A Novel Iron-catalyzed One-pot Synthesis of 3-Amino-1,2,4-triazoles

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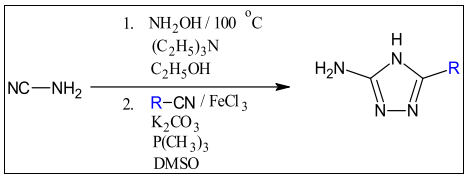

A novel one-pot synthesis of 3-amino-1,2,4-triazole developed *via* iron (III) catalyzed route is reported. The new method is more efficient, simple, and convenient and presents a concise new strategy for the synthesis of 3-amino-1,2,4-triazole derivatives. The iron (III) complex intermediate assisted in the intramolecular bond cyclization owing to its Lewis acidity or oxidizing properties. A series of aromatic nitriles bearing different electron-donating and electron-withdrawing groups substituted at para and/or ortho positions were also investigated. The position of the substituents affected the yield of the final compound, with the para-substituted substrates giving relatively higher yields.

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INTRODUCTION

1,2,4-Triazoles are important heterocyclic compounds that have applications in diverse areas such as medicinal chemistry, materials sciences, agrochemistry, and organocatalysis [1,2]. Compounds with 1,2,4-triazole moiety in its molecular skeleton are known to exhibit antiarthritic, antipyretic [3], antibacterials [4], anticancer [5], anti-inflammatory [6], analgesic [7], and antimicrobial [8] activities. The importance of these biological activities has prompted the development of many methods to construct the 1,2,4-triazole structural motif [9–11]. Existing approaches allow access to a wide variety of 1,2,4-triazoles, but these typically involve a multistep synthetic route.

Multicomponent reactions, featuring experimental simplicity and flexibility toward assemblage of three or more reactants and rapidly converting them into higher molecular weight compounds in one pot [12], have become ubiquitous in the discovery of novel biologically active compounds [13]. The one-pot synthesis of 3-amino-1,2,4-triazoles through multicomponent reactions of hydrazine, hydride, and ketones was reported previously using copper as a catalyst [14–16]. Three-component one-pot pathways were also used to synthesize 1-aryl-3-amino-1,2,4-triazoles [17].

The present study is aimed at developing practical synthetic routes toward fused heterocyclic compounds from nitrile compounds. Here, we report a multicomponent one-pot methodology for the synthesis of aryl-3-amino-1,2,4-triazoles from nitriles and hydroxylamine using $FeCl_3$ as a catalyst.

RESULTS AND DISCUSSION

In our search for new heterocycle formation reactions using nitrile compounds, we found that, in the presence of $FeCl_3$ and a base, hydroxylamine react with two nitrile compounds to give 5-aryl-3-amino-1,2,4-triazole derivatives (Table 1).

In an effort to optimize the reaction conditions, we have tried several bases and solvents. Potassium carbonate (K_2CO_3) and sodium hydroxide (NaOH) bases and dimethylformamide and acetonitrile solvents gave trace amount of the desired 5-substituted-3-amino-1,2,4-triazole. In the iron-catalyzed one-pot coupling, we used a phosphine ligand known to be efficient for iron (III), but without any additive.

The scope of the iron-catalyzed one-pot synthesis of 3-amino-1,2,4-triazole derivatives was investigated as shown in Scheme 1. A series of aromatic nitriles bearing different electron-donating groups (Me, OMe; entries 2–6) and electron-withdrawing groups (Cl, Br, F, and NO_2; entries 7–10) were engaged in the reaction with aminonitrile, leading to the desired 3-amino-1,2,4-triazoles (Table 2).

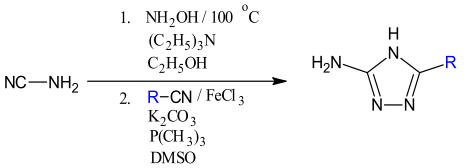
Table 1

Optimization of the reaction.

Temp (°C)	Solvent	Trimethylphosphite	Base	Yield
80	DMSO	YES	Na_2CO_3	16
100	DMSO	YES	Na_2CO_3	21
120	DMSO	YES	Na_2CO_3	10
140	DMSO	YES	Na_2CO_3	8
80	DMSO	YES	K_3PO_4	20
100	DMSO	YES	K_3PO_4	24
120	DMSO	YES	K_3PO_4	27
140	DMSO	YES	K_3PO_4	31
100	THF	YES	Na_2CO_3	5
	THF	YES	K_3PO_4	9
100	EtOH	YES	Na_2CO_3	32
			K_3PO_4	8
100	MeOH	YES	Na_2CO_3	8
			K_3PO_4	13
100	THF/DMSO	YES	Na_2CO_3	7
			K_3PO_4	10
100	EtOH/DMSO	YES	Na_2CO_3	31
			K_3PO_4	34
100	MeOH/DMSO	YES	Na_2CO_3	21
			K_3PO_4	25

DMSO, dimethylsulfoxide; THF, terahydrofuran; EtOH, ethanol; MeOH, methanol.

