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MANGANESE CHLORIDECATALYSED SYNTHESIS OF 3-(1*H*-INDOL-3-YL)-1, 3-DIPHENYLPROPAN-1-ONES IN WATER UNDER MICROWAVE IRRADIATION METHOD

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Abstract

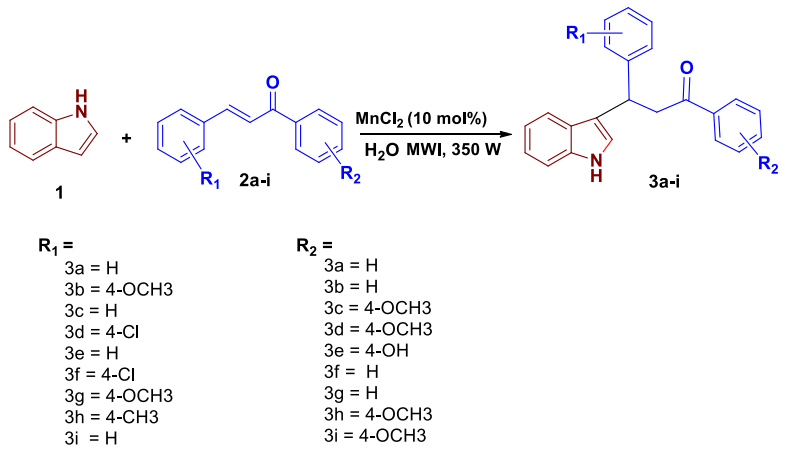
Manganese (II) Chloride has been used as an efficient catalyst for an improved synthesis of 3-(1*H*-indol-3-yl)-1, 3-diphenylpropan-1-ones in excellent yields using water as a reaction medium. This aqueous mediated reaction of various Chalcone with indole using catalytic amounts of manganese chloride avoids the use of expensive, corrosive reagents, toxic solvents, and provides operational simplicity.

Keywords: Water, Manganese chloride, Chalcone, 3-substituted indole, Microwave irradiation method.

Introduction

The nucleophilic addition to carbon-carbon multiple bond of α, β carbonyl compound for the new C-C bond formation in synthetic organic chemistry. It provides an easy route to produce Chalcone derivatives with Indole, which are more attractive for their biological activities[i] physiological properties[ii]. They are also used in the synthesis of natural products and its important building blocks substructures[iii].

Manganese Chloride catalyst is used in some organic transformations[iv-v]. In addition to using of green solvent, microwave irradiation reactions were performed and reduced the time compared to thermal reactions[vi-xiv]. Herein, we report a facile, mild and effective methodology by using environmentally benign catalyst and solvent under microwave irradiation method for the synthesis of 3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-ones.



Scheme 1. Synthesis of 3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-ones

In continuation of our earlier research work to search an environmentally benign protocol[xv-xviii]. Herein, we wish to report a new access for the synthesis of a series 3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-one **3a-i** by using Manganese chloridean efficient catalyst on water under microwave irradiation method (**Scheme 1**).

In the past, few methods have been reported for the synthesis of 3-substituted indoles by using different catalysts such as molecular iodine[xix] $CuBr_2$[xx], $InBr_3$[xxi], GaI_3 and $GaCl_3$[xxii], $CeCl_3$•7 H_2O– NaI[xxiii], SmI_3[xxiv], $ZrCl_4$[xxv], CAN[xxvi], ionic liquids[xxvii], and sodium dodecyl sulphate(SDS)[xxviii]. Use of lanthanide triflates[xxix] and Amberlite IR 120[xxx]. However, these suffer from disadvantages such as hazardous, toxic, and expensive reagent and solvent. There is no any report the reaction was performed in $MnCl_2$ as catalyst. Thus, we decide to carry out the reaction in water using Manganese chloride as a catalyst.

