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COMMUNICATION

Synthesis of New Tetracyclic Benzodiazepine-Fused Isoindolinones Using Recyclable Mesoporous Silica Nanoparticles

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Pseudo natural products (NPs) feature structural novelty and diversity and thus are a new source of lead compounds for drug discovery. We first report the mesoporous silica nanoparticles (MSNs)-catalyzed *de novo* combination of benzodiazepine and isoindolinone in a three-dimensional manner, giving biologically relevant and structurally complex tetracyclic benzodiazepine-fused isoindolinone pseudo natural products (21 examples, 55-91% yields) from readily available starting materials. The benzodiazepine and isoindolinone rings are formed simultaneously, with several advantages such as no use of pre-functionalized starting materials, metal-free conditions, gram-scale reactions and recyclable catalysts. The work has also demonstrated that MSNs are efficient acidic catalysts for multi-component reactions enabling rapid access to novel scaffolds for biological testing.

Pseudo natural products (NPs) refer to a cluster of compound classes with structural novelty and diversity that are not accessible through known biosynthesis pathways.[1] Pseudo NPs are obtained via the *de novo* combination of NP fragments derived from biologically diverse and interesting NPs (Figure 1A),[2] thus covering larger chemical space and possessing novel bioactivities.[3] Representative pseudo NPs are indomorphans,[4] chromopynones,[1] pyrano-furo-pyridones,[5] and indotropanes[6] that show interesting biological profiles as inhibitors of glucose transporters GLUT-1/3, mitochondrial complex I, and myosin lightchain kinase 1 (Figure 1B). Benzodiazepine and isoindolinone scaffolds are frequently found in many drug molecules and natural products with diverse and interesting biological activities. Selected representative examples are anthramycin,[7] sclerotigenin,[8] tilivalline,[9] (±)-lennoxamine,[10] (±)-pestalachloride A,[11] and fumaridine[12] (Figure 1C). Due to their interesting biological profiles of benzodiazepines and isoindolinones, appropriate combination of these two heteroatom-rich fragments could give new structures with novel biological profiles. Intriguingly, Kirk *et al.* reported that the benzodiazepine-fused isoindolinone MMV000917 (Figure 1C) could disrupt ion homeostasis in the malaria parasite.[13]

Benzodiazepine-fused isoindolinone pseudo NPs show potential for therapeutics. However, the efficient syntheses of such pseudo NPs have not been extensively explored and remain at a very early stage, thus limiting further biological investigation of such compounds.[14] In 1974, Kamiya *et al.* achieved the synthesis of benzodiazepine-fused isoindolinones from fused hydrazinium salts via the Stevens-type rearrangement (Scheme 1A).[15] In 2004, Daïch and co-workers successfully obtained *α*-hydroxylactam precursors through two-step synthesis, which were then transformed into benzodiazepines-fused isoindolinones through trifluoroacetic acid (TFA)-catalyzed intramolecular substitution reaction (Scheme 1B).[16] In 2013, Patil and co-workers successfully synthesized the benzodiazepine-fused isoindolinones through $Ph_3PAuOTf$-catalyzed relay branching cascade strategy (Scheme 1C).[17] Evidently, these approaches start from highly functionalized precursors that need multi-step synthesis and purification and/or use of expensive metal catalysts. Therefore, the efficient synthesis of such pseudo NPs remain highly desirable.

