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The synthesis of 5-amino-4-arylazo-3-methyl-1*H*-pyrazoles and 5-aryl-3-methylpyrazole[3,4-e][1,2,3,4]tetrazines

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ABSTRACT

$AlCl_3$-catalyzed coupling of 3-amino-5-methyl-1*H*-pyrazole in water with different aryldiazonium compounds yielded 5-amino-4-arylazo-3-methyl-1*H*-pyrazole derivatives in high yield; subsequent diazotization and cyclization realised the 5-aryl-3-methylpyrazole[3,4-e][1,2,3,4]tetrazine derivatives. The structure of these novel, hetarylazo dyes was confirmed by UV–vis, FT-IR, and ^{1}H NMR spectroscopic techniques and elemental analysis. Optimal preparation conditions for 5-amino-4-phenylazo-3-methyl-1*H*-pyrazole were determined with respect to the effects of the $AlCl_3$-catalyst, pH and temperature; the reaction mechanism of formation of the 5-aryl-3-methylpyrazole[3,4-e][1,2,3,4]tetrazines is discussed and the colours of the aminopyrazoles and pyrazolo-tetrazine dyes in a range of solvents are also discussed.

1. Introduction

Aminopyrazoles are very important class of heterocycles due to their biological and pharmacological activities [1,2]. These compounds often exhibit anti-inflammatory, herbicidal, fungicidal, bactericidal, and antipyretic activities, and also can be used as plant growth regulating agents as well as protein kinase inhibitors [3–7]. As derivatives of aminopyrazoles, the condensed heterocyclic compounds especially containing the triazine and tetrazine moiety have received much attention owing to the reported antibacterial, antiviral and antihypertensive activities [8,9]. Moreover, they are used as key starting material for the synthesis of commercial arylazopyrazolone dyes and purine analogues [10–18].

In recent years, with the increase of environmental consciousness in chemical research and industry, efficient, economic and clean procedures have received increased attention. Thus, water has become an intriguing reaction medium, and has particularly captured the interest of organic chemists [19–23]. Reactions previously thought impossible in water are now a reality. In many cases the catalyst and/or the aqueous medium can be recovered and reused, thereby reducing the environment impact of the reaction process [24–26]. Many Lewis acids work well in aqueous medium [27,28], and even $AlCl_3$, $SnCl_2$ and $TiCl_4$ which are previously used under anhydrous conditions are excellent catalysts in water [21].

Recently, Karci et al. reported that 2-arylhydrazone-3-ketimin obutyronitriles reacted with hydrazine hydrate to afford 5-amino-4-arylazo-3-methyl-1*H*-pyrazole derivatives [29,30]. In our previous work, $AlCl_3$-catalyzed diazocoupling of 1-phenyl-3-hydroxy-5-pyrazolone in water with different aryldiazonium salts yielded 1-phenyl-3-hydroxy-4-arylazo-5-pyrazolone derivatives. According to the same procedure, we successfully synthesized 5-amino-4-arylazo-3-methyl-1*H*-pyrazole derivatives (**2a**–**m**) using $AlCl_3$-catalyzed diazocoupling of 3-amino-5-methyl-1*H*-pyrazole (**1**) in water with different aryldiazonium salts with high yields.

The compounds (**2a**–**m**) were diazotized and cyclized into 13 novel 5-aryl-3-methylpyrazolo[3,4-e][1,2,3,4]tetrazines (**3a**–**m**) (Scheme 1).

2. Experimental

2.1. General

All melting points reported are uncorrected. IR spectra were recorded using Perkin Elmer Spectrum RXIFT-IR spectrophotometer on a KBr disc (ν in cm^{-1}), Ultraviolet–visible (UV–vis) absorption spectra were recorded on an ATI Unicam UV-100 spectrophotometer at the wavelength of maximum absorption (λ_{max}) in

