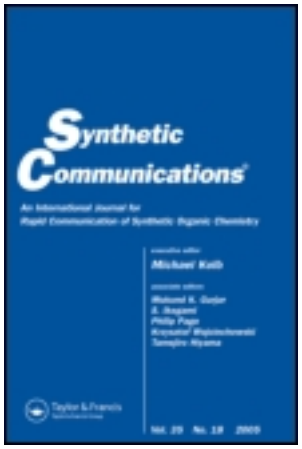

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SYNTHESIS OF NEW PYRAZOLOPYRIMIDINEDITHIONES AND PYRAZOLOPYRIMIDINEPHOSPHINES FROM AMINOCYANOPYRAZOLES

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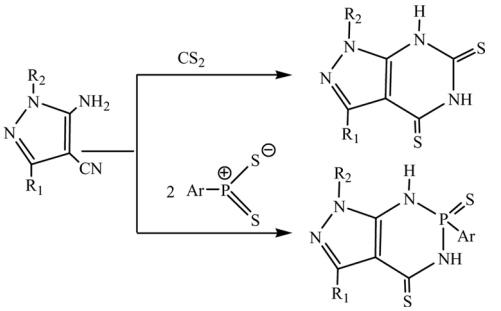
GRAPHICAL ABSTRACT



Abstract *A general, high-yielding synthetic protocol for the expedited synthesis of functionalized pyrazolopyrimidine dithione* ***2*** *and pyrazolodiazaphosphininethione* ***3*** *from amino-cyano pyrazole* ***1*** *precursors is presented.*

Keywords Pyrazole; pyrazolopyrimidinedithione; pyrazolopyrimidinephosphine

INTRODUCTION

The pyrazole ring has attracted great attention[1–5] as it has become fairly accessible, and it shows diverse properties. These heterocyclic compounds are not only interesting because of their biological activities as potential inhibitors of HIV[6] and herbicides,[7] but also they are important and useful as starting materials for the synthesis of other fused heterocyclic pyrazolopyrimidine derivatives of

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considerable chemical and pharmacological importance.[8–14] In this work, a classical method of pyrazole synthesis was applied for the preparation of compounds **1**. These aminocyanopyrazoles **1** possess two reactive sites, a cyano group and amine group, which react with carbon disulfide and Lawesson reagent to yield a new class of condensed heterocycles **2** and **3**.

RESULTS AND DISCUSSION

Synthesis of 5-Amino-4-cyano-1-substituted Pyrazoles 1

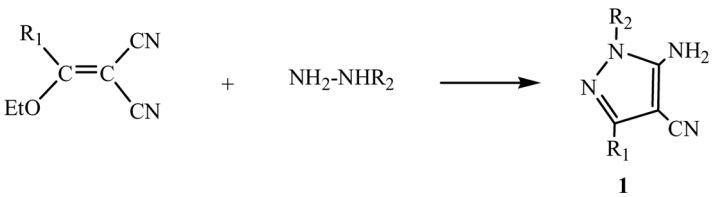
Several works mention the synthesis of the 5-amino-4-cyano pyrazoles.[15–16] These products were prepared via a standard addition of hydrazine derivatives to ketene ethoxymethylene compounds. To generalize the synthesis of 5-amino-4-cyano-1-substituted pyrazoles **1**, we have prepared a variety of ketene ethoxymethylene compounds in good yields, and the corresponding pyrazoles as shown in Scheme 1.

Reaction of Carbon Disulfide on Compound 1

The formation of pyrazolopyrimidine dithione from pyrazoles derivatives is well documented.[17–19] In this article, we report the synthesis of a variety of substituted pyrazolopyrimidine dithione obtained by refluxing aminocyanopyrazoles **1** with carbon disulfide in anhydrous pyridine. Analysis of spectral and bibliographic data shows that the reaction produced the corresponding substituted pyrazolopyrimidine. The formation of these compounds is the result of Dimroth's rearrangement. This type of transposition has been already reported by other authors[20–22] (Scheme 2).

