Highly Stereoselective Synthesis of 2-Aminobenzylidene Derivatives by a Convergent 3-Component Approach

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Abstract: An one-pot stereoselective synthesis of 2-aminobenzylidene derivatives from readily available 5-nitro/cyano-activated 2-halobenzaldehydes (2-chloro-5-nitrobenzaldehyde, 2-bromo-5-nitrobenzaldehyde, 2-fluoro-5-nitrobenzaldehyde, 5-cyano-2-fluorobenzaldehyde), the active methylidene compounds (cyanoacetamide and ethyl cyanoacetate), and secondary cycloamines via a novel parallel convergent Knoevenagel–nucleophilic aromatic substitution and nucleophilic aromatic substitution–Knoevenagel condensation cascade approach under mild conditions has been developed with high stereoselectivity and in 52–88% yields.

Key words: convergent cascade, Knoevenagel–S_NAr reaction, one-pot reaction, 2-halobenzaldehyde

The development of fast, highly efficient, and environmentally benign synthetic protocol is of particular significance. The one-pot multicomponent reactions (MCR) have prominent advantages over the classical multistep syntheses in their higher synthetic efficiency.[1] Therefore, in the last decade research in academia and industry has increasingly emphasized the application of MCR in industrialization.[1,2]

Compounds containing a benzylidene scaffold could covalently bond to the SH group of cysteine residue at the ATP moiety of epidermal growth factor receptor (EGFR) or other nucleophiles at different receptors by Michael addition.[3] Therefore, 2-amino-5-nitrobenzylidene and 2-amino-5-cyanobenzylidene derivatives could be potential intermediates of EGFR inhibitors (EGFRi, Figure 1).

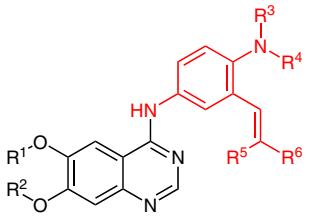

Figure 1 Potential side chains on the scaffold of EGFR inhibitors

They were usually prepared by stepwise S_NAr[4] and subsequent Knoevenagel reaction. Developping highly efficient facile one-pot, three-component synthetic methods from simple readily available materials under mild conditions is particularly valuable for such a process. Herein we report a three-component access to 2-amino-5-nitrobenzylidene and 2-amino-5-cyanobenzylidene derivatives **4** from readily available 2-halo-5-nitrobenzaldehyde (**1a**–**c**), 5-cyano-2-fluorobenzaldehyde (**1d**), cyanoacetamide (**2a**), and ethyl cyanoacetate (**2b**), and secondary cycloamines **3** via a novel parallel convergent Knoevenagel–nucleophilic aromatic substitution and nucleophilic aromatic substitution–Knoevenagel condensation cascade approach under mild conditions with high *E* selectivity and in 52–88% yields. To the best of our knowledge, this is the first example of parallel convergent Knoevenagel–nucleophilic aromatic substitution and nucleophilic aromatic substitution–Knoevenagel condensation cascade access to benzylidene-scaffold derivatives.

Our previous investigation of one-pot MCR and cascade reactions[5] has revealed the three-component Knoevenagel–nucleophilic aromatic substitution reactions and verified the first Knoevenagel condensation and subsequent S_NAr process. 4-Fluorobenzaldehyde can participate in such three-component reaction smoothly (Scheme 1, eq. 1).[5a] However, when the substrate was replaced by 2-fluorobenzaldehyde, the expected S_NAr reaction hardly occurred (Scheme 1, eq. 2).[6] In order to promote the aforementioned reaction, an electron-withdrawing group such as NO_2 or CN was added to the benzene ring. By this, the reaction goes as anticipated (Scheme 1, eq. 3).

