The Divergent Transformations of Aromatic *o*-Aminonitrile with Carbonyl Compound

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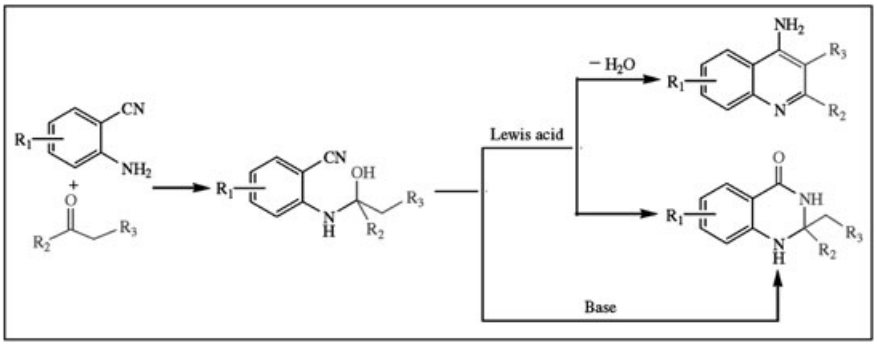

A modified Friedländer conversion of the cyclocondensation of aromatic *o*-aminonitriles with carbonyl compounds was discovered. Systematic studies reveal that both the new transformation and the classic Friedländer annulation in the presence of $ZnCl_2$ constitute a pair of divergent reaction, and thecontrolled PDF transformation of this divergent reaction was achieved in the present of bases.

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INTRODUCTION

The Friedländer annulation is one of the most simple and straightforward approaches for the synthesis of polysubstituted quinolines and related azaheterocycle or aza-aromatic compounds [1]. The Friedländer cyclocondensation of *o*-aminobenzonitriles with ketones has been widely explored [2]. Quinoline and similar compounds prepared by this method possessed interesting pharmacological properties such as acetylcholinesterase inhibitor [3,4], insecticides [5], antitumor agents [6], a nociceptin receptor antagonists [7], the affinity for α_1-adrenoreceptors [8], capable of intercalative binding to double-stranded DNA [9]. For this kind of Friedländer reaction, there are two points should be concerned. One is the catalyst, which are mainly divided into two categories: the proton acid [10–12] and Lewis acids [13–17]. The other point is that the structures of normal Friedländer condensation product is pyridine or quinoline skeleton. In other word, only those compounds containing quinoline/pyridine skeleton can be synthesized by this method.

In our study of tacrine derivatives by the Friedländer condensation of substituted 2-aminobenzo-nitrile with ketones, we realized that a new conversion to afford a new skeleton of compound was existed in this kind of normal Friedländer [18]. And further investigations revealed that this phenomenon was rather a certain generality. Herein, we wish to report these results in details.

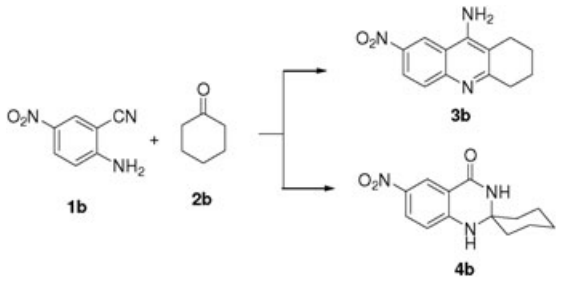
RESULTS AND DISCUSSION

Optimization of reaction conditions. The condensation of 2-amino-5-nitrobenzonitrile with cyclohexanone was chosen as a model reaction. A survey of Lewis acid catalysts indicates that the choice of the catalyst played a crucial role. Aluminum chloride and *p*-toluenesulfonic acid favor the product of Friedländer condensation in major and product of new conversion as minor (Table 1, entries 1 and 2), whereas zinc chloride, cuprous chloride, and copper chloride favor the formation of products **4b** (Table 1, entries 3–5, 10, and 11), and the yield of product **4b** has not obvious variety with the longer time (compare entries 5–9 in Table 1). The best catalyst, anhydrous zinc chloride, is choice as a catalyst for this new divergent transformation.

Intrigued by these results, this bifurcation reaction was subsequently examined by condensation of various

Table 1

Optimization of reaction conditions.[a,b]



Entries	Catalyst (equiv.)	Time (h)	**3b** Yield (%)	**4b** Yield (%)
1	$AlCl_3$	1	70	0
2	p-$MeC_6H_4SO_3H$	1	47	13
3	$CuCl_2$	1	7	32
4	CuCl	1	6	38
5	$ZnCl_2$	1	10	75
6	$ZnCl_2$	0.5	8	40
7	$ZnCl_2$	2	12	76
8	$ZnCl_2$	3	15	76
9	$ZnCl_2$	4	14	75
10	$ZnCl_2$ (0.5 equiv)	1	7	39
11	$ZnCl_2$ (1.5 equiv)	1	12	75

[a]Reaction condition: 2-amino-5-nitrobenzonitrile (6 mmol), cyclohexanone (15 mL), catalyst (6 mmol) at reflux.
[b]Yield of isolated product.

aromatic *o*-aminobenzonitriles **1** with cycloketones **2**. The selected examples are summarized in Table 2. As shown in Table 2, all the data suggested a high generality of the bifurcation reaction. Cycloketones were allowed to react with substituted *o*-aminobenzonitriles in the presence of $ZnCl_2$ to give two kinds of heterocycles: a quinazolinone produced *via* the new conversion route as the major products, meanwhile a quinoline built up through the normal Friedländer reaction as a minor one. The results also showed that *o*-aminobenzonitriles **1** having strong electron-withdrawing substituent or unsubstituent on the aromatic ring were cyclized with ketones to give the corresponding quinolines **3** in lower yields but quinazolinones **4** in better yields than other electron-donating substituted *o*-aminobenzonitriles. This probably suggested that electron-withdrawing groups on the aromatic ring would facilitate the new conversion.

