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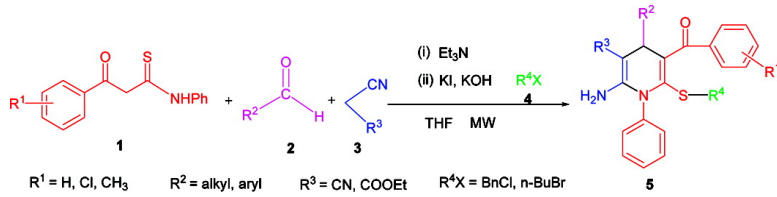

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Microwave-Assisted Combinatorial Synthesis of Hexa-Substituted 1,4-Dihydropyridines Scaffolds Using One-Pot Two-Step Multicomponent Reaction followed by a S-Alkylation

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A sequential one-pot two-step protocol for microwave-assisted synthesis of Hantzsch-type hexa-substituted 1,4-dihydropyridines has been developed. The three-component reactions of β-aroylthioamides with aldehydes and acetonitrile derivatives produce the intermediates in situ followed by a S-alkylation to afford hexa-substituted 1,4-dihydropyridines. The reaction presumably proceeds via a Knoevenagel condensation−Michael addition−cyclocondensation−rearrangement−S_N2 reaction sequence. Target compounds were obtained in high yields and simply purified by recrystallization. The novel method is complementary to the classical Hantzsch synthesis in that it is well-suited to the preparation of hexa-substituted 1,4-dihydropyridines.

Introduction

1,4-Dihydropyridines, as an important "privileged scaffold", are very attractive targets for combinatorial library synthesis because of their wide range of pharmaceutical activities; they have been reported to be vasodilators, antihypertensives, and bronchodilators and to possess antiatherosclerotic, antioxidant, hepatoprotective, antitumor, antimutagenic, antidiabetic, geroprotective, and photosensitizing activities.[1] They are also important reducing agents toward the application of the nicotinamide adenine dinucleotide coenzyme [NAD(P)H] models.[2] Many examples of privileged medicinal scaffolds have 1,4-dihydropyridine scaffolds, such as nifedipine,[3] which has been in use in clinical medicine since 1975. More recently, many novel second-generation calcium antagonists have emerged with improved bioavailability and tissue selectivity/stability (such as benidipine and lacidipine),[4] and calcium agonists (such as BAY K 8644) have been discovered[5] (Figure 1).

The synthesis of multisubstituted 1,4-dihydropyridines has attracted much attention, and a number of procedures have been developed.[6] The best known method for the preparation of 1,4-dihydropyridines is the classical Hantzsch synthesis,[7] a multicomponent condensation involving the original version (Scheme 1a). Another version is Menéndez synthesis,[8] ceric ammonium nitrate (CAN) catalyzed the three-component domino reaction from aromines, α,β-unsaturated aldehydes, and ethyl acetoacetate, providing an efficient new entry into the *N*-aryl-1,4-dihydropyridine class (Scheme 1b). Ishar et al.[9] reported that heating an azadiene and an allenic ester in dry refluxing benzene by a regioselective (4 + 2)-cycloaddition led to the formation of *N*-aryl-1,4-dihydropyridine. Wang et al.[10] developed a novel synthesis of N-substituted 1,4-dihydropyridines from salicaldehydes, ethyl propiolate, and amines. Sambr et al.[11] found a new protocol for the synthesis of various 1,2,3,4-tetrasubstituted 1,4-dihydropyridines from enamino or carbonylic derivatives promoted by $Mg(ClO_4)_2$. Although numerous synthesis have been developed for 1,4-dihydropyridines, it is still challenging to explore new and efficient synthetic routes for this class of compounds, particularly those with wide general applicability to achieve more flexible substitution pattern.

