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1-(3-NITROBENZENESULFONYL)-3,4-DIMETHYLIMIDAZOLINIUM IODIDE: A MORE ACTIVE TETRAHYDROFOLATE COENZYME MODEL

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Abstract—Reaction of tetrahydrofolate coenzyme model, 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (**2**) with a series of aromatic amines produced *N,N,N'*-trisubstituted-2-methylethylenediamine derivatives (**3-7**). Reaction of the model with indole or carbazole in the presence of NaH provides two imidazolidine derivatives. The action of one-carbon transfer of the model with several bifunctional nucleophiles is also tested.

INTRODUCTION

Tetrahydrofolate coenzyme was responsible for transfer of one-carbon fragment in the biological synthesis and metabolism.¹ Thus the study on the tetrahydrofolate coenzyme model [Figure 1(a)] may provide a valuable class of reagents for group transfer reactions for practical utility.^{2,3} In our earlier research, a series of 1-aryl-4,5-dihydroimidazolium iodides and 1-arenesulfonyl-4,5-dihydroimidazolium iodides had been synthesized as the tetrahydrofolate coenzyme model to improve their potential in one-carbon unit transfer reactions.⁴⁻⁷ These research showed that *N*(1)-arenesulfonyl-substituted models is more active than those *N*(1)-aryl-substituted ones, and *C*(2)-methyl-substituted models were superior to those *C*(2)-phenyl-substituted ones. Consequently, we presumed that the reactivity of our tetrahydrofolate

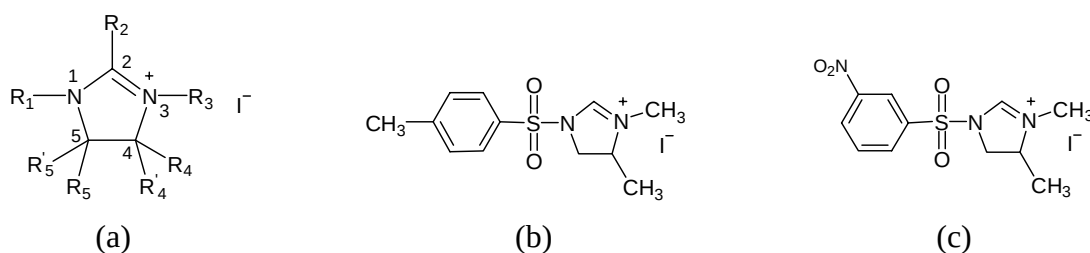


Figure 1 (a) General tetrahydrofolate coenzyme models. (b) 1-Tosyl-3,4-dimethylimidazolinium iodide (**1**). (c) 1-(3-nitro-benzenesulfonyl)-3,4-dimethylimidazolinium iodide (**2**)

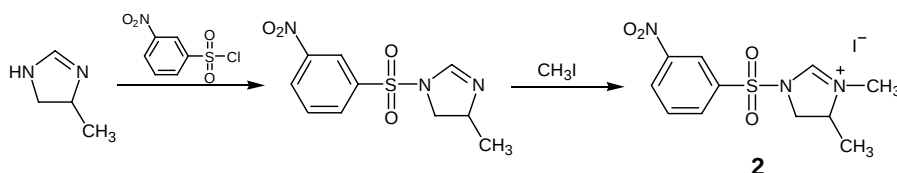
coenzyme models could obviously be affected by the steric hindrance on C(2) and induced effect in N(1).⁶⁻⁹ Moreover, we noted that in the literatures, 1-tosyl-3,4,4-trimethylimidazolinium iodide showed the higher reactivity than 1-tosyl-3,4,4,5,5-pentamethylimidazolinium iodide.¹⁰ Thus, we synthesized 1-tosyl-3,4-dimethylimidazolinium iodide (**1**), which have only a methyl at C(4) atom, and attempted its reactivity with a series of different nucleophilic reagents.^{11,12} The result obtained showed that the model was more electrophilic than those reported before.

Based on the above research, we recently synthesized a new tetrahydrofolate coenzyme model, 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (**2**). Compared with the structure of model (**1**), 3-nitrobenzenesulfonyl was expected by us to have stronger induced effect than tosyl, thus, make model (**2**) more active than model (**1**). In this paper, we report the synthesis and reaction features of model (**2**) as tetrahydrofolate coenzyme model.

