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ARTICLE

$MgSiO_3$ nanoparticle-catalyzed 1,3-dipolar cycloaddition reactions in the synthesis of novel spiroindane-1,3-diones derived from substituted chalcones

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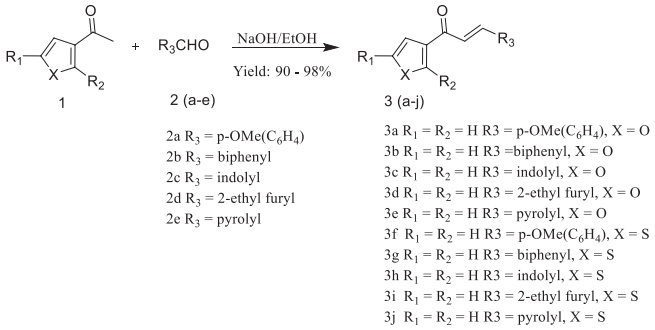
Employment of metal nanoparticles has been one of the most promising synthetic strategies for a number of chemical transformations. New spiroindane-1,3-diones were synthesized through [3 + 2] cycloaddition in moderate to high yields by a three-component reaction of heterocyclic chalcone derivatives, ninhydrin, and sarcosine/L-proline. The presence of heterogenous $MgSiO_3$ nanoparticles (NPs) under microwave irradiation showed a robust effect in improving the yield of the desired products. Furthermore, the catalyst may be recovered and reused without significant loss of activity.

KEYWORDS
1,3-dipolar cycloaddition, heterocyclic Chalcone derivatives, L-proline, $MgSiO_3$NPs, sarcosine

1 | INTRODUCTION

The evolution of nanoparticle-catalyzed cycloaddition has sprung into prominence opening up new prospects in various fields such as supramolecules,[1] polymers,[2] functional coatings,[3]and chemical synthesis.[4,5] Furthermore, nanocatalysts can be extensively used in organic transformation because of their high selectivity, reactivity, and stability.[6] The emergence of the metal oxide nanoparticles (NPs), for the synthesis of stable heterocyclic compounds via click chemistry, has been of intense interest and recently enolate-mediated organo click reaction for the synthesis of substituted triazoles has been reported.[7] For instance, our laboratory reported the application of $MgSiO_3$ NPs for the stereoselective synthesis of polycyclic aromatic hydrocarbons by intramolecular 1,3-dipolar cycloaddition reaction [1,3-DC].[8,9] We anticipated that this methodology could be extended to prepare spirocyclic compounds via 1,3-dipolar cycloaddition with diverse dipolarophile.

Chalcones because of their widespread applications, pharmacological activity, and their ease of preparation compelled us to consider them as dipolarophiles. Moreover, the newly synthesized chalcones were found to have excellent cytotoxic activity toward hepatocellular carcinoma cell lines (HepG2 cell lines).[10] Based on the initial findings and to explore the new class of functionalized spiroheterocyclic derivatives and also to study their biological applications, 1,3 DC on chalcone substrates was chosen. In recent years, a renaissance of interest in the development of methods for the synthesis of bioactive natural products and medicines comprising spiroindene motif has been observed.[11–14] These ring systems, which are connected through one atom, are a



SCHEME 1 Synthesis of chalcone derivatives **3a–j**. a. NaOH (1.5 eq), methanol, rt, 2 hr

TABLE 1 Reaction of dione azomethine ylide with dipolarophile **(3d)** under varied conditions

Reaction conditions	Time (hr)	Isolated yield (%)
Acetonitrile/reflux	24	10
Dioxane/reflux	12	15
Xylene/reflux	10	0
Toluene/reflux	8	15
Methanol/reflux	12	30
Methanol, $MgSiO_3$NPs (10 mol%) reflux	12	60
Methanol/MW, $MgSiO_3$NPs (10 mol%)	0.75	75

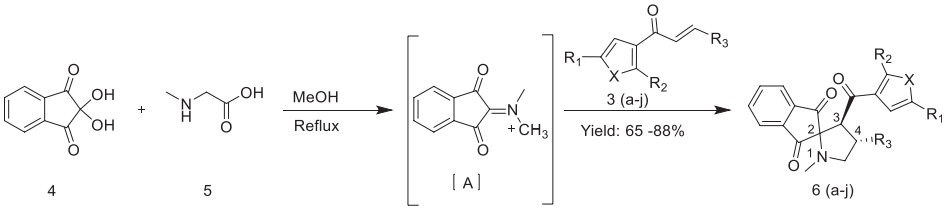
unique kind of structure in organic compounds. However, there are fewer reports related to the rationalizing azomethine-chalcone cycloadditions. Our initial concept for the preparation of spiroindene was inspired by traditional syntheses.[15–18] A number of methods have been developed for constructing enantioselective spiro compounds through 1,3-dipolar cycloaddition reaction via azomethine ylide[19–21] and organocatalytic reactions.[22] Consequently, we believed that the incorporation of chalcone framework into the more complex structures would be worthwhile to design new potentially bioactive compounds.

