Novel Synthesis of 5-Amino-1-arylsulfonyl-4-pyrazolin-3-ones as a New Class of *N*-Sulfonylated Pyrazoles†

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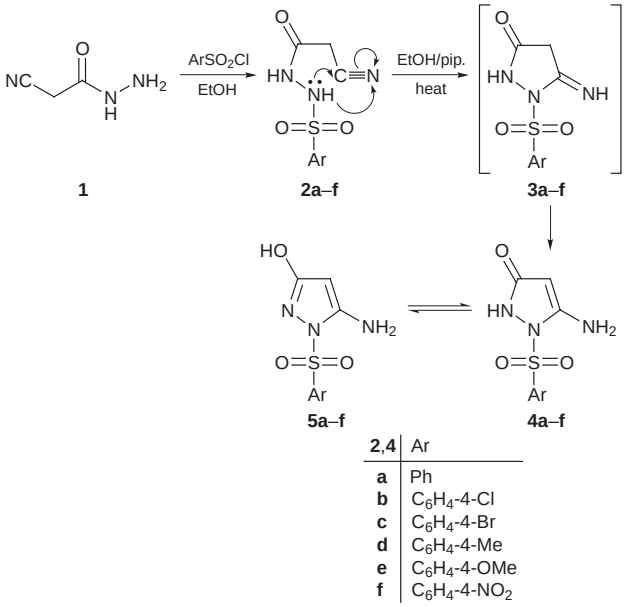
A novel synthesis of 5-amino-1-arylsulfonyl-4-pyrazolin-3-ones *via* intramolecular cyclization of cyanoaceto-*N*-arylsulfonylhydrazides is reported and the synthetic potential of the method is demonstrated.

Recent reports from our laboratory and others have demonstrated the effectiveness of a variety of *N*-sulfonylated heterocycles and other antimetabolites as antiplastic agents in a number of experimental murine tumor systems.[1–5] These compounds have been shown to cause inhibition of thymidine and uridine incorporation into DNA and RNA and appear to constitute a new class of antimetabolites. It was of interest to study their stereostructure and evaluate the effects of various structural modifications on biological activity. Recently, *N*-carboxyamidated pyrazoles were prepared in low yields from cyanoaceto-*N*-arylaminohydrazides.[6] The present investigation reports a new, one-step synthesis of *N*-sulfonylated pyrazoles *via* intramolecular cyclization of cyanoaceto-*N*-arylsulfonylhydrazides.



1 **2a–f** **3a–f** **4a–f** **5a–f**

2,4	Ar
a	Ph
b	C_6H_4-4-Cl
c	C_6H_4-4-Br
d	C_6H_4-4-Me
e	C_6H_4-4-OMe
f	C_6H_4-4-NO_2

Thus, it has been found that cyanoacetohydrazide **1** reacts with arylsulfonyl chloride in ethanol to afford the corresponding cyanoaceto-*N*-arylsulfonylhydrazides **2** in good yields. The structures of **2** were established and confirmed on the basis of their elemental analysis and spectral data (mass, IR, ^{1}H NMR). The analytical data for **2a** revealed a molecular formula $C_9H_9N_3O_3S$ (M^+, *m/z* 239), ^{1}H NMR spectroscopy was used to confirm this structure. Thus, a band at δ 3.63 was assignable to the CH_2 group, a multiplet at δ 7.56–7.86 to aromatic protons and two broad singlets at δ 10.11 and 10.40 to two NH groups (D_2O exchangeable). Compounds **2** on refluxing in ethanol containing catalytic amounts of piperidine undergo intramolecular cyclization to give the 5-amino-1-arylsulfonyl-4-pyrazolin-3-ones **4** or the tautomeric 5-amino-1-arylsulfonyl-3-hydroxypyrazole structures **5**. The hydroxy form **5** would be expected to be more stable, because of the weakened basicity of the ring nitrogen at the 2 position, in turn arising from the adjacent heteroatom and the oxygen at the 3 position, however spectral studies indicated the presence of the NH tautomer in solution for all products, thus, the ^{13}C NMR for **4a** revealed a signal at δ 170.81 assigned to a carbonyl carbon atom, and its ^{1}H NMR revealed a broad singlet at δ 10.00 assigned to an NH group (D_2O exchangeable). No significant amounts of the alternative tautomer **5** could be detected in solution.

Experimental

Melting points were uncorrected. IR spectra were obtained (KBr disc) on a Pye Unicam Spectra-1000 spectrophotometer, ^{1}H and ^{13}C NMR spectra on Wilmad 270 MHz or Varian 400 MHz spectrometers for solutions in DMSO-d_6 using $SiMe_4$ as internal standard and mass spectra on a Varian MAT 112 spectrometer. Analytical data were obtained from the Microanalytical Data Center at Cairo University.

