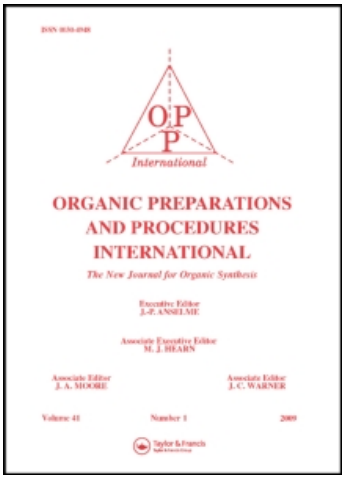

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R. B. Toche[a]; M. A. Kazi[a]; M. N. Jachak[a]
[a] Organic Chemistry Research Centre, Department of Chemistry, K. T. H. M. College, Nashik, MS, INDIA

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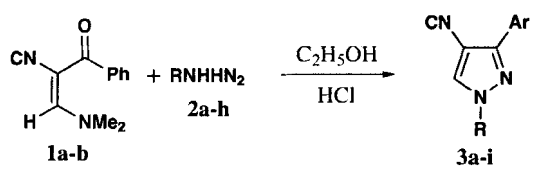
SYNTHESIS OF 4-CYANO- AND 5-AMINOPYRAZOLES AND DEAMINATION OF 5-AMINOPYRAZOLES

R. B. Toche*, M. A. Kazi and M. N. Jachak

Organic Chemistry Research Centre, Department of Chemistry,
K. T. H. M.College, Gangapur Road, Nashik 422002, MS, INDIA
e-mail: raghunath_toche@rediffmail.com

The 1,3,4-trisubstituted pyrazoles are important compounds in the preparation of 1,5-diphenylpyrazole non-nucleoside derivatives, which are used as HIV-1 non-nucleoside reverse transcriptose inhibitors.[1] 4-Cyanopyrazoles show significant biological activity in inhibiting alcohol dehydrogenase.[2] These compounds also produce skeletal muscle relaxation on administration to animals.[3] Hasseneen and co-workers[4] prepared these compounds by the reaction of nitrilimines with fumaronitrile. Junek and co-workers[5] reported the synthesis of 4-cyanopyrazoles from cyanoacetaldehyde. Previous syntheses involve refluxing 3-dimethylamino-2-benzoylpropenenitrile (**2a**) with phenylhydrazine or hydrazine in ethanol. However, the products were always a mixture of 4-cyano- and 5-aminopyrazole derivatives, which had to be separated by column chromatography.[6] We now report a new chemoselective method to synthesize 4-cyano or 5-aminopyrazoles.

Reflux of 3-dimethylamino-2-benzoylpropenenitriles (**1**) and hydrazines (**2**) in ethanol in the presence of catalytic amount of hydrochloric acid furnished 4-cyanopyrazoles (**3**) as the sole products in 60-70% yield; 5-aminopyrazoles were not detected. The structure of **3** was established by analytical and spectral methods (*Scheme 1*). The IR spectra show distinct usually

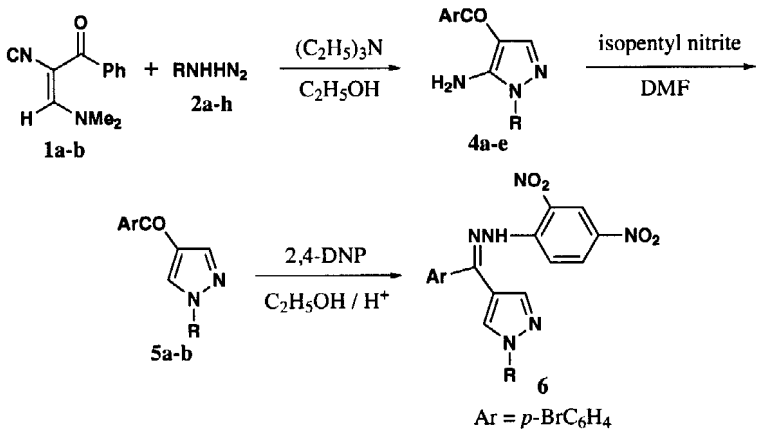


1a-b **3a-i**

a) Ar = R = C_6H_5; b) Ar = C_6H_5, R = *p*-MeC_6H_4; c) Ar = Ph, R = *p*-ClC_6H_4; d) Ar = Ph, R = *p*-$NO_2C_6H_4$; e) Ar = Ph, R = *p*-$MeOC_6H_4$; f) Ar = Ph, R = H; g) Ar = *p*-BrC_6H_4, R= CH_2CH_2OH; h) Ar = *p*-BrC_6H_4, R= CH_2CH_2OH; i) Ar = *p*-BrC_6H_4, R = C_6H_5