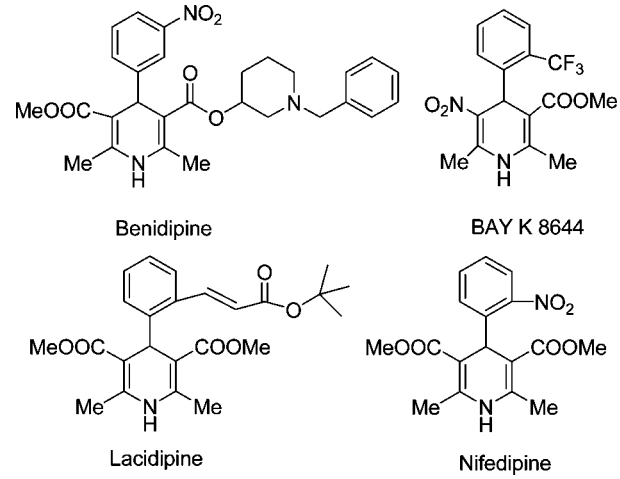

Figure 1. Examples of 1,4-dihydropyridine heterocyclic-containing therapeutics.

With the emergence of high-throughput pharmaceutical screening, there are increasing demands for the rapid generation of libraries of small molecules, especially heterocyclic compounds.[12] Multicomponent reaction[13] is an excellent strategy to prepare libraries of high molecular diversity not only because of their convergent nature, superior atom economy, and straightforward experimental procedures but also because of their value to the pharmaceutical industry for construction of small molecular weight compound libraries.

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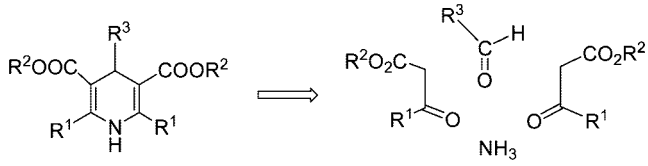
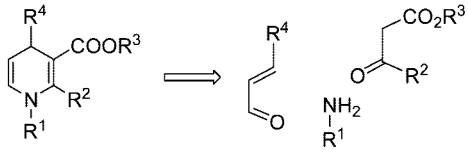
Polarized ketene N, S-,[14] N, N-,[15] and S, S-acetals,[16] as a new class of highly versatile functionalized enamines in complex heterocyclic synthesis, may be one of the good reactants that will lead to the formation of new heterocyclic compounds.[17] Although two-component reactions of β-aroylthioamides with various binucleophilic species have been developed,[18] to the best of our knowledge, there has been no report on the sequential one-pot two-step multicomponent reaction from β-aroylthioamides to synthesize novel hexa-substituted 1,4-dihydropyridines. Herein we report a facile one-pot two-step multicomponent reaction including β-aroylthioamides, aldehydes, acetonitrile derivatives, and alkyl halides by an integrated strategy using a combinatorial approach from readily available building blocks, to access highly functionalized hexa-substituted 1,4-dihydropyridines derivatives (Scheme 1c), and it is complementary to the Hantzsch reaction.

Scheme 1. Components used for the Synthesis of 1,4-Dihydropyridines

(a) Hantzsch synthesis:



(b) Menéndez synthesis:



(c) our work:

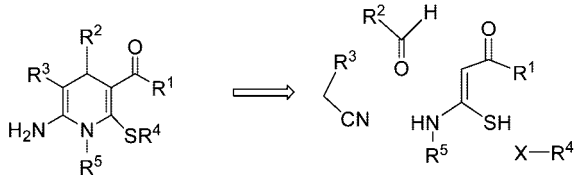


Table 1. Base Optimization for the Step 1 to Synthesize Intermediate **8a**[a]

entry	base (equiv)	time (min)	yield (%)[b]
1	Et_3N (0.5 mmol)	5	61
2	Et_3N (1 mmol)	5	85
3	Et_3N (2 mmol)	5	80
4	pyridine (1 mmol)	7	76
5	piperidine (1 mmol)	9	80
6	DABCO (1 mmol)	6	74
7	K_2CO_3 (1 mmol)	8	69
8	Na_2CO_3 (1 mmol)	8	61
9	Cs_2CO_3 (1 mmol)	8	64
10	KOH (1 mmol)	6	75

