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Thiocyanation of α-amino carbonyl compounds for the synthesis of aromatic thiocyanates

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Abstract

A procedure for $K_2S_2O_8$-mediated thiocyanation of α-amino carbonyl compounds has been developed for the synthesis of aromatic thiocyanates. A series of α-amino carbonyl compounds have been investigated, and the desired products are obtained in 74%–93% yields. This strategy has the advantages of simple reaction conditions without use of a transition-metal catalyst, high regioselectivity, and high efficiency. Moreover, we found that arylamine thiocyanates can also be obtained from α-amino carbonyl compounds and potassium thiocyanate in the presence of $CoCl_2 \cdot 6H_2O$, I_2, and dimethyl sulfoxide through the cleavage of the C–N bond. To explore the reaction mechanism, we designed several control experiments and proposed a possible mechanism using the experimental results and related literature reports.

Keywords

α-amino carbonyl compounds, aromatic thiocyanates, thiocyanation reaction

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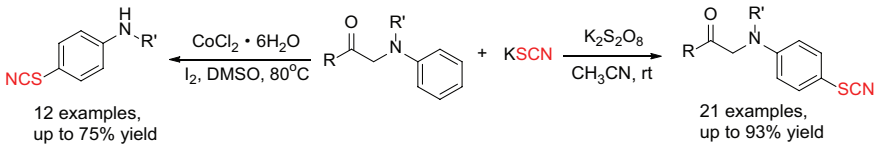

Introduction

As an important structural unit, the α-amino carbonyl fragment exists in numerous natural products and pharmaceutical compounds,[1–7] and it is a versatile precursor for the synthesis of various heterocyclic compounds.[8–14] Glycine, the simplest α-amino carbonyl compound, is one of the essential amino acids in the human body. Besides, amoxicillin and clopidogrel demonstrate the application of α-amino carbonyl compounds in medicine and provide resistance to some diseases. α-Amino carbonyl compounds are involved in many reactions, the most important among which are the reactions with nucleophiles, which include alcohols,[15] thiols,[15] amines,[16,17] phosphites,[18,19] nitromethane,[20] ketones,[21] 1,3-dicarbonyl compounds,[22–24] (hetero) arenes,[25–31] and others.

To the best of our knowledge, there are no reports on the thiocyanation of α-amino carbonyl compounds. Organic thiocyanates are well known in the area of organosulfur chemistry and have become a hot research field in organic synthetic chemistry, since they are not only the substructures or building blocks of bioactive natural products[32–35] but also versatile synthetic precursors for the synthesis of sulfur-containing compounds such as thiols,[36,37] thioethers,[38,39] and disulfides.[40,41] Therefore, it is worthwhile to develop a simple and efficient method to achieve the thiocyanation of α-amino carbonyl compounds for the synthesis of organic thiocyanates.

As a continuation of our research on α-functionalized carbonyl compounds,[17,20,42–48] herein, we describe a straightforward synthesis of aromatic thiocyanates through $K_2S_2O_8$-mediated thiocyanation of α-amino carbonyl compounds using KSCN as the thiocyanation reagent (Scheme 1A). Moreover, we can prepare arylamine thiocyanates from α-amino carbonyl compounds and KSCN in the presence of

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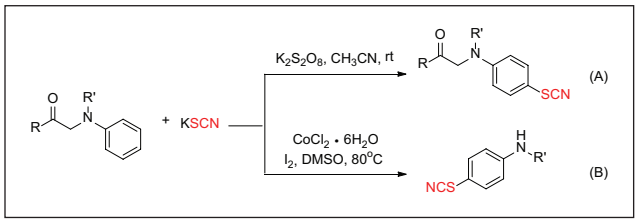
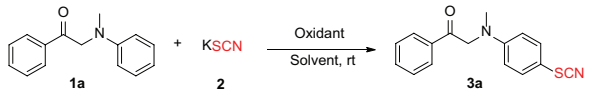


Scheme 1. Thiocyanation of α-amino carbonyl compounds.

Table 1. Optimization of reaction conditions.[a]



Entry	[SCN] (equiv.)	Oxidant (equiv.)	Solvent	Yield (%)[b]
1	KSCN (3)	$PhI(OAc)_2$ (3)	CH_3CN	28
2	KSCN (3)	DTBP (3)	CH_3CN	Trace
3	KSCN (3)	TBHP (3)	CH_3CN	12
4	KSCN (3)	DDQ (3)	CH_3CN	73
5	KSCN (3)	$K_2S_2O_8$ (3)	CH_3CN	87
6	KSCN (3)	O_2 (balloon)	CH_3CN	0
7	KSCN (3)	$K_2S_2O_8$ (3)	DMF	54
8	KSCN (3)	$K_2S_2O_8$ (3)	DMSO	31
9	KSCN (3)	$K_2S_2O_8$ (3)	$CHCl_3$	80
10	KSCN (3)	$K_2S_2O_8$ (3)	EtOH	9
11	KSCN (3)	$K_2S_2O_8$ (3)	Dioxane	45
12	KSCN (3)	$K_2S_2O_8$ (3)	Toluene	82
13	KSCN (3)	$K_2S_2O_8$ (1)	CH_3CN	54
14	KSCN (3)	$K_2S_2O_8$ (2)	CH_3CN	81
15	KSCN (3)	$K_2S_2O_8$ (4)	CH_3CN	87
16	KSCN (1)	$K_2S_2O_8$ (3)	CH_3CN	51
17	KSCN (2)	$K_2S_2O_8$ (3)	CH_3CN	70
18	**KSCN (4)**	**$K_2S_2O_8$ (3)**	**CH_3CN**	**93**
19	NH_4SCN (4)	$K_2S_2O_8$ (3)	CH_3CN	76
20[c]	KSCN (4)	$K_2S_2O_8$ (3)	CH_3CN	85
21[d]	KSCN (4)	$K_2S_2O_8$ (3)	CH_3CN	71

[a]Reaction conditions: **1a** (0.2 mmol), KSCN, oxidant, and solvent (2 mL) in a sealed tube at room temperature for 16 h.
[b]Isolated yields based on **1a**.
[c]At 50 °C.
[d]At 80 °C.
Bold figure represents the best conditions.