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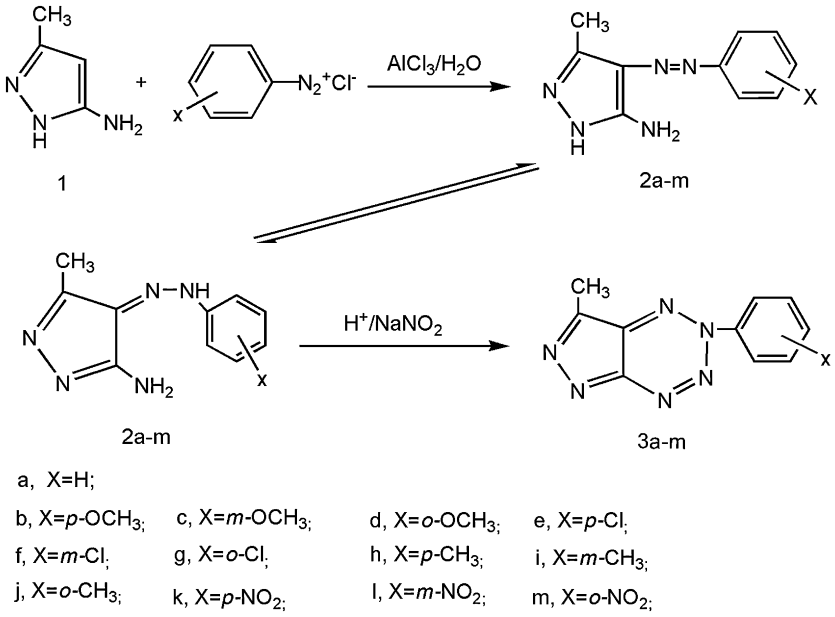


a, X=H;

b, X=*p*-OCH_3; c, X=*m*-OCH_3; d, X=*o*-OCH_3; e, X=*p*-Cl;

f, X=*m*-Cl; g, X=*o*-Cl; h, X=*p*-CH_3; i, X=*m*-CH_3;

j, X=*o*-CH_3; k, X=*p*-NO_2; l, X=*m*-NO_2; m, X=*o*-NO_2;

Scheme 1. 5-aryl-3-methylpyrazolo[3,4-e][1,2,3,4]tetrazines.

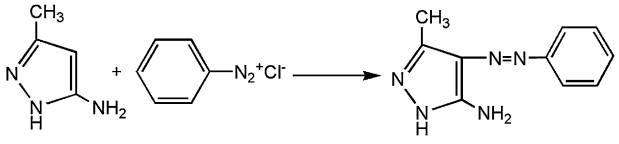
a range of solvents, The ^{1}H NMR spectra were recorded on Bruker Avance VXR-300 instrument, using DMSO-d_6 as a solvent and TMS as an internal standard (chemical shifts in δ values in ppm). Elemental analyses were preformed on Perkin Elmer 2400, series II micro-analyzer. The chemicals used for the synthesis of the compounds were obtained from Aldrich–Sigma Chemical Co. (USA) without further purification.

2.2. Synthesis of 5-amino-4-arylazo-3-methyl-1H-pyrazoles

The 5-amino-4-arylazo-3-methyl-1*H*-pyrazoles (**2a**–**m**) were prepared according to published procedures [18]. All melting points accorded with those reported in the literature [29].

2.3. Synthesis of 5-aryl-3-methylpyrazolo[3,4-e][1,2,3,4]-tetrazines (*3a*–*m*)

Nitrosylsulphuric acid was prepared by dissolving sodium nitrite (1 g) in concentrated sulphuric acid (7 ml) at 70 °C. 5-Amino-3-methyl-4-phenylazo-1*H*-pyrazole 0.45 g (0.002 mol) was dissolved in hot glacial acetic acid (2.5 ml) and was rapidly cooled in an ice–salt bath to 0 °C. The solution was then added in portions over 30 min to nitrosylsulphuric acid at 0–5 °C and the mixture was stirred for a further 1 h at this temperature. The resulting diazonium solution was mixed with a solution of ethanol (50 ml) and sodium acetate (3 g). The mixture was kept at room temperature overnight. The resulting solid was filtered, washed with cold water and dried. Recrystallisation from aqueous ethanol gave brown crystal of the product (**3a**). This procedure was also used to synthesize **3b**–**m**.



Scheme 2. Preparation of 5-amino-4-arylazo-3-methyl-1*H*-pyrazole.

