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Research Article

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Comparison of two routes for synthesis 5-aminopyrazole derivative

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ABSTRACT

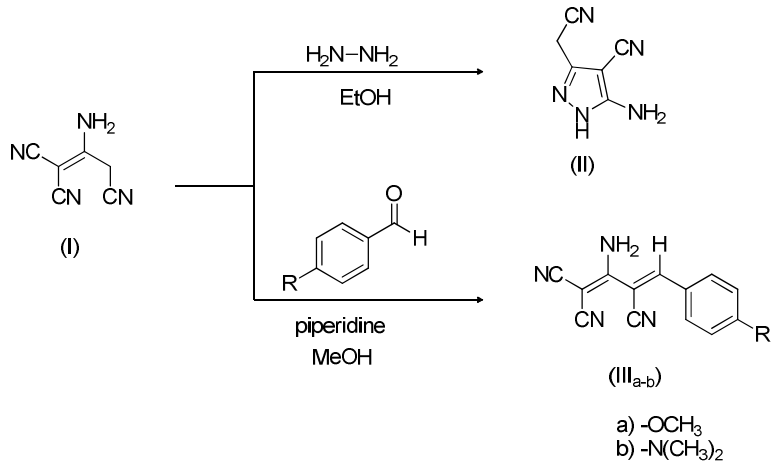
Attempting to synthesis 5-aminopyrazole derivatives by two routs carried in same condition, but in reverse sequence in reagent addition, this lead to completely different products, to identify the formed product NMR, IR and Mass spectroscopy techniques used.

Keywords: 5-aminopyrazole, malononitrile dimer, donor-acceptor dyes, push-pull dyes.

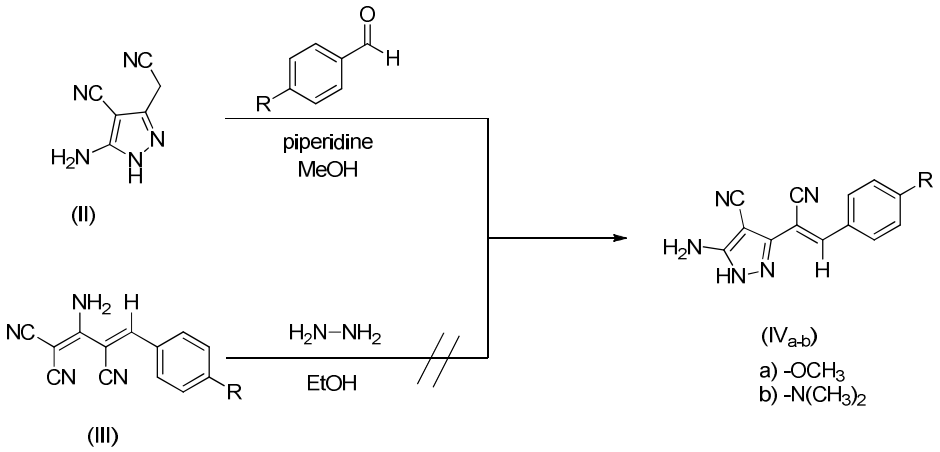
INTRODUCTION

Pyrazolesare well known compoundsforhaving pharmacological effects on human and used for drug preparation,also as potentinsecticides and herbicides, and as antitumor, anti-inflammatory, antimicrobial and antipsychotic agents.

The synthesis of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile (II)was reported,[1-3]and the procures for this compound was malononitrile dimer (I) and hydrazine hydrate.[4]On the other hand reaction of malononitrile dimer with aromatic aldehyde had been reported[1,5] to give 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (III).



Our interest was to prove that reaction of malonitrile dimer first with hydrazine followed by the aldehyde or with aldehyde followed by hydrazine would give the same result.



