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COMMUNICATION

A grinding-induced catalyst- and solvent-free synthesis of highly functionalized 1,4-dihydropyridines *via* a domino multicomponent reaction†

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A grinding-induced catalyst- and solvent-free domino multicomponent reaction for the synthesis of 1,4-dihydropyridines has been developed using aldehydes, amines, DEAD (diethyl acetylenedicarboxylate), and malononitrile/ethyl cyanoacetate. The synthesized 1,4-dihydropyridines were efficiently converted into novel tacrine analogs 7a–7e using micelle-promoted microwave irradiation.

Green chemistry has become a powerful tool in organic chemistry in the last decade,[1] and current areas of interest are the generation of complex molecular systems *via* multicomponent reactions (atom economy), catalyst and solvent-free syntheses,[2] and reactions in/on water.[3] The avoidance of catalysts and solvents in chemical processes, or the replacement of hazardous solvents with more benign solvents, have become major concerns in academia and industry, and the need for green reactions is now globally accepted. Catalyst- and solvent-free multicomponent syntheses are particularly attractive, because they incorporate many green chemistry principles.

In recent years, multicomponent reactions have been much utilized for the synthesis of diverse highly functionalized molecules,[4] *via* the formation of carbon–carbon and carbon–heteroatom bonds in one pot; as a consequence, they have emerged as a significant tool in organic synthesis.[5] These reactions are straightforward one-step transformations involving a pair of reactions in which the product of the first is a substrate for the second. The development of several methods for the generation of libraries of structurally complex and diverse small molecules has provided new applications for the "chemical genetic" approach,[6] as well as playing an important part in drug discovery, namely the rapid identification and optimization of biologically active lead compounds.[7]

Researchers have long been fascinated by the biological activity of 1,4-dihydropyridines (1,4-DHPs) (**I**), tacrine (**II**) and their derivatives. 1,4-Dihydropyridines are a very important class of heterocyclic compounds due to a variety of biological activities.[8] Initially, these compounds were found to be calcium channel modulators, and were developed as cardiovascular and antihypertensive drugs, which include felodipine, amlodipine, nifedipine and nicardipine (Fig. 1).[9] Recently, tacrine analogs were found to be potent acetylcholinesterase inhibitors, and even stronger inhibitors of butyrylcholinesterase.[10]

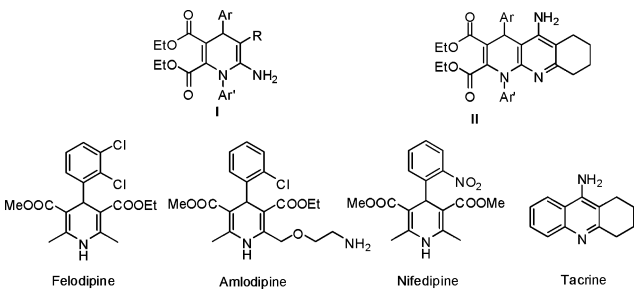

Fig. 1 Some biologically important dihydropyridines.

The vast biological importance of dihydropyridines and tacrine analogs inspired us to develop a novel protocol for the efficient synthesis of new 1,4-dihydropyridines *via* a domino multicomponent synthesis of DEAD (diethyl acetylenedicarboxylate), aldehyde, aniline and malononitrile/ethyl cyanoacetate/cyanoacetamide. During the synthesis of dihydropyridines, Yan and coworkers reported the same class of compound[11] using triethylamine as a base, but this required a long reaction time, as well as solvent and catalyst.

Our experience in the area of multicomponent reactions[12] and the success of our environmentally friendly synthesis of tryptanthrin[13] inspired us to search for environmentally friendly conditions for the synthesis of 1,4-dihydropyridines under catalyst- and solvent-free conditions.

In our initial studies, we attempted to optimize the reaction conditions for the domino multicomponent reaction between benzaldehyde, aniline, DEAD, and malanonitrile as model substrates (Scheme 1). Solvent-free syntheses[14] and Knoevengel condensation[15] under solventless conditions have gathered much interest, so we examined this reaction under solvent-free conditions. The reaction proceeded successfully in a porcelain mortar and pestle without any catalyst. Interestingly, 100% conversion in the synthesis of **5a** was found on grinding for 15 min, but no reaction was observed in ethanol (in the absence of catalyst). An

