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Microwave-assisted three-component Knoevenagel-nucleophilic aromatic substitution reactions

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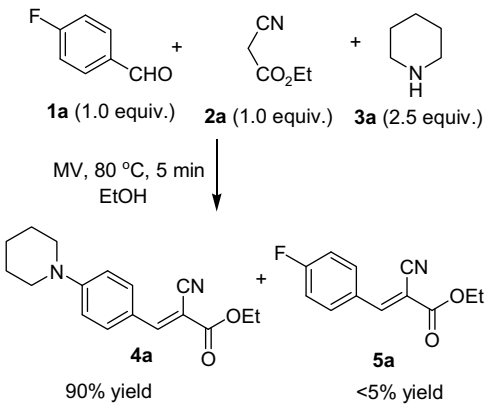
ABSTRACT

A powerful microwave-assisted three-component Knoevenagel-nucleophilic aromatic substitution reaction of 4-halobenzaldehydes, cyanoacetatic acid esters/cyanoacetamides, and cyclic secondary amines has been developed.

The development of atom-economic and synthetically efficient strategies is an important goal in contemporary organic synthesis. In the recent past, the use of microwave energy to facilitate chemical reactions has become increasingly popular in organic synthesis.[1,2] It has been demonstrated in many cases that the reaction efficiency has significantly improved in terms of reaction time and yield. On the other hand, atom-economic and efficient multicomponent reactions involving three or more reactants in a single reaction vessel enable to create complex molecular architectures.[3] Combining these two powerful tools is a particularly attractive strategy in practice of modern organic synthesis. Such tactic allows for rapidly producing molecular complexity and diversity from simple and readily accessible chemical substances. In this Letter, we wish to report an unprecedented microwave-assisted three-component Knoevenagel-nucleophilic substitution process from simple and readily accessible chemical substances, which provides a 'one-pot' procedure for the preparation of 4-aminobenzylidene derivatives in high efficiency.

Secondary amines such as piperidine are commonly used bases in the Knoevenagel reaction.[4] It is known that amines also often serve as nucleophiles in organic synthesis. We envisioned that taking advantage of their basicity and nucleophilicity and through the careful design of substrates, it is possible to develop a new Knoevenagel/aromatic nucleophilic substitution (S_NAr) reaction.

To demonstrate the feasibility of the proposed process, a model reaction of 4-fluorobenzaldehyde **1a** with ethyl cyanoacetate **2a** in the presence of piperidine **3a** was carried out with a ratio of 1:1:2.5 in ethanol under a microwave (MV) irradiation at 80 °C (Scheme 1).[5] 4-Fluorobenzaldehyde was selected as one of the three components since it is more reactive for S_NAr reaction.[6] It was found that the process proceeded smoothly to give the desired product **4a** with thermodynamically stable (*E*) configuration in 90% yield.[7] Notably, the reaction was completed in 5 min, whereas under the traditional heating reaction conditions it took 3 h. In addition, a small amount of **5a** was isolated (<5% yield).



Scheme 1. Microwave (MV)-facilitated three-component Knoevenagel/aromatic nucleophilic substitution reaction.

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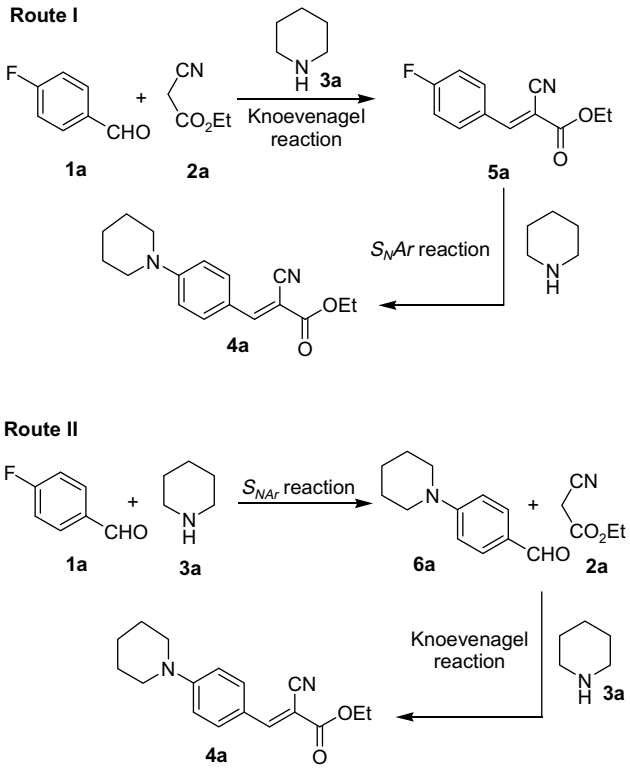
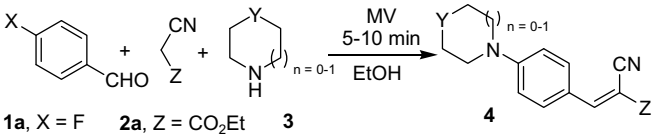
Encouraged by the results presented above, we next probed the scope of the reaction with a variety of halogen-substituted aromatic aldehydes **1**, stabilized carbanions, **2**, and amines **3** (Table 1). All reactions were conducted in EtOH at 80 °C with MV irradiation. In each case, smooth reactions occurred to generate desired products **4** in high yields (72–90%) with short reaction times. Variations in the form of cyanoacetic acid esters/cyanoacetamides **2** and cyclic secondary amines **3** used in reaction with 4-fluorobenzaldehyde **1a** had a limited effect on reaction yields (Table 1, entries 1–12). It is realized that when acyclic secondary and primary amines were employed, a complicated reaction mixture was observed. One possible reason is that generally higher reaction yields are achieved for Knoevenagel condensation with cyclic secondary amines than non-cyclic secondary and primary amines. More significant was the observation that the MV-facilitated three-component reactions could apply for much less reactive chloro- and bromo-aromatic aldehyde substrates for S_NAr reactions (entries 13 and 14). In these instances, the reaction occurred in good yields (72% and 83%, respectively) in spite of relatively long reaction times. However, no reactions were seen when the reaction was performed under traditional heat conditions.