$CoCl_2{\cdot}6H_2O$, I_2, and dimethyl sulfoxide (DMSO) through the cleavage of the C–N bond (Scheme 1B). The α-amino carbonyl compounds can be easily fabricated from ketones and amines[49,50] and are used as raw materials for the synthesis of a wide range of compounds.[51]

Results and discussion

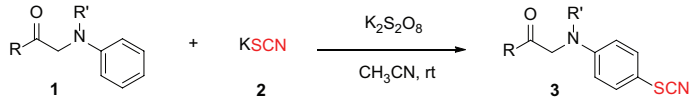
We began the investigation using 2-(methyl(phenyl)amino)-1-phenylethan-1-one (**1a**) and KSCN (**2**) as model substrates (Table 1). The desired product **3a** was obtained in 28% yield using $PhI(OAc)_2$ (3 equiv.) and CH_3CN (2 mL) in a sealed tube at room temperature for 16 h (entry 1). This result greatly encouraged us to further explore the reaction. First, we investigated different oxidants for the reaction, including DTBP (di-*tert*-butylperoxide), TBHP (*tert*-butyl hydroperoxide, 70% in water), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), $K_2S_2O_8$, and O_2. The oxidant $K_2S_2O_8$ was the best, giving the product in 87% yield (entries 2–6). Solvents often have a large effect on reactions, so we screened the effect of different solvents on the reaction. Common solvents such as DMF (*N,N*-dimethylformamide), DMSO, $CHCl_3$, EtOH, 1,4-dioxane, and toluene were selected for this reaction. Among them, the reaction using $CHCl_3$ or toluene was better, but it was still inferior to the use of acetonitrile (entries 7–12). Next, we explored the effect of the amount of $K_2S_2O_8$ on the reaction. As the amount of $K_2S_2O_8$ increased, the corresponding yield also increased, and the yield reached a maximum when $K_2S_2O_8$ (3 equiv.) was used (entries 13–15). Besides, when the amount of KSCN was increased from 1 equiv. to 4 equiv., the corresponding yield was also increased, up to 93% (entries 16–18). When NH_4SCN was selected as the SCN reagent, the yield of **3a** was reduced to 76% (entry 19). The temperature had a great effect on the reaction, and as the temperature increased, the yield decreased, mainly due to the formation of by-products (entries 20 and 21). Therefore, the optimal conditions for the reaction are **1a** (1 equiv.), **2** (4 equiv.), $K_2S_2O_8$ (3 equiv.), and CH_3CN (2 mL) in a sealed tube at room temperature for 16 h (entry 18).

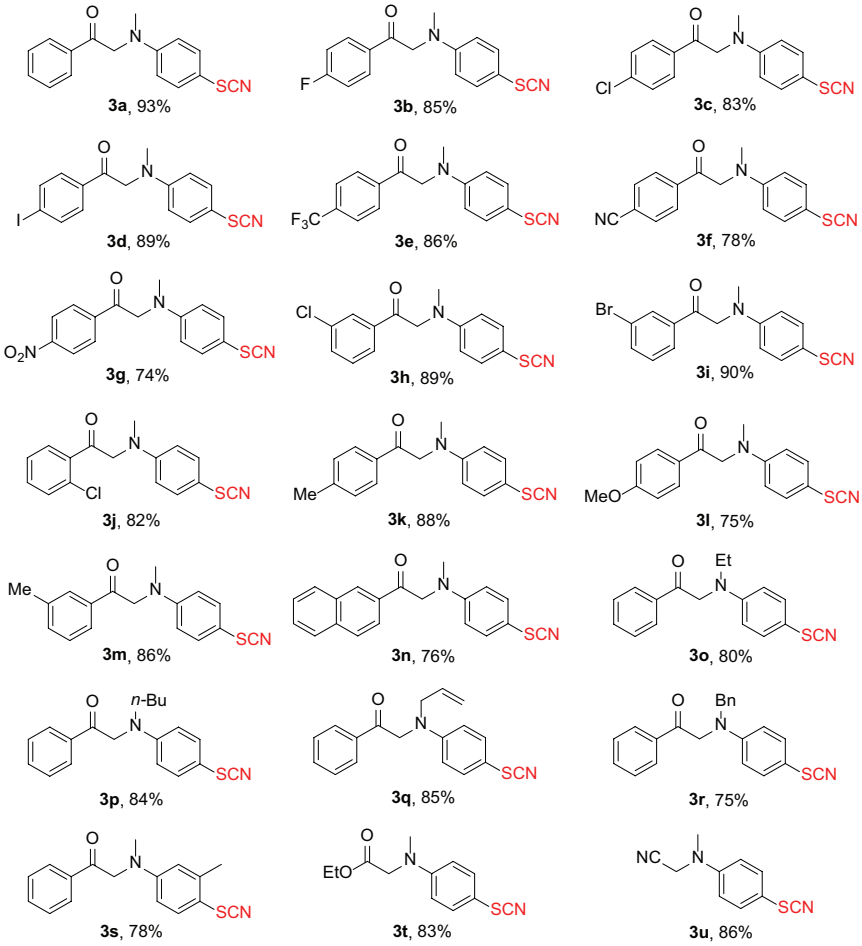
With the optimal conditions in hand, we then investigated the substrate scope of the transformation (Table 2). First, we screened the substituents on the aromatic ring of the 1-arylethanone moiety. For the substrates bearing electron-withdrawing substituents on the aromatic ring, including F–, Cl–, I–, CF3–, CN–, and NO_2– at the *p*-position, the protocol was applicable, and the corresponding products were obtained in moderate to good yields (**3b**–**3g**). In the cases of substrates having electron-withdrawing substituents at the *m*- or *o*-position, the desired products were also obtained in good yields (**3h**–**3j**). By comparing the yields of **3c**, **3h**, and **3j**, it was deduced that steric effects have little effect on the reaction. For the substrates bearing electron-donating substituents such as methyl (**1k** and **1m**) and methoxy (**1l**), these substituents were also tolerated under the reaction conditions.