Scheme 1

moderate to weak absorption between 2231-2245cm^{-1} (CN). The condensation product of **1a** with methyl carbazate (**2f**) furnished 1-methyl ester derivative of **3f** which was hydrolyzed to the carboxylic acid which underwent spontaneous decarboxylation to give **3f.** In contrast, compounds **1a** and **1b** upon reflux with hydrazines **2** in ethanol in presence of triethylamine led to 5-aminopyrazoles (**4a-e**) in 50-60% yield as the sole products within 1-2 hrs.



a) Ar = R = C_6H_5; b) Ar = C_6H_5, R= -C (=S) NHPh; c) Ar = Ph, R = CO (*P*-ClPh); d) Ar = *p*-BrC_6H_4, R = Ph; e) Ar = C_6H_5, R = 2,4-DNP

Scheme 2

In this reaction, the condensation occurs by replacement of dimethylamino group and cyclization by attack of the hydrazine on nitrile function. The 4-cyanopyrazoles were not formed in these medium. The ^{1}H NMR spectra, IR and elemental analysis were also in agreement with the proposed structures. For example the IR spectrum of **4d** shows absorption bands at 3445 and 3221 cm^{-1} due to NH_2 group and at 1695 cm^{-1} due to carbonyl group. The ^{1}H NMR of **4d** in $CDCl_3$ shows that the NH_2 is split in two singlets at δ 8.30 and 11.82, supports H-bonding between NH_2 (exchangeable with D_2O) and adjacent carbonyl group. The time required for cyclization is between 1-3 hrs compared to 2-18 hrs for the synthesis of 5-aminopyrazole.[7] To support the proposed structures of **4**, we have carried out reactions of amino group and carbonyl of the benzoyl group.

The carbonyl group of **4** is less reactive due to H-bonding to the adjacent amino group and hence does not condense with hydrazines. The amino group of **4a** was deaminated by the method of Nishiwaki *et al.*[8] and Doyle *et al.*[10] Thus, the amino group in pyrazoles **4a** and **4d** on treatment with isopentyl nitrile in DMF furnishes deaminated pyrazoles **5a**, **5b** in good yields. Kornblum[9] had suggested that free radical mechanism for deamination of primary aromatic amines. ^{1}H NMR, IR and elemental analysis confirmed the structures of **5a**,**b**. The IR spectra of **5b** show absence of peaks at 3370 and 3320 cm^{-1} for NH_2 group. The increase in carbonyl absorption from 1690 to 1720 cm^{-1}due to free carbonyl group indicate the loss of the amino group. The ^{1}H NMR of **5b**, in $CDCl_3$ shows singlet for C_3-H and C_5-H at δ 8.13 and 8.43 as

expected. The four aromatic protons show a *para* substituted pattern at δ 7.63, 7.97 as two doublets (J = 8 Hz) and five protons of phenyl ring shows multiplet at δ 7.22-7.55. After deamination, the products were easily converted 2,4-DNP derivatives **6**.

EXPERIMENTAL SECTION

Melting points were determined on a Gallenkamp melting point apparatus in open capillary tubes and are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL- 300 spectrometer (300 MHz). Chemical shifts are reported (internal tetramethylsilane) in δ units. The solvent for NMR spectra was $CDCl_3$ and DMSO-d_6. Infrared spectra were taken on a Shimadzu FTIR-408 in potassium bromide pellets. Elemental analyses were performed on a Hosli CH-Analyzer and are within ± 0.3 of the theoretical percentages. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Starting materials were obtained from commercial suppliers and used without further purification. Common reagent grade chemicals are either commercially available and are used without further purification or prepared by standard literature procedures.

