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Design and Synthesis of Novel 5-Sulfoxide-substituted Pyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3H)ones

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Abstract: A series of novel 5-sulfoxide-substituted pyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3*H*)ones **4a-j** were designed and efficiently synthesized *via* a diazotization of 5-amine-3-methylsulfinyl-1H-pyrazole, followed by cycloaddition with aryl isocyanate. A possible reaction mechanism is outlined and discussed. These new compounds exhibit some biological activity as preliminary bioassay indicated. Their structures were confirmed with ^{1}H NMR, IR and elemental analysis.

Keywords: Sulfoxide-substituted nitrogen heterocycle, diazotization, cycloaddition.

Heterocyclic nitrogen compounds and their fused analogs represent an important class of heterocyclic compounds. They exist in numerous natural products[1], displaying wide range of biological and pharmaceutical activities[2-4], and have been attracted considerable attention. For example, indolo[1,2-*c*]benzo[1,2,3]triazines exhibit antitumor and antimicrobial activity[5]. Some of nitrogen heterocycles are also important chiral ligands or catalysts and can be used efficiently in asymmetric reactions[6]. They are also widely used in textiles as dyes, daylight fluorescent pigments, and laser dyes due to their excellent color characteristics and high photostability[7]. Considering the sulfoxide nucleus is a key unit distributed in the plant kingdom[8] and plays an important role in many pharmacologically active compounds[9], in heterocyclic nitrogen compounds to introduce sulfoxide moiety may improve their acitivities[10]. Herein, we report our strategy to design and synthesize sulfoxide-substituted pyrazolo[5,1-*d*][1,2,3,5]tetrazin-4(3H)ones **4a-j** (**Scheme 1**).

5-Amino-4-ethoxycarbonyl-3-methylsulfinyl-1H-pyrazole **2** was easily prepared according to the reported method [11]. The diazotization of compound **2** using nitrous acid at –10 °C followed by neutralization with saturated aqueous sodium carbonate gave 5-diazo-4-ethoxycarbonyl-3-methylsulfinyl-1H-pyrazole **3**. 3-Aryl-8-ethoxycarbonyl-7-methylsulfinyl-pyrazolo[5,1-*d*] [1,2,3,5]tetrazin-4(3H)ones **4a-j** were obtained by the cycloaddition of compound **3** with aryl isocyanates in anhydrous CH_2Cl_2 at room temperature in high yield.

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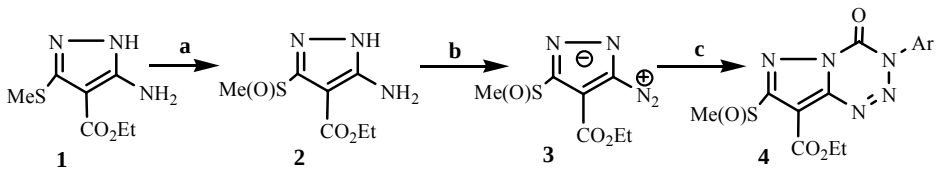
Scheme 1 Synthetic route of the title compounds **4**



Reaction conditions: a**.** AcOH, H_2O_2, 40-0 °C; b**.** (1) $NaNO_2$, HCl, -10 °C; (2) Na_2CO_3; c**.** ArNCO, CH_2Cl_2. **Ar: 4a** = 4-FC_6H_4; **4b** = 2-FC_6H_4; **4c** = 3-ClC_6H_4; **4d** = 4-ClC_6H_4; **4e** = 2,4-$Cl_2C_6H_3$; **4f** = 4-CNC_6H_4; **4g** = 4-$NO_2C_6H_4$; **4h** = 2-$NO_2C_6H_4$; **4i** = 2-$CF_3C_6H_4$; **4j** = 4-$EtO_2CC_6H_4$.

Table 1 Synthesis of compounds **4** *via* cycloaddition of compound **3** with aryl isocyanates

entry	Ar	Reaction time(d)	**4**	m.p. (°C)	yield (%)
1	4-FC_6H_4	6	**4a**	177-178	83
2	2-FC_6H_4	7	**4b**	172-173	78
3	3-ClC_6H_4	5	**4c**	164-165	87
4	4-ClC_6H_4	4	**4d**	174-175	91
5	2,4-$Cl_2C_6H_3$	2	**4e**	165-166	90
6	4-CNC_6H_4	0.5	**4f**	151-152	95
7	4-$NO_2C_6H_4$	0.5	**4g**	158-159	93
8	2-$NO_2C_6H_4$	1	**4h**	154-155	91
9	2-$CF_3C_6H_4$	1	**4i**	170-171	97
10	4-$EtO_2CC_6H_4$	0.5	**4j**	157-158	98
11	4-MeO	10			0

Various aryl isocyanates were investigated the scope and limitation of this cycloaddition. As **Table 1** indicated, the yields were good when aryl isocyanates bearing weak electron-drawing groups such as halogen (entry 1-5), and the products were purified by recrystallization from dichloromethane/diethyl ether; if the aryl isocyanates bearing strong electron-drawing groups such as ethoxycarboryl, nitro, cyano, *etc*, the yields were further raised(entry 6-10). The products were recrystallized from DMSO/ethanol; when the aryl isocyanates bearing electron-donating groups such as methoxy (entry 11), no any cycloaddition product could be obtained.

