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A Very Efficient Nano-crystalline Magnesium Oxide Mediated Catalytic Protocol for the Synthesis of Sulfinamides

Rajashree Chakravarti
Department of Materials Science and Engineering, University of California, Berkeley, CA, 94720-5800, USA
E-mail: rajashree@berkeley.edu

Abstract
A new protocol for the synthesis of aryl sulfinamides has been realized using highly basic nanocrystalline magnesium oxide (MgO) as a highly efficient catalytic platform. Good to excellent yields of the products have been realized and the catalyst could be recycled without the loss of activity for several cycles.

Keywords: catalyst, magnesium oxide, nanocrystalline, recyclable, sulfinamides

Sulfinamides are one of the most important molecules in synthetic organic chemistry.[1] In the recent years, several new methodologies for the synthesis of sulfoxides and sulfinamides have emerged. Sulfinamides are useful compounds and can be transformed to a number of other important functional groups such as sulfonimidoyl chlorides and cyclic sulfonimidates, which are valuable starting materials in the synthesis of various oxa- and aza-heterocyclic compounds.[2] N-chloro sulfinamides were found to be the reactive intermediates in the oxidative chlorination of sulfinamides with *tert*-butyl hypochlorite.[3] Several biologically active naturally occurring molecules like L-1-deoxyallonojirimycin and L-1-deoxymannojirimycin have sulfinamide moiety as an intermediate in their syntheses.[4]

Various procedures have been reported for the preparation of sulfinamides. The conventional synthesis of these compounds refer to the treatment of sulfinyl chlorides with secondary amines or with Grignard reagents.[5] Another method reported for the synthesis of these compounds is by the reaction of sulfinyl pthalimides with primary and secondary amines.[6] But low yields of the desired products due to unstable precursor formation and concomitant side reactions were the major drawbacks of these methods.

Furukawa et al.[7] reported the synthesis of sulfinamides from sulfinic acids using dicyclohexylcarbodiimide(DCC) as a dehydrating agent and 2-chloro-1-methylpyridinium iodide as a coupling reagent. Davis et al.[8] showed the synthesis of enantiopure sulfinimines from p-toluenesulfinate ester. Ellman and co-workers reported the synthesis of *tert*-butanesulfinamides via the oxidation of the corresponding disulfides.

Malacria and co-workers reported the synthesis cyclic sulfinates and sulfonamides through a hemolytic substitution at the sulfur atom.[9]

These reactions often require two or more synthetic steps. In order to render this reaction more useful, an elegant single step process is desired.[10] One recently reported but widely used method for the synthesis of sulfinamides is by amination of sulfinyl chlorides. Although, the preparation of sulfinyl chlorides is not exceptionally difficult, they are sensitive to hydrolysis and require preparation using highly toxic reagents as thionyl chloride. Therefore, mild and easier methods for the synthesis of sulfinamides are desired. Recently, much effort has been directed towards a mild synthesis of these sulfinamides. Sharpless and co-workers reported the synthesis of sulfinate esters from sulfonyl chlorides by a one-pot reductive esterification reaction using phosphites as the reducing agents.[11] Among the recent ones mention may be made of the work done by Harmata et al.[10] on the synthesis of sulfinamides from sulfonyl chlorides, using triphenylphosphine as the reductant and

triethylamine as the base. This method was successful in affording the sulfinamide products in good yields.

