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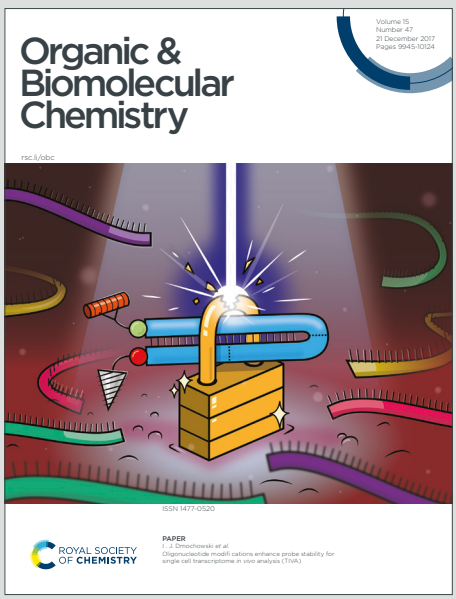

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Base-Promoted Addition of DMA with 1,1-diarylethylenes: Application to a Total Synthesis of (-)-Sacidumlignan B

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A base-promoted addition of DMA (N,N-dimethylacetamide) to 1,1-diarylethylenes has been developed, which provides a new strategy for the synthesis of N,N-dimethyl-4,4-diarylbutanamides from 1,1-diarylethylenes at room temperature. This method allows us to achieve the goal of synthesizing (-)-sacidumlignan B, and provides a simple operation and broad substrate scope by avoiding the use of transition metal catalysts.

The plant *Sarcostemma acidum* (Roxb.) is distributed in the coastal areas of Hainan Province, China, which has been used to treat chronic cough and postnatal hypogalactia by local residents.[1] In 2005, Yue and co-workers reported that four new lignans, namely, sacidumlignans A–D had been separated from the plant *Sarcostemma acidum* and their structures and relative configuration were proposed by 2D NMR experiments.[2] The sacidumlignans A–C possess naphthalene and di- and tetra-hydronaphthalene backbone, furthermore, the sacidumlignan D is a rearranged tetrahydrofuran lignan (Figure 1). Ramana group reported the synthesis of sacidumlignans A, B and D.[3] Moreover, the sacidumlignan A and (±)-sacidumlignan D have been synthesized in our group.[4] In continuation, we were interested in developing a more efficient synthesis route for (-)-sacidumlignan B. It is not difficult to find (-)-sacidumlignan B with dihydronaphthalene skeleton can be synthesized by intramolecular Friedel-Crafts reaction using diarylbutyr-aldehyde, which can be synthesized by functional group conversion utilizing diarylbutanamides. As we know, amides are not only important tools for extending alkyl chains, but also can be easily converted into carbonyl compounds, so we hope to develop an approach to synthesize them to achieve the goal of

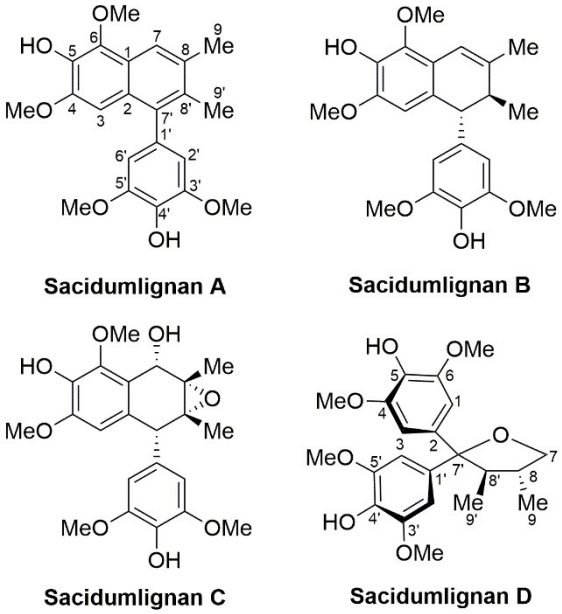

Figure 1 Structures of sacidumlignans A–D.

