydropyranyl groups are also preferred protective groups of choice in peptide, nucleotide, carbohydrate and steroid chemistry[3].

Most of the reported methods for the THP protection for amines, phenols and alcohols use acidic reagents generally used in an aprotic solvent such as CH_2Cl_2, THF, acetone and toluene[4]. At times their formation has been carried out in ionic liquids[5]. Although these methods are suitable for many synthetic conditions, some of these methods suffer from use of excess amounts and/or toxic catalysts, volatile organic solvents and large amounts of solid supports which ultimately result in the generation of considerable amounts of toxic wastes. Tetrahydropyranylation is usually performed in anhydrous aprotic organic solvents because of the longer reaction time and poor yields of products obtained in the presence of water.

Indazole is a ten-π electron aromatic heterocyclic system. Like the pyrazole molecule, indazole resembles both pyridine and pyrrole and its reactivity reflects this dual behaviour[6]. The indazole ring has two nitrogen atoms and presents annular tautomerism with regards to the position of the NH hydrogen atom. Due to the difference in energy between the tautomers, the 1*H*-tautomer (the benzenoid form **1a**) predominates in the gas-phase, solution and solid state and its derivatives are usually thermodynamically more stable than the corresponding 2*H*-forms (the quinonoid form **1b**)[6] (Fig. 1).

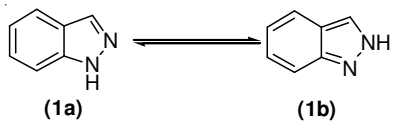
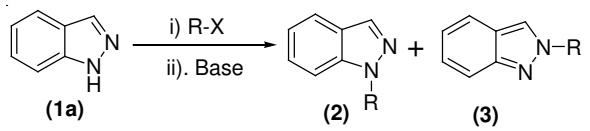


Fig. 1. Annular tautomerism of indazole (**1a**: benzenoid 1*H*-indazole tautomer; **1b**: quinonoid 2*H*-indazole tautomer)

Several studies for the alkylation of 1*H*-indazole (**1**) reveal that the acidity or basicity of the medium, use of protic or aprotic solvents, as well as electronic and steric effects the ratio of N-1 and N-2 alkylated isomers. Generally, the N-1 isomers are thermodynamically more stable, whereas N-2 isomers are kinetically favoured[7]. The regioselectivity of the reaction is also dependent on the nature of the alkylating agents being used. Recently Cheung *et al.*[8] reported an efficient and regioselective synthesis of N-2 alkylated isomers using trimethyloxonium tetrafluoroborate or trimethyloxonium

hexafluorophosphonate as alkylating agents. NMR spectroscopy is very useful to assign the structures of 1- and 2-substituted indazoles, as the ^{1}H NMR spectra of the two isomers are significantly different and can be used as diagnostic tools to establish the position of substitution. Substituted indazole derivatives at N1 and N2 positions (**2** and **3**) (**Scheme-I**).



Scheme-I

In this communication we wish to report regioselective protection with dihydropyran (DHP) group on various substituted 1*H*-indazole derivatives in solution phase as well as under solvent-free conditions using pyridinium *p*-toluenesulfonate as a mild catalyst (PPTS).

EXPERIMENTAL

Melting points were determined in open capillaries using Buchi melting point apparatus and are uncorrected. All ^{1}H NMR spectra were recorded on a VARIAN 200 MHz instrument with an internal standard of tetramethylsilane. Mass spectra were recorded on Agilent-LC-MS instrument giving only M^+ values using (M^++1) mode. Analytical TLC was performed with silica gel GF-254 from Merck & Co., (Germany). Spots were detected with UV-light or in iodine. The following experimental procedures are representive of the general procedures used to synthesize all compounds.

