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Molecular Iodine as an efficient catalyst for the synthesis of indazole

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Abstract: An efficient approach for the synthesis of indazoles from ortho alkoxy acetophenone, hydrazine hydrate by using DMSO and molecular iodine has been described. This reaction was performed in different solvents such as Methanol, Ethanol, Acetonitrile, Toluene, THF, DMF and DMSO. But DMSO gives good yield in comparison to the other solvents by using catalytic amount of molecular iodine. In comparison to the reported methods, this reaction is rapid and gives good yield of the product.

Keywords: Ortho Alkoxy Acetophenone, Hydrazine hydrate, Molecular Iodine and DMSO.

Introduction

The indazole derivatives are pharmacologically important compounds as their ring system forms large number of drug molecules, such as granisetron, $5HT_3$ receptor antagonist, which are used as an anti-emetic in cancer chemotherapy and benzydamine as an anti-inflammatory agent[1]. Recently various methods have been reported for the synthesis of substituted indazoles by cyclization of 2,6-dihydroxyacetophenone hydrazones in the presence of polyphosphoric acid[2], using chromium tricarbonyl complex[3], $NaHSO_3$ / DMF[4], Pd-catalyzed intramolecular amination reaction of *N*-Tosylhydrazonestrimethylsilylindazole[5], trimethylsilylindazole / CsF[6], 3-carboxyindazole[7], indazole-N-oxides via the 1,7-electrocyclization of azomethine ylides[8], deoxygenated in the presence of Pd/C[9], Palladium-Catalyzed intramolecular amination of aryl halides[10], synthesis of indazoles via condensation of ortho fluorobenzaldehydes and their ortho methyloxime with hydrazine[11] ,3-substituted indazoles and benzoisoxazoles via Pd-catalyzed cyclization reactions[12], but however as far as we know, an efficient synthesis of indazoles in reasonable yield has not yet been reported. We report here the synthesis of indazoles from ortho alkoxyacetophenone by using hydrazine hydrate in different solvents like Methanol, Ethanol, Acetonitrile, Toluene, THF, DMF and DMSO. But DMSO gives good yield in comparison to the other solvents by using catalytic amount of molecular iodine. In comparison to the reported methods, this reaction was rapid and gives good yields of the products. Various indazoles were obtained in moderate to excellent yields.

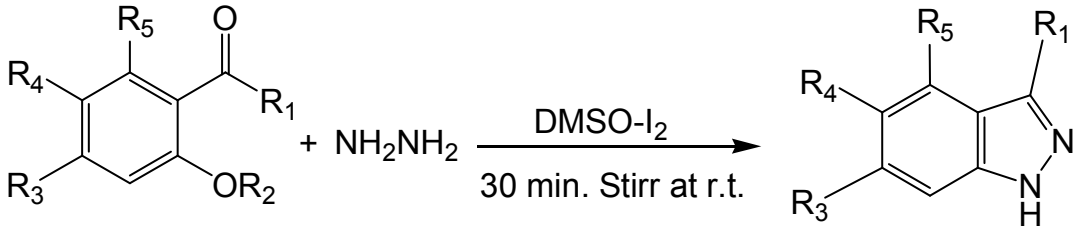
In recent years, the use of molecular iodine in organic synthesis has received considerable attention as an inexpensive, non-toxic, readily available mild Lewis acid catalyst for organic synthesis of benzothiophens[13], bis indoles[14], quinoxaline derivatives[15], deprotection of acetals[16], esterification[17], Transestrification[18] and Michel addition[19]. Recently we have reported the use of Iodine for the synthesis of an aromatic nitrile[20].

Results and Discussion

In a model condensation reaction ortho alkoxy acetophenone and hydrazine hydrate in DMSO were stirred at room temperature using catalytic amount of molecular iodine. The progress of the reaction was monitored by TLC. Completion of the reaction after 30 minutes afforded substituted indazoles in 90% yield. To evaluate the use of this procedure a variety of substituted indazoles were synthesized. The results and spectral data's are shown in Table-2 and Table-3. The reaction proceeds effectively at room temperature and no undesirable side products were obtained. In the absence of iodine, the reaction cannot proceed, even after time period of 24 h.

We have demonstrated an efficient and mild protocol for the synthesis of substituted indazoles in DMSO using catalytic amount of molecular iodine in excellent yields at room temperature.

Scheme



Where
R_1 = H,CH_3

Table:-1, Optimization of the catalytic activity of iodine and reaction Condition and yield of indazole

Entry	Amount of iodine (mmoles)	Temp (^{0}C)	Time (min)	Yield %
1	10	100	30	Trace Amount
2	08	100	60	30
3	06	70	80	35
4	04	40	100	60
5	02	r.t.	120	92

Table:- Effect of solvent on the yield of indazole

Entry	Solvents	Yield (%)
1	Methanol	10
2	Ethanol	13
3	Acetonitrile	24
4	Toluene	34
5	THF	45
6	DMF	60
7	DMSO	92