Synthesis of Pyrazolopyrimidinedithiones 2

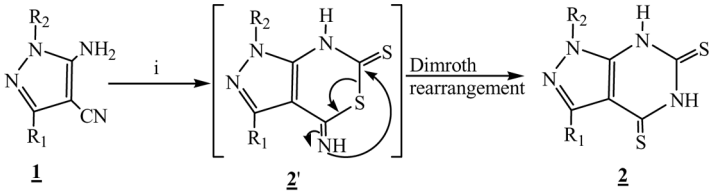
The structures of compounds **2** were deduced by infrared (IR), ^{1}H NMR, ^{13}C NMR, and mass spectra. Indeed, IR spectra of these compounds showed two bands (3330 and 3200 cm^{-1}) due to the vibration of the amino group, and we report the disparities of the CN band of aminocyanopyrazoles. ^{1}H and ^{13}C NMR of these compounds confirm the structure of the obtained products.



1

1a	R_1: H	R_2:Ph	**1d**	R_1 :H	R_2:p-SO_2PhCH_3
1b	R_1: Me	R_2:Ph	**1e**	R_1:Me	R_2:p-SO_2PhCH_3
1c	R_1: Et	R_2:Ph	**1f**	R_1:Et	R_2:p-SO_2PhCH_3

Scheme 1. Reagents and conditions: EtOH/H^+, reflux, 2 h.



2a	R_1: H	R_2:Ph	**2d**	R_1 :H	R_2:p-SO_2PhCH_3
2b	R_1: Me	R_2:Ph	**2e**	R_1:Me	R_2:p-SO_2PhCH_3
2c	R_1: Et	R_2:Ph	**2f**	R_1:Et	R_2:p-SO_2PhCH_3

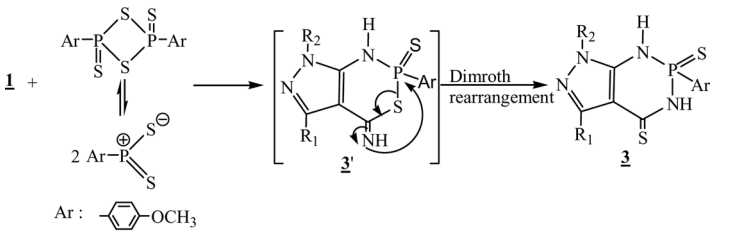
Scheme 2. Reagents and conditions: (i) CS_2/pyridine, reflux, 7 h.

Synthesis of Pyrazolopyrimidines Phosphines 3

Lawesson's reagent is known to react at both electrophilic and nucleophilic sites.[23–26] The cyclization reaction between Lawesson's reagent and aminocyanopyrazoles (**1a–f**) gave the corresponding pyrazolopyrimidine phosphine **3** from the aminocyanopyrazole precursors. This condensation was carried out in boiling toluene (Scheme 3).

The structures of compounds **3** were determined from their IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and mass spectra. IR spectra in particular revealed the absence of the absorption band corresponding to the nitrile group (2200 cm^{-1}) while exhibiting bands corresponding to C=S and P=S. ^{31}P NMR of compound **3** gave as useful information about the presence of phosphorus in this molecule; thus the signal at 55 ppm is indicative of the P=S group. Similarly, ^{1}H NMR spectra confirmed the structure of compound **3** and revealed signals indicative for the NH and OCH_3 groups.

In summary, we have used carbon disulfide and Lawesson's reagent for the preparation of pyrazolopyrimidine dithione **2** and pyrazolopyrimidine phosphine **3** from the amino pyrazoles precursors. In each case, reaction time and/or yield was



3a	R_1: H	R_2:Ph	**3d**	R_1 :H	R_2:p-SO_2PhCH_3
3b	R_1: Me	R_2:Ph	**3e**	R_1:Me	R_2:p-SO_2PhCH_3
3c	R_1: Et	R_2:Ph	**3f**	R_1:Et	R_2:p-SO_2PhCH_3

Scheme 3. Reagents and conditions: toluen, reflux, 7 h.

dramatically improved under this protocol. Moreover, this new protocol was employed for the rapid synthesis of **2** and **3**. Biological data for these products will be reported in due course.