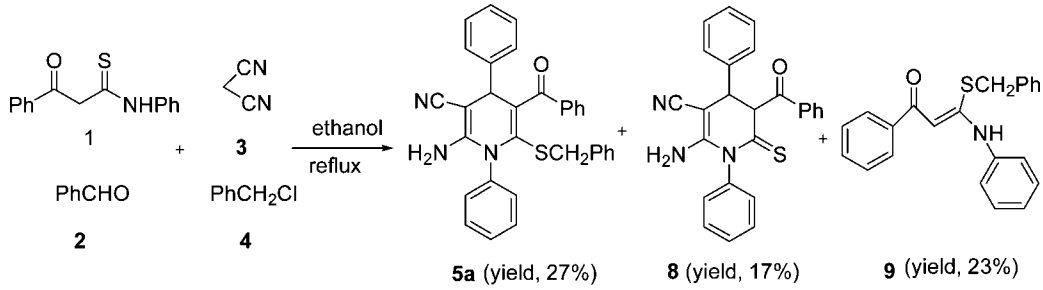
[a] Reagents and reaction conditions: 3-oxo-*N*,3-diphenylpropanethioamide (1mmol), benzaldehyde (1mmol), malononitrile (1mmol), base, 78 °C, EtOH (10 mL), MW 500 W. [b] Isolated yields.

Results and Discussion

In initial studies, we envisioned the synthesis of hexa-substituted 1,4-dihydropyridines by a straightforward one-pot four-component reaction in the presence of Et_3N in ethanol under conventional heating. Unfortunately, the reaction led to the formation of three products after analysis of the crude reaction mixture by silica gel column chromatography: the expected product, 2-amino-5-benzoyl-6-(benzylthio)-1,4-diphenyl-1,4-dihydropyridine-3-carbonitrile **5a** in a yield of only 27% and, simultaneously, two side-products, one of which was found to be 2-amino-5-benzoyl-1,4-diphenyl-6-thioxo-1,4,5,6-tetra hydropyridine-3-carbonitrile **8** in 17% yield and the other was (*Z*)-3-(benzylthio)-1-phenyl-3-(phenyl- amino)prop-2-en-1-one **9** with a yield of 23% (Scheme 2).

To address this problem, we adopted a combinatorial synthesis of hexa-substituted 1,4-dihydropyridines using a sequential one-pot two-step reaction, in which both processes

Scheme 2. Synthesis of Hexa-Substituted 1,4-Dihydropyridines by Straightforward Four-Component Reaction



Scheme 3. Microwave-Assisted Synthesis of Hexa-Substituted 1,4-Dihydropyridines Strategy by Sequential One-Pot Two-Step Reaction

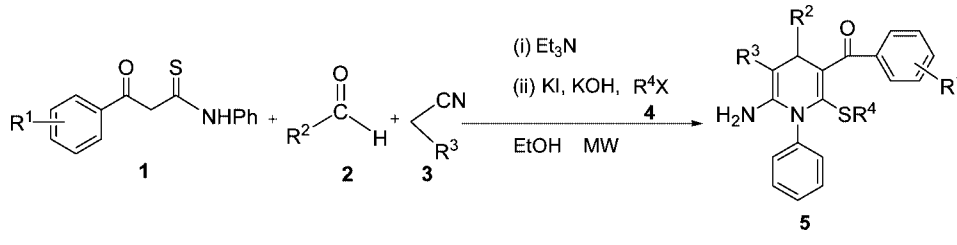


Table 2. Base Optimization for the Step 2 to Synthesize Product **5a**[a]

entry	base (equiv)	time (min)	yield (%)[b]
1	Et_3N (1 mmol)	18	41
2	pyridine (1 mmol)	17	29
3	piperidine (1 mmol)	19	33
4	DABCO (1 mmol)	18	45
5	Na_2CO_3 (1 mmol)	18	35
6	Cs_2CO_3 (1 mmol)	18	39
7	K_2CO_3 (1 mmol)	18	44
8	KOH (1 mmol)	16	53
9	KOH (2 mmol)	16	59
10	KOH (3 mmol)	16	64
11	KOH (4 mmol)	16	60
12	KOH (5 mmol)	16	57

[a] Reagents and reaction conditions: (step 1) 3-oxo-*N*,3-diphenylpropanethioamide (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol), Et_3N (1 mmol), EtOH (10 mL), 78 °C, MW 500 W, 5 min; (step 2) benzyl chloride (2 mmol), KI (1 mmol), base, 78 °C, MW 500 W. [b] Isolated yields.