Table 1. Yield, mps and Elemental Analysis, Spectral data of Compounds **3**.

Cmpd.	Yield (%)	mp. (°C)	Elemental Analysis (Found) C	H	N	IR (cm^{-1})	^{1}H NMR (δ)
3a	65	134-135	*lit.*[11] mp. 134-135°C				
3b	68	123-124	78.74 (79.07)	5.05 (5.34)	16.20 (15.91)	2230, 1520	2.35 (s, 3H,CH_3), 7.10 -7.60 (m, 9H, Ar-H)
3c	75	141-142	68.70 (68.45)	3.86 (3.75)	15.02 (14.80)	2230, 1480, 1240	7.16-7.50 (m, 5H, Ar-H), 7.60-7.71(d, J = 8 Hz, 4H, Ar-H), 8.42 (s, 1H, C_5-H)
3d	70	223-224	*lit.*[5] mp. 225°C				
3e	75	125-126	74.16 (74.39)	4.76 (4.95)	15.26 (15.20)	2228, 1510, 1230	3.75 (s, 3H, CH_3), 6.90-7.02(m, 9H, Ar-H), 8.07 (s, 1H, C_5-H)
3f	60	131-132	70.99 (71.10)	4.17 (4.36)	24.53 (24.61)	3150, 2960, 2240, 1510	7.40-7.95 (m, 5H, Ar-H), 8.02 (s, 1H, C_5-H), 11.52 (s, 1H, NH)
3g	65	106-107	67.59 (67.86)	5.19 (5.45)	19.70 (19.90)	2228, 1510, 1268	3.65 (t, J = 7 Hz, CH_2), 4.21 (t, J = 7 Hz, 2H, CH_2), 7.65 (m, 4H, Ar-H), 8.08 (s, 1H, C_5-H)
3h	63	135-136	49.33 (49.50)	3.45 (3.56)	14.38 (14.43)	3493, 2909, 2231, 1563,	3.67 (t, J = 7Hz, CH_2), 4.25 (t, J = 7 Hz, 2H, CH_2), 7.24-7.65 (m, 4H, Ar-H), 7.95 (s, 1H, C_5-H)
3i	68	210-210	58.28 (58.46)	3.10 (3.30)	12.96 (13.03)	2231, 1593, 1580	7.05-7.95 (m, 5H, ArH), 7.42-7.65 (d, J = 8 Hz, 4H, Ar-H), 8.55 (s, 1H, C_5-H)

Table 2. Yield, mps and Elemental Analysis, Spectral Data of Compounds **4, 5, 6**

Cmpd.	Yield (%)	mp. (°C)	Elemental Analysis (Found) C	H	N	IR (cm^{-1})	^1H NMR (δ)
4a	65	179-180	*lit.*[7] mp. 183°C			3280, 3275, 1620, 1540	7.40-7.75 (m, 5H, Ar-H), 7.40-7.75 (m, 5H, Ar-H), 7.86 (s, 1H, C_3-H), 7.90 (s, 2H, $-NH_2$).
4b	45	127-128	63.34 (63.25)	4.38 (4.60)	17.38 (18.61)	3380, 3300, 3140, 1640,	7.28-7.93 (m, 5H, Ar-H), 8.04 (s, 1H, C_3-H), 9.20-11.82 (s, 2H, NH_2), 12.5 (bs, 1H, NH)
4c	65	199-200	70.41 (70.60)	4.17 (4.46)	14.49 (14.61)	3370, 3220, 3040, 1690, 1630	7.28-7.94 (m, 5H, Ar-H), 8.04 (s, 1H, C_3-H), 9.2-11.82 (s, 2H, NH_2), 12.5 (bs, 1H, NH)
4d	60	217-218	56.14 (56.28)	3.53 (3.28)	12.28 (12.51)	3445, 3221, 2922, 1695	7.63-7.69 (m, 5H, Ar-H), 7.71-7.76 (d, J = 8 Hz, 4H, Ar-H), 8.02 (s, 1H, C_5-H), 8.30-11.82 (s, 2H, NH_2)
4e	50	186-187	44.45 (43.65)	2.33 (2.45)	16.20 (15.89)	3370, 3320, 3040, 1690, 1630	7.02-7.56 (m, 4H, Ar-H), 7.26-7.63 (m, 5H, Ar-H), 8.02 (s, 1H, C_3-H), 8.25-11.75 (s, 2H, $-NH_2$)
5a	55	123-124	*lit*[8]. mp. 123-124°C				
5b	65	198-199	58.73 (58.97)	3.39 (3.45)	8.56 (8.47)	1749, 1626, 1582	7.22-7.75 (m, 5H, Ar-H), 7.63-7.97 (d, 4H, Ar-H), 8.13 (s, 1H, C_3-H), 8.43 (s, 1H, C_5-H).
6	76	220-221	52.08 (52.32)	2.98 (3.06)	16.57 (16.50)	3279, 1610, 1588, 1562, 1461	7.22-7.51 (m, 5H, Ar-H), 7.83-7.86 (d, J = 8.2 Hz, 4H, Ar-H), 7.97 (s, 1H, C_3-H), 8.04 (s, 1H, C_5-H), 8.09 (dd, J = 8.3 Hz, 1H, Ar-H), 8.22 (d, J = 8.4 Hz, 1H, Ar-H), 9.13 (d, J = 3 Hz, 1H, Ar-H), 11.33 (s, 1H, NH)