A possible reaction mechanism is outlined in **Scheme 2** according to the published paper[12]. The cycloaddition of 5-diazo-4-ethoxycarboryl-3-methylsulfinyl-1H-pyrazole **3** to the electron deficient C=N double bond of various aryl isocyanates can be understood as a [7+2] cycloaddition, which consists two mechanisms (i) ring nitrogen acylation from 1,9-dipole followed by intramolecular coupling, (ii) [3+2] cycloaddition of compound **3** to the aryl isocyanates with subsequent [1,5] shift.

Since the cycloaddition is easy to complement when using aryl isocyanates bearing strong electron-drawing groups indicated by **Table 1**, the route (ii) should be the major mechanism because aryl isocyanate bearing strong electron-drawing group is disadvantage for nucleophilic attack.

Scheme 2 Proposed mechanism of the cycloaddition

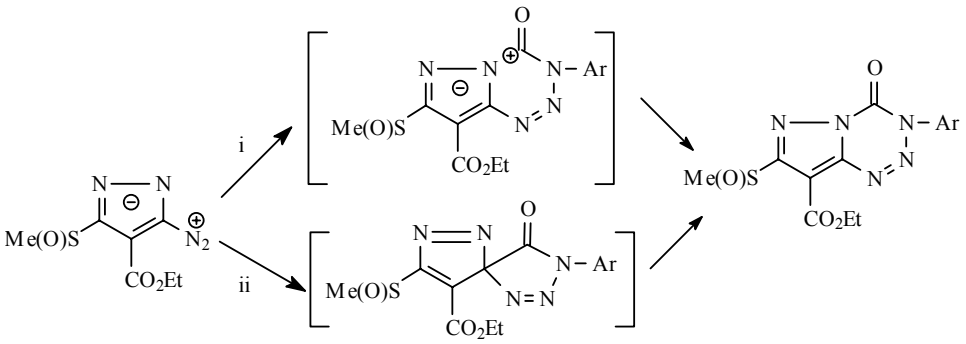


Table 2 Bioassay test of compounds **4a-e** against rape

Compound	**4a**	**4b**	**4c**	**4d**	**4e**	**Atriazine**
Activity (%)	70.0	66.7	60.6	61.3	68.6	100

Compounds **4a-e** were selected for testing against rape *in vivo* at 200 ppm. Their biological activity was indicated in **Table 2**. Further bioassay test and structural modification as well as synthetic applications of this new strategy are in progress in our laboratory.

Acknowledgments

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13. All reactions were performed under a dry nitrogen atmosphere with magnetic stirring. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. ^{1}H NMR spectra were measured on a Bruker AC-P200. Infrared (IR) spectra were recorded on a Shimadzu-435 spectrophotometer. Elemental analysis was performed on Yanaco-CHN CORDER elementary analyzer. Melting points

were measured on the Thomas-Hoover apparatus and the thermometer was not corrected.

2: 95.0% yield; white crystals; mp = 210-212 °C; ^{1}H NMR (200MHz, $CDCl_3$, δ ppm): 1.33 (t, 3H, *J*=7.02Hz), 2.98 (s, 3H), 4.28 (q, 2H, *J*=7.02Hz), 8.25 (s, br, 3H).

3: 67.0% yield; white crystals; mp = 109-110 °C; ^{1}H NMR(200MHz, $CDCl_3$, δ ppm): 1.40 (t, 3H, *J*=7.15Hz), 3.16 (s, 3H), 4.42 (q, 2H, *J*=7.15Hz); IR (KBr) ν 2996, 2217, 1718, 1523, 1271, 1061, 972, 770 cm^{-1}; Anal. Calcd. for $C_7H_8N_4O_3S$: C, 36.84; H, 3.53; N, 24.55. Found: C, 36.65; H, 3.49; N, 24.55.

4a: ^{1}H NMR (200MHz, $CDCl_3$, δ ppm): 1.45 (t, 3H, *J*=6.97Hz), 3.13 (s, 3H), 4.50 (q, 2H, *J*=6.97Hz), 7.24-7.62 (m, 4H); IR (KBr) ν 3070, 1775, 1707, 1566, 1507, 1265, 1176, 1051, 948 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}FN_5O_4S$: C, 46.03; H, 3.31; N, 19.17. Found: C, 45.86; H, 3.26; N, 19.10.

4b: ^{1}H NMR (200MHz, $CDCl_3$, δ ppm): 1.45 (t, 3H, *J*=6.91Hz), 3.15 (s, 3H), 4.51 (q, 2H, *J*=6.91Hz), 7.24-7.57 (m, 4H); IR (KBr) ν 3037, 1778, 1707, 1564, 1502, 1266, 1100, 1052, 948 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}FN_5O_4S$: C, 46.03; H, 3.31; N, 19.17. Found: C, 45.85; H, 3.25; N, 19.30.