EXPERIMENTAL SECTION

H^1-NMR spectra were measured in hexadeuterodimethylsulfoxid (DMSO-d_6) , deuterochloroform ($CDCl_3$), hexadeuteroacetond(CD_3COCD_3) and heptadeuterodimethylformamaide (($(CD_3)_2NCDO$) solution, on Bruker DPX 300 & 400 MHz NMR and jeol-ECA500 Japan 500MHz with chemical shift (δ) expressed in ppm down field from tetramethylsilane as an internal stander (TMS δ =0). The multiplicity of the signal is as follow: s (Singlet), d (Doublet).

C^{13}-NMR were measured on Bruker DPX 75&100 MHz NMR and jeol-ECA500 Japan 125MHz; internal reference TMS δ= 0.

FT-IR measurements were measured using a Perkin Elmer 2000 FT-IR system. The positions of absorptions have been expressed in wave number units (cm^{-1}).

Mass spectroscopy was done using direct inlet unit (DI-50) of shimadzu GC/MS – QP5050A, Ionization mode: EI, Ionization voltage: 70 ev.

Melting points (m.p) of the synthesized compounds were determined in capillary tubes using Stuart scientific apparatus and are uncorrected.

Analytical glass and aluminum plates were used with Kieselgel G or Kieselgel GF 254 (Merck). The plates were run in the following systems: (Ethyl acetate) and (Chloroform – methanol) different ratios, and examined under ultra-violet light Model UV GL-58/50 Hz Lampe.

Synthesis of malononitrile dimer [I].
The synthesis of malononitrile dimer was carried out using Mittelbach[4] methods. Yield: 2.7g (82%),; mp. : 169-172°C (water); IR: 3345, 3199, 2952, 2914, 2263, 2226, 2210, 1658,1551 cm^{-1}.;H^1 NMR (300MHz, DMSO-d6): δ: 3.82 (2H, s, CH_2); 8.9 & 9.0 (2H, s, exchangeable, NH_2).; C^{13} NMR (75MHz, DMSO-d6): δ: 22.18(1C), 49.92(1C), 114.21(1C), 114.57(1C), 115.33(1C), 164.70(1C).; MS(EI): m/z= 132.10 , 92.8, 65.20.

Synthesis of 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile [II].
To a solution of (2.64g, 0.02 mol) of 2-aminoprop-1-ene-1,1,3-tricabonitrile(I) in 20 ml. of boiling ethanol was added (1.1 g, 0.022 mol) 85% hydrazine hydrate at such a rate that the reaction mixture continued to boil without external heating. The strongly exothermic reaction was accompanied by a vigorous evolution of ammonia. After addition of the hydrazine hydrate was completed, the reaction mixture was heated under reflux for an additional 15 mints and then allowed to cool slowly to room temperature. It was then chilled, filtered and recrystallized from glacial acetic acid to give compound (II). Yield: (71%); mp. : 197-199°C.; IR:. 3397, 3355, 3199, 2268, 2216, 1686, 1657, 1598, 1536 cm^{-1}. ;H^1 NMR (300MHz, Acetone-d_6): δ: 3.9 (2H, s, CH_2); 6.09(2H, s, D_2O exchangeable, NH_2);

11.35(1H, s, D_2O exchangeable NH). ;C^{13} NMR (75MHz, Acetone-d_6): δ:16.08(1C), 73.08(1C), 113.07(1C),115.82(1C), 143.70(1C), 154.03(1C). MS (EI): m/z = 147.20, 91.15, 63.80, 66.

Synthesis of 4-aryl-2-aminobut-1,3-diene-1,1,3-tricarbonitrile[IIIa-b]

General procedure:2-aminoprop-1-ene-1,1,3-tricabonitrile and substituted benzaldehyde were refluxed in10 ml methanol with few drops of selected base. On cooling to room temperature the product was precipitated, filtered and washed with cold methanol.

No.	Ar	base	Mole ratio	R. time
(III_a)	4-methoxyphenyl	piperidine	1:1	90 mins.
(III_b)	4-N,N-dimethylaminophenyl	piperidinium acetate	1:2	60 mins.