Table 3. Solvent and Reaction Temperature Optimization for the Synthesis of **5a** under MW[a]

entry	solvent	temp (°C)	time (min)	yield (%)[b]
1	ethanol	78	21	64
2	acetonitrile	81	21	53
3	benzene	80	21	42
4	toluene	110	21	35
5	DMF	152	21	51
6	NMP	204	21	39
7	1,4-dioxane	101	21	55
8	THF	35	21	27
9	THF	50	21	52
10	THF	65	21	68
11	THF	75	21	62

[a] Reagents and reaction conditions: (step 1) 3-oxo-*N*,3-diphenylpropanethioamide (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol), Et_3N (1 mmol), solvents (8 mL), MW 500 W; (step 2) benzyl chloride (2 mmol), KOH (3 mmol), KI (1 mmol), MW 500 W. [b] Isolated yields.

Table 4. MW Power Optimization for the Synthesis of **5a** at 65 °C in THF[a]

entry	power (W)	time (min)	yield (%)[b]
1	200	21	35
2	300	21	42
3	500	21	61
4	600	21	71
5	700	21	66
6	800	21	62

[a] Reagents and reaction conditions: (step 1) 3-oxo-*N*,3-diphenylpropanethioamide (1 mmol), benzaldehyde (1 mmol), malononitrile (1 mmol), Et_3N (1 mmol), THF (8 mL); (step 2) benzyl chloride (2 mmol), KOH (3 mmol), KI (1 mmol). [b] Isolated yields.

are carried out in the same flask, without the isolation of intermediates. The resulting chemical system constitutes a very appealing reaction manifold for the synthesis of the hexa-substituted 1,4-dihydropyridine scaffold. (Scheme 3)

The reactions were carried out by mixing benzaldehyde, malononitrile, and 3-oxo-*N*,3-diphenyl-propanethioamide in ethanol at 78 °C under conventional heating; the corresponding intermediates **8** was produced after 2 h. Then benzyl chloride and KI were added to the mixture, and it was stirred for 24 h; the reaction was completed as indicated by TLC. However, the overall yield of the product **5a** was only 39%. It is well-known that microwave irradiation favors reactions involving more polar transition states and often leads to different product selectivity than the thermal reactions, further, reactions under microwave irradiation often proceed

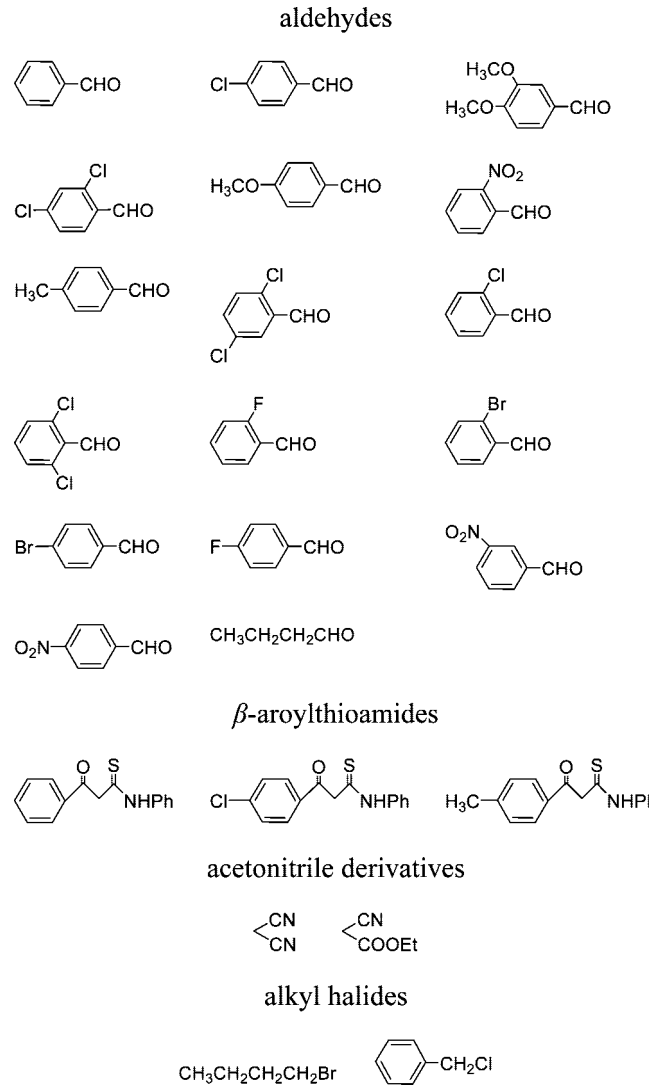


Figure 2. Building block for the hexa-substituted 1,4-dihydropyridines.