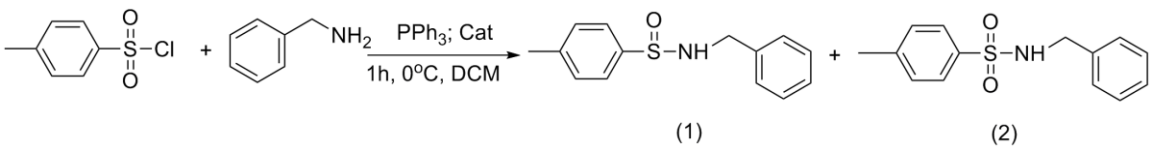
The current trend in methodology research is the search of cleaner technologies for synthetically important methods, designing of methodologies using reusable catalysts and eco benevolent solvents have seen many researcher working in the pursuit of them.[12] In similar lines we have earlier reported the synthesis of sulfinamides using mesoporous carbon supported MgO nanoparticles.[13] This catalyst was efficient and resulted in good to excellent yields of the products. But the catalyst requires very specialized synthesis techniques, which might not be always executable. We therefore have then taken the initiative of searching for a more readily available heterogenenous catalyst which affords the sulfinamides efficiently under mild reaction conditions. Nanocrystalline MgO has been recently used successfully as a catalyst in many organic reactions.[14] Hereby we report a very practical protocol for the synthesis of sulfonamides under mild conditions using nanocrystalline MgO. The catalyst can be isolated and reused for several cycles without the loss of its activity.

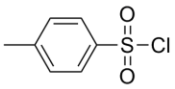
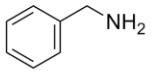
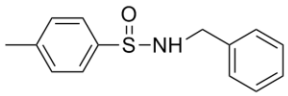
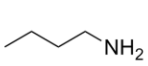
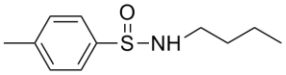
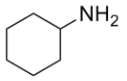
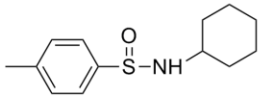
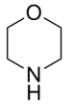
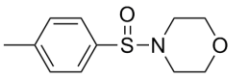
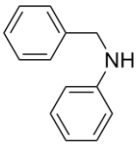
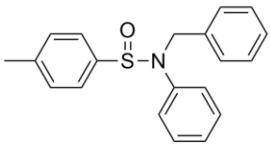
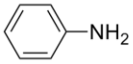
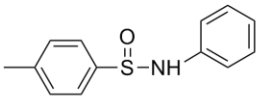
A large number of control experiments or optimization experiments are required to establish a successful protocol. The first set of experiments in this work being the optimization of the catalyst. NAP-MgO catalyst (SA: 600 m^2/g)[15] was applied to the synthesis of sulfinamides. The reactivity of this catalyst was compared to commercially available MgO (SA: 25 m^2/g). It was observed that a mere 20% of the corresponding product could be isolated, when commercial MgO was used as the catalyst in the reaction of *p*-toluenesulfonyl chloride with benzyl amine in presence of triphenylphosphine as the reducing agent, whereas the yield of the corresponding product was 72% when NAP-MgO was used as the catalyst. The earlier reports of the synthesis of the sulfinamides suggest that basic sites are necessary in the catalyst to trigger this reaction.[15] In this context, a thorough insight into the structure of MgO suggests that it is composed of Lewis acidic Mg^{2+} and Lewis basic O^{2-}.[16] This greater reactivity may be attributed to the higher surface area of the catalyst, which in its turn exposes a greater number of basic sites. Moreover the typical icosahedral shape of the particles in the catalyst helps in adhering isolated hydroxyl groups, whose basic nature helps in achieving the reaction.

Screening of various solvents for this reaction showed that in acetonitrile chloroform, toluene and THF, only a trace amount of conversion of the starting materials could be achieved using NAP-MgO as the catalyst and *p*-toluenesulfonyl chloride, benzyl amine and triphenylphosphine as the model substrates. It was found that the reaction proved to be most facile when dichloromethane was used as solvent. The selectivity of the reaction was found to be the maximum towards the formation of the corresponding sulfinamide when a mixture of benzyl amine and triphenylphosphine in dichloromethane was added slowly over 1 h to a stirred solution of the catalyst and *p*-toluenesulfonyl chloride in DCM at 0^oC.

Therefore with these optimized conditions, the scope of the reaction was then expanded over a large number of amines having diverse chemical nature. The results are furnished in the **Table 1** below.