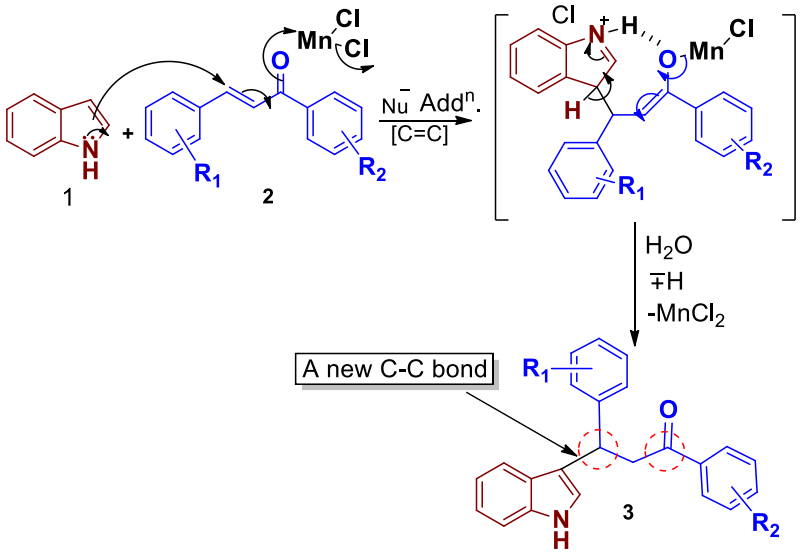


Figure 1.A proposed mechanism for nucleophilic addition of Indole to α, β carbonyl compound (Chalcone) with $MnCl_2$ and water

Results and Discussion

Hydrated manganese chloride ($MnCl_2$. $4H_2O$), a very inexpensive and easily available Lewis acid, is very easy to handle and relatively insensitive to air and moisture. In continuation of our work[xv-xviii] on the development of new synthetic methodologies, we found that manganese chloride could catalyze the addition of a variety of aliphatic and aromatic

amines to electron deficient α, β carbonyl compound in water to produce the corresponding indole derivatives in excellent yields may due to the solubility of different substrates.

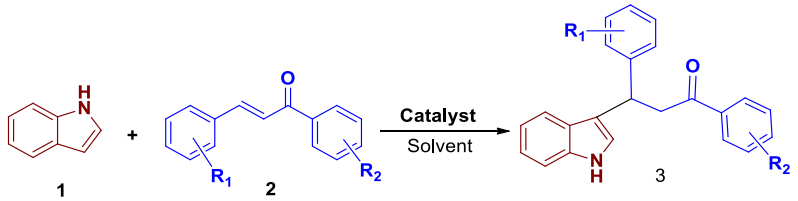
Table 1. Optimization of reaction conditions for synthesis of compound **3** in Selected catalyst under conventional and microwave irradiation method.

Entry	Catalyst (mol %)	Solvent	Reaction Condition	
			Conventional (h)	Microwave (min)
1	$MnCl_2$	DCM	8/30	4/30
2	$MnCl_2$	DMSO	8/20	4/20
3	$MnCl_2$	Toluene	8/38	4/38
4	$MnCl_2$	THF	6/58	4/68
5	$MnCl_2$	EtOH	4/78	4/78
6	$MnCl_2$	MeOH	4/70	4/70
7	$MnCl_2$	CH_3CN	5/75	4/75
8	$MnCl_2$ (0)	H_2O	8/00	6/00
9	$MnCl_2$ (2)	H_2O	5/80	4/80
10	$MnCl_2$ (5)	H_2O	5/80	4/80
11	**$MnCl_2$ (10)**	**H_2O**	**3/99**	**3/99**
12	$MnCl_2$ (15)	H_2O	3/99	3/99
13	$MnCl_2$ (20)	H_2O	2/99	2/99

[b]Isolated yield. (1) Reaction condition: Stirred and Heat at 100°C. (2) MWI=350 watt; 80° C

Literature survey reveals that there is no any report synthesis of 3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-ones using selected manganese chloride as catalyst under the microwave irradiation method. Initially, we screened various solvents for the synthesis of compound **3** as model reaction Indole **1** (10mmol) and chalcone **2** (10mmol) are mixed with manganese chloride (1.2 mmol) in water (12 ml) (**Table 1**,**Scheme 1**) with different time interval, series of solvents DCM, DMSO, Toluene, THF, EtOH, MeOH, CH_3CN, and water with selected $MnCl_2$ catalyst and we found that the used of polar protic solvents such as EtOH and MeOH forcefully reduces the reaction time with improved yield of product at reflux and microwave irradiation method, more especially with water (**Table 1,** entry 11).

Table 2. Synthesis of 3 substituted indoles under microwave irradiation method.