4c: ^{1}H NMR (200MHz, $CDCl_3$, δ ppm): 1.45 (t, 3H, *J*=6.26Hz), 3.14 (s, 3H), 4.53 (q, 2H, *J*=6.26Hz), 7.48-7.76 (m, 4H); IR (KBr) ν 3065, 2927, 1780, 1707, 1566, 1474, 1263, 1069, 1053, 958 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}ClN_5O_4S$: C, 44.04; H, 3.17; N, 18.34. Found: C, 43.86; H, 3.14; N, 18.15.

4d: ^{1}H NMR (200MHz, $CDCl_3$, δ ppm): 1.45 (t, 3H, *J*=7.19Hz), 3.13 (s, 3H), 4.49 (q, 2H, *J*=7.19Hz), 7.58 (d, 2H, J=3.26Hz), 7.63 (d, 2H, *J*=3.26Hz); IR (KBr) ν 3097, 2925, 1774, 1709, 1565, 1490, 1263, 1110, 1050, 946 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}ClN_5O_4S$: C, 44.04; H, 3.17; N, 18.34. Found: C, 43.97; H, 3.00; N, 18.44.

4e: ^{1}H NMR (200MHz, $CDCl_3$, δ ppm): 1.47 (t, 3H, *J*=6.91Hz), 3.16 (s, 3H), 4.53 (q, 2H, *J*=6.91Hz), 7.51~7.66 (m, 3H); IR (KBr) ν 3086, 2984, 1780, 1705, 1565, 1479, 1261, 1060, 947 cm^{-1}; Anal. Calcd. for $C_{14}H_{11}Cl_2N_5O_4S$: C, 40.40; H, 2.66; N, 16.83. Found: C, 40.45; H, 2.50; N, 16.81.

4f: ^{1}H NMR (200MHz, DMSO, δ ppm): 1.32 (t, 3H, *J*=6.71Hz), 3.03 (s, 3H), 4.38 (q,2H, *J*=6.71Hz), 7.86 (d, 2H, *J*=7.92Hz), 8.12 (d, 2H, *J*=7.92Hz); IR (KBr) ν 3030, 1784, 1707, 1567, 1433, 1261, 1175, 1051, 945 cm^{-1}; Anal. Calcd. for $C_{15}H_{12}N_6O_4S$: C, 48.38; H, 3.25; N, 22.57. Found: C, 48.45; H, 3.09; N, 22.36.

4g: ^{1}H NMR (200MHz, DMSO, δ ppm): 1.37 (t, *J*=6.84Hz, 3H), 3.07 (s, 3H), 4.42 (q, *J*=6.84Hz, 2H), 7.98 (d, *J*=8.47Hz, 2H), 8.51 (d, *J*=8.47Hz, 2H); IR (KBr) ν 3042, 1789, 1704, 1525, 1349, 1261, 1174, 1051, 945 cm^{-1}; Anal. Calcd. For $C_{14}H_{12}N_6O_6S$: C, 42.86; H, 3.08; N, 21.42. Found: C, 42.85; H, 3.19; N, 21.34.

4h: ^{1}H NMR (200MHz, DMSO, δ ppm): 1.36 (t, 3H, *J*=7.05Hz), 3.08 (s, 3H), 4.42 (q, 2H, *J*=7.05Hz), 7.93-8.41 (m, 4H); IR (KBr) ν 3028, 1779, 1704, 1541, 1358, 1261, 1051, 945 cm^{-1}; Anal. Calcd. for $C_{14}H_{12}N_6O_6S$: C, 42.86; H, 3.08; N, 21.42. Found: C, 42.68; H, 3.04; N, 21.34.

4i: ^{1}H NMR (200MHz, DMSO, δ ppm): 1.35 (t, 3H, *J*=7.05Hz), 3.06 (s, 3H), 4.41 (q, 2H, *J*=7.05Hz), 7.54-7.74 (m, 4H); IR (KBr) ν 2924, 1784, 1707, 1564, 1502, 1266, 1055, 947 cm^{-1}; Anal. Calcd. for $C_{15}H_{12}F_3N_5O_4S$: C, 43.38; H, 2.91; N, 16.86. Found: C, 43.38; H, 2.93; N, 16.70.

4j: ^{1}H NMR (200MHz, DMSO, δ ppm): 1.32~1.44 (m, 6H), 3.09 (s, 3H), 4.31-4.51 (m, 4H), 7.71 (d, 2H, *J*=7.57Hz), 8.20 (d, 2H, *J*=7.57Hz); IR (KBr) ν 2925, 1768, 1715, 1606, 1563, 1276, 1110, 1045, 948 cm^{-1}; Anal. Calcd. for $C_{17}H_{17}N_5O_6S$: C, 48.68; H, 4.09; N, 16.70. Found: C, 48.45; H, 3.95; N, 16.50.

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