RESULTS AND DISCUSSION

Preparation of model (**2**) was accomplished in two steps from 4-methylimidazoline: First, sulfonylation of 4-methylimidazoline with 3-nitrobenzenesulfonyl chloride in dichloromethane under basic conditions produced 1-(3-nitrobenzenesulfonyl)-4-methylimidazoline. Second, methylation of 1-(3-nitrobenzenesulfonyl)-4-methylimidazoline with excess iodomethane in dichloromethane produced model (**2**) with moderate yield (Scheme 1).

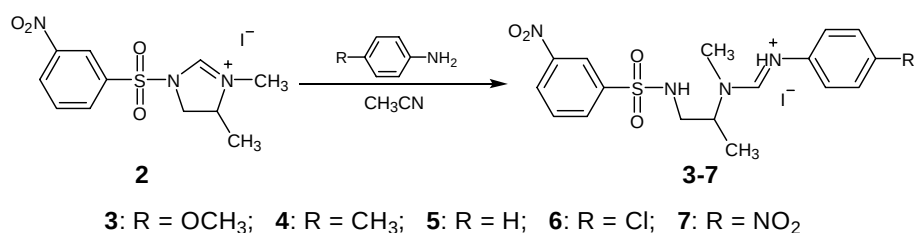
Scheme 1



In order to test the activity of model (**2**), we attempted its reactivity with a series of different nitrogen nucleophilic reagents. Generally, 4,5-dihydroimidazolium salts were commonly believed not active enough toward amino nucleophiles, especially aromatic amine. 2,3-Diarylimidazolinium salts could only react with primary aliphatic amines.⁶⁻⁹ We found that 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (**2**) could react not only with active aromatic amines but also with inactive aromatic amines, such as 4-nitroaniline and 4-chloroaniline, and afforded a series of functionalized ethylenediamine derivatives (**3-7**) as ring-opened products (Scheme 2). Compared with our recent results where model (**1**) was inert to aromatic amines, model (**2**) was proved to be more electrophilic under the same conditions.

In terms of the good reaction abilities of model (**2**) with aromatic amines, we further attempted the reactions of **2** with less nucleophilic indole and carbazole in the presence of NaH. Two substituted imidazolidines (**8** and **9**) were obtained in 78% and 75% yields, respectively, via an addition

Scheme 2

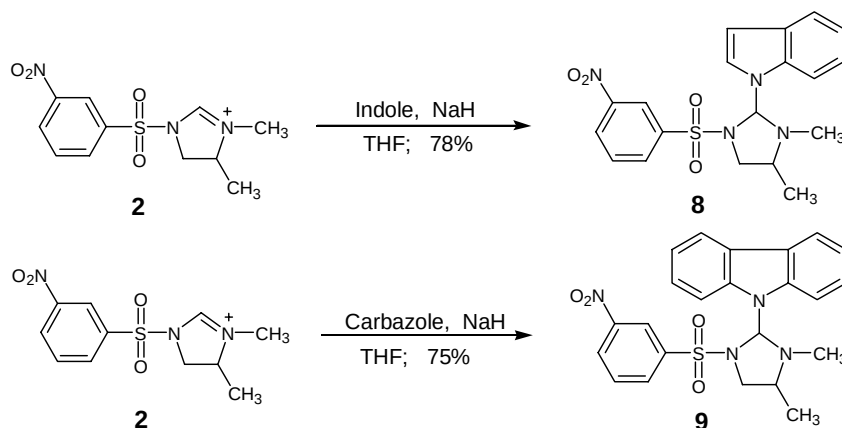
**Table 1** Nucleophilic Addition of Model Compound (**2**) with Amines^a

Product	Reagent	Temperature	Time (h)	Yield (%)
3	<i>p</i> -anisidine	rt	0.5	95
4	<i>p</i> -toluidine	rt	0.5	96
5	aniline	rt	1	88
6	<i>p</i> -chloroaniline	rt	1	67
7	<i>p</i> -nitroaniline	reflux	7	46