2-amino-4-(4-methoxyphenyl)buta-1,3-diene-1,1,3-tricarbonitrile (IIIa): Yield: (34%); mp. : 198-200°C (methanol).; IR: 3342, 3217, 2231, 2216, 2203, 1679, 829 .cm^{-1}. ;H^1 NMR (300MHz, DMSO-d_6): δ:3.84 (3H, s, CH_3); 7.14&7.17 (2H, d, Ar-H); 7.92(1H, s, CH); 7.96&7.99(2H, d, Ar-H);8.96&9.02 (2H, s, D_2O exchangeable, NH_2).; C^{13} NMR (75MHz, DMSO-d_6): δ: 49.45(1C), 55.68(1C), 98.26(1C), 114.79(1C), 114.94(1C), 115.38(1C), 115.58(2C), 124.10(1C), 132.59(2C), 152.73(1C), 163.09(1C), 165.90(1C).; MS (EI): m/z = 250.75, 224.75, 66.15.

2-amino-4-(4-(dimethylamino)phenyl)buta-1,3-diene-1,1,3-tricarbonitrile(III_b): Yield: (85%)
mp. : 268-269 °C (ethanol).; IR: 3342, 3210, 2227, 2213, 2195, 1680, 1615, 1577, 1518.cm^{-1}. ;
H^1 NMR(300MHz, DMSO-d_6): δ:3.807 (6H, s, $2CH_3$); 6.82&6.85 (2H, d, Ar-H); 7.75(1H, s, CH); 7.86&7.89(2H, d, Ar-H);8.74 (2H, s, D_2O exchangeable, NH_2).;C^{13} NMR(62.5MHz, DMSO-d_6): δ: 48.22(2C), 92.10(1C), 111.62(1C), 115.41(1C), 115.95(1C), 116.56(1C), 118.42(2C), 120.61(1C), 133.10(2C), 152.73(1C), 153.37(1C), 166.79(1C).
MS (EI): m/z = 263.4, 248, 219.

Synthesis of 5-amino-3-(1-cyano-2-(4-aryl)vinyl)-1H-pyrazole-4-carbonitrile

General procedure: A mixture of 5-amino-3-cyanomethyl-1H-pyrazole-4-carbonitrile (10 mmol) and 4-substituted benzaldehyde (10mmol) were refluxed in 50 ml methanol and few drops of selected base for 3-4hurs. On cooling to room temperature a precipitate was formed, filtered and washed with cold methanol.

No.	Ar	base	Mole ratio	R. time
(IV_a)	4-methoxyphenyl	piperidine	1:1	4 hrs.
(IV_b)	4-N,N-dimethylaminophenyl	piperidinium acetate	1:2	6hrs.

5-amino-3-(1-cyano-2-(4-(dimethylamino)phenyl)vinyl)-1H-pyrazole-4-carbonitrile [IV_a]

Yield: (34%); mp. : 267-269^{o}CDec.; IR: 3332, 3246, 3195, 2214, 1645cm^{-1}.; H^1 NMR (300M3Hz, DMSO-d_6): δ: 3.02 (6H, s, CH_3); 6.56(2H, s, D_2O exchangeable NH_2), 6.79 &6.82(2H, d, Ar-H); 7.67(1H, s,CH_2) 7.75 & 7.77(2H, d, Ar-H), 12.20(1H, s, D_2O exchangeable NH).; C^{13} NMR(100MHz, DMSO-d_6): δ: 47.23(2C), 95.95(1C), 111.60(2C), 115.37(1C), 117.38(1C), 119.88(1C), 131.20(2C),131.50(1C), 142.15(1C), 152.00(1C), 152.31(1C), 154.66(1C).; MS (EI): m/z = 278.40, 206.2, 178.55, 75.90, 65.10, 51.10.