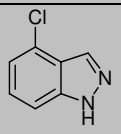
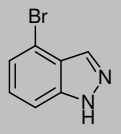
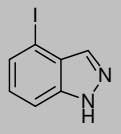
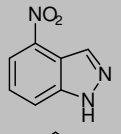
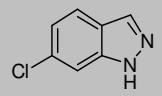
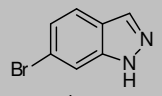
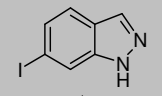
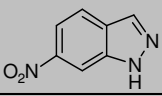
General procedure 5/6 (in solution phase): To a solution of indazole **4** (1.0 eq.), DHP (1.2 eq.) and PPTS (0.01 eq.) were taken in dry DCM (20 mL) at room temperature. The reaction mixture was stirred at 45-50 °C for appropriate time (Table-1), different timings for N-1 and N-2 isomers). The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature. Add water and separate the layers and aqueous layer was extracted into DCM (20 mL). The combined organic extracts were washed with water (2 × 20 mL), brine and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in vacuum and the resulting yellow coloured solid was obtained as crude product. Further it was washed with *n*-hexane to get the pure product in good yields (Table-1).

General procedure 5/6 (under solvent-free conditions): A mixture of indazole **4** (1.0 eq.), DHP (1.2 eq.) and PPTS (0.01 eq.) were added, in an open pyrex-glass vessel was subjected to microwave irradiation for appropriate time (Table-1). After completion of the reaction checked by TLC, water (20 mL) was added and filter the product (Table-1).

Spectral data for 5, 6 compounds

4-Chloro-1-tetrahydro-2*H*-2-pyranyl-1*H*-indazole (5a): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52-1.80 (m, 2H, CH_2), 1.90-2.10 (m, 2H, CH_2), 2.30-2.50 (m, 2H, CH_2), 3.67-3.87 (dd, 2H, CH_2), 5.80-5.90 (d, 1H, CH), 7.17-7.22 (d, 1H, Ar-H), 7.35-7.41 (t, 1H, Ar-H), 7.65-7.73 (d, 1H, Ar-H), 8.15 (s, 1H, pyrazole-H); M/z (M^++1): 237 (M^++1), 259 (M^++Na): FTIR (KBr) cm^{-1}: 3419, 2944, 2858. Anal. calcd. (%) ($C_{12}H_{13}N_3O_4$) requires: C, 54.75; H, 4.98; N, 15.96; Found (%): C, 54.05; H, 4.96; N, 15.89.

TABLE-1
PHYSICAL CHARACTERIZATION DATA FOR COMPOUNDS **5** AND **6** IN SOLUTION PHASE AS WELL AS UNDER SOLVENT-FREE CONDITIONS

Entry	Indazole	Product	Solution phase		Solvent free		m.p. (°C)
			Time (h)	Yield (%)[a]	Time (min)	Yield (%)[b]	
1		**5a**	1.5	80	15	92	55-56
		6a	16	78	1.5	90	62-63
2		**5b**	1.6	75	17	91	51-52
		6b	18	75	2.0	88	77-78
3		**5c**	1.5	78	15	93	83-85
		6c	18	72	2.0	85	89-90
4		**5d**	1.7	72	25	88	90-92
		6d	20	70	2.0	82	98-101
5		**5e**	1.5	82	17	94	60-61
		6e	17	76	1.75	92	68-69
6		**5f**	1.5	80	15	92	54-55
		6f	18	78	2.0	90	64-65
7		**5g**	1.5	75	15	90	74-77
		6g	17	75	1.75	92	98-102
8		**5h**	1.7	70	25	88	114-15
		6h	18	72	2.0	88	110-11

[a]Yields refers to pure products obtained in solution phase conditions.
[b]Yields refers to pure products obtained under solvent free conditions.