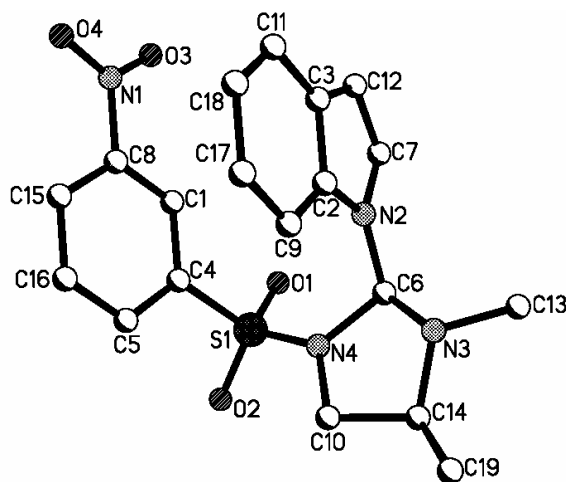
^a All reactions were performed in acetonitrile.

reaction (Scheme 3). The two products were identified by IR, ¹HNMR, EI-MS spectrum and elemental analysis. The structure of compound (**8**) could further been demonstrated by X-Ray spectra (Figure 2). A survey of literatures shows that imidazolidine motifs have widespread been found in biologically active compounds.¹³⁻¹⁵ Also, this type of compounds is usually used as carriers of pharmacologically active carbonyl compounds.¹⁶⁻¹⁷

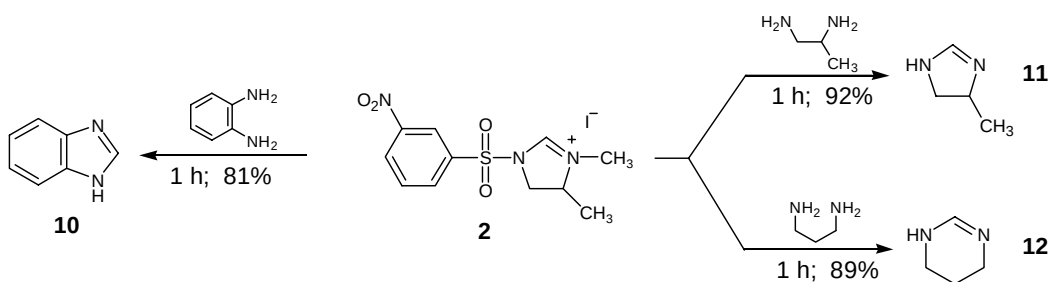
Scheme 3



Next, we tested the action of one-carbon transfer of model (**2**) with several bifunctional nucleophiles in our conditions (Scheme 4). When model (**2**) was treated with 1,2-diaminopropane, 1,3-diaminopropane and *o*-phenylenediamine, the corresponding transfer productions (**10-12**) were obtained in the yields of 81

Figure 2 X-Ray structure of compound (**8**)

-92%. The known products (**10-12**) shown in Scheme 4 were confirmed by ^1H NMR spectrum analyses. These simple reactions demonstrated that one-carbon unit in model (**2**) can easily be transferred to suitable acceptors at mild conditions.

Scheme 4

In conclusion, 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (**2**) reacted smoothly with a series of aromatic amines to provide the *N,N,N'*-trisubstituted 2-methylethylenediamine derivatives (**3-7**), and with indole or carbazole in the presence of NaH to provide two imidazolidine derivatives (**8,9**). Further, the model compound shows good reactivity for the one-carbon transfer with several diamines. The model was proved to be the more active than those reported before.

EXPERIMENTAL

MS spectra were obtained on a JMS-D300 GC/MS spectrometer. The ^1H NMR spectra were recorded at 300 MHz with TMS as a spectra standard and *J* values are given in Hz. Combustion analyses were performed on a Perkin-Elmer 240C or a MOD 1106 instrument. IR spectra were obtained on a Shimadzu IR-1700 spectrometer. X-Ray data were collected on a Bruker AXS SMART APEX CCD diffractometer, using Mo-K α radiation ($\lambda = 0.71073 \text{ \AA}$). The TLC was carried out on silica gel GF-254 20*20 cm² plate. Melting points were uncorrected. All reactions were performed under an inert atmosphere of nitrogen, all reagents and solvents were purified and dried as required.