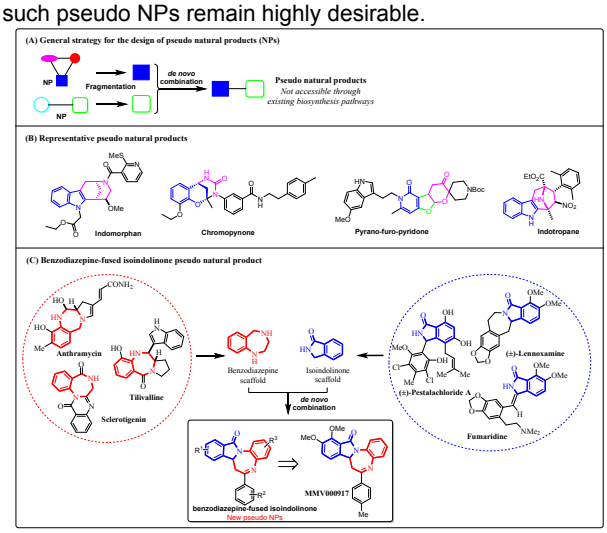

Figure 1. Design of biologically relevant benzodiazepine-fused isoindolinone pseudo natural products (NPs). (A) General strategy for the design of pseudo NPs. (B) Reported representative pseudo NPs. (C) Benzodiazepine-fused isoindolinone pseudo NPs.

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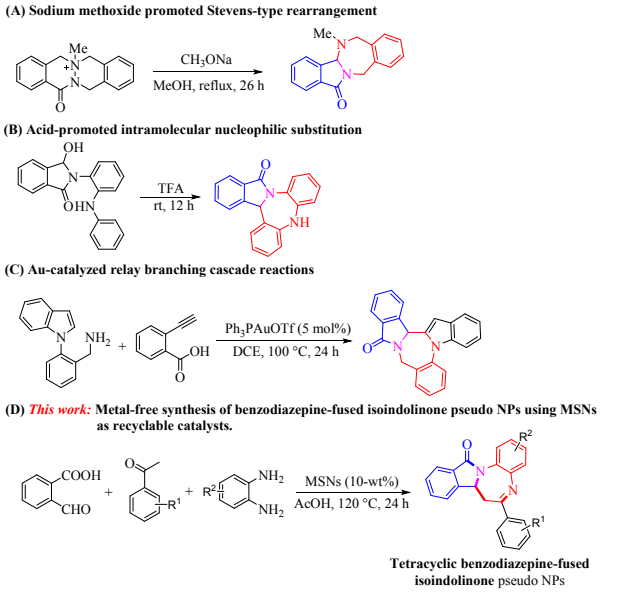
Mesoporous silica nanoparticles (MSNs) are catalytically active because of the strong Lewis acid properties, low coordinating sites and high surface area, and show excellent stability, efficient recovery and recyclability, thus making such catalysts widely used in organic chemistry.[18] Bunce and co-workers demonstrated an environmentally friendly Strecker approach for the construction of 3-oxoisoindolines from 2-carboxybenzaldehyde, TMSCN and benzylic or aliphatic amines by employing hexagonal MSN (OSU-6) as the recycled catalyst.[19] Subsequently, they also successfully realized the metal-free synthesis of 5-benzyl and 5-aryl-1*H*-tetrazoles through the heterogeneous OSU-6 catalyzed click reaction.[20] OSU-6 can also catalyze the conversion of acids and esters to amides as well as transamidations of primary amides.[21] In light of the catalytic properties of MSNs, we speculate that MSNs could effectively catalyze the reactions, including the condensation, amide formation, and dehydration, *etc*. Herein, we report the first metal-free multi-component reactions (MCRs) for the synthesis of biologically interesting benzodiazepine-fused isoindolinone pseudo NPs from commercially available 2-formylbenzoic acid, acetophenone and 1,2-diaminobenzene using MSNs as green and recyclable catalysts. In this reaction, a bicyclic pyrrolidin-2-one fused 1,5-diazepine ring system is formed accompanied by formation of one C-C bond, two C-N single bonds, and one C-N double bond (Scheme 1D). Of note, the tetracyclic pseudo-NPs are combined in a three-dimensional manner and possess multiple heteroatoms, meeting with pseudo-NP design principles.[3] Compared to previously reported methods (Scheme 1A-1C), this method has several advantages: (a) Synthesis of structurally complex benzodiazepine-fused isoindolinone pseudo NPs from readily available starting materials; (b) Avoids the use of precious metal catalysts; (c) Metal-free MCRs; (d) Recyclable MSNs catalysts; (e) High reactivity (up to 91% yield) and gram-scale.