Moreover, we explored the reactivity of α-amino carbonyl compounds having substituents on the nitrogen atom. The reaction can proceed smoothly when other alkyl groups are attached to the nitrogen atom, such as ethyl, *n*-butyl, allyl, and benzyl (**3o**–**3r**). It is worth noting that the carbon–carbon double bond of allyl is not affected during the reaction (**3q**). For the substrate having an aromatic group at the nitrogen atom (**3s**), the method was successful and the corresponding product was obtained in moderate yield. Unfortunately, 1-phenyl-2-(phenylamino)ethan-1-one was not applicable to the reaction. When ethyl *N*-methyl-*N*-phenylglycinate (**1t**) and 2-(methyl(phenyl)amino) acetonitrile (**1u**) were chosen as the substrates, the corresponding products **3t** and **3u** were obtained in good yields, which further increased the scope of the reaction.

Furthermore, we found that arylamine thiocyanates can also be obtained from α-amino carbonyl compounds and KSCN. After screening, the catalyst system $CoCl_2{\cdot}6H_2O$ (10 mol%)/I_2 (2 equiv.)/DMSO was shown to be the best

Table 2. Substrate scope for the reaction.[a,b].





[a]Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $K_2S_2O_8$ (0.6 mmol), and CH_3CN (2 mL) in a sealed tube at room temperature for 16 h.
[b]Isolated yields based on **1**.

combination. Then, we investigated the substrate scope of this transformation (Table 3). For the carbonyl moiety, regardless of whether an electron-donating or electron-withdrawing group was attached to the benzene ring, the product **4a** was obtained in moderate yields. For the amino moiety, when a substituent is attached to the *ortho* or *meta* position of the benzene ring, the target product can also be obtained in a moderate yield (**4b**–**e**). Unfortunately, as the alkyl chain on the nitrogen atom increases, the reaction efficiency decreases. When 2-(*n*-butyl(phenyl)amino)-1-phenylethan-1-one was used as the substrate, the target product **4g** was only obtained in a low yield.

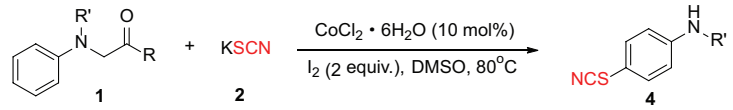
To explore the reaction mechanism, several control experiments were carried out (Scheme 2). When the radical inhibitor TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction under the optimal conditions, the product **3a** was obtained in 84% yield (Scheme 2A). When the radical inhibitor BHT (2,6-di-*tert*-butyl-4-methylphenol) was added, the yield of **3a** was almost unaffected (Scheme 2B). These two results indicate that the reaction might not be a radical process and may involve an ionic pathway. Moreover, when compound **5** was chosen as the substrate instead of **1a**, none of the products **3a** or **6** were detected (Scheme 2C). When **3a** was chosen as the substrate in the presence of $CoCl_2 \cdot 6H_2O$, I_2, and DMSO, product **4a** was obtained in 67% yield and benzoylformic acid was detected by gas chromatography–mass spectrometry (GC-MS; Scheme 2D).

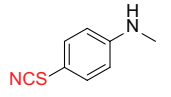
Based on these experimental results and previous repo rts,[52–60] a possible mechanism for the thiocyanation of α-amino carbonyl compounds is proposed (Scheme 3). Initially, $^+$SCN is formed from the KSCN by the oxidant and adds to the substrate **1a** to afford intermediate **I**. The intermediate **I** is unstable and converts into the product **3a** by losing a hydrogen ion. The product **4a** was obtained from **3a** under the conditions of cobalt catalyst, I_2, and DMSO.

Conclusion

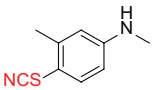
In conclusion, we have demonstrated a novel procedure for the synthesis of aromatic thiocyanates through $K_2S_2O_8$-mediated thiocyanation of α-amino carbonyl compounds.

Table 3. Substrate scope for the synthesis of arylamine thiocyanates.[a,b].

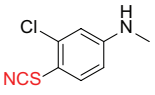




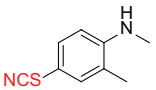
4a: R = Ph, 76%
4a: R = 4-MeC$_6$H$_4$, 75%
4a: R = 4-ClC$_6$H$_4$, 72%
4a: R = 4-CF$_3$C$_6$H$_4$, 65%
4a: R = 3-BrC$_6$H$_4$, 68%
4a: R = 2-MeC$_6$H$_4$, 72%
4a: R = OEt, 67%