The preparation of 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (2):

4-Methylimidazoline (8.4 g, 0.1 mol) was dissolved in 20 mL of dry dichloromethane at 0 °C, followed by the addition of triethylamine (10.1 g, 0.1 mol). Then this solution was added dropwise a solution of 3-nitrobenzenesulfonyl chloride (22.15 g, 0.1 mol) in 15 mL of dichloromethane. After the addition, the reaction mixture was warmed to rt for an additional 2 h. The resulted solution was treated with 5% sodium hydroxide solution (50 mL). After stirring for 0.5 h, the mixture was extracted with dichloromethane, and the organic layers were washed with the saturated brine (50 mL), dried over anhydrous sodium sulfate. Evaporation of dichloromethane in vacuo gave a crude solid, which was recrystallized from ethyl alcohol to yield 13.5 g (50%) of 1-(3-nitrobenzenesulfonyl)-4-methylimidazoline as white crystals. mp 99~102 °C; ¹H-NMR (300 MHz, δ, CDCl₃) 1.23 (d, *J* = 5.86, 3H), 3.09 (m, 1H), 3.63 (m, 1H), 4.28 (br, 1H), 7.34 (s, 1H), 7.83 (m, 1H), 8.16 (d, *J* = 6.9, 1H), 8.52 (d, *J* = 7.0, 1H), 8.71 (s, 1H); IR (KBr) cm⁻¹: 3082, 2972, 1618, 1527, 1461, 1429, 1363, 1176; MS *m/z*: 269(M⁺). *Anal.* Calcd for C₁₀H₁₁N₃O₄S: C, 44.57; H, 4.12; N, 15.60. Found C, 44.50; H, 4.28; N, 15.43.

1-(3-Nitrobenzenesulfonyl)-4-methylimidazoline (2.69 g, 10 mmol) and iodomethane (1.9 mL, 30 mmol) were refluxed in 20 mL of dry dichloromethane for 4 h. After cooled to rt, the yellow solid was collected by vacuum filtration and recrystallized from ethyl alcohol to give 2.96 g (72%) of 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (2) as a yellowish powder; mp 186~189 °C; ¹H-NMR (300 MHz, δ, CDCl₃): 1.13 (d, *J* = 6.7, 3H), 2.83 (s, 3H), 3.01-3.12 (m, 2H), 3.77 (m, 1H), 7.89 (m, 2H), 8.21 (d, *J* = 7.6, 1H), 8.44 (d, *J* = 8.0, 1H), 8.57 (s, 1H); IR (KBr) cm⁻¹: 3112, 2983, 1643, 1608, 1585, 1531, 1404, 1330, 1163; MS *m/z*: 284 ([M-I]⁺). *Anal.* Calcd for C₁₁H₁₄N₃O₄IS: C, 32.13; H, 3.43; N, 10.22. Found: C, 32.04; H, 3.59; N, 10.30.

General procedure for the reaction of 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (2) with aromatic amines:

A solution of 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (2) (0.411 g, 1 mmol) and aromatic amines (1 mmol) in 10 mL of dry acetonitrile was refluxed or stirred in rt for 0.5-7 h, white solids were observed. The white solids were collected and recrystallized from ethyl ether/acetone to afford white crystals (3-7).

Compound (3): yield (95%) as yellow crystals, mp 210-212 °C; ¹H-NMR (300 MHz, δ, DMSO-*d*₆): 1.22 (d, *J* = 4.9, 3H), 2.98 (s, 3H), 3.07 (m, 1H), 3.15 (m, 1H), 3.77 (s, 3H), 4.03 (m, 1H), 7.04 (d, *J* = 7.7, 2H), 7.33 (d, *J* = 7.9, 2H), 7.90 (m, 1H), 8.20 (d, *J* = 7.1, 1H), 8.30 (s, 1H), 8.46 (m, 3H), 10.91 (br, 1H); IR (KBr) cm⁻¹: 3286, 3024, 2939, 1683, 1600, 1533, 1506, 1448, 1353, 1168; MS *m/z*: 406 ([M-HI]⁺). *Anal.* Calcd. for C₁₈H₂₃N₄O₅IS: C, 40.46; H, 4.34; N, 10.48. Found C, 40.63; H, 4.39; N, 10.76.

Compound (4): yield (96%) as yellowish crystals; mp 189-192 °C; ¹H-NMR (300 MHz, δ, DMSO-*d*₆): 1.22 (d, *J* = 6.2, 3H), 2.31 (s, 3H), 2.99 (s, 3H), 3.08 (m, 1H), 3.13 (m, 1H), 4.04 (m, 1H), 7.30 (s, 4H),

7.87 (t, $J = 7.8$, 1H), 8.20 (d, $J = 7.7$, 1H), 8.29 (m, 1H), 8.46 (m, 1H), 8.50 (s, 1H), 8.59 (s, 1H), 10.96 (br, 1H); IR (KBr) cm^{-1} : 3263, 3006, 1683, 1606, 1533, 1506, 1456, 1350, 1168; MS m/z : 390 ($[\text{M-HI}]^+$). *Anal.* Calcd for $\text{C}_{18}\text{H}_{23}\text{N}_4\text{O}_4\text{IS}$: C, 41.71; H, 4.47; N, 10.81. Found C, 41.83; H, 4.59; N, 10.76.