synthesizing (-)-sacidumlignan B. Generally, amides are prepared from carboxylic acid by reaction with DMF and thionyl chloride. However, Pines group developed potassium *tert*-butoxide catalyzed addition of N-methyl-2-pyrrolidinone and N-methyl-2-piperidone with olefins to synthesize lactams.[5] Furthermore, with the continuous development and innovation of addition,[6] more and more pioneers have applied new methods to synthesize amides (Scheme 1).[7] Lee group reported rhodium-catalyzed oxygenative addition of terminal alkynes, providing amides.[8] Kobayashi and co-workers have done a lot of excellent works on the catalytic addition of carbonyl compounds with alkenes, and they recently reported catalytic alkylation reactions of weakly acidic carbonyl and related pronucleophiles in the presence of potassium hexamethyl-disilazide (KHMDS) and 18-crown-6 ether.[9] These successful

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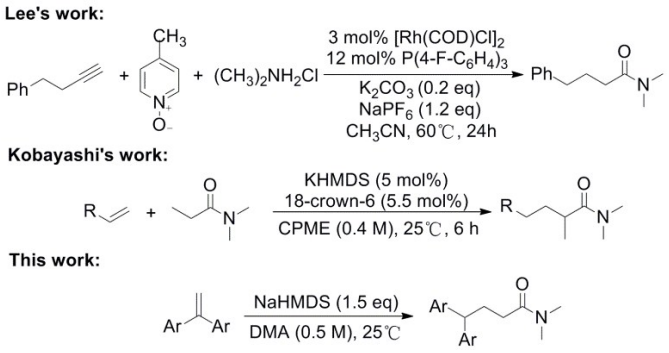
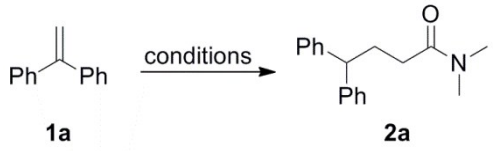


Scheme 1 Strategies for the synthesis of amides from alkenes

work greatly inspired us to develop a method for the synthesis of N,N-dimethyl-4,4-diarylbutanamides via a base-promoted addition of DMA (N,N-dimethylacetamide) to 1,1-diarylethylenes, which makes the experimental operation easier and allows for gram scale of amides, and makes the reaction more practical in organic synthesis.

Table 1. Optimization of the reaction conditions.