4-Bromo-1-tetrahydro-2*H*-2-pyranyl-1*H*-indazole (5b): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52-2.48 (m, 6H, CH_2), 3.67-6.87 (m, 2H, CH_2), 5.84-5.88 (d, 1H, CH), 7.32-7.35 (d, 1H, Ar-H), 7.46-7.51 (t, 1H, Ar-H), 7.70-7.73 (d, 1H, Ar-H), 8.22 (s, 1H, pyrazole-H); M/z (M^++1): Anal. calcd. (%) for ($C_{12}H_{13}N_3O_4$) requires: C, 54.75; H, 4.98; N, 15.96; Found (%): C, 54.05; H, 4.96; N, 15.89.

4-Iodo-1-tetrahydro-2*H*-2-pyranyl-1*H*-indazole (5c): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.50-2.47 (m, 6H, CH_2), 3.65-6.84 (m, 2H, CH_2), 5.86-5.90 (d, 1H, CH), 7.20-7.23 (d, 1H, Ar-H), 7.34-7.39 (t, 1H, Ar-H), 7.68-7.71 (d, 1H, Ar-H), 8.10 (s, 1H, pyrazole-H); M/z (M^++1): Anal. calcd. (%) for ($C_{12}H_{13}N_3O_4$) requires: C, 54.75; H, 4.98; N, 15.96; Found (%): C, 54.05; H, 4.96; N, 15.89.

4-Nitro-1-tetrahydro-2*H*-2-pyranyl-1*H*-indazole (5d): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55-1.73 (m, 3H, CH_2), 2.12-2.16 (m, 2H, CH_2), 2.53-2.56 (m, 1H, CH_2), 3.75-4.00 (m, 2H, CH_2), 5.79-5.83 (d, 1H, CH), 7.48-7.53 (t, 1H, Ar-H),

7.98-8.01 (d, 1H, Ar-H), 8.15-8.17 (d, 1H, Ar-H), 8.64 (s, 1H, pyrazole-H); M/z: 248 (M^++1), 270 (M^++Na).

6-Chloro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5e): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.62-1.8 (m, 3H, THP), 2.13-2.32 (m, 3H, THP), 3.77-3.84 (m, 1H, THP), 4.20-4.23 (m, 1H, THP), 5.67-5.72 (m, 1H, THP), 7.34-7.37 (d, 1H, Hr-H), 7.43-7.45 (d, 1H, Hr-H), 8.11 (s, 1H, Hr-H), 8.16 (s, 1H, pyrazole). M/z (M^{-+}+1): 238. Anal. calcd. (%) for ($C_{12}H_{13}ClN_2O$) requires: C, 60.89; H, 5.54; N, 11.84; Found (%): C, 60.87; H, 5.50; N, 11.81.

6-Bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5f): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60-1.79 (m, 3H, THP), 2.11-2.30 (m, 3H, THP), 3.76-3.83 (m, 1H, THP), 4.19-4.21 (m, 1H, THP), 5.66-5.71 (m, 1H, THP), 7.34-7.35 (d, 1H, Hr-H), 7.42-7.43 (d, 1H, Hr-H), 7.91 (s, 1H, Hr-H), 8.10 (s,1H, pyrazole). M/z (M^{-+}+1): 282. Anal. calcd. (%) for ($C_{12}H_{13}BrN_2O$) requires: C, 51.26; H, 4.66, N, 9.96; Found (%): C, 51.22; H, 4.62, N, 9.93.

6-Iodo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5g): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.61-1.8 (m, 3H, THP), 2.12-2.31 (m, 3H, THP), 3.75-3.82 (m, 1H, THP), 4.18-4.20 (m, 1H, THP), 5.65-5.70 (m, 1H, THP), 7.33-7.34 (d, 1H, Hr-H), 7.41-7.42 (d, 1H, Hr-H), 8.1 (s, 1H, Hr-H), 8.15 (s, 1H, pyrazole). M/z (M^{-+}+1): 329. Anal. calcd. (%) for ($C_{12}H_{13}IN_2O$) requires: C, 43.92; H, 3.99, N, 8.54; Found (%): C, 43.87; H, 3.92, N, 8.49.