To explore the feasibility of the newly proposed three-component reaction, we carried out a model reaction between 2-chloro-5-nitrobenzaldehyde (**1a**), cyanoacetamide (**2a**), and piperidine (**3a**) in ethanol (Table 1, entry 1). As disclosed by researches on S_NAr reactions, the major influencing factors in nucleophilic reactivity of amines is their basicity and bulkiness, and cyclic secondary amines were found to be the most reactive.[5a,7] In S_NAr reactions, the amine plays the dual role of nucleophile and base.[8] To neutralize the HX generated in reaction, an excess of amine or additional base is needed to facilitate the reaction. Therefore, the feeding ratio of **1a** (1 equiv), **2a** (1 equiv), and **3a** (2.5 equiv) was selected as optimized reaction conditions. It is noteworthy that in this procedure solvents have meaningful impact on the yield of this process. Although the reactions were not satisfying in H_2O (Table 1, entries 2 and 3), it was found that the process

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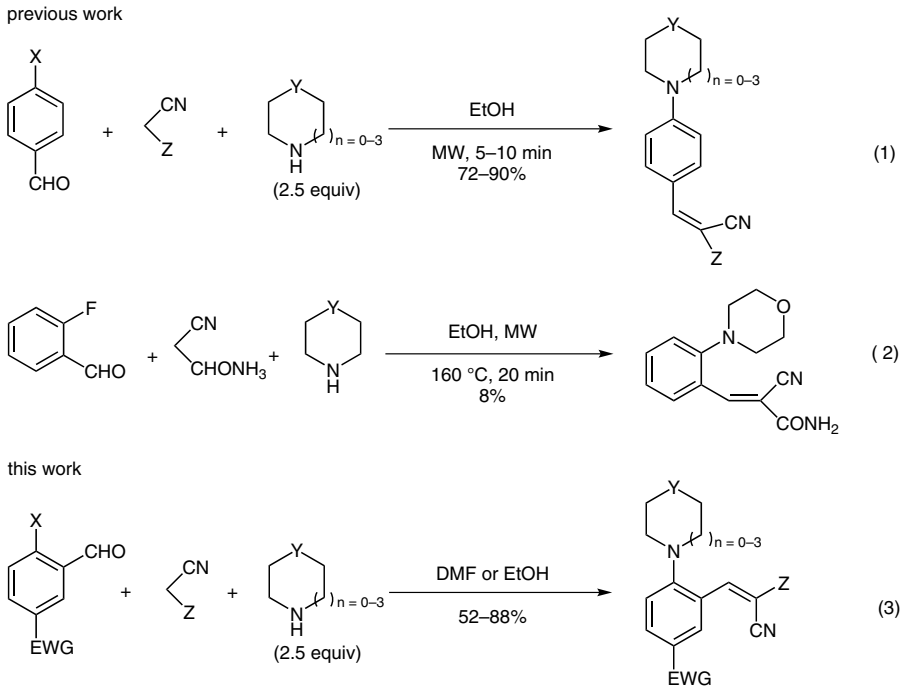
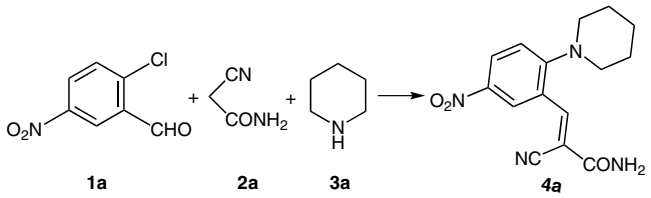


Scheme 1 A cascade three-component approach

performed in DMF generally afforded moderate to good yield (Table 1, entries 4–8).

Table 1 Optimization of Reaction Conditions[a]



1a **2a** **3a** ***4a***

Entry	Solvent	Temp (°C)	Time (min)	Yield (%)[b]
1	EtOH	78	90	64
2	H_2O	40	40	34
3	H_2O	100	40	36
4	DMF	90	35	76
5	DMF	70	40	77
6	DMF	110	35	75
7	DMF	70	40	72[c]
8	DMF	90	40	69[d]

