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Graphical Abstract

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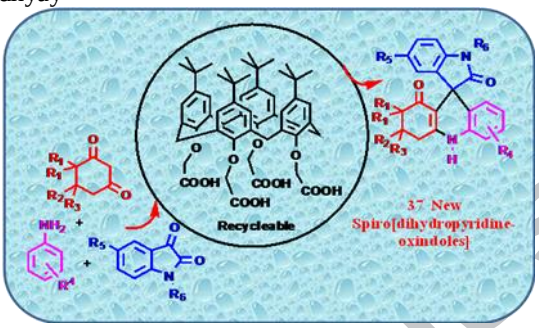

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Nano-ranged calix[4]arene tetracarboxylic acid catalyzed expeditious protocol for spiro[dihydropyridine-oxindoles] synthesis

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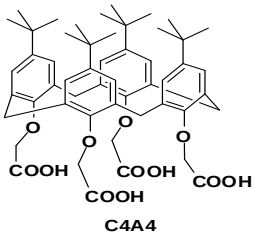
ABSTRACT

Calix[4]arene tetracarboxylic acid has been successfully established as the nanoranged organocatalyst for the synthesis of spiro[dihydropyridine-oxindoles]. Here we report a sustainable protocol for the synthesis of spiro[dihydropyridine-oxindoles], an Mannich type multi-component reaction involving the ortho-H of activated as well as un-activated aniline derivatives. A library of new spiro derivatives have been synthesized in very high yields in eco-friendly solvent water in one-pot multicomponent fashion.

Nano-organocatalyst, being a metal-free approach, becomes the area of global interest in the recent decade. Water dispersed nanoranged organic particle synthesis is a great challenge as they have high affinity towards coagulation in aqueous phase. Gratifyingly, calixarenes provide the opportunity to be nano-ranged catalyst as they disperse in nano-range in water and this nano-range dispersion is sufficiently stable for long time.[1] Calix[4]arene derivatives appears at 100-200 nm range in water at room temperature (30 ºC). Hence we tried to survey their catalytic ability for some important organic transformations.[2] Recently, we have reported *p*-tert-butylcalix[4]arene-tetra-O-acetate as an efficient nanoreactor for the synthesis of the cross azo-compounds.[1c] Next, we focused to synthesise some biologically important heterocyclic cores with the aid of the calixarene derivatives in greener fashion.



C4A4

Figure 1: Calix[4]arene tetracarboxylic acid

Recently, the development of spiro compounds has emerged as a field of strong attention owing to their attractive conformational features, potential medicinal applications, catalysis and optical materials.[3] The derivatives of spirooxindole ring systems are highly effective as antimicrobial, antitumor agents and as inhibitors of the human NKI receptor.[4] Some alkaloids like horsifiline and alstonisine (Figure 2) contain spirooxindole system as their structural motif.[5] On the other hand, 1,4-dihydropyridine scaffolds are ubiquitous structural motifs found in a multitude of pharmaceuticals, basically as calcium channel blockers, such as, Nifedipine, Felodipine, Nicardipine, Nimodipine etc. (Figure 2).[6] In addition, this is the common core structure of various biologically active compounds having selective adenosine-A3 receptor antagonism, along with radioprotective activity, anticonvulsant activity, sirtuin activation and inhibition etc.[7] Because of the intense utility of these two cores, we were interested to prepare oxindole-dihydropyridine fused spiro derivatives i.e., spiro[dihydropyridine-oxindoles]. With our continuous effort, we synthesized spiro[dihydropyridine-oxindoles] derivatives using 1,3-cyclohexanediones, substituted aniline derivatives and N-substituted isatins where the ortho- attack of the aniline system occurs to form the spiro centre. From the literature survey, we found very few report on the synthesis of this spiro core involving the naphthalen-2-amine where the reactive α–positional attack has taken place.[5,8]

Only one report has been published using *p*-substituted anilines, N-substituted isatins and 1,3-cyclopentanedione.[9] In this case, 1,3-cyclopentanedione is a highly reactive system and they used harsh condition, acetic acid as solvent and catalyst. So, there