Recently, a spirooxindole system obtained from various approaches has been outlined for its application as anti-tumor, antimicrobial, and anti-HIV agents as well as antipyretics.[23] Herein, we report an efficient, atom economic, regioselective, and high yielding multicomponent reaction (MCR) protocol for the one-pot facile synthesis of functionalized spiroindane-1,3-diones. A new synthetic methodology was implemented by the application of $MgSiO_3$ NPs for heterocyclic chalcones by the reaction of ninhydrin with sarcosine/proline, in methanol under microwave irradiation.

2 | RESULTS AND DISCUSSION

Our experimental efforts began with the synthesis of a variety of biologically active heterocyclic chalcones **3a–j** as larger dipolarophiles under the standard condition as described in the preceding literature procedure.[10] To evaluate the feasibility of the approach, outlined in Scheme 2, we targeted initially with the thiophene-based system synthesized from the readily available 3-acetyl thiophene **1** (Scheme 1).

With chalcone derivative **3d** in hand, we turned our attention to the implementation of 1,3-dipolar cycloaddition reaction. Primarily, we attempted a few experiments of **3d** in various solvents viz. acetonitrile, toluene dioxane, and xylene



SCHEME 2 Synthesis of spiroindane-1,3-dione derivatives **6a–j**. a. 4 (3.0 eq), 5 (3.0 eq), 3 (1.0 eq), 10 Mol% $MgSiO_3$ NPs, methanol, MW, and 0.5–1 hr

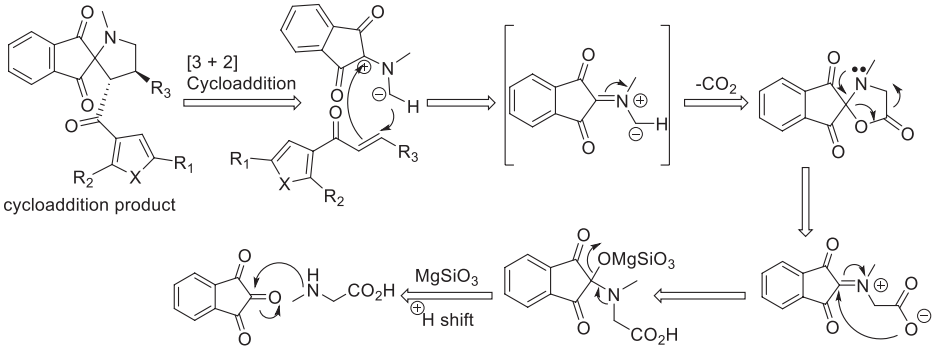
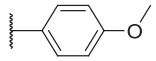
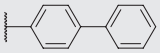
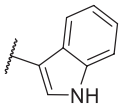
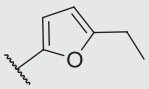
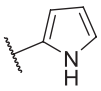
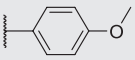
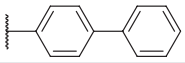
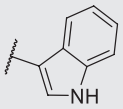
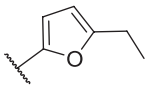
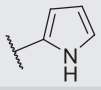


FIGURE 1 Retrosynthetic strategy for the synthesis of spiroindane-1,3-diones

TABLE 2 Spiroindane-1,3-dione hybrids **6a–j** from $MgSiO_3$NP-catalyzed 1,3-dipolar cycloaddition[a]