Entry	R_1	R_2	Time (min)	Yield[a] (%)	M.P. Found	M.P. Reported
3a	H	H	3	99	128-130	127-128[28(a)]
3b	4-OCH_3	H	3	99	126-128	128-130[31]
3c	H	4-OCH_3	3.5	99	170-172	174-177[28(b)]
3d	4-Cl	4-OCH_3	3.5	96	200-202	202-205[28(b)]
3e	H	4-OH	3.5	95	121-123	122-126[31]
3f	4-Cl	H	3.5	94	120-122	118-121[28(b)]
3g	4-OCH_3	H	3.5	94	121-123	120-122[31]
3h	4-CH_3	4-OCH_3	3	98	178-180	183-186[28(b)]
3i	H	4-OCH_3	5	99	128-130	This work

[a]Isolated yield.; Indole 1 (10mmol) and chalcone 2 (10mmol) are mixed with Manganous chloride (1.2 mmol) in

water(12 ml), at 80ºC, 350 watt 3-4 min by microwave method.

Without catalyst reaction didn't detected (**Table 1,** entry **8**). Further we observed that good to excellent yield was obtained in very less time of reaction in water medium (**Table 1**, entry **11**). If we compared both methods an excellent yield was obtained in very short time of reaction under microwave irradiation method (**Table 1**).
In our observation from the model reaction an excellent yield was obtained in presence of manganese chloride in presence of water in very less time of reactions under microwave irradiation, thus all examples were tested reasonably good to excellent yield in manganese chloride and water under microwave irradiation method (**Table 2**). The product **3a-3i**were purified by simple filtration and recrystallization from ethyl alcohol. Finally, the structure of the compounds **3** were confirmed by NMR spectroscopy and mass spectrophotometer compared with those reported methods (**Table 2**). The proposed mechanism has been shown in **Figure 1.** According to our observation, summarized data, the presence of compared chloride catalyst on water as solvent for the synthesis of compound **3** under microwave method can be considered as an efficient, total environmentally benign method for the preparation of desired product in high yield, short reaction time and environmentally safe conditions using a environmentally benign catalyst and solvent.

Conclusions

In conclusion, we have successfully developed green strategy for the synthesis of 3-(1*H*-indol-3-yl)-1, 3-diphenylpropan-1-ones using manganese chloride catalyzed in water under microwave irradiation method. The reaction was performed cleaner, no side product, good to excellent yield for all derivatives of Indole in very less time of reaction.

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Experimental

4.1. Materials and Methods

All chemicals were purchased from SD Fine chemicals. All the reported products were characterized and confirmed by comparison with those reported literature. NMR spectra were recorded on a Bruker advance spectrometer 300 MHz, DMSO-d_6 as a solvent,Chemical shifts are reported as δ_{ppm} unitsand Mass spectra were recorded QUART-MASS JEOL-Accu TOF JMS-T 100LC Mass spectrometer. Microwave reactions have been carried out in MicroSYNTH Lab station of Ethusi Milestone. All the compounds were checked for purity by thin layer chromatography.

General procedure for the synthesis of 3-(1H-indol-3-yl)-1,3-diphenylpropan-1-ones:

Indole **1** (10mmol) and chalcone **2** (10mmol) are mixed with manganese chloride (1.2 mmol) in water (12ml) was subjected to microwave irradiation 350 watt at 80°C for the appropriate time mentioned in Table **2**. The completion of reaction was monitored by Thin Layer Chromatography System, solvent system-ethyl acetate: hexane (4:6). After completion of the reaction, the reaction mixture was cooled and poured over ice water (30 ml). The solid crude product, which separated out, was filtered, washed with water and dried to give the desired compound and purified by recrystallization from ethanol. All synthesized compounds were characterized with ^{1}H NMR and mass spectrometry. Also the melting points recorded were compared with the corresponding literature melting points and found to be matching.

Physical and Spectral Data of selected compound:
3-(1H-indol-3-yl)-1,3 -diphenylpropan-1-one (3a):
M.P 129-130^{o}C; ^{1}H NMR (400 MHz,$CDCl_3$): δ = 3.63 (d, J = 7.6 Hz, 2 H); 4.52 (t, J = 6.8 Hz, 1 H), 6.98 (s, 1 H), 9.98 (s, 1 H, -NH), 7.01 (t, 1 H), 6.92 (t, 1 H), 7.50 (d, 1 H), 7.93 (d, 1 H), 7.18–7.44 (m, 5 H), 7.56–7.98 (m, 5 H); MS: m/z = 325.12.; M. F.: $C_{23}H_{19}NO$

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