# Organic & Biomolecular Chemistry



View Article Online

# COMMUNICATION

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Cite this: DOI: 10.1039/d0ob00284d

Received 8th February 2020, Accepted 3rd March 2020 DOI: 10.1039/d0ob00284d rsc.li/obc

# Magnetically recoverable silica catalysed solventfree domino Knoevenagel-hetero-Diels–Alder reaction to access divergent chromenones†

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A three-component domino Knoevenagel-hetero-Diels-Alder (DKHDA) reaction between 1,3-dicarbonyl, aldehydes/ketones, and alkenes/alkynes leading to the divergent synthesis of chromenones, dihydrochromenones, and spirocyclic chromenones is reported. The reaction was carried out under solvent-free conditions using a magnetically separable silica (Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>) catalyst. While two component DKHDA reactions are known, this is the first example of a three component DKHDA reaction involving 1,3dicarbonyl, ketones, and alkynes producing spirocyclic pyranone derivatives. Twenty-six different highly substituted chromenones were synthesized using this methodology. A wide substrate scope due to the multicomponent nature of the reaction, high atom economy, the use of inexpensive and non-toxic recyclable silica as the catalyst, and solvent free reaction conditions make it an advantageous process. The catalyst was characterized using different analytical techniques such as XRD, IR, HRTEM, VSM, and TGA. Based on the earlier reports a mechanism has also been proposed.

#### Introduction

The chromene core is exemplified as a privileged moiety in a variety of natural products such as flavonoids, alkaloids and anthrocyanins and is known to possess fascinating therapeutic properties.<sup>1</sup> For example, calanolide A and B show prominent HIV-1 inhibitory activity (Fig. 1).<sup>2</sup> Ethuliacoumarion A and its derivatives show anticancer, molluscicidal and anthelmintic activities.<sup>3</sup> Ferprenin is a specific inhibitor of the enzyme VKORC1 which is responsible for the recycling of vitamin K, a

vitamin essential for blood clotting,<sup>4</sup> and trigolutes show AChE inhibitory activity.<sup>5</sup> Synthetic chromene derivatives also show antioxidant,<sup>6</sup> anticancer,<sup>7</sup> antimicrobial,<sup>8</sup> and molluscicidal activities.<sup>9</sup>

In recent years, the domino Knoevenagel-hetero-Diels-Alder (DKHDA) reaction has gained immense interest due to its application in the construction of synthetic drugs,<sup>10</sup> natural products<sup>11</sup> and poly-heterocyclic compounds<sup>12</sup> incorporating pyran-based frameworks with high atom economy. Following the pioneering works by Tietze,<sup>12a-c</sup> several methods have been reported in the literature employing the DKHDA strategy leading to the construction of a vast array of highly diverse pyran-fused carbocycles.13 Although intramolecular or two component DKHDA reactions between various aromatic and aliphatic aldehydes and 1,3-dicarbonyl compounds have been widely reported,<sup>10-13</sup> examples of intermolecular three component reactions involving 1,3dicarbonyl, aldehydes/ketones, and alkenes/alkynes are comparatively less.14 Moreover, reactions with non-activated terminal alkynes are limited compared to alkenes. To our knowledge there are no reports on DKHDA reactions involving 1,3-



Fig. 1 Biologically active natural products containing chromenones.

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 $<sup>\</sup>dagger$  Electronic supplementary information (ESI) available: Experimental details, catalyst characterization and spectra of all new products. See DOI: 10.1039/ d0ob00284d

Traditional intramolecular or two component DKHDA reaction



Our work: Intermolecular three component DKHDA reaction



Scheme 1 The domino Knoevenagel-hetero-Diels-Alder (DKHDA) reaction.

dicarbonyl, ketones, and alkynes producing spirocyclic pyranone derivatives (Scheme 1).

The use of silica as a catalyst for organic reactions is a relatively less explored area.<sup>15</sup> Because of its non-toxicity, porous structure, large specific area, low cost, high stability and wide availability, there is a wide scope for the utilization of silica as a recyclable heterogeneous catalyst. In continuation of our work on the development of recyclable heterogeneous catalyst for different organic transformations,<sup>16</sup> herein, we report a silica catalyzed three component domino-Knoevenagel-hetero-Diels– Alder reaction for the efficient synthesis of highly substituted chromenones/dihydrochromenones/spirochromenones. For operational simplicity in recycling, the silica catalyst has been prepared as a magnetically active catalyst using *in situ* generated  $Fe_3O_4$ . Moreover, the reaction has been performed under solvent free conditions, which meets the recent green chemistry trends to develop green and sustainable chemical processes.

The Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> catalyst was prepared using a modified literature procedure<sup>17</sup> starting from silicic acid, iron( $\pi$ ) chloride and iron( $\pi$ ) chloride (see the ESI†).<sup>17</sup> Characterization of the prepared catalyst was carried out using XRD (Fig. S1†), FTIR (Fig. S2†) and HRTEM (Fig. S3†). The magnetic nature was studied using a vibrating sample magnetometer (Fig. S4†). The thermal stability was determined using TGA (Fig. S5†).

To identify the optimal reaction conditions, 1,3-cyclohexanedione (1a), benzaldehyde (2a), and phenylacetylene (3a) were used as model substrates. The reaction mixture was refluxed for 3 h using acetonitrile as the solvent and the chromenone product was obtained in 50% yield (Table 1, entry 1). Although the yield could not be improved significantly by varying the solvents (Table 1, entries 2-5), the reaction provided a significantly good yield (82%) of the product under solvent free conditions (Table 1, entry 11). The optimal temperature was found to be 100 °C and the reaction was completed in 2 h (Table 1, entries 6-11). The ideal catalyst amount was 10 wt% with respect to 1a. The role of the catalyst was confirmed by performing the reaction in the absence of the catalyst wherein no product formation could be observed (Table 1, entry 12). The reaction did not afford any product when performed in the presence of Fe<sub>3</sub>O<sub>4</sub>, FeCl<sub>2</sub> or FeCl<sub>3</sub> (Table 1, entries 14-16). This observation confirmed the role of the

Table 1	Synthesis of chromenones and optimization of the reaction conditions <sup>a</sup>	
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0 +	СНО	+		catalysttemperature, time	
1a	2a		39		4a

Entry	Catalyst	Solvent	Temperature (°C)	Catalyst amount (wt%)	Yield <sup>b</sup> (%)
1	Fe <sub>2</sub> O <sub>4</sub> @SiO <sub>2</sub>	CH_CN	80	20	50
2	Fe <sub>3</sub> O <sub>4</sub> @SiO <sub>2</sub>	DMSO	110	20	52
3	$Fe_3O_4(a)SiO_2$	H	100	20	38
4	Fe <sub>2</sub> O <sub>4</sub> @SiO <sub>2</sub>	C <sub>2</sub> H <sub>2</sub> OH	80	20	45
5	$Fe_2O_4 @SiO_2$	Toluene	110	20	18
6	$Fe_2O_4(0)SiO_2$	None	80	20	73
7	$Fe_2O_4$ (a) $SiO_2$	None	100	20	82
8	$Fe_3O_4(a)SiO_2$	None	120	20	79
9	$Fe_3O_4(a)SiO_2$	None	100	15	82
10	Fe <sub>3</sub> O <sub>4</sub> (a)SiO <sub>2</sub>	None	100	5	79
11	Fe <sub>3</sub> O <sub>4</sub> (a)SiO <sub>2</sub>	None	100	10	82
12	No catalyst (only silicic acid)	None	100	10	0
13	SiO <sub>2</sub> without Fe <sub>3</sub> O <sub>4</sub> (prepared using identical conditions)	None	100	10	82
14	$Fe_2O_4$	None	100	10	0
15	FeCl <sub>3</sub>	None	100	10	0
16	FeCl <sub>2</sub> ·H <sub>2</sub> O	None	100	10	0

<sup>*a*</sup> All the reactions were carried out using 0.9 mmol each of 1,3-cyclohexanedione (1a), benzaldehyde (2a), and phenylacetylene (3a). <sup>*b*</sup> Isolated yield.

silica as the active catalyst. For further confirmation, a catalyst was prepared from silicic acid without the addition of iron salt. The newly formed silica catalyst showed identical activity to the original  $Fe_3O_4$ (a)SiO<sub>2</sub> (Table 1, entry 11).