EXPERIMENTAL

Spectra IR were determined for KBr on a Jasco Fourier transform (FT)–IR 420 spectrometer with precision of $2\,cm^{-1}$ covering field 400–4000 cm^{-1}.

The spectra of ^{1}H NMR and ^{13}C NMR were recorded in solution in $CDCl_3$ or in dimethylsulfoxide (DMSO-d_6) on a Bruker spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz). The chemical shifts are expressed in parts per million (ppm) by using tetramethylsilane (TMS) as internal reference. The multiplicities of the signals are indicated by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quadruplet; and m, multiplet, and coupling constants are expressed in hertz.

The melting points were determined in an Electrothermal 9100 apparatus and are not corrected.

The reactions were monitored by thin-layer chromatography (TLC) using aluminium sheets with silica gel 60 F_{254} from Merck.

The mass spectrometer was operated in electrospray ionization (EI) mode at 70 eV, and mass (MS) spectra were recorded from m/z 50 to 650.

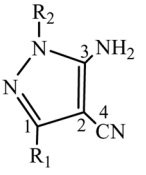
General Procedure for Synthesis of Aminocyanopyrazoles (1)

A mixture of aryl hydrazine (33 mmol) and ethoxymethylene malononitrile (33 mmol) was heated at reflux for 2 h in ethanol (30 mL). The product, which precipitates, was filtered and recrystallized from ethanol (Scheme 4).

Data for Compounds 1

5-Amino-1-phenyl-1*H*-pyrazolo-4-carbonitrile (1a). Yield: 83%, white solid. Mp 166 °C (methanol). IR (cm^{-1}): $\nu = 1594$, 1640, 2217 (CN), 2917, 3432, 3221. ^{1}H NMR (DMSO-d_6): δ (ppm) 6.82 (s, 2H), 7.40–7.55 (m, 6H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_1 144.60; C_2 73.48; C_3 152.74; C_4 114.17; C arom 117.08–137.52.

5-Amino-3-methyl-1-phenyl-1*H*-pyrazolo-4-carbonitrile (1b). Yield: 85%, white solid. Mp 133 °C (methanol). IR (cm^{-1}): $\nu = 1598$, 1645, 2215 (CN), 3331, 3227. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.15 (s, 3H), 6.66 (s, 2H), 7.35–7.52



R_1:H , $\overset{5}{CH_3}$, $\overset{6}{CH_2}$-$\overset{7}{CH_3}$

R_2: Ph , Ts:SO_2-C_6H_5-$\overset{8}{CH_3}$

(Ts: tosyl)

Scheme 4.

(m, 5H).^{13}C NMR (DMSO-d_6): δ (ppm): C_1 151.96; C_2 74.23; C_3 150.56; C_4 115.57; C arom 124.40–138.03; MS: $m/e = 199$ $[M+1]^+$, 100%.

5-Amino-3-ethyl-1-phenyl-1*H*-pyrazolo-4-carbonitrile (1c). Yield: 82%, white solid. Mp 137 °C (methanol). IR (cm^{-1}): $\nu = 1597$, 1647, 2209 (CN), 3433, 3296. ^{1}H NMR (DMSO-d_6): δ (ppm) 1.18 (t, 3H), 2.53 (q, 2H), 6.61 (s, 2H), 7.35–7.53 (m, 5H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_7 12.88; C_6 21.13; C_1 155.58; C_2 73.22; C_3 152.13; C_4 115.47; C arom 124.43–138.11. MS: $m/e = 213$ $[M+1]^+$, 100%; 158 $[M-54]^+$, 5%.

5-Amino-1-tosyl-1*H*-pyrazolo-4-carbonitrile (1d). Yield: 70%, white solid. Mp 192 °C (methanol). IR (cm^{-1}): $\nu = 1527$, 1616, 2211 (CN), 3347, 3225. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.27 (s, 3H), 7.11 (s, 2H), 7.13–7.51 (m, 5H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_8 21.28; C_1 138.58; C_2 75.51; C_3 145.55; C_4 113.81; C arom 124.66–129.07.