more rapidly than the conventional thermal reactions with diminished decomposition of the reactants, products, or both, thus minimizing the waste and enhancing the yield.[19] So the synthesis of **5a** was carried out under the microwave irradiation. The result showed the reaction was efficiently promoted by MW irradiation, and the reaction time was strikingly reduced to 2 min from the over 26 h time required under traditional heating conditions, and the yields were increased to 41% from 39%.

Various reaction conditions including bases, solvents, temperature, and power of microwave irradiations were screened with the aim to obtain a versatile and high-yielding route.

For the sequential one-pot reaction, the choice of base is very important. The reactions of 3-oxo-*N*,3-diphenylpropanethioamide **1a**, benzaldehyde **2**, and malononitrile **3** (step 1) were carried out in the presence of Et_3N, pyridine, piperidine, DABCO, potassium carbonate, sodium carbonate, cesium carbonate, and potassium hydroxide, respectively, under microwave irradiation (Table 1).

As can be seen from Table 1, the yield of intermediate **8** was the highest in the presence of Et_3N (Table 1, entry 2). Therefore, for step 1, the most suitable base should

Table 5. Microwave-Assisted Synthesis of **5** by Sequential One-Pot Two-Step Reaction[a]

entry	**5**	R^1	R^2	R^3	time (min)	yield (%)[b]	ESI-MS $[M + H]^+$
1	**5a**	H	C_6H_5	CN	21	71	500.2
2	**5b**	H	4-ClC_6H_4	CN	22	74	534.6
3	**5c**	H	4-$MeOC_6H_4$	CN	24	69	530.5
4	**5d**	H	3,4-$(MeO)_2C_6H_3$	CN	25	67	560.4
5	**5e**	H	2,4-$Cl_2C_6H_3$	CN	20	75	568.1
6	**5f**	H	3-$NO_2C_6H_4$	CN	19	80	545.3
7	**5g**	H	2-$NO_2C_6H_4$	CN	20	81	545.3
8	**5h**	4-Cl	C_6H_5	CN	21	75	534.2
9	**5i**	4-Cl	4-$MeOC_6H_4$	CN	23	72	564.4
10	**5j**	4-Cl	4-$CH_3C_6H_4$	CN	22	71	548.3
11	**5k**	4-Cl	2,4-$Cl_2C_6H_3$	CN	19	78	602.5
12	**5l**	4-Cl	2,5-$Cl_2C_6H_3$	CN	20	74	602.5
13	**5m**	4-Cl	2-ClC_6H_4	CN	21	72	568.7
14	**5n**	4-Cl	2-$NO_2C_6H_4$	CN	18	84	579.5
15	**5o**	4-Cl	2,6-$Cl_2C_6H_3$	CN	18	77	602.3
16	**5p**	4-Cl	2-FC_6H_4	CN	20	75	552.3
17	**5q**	4-Cl	2-BrC_6H_4	CN	21	78	612.1
18	**5r**	4-Cl	4-BrC_6H_4	CN	20	79	612.5
19	**5s**	4-Cl	4-FC_6H_4	CN	21	73	552.4
20	**5t**	4-Cl	3-$NO_2C_6H_4$	COOEt	18	83	626.4
21	**5u**	4-Cl	4-$NO_2C_6H_4$	COOEt	19	84	626.3
22	**5v**	4-Cl	2-ClC_6H_4	COOEt	22	80	615.4
23	**5w**	4-Cl	2-ClC_6H_4	CN	21	78	534.3
24	**5x**	4-Cl	-$CH_2CH_2CH_3$	CN	24	41	500.6
25	**5y**	4-CH_3	4-ClC_6H_4	CN	20	68	548.6
26	**5z**	4-CH_3	3,4-$(MeO)_2C_6H_3$	CN	23	59	574.6
27	**5aa**	4-CH_3	4-$MeOC_6H_4$	CN	22	69	544.4
28	**5ab**	4-CH_3	2-ClC_6H_4	CN	21	71	548.3
29	**5ac**	4-CH_3	4-$NO_2C_6H_4$	CN	20	79	559.3
30	**5ad**	4-CH_3	3-$NO_2C_6H_4$	CN	20	77	559.3
31	**5ae**	4-CH_3	4-FC_6H_4	CN	20	71	532.3
32	**5af**	4-CH_3	-$CH_2CH_2CH_3$	CN	23	48	480.4
33	**5ag**	4-CH_3	-CH_3	CN	23		