The same trend was observed for aliphatic ketones (Table 3), quinazolinones obtained from the new transformation were major product, and meanwhile quinoline derivatives from Friedländer were minor product. Different ketones could be used and had no little influence on the yield of product **7** except for those with bulky substituent and less of the number of carbon atoms of aliphatic ketones, the lower of the yield of product **7**.

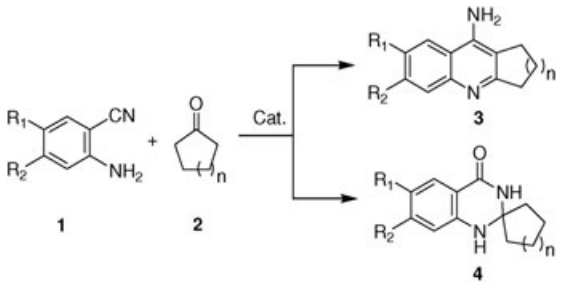
Based on these observations, a plausible mechanism for the simultaneous formation of quinoline **6** and quinazolinone **7** was proposed and depicted in Scheme 1. The formation of pyridine ring compound is *via* the normal Friedländer reaction (A), whereas the new modification may proceed *via* a different route (B) after the key intermediate **I** is formed by addition of the amino group of the *o*-aminonitrile onto the carbonyl of cyclohexanone. The hydroxyl group of intermediate **I** then attack the nitrile group (*i.e.,* Pinner reaction) to afford a benzoxazine, which subsequently rearranges to give the new conversion product **7** (Dimroth rearrangement). We called this new conversion as the PDF pathway [19].

Controlled transformation of the divergent reaction. Now, we clearly dissolve that the cyclocondensation of aromatic *o*-aminonitriles with ketones in the catalyst of $ZnCl_2$ constitutes a new divergent reaction. And either quinoline/pyridine or quinazolinone units provided by this divergent conversion represent a core structural motif found in natural products and biologically relevant compounds [20,21]. Molecules containing these motifs are the subject of considerable interest as useful biological and medicinal activities; they can be used as hypnotic, sedative, analgesic, anticonvulsant, antitussive, antibacterial, antidiabetic, antiinflammatory, and antitumor agents [22,23].

The control of selectivity is of fundamental importance in organic synthesis, especially with regard to the generation

Table 2

Divergent reaction of *o*-aminobenzonitriles with cycloketones.[a,b]



Entries	R_1	R_2	*N*	*T* (°C)	Time (h)	**3** Yield (%)	**4** Yield (%)
a	NO_2	H	1	Reflux	1	15	70
b	NO_2	H	2	Reflux	1	10	75
c	NO_2	H	3	Reflux	1	7	80
d	H	Cl	1	Reflux	2	12	67
e	H	Cl	2	Reflux	1.5	15	70
f	H	H	1	Reflux	2.5	25	62
g	H	H	2	Reflux	2.5	21	64
h	H	CH_3	1	160	4	11	25
i	CH_3	H	2	160	4	12	23
j	OCH_3	OCH_3	1	160	4	15	28
k	OCH_3	OCH_3	2	160	4	10	25

[a]Reaction condition: *o*-aminobenzonitrile (6 mmol), cycloketone(15 mL), catalyst ($ZnCl_2$, 6 mmol).
[b]Yield of isolated product.

of complex target structures. The most successful modern synthetic methodologies deliver the desired products in excellent yields and with efficient control of the diverse selectivities. This divergent reaction can simultaneously give two kinds of compounds in one pot, but their purifications are usually through silica gel column chromatography. So, that will be appreciated if two compounds could be obtained separately through the control transformation.

According to the mentioned mechanism, we envisioned that the control transformation is whether the intermediate **I** is dehydrated or not, and the regulation of pH value of reaction system is the key. So, the model conversion was reinvestigated in varieties of catalysts such as base, and the results were listed in Table 4. The results revealed that all bases selected except both $NaHCO_3$ and pyridine gave the appreciated products of quinazolinone, and potassium *tert*-butoxide was the best one.

Applications of PDF conversion. ***PDF conversion of the aromatic o-aminonitiles with aldehydes in the catalysis of*** $ZnCl_2$. Based on the above results, we first thought that the sole 1,2-dihydro-quinazolin-4(3*H*)-ones through the PDF conversion could be afforded from the cyclocondensation of aromatic *o*-aminonitriles with aromatic aldehydes instead of ketones.

After different conditions screening, we were delight to find the 1,2-dihydroquinazolin-4(3*H*)-one derivative **9c** was obtained from the condensation of 2-amino-5-nitrobenzonitrile **1b** with 3-nitrobenzoaldehyde **8c** in the catalyst of $ZnCl_2$ in suitable boiling solvent (Scheme 2), and DMF was the best solvent, meanwhile DMSO was also suitable for this annulation.

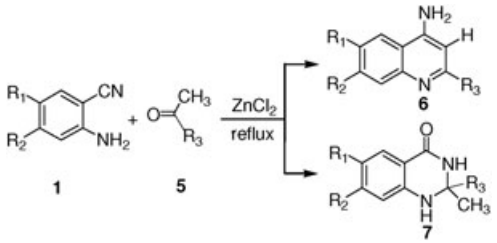
Next, various aldehydes **8**, including aromatic or aliphatic aldehydes with either electron donating or withdrawing substitutents, were subjected to react with **1** to investigate the reaction scope, and the representative results were summarized in Table 5.

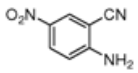
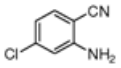
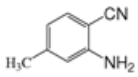
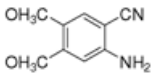
1,2-Dihydroquinazolin-4(3*H*)-one derivatives **9a–z** (Table 5) were formed by the reactions of aromatic *o*-aminonitriles with aldehydes in refluxed DMF in good yields. The position and electronic nature of the substituent on the phenyl ring of aryl aldehydes had no relevance to quinazolinone yield. Aliphatic aldehydes were also cyclized with **1** to afford quinazolinones in 60–80% yield. The new conversion proceeded better when *o*-aminonitriles **1** having electron withdrawing substituents.