Scheme 1. Scope of the iron-catalyzed reaction. [Color figure can be viewed at wileyonlinelibrary.com]

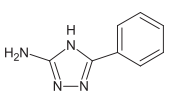
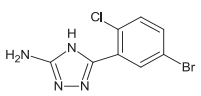
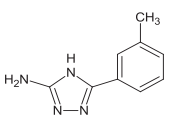
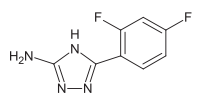


The position of the substituents on the aryl group (para vs meta position) affected the yield of the final compound, with the para-substituted substrates giving higher yields (compare entries 7 and 8). Various functional groups such as ether (entry 5), C−F bond (entries 11–13) and nitro group (entries 14–16) are tolerated. In addition, alkylnitriles employed in this reaction (methylnitrile and butyronitrile) have successively achieved the desired alkylaminotriazoles (entries17 and 18), in good yields.

A plausible mechanism for the synthesis of 3-amino-1,2,4-triazoles is shown in Scheme 2. First, the intermolecular nucleophilic addition of the amino group of hydroxylamine to the cyano group of R-CN in the presence of triethylamine leads to an amidoxime **a**, which couples with the iron complex of R-CN **b** to give an

Table 2

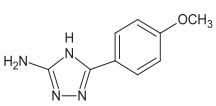
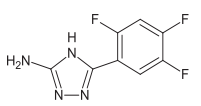
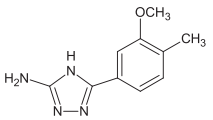
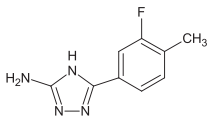
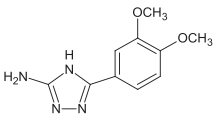
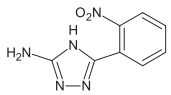
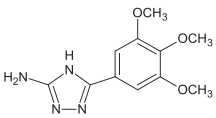
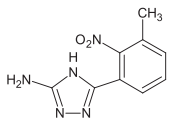
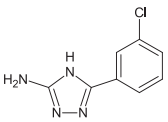
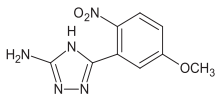
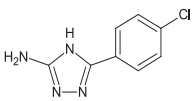
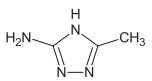
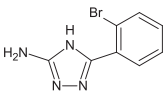
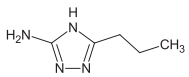
Reaction conditions: The aminonitrile (0.5 mmol), hydroxylaminehydrochloride (0.6 mmol, 34.7 mg), triethylamine (1 mmol), and ethanol (2 mL)were added to a 25 mL Schlenk. The reaction mixture was stirred at 100 °C for12 h under nitrogen atmosphere. The alkyl nitrile (0.25 mmol), FeCl3 (0.05mmol), K2CO3 (1 mmol), trimethylphosphite (0.10mmol) and anhydrous DMSO (1.5 mL) were added to the Schlenk tube, and themixture was stirred at 100 °C for another 12 h in the sealed Schlenk tube.

Entries	R	Compound	Yield	Entries	R	Compound	Yield
1	phenyl		81	10	2-chloro-5-bromophenyl		83
2	m-methylphenyl		83	11	2,4-difluorophenyl		77

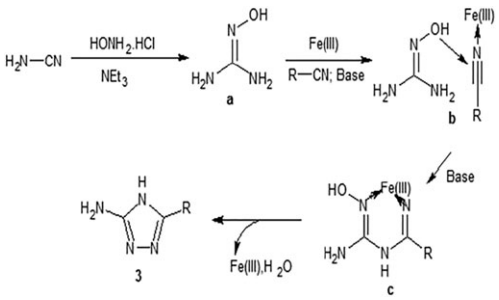
(*Continues*)

Table 2

(*Continued*)