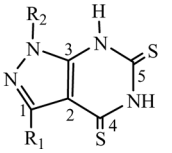
5-Amino-3-methyl-1-tosyl-1*H*-pyrazolo-4-carbonitrile (1e). Yield: 72%, white solid. Mp 185 °C (methanol). IR (cm^{-1}): $\nu = 1534$, 1628, 2216 (CN), 3381, 3227. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.04 (s, 3H); 2.39 (s, 3H), 7.63 (s, 2H), 7.47–7.87 (m, 4H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_5 13.06; C_8 21.53; C_1 146.80; C_2 73.97; C_3 154.87; C_4 113.71; C arom 127.89–133.44.

5-Amino-3-ethyl-1-tosyl-1*H*-pyrazolo-4-carbonitrile (1f). Yield: 74%, white solid. Mp 178 °C (methanol). IR (cm^{-1}): $\nu = 1526$, 1643, 2215 (CN), 3346, 3222. ^{1}H NMR (DMSO-d_6): δ (ppm) 0.87 (t, 3H), 2.16 (q, 2H); 2.38 (s, 3H), 7.38–7.68 (m, 6H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_7 10.81; C_6 21.52; C_8 23.30; C_1 143.49; C_2 73.50; C_3 144.26; C_4 114.32; C arom 128.20–136.42.

Data for Compounds 2

General procedure for synthesis of pyrazolo-pyrimidine dithione (2). A mixture of 5-amino-4-cyano-1-substituted pyrazole **1** (0.2 mol), disulfur of carbon (0.25 mol), and anhydrous pyridine (10 mL) was heated under reflux for 7 h and then evaporated under reduced pressure. The residue was treated with ethanol, and the solid product so formed was collected by filtration and washed with ether (Scheme 5).

1-Phenyl-1,7-dihydro-pyrazolo[3,4-*d*]pyrimidine-4,6-dithione (2a). Yield: 79%, white solid. Mp 302 °C (methanol). IR (cm^{-1}): $\nu = 1199$, 1147 (C=S), 1569, 1510 (C=N), 3480 (N-H). ^{1}H NMR (DMSO-d_6): δ (ppm): 2.70 (s, 1H), 2.86



R_1:H , $\overset{6}{CH_3}$, $\overset{7}{CH_2}$-$\overset{8}{CH_3}$

R_2: Ph , Ts: SO_2-C_6H_5-$\overset{9}{CH_3}$

Scheme 5.

(s, 1H), 7.22–7.92 (m, 6H). ^{13}C NMR (DMSO-d_6): δ (ppm), C_1 153.15; C_2 112.51; C_3 142.12; C_4 174.00; C_5 162.26; C arom 124.44–136.49.

3-Methyl-1-phenyl-1,7-dihydro-pyrazolo[3,4-*d*]pyrimidine-4,6-dithione (2b). Yield: 80%, white solid. Mp 305 °C (methanol). IR (cm^{-1}): $\nu = 1193$, 1162 (C=S), 1562, 1515 (C=N), 3472 (N-H). ^{1}H NMR (DMSO-d_6): δ (ppm) 2.40(s, 3H), 7.43–7.68 (m, 7H); ^{13}C NMR (DMSO-d_6): δ (ppm) C_6 14.71; C_1 148.74; C_2 113.73; C_3 129.33; C_4 181.11; C_5 163.36; C arom 121.80–137.66.

3-Ethyl-1-phenyl-1,7-dihydro-pyrazolo[3,4-*d*]pyrimidine-4,6-dithione (2c). Yield: 76%, white solid. Mp 280 °C (methanol). IR (cm^{-1}): $\nu = 1197$, 1143 (C=S), 1565, 1512 (C=N), 3470 (N-H). ^{1}H NMR (DMSO-d_6): δ (ppm) 1.23 (t, 3H), 2.71 (s, 1H), 2.87 (s, 1H), 3.01 (q, 2H), 7.43–7.93 (m, 5H); ^{13}C NMR (DMSO-d_6): δ (ppm) C_8 13.05; C_7 21.78; C_1 153.94; C_2 112.31; C_3 137.84; C_4 181.41; C_5 162.25; C arom 121.90–129.42. MS: $m/e = 289$ $[M+1]^+$, 100%; 272 $[M-16]^+$, 7%; 255 $[M-33]^+$, 5%, 230 $[M-58]^+$, 9%.