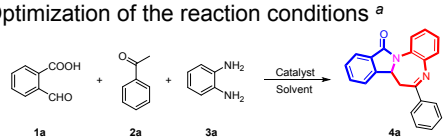


Scheme 1. Approaches for the synthesis of benzodiazepine-fused isoindolinone pseudo NPs.

MSNs catalysts were synthesized following a previously reported sol-gel method,[22] in which base was used as catalyst, hexadecyltrimethylammonium bromide (CTAB) as template, and tetraethyl orthosilicate (TEOS) as silica precursor. The preparation and characterization including transmission electron microscopy (TEM), scanning electron microscope (SEM), the hydrodynamic diameter, zeta potential, nitrogen adsorption-desorption and pore size distribution are provided in supporting information (Figure S1 and Table S1).

Initially, 2-formylbenzoic acid **1a** (0.5 mmol), acetophenone **2a** (0.5 mmol) and 1,2-diaminobenzene **3a** (1.5 mmol) were used as model substrates to optimize the reaction conditions in the presence of 10-wt% MSNs (Table 1). Compound **4a** was obtained in 9% yield when the reaction was performed in DCE (Table 1, entry1). Encouraged by this result, we further examined the reactivity in other solvents (Table 1, entries 2-7). To our satisfaction, product **4a** was afforded in 88% yield when the reaction was carried out in acetic acid (Table 1, entry 7). Other solvents such as EtOH, DMSO, DMF, H_2O and toluene turned out to be less efficient, and failed to generate compound **4a** (Table 1, entries 2-6). Other solid catalysts, such as SiO_2, amberlyst-15 (A-15) and montmorillonite-K10 (Mont-K10) could also catalyze this transformation, giving compound **4a** in 35-59% yields (Table 1, entries 8-10). We also found that compound **4a** was afforded in 33% yield when the reaction was carried out in AcOH only (Table 1, entry 11), indicating the effectiveness of the MSNs catalysts. According to above optimizations, the optimal reaction conditions entailed 2-formylbenzoic acid **1a** (0.5 mmol), acetophenone **2a** (0.5 mmol),1,2-diaminobenzene **3a** (1.5 mmol), MSNs (10-wt%), AcOH (2 mL), 100 ℃, 24 h (Table 1, entry 7).

Table 1. Optimization of the reaction conditions [a]



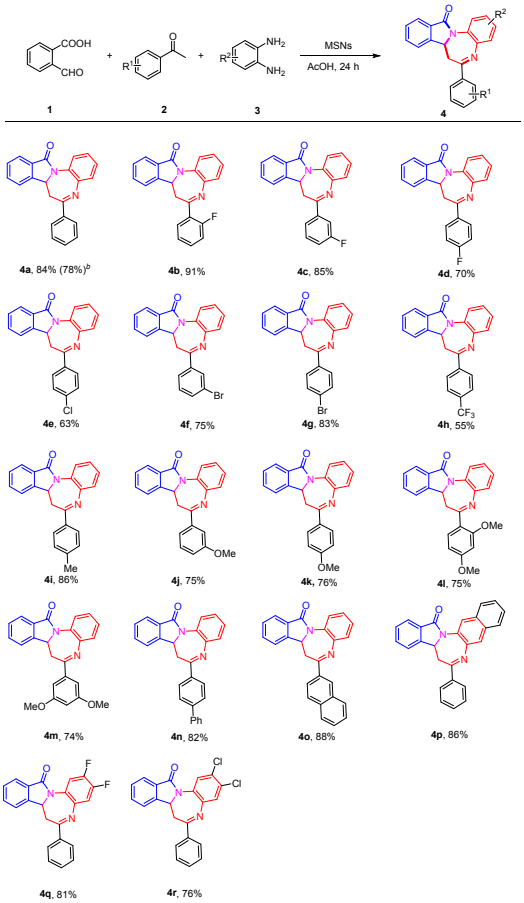
Entry	Catalyst (wt%)	Solvent	T (℃)	**4a** (%)[b]
1	MSNs	DCE	80	9
2	MSNs	EtOH	80	0
3	MSNs	DMSO	80	0
4	MSNs	DMF	80	0
5	MSNs	H_2O	80	0
6	MSNs	Toluene	80	0
7	**MSNs**	**AcOH**	**100**	**88**
8	SiO_2	AcOH	100	59
9	A-15	AcOH	100	35
10	Mont-K10	AcOH	100	39
11	-	AcOH	100	33

