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β–Enaminonitriles in heterocyclic synthesis: Synthesis of new 1, 4-dihydropyridine, amino-pyrazole and pyrazolopyrimidine derivatives

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ABSTRACT

Utility of 3-amino-2-pentenonitrile **(1)** in the synthesis of new 1,4-dihydro pyridines, aminopyrazoles and pyrazolopyrimidines.

KEYWORDS

β-Enaminonitriles;
Aminopyrazoles;
Pyrazolopyrimidines.

INTRODUCTION

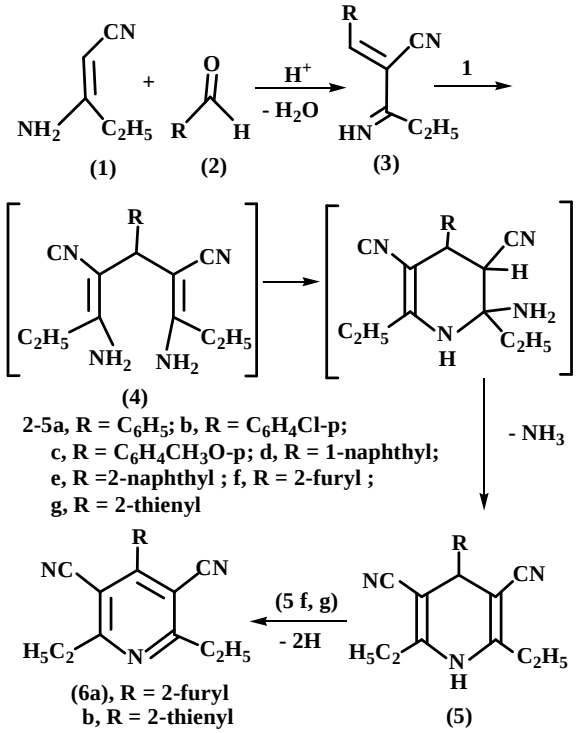
In conjunction with our interest in the synthesis of functionally substituted heterocyclic compounds as potential pharmaceuticals, the synthesis of new dihydropyridines analogous to nifedipine and amlodipine as potential calcium channel blockers in the treatment of angina and hypertension[1-9], seemed interesting. Recently we[10,11] have checked the synthetic potentiality of 2-aminocrotononitrile and 3-aminocinnamonitrile in the preparation of such dihydropyridines. In the course of this synthesis, it was noticed that only one product was detected by TLC which is considered of a great advantage on the commercial scale. In continuation to this and as a part of our biological chemistry programme 3-amino-2-pentenonitrile (1) was prepared and underwent several chemical transformations[12]. Thus, it has been found that 3-amino-2-pentenonitrile (1) condensed with benzaldehyde in acetic acid and in the presence of ammonium acetate to give 1,4-dihydropyridine **(5a)** which is believed to be formed via initial condensation of **(1)** with benzaldehyde to give the unstable benzylidene **(3)** which, in turn, reacts with another molecule of **(1)** via cyclization and subsequent elimination of ammonia. Establishing of structure **(5a)** was based on its elemental analysis and spectral data. Similarly, aldehydes **(2b-e)** reacted with 1 in the same reaction condition to afford 1,4-dihydropyridine derivatives **(6b-e)**.

In contrast to the behaviour of aromatic aldehydes towards 1, heteroaromatic aldehydes such as 2-furaldehyde and 2-thiophenaldehyde[11] reacted with 1 to give pyridine derivatives **(6a,b)** via intermediacy of **(5f,g)**. Trial to isolate dihydropyridines **(5f,g)** failed.

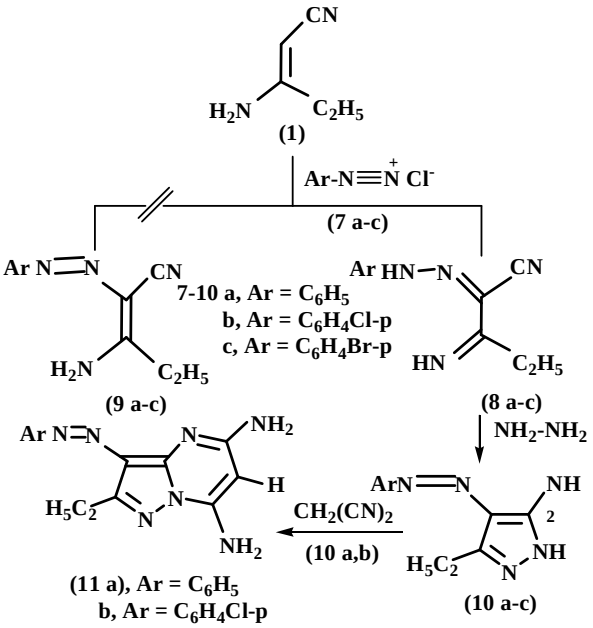
Compound **(1)** coupled readily with aromatic diazonium salts **(7a-c)** affording the corresponding coupling products that were assigned as the arylhydrazo enaminonitrile derivatives **(8a-c)** rather than potentially tautomeric structures **(9a-c)** based on ^{1}H NMR that revealed the presence of signals for enamino functions at δ= 10.3 ppm and at δ = 12.2 ppm.