With the aforementioned optimised reaction conditions in hand, we further examined the substrate scope by reacting 1,3cyclohexanedione with different aromatic aldehydes and terminal alkynes/alkenes (Table 2). It was observed that aldehydes and alkynes containing electron withdrawing as well as electron donating groups performed well to give the corresponding tetrahydro-5H-chromen-5-ones 4a-4s under the given reaction conditions. Not only aromatic aldehydes, but also phenylacetaldehyde under the given optimised conditions provided the desired products 4i and 4l. 4-Allyloxybenzaldehyde reacted well to give the corresponding tetrahydro-5H-chromen-5-one 4j without any side reaction. Other 1,3-diones such as cyclopentane-1,3-dione, dimedone, and chromane-2,4-dione were coupled with aldehydes and alkynes to give the corresponding chromenones 4k-4p in very good yields. Styrene derivatives also participated in the same reaction producing the corres-

 Table 2
 Synthesis of chromenones from 1,3-diketones, aldehydes, and alkynes or alkenes



ponding hexahydro-5*H*-chromen-5-ones **4q–4s**. All the compounds were characterized with the help of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra. Their molecular formulae were confirmed with the HRMS data. The melting point data of the reported compounds matched with those in the literature.

After the successful exploration of  $Fe_3O_4(@SiO_2 towards the synthesis of chromenones, we further extended our study towards cyclic ketones. It was observed that the reaction between 1,3-diketones, alkynes or alkenes and cyclic ketones provided the corresponding spirocyclic chromenones$ **6a–g**in good to excellent yields (Table 3). Both cyclobutanone and cyclopentanone provided the corresponding spirochromenes in good yields. Unfortunately, cyclohexanone and larger cyclic ketones did not participate in the reaction. This fact may be explained by the difficulty in the formation of the Knoevenagel

 Table 3
 Synthesis of spirochromenones from 1,3-diketones, ketones, and alkynes or alkenes



Scheme 2 A plausible mechanism for the  $Fe_3O_4@SiO_2$  catalyzed Knoevenagel-hetero-Diels-Alder reaction.

product with cyclohexanone and larger counterparts. Simple acyclic ketones also didnot participate under the given reaction conditions. All the prepared compounds were duly characterized with the help of NMR and mass spectral data.

Based on the earlier report of the participation of silica as the catalyst in Knoevenagel reaction,<sup>15c</sup> a plausible mechanism is proposed in Scheme 2. Firstly, a SiO<sub>2</sub> catalyzed Knoevenagel condensation between 1,3-dicarbonyl **1a** and aldehyde **2a** produces enone intermediate **A**. In the second step, the 1,3-heterodiene undergoes subsequent thermal [4 + 2] cycloaddition with alkyne **3a** to produce chromenone **4a**. It is to be noted that this type of thermal hetero-Diels–Alder reaction is known in the literature.<sup>13a</sup>

The recyclability of the prepared catalyst was also studied by filtration and reuse after drying. It was observed that the catalyst could be reused up to five consecutive catalytic cycles without any significant loss in the activity (Fig. S6†).

## Conclusion

In summary, we have developed a simple, one-step three component DKHDA reaction between 1,3-cycloalkanediones, aldehydes/ketones and terminal alkynes/alkenes to produce chromenone derivatives. Simple magnetically active silica, prepared from silicic acid, iron(II) chloride and iron(III) chloride, acted as the catalyst for the reaction. The shape, size, structure, thermal stability, and magnetic properties of the catalyst were determined by XRD, HRTEM, IR, TGA, and VSM, respectively (see the ESI<sup>†</sup>). One of the major advantages of the process is the ability to carry out the reactions under solvent-free conditions, thereby providing scope for waste reduction and energy efficiency. Nineteen different chromenone/dihydrochromenone and seven different spirochromeone derivatives were prepared using this methodology. Unfortunately, the reaction was not suitable for acyclic ketones, cyclohexanones and larger cyclic ketones. A tentative mechanism has been discussed where silica acts as the acidic catalyst for initial Knoevenagel reaction. Recyclability of the catalyst has also been studied. Studies on the application of the catalytic system for the synthesis of other fascinating N-heterocycles are in progress.

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

This work is financially supported by the SERB, New Delhi, India (GPP0356) and CSIR, New Delhi, India (OLP2020 and HCP021). The authors are thankful to the analytical facility, CSIR-NEIST, for recording all the analytical data.

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