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An expedient, fast and competent synthesis of organic dithiocarbamates over nanocrystalline MgO in water at room temperature

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ABSTRACT

A new, expeditious, efficient and eco-friendly method for the synthesis of organic dithiocarbamates has been achieved at room temperature using basic nanocrystalline MgO catalyst in aqueous condition. The method has been applied for the synthesis of a range of compounds with variable functionalities in excellent yield and selectivity.

In recent times increased attention is being focused on the development of eco-friendly solid acid/base catalysts for organic synthesis. Removing organic solvents has become an important factor towards developing benign chemical technologies due to their high toxicity. As a result, organic reactions in aqueous media have gained high priority in view of green methodology.[1] The use of water is also preferred due to its abundance, being economical and high polarity. It shows higher reactivity and selectivity compared to other conventional organic solvents due to its strong hydrogen bonding ability.[2] The use of water in multicomponent organic reactions has gained much importance.[3]

Organic dithiocarbamates have received much attention due to their interesting chemistry and wide utility. These compounds have shown wide applications as pesticides, fungicides in agriculture,[4] in the vulcanization of rubber,[5] and in radical chain transfer agents in the reversible addition fragmentation chain transfer (RAFT) polymerizations.[6] They have been extensively used as intermediates in organic synthesis,[7] for the protection of amino groups in peptide chemistry,[8] as linker in solid phase organic synthesis,[9] and recently in the synthesis of ionic liquids.[10] Dithiocarbamates are widely used in the synthesis of trifluoromethylamines, thioureas, aminobenzimidazoles, isothiocyanates, alkoxyamines and 2-imino-1,3-dithiolanes.[11] They also have antihistaminic, antibacterial and anticancer activities.[12]

The classical synthesis of dithiocarbamates involves the use of thiophosgene and its substituted derivatives,[13] which are costly and toxic. Dithiocarbamates can be easily synthesized by coupling an amine, CS_2 and an electrophilic reagent. Several methods have been developed for the preparations of dithiocarbamates in view of their importance. Some of the methods involve the use of various homogeneous bases and solvents like DMSO, DMF, MeOH to promote the reaction which are not considered as eco-friendly.[14] Several researchers[15–17] have developed some green protocol for the synthesis of these compounds. However, these methods suffer from the disadvantage that they take a long time for completion. We have developed the synthesis of dithiocarbamates following an eco-friendly pathway in very short time, involving Michael addition as an intermediate step catalysed over nanocrystalline MgO.

In continuation of our efforts for the developing synthetic methodologies for the production of various biologically important moieties using heterogeneous nanocatalysts,[18] we wish to report for the first time use of nanocrystalline MgO catalysed one-pot three component synthesis of dithiocarbamates in water under ambient conditions in high yield (Scheme 1). Recently, we have published our work for the synthesis of Betti bases over nanocrystalline MgO at aqueous condition.[19] Structural characterization, active sites and method of synthesis of NP MgO have been discussed in detail in the earlier work.

A very simple protocol was followed in the reaction process.[20] A mixture of an amine (1.0 mmol), CS_2 (3.0 mmol) and a Michael acceptor (1.3 mmol) was stirred in water at room temperature over nano MgO catalyst. The progress was checked by TLC and after work-up excellent yields of the product was obtained. No other additive was necessary to promote the reaction.

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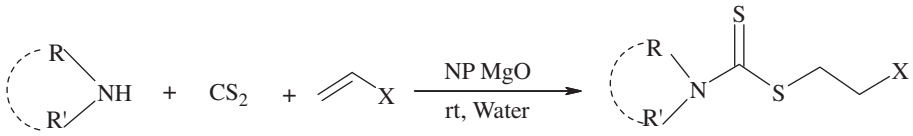

Scheme 1. Synthesis of dithiocarbamates over nanocrystalline MgO in water.