3. Result and discussion

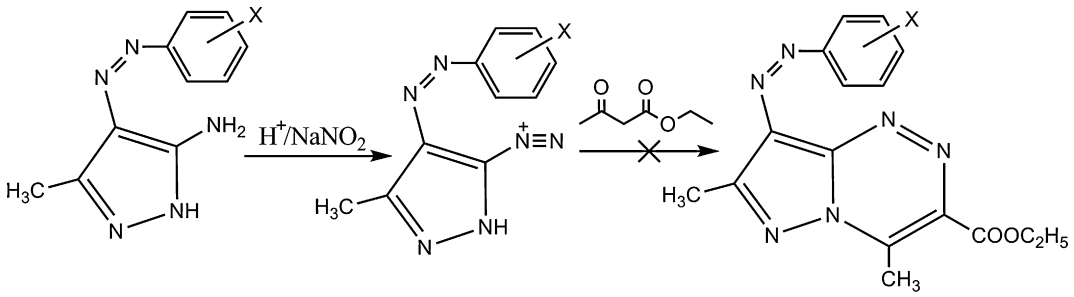
3.1. Synthesis and characterizations

Initially, we used the preparation of **2a** (Scheme 2) as a model reaction to optimize reaction conditions using TLC. After investigations with different metal salts at various pH values, acidic conditions at pH 5.0 resulted in the heterogeneous coupling of aromatic diazonium chlorides with 5-amino-3-methyl-1*H*-pyrazole at 0–5 °C in the presence of aluminum chloride ($AlCl_3$) as the catalyst, presented the colored 5-amino-4-phenylazo-3-methyl-1*H*-pyrazole (**2a**). No coloration or formation of azopyrazole in aqueous medium in the absence of $AlCl_3$ was observed. The reason for $AlCl_3$ catalysis might be that the $AlCl_3$ was hydrolysed, thereby enhancing the acidity of the reaction medium. The reaction mechanism is still needed further study. Under the optimized conditions, 5-amino-3-methyl-1*H*-pyrazole was coupled with various aromatic diazonium salts to afford the 5-amino-4-arylazo-3-methyl-1*H*-pyrazole derivatives (**2b**–**m**). Characterization data for each of the compounds are shown in Table 1.

Diazotisation of 5-aminopyrazoles in strong acids has been reported to afford the corresponding diazonium salts which undergo coupling reaction with phenols to yield pyrazolo[5,1-c][1,2,4]tetrazines by intramolecular condensation [31,32]. In our

Table 1
Capability of compounds **2a**–**m**.

Entry	M.p. (°C)	Yield (%)	Colour
2a	165–167	91	Orange
2b	187–189	90	Orange
2c	182–184	92	Orange
2d	166–168	94	Orange
2e	181–183	87	Orange
2f	187–189	88	Orange
2g	194–195	85	Orange
2h	170–172	86	Brown
2i	145–147	85	Brown
2j	155–157	84	Brown
2k	226–228	89	Brown
2l	221–223	87	Brown
2m	191–193	86	Brown



Scheme 3. Failure of synthesis of 3-methylpyrazolo[5,1-c][1,2,4]tetrazines.

present work, attempts to diazotize compounds **2a**–**m** to afford the corresponding diazonium salts which may undergo coupling reaction with active methylene reagents such as acetyl acetone, ethyl acetoacetate to synthesize 3-methylpyrazolo[5,1-c][1,2,4]tetrazines by intramolecular condensation were unsuccessful (Scheme 3). Under various conditions, the 3-methylpyrazolo[3,4-e][1,2,3,4]tetrazines derivatives (**3a**–**m**) were the only products which were isolated. The formation of **3** may be easier and assumed to proceed via formation of the intermediate resonance stabilized diazobetaine (**4**) which undergoes intramolecular cyclization to afford **3** (Scheme 4).

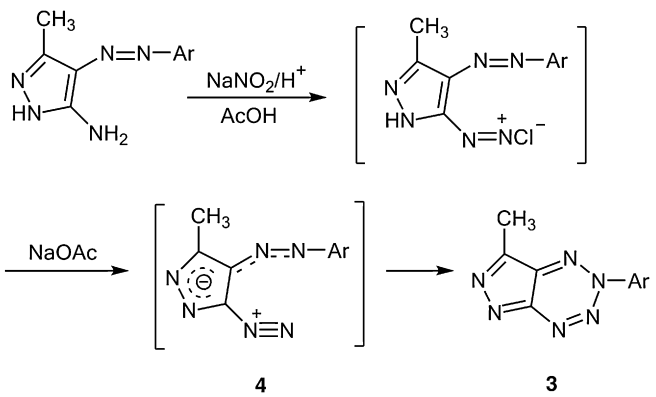
The FT-IR absorption spectra of compounds (**3a**–**m**) showed absorption bands at ν (cm^{-1}): 1225–1249 (C═N exocyclic), 1361–1497 (N═N sym), 1548–1552 (N═N asym), 1595–1604 (C═C, C═N), 2612–3002 (CH) and 1556, 1328 (**3k**–**m** NO_2).

The structures of 5-aryl-3-methylpyrazolo[3,4-e][1,2,3,4]tetrazines (**3a**–**m**) have been confirmed by ^{1}H NMR (Table 2) and elemental analysis(Table 3).

3.2. Solvent effects

UV–vis absorption spectra were recorded using an ATI Unicam UV-100 spectrophotometer in the wavelength range between 350 and 700 nm. Absorption maxima spectra of dyes **2a**–**m** and **3a**–**m** were recorded in a range of solvents at a concentration of 10^{-6}–10^{-8} M and these are all run at different concentrations. The molar extinction coefficient of these dyes was also determined and the results are summarized in Table 4.