PDF conversion of the aromatic o-aminonitriles with ketones in the catalysis of base. To determine the selective PDF conversion of this divergent reaction, we studied the cyclocondensation of aromatic *o*-aminonitriles with cycloketones in the presence of KOBu-*t* or NaOMe, and the results were shown in Table 6. The PDF conversion of compound **1b** substituted by electron-withdrawing

Table 3

Divergent reaction of *o*-aminobenzonitriles with aliphatic ketones.[a,b]



Entries	**1**	R_3	Time (h)	**6** Yield (%)	**7** Yield (%)
a		CH_3	1	7	82
b		C_2H_5	1	7	80
c		*n*-C_3H_8	1	10	75
d		$CH_2CH(CH_3)_2$	1	Trace	76
e		C_6H_5	2	Trace	78
f		CH_3	1.5	10	71
g		C_2H_5	1.5	8	74
h		*n*-C_3H_8	1.5	15	70
i		$CH_2CH(CH_3)_2$	1.5	Trace	75
j		C_6H_5	2.5	12	70
k		(*p*-OCH_3)C_6H_5	2.5	Trace	75
l		CH_3	3	20	62
m		C_2H_5	2.5	15	65
n		C_6H_5	2.5	Trace	67
o		CH_3	4	Trace	20
p		CH_3	3	Trace	25

[a]All reactions were carried out using **1** (6 mmol), **5** (4 mL), $ZnCl_2$ (6 mmol), and DMF (8 mL).
[b]Isolated yield.

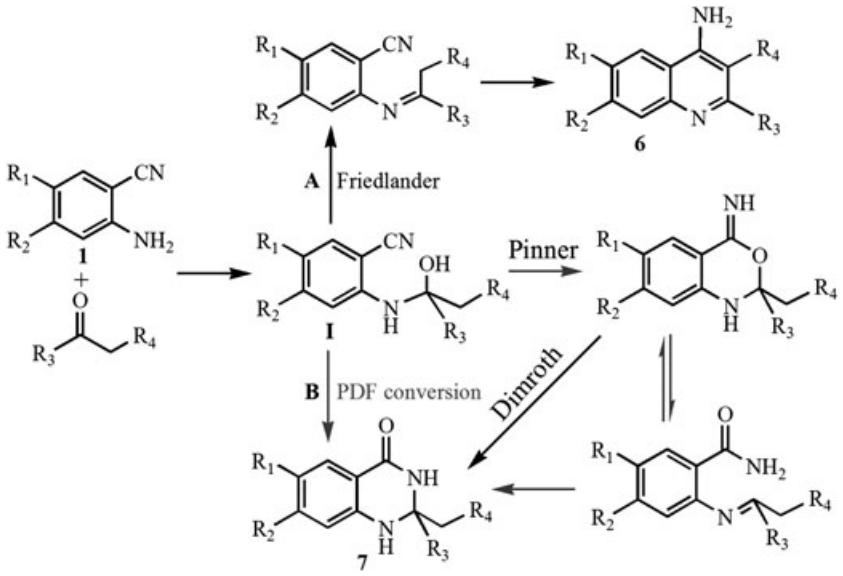
groups or unsubstituted with cycloketones in the catalyst of KOBu-*t* provided good to excellent results. The yield of cyclohexanone was higher than that of cyclopentanone.

The control PDF conversion of the divergent reaction was also successfully applied for the cyclocondensation of various aliphatic ketone with compounds **1** to give the corresponding quinazolinones in moderate yields (Table 7). For the aliphatic ketones, the catalytic effect of alcohol sodium or potassium was worse than those of $ZnCl_2$. The substituted effect on the aromatic is not obvious. These results shown that the PDF conversion of aromatic *o*-aminonitriles with ketones in the presence of base is a facile and one-pot procedure for the convenient synthetic methodology of 1,2-dihydroquinazolin-4(3*H*)-one derivatives.

CONCLUSIONS

A modified conversion was discovered in the normal Friedländer annulation of aromatic *o*-aminonitriles with carbonyl compounds. Both modified transformation and normal Friedländer annulation constitutes a new interesting divergent reaction, and this divergent reaction was first studied systematically. In the stronger base condition, controllable PDF conversion pioneered perfectly and found it possessed the broad scope with present to the facile preparation of 1,2-dihydroquinazolin-4(3*H*)-one derivatives by one-pot reaction of aromatic *o*-aminonitriles with carbonyl compound. The formation of 1,2-dihydroquinazolin-4(3*H*)-one skeleton is the tandem intermolecular Pinner and followed by a Dimroth rearrangement through the same intermediate. Further application studies are in progress.

Scheme 1. Proposed mechanism.



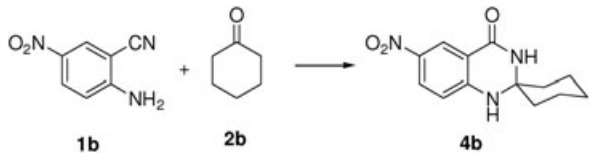
EXPERIMENTAL

General information. Melting points were determined using XT4 microscope melting point apparatus (uncorrected). Infrared (IR) spectra were recorded on a Perkin Elmer FTIR spectrophotometer with KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded at a Bruker 400 (400 MHz) spectrometer with TMS as the internal standard. ESI-MS were recorded with a ZAB-HS mass spectrometer in the positive ion mode. Elemental analyses were performed on an Elementar Vario EL (within ±0.4% of theoretical values).