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (1.5 mmol), catalyst (10-wt%), solvent (2 mL), 24 h. [b] NMR yields determined by ^{1}H NMR using the triphenylmethane as an internal standard.

With the optimized reaction conditions in hand, we next examined the scope for the synthesis of benzodiazepine fused isoindolinones (Table 2). As shown in Table 2, compounds **4a-r** were obtained in good to excellent yields (55-91%) regardless of their substitution patterns and electronic nature. Various R^1 substitutions attached to the ketones were well tolerated in these reactions. When R^1 was halogen, the corresponding products **4b-4g** were generated in good yields (up to 91% yield), the halogen atom could be used for further functionalization. Delightfully, both

electron-deficient and electron-rich aromatic ketones proceeded well under the optimized conditions and furnished compounds **4b-o** in moderate to excellent yields (55-91% yield). For 1,2-diaminobenzene bearing additional substituents, the corresponding products **4p-r** were formed in 76-86% yields. Finally, 2-formylbenzoic acid **1a** (3 mmol), acetophenone **2a** (3 mmol) and 1,2-diaminobenzene **3a** (9 mmol) were employed to examine the scalability. To our satisfaction, the desired product **4a** was formed in 78% yield under the standard reaction conditions. Collectively, the MSNs catalysts could catalyze the reactions efficiently even at a gram scale.

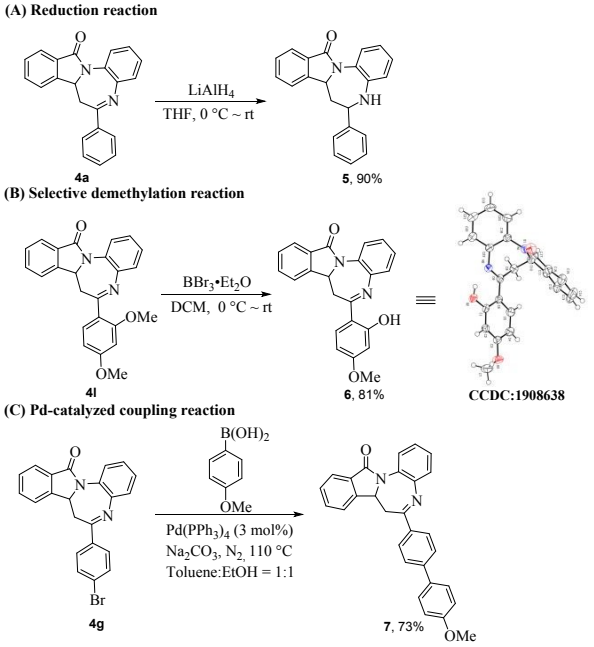
Table 2. Construction of 6-aryl-7,7*a*-dihydro-12*H*-benzo[2,3][1,4]diazepino[7,1-*a*]isoindol-12-ones [a]



[a] Reaction conditions:**1** (0.5 mmol), **2** (0.5 mmol), **3** (1.5 mmol), MSNs (10-wt%), AcOH (2 mL), 120 ℃, 24 h. [b] **1** (3 mmol), **2** (3 mmol), **3** (9 mmol), MSNs (10-wt%), AcOH (10 mL), 120 ℃, 24 h.

