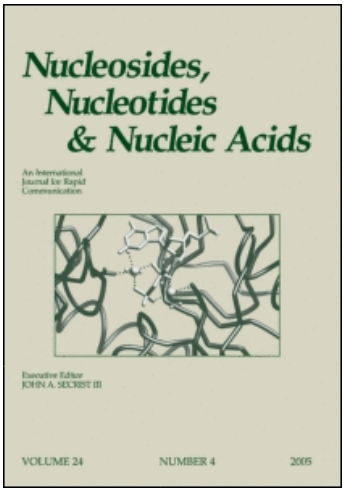

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Abd El-Hamid Ismail[a]; Abdel Aleem Hassan Abdel Aleem[a]; Hamed Abdel Bary[a]; Samy El-Assaly[a]
[a] Chemistry Department, Menoufia University, Shebin El-Koom, Egypt

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SYNTHESIS OF 1-(2-NAPHTHYLSULFONYL)PYRAZOLE-*C*-GLYCOSIDES

Abd El-Hamid Ismail,* Abdel Aleem Hassan Abdel Aleem, Hamed Abdel Bary, and Samy El-Assaly

Chemistry Department, Faculty of Science, Menoufia University, Shebin El-Koom, Egypt

ABSTRACT

2-Naphthylsulfonylhydrazine was reacted with aromatic aldehydes or aldehydo sugars to give the corresponding hydrazones which undergo Michael addition reactions with malononitrile or ethyl cyanoacetate to form pyrazole derivatives.

INTRODUCTION

Some pyrazoles are biologically active and have been used as analgesic anti-inflammatory,[1] chemical control substance for pharmacological characterization of histamine receptors,[2] antibacterial activity against Escherichia coli,[3] sedative and hypontic,[4] saluretic effect,[5] a good activity as platelet aggregation inhibitor,[6] a prostaglandin synthetase inhibitor[7] and an antirheumatic drug.[8]

*Fax: 20 48 235689

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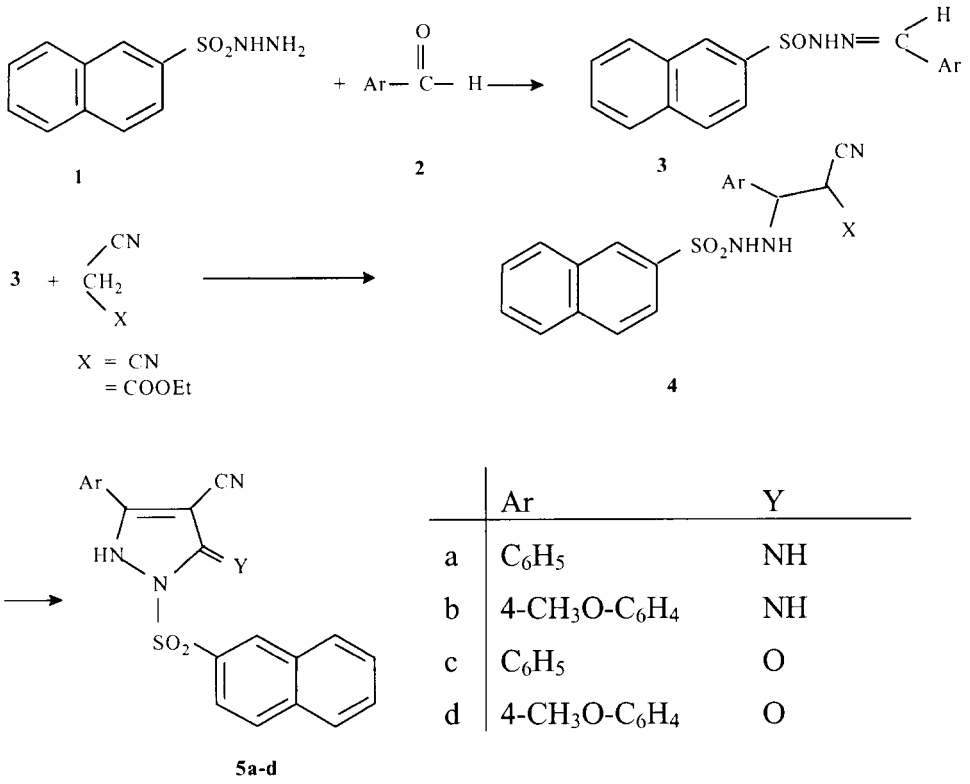
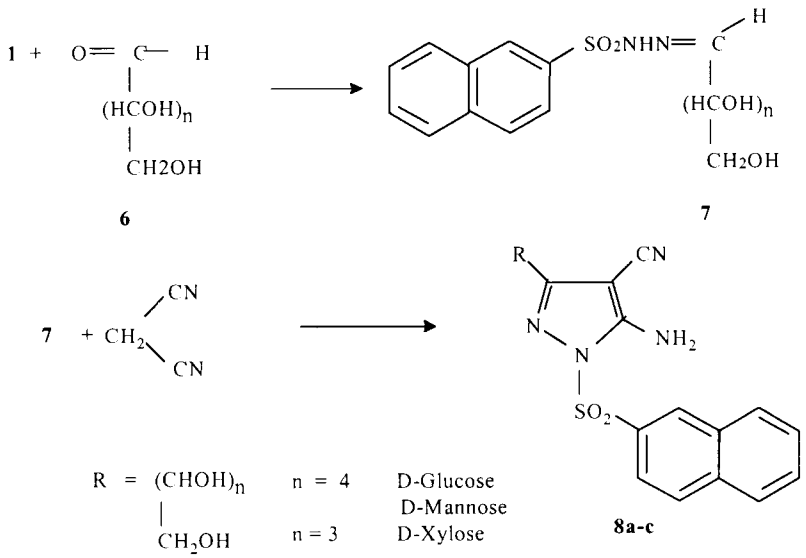
RESULTS AND DISCUSSION