Table 1
Screening of catalysts in the synthesis of dithiocarbamates over nano MgO[a]

Entry	Catalyst	Time (h)	Yield (%)
1	CuO nanopowder	6	52
2	Basic Al_2O_3	20	95[17]
3	Silica gel	20	84[17]
4	SBA 15	12	73
5	TUD-1	12	68
6	Bulk MgO	1.0	78
7	**Nano MgO**	**1.0**	**92**

[a] Reagents and conditions: pyrrolidine/methyl acrylate/CS_2 = 1.0:1.2:3.0, catalyst 10 mg, room temperature, water, isolated yield, bold entry signifies the best condition.

Table 2
Screening of solvents in the synthesis of dithiocarbamates over nano MgO[a]

Entry	Solvent	Time (h)	Yield (%)
1	*n*-Hexane	6	n.r
2	THF	6	n.r
3	MeOH	3	76
4	**Water**	**1**	**92**

[a] Reagents and conditions: pyrrolidine/methyl acrylate/CS_2 = 1.0:1.2:3.0, catalyst 10 mg, room temperature, isolated yield, bold entry signifies the best condition.

During the course of the reaction, standardization of reaction conditions appeared important. The reaction between pyrrolidine, carbon disulphide and methyl acrylate as the Michael acceptor was chosen as a probe. Optimization started with the study of catalyst variation. A wide range of catalysts viz., CuO nanopowder, basic Al_2O_3, silica gel, mesoporous silica, bulk MgO and nanocrystalline MgO was used in the reaction in aqueous condition at room temperature. Notably, nano MgO afforded the best results amongst the different kinds of solid media used. These have been shown in Table 1. It seems interesting to mention that CuO provided the corresponding aza-Michael product in major amount compared to the desired dithiocarbamate. Basic alumina, although efficient, took longer reaction time. With silica gel and mesoporous silica (SBA-15 and TUD-1) only moderate yields were obtained. However, with bulk MgO some undetected byproduct was produced along with the desired compound. So, nanocrystalline MgO proved to be the best catalyst in water.

Nano MgO worked best in aqueous condition as shown in Table 2. Among the different tested conventional organic solvents like *n*-hexane, THF and methanol, none of the solvents proved satisfactory in terms of reaction time and yield. With hexane and THF the reaction did not proceed at all.

After standardization of the reaction conditions, the scope and generality of these conditions with other substrates were examined by using a variety of primary and secondary amines and different electrophiles (Michael acceptors or α,β-unsaturated compounds). The results have been summarized in Table 3. All the reactions were performed smoothly under optimized conditions by stirring all reagents together in water in the presence of nanocrystalline MgO and all the reactions were satisfactorily completed within 1.0–2.0 h at ambient conditions. Using pyrrolidine as cyclic secondary amine reactions were carried out with different Michael acceptors like methyl acrylate, acrylonitrile, acrylamide, ω-nitro styrene, benzyledene acetophenone and 4-nitro benzyledene acetophenone (Table 3, entries 1–6). In all the cases excellent yields were obtained in short time except with 4-nitrobenzyledene acetophenone which afforded comparatively lower yield due to its lower electrophilicity (entry 6). Similarly, other aliphatic amines like piperidine, morpholine, cyclohexyl amine and benzyl amine also reacted with different electrophiles efficiently generating high yields (Table 3, entries 7–16).

Table 3
Synthesis of dithiocarbamates over nanocrystalline MgO[a]