General procedure for divergent synthesis of quinolines and quinolinones by the catalyst of zinc chloride. ***Divergent reaction of o-aminobenzonitriles with cycloketones.*** The appropriate *o*-aminobenzonitrile (6 mmol), cycloketones (15mL), and zinc chloride (6 mmol) were added into a 50-mL flask. The mixture was heated at certain temperature for the specified time (see Table 2). After completion of the reaction as indicated by TLC (eluent: petrolum ether/ethyl acetate 1:1), the cooled reaction mixture was quenched with water (10 mL) and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the solid was dissolved in acetone; the organic phase

Table 4

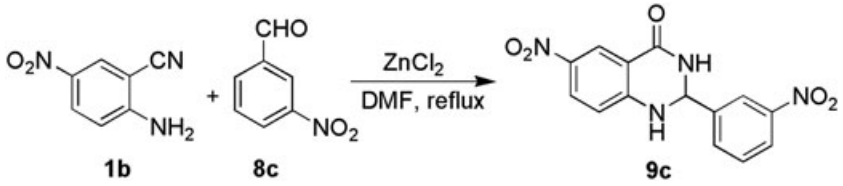
The yield based of the different catalyst.[a,b]



Entries	Catalyst	*T* (°C)	Time (h)	**3b** Yield (%)	**4b** Yield (%)
1	MeONa	60	1	0	74
2	EtONa	60	1	0	67
3	KOBu-t	60	1	0	84
4	Na_2CO_3	Reflux	2	0	Trace
5	$NaHCO_3$	Reflux	4	0	0
6	Pyridine	100	3.5	0	0

[a]Reaction condition: 2-amino-5-nitrobenzonitrile (1 mmol), cyclohexanone (3 mL), catalyst (0.2–0.4 mmol).
[b]Yield of isolated product.

Scheme 2. Condensation of 2-amino-5-nitrobenzonitrile with 3-nitrobenzoaldehyde.



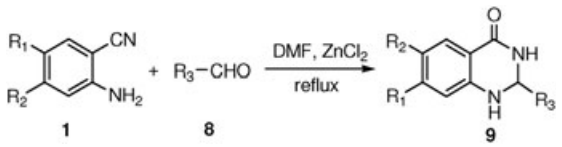
obtained was combined with the extracted component of filtrate (using EtOAc) and evaporated *in vacuo*. The product was purified by silica gel column chromatography (200–300 mesh silica gel, ethyl acetate: petroleum = 1:3/v:v) to afford quinolines **3** and quinazolinone derivatives **4**.

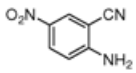
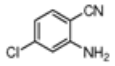
4c. 6′-Nitro-1′H-spiro[cycloheptane-1,2′-quinazolin]-4′(3′H)-one. M.p. 298–300°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.54 (s, 8H; CH_2), 1.94 (s, 4H; CH_2), 6.82 (d, 1H; J = 8.8 Hz, ArH), 8.09 (dd, 1H; J = 2.8, 8.8 Hz, ArH), 8.26 (s, 1H; NH), 8.40 (d, 1H; J = 2.8 Hz, ArH), 8.55 (s, 1H; NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 20.8, 20.8, 29.2, 29.2, 41.9, 41.9, 72.7, 112.2, 114.3, 124.1, 128.8, 136.7, 151.2, 160.9; IR (KBr): ύ = 3325, 3195, 2920, 1669, 1617, 1537, 1306 cm^{-1}; MS (ESI): m/z (%) = 276.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C 61.08, H 6.22, N 15.26; found C 61.11, H 6.33, N 15.18.

4d. 7′-Chloro-1′H-spiro[cyclopentane-1,2′-quinazolin]-4′(3′H)-one. Mp 250–251°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.66–1.80 (8H; m, C_4H_8), 6.64 (1H; dd, J = 8.0, 2.0 Hz, ArH), 6.73 (1H; d, J = 2.0 Hz, ArH), 7.04 (1H; s, NH), 7.56 (1H; d, J = 8.0 Hz, ArH), 8.21 (1H; s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 20.9

Table 5

The results of the reaction of *o*-aminonitriles with various aldehydes in DMF.[a,b]

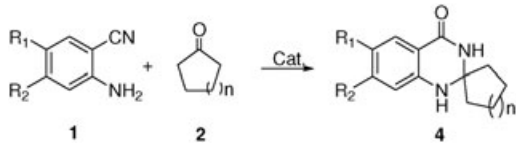


Entries	1	R_3	Time (h)	**9** Yield (%)
a		Ph	1	80
b		(*o*-NO_2) Ph	1	74
c		(*m*-NO_2) Ph	1	80
d		(*p*-NO_2) Ph	1	71
e		(*o*-OH) Ph	1	76
f		(*m*-OCH_3) Ph	1	86
g		(*p*-OCH_3) Ph	1	82
h		(*p*-Cl) Ph	1	80
i		$CH_3CH_2CH_2$	1	75
j		$(CH_3)_2CH$	1	73
k		$CH_3CH_2CH_2CH_2$	1	80
l		Ph	2	75
m		(*m*-NO_2) Ph	2	78
n		(*p*-NO_2) Ph	2	70
o		(*p*-OCH_3) Ph	2	76
p		(*p*-Cl) Ph	2	75
q		$CH_3CH_2CH_2$	2	72
r		Ph	2.5	71
s		(*o*-NO_2) Ph	2.5	69
t		(*m*-NO_2) Ph	2.5	73
u		(*p*-NO_2) Ph	2.5	67
v		(*o*-OH) Ph	2.5	72
w		(*m*-OCH_3) Ph	2.5	78
x		(*p*-OCH_3) Ph	2.5	73
y		(*p*-Cl) Ph	2.5	70
z		$CH_3CH_2CH_2$	2.5	60

[a]All reactions were carried out using **1** (2.5 mmol), **8** (3.0 mmol), $ZnCl_2$ (3.0 mmol), and DMF (3 mL).
[b]Isolated yield.