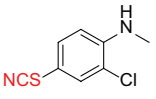
4b,70%



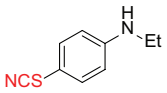
4c, 67%



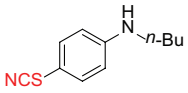
4d, 68%



4e, 53%

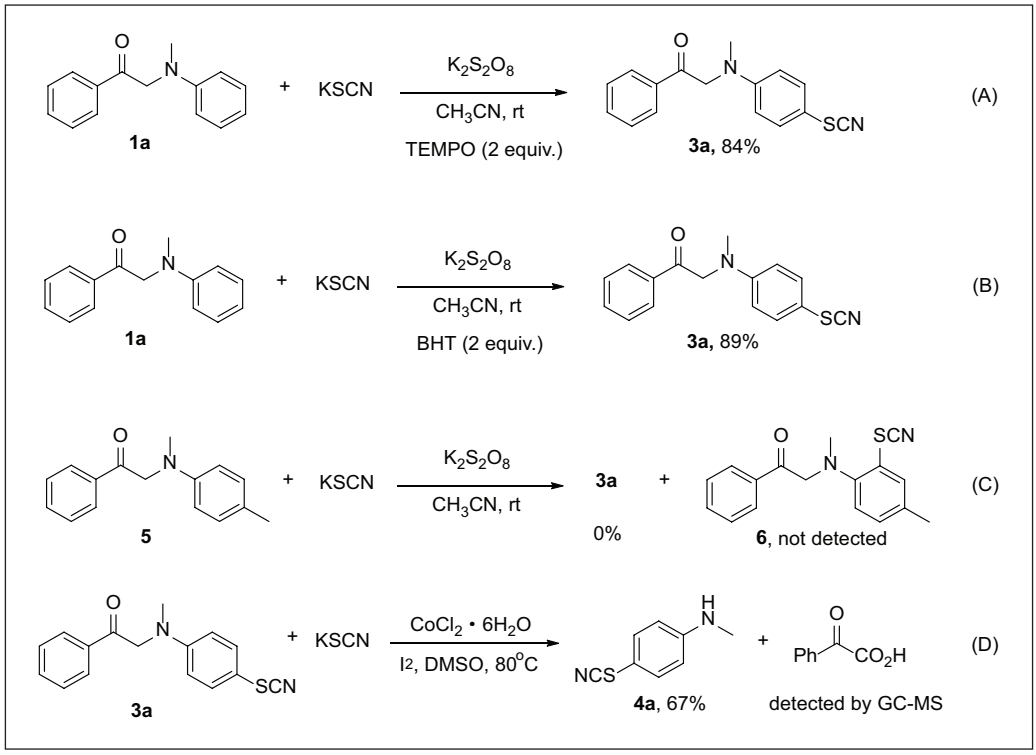


4f, 36%



4g, trace

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.3 mmol), $CoCl_2 \cdot 6H_2O$ (10 mol%), I_2 (0.6 mmol), and DMSO (2 mL) in a sealed tube at 80 °C for 16 h.
[b]Isolated yields based on **1**.



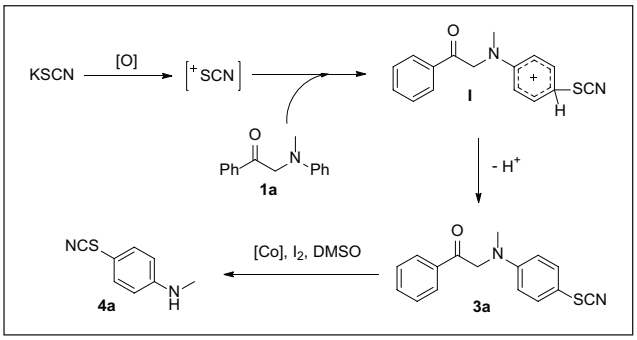
Scheme 2. Control experiments.

This strategy has the advantages of simple reaction conditions without the use of a transition-metal catalyst, high regioselectivity, and high efficiency. Moreover, arylamine thiocyanates can also be obtained from α-amino carbonyl compounds and potassium thiocyanate in the presence of cobalt catalyst, I_2, and DMSO through the cleavage of the C–N bond. These reactions expand further the use of α-amino carbonyl compounds in organic synthesis. Studies to gain insights into the reaction mechanism and application of the protocol for the synthesis of bioactive molecules are currently underway.

Experimental section

General information

Commercially available reagents were purchased from commercial suppliers and used without further purification.



Scheme 3. Possible mechanism.

Reactions were monitored by thin-layer chromatography (TLC). Flash column chromatography was performed over silica gel (200–300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR plus spectrometer using residue solvent peaks as internal standards. High-resolution mass spectra were obtained using a GCT time of flight (TOF) instrument with the electron ionization (EI) source. Melting points are uncorrected.

General procedure for the synthesis of product 3

To a sealed tube were added α-amino carbonyl compound **1** (0.2 mmol), KSCN (0.8 mmol), $K_2S_2O_8$ (0.6 mmol), and CH_3CN (2 mL). Then, the tube was stirred at room temperature for 16 h. After completion of the reaction, the resulting mixture was concentrated in vacuo and purified by column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the desired product **3**.

2-(Methyl(4-thiocyanatophenyl)amino)-1-phenylethan-1-one (**3a**): White solid, 93% yield (52 mg), m.p.= 145–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J*=5.6 Hz, 2H), 7.62–7.66 (m, 1H), 7.50–7.53 (m, 2H), 7.39 (d, *J*= 7.2 Hz, 2H), 6.63 (d, *J*=7.2 Hz, 2H), 4.83 (s, 2H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 150.7, 134.9, 134.4, 133.9, 128.9, 127.7, 113.2, 112.3, 107.7, 58.4, 39.7; high resolution mass spectrometry (HRMS) (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{14}N_2OS$: 282.0822, found: 282.0824.

1-(4-Fluorophenyl)-2-(methyl(4-thiocyanatophenyl) amino)ethan-1-one (**3b**): White solid, 85% yield (51 mg), m.p.=160–162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–8.02 (m, 2H), 7.38 (d, *J*=7.6 Hz, 2H), 7.16–7.20 (m, 2H), 6.62 (d, *J*=6.8 Hz, 2H), 4.79 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 166.0 (d, *J*=203.7 Hz), 150.7, 134.3, 131.3 (d, *J*=2.9 Hz), 130.4 (d, *J*=7.2 Hz), 116.1 (d, *J*=17.3 Hz), 113.2, 112.3, 107.7, 58.3, 39.6; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}FN_2OS$: 300.0728, found: 300.0723.