Entries	R	Compound	Yield	Entries	R	Compound	Yield
3	p-methoxy phenyl		92	12	2,4,5-trifluorophenyl		71
4	[3-methoxy(4-methylphenyl)]		87	13	3-fluoro-4-methylphenyl		74
5	3,4-dimethoxy phenyl		91	14	o-Nitro phenyl		80
6	3,4,5-trimethoxy phenyl		94	15	2-nitro-3-methylphenyl		83
7	m-chloro phenyl		84	16	2-nitro-5-methoxyphenyl		86
8	p-chlorophenyl		87	17	Methyl		59
9	o-bromophenyl		90	18	Propyl		65

Scheme 2. Plausible mechanism for the synthesis of 3-amino-1,2,4-triazoles.



intermediate **c**. Finally, intramolecular cyclization, which is a dehydration of **c**, afforded the desired targets 3-amino-1,2,4-triazoles **1**–**18**.

CONCLUSION

We have developed a concise and a convenient new strategy for the synthesis of 3-amino-1,2,4-triazoles. This methodology consists in an iron (III) chloride mediated catalyzed one-pot reaction of aminonitrile with various alkyl and arylnitriles. Trimethylphosphine is used as ligand without any other additive. This method is mild and convenient for the preparation of a wide range of aryl-3-amino-1,2,4-triazoles in a one-pot operation in excellent yields. This novel method is highly sustainable as compared to previously described methods. We anticipate this procedure to be used advantageously in the synthesis of 3-amino-1,2,4-triazole needed for pharmaceutical or medicinal needs.

EXPERIMENTAL

General. Melting points were determined by open tube capillary method. The completion of the reaction was monitored throughout by thin layer chromatography, and the spots were located under UV light. IR spectra were obtained on a Shimadzu 8201 PC, FTIR spectrometer using KBr pellets. ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker-300 Avance instrument operating at a frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C using tetramethylsilane as internal standard in DMSO-d_6. Mass spectra were recorded on a Bruker Esquire LCMS using ESI and elemental analyses were performed on Perkin-Elmer 2400 Elemental Analyzer.

General procedure for the synthesis of 1,2,4-triazoles. The aminonitrile (0.5 mmol), hydroxylamine hydrochloride (0.6 mmol, 34.7 mg), triethylamine (1 mmol), and ethanol (2 mL) were added to a 25-mL Schlenk. The reaction mixture was stirred at 100°C for 12 h under nitrogen atmosphere. The alkyl nitrile (0.25 mmol), $FeCl_3$ (0.05 mmol), K_2CO_3 (1 mmol), trimethylphosphite (0.10 mmol), and anhydrous DMSO (1.5 mL) were added to the Schlenk tube, and the mixture was stirred at 100°C for another 12 h in the sealed Schlenk tube. The resulting solution was concentrated on a rotary evaporator, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate as the eluent to give the desired target product **1**–**18**.

5-Phenyl-1,2,4-triazol-3-amine (1). This compound was obtained as white solid, yield: 81%; mp 163–164°C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.02–7.97 (2 H, m), 7.67 (1 H, t, J = 7.4 Hz), 7.60 (2 H, t, J = 7.4 Hz), 6.43 (2 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 173.45, 169.47, 133.12, 129.85, 127.81, 124.55; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_7N_4$ $[M + H]^+$: 160.1679, found $[M + H]^+$: 160.1682.

5-(M-tolyl)-1,2,4-triazol-3-amine (2). This compound was obtained as white solid, yield: 83%; mp 145–146°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.81 (1 H, s), 7.80–7.76 (1 H, m), 7.48 (2 H, d, J = 5.0 Hz), 6.40 (2 H, s), 2.40 (3 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 173.55, 169.44, 139.32, 133.75, 129.75, 128.15, 124.99, 124.49, 21.28; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_9H_9N_4$ $[M + H]^+$: 174.1945,found $[M + H]^+$: 174.0750.

5-(4-Methoxyphenyl)-1,2,4-triazol-3-amine (3). This compound was obtained as pale yellow solid, yield: 92%; mp 156–157°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.93 (2 H, d, J = 8.9 Hz), 7.13 (2 H, d, J = 8.9 Hz), 6.33 (2 H, s), 3.85 (3 H, s); ^{13}C-NMR (75 MHz DMSO-d_6): δ 173.00, 169.05, 162.68, 129.44, 116.66, 114.93, 55.75; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_9H_9N_4O$ $[M + H]^+$: 190.1939, found $[M + H]^+$: 190.1942.