Table 6

The reaction of aromatic *o*-aminonitriles with cycloketones by bases.[a,b]



Entries	R_1	R_2	*n*	*T* (°C)	Time (h)	**4** Yield (%)
a	NO_2	H	1	60	1.0	62
b	NO_2	H	2	60	1.0	84
c	NO_2	H	3	60	1.0	55
d	H	Cl	1	60	0.5	67
e	H	Cl	2	60	0.2	91
f	H	H	1	r.t.	2	70
g	H	H	2	r.t.	0.2	92
h	H	CH_3	1	reflux	2	35
i	CH_3	H	2	reflux	2	42
j	CH_3O	CH_3O	1	reflux	2	38
k	CH_3O	CH_3O	2	reflux	2	45

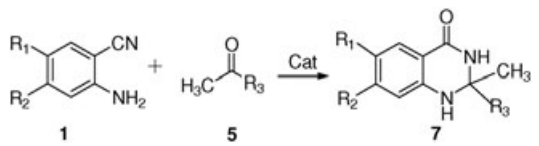
[a]Reaction condition: *o*-aminobenzonitrile (6 mmol), cycloketone(2 mL), catalyst (0.2–0.4 mmol).
[b]Yield of isolated product.
[c]**a-g** catalyzed by KOBu-t, **h-k** catalyzed by $NaOCH_3$.

(2C), 39.0 (2C),72.1, 113.0, 113.2, 116.1, 129.0, 136.9, 147.2, 162.0; IR (KBr): ύ = 3310, 3181, 2942, 1648, 1608, 1481 cm^{-1};MS (ESI): *m/z* (%) = 237.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{12}H_{13}N_2OCl$: C 60.89, H 5.53, N 11.83; found C 60.51, H 5.46, N 11.48.

4f. 1′H-spiro[cyclopentane-1,2′-quinazolin]-4′(3′H)-one. M.p. 268~ 270°C. ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.75–2.08 (8H; m, C_4H_8), 6.07 (1H; s, NH), 6.73 (2H; dd, *J* = 7.8, 8.0 Hz, ArH), 7.19 (1H; s, NH), 7.24–7.26 (1H; m, *J* = 7.2 Hz, ArH), 7.73 (1H; d, *J* = 8.0 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 21.9 (2C),

Table 7

The reaction of aromatic *o*-aminonitriles with aliphatic ketones by base.[a,b,c]



Entries	R_1	R_2	R_3	*T* (°C)	Time (h)	**7** Yield (%)
a	NO_2	H	CH_3	60	5	56
b	NO_2	H	C_2H_5	80	1	43
d	NO_2	H	$(CH_3)_2CHCH_2$	80	2	30
e	NO_2	H	Ph	150	5	17
f	H	Cl	CH_3	60	1.5	48
g	H	Cl	C_2H_5	80	1.5	40
l	H	H	CH_3	60	1	35
m	H	H	C_2H_5	80	1	32
n	H	H	Ph	150	5	20
o	H	CH_3	CH_3	Reflux	3	45
q	H	CH_3	C_2H_5	Reflux	3	47
r	H	CH_3	Ph	Reflux	3	Trace
p	OCH_3	OCH_3	CH_3	Reflux	3	50
s	OCH_3	OCH_3	C_2H_5	Reflux	3	55

[a]Reaction condition: *o*-aminobenzonitrile (6 mmol), ketone(2 mL), and catalyst (1.2–2.4 mmol).
[b]Yield of isolated product.
[c]**a-m** catalyzed by KOBu-*t*, **n-s** catalyzed by $NaOCH_3$.

38.9 (2C), 77.1, 114.3, 114.6, 116.5, 127.2, 133.0, 147.5, 163.4; IR (KBr): ύ = 3292, 3165, 2935, 1639, 1615, 1518, 1485 cm^{-1}; MS (ESI): *m/z* (%) = 203.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{12}H_{14}N_2O$: C 71.26, H 6.98, N 13.85; found C 71.38, H 6.71, N 13.49.

4h. 7′-Methyl-1′H-spiro[cyclopentane-1,2′-quinazolin]-4′(3′H)-one. M.p. 89–90°C; IR (KBr): ύ = 3279, 2948, 1634, 1532, 1488, 1420 cm^{-1}; MS (ESI): *m/z* (%) = 217.1 (100) $[M+H]^+$;Anal. Calcd. for $C_{13}H_{16}N_2O$: C 72.19, H 7.46, N 12.95.

4j. 6′,7′-Dimethoxy-1′H-spiro[cyclopentane-1,2′-quinazolin]-4′(3′H)-one. M.p. 177–179°C; IR (KBr): ύ = 3332, 3165, 2950, 1638, 1618, 1507, 1415 cm^{-1}; MS (ESI): *m/z* (%) = 263.1 (100) [M+H]+; Anal. Calcd. for $C_{14}H_{18}N_2O_3$: C 64.10, H 6.92, N 10.68.

Divergent reaction of o-aminobenzonitriles with linear aliphatic ketones. The appropriate *o*-aminobenzonitrile (6 mmol), linear aliphatic ketone (4 mL), zinc chloride (6 mmol), and DMF (8 mL) were added into a 50-mL flask. The mixture was heated at certain temperature for the specified time (See Table 3). After completion of the reaction as indicated by TLC (eluent: petrolum ether/ethyl acetate 1:1/v:v), the mixture was quenched with water (10 mL) and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the solid was dissolved in acetone, the organic phase obtained was combined with the extracted component of filtrate (using EtOAc) and evaporated *in vacuo*, and silica gel column chromatographed (200–300 mesh silica gel, ethyl acetate: petroleum = 1:3) to afford quinolines **6** and quinazolinone derivatives **7**.