1-(4-Chlorophenyl)-2-(methyl(4-thiocyanatophenyl) amino)ethan-1-one (**3c**): White solid, 83% yield (52 mg), m.p.=156–157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J*=7.2 Hz, 2H), 7.49 (d, *J*=7.2 Hz, 2H), 7.39 (d, *J*=6.8 Hz, 2H), 6.62 (d, *J*=7.2 Hz, 2H), 4.78 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 150.6, 140.4, 134.4, 133.2, 129.3, 129.1, 113.2, 112.3, 107.9, 58.4, 39.7; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}ClN_2OS$: 316.0432, found: 316.0436.

1-(4-Iodophenyl)-2-(methyl(4-thiocyanatophenyl) amino)ethan-1-one (**3d**): White solid, 89% yield (72 mg), m.p.=163–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J*= 6.8 Hz, 2H), 7.67 (d, *J*=6.4 Hz, 2H), 7.38 (d, *J*=7.2 Hz, 2H), 6.61 (d, *J*=6.8 Hz, 2H), 4.76 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 150.6, 138.2, 134.4, 134.1, 129.0, 113.2, 112.3, 107.9, 102.0, 58.3, 39.6; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}IN_2OS$:407.9788, found: 407.9789.

2-(Methyl(4-thiocyanatophenyl)amino)-1-(4-(trifluoromethyl)phenyl)ethan-1-one (**3e**): Light yellow solid, 86% yield (60 mg), m.p.=143–144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J*=6.0 Hz, 2H), 7.79 (d, *J*=6.4 Hz, 2H), 7.40 (d, *J*=7.2 Hz, 2H), 6.63 (d, *J*=7.2 Hz, 2H), 4.84 (s, 2H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 150.5, 137.5, 135.1 (q, *J* = 26.0 Hz), 134.4, 128.1, 126.0 (q, *J*=2.9 Hz), 123.4 (q, *J*=216.6 Hz), 113.3, 112.2, 108.2, 58.7, 39.7; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{13}F_3N_2OS$: 350.0696, found: 350.0691.

4-(*N*-Methyl-*N*-(4-thiocyanatophenyl)glycyl)benzonitrile (**3f**): Yellow solid, 78% yield (48 mg), m.p.=151–152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J*=6.8 Hz, 2H), 7.82 (d, *J*=6.4 Hz, 2H), 7.40 (d, *J*=7.2 Hz, 2H), 6.62 (d, *J*=7.6 Hz, 2H), 4.82 (s, 2H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 150.4, 137.7, 134.4, 132.8, 128.2, 117.6, 117.1, 113.3, 112.2, 108.4, 58.8, 39.7; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{13}N_3OS$: 307.0772, found: 307.0766.

2-(Methyl(4-thiocyanatophenyl)amino)-1-(4-nitrophenyl)ethan-1-one (**3g**): Yellow solid, 74% yield (48 mg), m.p.=162–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J*=6.8 Hz, 2H), 8.12 (d, *J*=7.2 Hz, 2H), 7.40 (d, *J*=7.2 Hz, 2H), 6.63 (d, *J*=7.2 Hz, 2H), 4.85 (s, 2H), 3.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 150.6, 150.4, 139.2, 134.4, 128.9, 124.1, 113.3, 112.2, 108.4, 58.9, 39.7; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}N_3O_3S$: 327.0673, found: 327.0670.

1-(3-Chlorophenyl)-2-(methyl(4-thiocyanatophenyl) amino)ethan-1-one (**3h**): White solid, 89% yield (56 mg), m.p.=127–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, *J*=1.2 Hz, 1H), 7.85–7.83 (m, 1H), 7.61–7.59 (m, 1H), 7.46 (t, *J*=6.4 Hz, 1H), 7.38 (d, *J*=7.2 Hz, 2H), 6.61 (d, *J*=7.6 Hz, 2H), 4.79 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 150.5, 136.3, 135.2, 134.3, 133.8, 130.2, 127.8, 125.7, 113.2, 112.3, 107.9, 58.5, 39.6; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}ClN_2OS$: 316.0432, found: 316.0433.

1-(3-Bromophenyl)-2-(methyl(4-thiocyanatophenyl) amino)ethan-1-one (**3i**): White solid, 90% yield (65 mg), m.p.=138–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (t, *J*=1.2 Hz, 1H), 7.88–7.89 (m, 1H), 7.74–7.76 (m, 1H), 7.37–7.41 (m, 3H), 6.61 (d, *J*=7.6 Hz, 2H), 4.78 (s, 2H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 150.5, 136.7, 136.5, 134.3, 130.8, 130.5, 126.2, 123.2, 113.2, 112.3, 107.9, 58.5, 39.6; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}BrN_2OS$: 359.9927, found: 359.9921.

1-(2-Chlorophenyl)-2-(methyl(4-thiocyanatophenyl) amino)ethan-1-one (**3j**): White solid, 82% yield (52 mg), m.p.=108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.47 (m, 3H), 7.40 (d, *J*=7.2 Hz, 2H), 7.33–7.37 (m, 1H),

6.65 (d, J=7.6 Hz, 2H), 4.72 (s, 2H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 150.4, 137.2, 134.3, 132.5, 130.9, 130.5, 129.1, 127.2, 113.2, 112.3, 107.9, 61.9, 39.6; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{16}H_{13}ClN_2OS$: 316.0432, found: 316.0430.