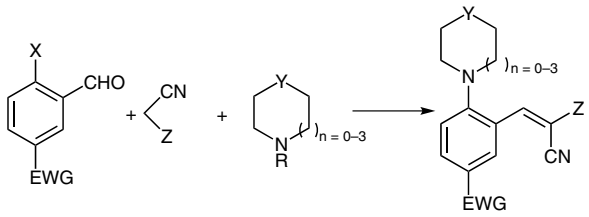
[a] Reaction conditions: Unless specified, a mixture of **1a** (1.0 mmol, 1.0 equiv), **2a** (1.0 mmol, 1.0 equiv), and **3a** (2.5 mmol, 2.5 equiv) in solvent (2 mL) was heated for a specified time.
[b] Isolated yield.
[c] Reaction conditions: **1a** (1.0 mmol, 1.0 equiv), **2a** (1.0 mmol, 1.0 equiv), and **3a** (2.0 mmol, 2.0 equiv).
[d] Reaction conditions: **1a** (1.0 mmol, 1.0 equiv), **2a** (1.0 mmol, 1.0 equiv), **3a** (1.0 mmol, 1.0 equiv), and Et_3N (1.5 mmol, 1.5 equiv).

As revealed in Table 2, the one-pot cascade protocol serves as a general method for the preparation of 2-aminobenzylidene-scaffold derivatives from 2-halo-5-nitrobenzaldehyde (**1a–c**), or 5-cyano-2-fluorobenzaldehyde (**1d**), cyanoacetamide (**2a**), or ethyl cyanoacetate (**2b**), and secondary cycloamines **3**.[9] Compared to 2-chloro-5-nitrobenzaldehyde (Table 2, entry 15) and 2-bromo-5-nitrobenzaldehyde (Table 2, entry 16), the reactions of 2-fluoro-5-nitrobenzaldehyde, active methylidene compounds, and secondary cycloamines in ethanol afforded higher isolated yields (Table 2, entries 17–21). Much to our surprise, we observed that the reactions of 2-chloro-5-nitrobenzaldehyde or 2-bromo-5-nitrobenzaldehyde with active methylidene compounds and secondary cycloamines got better yield in DMF (Table 2, entries 1–14) than in ethanol (Table 2, entries 15 and 16). Among the used secondary cycloamines, the reactions of heptamethyleneimine with 5-nitro- or 5-cyano-activated 2-halobenzaldehydes **1** and active methylidene compounds **2** got the lowest yield owing to its spatial hindrance, while the reactions of 2-fluoro-5-nitrobenzaldehyde are faster than those of 2-fluoro-5-cyanobenzaldehyde because the nitro group has a stronger electron-withdrawing effect than the cyano group does. The Knoevenagel condensation products and final products should have the same configuration (*E* configuration[10]) for the carbon–carbon double bonds that are stiff and nonrotatable.

In the course of the above cascade access to **4a**, both intermediates **5a** and **6a** were detected and transferred to **4a**, respectively, by the fractional-step reactions. Remarkably, the above one-pot processes proceeded in a convergent cascade manner (Scheme 2): first, 2-chloro-5-

nitrobenzaldehyde (**1a**) reacted with piperidine (**3a**) and followed by the S_NAr product 5-nitro-(piperidin-1-yl)benzaldehyde (**5a**) condensed with ethyl cyanoacetate (**2a**) to yield ethyl (*E*)-2-cyano-3-(5-nitro-2-(piperidin-1-yl)phenyl)acrylate (**4a**). Alternatively, **1a** condensed with **2a** catalyzed by pyrrolidine, and then **3a** reacted as nucle-

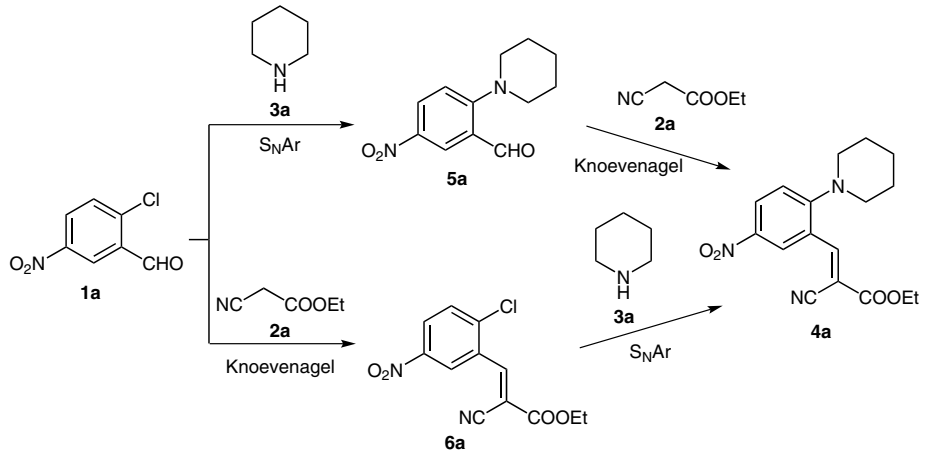
Table 2 Scope of Three-Component Knoevenagel–Nucleophilic Aromatic Substitution Reactions