7a. 2,2-Dimethyl-6-nitro-2,3-dihydroquinazolin-4(1H)-one. M.p. 291–293°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.45 (6H; s, CH_3), 6.74 (1H; d, *J* = 8.8 Hz, ArH), 8.09 (1H; dd, *J* = 2.7, 8.8 Hz, ArH), 8.24 (1H; s, NH), 8.41 (1H; d, *J* = 2.7 Hz, ArH), 8.56 (1H; s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 29.7 (2C), 67.6, 111.7, 114.1, 124.2, 128.9, 136.7, 151.3, 160.9; IR (KBr): $\bar{\nu}$= 3322, 3177, 1671, 1618, 1534, 1306, 1149 cm^{-1}; MS (ESI): *m/z* (%) = 222.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C 54.29, H 5.01, N 18.99; found C 54.41, H 5.12, N 18.78.

7b. 2-Ethyl-2-methyl-6-nitro-2,3-dihydroquinazolin-4(1H)-one. M.p. 283–285°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 0.88 (3H; t, *J* = 7.2 Hz, CH_3), 1.43 (3H; s, CH_3), 1.64–1.73 (2H; m, *J* = 7.2 Hz, CH_2), 6.75 (1H; d, *J* = 8.8 Hz, ArH), 8.08 (1H; dd, *J* = 2.7, 8.8 Hz, ArH), 8.17 (1H; s, NH), 8.36 (1H; s, NH), 8.40 (1H; d, *J* = 2.7 Hz, ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 7.9, 28.6, 35.0, 70.3, 111.4, 113.8, 124.1, 128.9, 136.4, 151.8, 161.0; IR (KBr): $\bar{\nu}$ = 3322, 3177, 2919, 1671, 1618, 1534, 1306, 1149 cm^{-1}; MS (ESI): *m/z* (%) = 236.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C 56.16, H 5.57, N 17.86; found C 55.98, H 5.67, N 17.48.

7d. 2-Isobutyl-2-methyl-6-nitro-2,3-dihydroquinazolin-4(1H)-one. M.p. 272–275°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88–0.91 (m, 6H; CH_3), 1.43 (s, 3H; CH_3), 1.53–1.65 (m, 2H; CH_2), 1.78–1.84 (m, 1H; CH), 6.72 (d, *J* = 9.2 Hz,1H; ArH), 8.08 (dd, *J* = 2.7, 9.2 Hz, 1H; ArH), 8.19 (s, 1H; NH), 8.37 (s, 1H; NH), 8.38 (d, *J* = 2.7 Hz, 1H; ArH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 23.4, 24.0, 24.1, 29.9, 50.2, 70.2, 111.1, 113.7, 124.1, 129.0, 136.4, 151.5, 160.7; IR (KBr): $\bar{\nu}$ = 3321, 3191, 3058, 2956, 1673, 1618, 1536, 1503, 1431, 1383, 1150, 1069 cm^{-1}; MS (ESI): *m/z* (%) = 264.2 (100) $[M+H]^+$; Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C 59.30, H 6.51, N 15.96; found C 59.34, H 6.69, N 15.41.

7f. 7-Chloro-2,2-dimethyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 227–229°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.52 (6H; s, CH_3), 6.57 (1H; s, NH), 6.71 (1H; dd, *J* = 2.0, 8.0 Hz, ArH), 6.80 (1H; d, *J* = 2.0 Hz, ArH), 7.70 (1H; d, *J* = 8.0 Hz, ArH), 8.16 (1H; s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 29.5 (2C), 69.7, 111.3, 112.8, 116.2, 129.1, 137.8, 148.3, 162.3; IR (KBr): $\bar{\nu}$ = 3311, 2978, 1627, 1602 cm^{-1}; MS (ESI): *m/z* (%) = 211.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{10}H_{11}N_2OCl$: C 57.01, H 5.26, N 13.30; found C 57.37, H 5.33, N 13.18.

7g. 7-Chloro-2-ethyl-2-methyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 174–176°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 0.86 (3H; t, *J* = 7.2 Hz, CH_3), 1.36 (3H; s, CH_3), 1.57–1.67 (2H; m, *J* = 7.2 Hz, CH_2), 6.60 (1H; dd, *J* = 2.0, 8.0 Hz, ArH), 6.67 (1H; d, *J* = 2.0 Hz, ArH), 6.89 (1H; s, NH), 7.54 (1H; d, *J* = 8.0 Hz, ArH), 8.00 (1H; s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 8.1, 27.6, 34.1, 69.6, 111.3, 112.9, 116.0, 129.1, 137.6, 148.2, 162.2; IR (KBr): $\bar{\nu}$ = 3297, 3188, 2971, 1640, 1606 cm^{-1}; MS (ESI): *m/z* (%) = 225.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_{13}N_2OCl$: C 58.80, H 5.83, N 12.47; found C 59.12, H 5.99, N 12.28.

7l. 2,2-Dimethyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 190–191°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.38 (6H; s, CH_3), 6.59 (1H; d, *J* = 7.6 Hz, ArH), 6.62 (1H; s, NH), 6.64 (1H; d, *J* = 1.6 Hz, ArH), 7.20–7.23 (1H; m, *J* = 1.6, 1.2, 7.6 Hz, ArH), 7.57 (1H; dd, *J* = 1.2, 7.6 Hz, ArH), 7.87 (1H; s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 28.9 (2C), 66.7, 113.8, 114.1, 116.3, 127.1, 133.1, 147.0, 162.9; IR (KBr): $\bar{\nu}$ = 3332, 3169, 3029, 1643, 1610 cm^{-1}; MS (ESI): *m/z* (%) = 177.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{10}H_{12}N_2O$: C 68.16, H 6.86, N 15.90; found C 68.50, H 6.98, N 15.74.