The aim of the work in this paper is the synthesis of naphthylsulfonylpyrazoles and naphthylsulfonylpyrazole-*C*-glycosides. We expect that the naphthylsulfonyl group will increase the biological activity of the pyrazole ring. Thus, treatment of 2-naphthalene sulphonyl chloride with hydrazine hydrate produced 2-naphthyl-sulfonylhydrazine **1**. Condensation of 2-naphthylsulfonylhydrazine **1** with equimolar amounts of aromatic aldehydes namely, benzaldehyde and anisaldehyde **2** in ethanol and in presence of glacial acetic acid as a catalyst yielded the corresponding hydrazones **3**. 2-Naphthyl-sulfonylhydrazones **3** were allowed to react with malononitrile and/or ethyl cyanoacetate to afford 1-(2-naphthylsulfonyl)pyrazoles **5a–d** after purification by column chromatography. The reaction may be occur as follows: Initial addition of active methylene moiety to the double bond of hydrazones **3** affords an acyclic Michael adduct **4**. The intermediate **4** cyclizes by internal addition to the cyano group or internal substitution at the ester carbonyl followed by aromatization form pyrazole derivatives **5a–d** (Sch. 1).



	Ar	Y
a	C_6H_5	NH
b	4-CH_3O-C_6H_4	NH
c	C_6H_5	O
d	4-CH_3O-C_6H_4	O

Scheme 1.



Scheme 2.

Pyrazole-*C*-glycosides were prepared via 1,3-dipolar cycloaddition reaction of nitrilimines with acetylene derivatives[9,10] and methylacrylate.[11] In our work 2-naphthylsulfonylhydrazine **1** was reacted with D-glucose, D-mannose or D-xylose **6** to form the corresponding hydrazones **7**. The sugar-hydrazones **7** were reacted with malononitrile in ethanol and with a catalytic amount of triethylamine via Michael addition to afford 1-(2-naphthylsulfonyl) pyrazole-*C*-glycosides **8** (Sch. 2).

EXPERIMENTAL

NMR spectra were recorded on a Bruker 250 FT NMR spectrometer, TMS as internal standard. The silica gel (0.040–0.63 mm) used for CC was purchased from Merck. Analytical TLC was performed on percolated TLC sheets (Merk silica gel 60 F_{254} 0.2 mm). Results of elemental analysis were in acceptable range.

General Procedure for Compound 5a–d

A mixture of 2-naphthylsulfonylhydrazones **3** (1 mmole) and malononitrile or ethyl cyanoacetate (1 mmole) in 10 mL of ethanol with a catalytic amount of triethylamine was boiled under reflux 6 h. The solvent was evaporated under vacuum. The residue was purified by column chromatography with chloroform/methanol (90:10, v/v) to give **5a–d**.