1 **2** **3** **4**

Entry	**1**	X	EWG	**2**	Z	Y	n	**4**	Time (min)	Temp (°C)	Yield (%)
1	**1a**	Cl	NO_2	**2a**	$CONH_2$	CH_2	1	**4a**	40	70	77
2	**1a**	Cl	NO_2	**2a**	$CONH_2$	CH_2	0	**4b**	80	90	72
3	**1a**	Cl	NO_2	**2a**	$CONH_2$	O	1	**4c**	40	108	88
4	**1a**	Cl	NO_2	**2a**	$CONH_2$	NMe	1	**4d**	50	90	76
5	**1a**	Cl	NO_2	**2a**	$CONH_2$	CH_2CO_2Me	1	**4e**	50	90	86
6	**1a**	Cl	NO_2	**2a**	$CONH_2$	CH_2	3	**4f**	50	90	55
7	**1a**	Cl	NO_2	**2b**	CO_2Et	CH_2	1	**4g**	130	70	78
8	**1a**	Cl	NO_2	**2b**	CO_2Et	CH_2	0	**4h**	40	90	76
9	**1a**	Cl	NO_2	**2b**	CO_2Et	O	1	**4i**	50	90	80
10	**1a**	Cl	NO_2	**2b**	CO_2Et	NMe	1	**4j**	50	90	78
11	**1a**	Cl	NO_2	**2b**	CO_2Et	$CHCO_2Me$	1	**4k**	60	90	78
12	**1a**	Cl	NO_2	**2b**	CO_2Et	CH_2	3	**4l**	60	90	57
13	**1a**	Cl	NO_2	**2b**	CO_2Et	NBn	1	**4m**	70	90	81
14	**1b**	Br	NO_2	**2a**	$CONH_2$	CH_2	1	**4a**	40	70	81
15	**1a**	Cl	NO_2	**2b**	CO_2Et	CH_2	1	**4g**	90	78	64[a]
16	**1b**	Br	NO_2	**2a**	$CONH_2$	CH_2	1	**4a**	60	78	69[a]
17	**1c**	F	NO_2	**2b**	CO_2Et	CH_2	1	**4g**	30	78	88[a]
18	**1c**	F	NO_2	**2b**	CO_2Et	CH_2	0	**4h**	40	78	86[a]
19	**1c**	F	NO_2	**2b**	CO_2Et	O	1	**4i**	50	78	82[a]
20	**1c**	F	NO_2	**2b**	CO_2Et	NMe	1	**4j**	60	78	78[a]
21	**1c**	F	NO_2	**2b**	CO_2Et	$CHCO_2Me$	1	**4k**	60	78	80[a]
22	**1d**	F	CN	**2b**	CO_2Et	CH_2	0	**4n**	120	78	54[a]
23	**1d**	F	CN	**2b**	CO_2Et	CH_2	1	**4o**	70	78	65[a]
24	**1d**	F	CN	**2b**	CO_2Et	O	1	**4p**	120	78	68[a]
25	**1d**	F	CN	**2b**	CO_2Et	NMe	1	**4q**	105	78	52[a]
26	**1d**	F	CN	**2b**	CO_2Et	$CHCO_2Me$	1	**4r**	60	78	74[a]
27	**1d**	F	CN	**2b**	CO_2Et	CH_2	0	**4s**	90	78	75[a]

[a] Reaction was carried out in EtOH and purified by recrystallization with EtOH.