6-Nitro-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole (5h): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56-1.80 (m, 3H, THP), 2.05-2.19 (m, 2H, THP), 2.27-2.32 (m, 1H, THP), 3.79-3.84 (m, 1H, THP), 4.13-4.16 (m, 1H, THP), 5.74-5.76 (m, 1H, THP), 7.78-7.80 (d, 1H, Hr-H), 7.89-7.90 (m, 1H, Hr-H), 8.30 (s, 1H, Hr-H), 8.73 (s,1H, pyrazole). M/z (M^{-+}+1): 249. (M+2). Anal. calcd. (%) for ($C_{12}H_{13}N_3O_3$) requires: C, 20.04; H, 1.82; N, 3.89; Found (%): C, 19.98; H, 1.78; N, 3.86.

4-Chloro-2-tetrahydro-2*H*-2-pyranyl-2*H*-indazole (6a): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55-1.80 (m, 3H, CH_2), 1.85-2.22 (m, 3H, CH_2), 3.65-3.98 (m, 2H, CH_2), 5.73-5.77 (d, 2H, CH) 7.11-7.13 (d, 1H, Ar-H), 7.20-7.25 (m, 1H, Ar-H), 7.58-7.61 (d, 1H, Ar-H), 8.56 (s, 1H, pyrazole-H); ^{13}C NMR (DMSO-d_6): 21.91, 24.87, 30.63, 67.41, 88.52, 117.05, 121.10, 121.3, 122.21, 124.98, 126.88, 148.43; M/z (M^++1): 237 (M^++1), 259 (M^++Na): FTIR (KBr) cm^{-1}: 3419, 2944, 2858.

4-Bromo-2-tetrahydro-2*H*-2-pyranyl-2H-indazole (6b): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52-2.48 (m, 6H, CH_2), 3.67-6.87 (m, 2H, CH_2), 5.84-5.88 (d, 1H, CH), 7.32-7.35 (d, 1H, Ar-H), 7.46-7.51 (t, 1H, Ar-H), 7.70-7.73 (d, 1H, Ar-H), 8.58 (s, 1H, pyrazole-H); M/z 282 (M^++1), 304 (M^++Na).

4-Iodo-2-tetrahydro-2*H*-2-pyranyl-2*H*-indazole (6c): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55-2.50 (m, 6H, CH_2), 3.75-3.85 (m, 2H, CH_2), 5.88-6.00 (d, 1H, CH), 7.20-7.23 (d, 1H, Ar-H), 7.34-7.39 (t, 1H, Ar-H), 7.68-7.71 (d, 1H, Ar-H), 8.45 (s, 1H, pyrazole-H); M/z 329 (M^++1), 351 (M^++Na).

4-Nitro-2-tetrahydro-2*H*-2-pyranyl-2*H*-indazole (6d): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.69-1.81 (m, 3H, CH_2), 2.07-2.28 (m, 3H, CH_2), 3.77-4.19 (m, 2H, CH_2), 5.72-5.77 (d, 1H, CH), 7.37-7.42 (t, 1H, Ar-H), 8.08-8.11 (d, 1H, Ar-H), 8.17-8.19 (d, 1H, Ar-H), 8.80 (s, 1H, pyrazole-H); ^{13}C NMR (DMSO-d_6): 21.81, 24.82, 30.65, 67.47, 88.65, 113.89, 121.32, 123.65, 125.34, 127.09, 140.67, 149.04; M/z: 270 (M^++Na). FTIR (KBr) cm^{-1}: 3158, 2944, 2860.

6-Chloro-2-tetrahydro-2*H*-2-pyranyl-2*H*-indazole (6e): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.60-1.79 (m, 3H, CH_2), 1.95-2.24 (m, 3H, CH_2), 3.74-4.15 (m, 2H, CH_2), 5.62-5.66 (d, 1H, CH), 7.00-7.03 (d, 1H, Ar-H), 7.57-7.60 (m, 1H, Ar-H), 7.69-7.70 (s, 1H, Ar-H), 8.13 (s, 1H, pyrazole-H); ^{13}C NMR (DMSO-d_6): 21.92, 24.91, 30.75, 67.37, 88.42, 116.63, 119.98, 122.74, 123.40, 123.68, 131.13, 147.96; M/z (M^++1): 237 (M^++1), 259 (M^++Na): FTIR (KBr) cm^{-1}: 3134, 3064, 2948, 2850.