[a] Entries 1−22, 24−33, R^4 X = $PhCH_2Cl$, entry 23, R^4X = *n*-BuBr. [b] Isolated yields.

be Et_3N, but it is disadvantage for the S_N2 reaction of **8** with benzyl chloride (step 2) (Table 2, entry 1). So other bases were also investigated for step 2 under microwave irradiation (Table 2).

From Table 2, in the presence of pyridine, piperidine, DABCO, sodium carbonate, cesium carbonate, or potassium carbonate, the corresponding product **5a** was obtained only in 29%, 33%, 45%, 35%, 39%, or 44% overall yields, respectively (Table 2, entries 2−7). To our satisfaction, the treatment of **8** with benzyl chloride in the presence of potassium hydroxide gave the highest yield (**5a**, 53%) (Table 2, entry 8). It is observed through further examination that the amount of potassium hydroxide increased from 1 equiv to 3 equiv, the yields of the products were improved from 53% to 64% (Table 2, entries 8−10), and when 4 or 5 equiv of KOH were employed, the yields were not further enhanced (Table 2, entries 11 and 12). We also found that for reactions when 1 equiv of alkylating agents (benzyl chloride or n-butyl bromide) were employed, the reaction did not proceeded completely. This problem was easily overcome by combination of a 2 equiv excess of alkyl halides and 1 equiv of potassium iodide in the reaction. Therefore, we chose 1 equiv of Et_3N for step 1 and 3 equiv of potassium hydroxide and 1 equiv of potassium iodide for step 2.

To search for the optimum solvent, the reaction of 3-oxo-*N*,3-diphenylpropanethioamide **1a**, benzaldehyde **2**, malononitrile **3**, benzyl chloride **4** was also tested in acetonitrile, benzene, toluene, DMF, NMP, 1,4-dioxane, or THF at the temperature of boiling point, respectively, under MW condition (Table 3, entries 1−7 and 10). As can be seen from Table 3, the reaction using THF as solvent provided the best yield (**5a**, 68%, entry 10). Next, the reaction in THF was also conducted at the temperature from 35 to 75 °C (Table 3, entries 8−11), the results showed the optimum reaction temperature is 65 °C.

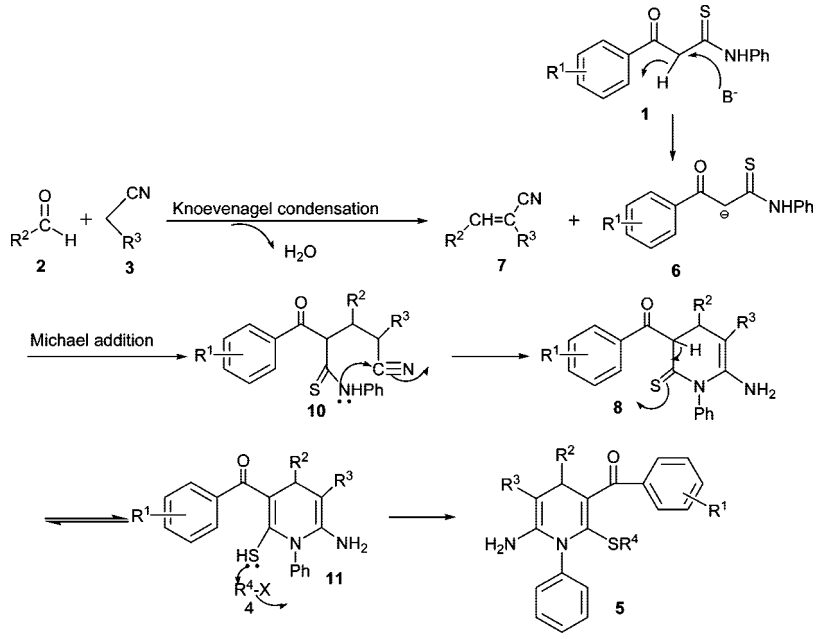
Further investigation was carried out for the evaluation of power of microwave irradiation from 200 to 800 W (Table 4). It is observed that the yield of product **5a** was improved, and the reaction time was shortened when the microwave irradiation was increased from 200 to 600 W. However, further increase of the power from 700 to 800 W failed to further improve the yield of product **5a**. So microwave power of 600 W was chosen as the optimum power (**5a**, 71%, Table 4, entry 4).