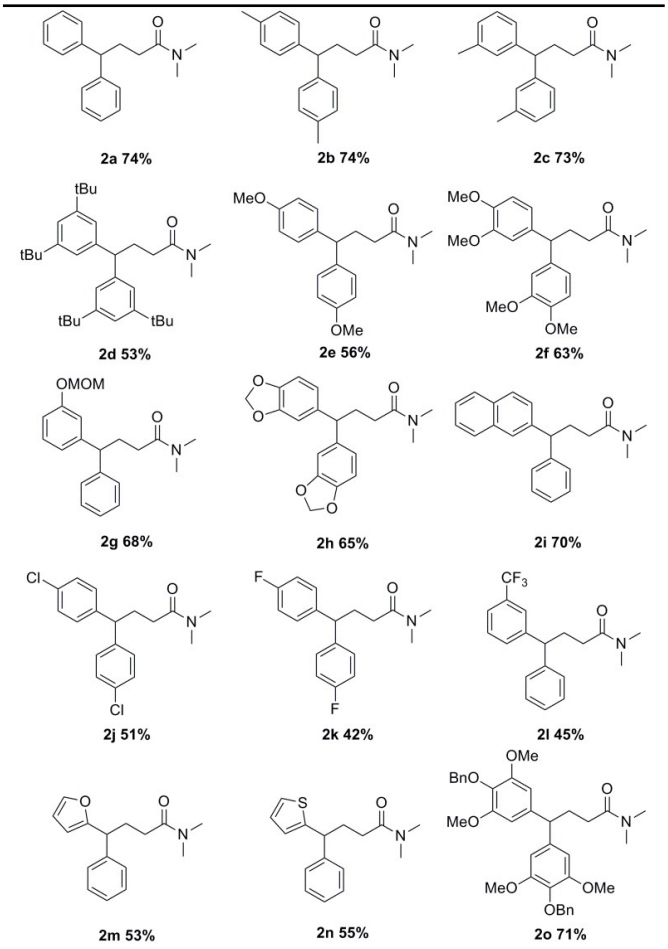


1a 2a

Entry	Base	Solvent	t/h	T/℃	Yield/%
1	NaHMDS (2.0 eq)	THF	8	-45	0
2	NaHMDS (2.0 eq)	THF	8	-15	0
3	NaHMDS (2.0 eq)	THF	8	0	0
4	NaHMDS (2.0 eq)	THF	8	25	0
5	NaHMDS (2.0 eq)	Toluene	8	25	0
6	NaHMDS (2.0 eq)	Benzene	8	25	0
7	NaHMDS (2.0 eq)	DMF	8	25	23
8	NaHMDS (2.0 eq)	DMSO	8	25	35
9	NaHMDS (2.0 eq)	DMA	3	25	73
10	KOH (2.0 eq)	DMA	8	25	5
11	*t*BuOK (2.0 eq)	DMA	8	25	15
12	LiHMDS (2.0 eq)	DMA	3	25	40
13	KHMDS (2.0 eq)	DMA	3	25	64
14	-	DMA	8	25	0
15	NaHMDS (1.5 eq)	DMA	3	25	74
16	NaHMDS (1.0 eq)	DMA	8	25	56
17	NaHMDS (3.0 eq)	DMA	2	25	65
18	NaHMDS (4.0 eq)	DMA	2	25	49

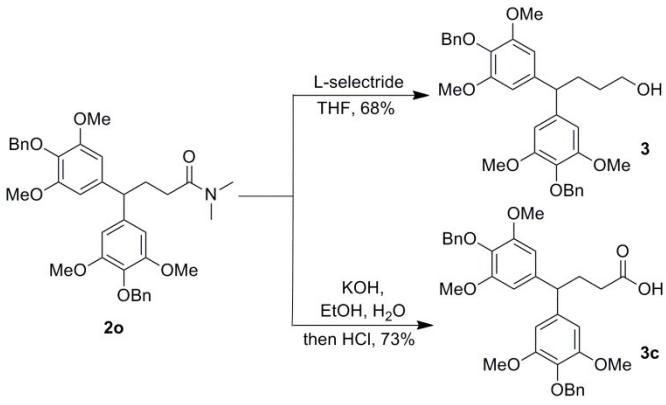
The reaction was conducted in solvent [0.5 M]. eq = equivalent. KOH = Potassium hydroxide. THF = Hydrofuran. NaHMDS = Sodium bis(trimethylsilyl)amide. LiHMDS = Lithium bis(trimethylsilyl)amide. KHMDS = Potassium bis(trimethylsilyl)amide. DMA = N, N-Dimethylacetamide. DMF = N, N-Dimethylformamide. *t*BuOK = Potassium butoxide. DMSO = Dimethyl sulfoxide.

Table 2 Substrate scope of alkenes



Reactions were performed with the alkenes (1.0 mmol) and NaHMDS (1.5 eq.) in DMA [0.5 M] at room temperature for 3.0 h.

Sodium bis(trimethylsilyl)amide (NaHMDS) is a base commonly used in organic synthesis, DMA is a widely used organic solvent, both of them are easy to be obtained, so we wanted to use these two reagents to achieve our method. We hypothesized that the addition of DMA to 1,1-diarylethylenes was allowed to proceed under an argon atmosphere by using NaHMDS as base (Scheme 1). In order to find a suitable reaction