General Procedure for Arylsulfonylcyanoacetohydrazides **2a–f**.—A mixture of cyanoacetohydrazide **1** (0.01 mol) and arylsulfonyl chloride (0.01 mol) in ethanol (30 ml) was stirred at room temperature for 24 h. The resulting solid product was filtered off and crystallized from EtOH.

2a: mp 170 °C, yield 88%. IR (KBr): ν/cm^{-1} 3407, 3284 (NH), 2215 (CN, s), 1686 (C=O, s). ^{1}H NMR (DMSO-d_6): δ 3.63 (s, 2H, CH_2), 7.56–7.86 (m, 5H, C_6H_5), 10.11 (s, br, 1H, NH), 10.40 (s, br, 1H, NH) *m/z* = 239 (Found: C, 45.36: H, 4.0; N, 17.75; S, 13.60. Calc. for $C_9H_9N_3O_3S$: C, 45.16; H, 3.79; N, 17.56; S, 13.40%).

2b: mp 222–224 °C, yield 95%. IR (KBr): ν/cm^{-1} 3400, 3320 (NH), 2220 (CN, s), 1688 (C=O, s). ^{1}H NMR (DMSO-d_6): δ 3.81 (s, 2H, CH_2), 7.50–8.10 (m, 4H, C_6H_4), 10.23 (s, br, 1H, NH), 10.93 (s, br, 1H, NH) *m/z* = 274 (Found: C, 39.67; H, 2.75; N, 15.55; S, 11.90. Calc. for $C_9H_8ClN_3O_3S$: C, 39.47; H, 2.94; N, 15.35; S, 11.71%).

2c: mp 211 °C, yield 92%. IR (KBr): ν/cm^{-1} 3380, 3300 (NH), 2221 (CN, s), 1687 (C=O, s). ^{1}H NMR (DMSO-d_6): δ 3.71 (s, 2H, CH_2), 7.44–8.15 (m, 4H, C_6H_4), 10.23 (s, br, 1H, NH), 11.05 (s, br, 1H, NH) *m/z* = 318 (Found: C, 33.74; H, 2.72; N, 13.00; S, 10.27. Calc. for $C_9H_8BrN_3O_3S$: C, 33.94; H, 2.53; N, 13.20; S, 10.07%).

2d: mp 180 °C, yield 85%. IR (KBr): ν/cm^{-1} 3380, 3220 (NH), 2220 (CN, s), 1680 (C=O, s). ^{1}H NMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 3.65 (s, 2H, CH_2), 7.11–7.77 (m, 4H, C_6H_4), 10.77 (s, br, 1H, NH), 11.21 (s, br, 1H, NH). *m/z* = 253 (Found: C, 47.60; H, 4.16; N, 16.80; S, 12.46. Calc. for $C_{10}H_{11}N_3O_3S$: C, 47.40; H, 4.37; N, 16.59; S, 12.66%).

2e: mp 166 °C, yield 90%. IR (KBr): ν/cm^{-1} 3480, 3400 3220 (NH), 2220 (CN, s), 1687 (C=O, s). ^{1}H NMR (DMSO-d_6): δ 3.62 (s, 2H, CH_2), 3.74 (s, 3H, OCH_3), 7.34–7.82 (m, 4H, C_6H_4), 11.21 (s, br, 1H, NH), 11.68 (s, br, 1H, NH). *m/z* = 269 (Found: C, 44.77; H, 4.31; N, 15.42; S, 11.71. Calc. for $C_{10}H_{11}N_3O_4S$: C, 44.55; H, 4.11; N, 15.61; S, 11.91%).

2f: mp 231–232 °C, yield 93%. IR (KBr): ν/cm^{-1} 3370, 3300 3250 (NH), 2221 (CN, s), 1688 (C=O, s). ^{1}H NMR (DMSO-d_6): δ 3.64 (s, 2H, CH_2), 7.38–8.02 (m, 4H, C_6H_4), 10.81 (s, br, 1H, NH) 11.31

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(s, br, 1H, NH), $m/z = 284$ (Found: C, 38.22; H, 2.64; N, 19.91; S, 11.48. Calc. for $C_9H_8N_4O_5S$: C, 38.01; H, 2.83; N, 19.71; S, 11.28%).

General Procedure for 5-*Amino*-1-*arylsulfonyl*-4-*pyrazolin*-3-*ones* **4a**–**f**.—A solution of **2a**–**f** (0.001 mol) in 30 ml EtOH and piperidine (0.3 ml) was refluxed for 3 h. The resulting solid product was filtered off and crystallized from EtOH–1,4-dioxane.

4a: mp 208–210 °C, yield 85%. IR (KBr): ν/cm^{-1} 3480, 3400 (NH_2, NH), 1615 (CO, s). ^1H NMR (DMSO-d_6): δ 4.34 (s, 1H, CH), 6.78 (s, br, 2H, NH_2), 7.63–7.85 (m, 5H, C_6H_5), 10.00 (s, br, 1H, NH), ^{13}C NMR (DMSO-d_6): δ 79.17 (C-4), 128.5–134.85 (ArC), 158.94 (C-5), 170.81 (C-3) $m/z = 239$ (Found: 45.36; H, 4.0; N, 17.36; S, 13.60. Calc. for $C_9H_9N_3O_3S$: C, 45.16; H, 3.79; N, 17.56; S, 13.40%).