Entry	Amines	Michael acceptor	Time (h)	Yield (%)
1	Pyrrolidine	Methyl acrylate	1.0	92
2	Pyrrolidine	Acrylonitrile	1.2	94
3	Pyrrolidine	Acrylamide	1.5	88
4	Pyrrolidine	ω-Nitro styrene	0.5	95
5	Pyrrolidine	Benzylidene acetophenone	1.0	92
6	Pyrrolidine	4-Nitrobenzylidene acetophenone	2.0	73
7	Piperidine	Acrylonitrile	1.2	88
8	Piperidine	Acrylamide	2.0	85
9	Piperidine	Methyl acrylate	1.5	90
10	Piperdine	Benzylidene acetophenone	1.2	91
11	Piperdine	ω-Nitro styrene	0.7	93
12	Morpholine	Acrylonitrile	1.0	88
13	Morpholine	Acrylamide	2.0	82
14	Morpholine	Methyl acrylate	1.5	85
15	Cyclohexylamine	Acrylonitrile	1.5	84
16	Benzylamine	Acrylonitrile	1.0	86

[a] Reagents and conditions: amine/Michael acceptor/CS_2 = 1.0:1.2:3.0, catalyst 10 mg, room temperature, water, isolated yield.

Table 4
Reusability study of MgO

Entry	Yield[a] (%)
1	94
2	92
3	88
4	87

[a] Isolated yield after each run.

Recyclability of nanocrystalline MgO was examined through the reaction of pyrrolidine, CS_2 and acrylonitrile in water. After completion of the reaction, the product was extracted with diethyl ether from the reaction mixture. The aqueous part containing the MgO catalyst was recovered and reused as such for subsequent reactions with fresh batch of reactants. It was found that MgO could be recycled three times without significant loss of yield. The reusability test has been shown in Table 4.

Nanocrystalline MgO contains large number of basic sites such as O^{2-} and O^- and Mg^{2+} as Lewis acid sites. The initial mechanism goes through the formation of dithiocarbamic acid where Mg^{2+} is involved in activating carbon disulphide. This acid anion then undergoes Michael addition promoted by Lewis and Bronsted basic sites with the different acceptors to give the dithiocarbamate as the final product.

In conclusion, an environmentally benign, highly efficient and simple protocol for the synthesis of various structurally divergent dithiocarbamate derivatives has been developed by one-pot

reaction of wide range of amines, carbon disulphide and an array of Michael acceptors with excellent yield in the presence of nanocrystalline MgO as catalyst. The reaction is (i) clean, (ii) highly expeditious, (iii) involves water as the green solvent and (iv) occurs at ambient conditions.

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20. A mixture of an amine (1.0 equiv), a Michael acceptor (1.2 equiv), and CS_2 (3.0 equiv) was stirred at room temperature in aqueous (just moist) condition in the presence of 10 mg of nano MgO catalyst. After completion of the reaction (indicated by TLC), the reaction mixture was extracted with diethyl ether. The extract was concentrated under reduced pressure and purified by column chromatography using 100–200 mesh silica gel with ethyl acetate/hexane (6–10%) as eluent. The isolated compounds were characterized from mp, IR, ^{1}H NMR, ^{13}C NMR spectrometry and spectral analysis (C, H, and N). Spectroscopic data for one of the characteristic compound has been provided below.
Pyrrolidine-1-carbodithioic acid-3-oxo-1,3-diphenylpropyl ester (entry 5, Table 3): Yield 460 mg; white solid; mp 125 °C; IR (KBr): 2956.5, 2366.9, 1677.9, 1432.4, 1228.0, 1113.7, 978.7, 685.8 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.91–2.06 (m, 4H), 3.56–3.62 (m, 2H), 3.70–3.79 (m, 1H), 3.92 (t, J = 6.75 Hz, 2H), 4.13 (dd, J_1 = 4.5 Hz and J_2 = 4.5, 1H), 5.72–5.77 (m, 1H), 7.19–7.31 (m, 3H), 7.4–7.56 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 24.2, 26.04, 45.1, 50.52, 50.61, 54.81, 127.59, 128.17, 128.35, 128.51, 128.55, 133.08, 136.6, 139.47, 191.20, 197.0; Anal. Calcd for $C_{20}H_{21}NOS_2$: C, 67.60; H, 5.91; N, 3.94. Found: C, 67.51; H, 6.02; N, 3.88.