Table 1: Synthesis of a series sulfinamides using *p*-toluenesulfonyl chloride and various amines[a]



Entry	Substrate	Amine	Product (1)	Yield (%)
1				72
2				72
3				70
4				65
5				68
6				81

[a]*Reaction conditions: p*-toluenesulfonyl chloride (1mmol), triphenylphosphine (1mmol), amine (1.5mmol), catalyst (20 mg), DCM (4 ml), stirred at 0^{o}C for 1h. All yield reported are isolated yields.

The reductive amination of the *p*-toluenesulfonyl chloride with various amines proceeded smoothly to afford the desired sulfinamides in moderate to good yields. In most of the cases aryl sulfonamides were formed as a minor side product. ^{1}H NMR and mass spectrometry of the resulting compounds revealed that benzyl amine resulted in 72% of the desired product in a very short reaction time (Table 1; entry 1). Aliphatic amines, like butyl amine showed a good selectivity towards the formation of the sulfinamide (Table 1; entry 2). Good yields of the aryl sulfinamides were also obtained in case of the cyclic primary amines, where as the side product, aryl sulfonamides were formed in a very small amount of only 10% (Table 1; entry 3). morpholine showed a much higher selectivity towards the formation of the corresponding sulfinamide product (Table 1; entry 4). Aniline was very selective and formed only the sulfinamide product (Table 1, entry 6).

After the completion of the reaction, the catalyst was separated by simple centrifugation and washed several times with ethyl acetate to remove any traces of organic compounds and was dried at 100^{o}C, in a hot air oven and re-used for further cycles without any re-activation. Yields of the products obtained in the consecutive reaction cycles are similar to that of the first one for five consecutive cycles.

Therefore the catalyst was highly successful in affording the desired sulfinamide products in good to excellent yield and the catalyst was seen to be very versatile and could achieve similar results with various amines with diverse chemical characteristics.

In order to provide an insight into the mechanism of the reaction, which might have made this new catalytic technique a successful one, NAP-MgO can be looked upon as an assembly of Mg^{2+} and O^{2-} ions.[16] The presence of both these ions on the catalyst surface helps in

stabilization of the incoming charges on the reagents in close proximity. This in turn results in a facile reaction, taking place affording the desired product in good yields.

In summary, an efficient and practical protocol for the synthesis of an important molecular moiety, sulfinamides, is designed. This method is environmentally benign using magnesium oxide and the catalyst is reusable for several cycles without the loss of activity.

Experimental Procedure

Methods and materials: All chemicals were obtained from commercial sources. Nanocrystalline magnesium oxide is obtained from Nanoscale Inc., USA. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates. All column chromatographies were performed using ACME silica gel 60-120 mesh.

Typical experimental procedure: To a stirred solution of *p*-toluenesulfonyl chloride (190 mg, 1 mmol) and NAP-MgO catalyst (20 mg) in dichloromethane (2 mL) at 0^{o}C, was added a solution of triphenylphosphine (262 mg, 1 mmol) and benzyl amine (160.5 mg, 1 mmol) in dichloromethane (2 ml) *via* a syringe over a period of 1h. The reaction was monitored by thin layer chromatography, by comparing with the starting materials. After the reaction was complete, the reaction mixture was centrifuged to remove the catalyst and washed several times with ethyl acetate. The combined organic extracts were concentrated under vacuum and subjected to purification by column chromatography over a silica gel column (eluent: 20% ethyl acetate: hexane) as white solid. The catalyst was washed and then dried in a hot air oven and subjected to the next run. The products were identified by NMR and mass spectroscopic analysis and comparison with the data available in the literatures.[16]

Representative examples

1-(*p*-tolylsulfinyl)-4-methoxyaniline (Table 4, entry 1).

Figure 8. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J*= 8.4 Hz, 2H), 7.18-7.31 (m, 7H), 4.24-4.30 (t, *J*= 5.5 Hz, 1H), 4.14 (dd, J=4.8, 13.2 Hz, 1H), 3.76 (dd, J=7.3, 13.5 Hz, 1H), 2.35 (s, 3H).

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