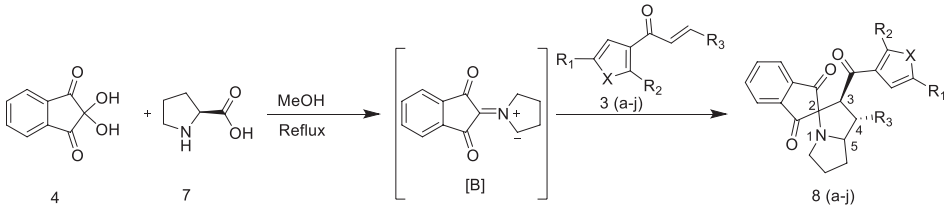
Entry	R_1	R_2	R_3	X	Time (hr)	Isolated yield (%)
6a	H	H		S	0.75	75
6b	H	H		S	0.75	72
6c	H	H		S	1	68
6d	H	H		S	0.5	88
6e	H	H		S	0.5	85
6f	CH_3	CH_3		O	0.75	75
6g	CH_3	CH_3		O	0.75	72
6h	CH_3	CH_3		O	1	65
6i	CH_3	CH_3		O	0.5	80
6j	CH_3	CH_3		O	0.5	80

[a]*Reaction conditions*: **3** (1 mmol), **4** (3.0 mmol), **5** (3.0 mmol), methanol (10 mL), 10 mol%$MgSiO_3$NPs, Methanol MW, and 0.5–1 hr.

under thermal conditions, which led to the formation of spiro products, but in low yields (Table 1). Eventually, we found that, the addition of a catalytic amount of nanocatalyst viz. $MgSiO_3$ to **3d** in methanol under refluxing conditions worked well and gave the desired cyclic adduct **6d** in 60% yield. There was a substantial increase in the yield of the cycloadducts under microwave irradiation with a decrease in reaction time to get a novel fused spiroindane-1,3-diones. The reaction progressed through in situ generation of azomethine ylide intermediate **A** (Scheme 2) followed by cyclization in completely regioselective and stereoselective manners. The $MgSiO_3$ NPs were prepared according to the reported protocol.[24] These nanoparticles were believed to act as Lewis acid by coordinating with chalcone for the formation of ylide intermediates, as shown in the retrosynthetic analysis (Figure 1).

The structure of **6d** was confirmed by the spectral data. The stereochemistry was assigned based on ^{1}H NMR and NOE studies. The confirmative protons of the proposed structure for **6d** are H3 and H4 protons. In ^{1}H NMR spectroscopy, the H4 proton appeared at δ 3.5 as a quartet with a coupling constant $J = 6.4$ Hz, whereas the characteristic H3 proton appeared as a multiplet at $\delta = 4.4$ ppm, respectively. The stereochemistry of the cycloadduct **6d** was presumed on the basis of 2D NOESY experiments. There is no NOESY between H4 and H3 of **6d** clearly proved *trans* stereochemistry. Two triplets at δ 3.8 and 4.5 correspond to N-CH_2 protons. The N-CH_3 peak appeared as a singlet at δ 2.3 ppm. This was further confirmed by carbonyl groups of indene and thiophene of ^{13}C NMR at δ 202.8, 200.5, and 191.7 ppm.

SCHEME 3 Synthesis of spiroindane-1,3-diones derivatives **8a–j**. a. 4 (3.0 eq), 7 (3.0 eq), 3 (1.0 eq), 10 Mol% $MgSiO_3$ NPs, methanol, MW, and 0.5–1 hr

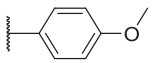
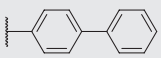
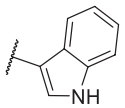
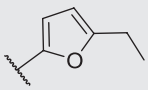
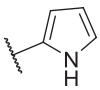
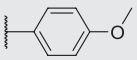
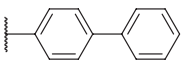
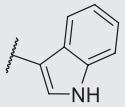
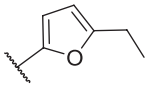
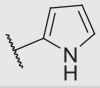


To expand the scope of this reaction, we explored the use of various chalcone derivatives (**3a–j**) under optimized reaction conditions, which led to the formation of the corresponding cycloadducts **6a–j** in good yields with complete regioselectivity (Table 2). We first began the reaction of **3a** with acyclic amino acid (sarcosine) **5**, ninhydrin **4** in methanol (10 vol) in the presence of $MgSiO_3$ NPs at 50°C, which efficiently afforded cyclic adduct **6a** as a single diastereoisomer in 75% yield (Table 2, entry 1).