4b: mp 255–256 °C, yield 90%. IR (KBr): ν/cm^{-1} 3600, 3520, 3400 (NH_2, NH), 1620 (CO, s). ^1H NMR (DMSO-d_6): δ 4.45 (s, 1H, CH), 6.51 (s, br, 2H, NH_2), 7.50–7.90 (m, 4H, C_6H_4), 10.62 (s, br, 1H, NH), ^{13}C NMR (DMSO-d_6): δ 80.01 (C-4), 127.8–133.92 (ArC), 158.53 (C-5), 170.25 (C-3) $m/z = 274$ (Found: C, 39.27; H, 2.75; N, 15.15; S, 11.90. Calc. for $C_9H_8ClN_3O_3S$: C, 39.47; H, 2.94; N, 15.35; S, 11.71%).

4c: mp 240–242 °C, yield 92%. IR (KBr): ν/cm^{-1} 3820, 3300 (NH_2, NH), 1625 (CO, s). ^1H NMR (DMSO-d_6): δ 4.41 (s, 1H, CH), 6.81 (s, br, 2H, NH_2), 7.34–7.80 (m, 4H, C_6H_4), 10.82 (s, br, 1H, NH), ^{13}C NMR (DMSO-d_6): δ 79.73 (C-4), 128.07–133.82 (ArC), 159.23 (C-5), 171.25 (C-3) $m/z = 318$ (Found: C, 33.74; H, 2.32; N, 13.40; S, 10.27. Calc. for $C_9H_8BrN_3O_3S$: C, 33.94; H, 2.53; N, 13.20; S, 10.07%).

4d: mp 203 °C, yield 84%. IR (KBr): ν/cm^{-1} 3550, 3500, 3420 (NH_2, NH), 1630 (CO, s). ^1H NMR (DMSO-d_6): δ 2.34 (s, 3H, CH_3), 4.48 (s, 1H, CH), 6.88 (s, br, 2H, NH_2), 7.41–7.92 (m, 4H, C_6H_4), 10.85 (s, br, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 18.22 (CH_3) 77.82 (C-4), 127.23–133.24 (ArC), 156.23 (C-5), 169.89 (C-3) $m/z = 253$ (Found: C, 47.20; H, 4.16; N, 16.39; S, 12.46. Calc. for $C_{10}H_{11}N_3O_3S$: C, 47.40; H, 4.37; N, 16.59; S, 12.66%).

4e: mp 217 °C, yield 91%. IR (KBr): ν/cm^{-1} 3620, 3580, 3410 (NH_2, NH), 1618 (CO, s). ^1H NMR (DMSO-d_6): δ 3.78 (s, 3H, OCH_3), 4.51 (s, 1H, CH), 6.70 (s, br, 2H, NH_2), 7.30–7.89 (m, 4H, C_6H_4), 11.12 (s, br, 1H, NH). $m/z = 269$ (Found: C, 44.77; H, 4.31; N, 15.42; S, 11.71. Calc. for $C_{10}H_{11}N_3O_4S$: C, 44.58; H, 4.11; N, 15.61; S, 11.91(%).

4f: mp 260–262 °C, yield 88%. IR (KBr): ν/cm^{-1} 3560, 3485, 3400 (NH_2, NH), 1628 (CO, s), cm^{-1}. ^1H NMR (DMSO-d_6): δ 4.55 (s, 1H, CH), 6.66 (s, br, 2H, NH_2), 7.41–7.92 (m, 4H, C_6H_4), 11.0 (s, br, 1H, NH). $m/z = 284$ (Found: C, 38.22; H, 2.64; N, 19.91; S, 11.48. Calc. for $C_9H_8N_4O_5S$: C, 38.01; H, 2.83; N, 19.71; S, 11.28%).

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References

1 G. E. H. Elgemeie, A. M. E. Attia, D. S. Farag and S. M. Sherif, *J. Chem. Soc., Perkin Trans.* 1, 1994, 1285.
2 G. E. H. Elgemeie and B. A. W. Hussain, *Tetrahedron*, 1994, **50**, 199.
3 G. E. H. Elgemeie, S. E. El-Ezbawy, H. A. Ali and A. K. Mansour, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 738.
4 P. Giori, A. C. Veronese, C. B. Vicentini and M. Guarneri, *J. Heterocycl. Chem.*, 1985, **22**, 1093.
5 T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P.W. Collina, S. Doctor, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Ragers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhultzen, Y. Y. Zhang and P. C. Isakson, *J. Med. Chem*., 1997, **40**, 1347.
6 J. T. Drummond and G. Johnson, *J. Heterocycl. Chem.*, 1988, **25**, 1123.