Synthesis of 4-Cyanopyrazoles (3a-e, 3g-i).- To a solution of **1a, b** (0.01mole) and hydrazines, **2a-e, 2g-i** (0.01 mole) in ethanol (30 mL), was added 0.2 mL of conc. hydrochloric acid and the reaction mixture was refluxed for 2-3 hrs. After completion of reaction (tlc check, toluene: acetone 8:2). The solvent was evaporated to dryness under reduced pressure and the resulting

solid obtained was stirred in cold ethanol (2 mL), collected, dried and recrystallized from ethanol. All the compounds were obtained as colorless solids.

Synthesis of 4-Cyanopyrazoles (3f).- To a solution of **1a** (0.01 mole) and methyl carbazate **2f** (0.90, 0.01 mole) in ethanol (30 mL), was added 0.2 mL of conc. hydrochloric acid and the reaction mixture was refluxed for 3 hrs. After completion of reaction (tlc check, toluene: acetone 8:2). The solvent was evaporated to dryness under reduced pressure. The resulting solid obtained was stirred in cold ethanol (2 mL), collected, dried and recrystallized from ethanol.

Synthesis of 1-Substituted-4-benzoyl-5-aminopyrazoles (4a-e). General Procedure.- To a solution of **2a** or **2b** (0.01 mole), hydrazines, **2a-h** (0.01 moles) in ethanol (30 mL), was added triethylamine (0.2 mL) and mixture refluxed for 2-3 hrs. After completion of reaction (tlc check, toluene: acetone 8:2), the solvent was evaporated to dryness under reduced pressure. The resulting solid obtained was stirred in cold ethanol (2 mL), collected, dried and recrystallized from ethanol. All the compounds obtained as colorless solids.

Deamination of 5-Aminopyrazoles (5a,b).- To a solution of **4a,b** (0.01 mole) in anhydrous dimethylformamide (5 mL) maintained at 60-65°C, isopentyl nitrite (0.015 mole) in anhydrous DMF (3 mL) was added over period of 10 minutes. The reaction mixture was stirred at 75-80°C for further 30 min and the solvent was evaporated under reduced pressure to dryness. The resulting solid obtained was stirred with petroleum ether, collected, recrystallized from ethanol.

2,4-Dinitrophenylhydrazone of 4-Benzoyl-N-phenylpyrazole (6).- To a solution of **5b** (0.02 mole), 2,4-dinitrophenylhydrazine (0.02 mole) in ethyl alcohol (10 mL), concentrated sulfuric acid (0.5 mL) was added and reaction mixture was refluxed for 2 hrs. After completion of reaction (tlc check, toluene: acetone 8:2), solvent was evaporated under reduced pressure to dryness. The resulting solid obtained was stirred in cold ethanol (2 mL), collected, dried and recrystallized from ethanol:DMF.

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