Compound (5): yield (88%) as yellowish crystals; mp 168-170 °C; $^1\text{H-NMR}$ (300 MHz, δ , $\text{DMSO-}d_6$): 1.23 (d, $J = 6.2$, 3H), 3.02 (s, 3H), 3.15 (m, 2H), 4.07 (m, 1H), 7.30-7.53 (m, 5H), 7.88 (t, $J = 7.8$, 1H), 8.21 (d, $J = 7.6$, 1H), 8.30 (m, 1H), 8.46 (m, 2H), 8.66 (s, 1H), 11.01 (br, 1H); IR (KBr) cm^{-1} : 3055, 1685, 1598, 1558, 1533, 1494, 1352, 1168; MS m/z : 376($[\text{M-HI}]^+$). *Anal.* Calcd for $\text{C}_{17}\text{H}_{21}\text{N}_4\text{O}_4\text{IS}$: C, 40.49; H, 4.20; N, 11.11. Found C, 40.53; H, 4.39; N, 10.96.

Compound (6): yield (67%) as white powder; mp 192-194 °C; $^1\text{H-NMR}$ (300 MHz, δ , $\text{DMSO-}d_6$): 1.25 (d, $J = 6.3$, 3H), 3.03 (s, 3H), 3.17 (m, 2H), 4.08 (m, 1H), 7.46 (d, $J = 8.4$, 2H), 7.59 (d, $J = 8.3$, 2H), 7.92 (t, $J = 7.8$, 1H), 8.22 (d, $J = 7.7$, 1H), 8.29 (m, 1H), 8.48 (m, 2H), 8.70 (s, 1H), 11.08 (br, 1H); IR (KBr) cm^{-1} : 3072, 2977, 1685, 1600, 1521, 1490, 1352, 1166; MS m/z : 410($[\text{M-HI}]^+$). *Anal.* Calcd for $\text{C}_{17}\text{H}_{20}\text{ClN}_4\text{O}_4\text{IS}$: C, 37.90; H, 3.74; N, 10.40. Found C, 37.96; H, 3.71; N, 10.45.

Compound (7): yield (46%) as white powder; mp 193-195 °C; $^1\text{H-NMR}$ (300 MHz, δ , $\text{DMSO-}d_6$): 1.25 (d, $J = 6.3$, 3H), 3.06 (s, 3H), 3.17 (m, 2H), 4.11 (m, 1H), 7.65 (d, $J = 8.1$, 2H), 7.92 (t, $J = 7.8$, 1H), 8.20 (d, $J = 7.8$, 1H), 8.30 (m, 1H), 8.37 (d, $J = 8.6$, 2H), 8.46 (m, 2H), 8.87 (s, 1H), 11.33 (br, 1H); IR (KBr) cm^{-1} : 3058, 2981, 1689, 1596, 1521, 1496, 1332, 1166; MS m/z : 421 ($[\text{M-HI}]^+$). *Anal.* Calcd for $\text{C}_{17}\text{H}_{20}\text{N}_5\text{O}_6\text{IS}$: C, 37.17; H, 3.67; N, 12.75. Found C, 37.23; H, 3.80; N, 12.66.

General procedure for the reaction of 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (2) with indole or carbazole:

50% Sodium hydride suspended in oil (67.2 mg, 1.4 mmol) was added into a solution of indole or carbazole (1 mmol) in 10 mL of dry tetrahydrofuran, which was cooled with an ice-water bath. The reaction mixture was stirred for 30 min, then 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (2) (0.411 g, 1 mmol) was added. The mixture was allowed to warm to rt for 1 h. Then the resulted solution was treated with water and extracted with dichloromethane, the combined organic layers were dried over anhydrous sodium sulfate. After evaporation of dichloromethane, the residue was purified by flash column chromatography (SiO_2 ; ethyl acetate/hexane, 1:5) to give the desired products (8) and (9).

