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Note

A Novel synthesis of nitrofuran containing 1,3,4,5-tetra substituted pyrazoles via 1,3-dipolar addition reaction

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A hitherto unreported novel series of nitrofuran containing 1,3,4,5-tetra substituted pyrazole derivatives are prepared by the 1,3-dipolar cycloaddition reaction between 1-aryl-3-(5-nitro-2-furyl)propynones **1** with 4-substituted-3-aryl sydnones **2**. The structures of these compounds are established by elemental analysis, IR, ^{1}H NMR and mass Spectral data. The new compounds are also screened for their antibacterial and antifungal activity and most of them showed significant activity.

Keyword: Sydnones, acetylinic ketone, pyrazoles, dipolar addition, biological activity

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Sydnones are novel class of mesoionic aromatic heterocycles which serves as versatile synthetic intermediates with a masked azo methine unit. Sydnones having 4-position free undergo electrophilic substitution reactions such as halogenation, nitration, sulfonation, acylation, formylation at this position[1].

The pyrazole nucleus constitutes an interesting class of organic compound with diverse chemical applications[2]. Pyrazole and nitrofuran derivatives have been found to have diverse applications in medicine and agriculture[3]. A number of patents and papers advocate the importance of pyrazole derivatives containing nitrofuran moiety[4]. However there are only few reports on the synthesis of pyrazoles carrying nitrofuran moiety[5]. Also it is difficult to functionalise pyrazole ring at position-5 by conventional methods. Any electrophilic substitution reaction involves preferential substitution of the pyrazole ring at position-4 and only when this position is substituted the other position react[6]. The 1,3-dipolar cycloaddition reactions offers a convenient synthetic route for pyrazole derivatives. Kepping in view of these observations it was planned to synthesize pyrazoles carrying bromo, acetyl or formyl group at position-5 and also carrying nitrofuran substituent by the 1,3-dipolar cycloaddition of sydnones carrying appropriate substituent at position-4 with acetylenic ketones carrying nitrofuran moiety.

In the present protocol 1-aryl-3-(5-nitro-2-furyl) propynones **1a-c** were choosen as the dipolarophile for the 1,3-dipolar cycloaddition. The propynones[7] **1a-c** and 3-aryl-4-substituted sydnones[8-11] **2a-e** were prepared following the literature method. The reaction between 1-aryl-3-(5-nitro-2-furyl) propynones **1a-c** with 4-substituted 3-aryl sydnones **2a-e** in xylene under reflux resulted in the regiospecific formation of 1-aryl-3-(5-nitro-2-furyl)-4-benzoyl-5-substituted pyrazoles **3** in yields ranging from 61-79% (**Table I** and **Scheme I**).

The reaction involves a 1,3-dipolar cycloaddition of sydnones behaving like a cyclic azomethine imine to the corresponding acetylenic compounds with the extrusion of carbondioxide followed by aromatization. The structure of these compounds **3** were confirmed by analytical and spectral data. The IR spectra of **3a** showed absorption bands in the region of 1798 cm^{-1} for the carbonyl stretching of the formyl group. The carbonyl stretching of the keto group appeared at 1635 cm^{-1}. The C-H stretching band was observed in the region of 2850-3051cm^{-1}. The mass spectrum of **3a** showed the molecular ion peak at *m/z* 401, consistent with the molecular formula $C_{22}H_{15}N_3O_5$. The ^{1}H NMR spectrum of **3a** showed the signals at δ 2.47 integrating for three protons of methyl group. The *ortho* and the *meta*-protons of the *p*-tolyl group appeared as two doublets centered at δ 7.11 (J = 3.8 Hz) and δ 7.37 (J = 3.8 Hz) each integrating for two protons. The nitrofuryl β-protons appeared as two doublets centered at δ, 7.35 (J = 8 Hz) and 8.07 (J = 8 Hz) integrating for one proton each. The remaining aromatic protons appeared as multiplets in the region of δ 7.52 to 7.77 integrating for 5-protons. The signal due to formyl proton appeared as a singlet at δ 9.59 integrating for one proton.

Biological activity

The newly synthesized compounds were evaluated for their antibacterial and antifungal activities by disk