1-Tosyl-1,7-dihydro-pyrazolo[3,4-*d*]pyrimidine-4,6-dithione (2d). Yield: 73%, white solid. Mp 290 °C (methanol). IR (cm^{-1}): $\nu = 1190$, 1151 (C=S), 1560, 1517 (C=N), 3475 (N-H). ^{1}H NMR (DMSO-d_6): δ (ppm) 2.28 (s, 3H); 6.90–7.53 (m, 7H); ^{13}C NMR (DMSO-d_6): δ (ppm) C_9 21.30; C_1 145.59; C_2 112.44; C_3 134.83; C_4 186.30; C_5 162.26; C arom 125.43–137.60.

3-Methyl-1-tosyl-1,7-dihydro-pyrazolo[3,4-*d*]pyrimidine-4,6-dithione (2e). Yield: 75% white solid. Mp 300 °C (methanol). IR (cm^{-1}): $\nu = 1194$, 1163 (C=S), 1562, 1519 (C=N), 3478 (N-H). ^{1}H NMR (DMSO-d_6): δ (ppm) 2.28 (s, 3H); 2.87 (s, 3H), 6.99–7.50 (m, 6H); ^{13}C NMR (DMSO-d_6): δ (ppm): C_6 11.30; C_9 21.30; C_1 145.59; C_2 112.44; C_3 134.83; C_4 186.30; C_5 162.26; C arom 125.43–137.60.

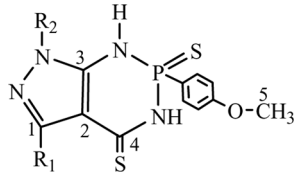
3-Ethyl-1-tosyl-1,7-dihydro-pyrazolo[3,4-*d*]pyrimidine-4,6-dithione (2f). Yield: 72%, white solid. Mp 306 °C (methanol). IR (cm^{-1}): $\nu = 1191$, 1142 (C=S), 1567, 1510 (C=N), 3481 (N-H). ^{1}H NMR (DMSO-d_6): δ (ppm) 2.28 (s, 3H); 1.24 (t, 3H); 2.81 (q, 2H); 6.99–7.50 (m, 6H); ^{13}C NMR (DMSO-d_6): δ (ppm) C_7 21.30; C_8 21.30; C_9 21.30; C_1 145.59; C_2 112.44; C_3 134.83; C_4 186.30; C_5 162.26; C arom 125.43–137.60.

General Procedure for Synthesis of Pyrazolo-Diazaphosphinine Thione (3)

A mixture of 5-amino-4-cyano-1-substituted pyrazole **1** (0.2 mol) and Lawesson's reagent (0.25 mol) in toluene (10 mL) was heated under reflux for 7 h and then evaporated under reduced pressure. The solid product so formed was collected by filtration and washed with ether (Scheme 6).

Data for Compounds 3

5-Methyl-2-(4-methoxyphenyl)-7-phenyl-2-thioxo-1,2,3,7-tetrahydro-pyrazolo[3,4-*d*] [1,3,2]diazaphosphinine-4-thione (3a). Yield: 79%, white solid. Mp 174 °C (methanol). IR (cm^{-1}): $\nu = 1226$ (P=S), 1190 (C=S), 1594, 3231,



R_1:H , $\overset{6}{CH_3}$, $\overset{7}{CH_2}$-$\overset{8}{CH_3}$

R_2: Ph , Ts: SO_2-C_6H_5-$\overset{9}{CH_3}$

Scheme 6.

3411. ^{31}P NMR: 56, 28. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.48 (s, 3H), 3.77 (s, 3H), 6.92–7.82 (m, 9H), 10.13 (s, 2H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_6 15.19; C_5 55.70; C_4 187.82; C_2 113.93; C_3 154.76; C arom 129.46–147.09.