7o. 2,2,7-Trimethyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 266–267°C; ^{1}H NMR (300 MHz, $CDCl_3$-d_3) δ_H: 1.54 (6H; s, $2CH_3$), 2.29 (3H; s, CH_3), 5.89 (1H; s, NH), 6.43 (1H; s, ArH), 6.64–6.66 (1H; d, ArH), 7.26 (1H; s, ArH), 7.75 (1H; s, NH); ^{13}C NMR (75 MHz, $CDCl_3$-d_3) δ_C: 21.7, 29.7, 30.9(2C), 67.7, 112.2, 114.9, 120.2, 128.4, 144.8, 145.8,164.2; IR (KBr): $\bar{\nu}$ = 3300, 3167, 3036, 2972, 1642, 1522, 1487, 1386 cm^{-1}; MS (ESI): *m/z* (%) = 191.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_{14}N_2O$: C 69.45, H 7.48, N 14.54; found C 69.45, H 7.42, N 14.73.

7p. 6,7-Dimethoxy-2,2-dimethyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 203–204°C. IR (KBr): $\bar{\nu}$ = 3265, 2976, 2840, 1735, 1618, 1507, 1384 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$-d_3) δ_H: 1.542 (6H, s, CH_3), 3.48–3.86(6H, s, OCH_3), 6.17 (1H, s, NH), 6.39 (1H, s, ArH), 7.28 (1H, s, ArH), 7.37 (1H, s, NH); ^{13}C NMR (75 MHz, $CDCl_3$-d_3) δ_C: 29.2(2C), 55.9, 56.2(2C), 67.7, 98.42, 106.8, 109.7, 141.3, 142.8, 154.2, 164.4; MS (ESI): *m/z* (%) = 237.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C 59.99, H 7.23, N 10.03; found C 61.00, H 6.83, N 11.86.

General procedure for controlled synthesis of quinolinones. ***Reaction of o-aminobenzonitriles with aldehydes by the catalyst of zinc chloride.*** The appropriate *o*-aminobenzonitrile (2.5 mmol), phenylaldehyde (3.0 mmol), and zinc chloride (3.0 mmol) and DMF (3 mL) were added into a 50-mL flask. The mixture was heated at reflux for the specified time (See Table 5, Schemes 5, 6, and 7). After completion of the reaction as indicated by TLC (eluent: petrolum ether/ethyl acetate 1:1), the cooled reaction mixture was quenched with water (10 mL) and titrated to pH 12–13 by 20% sodium hydroxide. After filtration, the solid was

dissolved in acetone; the organic phase obtained was combined with the extracted component of filtrate (using EtOAc) and evaporated *in vacuo*, and chromatographed (200–300 mesh silica gel, ethyl acetate:petroleum = 1:3) to afford product **9**.

9b. 6-Nitro-2-(2-nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one. M.p. 278–279°C; ^{1}H NMR (DMSO-d_6) δ_H: 6.59 (1H; s, ArCH), 8.46–6.87 (7H; m, ArH), 8.47 (1H; s, NH), 8.62 (1H; s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 62.24, 112.05, 114.57, 124.06, 124.78, 128.84, 129.03, 130.33, 134.42, 135.23, 137.40, 147.28, 151.60, 161.01; IR (KBr): $\bar{\nu}$ = 3381, 3183, 1688, 1617, 1532, 1329 cm^{-1}; MS (ESI): *m/z* (%) =315.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{14}H_{10}N_4O_5$: C 53.51, H 3.21, N 17.82; found C 53.69, H 3.30, N 17.62.

9f. 2-(3-Methoxyphenyl)-6-nitro-2,3-dihydroquinazolin-4(1H)-one. M.p. 208–210°C; ^{1}H NMR (DMSO-d_6) δ_H: 3.76 (3H; s, CH_3), 5.99 (1H; s, CH), 6.85 (1H; d, *J* = 8.0 Hz, ArH), 6.94–6.97 (1H; m, ArH), 7.03 (2H; t, *J* = 1.6, 1.6 Hz, ArH), 7.34 (1H; t, *J* = 8.0, 8.0 Hz, ArH), 8.11 (1H; dd, *J* = 2.8, 8.0 Hz, ArH), 8.43 (1H; d, *J* = 2.8 Hz, ArH), 8.59 (1H; s, NH), 8.78 (1H; s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 55.13, 66.01, 112.30, 112.66, 114.05, 114.23, 118.47, 124.13, 128.93, 129.80, 137.11, 142.65, 152.08, 159.36, 161.29; IR (KBr): $\bar{\nu}$ = 3457, 3190, 1653, 1615, 1490, 1323 cm^{-1}; MS (ESI): *m/z* (%) = 300.4 (100) $[M+H]^+$; Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C 60.10, H 4.38, N 14.04; found C 59.80, H 4.42, N 13.78.

9i. 6-Nitro-2-propyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 235–237°C; ^{1}H NMR (DMSO-d_6) δ_H: 0.90 (3H; t, *J* = 7.2 Hz, CH_3), 1.38–1.42 (2H; m, CH_2), 1.61–1.67 (2H; m, CH_2), 4.94 (1H; t, *J* = 5.0 Hz, CH), 6.80 (1H; d, *J* = 8.8 Hz, ArH), 8.08 (1H; dd, *J* = 2.7, 8.8 Hz, ArH), 8.13 (1H; s, NH), 8.36 (1H; s, NH), 8.39 (1H; d, *J* = 2.7 Hz, ArH); ^{13}C NMR (DMSO-d_6) δ_C: 13.66, 16.21, 38.18, 63.94, 112.64, 114.12, 124.19, 128.76, 136.76, 152.76, 161.57; IR (KBr): $\bar{\nu}$ = 3362, 3190, 2927, 1689, 1623, 1515, 1450, 1324, 1302 cm^{-1}; MS (ESI): *m/z* (%) = 236.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C 56.16, H 5.57, N 17.86; found C 56.19, H 5.48, N 17.46.