Scheme 2 Versatile transformations of the amide **2o**

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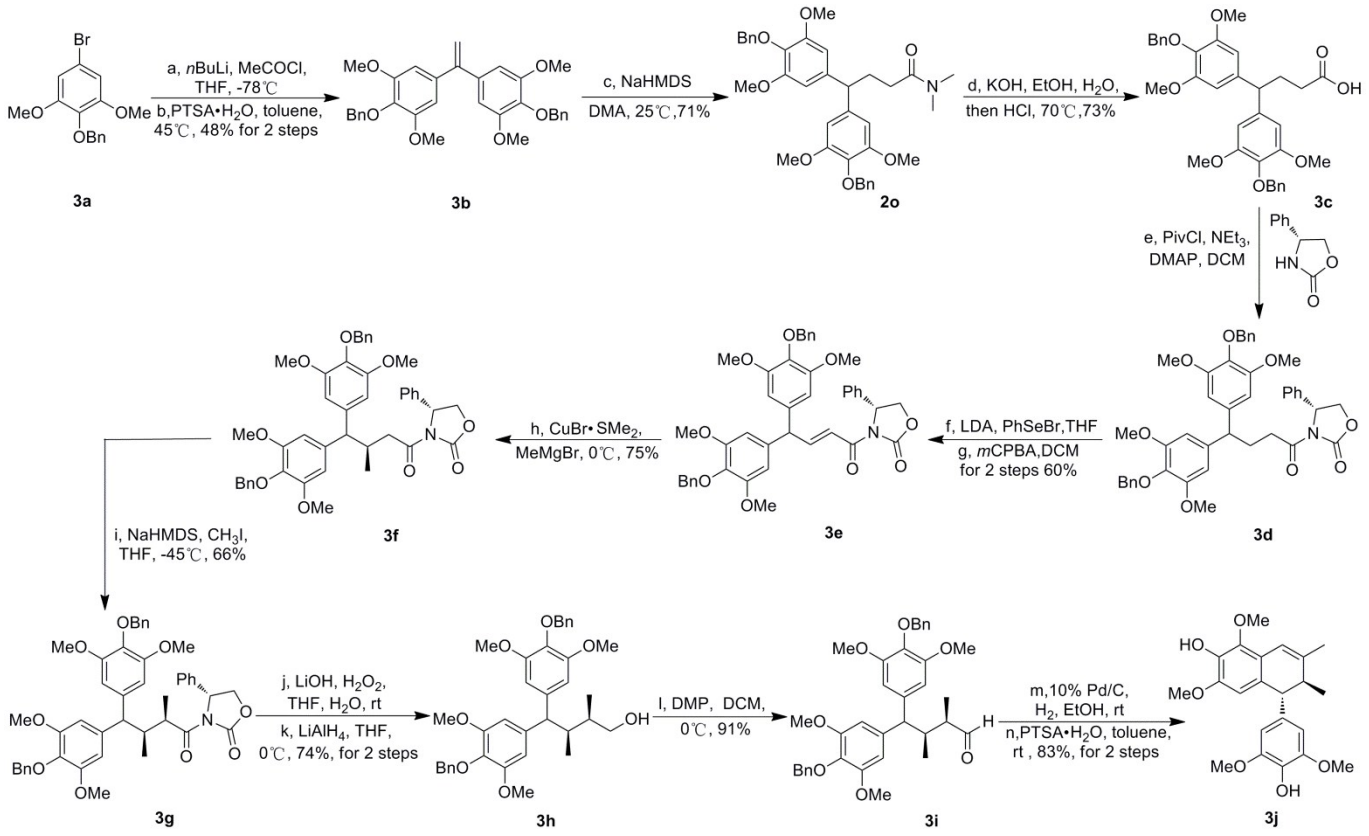

Scheme 3 Total synthesis of (-)-sacidumlignan B (**3j**)

temperature, we initially investigated 1,1-diphenylethylene and DMA (4.0 eq.) as test substrates, the reaction was conducted in THF at −45°C in the presence of NaHMDS with 2 equivalents, disappointingly, 1,1-diphenylethylene was not consumed (Table 1, entry 1). After increasing the temperature, the results did not change (Table 1, entries 2, 3). Small amount of substrate was exhausted, but the desired amide was not obtained at room temperature (Table 1, entry 4). Considering that solvent had an effect on the reaction, we tried to experiment with toluene and benzene, but failed to afford the corresponding product (Table 1, entries 5, 6). To our delight, we used DMF as solvent and successfully obtained N,N-dimethyl-4,4-diphenylbutanamide (**2a**) with poor yield (Table 1, entry 7). Although the yield was still low, it was improved under the conditions of DMSO, which indicated that solvent had huge impact on the reaction (Table 1, entry 8). Delightfully, the yield dramatically increased to 73% in DMA, while the reaction time was greatly shortened at room temperature, which proved DMA was better solvent (Table 1, entry 9). Screening of different bases indicated that KOH, LiHMDS and KHMDS were also capable of promoting the addition, but NaHMDS gave better yield (Table 1, entries 10−13). A control experiment showed that the reaction did not occur without a base (Table 1, entry 14). Moreover, we examined the amount of NaHMDS, and found that 1.5 equivalents of NaHMDS as the base effectively promoted the reaction smoothly (Table 1, entries 15−18). On the other hand, we noticed that the commercially available NaHMDS was dissolved in THF, while the amount of DMA was too low, the substrate was difficult to completely react, and the amount of DMA was too high, which brought great trouble for experimental operation. After screening, we found that substrate concentration of 0.5 M was a better choice. The substrate scope of 1,1-diarylethylenes was examined under the optimized conditions, as listed in Table 2. We found 1,1-diarylethylenes with various alkyl- and alkoxy- substituents on the aromatic ring gave good yields of the amides (**2a**–**2h**), and substrates bearing electron-withdrawing groups gave medium yields (**2i**, **2j**, **2k**). Excitingly, 1,1-diphenylethylene with CF_3-groups was employed, the desired adduct (**2l**) was obtained successfully, and heterocyclic substrates gave the corresponding amides (**2m**, **2n**) in moderate yields. Pleasingly, we provided gram scale (5.12 g) of the amide (**2o**) under our