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is an extreme need of a new protocol for the synthesis of spiro[dihydropyridine-oxindoles] derivatives involving electron withdrawing or donating group substituted anilines with different

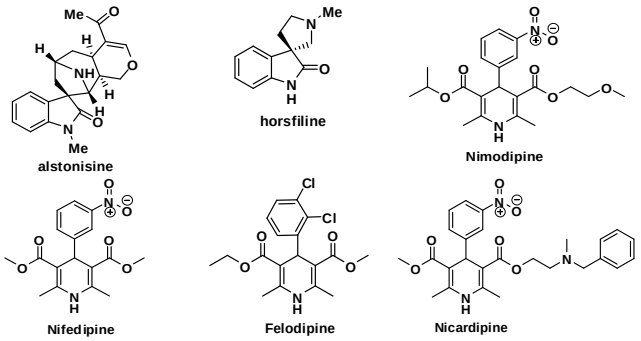


Figure 2: First two are alkaloids containing spirooxindole and rests are highly recommended calcium channel blockers containing 1,4-dihydropyridine system

1,3-diones. For this purpose, we wanted to involve the water dispersed nano-ranged acid graphed calix[4]arene derivatives. Delightfully, we reached our goal i.e., we successfully done the Mannich type multi-component reaction with calix[4]arene tetracarboxylic acid (**C4A4**) (Figure 1) as catalyst in water, with approximately full conversion in a chromatography-free multicomponent fashion.

In the beginning, we tried to find out the way of dispersion of the calixarene derivatives in water. To our delight, just 5 minute ultra-sonication provided the nano ranged dispersion of **C4A4** in water. The particle size was confirmed by SEM experiment as 80-100 nm and furthermore, the size remained around 190 nm after keeping the solution intact for 2-3 days (Figure 3). So, calixarene derivatives possess the possibility to be a nano-catalyst.

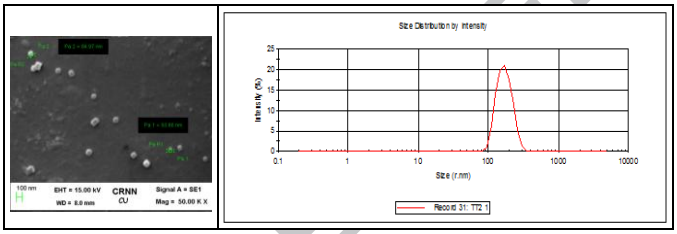


Figure 3: SEM image and DLS data of **C4A4**

To optimize the reaction conditions, the equimolar (1 mmol of each) mixture of the dimethyl-1,3-cyclohexanedione, *p*-toluidine and N-allylisatin were chosen as the starting materials. As central to our objective is the reactivity of the catalyst, we investigated the activity of the heterogeneous catalyst, spherical mesoporous silica nanoparticle supported carboxylic acid (SMSNP-CA, Figure 4a) and porous silica nanoparticle supported carboxylic acid (PSNP-CA, Figure 4b), but they failed to show mentionable reactivity. Then we tried to emphasize the particular effect of the cavity and the acid group on this reaction. Unfortunately, neither the simple calix[4]arene nor the monomer, **MC4A4** (Figure 4c), could perform the desired reaction. So, the combination of both the cavity and the acid substitution were absolutely necessary for the effectiveness of this protocol.

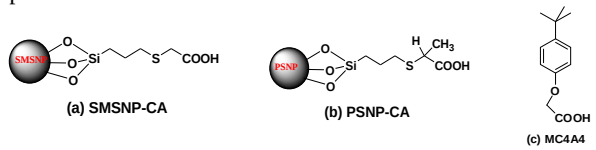
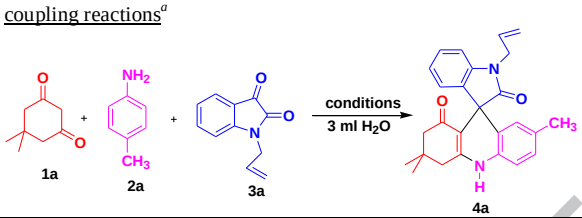