9m. 7-Chloro-2-(3-nitrophenyl)-2,3-dihydroquinazolin-4(1H)- one. M.p. 258–260°C; ^{1}H NMR (DMSO-d_6) δ_H: 6.02 (1H; s, CH), 6.72 (1H; dd, *J* = 1.8, 8.0 Hz, ArH), 6.83 (1H; d, *J* = 1.8 Hz, ArH), 7.61 (2H; t, *J* = 4.0, 4.0 Hz, ArH), 7.72 (1H; t, *J* = 7.8, 7.8 Hz, ArH), 7.93 (1H; d, *J* = 8.0 Hz, ArH), 8.21–8.23 (1H; m, *J* = 1.6, 1.6 Hz, ArH), 8.35 (1H; s, NH), 8.66 (1H; s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 65.09, 113.58, 113.63, 117.47, 121.48, 123.40, 129.42, 130.17, 133.18, 138.05, 143.94, 147.75, 148.22, 162.46; IR (KBr): $\bar{\nu}$ = 3301, 3166, 1665, 1609, 1523, 1345 cm^{-1}; MS (ESI): *m/z* (%) = 304.0 (100) $[M+H]^+$; Anal. Calcd. for $C_{14}H_{10}N_3O_3Cl$: C 55.37, H 3.32, N 13.84; found C 55.76, H 3.35, N 13.75.

9p. 7-Chloro-2-(4-chlorophenyl)-2,3-dihydroquinazolin-4(1H)- one. M.p. 242–244°C; ^{1}H NMR (DMSO-d_6) δ_H: 5.85 (1H; s, CH), 6.70 (1H; dd, *J* = 2.0, 8.4 Hz, ArH), 6.80 (1H; d, *J* = 2.0 Hz, ArH), 7.43 (1H; s, NH), 7.47–7.52 (4H; m, *J* = 2.4 Hz, ArH), 7.61 (1H; d, *J* = 8.4 Hz, ArH), 8.48 (1H; s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 65.69, 113.51, 113.59, 117.20, 128.42 (2C), 128.65 (2C), 129.36, 133.15, 137.93, 140.34, 148.56, 162.61; IR (KBr): $\bar{\nu}$ = 3251, 3166, 1649, 1609, 1484 cm^{-1}; MS (ESI): *m/z* (%) = 294.0 (100) $[M+H]^+$; Anal. Calcd. for $C_{14}H_{10}N_2OCl_2$: C 57.36, H 3.44, N 9.56; found C 57.51, H 3.47, N 9.66.

9q. 7-Chloro-2-propyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 222–223°C; ^{1}H NMR (DMSO-d_6) δ_H: 0.93 (3H; t, *J* = 7.2 Hz, CH_3), 1.71–1.77 (2H; m, CH_2), 2.56–2.59 (2H; m, CH_2), 5.38 (1H; t, *J* = 5.0 Hz, CH), 7.48 (1H; dd, *J* = 2.0, 8.4 Hz, ArH), 7.64 (1H; d, *J* = 2.0 Hz, ArH), 8.06 (1H; d, *J* = 8.4 Hz, ArH), 8.19 (1H; s, NH), 8.38 (1H; s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 13.40, 20.08, 36.31, 65.21, 125.89, 126.14, 127.73, 138.83, 150.02, 159.00, 161.14; IR (KBr): $\bar{\nu}$ = 3285, 3180, 2920, 1674, 1602 1447 cm^{-1}; MS (ESI): *m/z* (%) = 225.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_{13}N_2OCl$: C 58.80, H 5.83, N 12.47; found C 59.20, H 5.48, N 12.21.

9s. 2-(2-Nitrophenyl)-2,3-dihydroquinazolin-4(1H)-one. M.p. 203–205°C; ^{1}H NMR (DMSO-d_6) δ_H: 6.49 (1H; s, ArCH), 8.32–6.75 (8H; m, ArH), 8.40 (1H; s, NH), 8.58 (1H; s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 62.18, 112.00, 114.23, 124.01, 124.59, 128.68, 128.96, 130.17, 134.38, 135.19, 137.35, 147.09, 151.49, 160.97; IR (KBr): $\bar{\nu}$ = 3378, 3176, 1679, 1610, 1530, 1321 cm^{-1}; MS (ESI): *m/z* (%) = 270.2 (100) $[M+H]^+$; Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C 62.45, H 4.12, N 15.61; found C 62.09, H 4.57, N 15.53.

9z. 2-Propyl-2,3-dihydroquinazolin-4(1H)-one. M.p. 213–215°C; ^{1}H NMR (DMSO-d_6) δ_H: 0.81 (3H; t, *J* = 7.2 Hz, CH_3), 1.05–1.11 (2H; m, CH_2), 1.30–1.37 (2H; m, CH_2), 4.24 (1H; t, *J* = 5.0 Hz, CH), 6.21 (1H; d, *J* = 1.6 Hz, ArH), 6.42 (1H; s, NH), 6.51 (1H; d, *J* = 1.6 Hz, ArH), 7.00–7.02 (1H; m, *J* = 1.6, 1.2, 7.6 Hz, ArH), 7.37 (1H; dd, *J* = 1.2, 7.6 Hz, ArH), 7.57 (1H; s, NH); ^{13}C NMR (DMSO-d_6) δ_C: 13.21, 18.21, 34.18, 66.45, 113.69, 114.19, 116.35, 127.16, 133.01, 146.89, 162.72; MS (ESI): IR (KBr): $\bar{\nu}$ = 3382, 3185, 2927, 1645, 1608, 1430 cm^{-1}; *m/z* (%) = 191.1 (100) $[M+H]^+$; Anal. Calcd. for $C_{11}H_{14}N_2O$: C 69.44, H 7.42, N 14.73; found C 69.30, H 7.25, N 14.92.

Reaction of o-aminobenzonitriles with ketones in the catalyst of base. *o*-Aminobenzonitrile, ketones and base were added into a 50-mL flask. The mixture was heated at certain temperature for the specified time (see Table 6 and 7). After completion of the reaction as indicated by TLC (eluent: petrolum ether/ethyl acetate 1:1), the cooled reaction mixture was quenched with water (10 mL), and the precipitate was separated by filtration, then the residue was used appropriate solvent for recrystallization, which can get the product.

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