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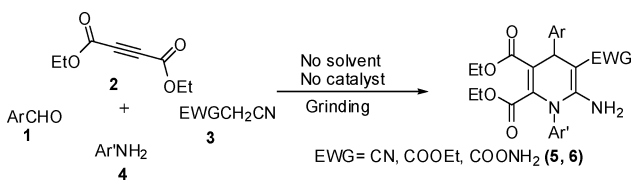
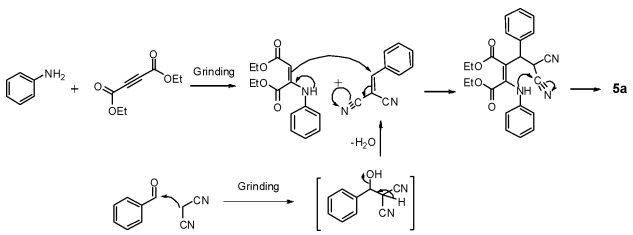
Table 1 Solvent- and catalyst-free domino synthesis of 1,4-dihydropyridines[a]

Entry	Ar	Ar′	EWG	Product	Yield (%)
1	C_6H_5	C_6H_5	CN	**5a**	92
2	p-$CH_3OC_6H_4$	p-$CH_3OC_6H_4$	CN	**5b**	88
3	p-$CH_3OC_6H_4$	p-ClC_6H_4	CN	**5c**	84
4	p-$CH_3OC_6H_4$	p-$CH_3C_6H_4$	CN	**5d**	92
5	3,4,5-$(CH_3O)_3C_6H_2$	p-$CH_3OC_6H_4$	CN	**5e**	99
6	3,4,5-$(CH_3O)_3C_6H_2$	p-ClC_6H_4	CN	**5f**	84
7	3,4,5-$(CH_3O)_3C_6H_2$	3,4,5-$(CH_3O)_3C_6H_2$	CN	**5g**	86
8	3,4,5-$(CH_3O)_3C_6H_2$	p-$CH_3C_6H_4$	CN	**5h**	93
9	3,4,5-$(CH_3O)_3C_6H_2$	2,4-$(CH_3)_2C_6H_4$	CN	**5i**	92
10	3,4,5-$(CH_3O)_3C_6H_2$	p-BrC_6H_4	CN	**5j**	95
11	3,4,5-$(CH_3O)_3C_6H_2$	C_6H_5	CN	**5k**	91
12	3,4-$(CH_3O)_2C_6H_3$	p-BrC_6H_4	CN	**5l**	94
13	3,4-$(CH_3O)_2C_6H_3$	p-ClC_6H_4	CN	**5m**	84
14	3,4-$(CH_3O)_2C_6H_3$	p-$CH_3OC_6H_4$	CN	**5n**	82
15	p-$CH_3OC_6H_4$	p-BrC_6H_4	CN	**5o**	88
16	p-$CH_3OC_6H_4$	p-$C_2H_5OC_6H_4$	CN	**5p**	92
17	p-ClC_6H_4	p-BrC_6H_4	CN	**5q**	93
18	2,4-$Cl_2C_6H_4$	p-BrC_6H_4	CN	**5r**	98
19	p-$(C_6H_5CH_2O)C_6H_4$	p-BrC_6H_4	CN	**5s**	95
20	p-$NO_2C_6H_4$	p-$CH_3C_6H_4$	CN	**5t**	96
21	Isatin	C_6H_5	CN	**5u**	0
22	Cyclohexanone	C_6H_5	CN	**5v**	0
23	3,4,5-$(CH_3O)_3C_6H_2$	p-$CH_3OC_6H_4$	COOEt	**6a**	91
24	p-ClC_6H_4	p-BrC_6H_4	COOEt	**6b**	93
25	p-$NO_2C_6H_4$	p-$CH_3C_6H_4$	COOEt	**6c**	91
26	p-ClC_6H_4	p-ClC_6H_4	COOEt	**6d**	84
27	p-ClC_6H_4	p-ClC_6H_4	$COONH_2$	**6e**	79

[a] Reagents and conditions: Aniline (1 mmol), aldehyde (1 mmol), malanonitrile/ethyl cyanoacetate (1 mmol), DEAD (1 mmol), grinding, 5–20 min.



Scheme 1 Synthesis of 1,4-dihydropyridines.