2-(Methyl(4-thiocyanatophenyl)amino)-1-(p-tolyl) ethan-1-one (**3k**): White solid, 88% yield (52 mg), m.p. = 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J=6.4 Hz, 2H), 7.37 (d, J=7.2 Hz, 2H), 7.31 (d, J=6.4 Hz, 2H), 6.62 (d, J=7.2 Hz, 2H), 4.79 (s, 2H), 3.11 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 150.8, 144.8, 134.3, 132.4, 129.5, 127.8, 113.1, 112.3, 107.3, 58.2, 39.6, 21.6; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{16}N_2OS$: 296.0978, found: 296.0975.

1-(4-Methoxyphenyl)-2-(methyl(4-thiocyanatophenyl) amino)ethan-1-one (**3l**): White solid, 75% yield (47 mg), m.p. = 125–126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J=8.8 Hz, 2H), 7.37 (d, J=8.8 Hz, 2H), 6.98 (d, J=8.8 Hz, 2H), 6.62 (d, J=8.8 Hz, 2H), 4.77 (s, 2H), 3.89 (s, 3H), 3.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 164.0, 150.8, 134.3, 130.0, 127.9, 114.0, 113.1, 112.4, 107.3, 58.0, 55.5, 39.7; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{16}N_2O_2S$: 312.0927, found: 312.0926.

2-(Methyl(4-thiocyanatophenyl)amino)-1-(m-tolyl) ethan-1-one (**3m**): White solid, 86% yield (51 mg), m.p. = 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J=7.2 Hz, 2H), 7.45 (d, J=6.0 Hz, 1H), 7.37–7.41 (m, 3H), 6.62 (d, J=6.8 Hz, 2H), 4.81 (s, 2H), 3.12 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 150.8, 138.8, 134.9, 134.6, 134.4, 128.7, 128.2, 124.8, 113.1, 112.4, 107.4, 58.4, 39.6, 21.3; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{16}N_2OS$: 296.0978, found: 296.0976.

2-(Methyl(4-thiocyanatophenyl)amino)-1-(naphthalen-2-yl)ethan-1-one (**3n**): White solid, 76% yield (50 mg), m.p. = 128–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.90–8.02 (m 4H), 7.63–7.67 (m, 1H), 7.58–7.61 (m, 1H), 7.40 (d, J = 6.8 Hz, 2H), 6.67 (d, J = 7.6 Hz, 2H), 4.97 (s, 2H), 3.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 150.8, 135.8, 134.4, 132.4, 132.2, 129.5, 129.4, 128.9, 127.9, 127.1, 123.3, 113.2, 112.4, 107.7, 58.5, 39.7; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{20}H_{16}N_2OS$: 332.0978, found: 332.0974.

2-(Ethyl(4-thiocyanatophenyl)amino)-1-phenylethan-1-one (**3o**): White solid, 80% yield (47 mg), m.p. = 134–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–8.01 (m 2H), 7.62–7.66 (m, 1H), 7.51–7.54 (m, 2H), 7.37 (d, J=7.2 Hz, 2H), 6.57 (d, J=7.6 Hz, 2H), 4.79 (s, 2H), 3.50 (q, J=5.6 Hz, 2H), 1.24 (t, J=5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 149.6, 134.9, 134.6, 133.8, 128.9, 127.7, 113.0, 112.4, 107.0, 56.4, 46.4, 12.2; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{16}N_2OS$: 296.0978, found: 296.0973.

2-(Butyl(4-thiocyanatophenyl)amino)-1-phenylethan-1-one (**3p**): Light yellow solid, 84% yield (54 mg), m.p. = 87–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–8.01 (m 2H), 7.62–7.66 (m, 1H), 7.50–7.53 (m, 2H), 7.35 (d, J=7.2 Hz, 2H), 6.56 (d, J=7.2 Hz, 2H), 4.80 (s, 2H), 3.41 (t, J=6.4 Hz, 2H), 1.61–1.68 (m, 2H), 1.34–1.42 (m, 2H), 0.97 (t, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 149.9, 134.8, 134.5, 133.8, 128.8, 127.7, 112.9, 112.4, 106.7, 56.8, 52.0, 29.3, 20.1, 13.8; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{19}H_{20}N_2OS$: 324.1296, found: 324.1291.

2-(Allyl(4-thiocyanatophenyl)amino)-1-phenylethan-1-one (**3q**): Light yellow solid, 85% yield (52 mg), m.p. = 73–75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–8.01 (m 2H), 7.62–7.66 (m, 1H), 7.50–7.53 (m, 2H), 7.36 (d, J=6.8 Hz, 2H), 6.59 (d, J=7.2 Hz, 2H), 5.85–5.92 (m, 1H), 5.21–5.26 (m, 2H), 4.80 (s, 2H), 4.04–4.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 150.1, 134.8, 134.3, 133.9, 132.7, 128.9, 127.7, 116.7, 113.4, 112.3, 107.6, 56.3, 54.3; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{18}H_{16}N_2OS$: 308.0978, found: 308.0982.

2-(Benzyl(4-thiocyanatophenyl)amino)-1-phenylethan-1-one (**3r**): Light yellow solid, 75% yield (54 mg), m.p. = 80–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.99 (m 2H), 7.63–7.66 (m, 1H), 7.50–7.53 (m, 2H), 7.34–7.38 (m, 4H), 7.27–7.31 (m, 3H), 6.63 (d, J=7.2 Hz, 2H), 4.87 (s, 2H), 4.69 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 150.8, 135.8, 134.4, 132.4, 132.2, 129.5, 129.4, 128.9, 127.9, 127.1, 123.3, 113.2, 112.4, 107.7, 58.5, 39.7; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{22}H_{18}N_2OS$: 358.1135, found: 358.1132.