Figure 4: silica nanoparticle supported carboxylic acid (a) SMSNP-CA & (b) PSNP-CA, tricarboxylic acid and monomer of **C4A4** (c) **MC4A4**

Table 1: Optimization of reaction conditions for the multicomponent coupling reactions[a]



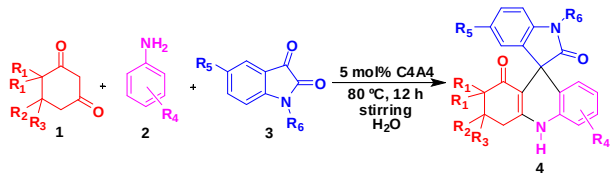
Entry	Catalyst	Temp. (ºC)	Time (h)	Yield[b] (%)
1	No catalyst	100	72	NF
2	SMSNP-CA	100	72	20
3	PSNP-CA	100	72	16
4	Calix[4]arene	100	72	NF
5	**MC4A4**[c]	100	72	NF
5	**C4A1**	100	72	26
6	**C4A2**	100	72	43
7	**C4A3**	100	72	73
8	**C4A4**	60	72	NF
9	**C4A4**	**80**	**12**	**93**
10	**C4A4**	80	24	93
11	**C4A4**	100	12	93

[a]Reaction conditions: mixture of 1.0 equiv. of each of dimedone (1 mmol), N-allylisatin (1 mmol) and *p*-toluidine (1 mmol) was heated with stirring in presence of different catalysts (10 mol% for heterogeneous catalysts and 5 mol% of calixarene catalysts) in 3 ml of solvent. [b]Isolated yield. [c]The monomer is used in 20 mol% amount. NF= not found.

Again, as we increased the acid substitution from mono to tetra, the yield increased gradually (Table 1, entries 5-9). We achieved our goal using **C4A4** (5 mol%) at 80 ºC in 12 h (Table 1, entry 9).

As mentioned previously, we were interested in exploring the generality and scope of this multicomponent reaction through a combination of a range of 1,3-diketones, anilines and N-substituted isatins. With our optimized conditions in hand, the synthesis of spiro[dihydropyridine-oxindoles] can be readily diversified and the results obtained are summarized in Table 2. Various types of activating (having electron donating substituent) and deactivating (having electron withdrawing substituent) aniline systems were used and interestingly all of them produced good to excellent outputs. Nitro-aniline derivatives provided the desired products with a little lowering of yields but still in good extent (77-80 %) (Table 2, **4a'-4d'**).

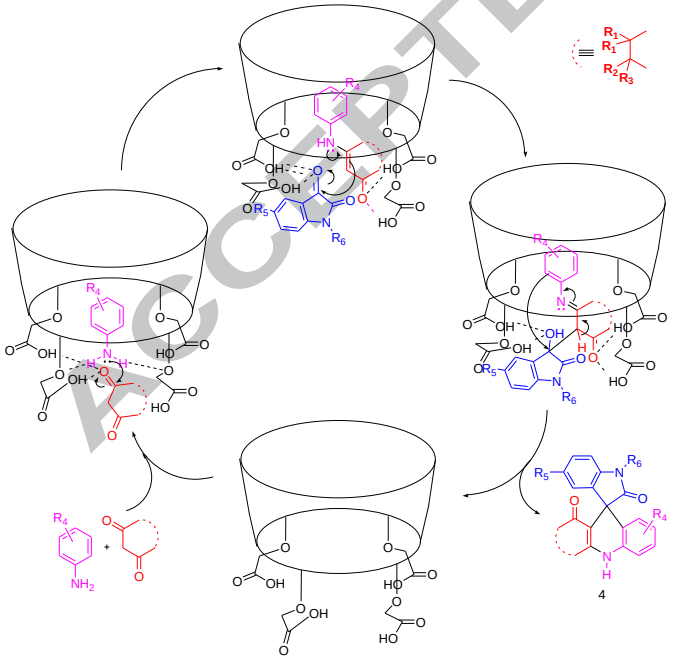
Table 2: scope of the reaction[a]