5-amino-3-(1-cyano-2-(4-methoxyphenyl)vinyl)-1H-pyrazole-4-carbonitrile [IV_b]

Yield: (30%); mp. : 231–233^{o}C Dec.; IR: 3449, 3333, 3198, 2222, 2210, 1646, 1599, 1566, 1515, 829 cm^{-1}.; H^1 NMR(300MHz, DMSO-d_6): δ: 3.84 (3H, s, CH_3); 6.62(2H, s, D_2O exchangeable NH_2), 7.09 &7.11(2H, d, Ar-H); 7.80(1H, s,CH_2) 7.84 & 7.86(2H, d, Ar-H), 12.15(1H, s, D_2O exchangeable NH).; C^{13} NMR(100MHz, DMSO-d_6): δ: 55.53(1C), 100.59(1C), 114.71(2C), 114.99(1C), 116.52(1C), 125.37(1C), 131.25(2C), 139.97(1C), 142.54(1C), 145.81(1C), 154.88(1C), 161.51(1C).; MS (EI): m/z = 265.15, 195, 139, 51.

Synthesis of 1,2-bis(4-x-benzylidene)hydrazine[V_{a-b}]:

General procedure: a mixture of 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile (10 mmol) and hydrazine hydrate (10 mmol) in ethanol (20 ml) was refluxed. The formed solid was collected by filtration and washed with ethanol; the product was pure enough for analysis.

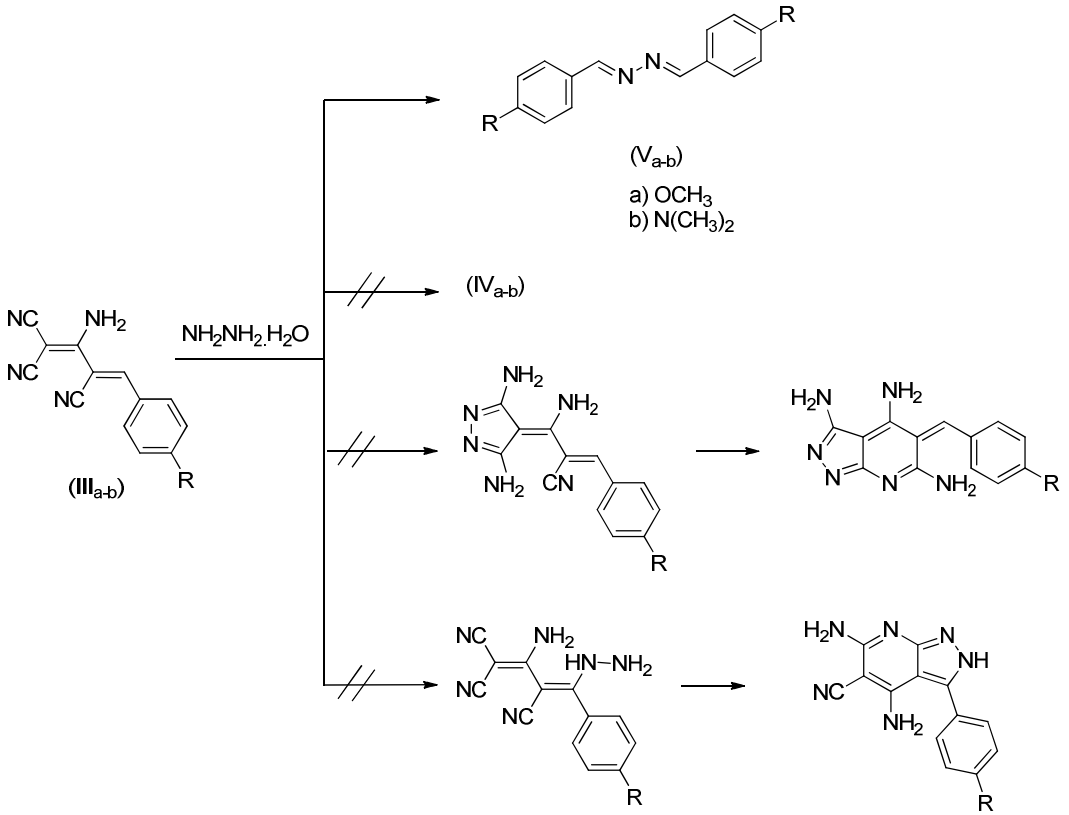
No.	Ar	base	R. time
(V_a)	4-methoxyphenyl	piperidine	3hrs
(V_b)	4-N,N-dimethylaminophenyl	piperidinium acetate	3hrs