Compound (8): yield (78%), recrystallized from EtOH/acetone as yellow crystals; mp 124-127 °C; $^1\text{H-NMR}$ (300 MHz, δ , CDCl_3): 1.34 (d, $J = 5.8$, 3H), 2.27 (s, 3H), 3.11 (m, 1H), 3.36 (t, $J = 9.2$, 1H), 4.23 (t, $J = 8.1$, 1H), 6.02 (s, 1H), 6.35 (s, 1H), 6.94 (m, 2H), 7.07 (d, $J = 8.0$, 1H), 7.18 (s, 1H), 7.35 (m, 3H), 7.84 (s, 1H), 7.93 (d, $J = 8.0$, 1H); IR (KBr) cm^{-1} : 2875, 1606, 1533, 1456, 1353, 1174; MS m/z : 284, 117. *Anal.* Calcd for $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$: C, 56.99; H, 5.03; N, 13.99. Found C, 56.81; H, 5.20; N, 13.92.

Compound (9): yield (75%), recrystallized from EtOH/acetone as yellowish powder; mp 152-154 °C; $^1\text{H-NMR}$ (300 MHz, δ , CDCl_3): 1.41 (d, $J = 5.7$, 3H), 2.28 (s, 3H), 3.14 (m, 1H), 3.52 (t, $J = 9.5$, 1H),

4.39 (t, $J = 8.1$, 1H), 6.42 (s, 1H), 6.75 (t, $J = 7.9$, 1H), 7.06 (d, $J = 7.8$, 1H), 7.12 (t, $J = 7.2$, 2H), 7.28 (s, 2H), 7.57 (m, 3H), 7.74 (m, 3H); IR (KBr) cm^{-1} : 3051, 2846, 1604, 1531, 1506, 1448, 1352, 1153; MS m/z : 284, 166, 167. *Anal.* Calcd for $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_4\text{S}$: C, 61.32; H, 4.92; N, 12.44. Found C, 61.51; H, 5.12; N, 12.32.

General procedure for the reaction of 1-(3-nitrobenzenesulfonyl)-3,4-dimethylimidazolinium iodide (2) with diamines:

A solution of 3,4-dimethyl-1-(3-nitrobenzenesulfonyl)imidazolinium iodide (**2**) (1 mmol) and diamine (1 mmol) in 10 mL of dry acetonitrile was refluxed for 1 h. The filtrate was concentrated, and the residue was purified by column chromatography (silica gel, gradient chloroform and methanol). The $^1\text{H-NMR}$ spectra of compounds (**10-12**) were in complete agreement with those of the authentic samples: benzimidazole (Aldrich), 4-methylimidazoline,¹¹ 1,4,5,6-tetrahydropyrimidine (Aldrich).

Compound (10): Yield (81%) as white crystals (water); mp 171.2°C-173.0 °C; $^1\text{H-NMR}$ (300 MHz, δ , CDCl_3): 7.31 (m, 2H), 7.67 (br, 2H) 8.10 (s, 1H), 10.21 (br, 1H).

Compound (11): Yield (92%) as yellow oil; $^1\text{H-NMR}$ (300 MHz, δ , CDCl_3): 1.12 (d, $J = 6.3$, 3H), 3.08 (m, 1H), 3.65 (m, 1H), 3.84 (m, 1H), 4.17 (s, 1H), 6.96 (s, 1H).

Compound (12): Yield (89%) as colorless oil; $^1\text{H-NMR}$ (300 MHz, δ , CDCl_3): 1.69 (m, 2H), 3.14 (t, 4H), 5.12 (br, 1H), 7.00 (s, 1H).

Crystal data for compound (8):

Empirical formula: $\text{C}_{19}\text{H}_{20}\text{N}_4\text{O}_4\text{S}$, crystal size: 0.40×0.40×0.20 mm, Monoclinic, $a = 10.599(2)\text{\AA}$, $b = 14.298(3)\text{\AA}$, $c = 13.415(3)\text{\AA}$, $\alpha = 90.00^\circ$, $\beta = 108.164(3)^\circ$, $\gamma = 90.00^\circ$, $V = 1931.6(7)$, $T = 293(2)\text{K}$, space group $P2(1)/n$, $Z = 4$, $d_{\text{calc}} = 1.377\text{ g/cm}^3$, $F(000) = 508$, 3390 reflections measured, 2408 unique. The final $R1 = 0.1514$ ($I > 2\sigma$), 0.1101 (all data), $wR2 = 0.3088$ ($I > 2\sigma$), 0.2777 (all data).

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