We next examined whether the catalyst could be recycled for the synthesis of compound **4a** under the optimal conditions. After the completion of the reaction, the MSNs catalysts were filtered and washed with EtOH:H_2O (1:1), followed by drying at 120 ℃ under vacuum for 24 h, and the catalytic efficiency of the MSNs slightly decreased after five consecutive cycles (Figure S2), giving compound **4a** in 81% yield.

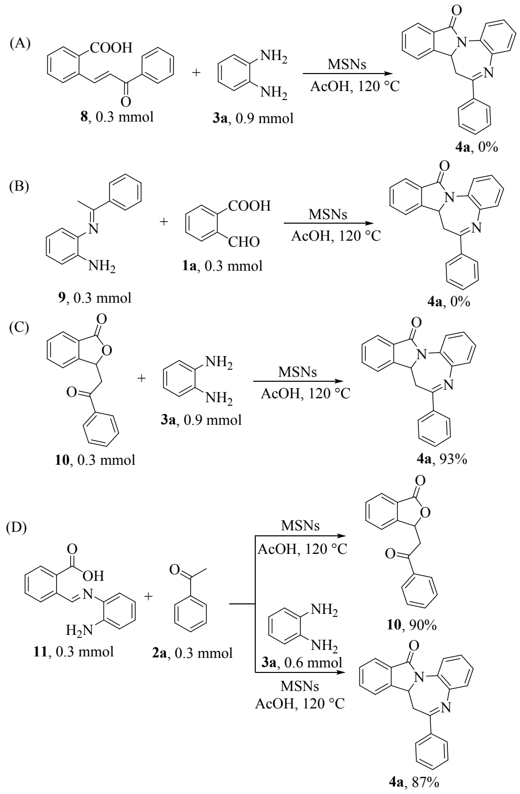
To showcase the synthetic utilities, late-stage diversification was performed (Scheme 2). As shown in Scheme 2A, by treating with $LiAlH_4$, compound **4a** was reduced to give **5** as a mixture of diastereomers in 90% yield. Treatment of **4l** with BBr_3•Et_2O led to selective demethylation, yielding compound **6** in 81% yield, which was characterized by X-ray crystallography (CCDC number: 1908638) (Scheme 2B). In the presence of $Pd(PPh_3)_4$, **4g** reacted smoothly with (4-methoxyphenyl)boronic acid, affording compound **7** in 73% yield (Scheme 2C).



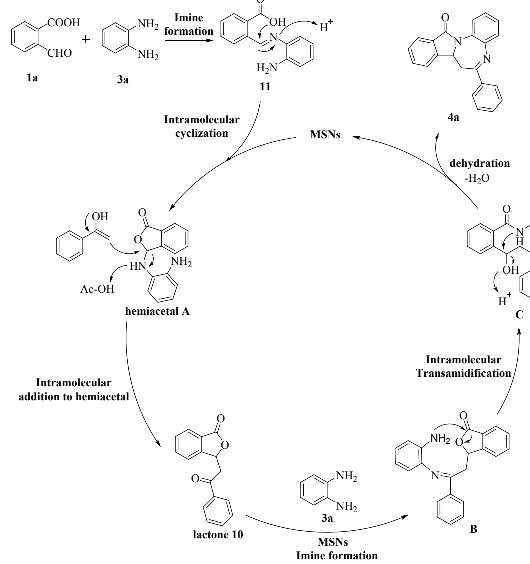
Scheme 2. Late-stage elaborations.