Table I — Characterization data of compounds **3a-j**

Compds	R_1	R_2	X	Mol.Formule (Mol.Wt)	Yield (%)	m.p °C	Found (Calculated)% C	H	N
3a	Me	H	CHO	$C_{22}H_{15}N_3O_5$ (401)	79	114-16	65.70 (65.83	3.72 3.74	10.41 10.47)
3b	Me	Me	CHO	$C_{23}H_{17}N_3O_5$ (415)	74.2	133-35	66.41 (66.50	4.10 4.09	10.11 10.12)
3c	Me	OMe	Br	$C_{22}H_{16}BrN_3O_5$ (481/483)	61.9	143-45	54.75 (54.77	3.30 3.31	8.72 8.71)
3d	OMe	OMe	Br	$C_{22}H_{16}BrN_3O_6$ (497/499)	68.8	120-22	52.93 (53.01	3.20 3.21	8.41 8.43)
3e	Me	H	Br	$C_{21}H_{14}BrN_3O_4$ (451/453)	72.9	160-62	55.69 (55.75	3.10 3.09	9.27 9.29)
3f	Me	Me	Br	$C_{22}H_{16}BrN_3O_4$ (465/467)	65.8	167-69	56.62 (56.65	3.39 3.43	9.03 9.01)
3g	OMe	Me	Br	$C_{22}H_{16}BrN_3O_5$ (481/483)	62.8	195-97	54.75 (54.77	3.32 3.31	8.70 8.71)
3h	H	Me	Br	$C_{21}H_{14}BrN_3O_4$ (451/453)	72.1	197-98	55.62 (55.75	3.1 3.09	9.3 9.29)
3i	OMe	H	$COCH_3$	$C_{23}H_{17}N_3O_6$ (431)	74.2	110-12	64.0 (64.03	3.92 3.94	9.72 9.74)
3j	OMe	OMe	$COCH_3$	$C_{24}H_{19}N_3O_7$ (461)	72.9	125-27	62.4 (62.47	4.11 4.12	9.10 9.11)

Solvent for recrystalization: Ethanol +DMF::10:1

diffusion technique.[12] The test organisms employed for antibacterial studies were *E.coli*, *P.aeruginosa*, *S.aureus* and *B.subtilis*. Furacin being the standard drug. The antifungal activity was studied against *Candida albicans.* Fluconazol was the standard. DMF was used as solvent control. The results of the biological studies were given in **Table II**. Compounds **3b** and **3f** showed highest activity among all the tested compounds. This shows that the presence of methyl group at position R_1 and R_2 has enhanced the activity.

Experimental Section

The melting points of the newly synthesized compounds were determined in open capillaries and are uncorrected. The IR spectra (KBr disc) were recorded on a JASCO FT IR 430 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AC 300F (300 MHz) NMR spectrometer using DMSO-d_6 as solvent and TMS as internal standard. The chemical shifts are expressed in δ scale downfield from TMS. Mass spectra were recorded either on a Jeol JMS-D 300 mass spectrometer or API 3000 LCMS instrument operating at 70 eV.

Preparation of 3 (General Procedure) 1-Aryl-3-(5-nitro-2-furyl)propynone **1** (0.01 mole) and 3-aryl-4-substituted sydnone **2** (0.01 mole) in xylene (10 mL) were refluxed for 3-4 hr. After completion of the reaction (Monitored by TLC and evolution of CO_2) the excess solvent was removed by distillation under reduced pressure. The crude product obtained was recrystallized from a mixture of ethanol and DMF to afford pure products **3a-j** in 61-79% yield **Table I**.