5-(3-Methoxy-4-methylphenyl)-1,2,4-triazol-3-amine (4). This compound was obtained as pale yellow solid, yield: 87%; mp 134–137°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.50 (1 H, d, J = 7.8 Hz), 7.45 (1 H, s), 7.36 (1 H, d, J = 7.8 Hz), 6.40 (2 H, s), 3.88 (3 H, s), 2.23 (3 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 173.50, 169.35, 157.99, 131.60, 131.57, 123.30, 119.90, 108.83, 55.84, 16.62; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_{10}H_{11}N_4O$ $[M + H]^+$: 204.2205, found $[M + H]^+$: 204.2209.

5-(3,4-Dimethoxyphenyl)-1,2,4-triazol-3-amine (5). This compound was obtained as yellow solid, yield: 91%; mp 164–165°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.56 (1 H, d, J = 8.4 Hz), 7.43 (1 H, s), 7.12 (1 H, d, J = 8.4 Hz), 6.31 (2 H, s), 3.81 (6 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 173.44, 169.36, 152.80, 149.37, 121.50, 116.85, 112.36, 110.32, 56.21, 56.02; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_{10}H_{11}N_4O_2$ $[M + H]^+$: 220.2199, found $[M + H]^+$: 220.2201.

5-(3,4,5-Trimethoxyphenyl)-1,2,4-triazol-3-amine (6). This compound was obtained as pale yellow solid, yield: 94%; mp 201–203°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ7.25 (2 H, s), 6.40 (2 H, s), 3.86 (6 H, s), 3.74 (3 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 173.29, 169.43, 153.76, 141.67, 119.66, 105.09, 60.68, 56.53; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_{11}H_{13}N_4O_3$ $[M + H]^+$: 250.2459, found $[M + H]^+$: 250.2462.

5-(3-Chlorophenyl)-1,2,4-triazol-3-amine (7). This compound was obtained as pale yellow solid, yield: 84%; mp 160–161°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.00–7.93 (2 H, m), 7.75 (1 H, d, J = 8.3 Hz), 7.64 (1 H, t, J = 7.9 Hz), 6.50 (2 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6); δ 171.80, 169.08, 134.03, 132.52, 131.51, 126.89, 126.11, 125.98; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_6ClN_4$ $[M + H]^+$: 194.6130, found $[M + H]^+$: 194.6134.

5-(4-Chlorophenyl)-1,2,4-triazol-3-amine (8). This compound was obtained as pale yellow solid, yield: 87%; mp 223–224°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.00 (2 H, d, J = 8.6 Hz), 7.67 (2 H, d, J = 8.6 Hz), 6.46 (2 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 172.36, 169.26, 137.69, 129.81, 129.41, 123.14; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_6ClN_4$ $[M + H]^+$: 194.6130, found $[M + H]^+$: 194.6132.

5-(2-Bromophenyl)-1,2,4-triazol-3-amine (9). This compound was obtained as white solid, yield: 90%; mp 167–168°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.91 (1 H, dd, J = 7.4, 2.1 Hz), 7.87 (1 H, dd, J = 7.6, 1.5 Hz), 7.61–7.54 (2 H, m), 6.51 (2 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 170.31, 169.38, 148.81, 134.12, 133.93.131.35, 125.03, 118.37; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_6BrN_4$ $[M + H]^+$: 238.0640, found $[M + H]^+$: 238.0643.

5-(5-Bromo-2-chlorophenyl)-1,2,4-triazol-3-amine (10). This compound was obtained as white solid, yield: 83%;

mp 173–175°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.13 (1 H, d, J = 2.4 Hz), 7.86 (1 H, dd, J = 8.6, 2.4 Hz), 7.66 (1 H, d, J = 8.6 Hz), 6.57 (2 H, s); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 170.79, 169.20, 136.64, 134.13, 133.60, 131.82, 125.70, 120.75. HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_5BrClN_4$ $[M + H]^+$: 272.5091, found $[M + H]^+$: 272.5095.

5-(2,4-Difluorophenyl)-1,2,4-triazol-3-amine (11). This compound was obtained as pale yellow solid, yield: 77%; mp 164–165°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.09 (1 H, dd, J = 15.1, 8.6 Hz), 7.62–7.54 (1 H, m), 7.34 (1 H, dd, J = 10.5, 8.6 Hz), 6.52 (2 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 169.45, 169.02, 164.99, 160.74, 132.42, 113.23, 109.62, 106.06; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_5F_2N_4$ $[M + H]^+$: 196.1201, found $[M + H]^+$: 196.1205.