2-(Methyl(3-methyl-4-thiocyanatophenyl)amino)-1-phenylethan-1-one (**3s**): White solid, 78% yield (46 mg), m.p. = 146–147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.99 (m 2H), 7.62–7.66 (m, 1H), 7.50–7.53 (m, 2H), 7.39 (d, J=6.8 Hz, 1H), 6.56 (d, J=2.0 Hz, 1H), 6.47 (dd, J=2.4, 6.8 Hz, 1H), 4.82 (s, 2H), 3.11 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.1, 151.3, 142.7, 136.0, 134.9, 133.8, 128.9, 127.7, 114.3, 111.9, 110.9, 107.4, 58.4, 39.6, 21.4; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{17}H_{16}N_2OS$: 296.0978, found: 296.0975.

Ethyl N-methyl-N-(4-thiocyanatophenyl)glycinate (**3t**): White solid, 83% yield (42 mg), m.p. = 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J=7.6 Hz, 2H), 6.66 (d, J=7.6 Hz, 2H), 4.18 (q, J=6.0 Hz, 2H), 4.06 (s, 2H), 3.08 (s, 3H), 1.25 (t, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 150.4, 134.3, 113.2, 112.2, 108.1, 61.1, 54.0, 39.5, 14.1; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{12}H_{14}N_2O_2S$: 250.0771, found: 250.0776.

2-(Methyl(4-thiocyanatophenyl)amino)acetonitrile (**3u**): White solid, 86% yield (35 mg), m.p. = 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 4.22 (s, 2H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 133.8, 115.2, 114.9, 112.1, 111.6, 41.4, 39.1; HRMS (EI): *m/z* $[M]^+$ calcd for $C_{10}H_9N_3S$: 203.0512, found: 203.0511.

General procedure for the synthesis of product 4

To a sealed tube were added α-amino carbonyl compound **1** (0.3 mmol), KSCN (0.3 mmol), $CoCl_2{\cdot}6H_2O$ (10 mol%), I_2 (0.6 mmol), and DMSO (2 mL). Then, the tube was stirred at 80 °C for 16 h. After completion of the reaction, a $Na_2S_2O_3$ solution was added, and the resulting mixture was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The resulting mixture was purified by column

chromatography on silica gel (petroleum ether/ethyl acetate) to afford the desired product **4**.

N-Methyl-4-thiocyanatoaniline (**4a**):[52,54] Light yellow oil, 76% yield (37 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 6.8 Hz, 2H), 6.58 (d, *J* = 7.2 Hz, 2H), 4.09 (s, 1H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 134.7, 113.3, 112.6, 107.4, 30.2.

N,3-Dimethyl-4-thiocyanatoaniline (**4b**): Light yellow solid, 70% yield (37 mg), m.p. = 48–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 1.6 Hz, 1H), 6.43–6.41 (m, 1H), 4.03 (s, 1H), 2.83 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 142.9, 136.3, 114.4, 112.2, 111.0, 107.1, 30.1, 21.1; HRMS (EI): *m/z* $[M]^+$ calcd for $C_9H_{10}N_2S$: 178.0560, found: 178.0557.

3-Chloro-N-methyl-4-thiocyanatoaniline (**4c**): White solid, 67% yield (40 mg), m.p. = 57–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 6.8 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 6.48–6.46 (m, 1H), 4.27 (s, 1H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 138.2, 135.4, 113.0, 112.1, 111.2, 106.1, 30.0; HRMS (EI): *m/z* $[M]^+$ calcd for $C_8H_7ClN_2S$:198.0013, found:198.0011.

N,2-dimethyl-4-thiocyanatoaniline (**4d**): Light yellow solid, 68% yield (36 mg), m.p. = 51–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.34 (m, 1H),7.26–7.25 (m, 1H), 6.56 (d, *J* = 6.8 Hz, 1H), 3.91 (s, 1H), 2.90 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 134.5, 132.8, 123.5, 112.7, 109.8, 106.9, 30.3, 17.1; HRMS (EI): *m/z* $[M]^+$ calcd for $C_9H_{10}N_2S$: 178.0560, found: 178.0556.

2-Chloro-N-methyl-4-thiocyanatoaniline (**4e**): White solid, 53% yield (31 mg), m.p. = 52–53 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.0 Hz, 1H), 7.39–7.37 (m, 1H), 6.62 (d, *J* = 7.2 Hz, 1H), 4.70 (s, 1H), 2.92 (d, *J* = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 133.4, 133.3, 119.5, 111.8, 111.1, 107.4, 30.0; HRMS (EI): *m/z* $[M]^+$ calcd for $C_8H_7ClN_2S$: 198.0013, found: 198.0011.

N-Ethyl-4-thiocyanatoaniline (**4f**):[52] White solid, 36% yield (19 mg), m.p. = 55–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 6.8 Hz, 2H), 6.57 (d, *J* = 6.8 Hz, 2H), 3.97 (s, 1H), 3.16 (q, *J* = 5.6 Hz, 2H), 1.26 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 134.7, 113.5, 112.6, 107.2, 37.9, 14.4.