As shown in Table 4, the dyes **2a**–**m** showed single or two absorption peaks in some solvents. For example, **2a** gave an absorption peak of 401 nm with a shoulder of 433 nm in methanol. It can be suggested that the dyes **2a**–**m** may exist as a mixture of tautomeric forms in various solvents, as shown in Scheme 1. The visible absorption maxima spectra of the dyes did not show regular variation with the polarity of solvents. It was observed that the absorption maxima of dyes **3a**, **3c**, **3f**, **3g**, **3k**–**m**, did not change significantly, however, the absorption maxima of dyes **3b**, **3d**, **3e**, **3h**–**j** shifted significantly in different solvents. For example, λ_{max} of **3b** appeared at 467 nm in acetonitrile but was shifted hypsochromically to 405 nm in chloroform and λ_{max} of **3j** was shifted bathochromically from 407 nm in methanol to 455 nm in acetonitrile.



Scheme 4. Mechanism of formation of 5-aryl-3-methylpyrazolo[3,4-e][1,2,3,4]tetrazines.

3.3. Substituent effects

As shown in Table 4, the introduction of an electron-donating group into the benzene ring resulted in bathochromic shifts in all solvents. For example, λ_{max} of **3a** was 438 nm in DMF, but when the electron-donating methoxyl group was introduced into the *para*-position of the benzene ring of **3b**, λ_{max} was shifted to 461 nm. Conversely the introduction of an electron-withdrawing group into the benzene ring resulted in hypsochromic shifts in all solvents, e.g. λ_{max} of **3a** was 438 nm in DMF, but when the electron-withdrawing chloro group was introduced into *para*-position of benzene ring (**3e**), it was 413 nm.

In summary, we have reported the synthesis of a series of 5-amino-4-arylazo-3-methyl-1*H*-pyrazole derivatives. In contrast

Table 2
Capability and ^{1}H NMR of compounds **3a**–**m**.

Entry	M.p. (°C)	Yield (%)	Colour	^{1}H NMR (DMSO-d_6) δ
3a	153–155	82	Brown	2.59 (s, 3H, CH_3, pyrazole), 7.56–8.23 (m, 5H, PhH)
3b	138–140	76	Brown	2.58 (s, 3H, CH_3, pyrazole), 3.78 (s, 3H, *p*-OCH_3), 7.35–8.12 (dd, 4H, ArH)
3c	145–146	78	Brown	2.61 (s, 3H, CH_3, pyrazole), 3.68 (s, 3H, *m*-OCH_3), 7.46–8.14(m, 4H, ArH)
3d	141–142	74	Brown	2.63 (s, 3H, CH_3, pyrazole), 3.98 (s, 3H, *o*-OCH_3), 7.16–8.13 (m, 4H, ArH)
3e	144–146	81	Orange	2.65 (s, 3H, CH_3, pyrazole), 7.51–8.13 (dd, 4H, ArH)
3f	135–137	82	Orange	2.67(s, 3H, CH_3, pyrazole), 7.41–8.03(m, 4H, ArH)
3g	130–132	75	Orange	1 2.67 (s, 3H, CH_3, pyrazole), 7.62–8.14 (m, 4H, ArH)
3h	123–125	78	Brown	2.67 (s, 3H, CH_3, pyrazole), 2.42 (s, 3H, *p*-CH_3), 7.36–8.01 (dd, 4H, ArH)
3i	137–139	73	Brown	2.58 (s, 3H, CH_3, pyrazole), 2.39 (s, 3H, *m*-CH_3), 7.25–8.13 (m, 4H, ArH)
3j	116–118	75	Brown	2.59 (s, 3H, CH_3, pyrazole), 2.40 (s, 3H, *o*-CH_3), 7.22–8.06 (m, 4H, ArH)
3k	124–126	81	Palebrown	2.71 (s, 3H, CH_3, pyrazole), 7.51–8.43 (dd, 4H, ArH)
3l	173–175	79	Palebrown	2.71 (s, 3H, CH_3, pyrazole), 7.46–8.44 (m, 4H, ArH)
3m	164–166	78	Palebrown	2.72 (s, 3H, CH_3, pyrazole), 7.52–8.51 (m, 4H, ArH)

Table 3
Elementary analysis of compounds **3a–m**.