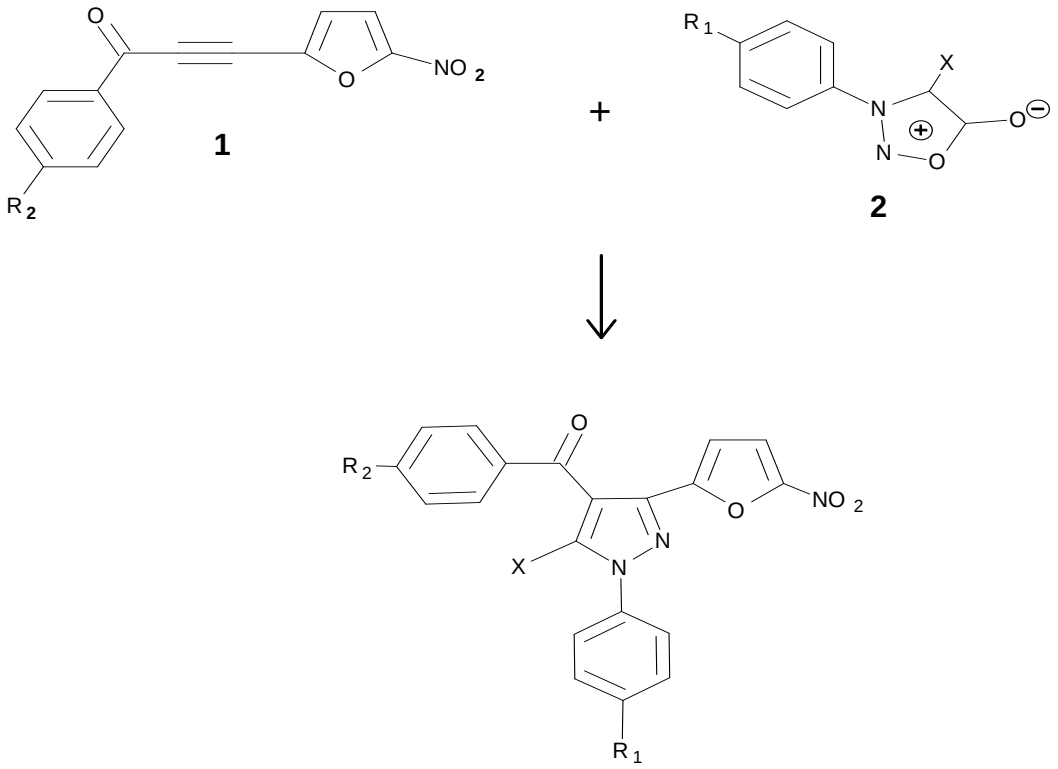
Spectral data for compounds 3b-3j

3b: ^{1}H NMR (DMSO-d_6): δ, 2.47 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 7.10-7.53 (m 8H Ar-H), 7.32 (d, 1H, NF-4H), 8.04 (d, 1H, NF-3H), 9.58(s, 1H, CHO); MS for $C_{23}H_{17}N_3O_5$; 415(M^+), 375 (M^+-NO_2), 347 (M+-NO_2-CO).

3d:^{1}H NMR (DMSO-d_6): δ, 3.81 (s, 3H, OCH_3) 3.98 (s, 3H, OCH_3), 6.87-7.87 (m, 10H, Ar-H, NF-3H & 4H), MS for $C_{22}H_{16}BrN_3O_6$: $M^{+\cdot}$ 497/499, 418 (M+-Br), 374 (M+-Br-NO_2).

3e: ^{1}H NMR (DMSO-d_6): δ, 2.43 (s, 3H, CH_3) 6.9 (d, 1H, NF-4H) 7.22-7.81 (m, 10H, Ar-H&NF-3H), MS for $C_{21}H_{14}BrN_3O_4$: M^+, 451/453; 405/407 (M+-NO_2); 326 (M^+-NO_2-Br).

3f: ^{1}H NMR (DMSO-d_6): δ, 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3); δ 7.29 (d, 2H, *ortho* protons of *p*-tolyl), 7.32 (d, 2H, *meta* protons of *p*-tolyl) 7.38 (d, 2H, *ortho* protons of *p*-methylbenzoyl), 7.50 (d, 2H, *meta*



3

1 a, R_2=H
b, R_2=Me
c, R_2=OMe

2 a, R_1=Me, X=CHO
b, R_1=Me, X=Br
c, R_1=OMe, X=Br
d, R_1=H, X=Br
e, R_1=OMe, X=$COCH_3$

Scheme I

Table II — Antibacterial and antifungal activity data of 1-aryl-3-(5-nitro-2-furyl)-4-benzoyl-5-substituted pyrazoles

Compd	Antibacterial activity MIC in µg/mL				Antifungal activity MIC in µg/mL
	E.coli	*B.subtilus*	*S.aureus*	*P.aeruginosa*	*C.albicans*
3a	6.25	3.125	12.5	6.25	6.25
3b	6.25	3.125	3.125	3.125	3.125
3c	3.125	6.25	6.25	6.25	6.25
3d	6.25	12.5	12.5	6.25	6.25
3e	3.125	6.25	6.25	6.25	6.25
3f	3.125	6.25	3.125	6.25	3.125
3g	12.5	12.5	12.5	12.5	12.5
3h	6.25	6.25	12.5	6.25	6.25
3i	6.25	6.25	12.5	6.25	6.25
3j	12.5	6.25	12.5	6.25	6.25
Furacin (Std)	6.25	6.25	6.25	6.25	-
Flucanazol(Std)	-	-	-	-	6.25

Index for Antibacterial and Antifungal activity:
MIC : Minimum inhibitory concentration
Incubation period : 24 hr at 37°C
Solvent control : DMF

protons of *p*-methylbenzoyl), 7.66 (d, 1H, NF-4H, *J*=8 Hz); 7.77 (1H, NF-3H, *J*=8 Hz); MS for $C_{22}H_{16}BrN_3O_4$: M^+, 465/467, 419/421 (M^+-NO_2), 386 (M^+-Br), 341 (M^+-Br-NO_2).

3g: MS for C22H16BrN3O4: M+ 481/483, 402 (M^+-Br).

3h: ^{1}H NMR ($CDCl_3$): δ, 2.44 (s, 3H, CH_3) 6.9-7.65 (m, 10H, Ar-H & NF-4H), 7.81 (d, 1H, NF-3H); MS for $C_{21}H_{14}BrN_3O_4$: M^+, 451/453, 372 (M^+-Br), 326 (M^+-Br-NO_2).

3i: ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H,-$COCH_3$), 3.92 (s, 3H, OCH_3), 7.02 (d, 2H, *ortho* protons, *p*-anisyl) 7.1 (d, 1H, NF-4H); 7.46-7.62 (m, 5H, Ar-H) 8.15 (d, 2H, *meta* protons of *p*-anisyl).

3j: ^{1}H NMR (DMSO-d_6): δ 2.58 (s, 3H,-$COCH_3$), 3.86 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3) 7.1-8.3 (m, 10H, Ar-H, NF-3H and 4H); MS for $C_{24}H_{19}N_3O_7$: M^+, 461, 415 (M^+-NO_2).

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