5-(2,4,5-Trifluorophenyl)-1,2,4-triazol-3-amine (12). This compound was obtained as pale yellow solid, yield: 71%; mp 164–165°C; ^{1} H-NMR (300 MHz, DMSO-d_6): δ 8.08 (1 H, dd, J = 15.5, 10.4 Hz), 7.90 (1 H, dd, J = 17.2, 10.6 Hz), 6.56 (2 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 169.32, 168.78, 118.57, 118.47, 108.85, 108.63, 108.57, 108.35; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_4F_3N_4$ $[M + H]^+$: 214.1393, found $[M + H]^+$: 214.1396.

5-(3-Fluoro-4-methylphenyl)-1,2,4-triazol-3-amine (13). This compound was obtained as pale grey solid, yield: 74%; mp 171–172°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.71 (1 H, d, J = 7.9 Hz), 7.66 (1 H, d, J = 10.0 Hz), 7.51 (1 H, t, J = 7.8 Hz), 6.43 (2 H, s), 2.31 (3 H, s): ^{13}C-NMR (75 MHz, DMSO-d_6): δ 172.50, 169.45, 162.25, 159.82, 133.25, 130.22, 123.84, 114.20, 14.86. HRMS (ESI-Q-TOF, *m/z*) calcd for $C_9H_8FN_4$ $[M + H]^+$: 192.1850, found $[M + H]^+$: 192.1854.

5-(2-Nitrophenyl)-1,2,4-triazol-3-amine (14). This compound was obtained as pale yellow solid, yield: 80%; mp 200–202°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.14 (1 H, dd, J = 5.9, 3.3 Hz), 8.04 (1 H, dd, J = 5.5, 3.6 Hz), 7.95–7.89 (2 H, m), 6.59 (2 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 161.96, 158.39, 149.32, 132.37, 130.60, 127.69, 117.51, 106.35, 55.53; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_8H_6N_5O_2$ $[M + H]^+$: 205.1655, found $[M + H]^+$: 205.1658.

5-(3-Methyl-2-nitrophenyl)-1,2,4-triazol-3-amine (15). This compound was obtained as white solid, yield: 83%; mp 173–174°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.98 (1 H, d, J = 7.5 Hz), 7.80 (1 H d, J = 7.4 Hz), 7.73 (1 H, t, J = 7.7 Hz), 6.58 (1 H, s), 4.14 (1 H, s), 2.34 (3 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 169.41, 148.95, 136.33, 131.75, 131.10, 128.21, 116.27, 16.92. HRMS (ESI-Q-TOF, *m/z*) calcd for $C_9H_8N_5O_2$ $[M + H]^+$: 219.1921, found $[M + H]^+$: 219.1915.

5-(5-Methoxy-2-nitrophenyl)-1,2,4-triazol-3-amine (16). This compound was obtained as yellow solid, yield: 86%; mp 141–142°C; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.20 (1 H, d, J = 9.1 Hz), 7.44 (1 H, d, J = 2 8 Hz), 7.39 (1 H, dd, J = 9.1, 2.8 Hz), 6.55 (2 H, s), 3.95 (3 H, s); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 170.90, 169.24, 163.21, 141.32, 128.00, 122.16, 118.16, 116.79, 57.12; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_9H_8N_5O_3$ $[M + H]^+$: 235.1915, found $[M + H]^+$: 235.1919.

5-Methyl-4H-1,2,4-triazol-3-amine (17). This compound was obtained as white solid, yield: 59%; mp 146–148°C; IR (KBr, cm^{-1}): 1041, 1289, 1468, 1581, 1657, 2984, 3257; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.67 (bs, 2H, NH_2), 2.15 (s, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 165.85, 148.82, 10.81; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_3H_6N_4$ $[M + H]^+$: 99.1065, found $[M + H]^+$: 99.1069.

5-Propyl-4H-1,2,4-triazol-3-amine (18). This compound was obtained as white solid, yield: 65%; mp 143°C; IR (KBr, cm^{-1}): 1091, 1267, 1360, 1461, 1588, 1644, 2949, 3266; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.56 (bs, 2H, NH_2), 2.42 (t, 2H, CH_2), 1.52–1.58 (q, 2H, CH_2), 0.82 (t, 3H, CH_3); ^{13}C-NMR (75 MHz, DMSO-d_6): δ 165.31, 151.81, 26.31, 20.61, 12.71; HRMS (ESI-Q-TOF, *m/z*) calcd for $C_5H_{10}N_4$ $[M + H]^+$: 126.1597, found $[M + H]^+$: 126.1596.

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