In the 'one-pot' transformation, two reaction pathways (routes I and II) could be possible (Scheme 2). In route I, the Knoevenagel condensation proceeds first and then is followed by the S_NAr substitution. Alternatively, the S_NAr process occurs prior to the Knoevenagel condensation (route II). To verify the reaction mechanism, we conducted two experiments and found that route I was a likely one. Treatment of pure preformed **5a**, produced from reaction of 4-fluorobenzaldehyde **1a** with ethyl cyanoacetate **2a** using Et_3N as catalyst, with piperidine in refluxing ethanol gave rise to the S_NAr product **4a** in high yield.[8] However, no reaction between 4-fluorobenzaldehyde **1a** and piperidine was observed under the same reaction conditions. The presumable reason for the Knoevenagel condensation and then subsequent S_NAr process is that the Knoevenagel condensation product (e.g., **5a**) is more reactive than aldehyde **1a** for the S_NAr substitution due to its strong electron-withdrawing ability in addition to resonance effect.



Scheme 2. Reaction pathways.

Table 1
Scope of MV-facilitated three-component Knoevenagel/aromatic nucleophilic substitution reaction[a]



1a, X = F **2a**, Z = CO_2Et **3**
1b, X = Cl **2b**, Z = CO_2Me Y = CH_2 and O, NR
1c, X = Br **2c**, Z = $CONH_2$

Entry	**1** and **2**	Amines **3**	**4**	*t* (min)	Yield[b] (%)
1	**1a,2a**	Piperidine	**4a**	5	90
2	**1a,2a**	Morpholine	**4b**	5	86
3	**1a,2a**	*N*-Methylpiperazine	**4c**	5	85
4	**1a,2a**	Pyrrolidine	**4d**	5	86
5	**1a,2a**	*N*-Ethylpiperazine	**4e**	5	80
6	**1a,2a**	*N*-Phenylpiperazine	**4f**	5	84
7	**1a,2b**	Piperidine	**4g**	10	85
8	**1a,2b**	Morpholine	**4h**	10	84
9	**1a,2b**	*N*-Methylpiperazine	**4i**	10	83
10	**1a,2c**	Piperidine	**4j**	5	75
11	**1a,2c**	Morpholine	**4k**	5	78
12	**1a,2c**	*N*-Methylpiperazine	**4l**	5	75
13	**1b,2a**	Piperidine	**4a**	30	72
14	**1c,2a**	Piperidine	**4a**	30	83

Reaction carried out in MeOH.
[a] Unless specified, see Ref. 5 for detailed reaction procedure.
[b] Isolated yield based crystallization without column chromatography.

In summary, we have developed a new microwave-assisted three-component Knoevenagel-nucleophilic aromatic substitution reaction of 4-halobenzaldehyde, cyanoacetic acid ester/cyanoacetamide, and cyclic secondary amines. The process affords one-pot process for the domino formation of one carbon-carbon double bond and one carbon–nitrogen bond. Taking the advantage of microwave irradiation, reaction times can be significantly reduced in high yields, and more significantly the less reactive 4-chloro and bromo-benzaldehydes can effectively participate in the process. Further expanding the scope of the powerful MV, assisted multi-component reactions is underway in our laboratory.

Acknowledgment

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5. *Typical experimental procedure under microwave irradiation:* Cyclic secondary amine (2.5 equiv) was treated with 4-fluorobenzaldehyde (1.24 mL, 11.6 mmol) and active methylidene (11.6 mmol) in EtOH (20 mL). The resulting mixture was placed into the microwave reactor for a specified reaction time. After the reaction was completed, the mixture was cooled down to rt and poured into 50 mL of water. Crude products were filtered off and purified by crystallization in EtOH.
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8. *For experimental procedure, see:* Et_3N (10 mol %) was treated with 4-fluorobenzaldehydes (11.6 mmol) and ethyl cyanoacetate (1.83 mL, 17.3 mmol) in ethanol (20 mL). The mixture was stirred and heated to reflux for 3–4 h. Then the mixture was cooled down to room temperature and poured into 50 mL of water. Crude products were filtered off and purified by crystallization in ethanol/water. Compound **5a** was isolated as pale yellow sheet, 2.36 g, 93%, mp: 97.6–97.8 °C, lit. 96–97 °C (Mečiarová, M.; Podlesná, J.; Toma, Š. *Monatsh. Chem.* **2004**, *135*, 419); MS (EI): 219 (M^+), ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.2 (s, 1H, C*H*), 8.03 (m, J = 5.3 Hz, 2H, Ar*H*), 7.02 (t, J = 8.4 Hz, 2H, Ar*H*), 4.39 (m, J = 7.1 Hz, 2H, OCH_2CH_3), 1.40 (t, J = 7.1 Hz, 3H, OCH_2CH_3). Then **5a** (2.54 g, 11.6 mmol) was dissolved in EtOH (20 mL). The resulting solution was treated with cyclic secondary amine (2.5 equiv) and heated to reflux for 3 h. Then the mixture was cooled down to room temperature and poured into 50 mL of water. Crude products were filtered off and purified by crystallization in EtOH.