To gain insight into the mechanism, control experiments were carried out (Scheme 3). Possible intermediates were synthesized and then examined for the synthesis of compound **4a**. When chalcone **8** and 1,2-diaminobenzene **3a** were treated with MSNs in AcOH, compound **4a** could not be detected (Scheme 3A). The reaction between **9** and **1a** was also tested under the standard reaction conditions and no desired product was obtained (Scheme 3B). These results indicated that **8** and **9** were not the intermediates in this reaction. Then the reaction between isobenzofuranone **10** and **3a** was carried out in the presence of MSNs, the desired product **4a** was obtained in 93% yield (Scheme 3C). Under the optimized reaction conditions, the imine **11** reacted with acetophenone **2a** smoothly, giving the intermediate **10** in 90% yield. Interestingly, in the presence of 1,2-diaminobenzene **3a**, compound **4a** was afforded in 87% yield (Scheme 3D). The findings strongly suggest compounds **10** and **11** are key intermediates during this transformation.

Based on the above results, a reaction pathway of this reaction is depicted in Scheme 4. Initially, the imine intermediate **11** was generated *in situ* from **1a** and **3a** through the condensation reaction. In the presence of the catalyst and/or AcOH, the intramolecular cyclization formed the hemiacetal **A**, followed by addition of acetophenone to **A**. The lactone intermediate **10** was then generated accompanied by the release of 1,2-diaminobenzene **3a**. Compound **3a** then reacted with the lactone **10** through the condensation reaction to form the intermediate **B** (detected by LC-MS). In the presence of the catalyst, the intermediate **B** underwent the intramolecular transamidification to form the lactam species **C**. Finally, dehydration of **C** gave the desired product **4a**. In this work, we first realized the multi-component assembly of 2-formylbenzoic acid, acetophenones and 1,2-diaminobenzenes in the presence of the catalyst MSNs to give structurally new and complex benzodiazepine-fused isoindolinone pseudo natural products. We further envisioned that the catalyst MSNs could catalyse the condensation, dehydration and transamidification reactions and may have wide applications in organic synthesis.



Scheme 3. Control experiments.



Scheme 4. Proposed reaction mechanism.

In conclusion, we have demonstrated that MSNs could catalyze multi-component reactions that enable efficient combination of benzodiazepine and isoindolinone NP fragments, yielding biologically relevant benzodiazepine-fused isoindolinone pseudo natural products (55-91% yields). Compared to previous reported methods, this protocol does not use pre-functionalized starting materials and is metal-free. The reaction could also be carried out on a gram-scale, giving compound **4a** in 78% yield. During this transformation, one C-C bond, three C-N bonds and two heterocycle ring systems (benzodiazepine and isoindolinone) were formed simultaneously. Additionally, the catalyst could be recycled for several times without significant loss of the catalytic activity. The title compounds could undergo late-stage modifications, showing the synthetic utility. We also proposed a mechanism based on the control experiments and further envisioned that MSNs may have wide applications in organic synthesis because of the catalytic efficiency. The title compounds are currently undergoing biological screening for potential therapeutics based on our unbiased cell-based phenotypic screening platforms.

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Conflicts of interest

There are no conflicts to declare.

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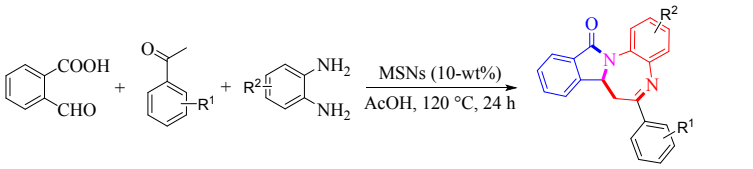

Tetracyclic benzodiazepine-fused isoindolinone pseudo NPs

- Novel tetracyclic benzodiazepine-fused isoindolinone scaffold
- 21 examples, up to 91% yield
- One C-C, two C-N, and one C=N bonds formed simultaneously
- Metal-free conditions
- Recycle MSNs catalyst
- Readily available starting materials
- Gram-scale synthesis

Mesoporous silica nanoparticles could catalyze *de novo* combination of benzodiazepine and isoindolinone, giving biologically relevant benzodiazepine-fused isoindolinone pseudo natural products.