Entry	R_1	R_2	R_3	R_4	R_5	R_6	Yield[b](%)
4a	H	CH_3	CH_3	*p*-CH_3	H	allyl	93
4b	H	CH_3	CH_3	*p*-Cl	H	allyl	90
4c	H	CH_3	CH_3	H	H	allyl	92
4d	H	H	H	*p*-Cl	H	allyl	87
4e	H	CH_3	CH_3	*p*-CH_3	H	benzyl	92
4f	H	H	H	*p*-Cl	H	benzyl	89
4g	H	H	H	m-OCH_3	H	benzyl	85
4h	H	H	H	*p*-OCH_3	H	benzyl	90
4i	H	H	H	m-OCH_3	H	allyl	92
4j	H	H	H	*p*-OCH_3	H	allyl	93

4k	H	CH_3	CH_3	*p*-Br	H	allyl	88
4l	H	CH_3	CH_3	m-CH_3	H	allyl	84
4m	H	CH_3	CH_3	*p*-Br	H	benzyl	90
4n	H	CH_3	CH_3	m-CH_3	H	benzyl	86
4o	H	H	H	m-CH_3	H	benzyl	92
4p	H	H	H	*p*-Br	H	benzyl	89
4q	H	H	H	m-CH_3	H	allyl	91
4r	H	H	H	*p*-Br	H	allyl	87
4s	H	H	H	*p*-CH_3, m-CH_3	H	allyl	82
4t	H	CH_3	CH_3	o-CH_3	H	allyl	90
4u	H	H	H	*p*-CH_3, m-CH_3	H	benzyl	83
4v	H	CH_3	CH_3	*p*-CH_3	H	butyl	89
4w	H	H	H	*p*-CH_3, m-CH_3	H	butyl	82
4x	H	H	H	*p*-Cl	H	butyl	86
4y	CH_3	H	H	*p*-CH_3	H	benzyl	94
4z	CH_3	H	H	*p*-CH_3	H	allyl	93
4a’	H	CH_3	CH_3	m-NO_2	H	benzyl	80
4b’	H	H	H	m-NO_2	H	benzyl	79
4c’	H	CH_3	CH_3	m-NO_2	H	allyl	79
4d’	H	CH_3	CH_3	*p*-NO_2	H	allyl	77
4e’	H	CH_3	CH_3	*p*-CH_3	H	phenyl	91
4f’	H	CH_3	CH_3	*p*-CH_3	H	methyl	89
4g’	H	CH_3	CH_3	*p*-CH_3	Br	allyl	78
4h’	H	CH_3	CH_3	*p*-CH_3	Cl	allyl	80
4i’	H	CH_3	CH_3	*p*-CH_3	Cl	benzyl	80
4j’	H	CH_3	CH_3	*p*-CH_3	Br	benzyl	77
4k’	H	Ph	H	*p*-CH_3	H	allyl	85

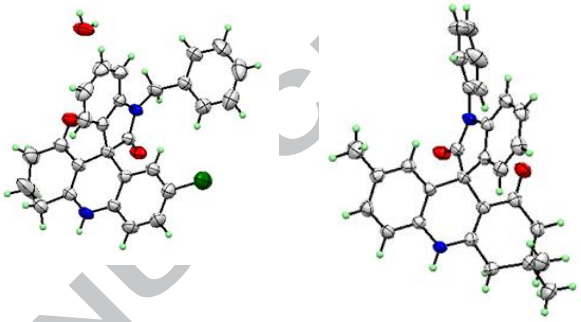
[a]Reaction conditions: mixture of 1.0 equiv. of each of 1,3-dione (1 mmol), isatin (1 mmol) and amine (1 mmol) was heated at 80 ºC with stirring in presence of 5 mol% **C4A4** in 3 ml water. [b]Isolated yield.