Table: -2, Substituents, Yields & m.p. for the compounds

Entry	R_1	R_2	R_3	R_4	R_5	m.p. ^{0}C (Lit)	% Yield
1	H	H	H	H	H	147(Lit)[21]	80
2	H	Me	H	H	H	147(Lit)[21]	90
3	H	Me	NH_2	H	H	205(206)	85
4	H	Me	H	NH_2	H	175(178)	87
5	H	Me	NO_2	H	H	180(Lit)[22]	75
6	H	Me	H	NO_2	H	208(210)	78
7	Me	H	H	H	OH	210(Lit)[23]	92
8	Me	Me	H	H	OMe	132(Lit)[23]	90
9	Me	Me	H	H	H	115(Lit)[24]	87
10	Me	Me	OMe	H	OMe	205(Lit)[23]	90
11	Me	Me	H	Me	H	220	84
12	Me	Me	Me	H	Me	208(206)	90
13	Me	Me	H	Cl	H	265	84
14	Me	Me	Cl	H	H	252	87

Table: -3, Molecular formula, molecular weight and spectroscopic Characterizations

Entryy	Molecular formula	Molecular weight	IR (cm^{-1})	H^1NMR ($CDCl_3$)
1 & 2	$C_7H_6N_2$	118.14	3382,3045 1689,1571	6.95 δ (1H,q, Ar-H) 7.03δ (1H,q, Ar-H) 7.35δ(1H,t, Ar-H) 7.37δ(1H,t, Ar-H) 8.25δ(1H,s) 8.79δ(1H,s, NH, D_2O, exchangeable);
8	$C_9H_{10}N_2O$	162.19	3171,1623 1596,1525	2.80δ(3H,s, CH_3) 4.07δ(3H,s, OCH_3) 6.60-7.67δ(3H,m, Ar-H) 8.56δ(1H,s, NH, D_2O, exchangeable);
9	$C_8H_8N_2$	132.16	3216,3018 1602,1560	2.61δ (3H, s) 6.94δ (1H, t, Ar-H) 7.02δ (1H, q, Ar-H) 7.37δ (1H, q, Ar-H) 7.63δ (1H, t, Ar-H) 7.27δ (1H, s, NH, D_2O exchangeable).
10	$C_{10}H_{12}N_2O_2$	192.22	3182,1636 1602,1531	2.87δ (3H, s, CH_3) 4.14δ (3H, s, OCH_3) 4.24δ (3H, s, OCH_3) 6.67-6.94δ (2H, m, Ar-H) 7.92δ (1H, s, NH, D_2O, exchangeable)
11	$C_9H_{10}N_2$	146.08	3224,3098 1670,1510	2.61δ (3H,s) 2.67δ (3H,s,Ar-CH_3) 6.95δ(1H,d,Ar-H) 7.20δ (1H,dd,Ar-H) 7.30δ (1H,d, Ar-H) 7.40δ (1H,s,NH, D_2O exchangeable)
12	$C_{10}H_{12}N_2$	160.22	3176,1622 1597,1445	2.64δ(3H,s, CH_3) 2.88δ(3H,s, Ar-H) 2.94δ(3H,s, Ar-CH_3) 7.45δ(2H,d, Ar-H) 7.87δ(1H,s, NH, D_2O, exchangeable)
13	$C_8H_7N_2Cl$	166.61	3228,3015 1602,1560	2.30δ (3H, s) 6.99δ (1H, d, Ar-H) 7.33 (1H, d, Ar-H) 7.90δ (1H, dd, Ar-H) 7.66δ (1H, s, NH, D_2O exchangeable)

All the products were characterized by IR, NMR and compaired to authentic samples.

Experimental:

All the melting points are determined in open capillaries and uncorrected. TLC routinely checked the purity of the synthesized indazoles on silica gel coated plates. IR spectra are recorded in KBr pellets on a Perkin-Elmer F.T.I.R.; PMR spectra are recorded on Perkin-Elmer Jeol FX 90 QC 300Mz instrument in $CDCl_3$. PMR chemical shifts are reported in δ values using tetramethyl silane (TMS) as an internal standard.

Typical procedure for the synthesis of 1H-Indazole A:

A mixture of Salicyldehyde1.22gm (1mol), hydrazine hydrates 0.64gm (2mol) and molecular iodine (2 mmol) in DMSO (10 mol) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice and stirred for 30 min. The solid, which separates, was filtered, washed with aqueous sodium thiosulfate solution to remove iodine and subsequently with water and then recrystallized from ethanol to afford pure 1H-indazole

M.P. = 147^0C Yield = 80%

Typical procedure for the synthesis of 3-methyl 1H-Indazole B:

A mixture of ortho methoxy acetophenone 1.50 gm (1mol), hydrazine hydrates 0.64gm (2mol) and molecular iodine (2mmol) in DMSO (10 mol) was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into crushed ice and stirred for 30 min. The solid, which separates, was filtered, washed with aqueous sodium thiosulfate solution to remove iodine and subsequently with water and then recrystallized from ethanol to afford pure 3-methyl 1H-indazole

M.P. = 190^0C Yield = 87%

Conclusion

Molecular iodine was found to be an efficient reagent for the synthesis of indazoles from corresponding substituted artho alkoxy acetophenone. The conversion was very efficient, fast and gives better yields of the product in comparison to previously reported methods. The reagent used is very mild and byproducts were not formed.

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