5-Amino-4-cyano-3-phenyl-1-(2-naphthylsulfonyl)pyrazole (**5a**)

Yield (54%); m.p. 182°C. ^{1}H-NMR (DMSO-d_δ): δ 11.64 (s, 1H, NH), 8.53-7.39 (m, 9H, ArH); Anal. Calcd for $C_{20}H_{14}N_4O_2S$ (374.42): C, 64.15; H, 3.27; N, 14.96. Found: C, 64.43; H, 3.76; N, 14.69.

5-Amino-4-cyano-3-(4-methyoxyphenyl)-1-(2-naphthylsulfonyl)pyrazole (**5b**)

Yield (56%); m.p. 188°C. ^{1}H-NMR (DMSO-d_δ): δ 11.50 (s, 1H, NH), 9.23-8.65 (m, 10H, ArH), 3.59 (s, 3H, C$\underline{H}_3$O); Anal. Calcd for $C_{21}H_{16}N_4O_3S$ (404.45): C, 62.34; H, 3.99; N, 13.85. Found: C, 62.66; H, 4.20; N, 13.69.

4-Cyano-3-phenyl-1-(2-naphthylsulfonyl)pyrazole-5-one (**5c**)

Yield (45%); m.p. 191°C. ^{1}H NMR (DMSO-d_δ): δ 11.53 (s, 1H, NH), 8.77-7.51 (m, 8H, ArH); Anal. Calcd for $C_{20}H_{13}N_3O_3S$ (375.4): C, 63.99; H, 3.49; N, 11.19. Found: C, 63.72; H, 3.40; N, 11.45.

4-Cyano-3-(4-methoxyphenyl)-1-(2-naphthylsulfonyl)pyrazole-5-one (**5d**)

Yield (54%); m.p. 182°C. ^{1}H NMR (DMSO-d_δ): δ 11.4 (s, 1H, NH), 8.50-7.86 (m, 11H, ArH), 3.11 (s, 3H, OC$\underline{H}_3$); Anal. Calcd for $C_{21}H_{15}N_3O_4S$ (404.43): C, 62.21; H, 3.72; N, 10.35. Found: C, 62.53; H, 3.60; N, 10.72.

General Procedure for Hydrazones 3a, b and 7a–c

A mixture of 2-naphthylsulfonylhydrazine (1 mmole) and D-Glucose, D-Mannose, D-Xylose, benzaldehyde or anisaldehyde in 10 mL of ethanol with a few drops of acetic acid was boiled under reflux for 1 h. After concentration and cooling, the separated precipitate was filtered off and crystallized from the appropriate solvents (**3a**, **b** from ethanol, **7a–c** from 1,4-dioxane).

Benzaldehyde (2-naphthylsulfonyl)hydrazone (**3a**)

Yield (81%); m.p. 188°C; Anal. Calcd for $C_{17}H_{14}N_2O_2S$ (310.40): C, 65.79; H, 4.55; N, 9.03. Found: C, 75.61; H, 4.80; N, 9.11.

Anisaldehyde (2-naphthylsulfonyl)hydrazone (**3b**)

Yield (70%); m.p. 192°C; Anal. Calcd for $C_{18}H_{16}N_2O_3S$ (340.36): C, 63.52; H, 4.74; N, 8.23. Found: C, 63.29; H, 4.81; N, 8.00.

D-Glucose 2-naphthylsulfonylhydrazone (**7a**)

Yield (76%); m.p. 173°C; Anal. Calcd for $C_{16}H_{20}N_2O_7S$ (384.4): C, 49.99; H, 5.24; N, 7.28. Found: C, 50.5; H, 5.40; N, 7.52.

D-Mannose 2-naphthylsulfonylhydrazone (**7b**)

Yield (72%); m.p. 179°C; Anal. Calcd for $C_{16}N_{20}N_2O_7S$ (384.4): C, 49.99; H, 5.25; N, 7.28. Found: C, 49.52; H, 5.00; N, 7.43.

D-Xylose 2-naphthylsulfonylhydrazone (**7c**)

Yield (73%); m.p. 168°C; Anal. Calcd for $C_{15}H_{18}N_2O_6S$ (354.37): C, 50.84; H, 5.12; N, 7.90. Found: C, 50.73; H, 5.30; N, 7.63.