We can conclude that the best condition is in THF at 65 °C under microwave irradiation of 600 W by 1 equiv of Et_3N for the step 1 and 3 equiv of potassium hydroxide and 1 equiv of potassium iodide for the step 2.

To examine the efficiency and the generality of this novel sequential one-pot two-step reaction, 18 aldehydes, 3 β-aroylthioamides, 2 acetonitrile derivatives, and 2 alkyl halides were investigated for synthesis of hexa-substituted 1,4-dihydropyridines under optimal conditions (Figure 2). Aldehydes, acetonitrile derivatives, and alkyl halides are all commercially available materials. Aroylthioamides were easily prepared according to the literature.[20] The results were summarized in Table 5.

The protocol could be applied to the aryl aldehydes with either electron-withdrawing groups or electron-donating groups and aliphatic aldehydes. As can be seen from Table

Scheme 4. Plausible Reaction Mechanism



5, the electronic effect of the substituted benzaldehydes has an insignificant impact on the conversion. The feasibility of employing aliphatic aldehydes instead of aryl aldehydes in the reaction was also investigated. Unfortunately, when butyl aldehyde was used, the products **5** were obtained in lower yields (**5x** 41%, **5af** 48%) (Table 5, entries 24 and 32). Even the use of acetaldehyde could not afford the expected product **5ag** (Table 5, entries 33). This may be considered as a limitation for practical achievement using aliphatic aldehydes in this reaction.

A plausible mechanism for the reaction was depicted in Scheme 4. Initially, a Knoevenagel condensation occurs by attacking the carbonyl group of aromatic aldehydes **2** with the α-carbon atom of acetonitrile derivatives **3**, leading to the formation of intermediate 2-arylidenemalononitrile **7**. Michael addition between β-aroylthioamide **6** and **7** then may undergo cyclozation in situ by nucleophilic attack of amino nitrogen at the cyano group to give a pyridine **8**, then a nucleophilic substitution (S_N2) of the alkyl halides **4** by attack of mercapto group leads to a new class of expected compounds **5** with elimination of hydrogen chloride. The reaction presumably proceeds in a cascade manner involving a sequence of chemical transformations, including Knoevenagel condensation, Michael addition, cyclization, rearrangement, elimination, and S_N2 reaction.

Conclusion

In summary, we have developed a new strategy that provides an efficient entry into hexa-substituted 1,4-dihydropyridine derivatives in a sequential one-pot two-step process from β-aroylthioamides, aldehydes, acetonitrile derivatives, and alkyl halides under microwave irradiation. Therefore, it is complementary to existing procedures, particularly to the Hantzsch synthesis. The systematic variation of every component led to a remarkable level of structural diversity. The β-aroylthioamides contribute diversity at R^1, the aldehydes contribute diversity at R,[2] the acetonitrile derivatives contribute diversity at R^3, and alkyl halides contribute diversity at R.[4] It is worth noting that all the target compounds were simply purified by recrystallization. This ease of purification makes this methodology facile, practical, and rapid to execute. Further studies on the biological activities of this type of 1,4-dihydropyridines are in progress. This method for construction of congested 1,4-dihydropyridines opens a new avenue for the generation of molecular diversity that can find application for chemical genomics or drug discovery research.

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Supporting Information Available. Details of experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, IR, MS, EA), ^{1}H and ^{13}C NMR spectra and partial MS spectra of all new compounds, and a comparison of microwave and thermal conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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