Furthermore, this catalytic system was effective for the methodology toward cyclic amino acid-derived ylides and regiochemistry. These results demonstrate that this reaction can be used to furnish novel corresponding cycloadducts **8a–j** in good yields with complete selectivity (Scheme 3). Only a single diastereomer was obtained throughout the series and the structures of which were completely established by ^1H, ^{13}C, and mass spectral studies (Table 3). The ^1H nuclear magnetic resonance (NMR) spectrum of compound **8a** shows multiplet signals in the region δ 1.77–2.64 for the protons of the pyrrolizidine system. The signals in the region δ 6.80–8.08 are for the protons of aryl groups. A doublet at δ 4.80 (1H, d, $J = 11.2$ Hz) indicates the presence of a methine proton, next to the thiophenecarbonyl group at C-3 of the pyrrolidine ring. The benzylic proton at C-4 resonates as a multiplet at δ 3.81 (1H, m). In the ^{13}C NMR spectrum of the cycloadduct **8a**, the carbonyl carbons of indene-1,3-dione and the thiophenecarbonyl group carbons exhibit signals at δ 201.4, 200.1, and 190.1, respectively. A molecular ion peak at m/z 458 (ESI-MS, M + 1) in the mass spectrum confirmed the formation of the cycloadduct. The regiochemistry of this type is established by the comparison with the analogous type of compound that has been reported in the literature.[9,13]

Finally, we also examined the catalytic effect of $MgSiO_3$ NPs on 1,3-dipolar cycloaddition reaction and its regiochemical outcome in terms of reusability. The catalyst was recovered from the reaction medium by simple filtration and was washed with cold methanol and further dried in the air overnight. In two runs, there is no substantial decrease in the isolated yield observed with recycled $MgSiO_3$NPs. An experimental work to assess the stability and efficiency of the reused dried catalyst was carried out on compound **6d**, by following the optimized protocol. The isolated yield was found to be 80%, after two runs and was achieved in 30 min., which is 15 min less than that of the original single-pot reaction. The reason for the sustained performance can be attributed to nanoparticle formation. However,

TABLE 3 Spiroindane-1,3-dione hybrids **8a–j** from $MgSiO_3$NP-catalyzed 1,3-dipolar cycloaddition[a]

Entry	R_1	R_2	R_3	X	Time (hr)	Isolated yield (%)
8a	H	H		S	0.75	70
8b	H	H		S	0.75	74
8c	H	H		S	1	63
8d	H	H		S	0.5	85
8e	H	H		S	0.5	82
8f	CH_3	CH_3		O	0.75	70
8g	CH_3	CH_3		O	0.75	72
8h	CH_3	CH_3		O	1	60
8i	CH_3	CH_3		O	0.5	82
8j	CH_3	CH_3		O	0.5	80

[a]*Reaction conditions*: **3** (1 mmol), **4** (3.0 mmol), **7** (3.0 mmol), methanol (10 vol), 10 mol%$MgSiO_3$NPs, Methanol, MW, 0.5–1 hr.

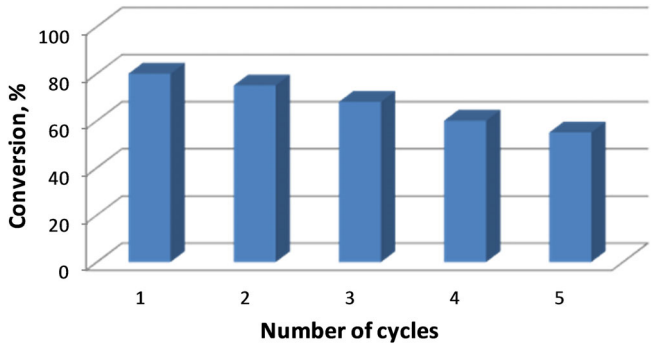


FIGURE 2 Recyclability study of the $MgSiO_3$NPs was tested for the reaction mentioned in Table 2, entry **6d**

after two runs the percentage in the isolated yield was dropped gradually till five runs (Figure 2).

3 | CONCLUSIONS

In this study, we performed 1,3-dipolar additions involving different heterocyclic chalcones as dipolarophiles and an azomethine ylide prepared from the decarboxylative condensation between N-substituted α-amino acids and ninhydrin in the presence of $MgSiO_3$ NPs under traditional as well as microwave irradiation. To the best of our knowledge, the application of $MgSiO_3$NPs and their reusability in these types of reactions are not known. These reactions produce diversely structured regioselective and stereoselective spiroindane-1,3-diones in moderate to high yields. Because of their antitumor, antimicrobial, and anticholinesterase properties, these compounds can be used as a scaffold for generating small-molecule libraries with potential or demonstrated activity in various areas.

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SUPPORTING INFORMATION

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