6-Bromo-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazole (6f): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55-1.8 (m, 3H, THP), 2.07-2.14 (m, 2H, THP), 2.47-2.53 (m, 1H, THP), 3.72-3.76 (m, 1H, THP), 4.01-4.03 (m, 1H, THP), 5.64-5.66 (m, 1H, THP), 7.44-7.46 (m, 2H, Hr-H), 7.96 (s,1H, Hr-H), 7.99 (s,1H, pyrazole). M/z (M^{-+}+1): 282. Anal. calcd. (%) for ($C_{12}H_{13}BrN_2O$) requires: C, 51.26; H, 4.66, N, 9.96; Found (%): C, 51.20; H, 4.62, N, 9.94.

6-Iodo-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazole (6g): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.56-1.8 (m, 3H, THP), 2.08-2.15 (m, 2H, THP), 2.49-2.54 (m, 1H, THP), 3.73-3.77 (m, 1H, THP), 4.02-4.04 (m, 1H, THP), 5.65-5.67 (m, 1H, THP), 7.45-7.47 (m, 2H, Hr-H), 7.97 (s,1H, Hr-H), 8.00 (s,1H, pyrazole). M/z (M^{-+}+1): 329. Anal. calcd. (%) for ($C_{12}H_{13}IN_2O$) requires: C, 43.92; H, 3.99, N, 8.54; Found (%): C, 43.91; H, 3.96, N, 8.50.

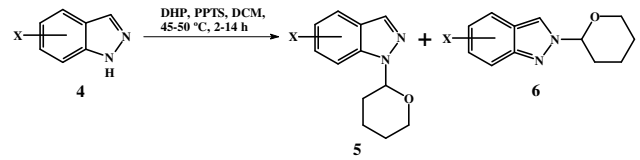
6-Nitro-2-tetrahydro-2*H*-2-pyranyl-2*H*-indazole (6h): ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.55-1.72 (m, 3H, CH_2), 1.90-195 (m, 1H, CH_2), 2.07-2.18 (m, 2H, CH_2), 3.69-4.00 (dd, 2H, CH_2), 5.82-5.86 (d, 1H, CH), 7.77-7.81 (d, 1H, Ar-H), 7.94-7.97 (d, 1H, Ar-H), 8.63 (s, 1H, Ar-H), 8.74 (s, 1H, pyrazole-H); ^{13}C NMR (DMSO-d_6): 21.71, 24.83, 30.74, 67.42, 88.84, 115.29, 115.63, 123.40, 123.91, 124.45, 145.78, 146.530 M/z: 248 (M^++1), 270 (M^++Na), 286 (M^++K). FTIR (KBr) cm^{-1}: 3402, 3131, 2931, 2865.

RESULTS AND DISCUSSION

Herein we report synthesis, starting from 4-substituted indazole (**4**), of several indazole derivatives substituted at the N-1 and N-2 positions with THP protected group. Their full characterization was achieved by multinuclear NMR and mass spectrometry, melting point and elemental analysis. Substituted indazole derivatives were prepared according to the literature reports[9]. Further, regioselective protection with THP group on indazoles derivatives was investigated in solution phase as well as under solvent free conditions with different time intervals using PPTS as a mild catalyst.