standard conditions in 71% yield, which greatly reflected the potential utility of the method. On the basis of previous literature reports, the possible mechanism seems to indicate that the reaction is a base-promoted nucleophilic addition of DMA to 1,1-diarylethenes.[10]

To illustrate the synthetic potentiality of the addition process, the amide (**2o**) was employed to prepare a series of functional molecules (Scheme 2). The selective reduction of **2o** using L-selectride as the reductant afforded **3** in a moderate yield.[11] Amidic hydrolysis of **2o** with KOH, followed by acidification of hydrochloric acid gave the corresponding carboxylic acid (**3c**).[12]

Synthesis (-)-sacidumlignan B (**3j**) is our goal, and then we applied this addition to the synthesis of (-)-sacidumlignan B (**3j**) to test our method (Scheme 3). We prepared the arylbromide (**3a**) using the method from our previous work published.[4] Treatment with *n*-butyllithium, the arylbromide underwent Lithium-bromine exchange to give the aryllithium species, which was treated sequentially with acetyl chloride to afford tertiary alcohol. It was then dehydrated under acidic conditions to give the 1,1-diarylethylene (**3b**). By our standard reaction conditions, the addition of DMA to 1,1-diarylethenes proceeded smoothly to give the amide (**2o**) in 71% yield. Treatment of the amide with KOH, followed by acidification of hydrochloric acid provided the carboxylic acid (**3c**). The acid with pivaloyl chloride and triethylamine reacted to give the mixed anhydride. Subsequently, the mixed anhydride with (*R*)-4-Phenyl-2-oxazolidinone provided the oxazolidinone (**3d**).[13] Next, the oxazolidinone (**3d**) was deprotonated with LDA and selenated with PhSeBr, followed by oxidative elimination with *m*CPBA to furnish **3e**. Conjugate addition of MeMgBr to the α,β-unsaturated imide (**3e**) produced 1,4-adducts (**3f**) (dr > 98: 2) in the presence of $CuBr{\bullet}SMe_2$. Treatment of **3f** with NaHMDS, followed by methylation of the sodium enolate obtained the oxazolidinone (**3g**) (dr = 94: 6).[14] Exposure of the oxazolidinone to LiOH and H_2O_2 provided the acid, then, the alcohol (**3h**) was afforded by reduction of the acid with $LiAlH_4$.[15] The hydroxy group of the alcohol was oxidized with Dess-Martin periodinane to give the aldehyde (**3i**). Finally, hydrogenation of **3i** with Pd/C and H_2 afforded the phenol, which was converted into (-)-Sacidumlignan B (**3j**) under acidic conditions.

In summary, we have reported an efficient and economical method for addition of DMA to 1,1-diarylethylenes in the absence of transition metal catalysts, and the addition proceeded smoothly to synthesize N,N-dimethyl-4,4-diarylbutanamides in good yields by using NaHMDS as a base in DMA under mild conditions. Amides are versatile intermediates for synthetic organic chemistry, we have used the approach to get the goal of synthesizing (-)-sacidumlignan B, which shows the practicability of our method.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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