Scheme 2 A convergent cascade mechanism

ophilic reagent with the Knoevenagel product ethyl (*E*)-α-cyano-3-(2-fluoro-5-nitro)acrylate (**6a**) to yield **4a**.

In summary, we have developed a one-pot convergent Knoevenagel–nucleophilic aromatic substitution reaction to prepare 2-aminobenzylidene derivatives, which features the domino formation of one carbon–carbon double bond and one carbon–nitrogen bond. The process proceeds highly stereoselectively and in good yields. The further transformations of these compounds are under way.

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(9) **Typical Experimental Procedure**
Cyclic secondary amine (2.5 equiv) was treated with 2-halobenzaldehyde (1 mmol) and active methylidene compound (1 mmol) in EtOH (2 mL) or DMF (2 mL). The mixture was stirred and heated to reflux. After the reaction was completed, the mixture was cooled down to r.t. and poured into H_2O (10 mL). Crude products were filtered off and purified by recrystallization in EtOH or by column chromatography on silica gel; 52–88% yield.

(*E*)-α-Cyano-3-[5-nitro-2-(piperidin-1-yl)phenyl]-acrylamide (4a)
Yield 81%; yellow solid; 0.24 g. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (1 H, d, *J* = 2.4 Hz), 8.36 (1 H, m, *J* = 2.4, 2.8 Hz), 8.08 (1 H, s), 7.96 (1 H, s), 7.84 (1 H, s), 7.24 (1 H, d, *J* = 9.2 Hz), 3.13 (4 H, s), 1.68 (4 H,s), 1.61 (2 H, s). ^{13}C NMR (101 MHz, DMSO-d_6) δ = 162.58, 158.82, 147.99, 140.06, 127.74, 125.50, 123.44, 119.09, 116.37, 106.10, 53.54, 25.98, 23.82.

(*E*)-α-Cyano-3-[5-nitro-2-(pyrrolidin-1-yl)phenyl]-acrylamide (4b)
Yield 72%; yellow solid; 0.24g. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.68 (1 H, d, *J* = 2.4 Hz), 8.31 (1 H, m, *J* = 2.4, 2.8 Hz), 8.13 (1 H, s), 7.99 (1 H, s), 7.85 (1 H, s), 7.31 (1 H, d, *J* = 8.8Hz), 3.78 (4 H, s), 3.16 (4 H, s). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.45, 157.87, 147.47, 140.88, 127.82, 125.53, 123.97, 119.29, 116.28, 109.10, 66.39, 52.66.

(*E*)-α-Cyano-3-[5-nitro-2-(morpholin-1-yl)phenyl]-acrylamide(4c)
Yield 88%; yellow solid; 0.25g. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.68 (1 H, d, *J* = 2.4 Hz), 8.31 (1 H, m, *J* = 2.4, 2.8 Hz), 8.13 (1 H, s), 7.99 (1 H, s), 7.86 (1 H, s), 7.32 (1 H, d, *J* = 9.2 Hz), 3.79 (4 H, m), 3.17 (4 H, m). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.44, 157.87, 147.47, 140.87, 127.80, 125.51, 123.98, 119.26, 116.28, 109.05, 66.39, 52.66.

(*E*)-α-Cyano-3-[5-nitro-2-(4-methylpiperazin-1-yl)phenyl]acrylamide(4d)
Yield 76%; yellow solid; 0.25g. ^{1}HNMR (400 MHz, DMSO-d_6): δ = 8.66 (1 H, d, *J* = 2.4 Hz), 8.26 (1 H, m, *J* = 2.2, 9.0 Hz), 8.08 (1 H, s), 7.97 (1 H, s), 7.84 (1 H, s), 7.27 (1 H, d, *J* = 9.2 Hz), 3.16 (4 H, s), 2.51 (4 H, s), 2.25 (3 H, s). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 162.47, 158.04, 147.70, 140.56, 127.77, 125.48, 123.72, 119.28, 116.32, 108.64, 54.74, 52.28, 45.99.

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