Based on literatures[10] introduction of a DHP group under mild acidic conditions led to a N-2 product after 5 h and subsequent reaction provided a mixture of N-1 and N-2 (3:1) after 18 h. We achieved excellent selectivity under mild acidic conditions at different time intervals by optimizing the reaction conditions. 4-Chloroindazole (**4a**) with dihydropyran and PPTS in dichloromethane under nitrogen atmosphere was stirred at 25 °C for 85-90 min (**Scheme-II**). Formation of the product was checked by TLC and showed a single spot, which is having 0.3 R_f on TLC plate. Reaction was continued to prolonged

time (*i.e.* more than 90 min) and formation of another spot (along with 0.3 R_f) on TLC was found (new spot R_f on TLC is 0.8), subsequently 0.3 R_f is converted to a 0.8 R_f over a period of time. At early times in the reaction, both isomers were present by TLC, but the unstable isomer (0.3 R_f) disappeared as the reaction progressed. This suggests that the reversible nature of the conjugate addition led to the thermodynamically preferred product.



Scheme-II

When we studied the protection of DHP group on substituted indazoles, we were getting selectively N-1/N-2 substituted THP indazole depending on the reaction time. Both isomers were separated at different time intervals (Table-2) and characterized by ^{1}H NMR, ^{13}C NMR and Mass. The isomers were characterized and the regioselectivity was unequivocally assigned through NOE studies. Based on these results we could further conclude that more stable isomer is the benzenoid form of the THP protected indazole which forms on prolonged heating conditions and less stable quinonoid form of the THP protected indazole results during short reaction times.

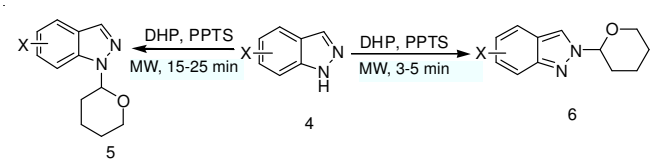
TABLE-2
REGIOSELECTIVE PROTECTION OF DHP ON
4-CHLOROINDAZOLE UNDER DCM, PPTS CONDITION

Entry	Reaction time (h)	Conversion (%)	Ratio (**5/6**)
1	1.0-1.5	100	0/1
2	2.0-10.0	100	1/1
3	16-18	100	1/0

N-1 Isomer: The signals at 8.15 (1H, s,), 7.72 (1H, d, J = 8.5), 7.39 (1H, t, J = 7.5), 7.24 (1H, d, J = 7.2) are aromatic protons in ^{1}H NMR spectroscopy, which are confirmed by DQCOSY NMR. In the NOESY1D NMR experiment on irradiation at 7.73 ppm (which corresponds to the aromatic proton at 7th position), the protons at 7.38 (6th position), 5.37 (10th position) were enhanced. Hence the connectivity of tetrahydropyran group was at 1st position on indazole

N-2 Isomer: In the NOESY1D NMR experiment on irradiation at 8.56 ppm (3rd position) the protons at 5.74 (10th position) and 2.21 ppm (11th position) were enhanced. Hence the connectivity of tetrahydropyran was at 2nd position on indazole.

As part of our ongoing investigations, we carried out the reactions under solvent-free conditions catalyzed by Microwave irradiation. Microwave irradiation has been frequently used in diverse organic transformations with a remarkable reduction in reaction times and in many cases, improving the yields and selectivities of the processes[11]. Reaction of **4a** with DHP and catalytic amount of PPTS under solvent-free conditions catalyzed by Microwave irradiation for 5 min, N-2 THP-protected indazole was exclusively formed (**Scheme-III**) and another confirmation it was identical with the solution phase product in all respect such as TLC, m.p. and NMR. Another reaction was carried out extended to 20 min, N-1 THP protected exclusively formed. Based on these results, when the reactions were carried out under microwave radiation conditions reactions precedes smoothly, shorter reaction periods, without volatile organic solvents, greater yields, simple work-up procedures.



Scheme-III

Conclusion

A simple and efficient method is developed for the regioselective protection of THP group on various substituted indazole derivatives in solution phase as well as under solvent-free conditions catalyzed by microwave irradiation at different time intervals using PPTS as a mild reagent to get N-1/ N-2 THP protected indazoles.

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