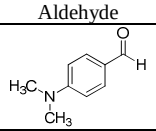
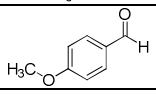
1,2-bis(4-methoxybenzylidene)hydrazine[V_a]
Yield :(74%) ; mp. : 168-170^{o}C.; IR: 2968, 29271615, 1602cm^{-1}.; H^{1}NMR(400 MHz, DMSO-d_6): δ: 3.82 (6H,s, CH_3); 7.03& 7.06 (4H, d, CH ar), 7.82& 7.79 (4H, d, CH ar), 8.62 (2H, s,CH). C^{13} NMR(100MHz, DMSO-d_6): δ: 55.39 (2C), 114.42 (4C), 126.58 (2C), 130 (4C), 160.54(2C), 161.69 (2C).; MS (EI): m/z = 278.40, 240.90, 160.90, 75.90, 65.10 51.10(100).

4,4'-(hydrazine-1,2-diylidenebis(methanylylidene))bis(N,N-dimethylaniline)) [V_b]
Yield:(78%); mp. : 214-216^{o}C.;IR: 2911, 1602, 1555cm^{-1}.;H^1 NMR(400 MHz, DMSO-d_6): δ: 2.97 (12H,s, CH_3); 6.73& 6.76 (4H, d, Ar-H), 7.61&7.64 (4H, d, Ar-H), 8.48 (2H, s, CH). C^{13}NMR(100MHz, DMSO-d_6): δ: 40.13(4C), 111.70(4C), 121.52(2C), 129.52(4C), 151.98(2C), 159.85(2C).; MS (EI): m/z = 294.60,266.75, 251.40, 236.35, 131.00, 118.10

RESULTS AND DISCUSSION

The chemistry of methylene group for 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile (II) had not sufficiently studied.[6] Whereas the chemistry of the same group for the malononitrile dimer had studied very well.[1,5,7-37]Our interest goes to condensation of methylene group of the 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile with aldehydes,the reaction was carried in the same condition that used with malononitrile dimer to insure that the methylene reactivity are the same or not.obviously it wasn't the same, since the reaction time for the dimer was much less than for the 5-amino-3-(cyanomethyl)-1H-pyrazole-4-carbonitrile, the yield was also different from each other as reported in Table (1).



compound	Aldehyde	Base	Solvent	Time	Yield
(I)		piperidinium acetate	MeOH	60 mins.	85%
(II)				6hrs.	34%
(I)		piperidine	MeOH	90 mins.	34%
(II)				4 hrs.	30%

On the other handthe chemistry of 4-aryl-2-aminobut-1,3-diene-1,1,3-tricabonitrile(III) had been poorly discovered.Little publication on this class of compoundswas published.[38-40]we also noted that all pervious reaction occurred at δ-carbon.considering the giving facts, our target was to get new pyrazole derivative from the reaction of these compounds with hydrazine hydrate, it was assumed that hydrazine attack 2-amino-4-arylbuta-1,3-diene-1,1,3-tricarbonitrile(III), followed by intermolecular attack of the second nitrogen of hydrazine, the first attack had occurred and the second nitrogen attacks another molculese rather than intermolecular attack leading to 1,2-dibenzylidenehydrazine derivative (V_{a-b})

CONCLUSION

We find that the reaction of malononitrile dimer with aldehyde followed by reaction with hydrazine derivatives, was completely different from reaction of malononitrile with hydrazine hydrate first then followed by reaction with aromatic substituted aldehydes.

We observed that the aliphatic aldehyde did not give any results under the same conditions.

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