5-Ethyl-2-(4-methoxyphenyl)-7-phenyl-2-thioxo-1,2,3,7-tetrahydro pyrazolo[3,4-*d*][1,3,2]diazaphosphinine-4-thione (3b). Yield: 75%, white solid. Mp 152 °C (methanol). IR (cm^{-1}): $\nu = 1239$ (P=S), 1197 (C=S), 1590, 3231, 3464. ^{31}P NMR: 54, 72, ^{1}H NMR (DMSO-d_6): δ (ppm) 1.22 (t, 3H), 3.07 (q, 2H), 3.81 (s, 3H), 7.09–7.88 (m, 9H), 10.29 (s, 1H), 10.90 (s, 1H). ^{13}C NMR (DMSO-d_6) δ (ppm) C_1 139.89; 140.43; C_8 12.79; C_7 22.50; C_5 56.11; C_4 187.82; C_2 114.30; C_3 156.22; C arom 125.31–140.42; 415 $[M+1]^+$, 100%; 381 $[M-33]^+$, 25%; 213 $[M-201]^+$, 40%.

2-(4-Methoxyphenyl)-7-phenyl-2-thioxo-1,2,3,7-tetrahydropyrazolo[3,4-*d*][1,3,2]diazaphosphinine-4-thione (3c). Yield: 76%, white solid. Mp 179 °C (methanol). IR (cm^{-1}): $\nu = 1251$ (P=S), 1143 (C=S), 1573, 3225, 3420. ^{1}H NMR (DMSO-d_6): δ (ppm) 4.42 (s, 3H), 7.06–7.89 (m, 9H), 10.29 (s, 1H), 10.69 (s, 1H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_1 133.35; C_5 55.61; C_4 180.56; C_2 113.79; C_3 161.60; C arom 124.60–133.35.

2-(4-Methoxyphenyl)-7-tosyl-2-thioxo-1,2,3,7-tetrahydropyrazolo[3,4-*d*]-[1,3,2]diazaphosphinine-4-thione (3d). Yield: 73%, white solid. Mp 160 °C (methanol). IR (cm^{-1}): $\nu = 1226$ (P=S), 1177 (C=S), 1565, 3225, 3424. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.20 (s, 3H), 4.40 (s, 3H), 7.06–7.89 (m, 9H), 10.29 (s, 1H), 10.69 (s, 1H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_1 133.35; C_5 55.61; C_4 180.56; C_2 113.79; C_3 161.60; C arom 124.60–133.35.

2-(4-Methoxyphenyl)-7-tosyl-2-thioxo-1,2,3,7-tetrahydropyrazolo[3,4-*d*]-[1,3,2]diazaphosphinine-4-thione (3e). Yield: 75%, white solid. Mp 170 °C (methanol). IR (cm^{-1}): $\nu = 1267$ (P=S), 1177 (C=S) 1598, 3218, 3475. ^{1}H NMR (DMSO-d_6): δ (ppm) 2.25 (s, 3H), 2.77 (s, 3H), 3.93 (s, 3H), 7.09–7.88 (m, 9H), 10.25 (s, 1H), 10.93 (s, 1H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_8 21.3; C_1 139.89; C_5 56.11; C_4 187.82; C_2 114.30; C_3 156.22; C arom 124.12–145.48.

5-Ethyl-2-(4-methoxyphenyl)-7-tosyl-2-thioxo-1,2,3,7-tetrahydropyrazolo[3,4-*d*][1,3,2] diazaphosphinine-4-thione (3f). Yield: 72%, white solid. Mp 164 °C (methanol). IR (cm^{-1}): $\nu = 1264$ (P=S), 1121 (C=S), 1597, 3218, 3425. ^{1}H NMR (DMSO-d_6): δ (ppm) 1.25 (t, 3H), 3.10 (q, 2H), 2.22 (s, 3H), 3.97 (s, 3H), 7.10–7.76 (m, 9H), 10.26 (s, 1H), 10.87 (s, 1H). ^{13}C NMR (DMSO-d_6): δ (ppm) C_8 21.7; C_1 138.29; C_5 56.22; C_4 188.12; C_2 115.13; C_3 157.28; C arom 125.42–146.78.

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