General Procedure for Compound 8a–c

A mixture of 2-naphthylsulfonylhydrazones **7** (1 mmole) and malononitrile (1 mmole) in 10 mL absolute ethanol and 1 mL triethylamine was boiled under reflux for 6 h. The solvent was evaporated under vacuum. The residue was purified by column chromatography with chloroform/methanol (90:10, v/v) to produce compounds **8a–c**.

5-Amino-4-cyano-3-(D-gluco-1,2,3,4,5,pentahydroxypentyl)-1-(2-naphthyl sulfonyl)pyrazole (**8a**)

Yield (53%); m.p. 180°C; ^{1}H-NMR (DMSO-d_δ): δ 9.77 (s, 1H, NH), 8.55-7.60 (m, 7H, ArH), 5.67 (s, 1H, OH-1′), 4.61 (s, 1H, H-1′), 4.35 (m, 3H, OH-2′, OH-3′ and OH-4′), 4.01 (m, 1H, OH-5′), 3.91 (m, 3H, H-2′, H-3′ and H-4′), 2.58 (m, 2 H,$\underline{CH_2}$OH). ^{13}C NMR (DMSO-d_δ): δ 136.58, 134.26, 131.65, 129.20, 128.81, 128.62, 128.44, 127.70, 127.36, 122.90 (C arom.), 112.11(C≡N), 89.96 (C-1′), 77.96 (C-2′), 76.80 (C-3′), 70.61 (C-4′), 61.77 C_5'); Anal. Calcd for $C_{19}H_{20}N_4O_7S$ (448.45): C, 50.88; H, 4.5; N, 12.49. Found: C, 50.71; H, 4.43; N, 12.62.

5-Amino-4-cyano-3-(D-manno-1-1,2,3,4,5,pentahydroxypentyl)-(2-naphthyl sulfonyl)pyrazole (**8b**)

Yield (55%); m.p. 178°C; ^{1}H-NMR (DMSO-d_δ): δ 9.02 (s, 1H, NH); 8.52-7.58 (m, 7H, ArH) 4.70 (m, 2H, OH-1′ and H-1′) 4.58 (m, 3H, OH-2′, OH-3′, OH-4′), 3.98 (m, 1H, OH-5′), 3.61 (m, 3H, H-2′, H-3′, H-4′); 2.89 (m, 1 H, C$\underline{H}_2$OH). ^{13}C NMR (DMSO-d_δ): δ 136.51, 134.33, 131.70, 129.22, 128.85, 128.41, 127.75, 127.32, 124.94, 122.80 (C arom.), 112.33 (C≡N), 91.71 (C-1′), 76.80 (C-2′), 70.28 (C-3′), 69.40 (C-4′), 66.75 (C-5′); Anal. Calcd for $C_{19}H_{20}N_4O_7S$ (448.48): C, 50.88; H, 4.50; N, 12.49. Found: C, 50.90; H, 5.00; N, 12.55.

5-Amino-4-cyano-3-(D-xylo-1,2,3,4,tetrahydroxybutyl)-1-(2-naphthyl sulfonyl)pyrazole (**8c**)

Yield (53%); m.p.; 188°C; ^{1}H-NMR (DMSO-d_δ): δ 11.39 (s, 1H, NH), 8.51-7.86 (m, 7H, ArH), 5.40 (s, 1H, OH-1′), 4.91 (s, 1H, H-1′), 4.45 (m, 1H, OH-2′), 4.12 (m, 1H, OH-3′), 3.94 (m, 1H, OH-4′), 3.60 (m, 2H, H-2′ and H-3′), 2.94 (m, 2H, C$\underline{H}_2$OH); ^{13}C NMR (DMSO-d_δ): δ 136.22, 134.39, 131.76, 129.29, 128.90, 127.84, 127.35, 123.07 (C arom.), 112.00 (C≡N), 91.20 (C-1′) 76.63 (C-2′), 70.18 (C-3′), 69.70 (C-4′); Anal. Calcd for $C_{18}H_{18}N_4O_6S$ (418.43): C, 51.66; H, 4.34; N, 13.38. Found: C, 15.50; H, 4.46; N, 13.22.

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