Scheme 1: Suggested mechanism for the **C4A4** catalyzed synthesis of spiro[dihydropyridine-oxindoles] derivative

In our previous report,[1c] we showed that the calix[4]arene moiety provides stability towards the aniline group. It is the main driving force of the mechanism from the same point of view. The hydrophilic lower rim part provides the favorable environment for the enaminoketone formation. Then two consecutive condensations occur, one, the active methylene carbon of the enaminoketone and secondly, the ortho-carbon of the aniline group, with isatin to provide our desired product (Scheme 1). The enaminoketone could be separated from the reaction mixture after 2h. This enaminoketone further produces the desired product under the same reaction condition. So, the mechanistic pathway obviously involves enaminoketone formation.

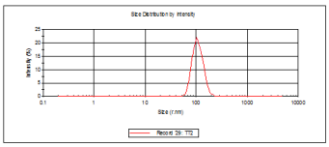
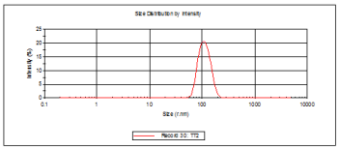
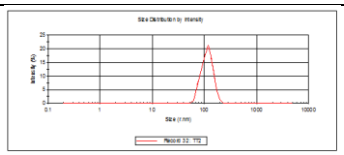
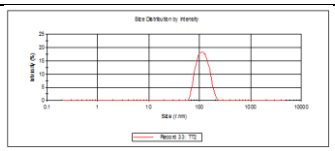
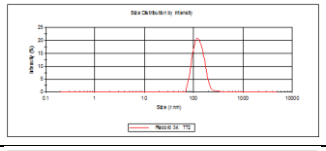
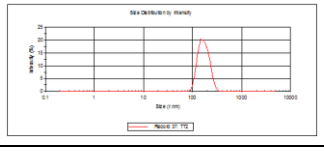
The structure of the compound **4** was confirmed by a single crystal X-ray analysis of compound **4f** and **4e’** (crystallized from DMSO) (Figure 5).



(a) (b)

Figure 5: X-ray single crystal structure of (a) **4f** (CCDC 1477349) and (b) **4e’** (CCDC 1477350).

Table 3: DLS data of the recovered catalyst

No. of run	DLS data	Size of the partiles (nm)
Initial		~105
1		~110
2		~110
3		~115-120
4		~120
5		~135

Next, we were concerned about the recovery of the catalyst. As the nano-ranged C4A4 was dispersed in water, it was not separable from water by filtration. Hence after the reaction the crude product was filtered and the C4A4 was then stayed at the filtrate. Also the residue was washed with a little water which was mixed with the filtrate. The presence of nano-ranged catalyst in the filtrate was confirmed by the DLS measurement. The mother liquor i.e., the filtrate was reused for further preparation of **4a** and in a test of six cycles; the catalyst could be reused at list five times without significant loss of catalytic activity (Figure 6). After every cycle the particle size was measured by DlS study and they are given in Table 3.

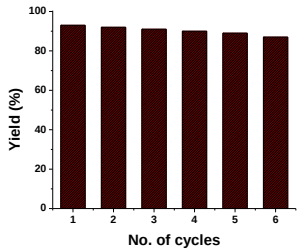


Figure 6: Recyclability of the **C4A4** for the synthesis of **4a**

In conclusion, we have developed a very simple, facile and green method for easy access to a wide range of new functionalized spiro[dihydropyridine-oxindoles]. This system synthesized here involves the ortho-H of various activated as well as un-activated (i.e., with electron donating or withdrawing substitutions) aniline derivatives. Here, the nano ranged calix[4]arene tetracarboxylic acid is used as efficient recyclable catalyst generating a high throughput yield of the products in environmentally benign solvent water. Moreover, the newly generated spiro[dihydropyridine-oxindoles] may provide effective biological activity in future studies.

Acknowledgments

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Supplementary Material

Electronic Supplementary Information (ESI) [CCDC 924313 and 924314] and Details of supplementary information (experimental procedure, spectral data and crystallographic data in CIF) are given in the Supplementary Section.

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Highlights

1. Facile sustainable new methodology for spiro[dihydropyridine-oxindoles] synthesis
2. nano-ranged tetra-acid grafted calix[4]arene derivative as efficient recyclable catalyst
3. Involvement of the ortho-H of activated as well as un-activated anilines
4. 37 new compounds are synthesized