Declaration of conflicting interests

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Supplemental material

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References

1. Elander RP. *Appl Microbiol Biotechnol* 2003; 61: 385.
2. Ohfune Y. *Acc Chem Res* 1992; 25: 360.
3. Gellman SH. *Acc Chem Res* 1998; 31: 173.
4. Beenen MA, Weix DJ and Ellman JA. *J Am Chem Soc* 2006; 128: 6304.
5. Walsh JJ, Metzler DE, Powell D, et al. *J Am Chem Soc* 1980; 102: 7136.
6. Schirlin D, Gerhart F, Hornsperger JM, et al. *J Med Chem* 1988; 31: 30.
7. Obrecht D, Altorfer M, Lehmann C, et al. *J Org Chem* 1996; 61: 4080.
8. For selected papers see: (a) Jiang W, Wang YJ, Niu PF, et al. *Org Lett* 2018; 20: 4649.
9. Li WP, Duan YQ, Zhang ML, et al. *Chem Commun* 2016; 52: 7596.
10. Zhu ZQ, Xie ZB and Le ZG. *J Org Chem* 2016; 81: 9449.
11. Li XD, Chen M, Xie X, et al. *Org Lett* 2015; 17: 2984.
12. Ishida N, Nečas D, Shimamoto Y, et al. *Chem Lett* 2013; 42: 1076.
13. Jia XD, Peng FF, Qing C, et al. *Org Lett* 2012; 14: 4030.
14. Wang Y, Xin X, Liang YJ, et al. *Eur J Org Chem* 2009; 2009: 4165.
15. Liu XX, Pu JH, Luo XL, et al. *Org Chem Front* 2018; 5: 361.
16. Liu XX, Wu ZY, He YQ, et al. *Adv Synth Catal* 2016; 358: 2385.
17. Chen C, Zhu MH, Jiang LH, et al. *Org Biomol Chem* 2017; 15: 8134.
18. Yang B, Yang TT, Li XA, et al. *Org Lett* 2013; 15: 5024.
19. Zhu ZQ, Xiao LJ, Guo D, et al. *J Org Chem* 2019; 84: 435.
20. Zhu MH, Chen D, Zeng S, et al. *Tetrahedron Lett* 2018; 59: 3214.
21. Xie J and Huang ZZ. *Angew Chem Int Ed* 2010; 49: 10181.
22. Zhao L and Li CJ. *Angew Chem Int Ed* 2008; 47: 7075.
23. Zhang G, Zhang YH and Wang R. *Angew Chem Int Ed* 2011; 50: 10429.
24. Gao XW, Meng QY, Li JX, et al. *ACS Catal* 2015; 5: 2391.
25. Wu JC, Song RJ, Wang ZQ, et al. *Angew Chem Int Ed* 2012; 51: 3453.
26. Xu ZW, Yu XQ, Feng XJ, et al. *J Org Chem* 2012; 77: 7114.
27. Segundo MS, Guerrero I and Correa A. *Org Lett* 2017; 19: 5288.
28. Wang ZQ, Hu M, Huang XC, et al. *J Org Chem* 2012; 77: 8705.
29. Jiao J, Zhang JR, Liao YY, et al. *RSC Adv* 2017; 7: 30152.
30. Salman M, Zhu ZQ and Huang ZZ. *Org Lett* 2016; 18: 1526.
31. Ramana DV, Chowhan LR and Chandrasekharam M. *ChemistrySelect* 2017; 2: 2241.
32. Dutta S, Abe H, Aoyagi S, et al. *J Am Chem Soc* 2005; 127: 15004.
33. Pina IC, Gautschi JT, Wang GYS, et al. *J Org Chem* 2003; 68: 3866.
34. Patil AD, Freyer AJ, Reichwein R, et al. *Tetrahedron Lett* 1997; 38: 363.
35. Castanheiro T, Suffert J, Donnard M, et al. *Chem Soc Rev* 2016; 45: 494.
36. Linderoth L, Fristrup P, Hansen M, et al. *J Am Chem Soc* 2009; 131: 12193.
37. Houk J and Whitesides GM. *J Am Chem Soc* 1987; 109: 6825.
38. Ke F, Qu Y, Jiang Z, et al. *Org Lett* 2011; 13: 454.
39. Still IWJ and Toste FD. *J Org Chem* 1996; 61: 7677.
40. Sengupta D and Basu B. *Tetrahedron Lett* 2013; 54: 2277.
41. Sengupta D and Basu B. *Tetrahedron Lett* 2013; 54: 2277.
42. Yi NN, Xiong Y, Huang QJ, et al. *Synlett* 2018; 29: 2422.

43. Xiong Y, Chen D, Zeng S, et al. *Synlett* 2018; 29: 2279.
44. Yi NN, Li JX, Zhang H, et al. *Synth Commun* 2017; 47: 2062.
45. Yi NN, Zhang H, Xu CH, et al. *Org Lett* 2016; 18: 1780.
46. Yi NN, Wang RJ, Zou HX, et al. *J Org Chem* 2015; 80: 5023.
47. Xiang JN, Yi NN, Wang RJ, et al. *Tetrahedron* 2015; 71: 694.
48. Tang RY, Guo XK, Xiang JN, et al. *J Org Chem* 2013; 78: 11163.
49. Borzecka W, Lavandera I and Gotor V. *J Org Chem* 2013; 78: 7312.
50. Pal M, Swamy NK, Hameed PS, et al. *Tetrahedron* 2004; 60: 3987.
51. Segundo MS and Correa A. *Synthesis* 2018; 50: 2853.
52. Yadav JS, Reddy BVS and Krishna BBM. *Synthesis* 2008; 23: 3779.
53. Zhang X, Wang CG, Jiang H, et al. *RSC Adv* 2018; 8: 22042.
54. Jiang HF, Yu WT, Tang XD, et al. *J Org Chem* 2017; 82: 9312.
55. Wu WL and Su WP. *J Am Chem Soc* 2011; 133: 11924.
56. Li HJ, He ZH, Guo XW, et al. *Org Lett* 2009; 11: 4176.
57. Guo SM, Qian B, Xie YJ, et al. *Org Lett* 2011; 13: 522.
58. Chen XL, Chen TQ, Li Q, et al. *Chem Eur J* 2014; 20: 12234.
59. Zhang L, Peng C, Zhao D, et al. *Chem Commun* 2012; 48: 5928.
60. Zhang XB, Yang WC and Wang L. *Org Biomol Chem* 2013; 11: 3649.