Entry	Molecular formula	Molecular mass	Elementary analysis, found (Calcd)%		
			C	H	N
3a	$C_{10}H_8N_6$	212.2	56.43(56.60)	3.59(3.77)	39.45(39.62)
3b	$C_{11}H_{10}N_6O$	242.3	54.32(54.55)	4.34(4.13)	34.54(34.71)
3c	$C_{11}H_{10}N_6O$	242.3	54.78(54.55)	4.35(4.13)	34.42(34.71)
3d	$C_{11}H_{10}N_6O$	242.3	54.23(54.55)	4.31(4.13)	34.49(34.71)
3e	$C_{10}H_7N_6Cl$	246.5	48.95(48.68)	2.51(2.84)	30.36(30.08)
3f	$C_{10}H_7N_6Cl$	246.5	48.34(48.68)	2.57(2.84)	30.32(30.08)
3g	$C_{10}H_7N_6Cl$	246.5	48.91(48.68)	2.62(2.84)	30.35(30.08)
3h	$C_{11}H_{10}N_6$	226.3	58.13(58.41)	4.20(4.42)	37.39(37.17)
3i	$C_{11}H_{10}N_6$	226.3	58.15(58.41)	4.64(4.42)	37.40(37.17)
3j	$C_{11}H_{10}N_6$	226.3	58.58(58.41)	4.69(4.42)	37.35(37.17)
3k	$C_{10}H_7N_7O_2$	257.2	46.47(46.69)	2.45(2.72)	38.45(38.13)
3l	$C_{10}H_7N_7O_2$	257.2	46.92(46.69)	2.50(2.72)	38.40(38.13)
3m	$C_{10}H_7N_7O_2$	257.2	46.46(46.69)	2.49(2.72)	38.41(38.13)

Table 4
Absorption maxima and extinction coefficients of dyes **2a–m** and **3a–m** in a range of solvents.

Dye No.	Methanol	DMF	Acetonitrile	Chloroform
	λ_{max} (nm) log ε	λ_{max} (nm) log ε	λ_{max} (nm) log ε	λ_{max} (nm) log ε
2a	401, 433s, 4.18	431, 460s, 4.27	419, 4.23	410, 4.31
2b	409, 427s, 4.21	413, 456s, 4.13	427, 4.05	401, 4.28
2c	404, 430s, 4.31	436, 467s, 4.08	414, 4.17	409, 4.30
2d	412, 447s, 4.25	440, 469s, 4.11	421, 4.07	444, 4.12
2e	398, 434s, 4.18	402, 457s, 4.09	410, 4.24	400, 4.09
2f	394, 440s, 4.10	399, 436s, 4.25	407, 4.36	411, 4.28
2g	401, 455s, 4.19	412, 460s, 4.08	409, 438s, 4.22	413, 4.30
2h	449, 481s, 4.27	432, 465s 4.17	418, 4.39	422, 4.15
2i	452, 498s, 4.00	440, 486s 4.43	422, 4.16	438, 4.08
2j	441, 476s, 4.18	453, 490s 4.29	437, 4.33	442, 4.11
2k	390, 432s, 4.09	421, 454s, 4.31	407, 424s, 4.11	407, 4.39
2l	400, 441s, 4.22	418, 465s, 4.14	389, 4.08	411, 4.07
2m	413, 462s, 4.39	422, 467s, 4.08	409, 4.13	402, 4.40
3a	412, 4.09	438, 4.29	400, 4.22	397, 4.14
3b	415, 4.11	461, 4.26	467, 4.18	405, 4.30
3c	409, 4.17	445, 4.09	437, 4.00	407, 4.07
3d	408, 4.22	453, 4.15	452, 4.03	416, 4.25
3e	405, 4.08	413, 4.11	452, 4.18	399, 4.13
3f	413, 4.11	440, 4.25	438, 4.32	417, 4.14
3g	406, 4.15	427, 4.30	398, 4.22	415, 4.12
3h	408, 4.02	433, 4.00	456 4.14	401, 4.11
3i	415, 4.26	454, 4.12	424, 4.07	406, 4.29
3j	407, 4.04	448, 4.02	455, 4.10	410, 4.03
3k	403, 4.40	425, 4.17	412, 4.00	408, 4.41
3l	402, 4.02	427, 4.15	396, 4.12	415, 4.04
3m	409, 4.10	426, 4.21	437, 4.08	400, 4.19

s: shoulder.

to the procedure of literature [29], the advantages of this method include (1) the use of water as solvent, which reduce the environment impact; (2) short reaction procedure and (3) high yields. Moreover, we have reported here the synthesis of some new 5-aryl-3-methylpyrazolo[3,4-e][1,2,3,4]tetrazines which might be used as commercial dyes or potentially chemotherapeutic purine analogues.

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