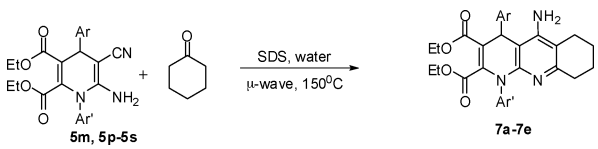
Scheme 2 Possible mechanistic pathway for the synthesis of 1,4-dihydropyridines.

exothermic reaction started immediately after grinding started, with liquification of the mixture, followed by solidification of the product **5a**, as explained by Scott and coworkers.[16] The purity of the product was high enough for spectroscopic analysis without any further purification, but all the compounds were nevertheless crystallized from ethanol.

In order to demonstrate the efficiency and the applicability of our method, we performed the reaction with a variety of arylaldehydes and aryl amines under solvent-free conditions (Table 1), without using any catalyst. No obvious electronic effects of the aldehyde or amine were observed, and the products were obtained in excellent yields. A limitation of the reaction is that complex mixtures of products were observed when ketones such as isatin and cyclohexanone were used in place of aldehydes. Using malononitrile instead of cyanoacetamide gave the desired product in very good yield (Scheme 1).

A possible mechanistic pathway is shown in Scheme 2, using **5a** as an example. Initially, coupling of the aldehyde with the active methylene compound, and the aza-Michael reaction of DEAD and aniline occur (and are known to take place under catalyst-free conditions). Rearrangement of the intermediates then generates the product **5a**. We observed the aza-Michael product as an oily compound after 1 min of grinding, but no hydroamination or Knoevenagel products were isolated. This indicates the fast rate of the aza-Michael reaction compared to the other possible reactions.

In order to synthesize tacrine analogs, the synthesized dihydropyridines were used in the micelle-promoted coupling of cyclohexanone, to yield hexahydrobenzo[*b*][1,8]naphthyridine derivatives in the presence of SDS (sodium dodecyl sulfate) as a catalyst in water (Scheme 3). We also tested sodium lauryl sulfate, Triton X-100 and dodecylsulfonic acid, to optimize the reaction conditions. The reaction of dihydropyridine **5m** and cyclohexanone using these catalysts gave **7a** in 43, 48 and 32% yields respectively (Scheme 3, Table 2).



Scheme 3 Synthesis of novel hexahydrobenzo[*b*][1,8]naphthyridines.

Table 2 Synthesis of hexahydrobenzo[*b*][1,8]naphthyridine derivatives *via* SDS-promoted reaction of dihydropyridines

Entry	Ar	Ar′	Product	Yield (%)
1	3,4-$(CH_3O)_2C_6H_3$	*p*-ClC_6H_4	**7a**	65, 43[a], 48[b], 32[c]
2	*p*-$CH_3OC_6H_4$	*p*-$C_2H_5OC_6H_4$	**7b**	52
3	*p*-ClC_6H_4	*p*-BrC_6H_4	**7c**	68
4	2,4-$Cl_2C_6H_4$	*p*-BrC_6H_4	**7d**	79
5	*p*-$(C_6H_5CH_2O)C_6H_4$	*p*-BrC_6H_4	**7e**	61

[a] Sodium lauryl sulfate (30 mol%) used as a catalyst. [b] Triton X-100 used as a catalyst. [c] Dodecylsulfonic acid (30 mol%) used as a catalyst.

Conclusions

In conclusion, a domino multicomponent reaction for the synthesis of dihydropyridines has been developed using solvent- and catalyst-free conditions. The features of this procedure are mild conditions, high yields, operational simplicity, and the environmental friendliness. In addition, the synthesized dihydropyridines could be efficiently converted into polyhydronaphthyridines in water.

Experimental

General procedure for synthesis of compounds 5a–v and 6a–e

A mixture of the appropriate aldehyde (1 mmol), aniline (1 mmol), DEAD (1 mmol), and malanonitrile (1 mmol) was ground in a mortar and pestle at room temperature. After two minutes, a syrupy solution was observed, which solidified upon completion of the reaction. Solid products were formed with high purity, and all the compounds were recrystallized from ethanol.

General procedure for synthesis of compounds 7a–e

An oven-dried microwave vial was charged with dihydropyridine **5** (1 mmol), cyclohexanone (3 mmol) and SDS (30 mol% solution in water, 3 ml), and irradiated in a microwave (power input 140 W) at 150 °C with stirring for 15 min. After completion of the reaction, the mixture was diluted with 5 ml ethyl acetate and washed with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ether, and the combined organic layers washed with brine and dried over Na_2SO_4. The solvent was evaporated to yield a crude residue, which was purified by silica gel column chromatography using EtOAc–hexane to give the pure product **7**.

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