Compounds **(8a-c)** reacted readily with hydrazine hydrate in refluxing ethanol to give aminopyrazole **(10a-c)**.

Moreover, the reaction of aminopyrazoles **(10a,b)** with malononitrile gave the corresponding pyrazol opyrimidines **(11a,b)**. Establishing structure **(11)** was

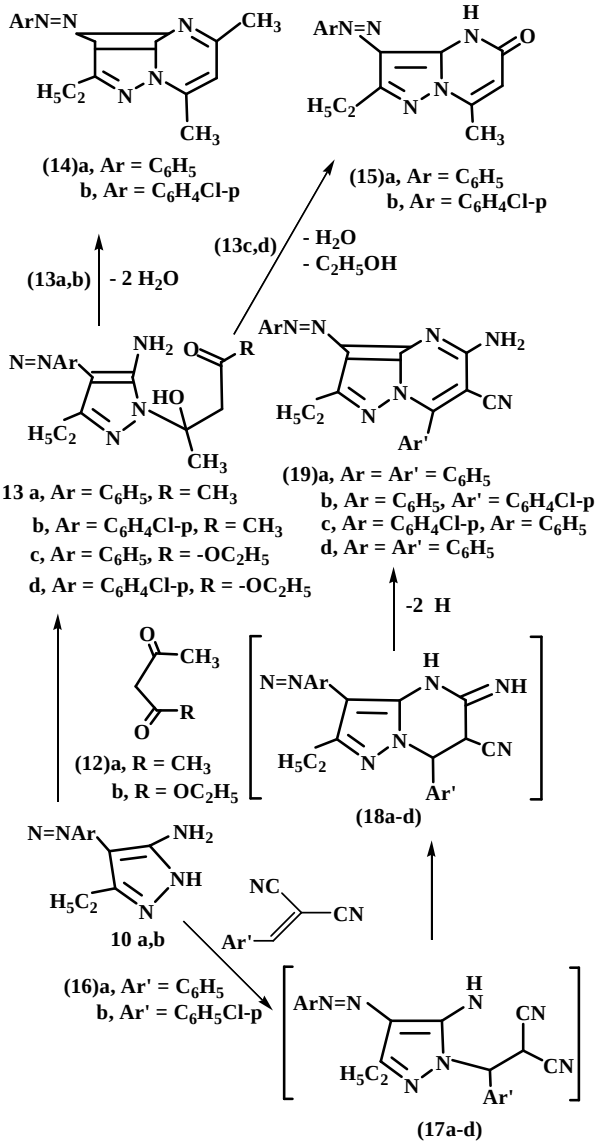


SCHEME 1



SCHEME 2

based on its spectral analysis. For example, ^{1}H NMR spectrum of 11a revealed the presence of a triplet signal at δ= 1.37 ppm corresponding to methyl function, a quartet signal at δ= 3.24ppm corresponding to methylene group, a broad function at δ=4.51ppm corresponding to amino and a multiplet signal at δ=7.48-7.89 ppm



SCHEME 3

corresponding to aromatic protons and alkenyl proton. The mass spectrum of the same product is in accordance with the proposed structure. Thus, it showed a very intense molecular ion peak at 281. The IR spectrum of the same product further supports the proposed structure.

Furthermore, the behaviour of aminopyrazoles **(10a,b)** towards some other active methylene reagents such as acetylacetone and ethylacetoacetate was also investigated. Thus, when a mixture of aminopyrazole **(10a)**, acetylacetone and ethanolic sodium ethoxide solution was refluxed for 6h, a product with a molecular formula $C_{16}H_{17}N_5$ 14a was obtained. Formation of **(14a)** from the reaction of **(10a)** and acetylacetone is

believed to be formed via initial addition and subsequent elimination of two molecules of water. Similarly, aminopyrazole **(10b)** reacted acetylacetone to pyrazolopyrimidine **(14b)**. In a similar manner aminopyrazoles **(10a,b)** reacted with ethylacetoacetate in the same reaction condition to give pyrazolopyrimi dinones **(15a,b)** respectively. Formation of **(15a,b)** from the reaction **(10a,b)** and ethylacetoacetate is believed to be formed via initial addition and subsequent elimination of water and ethanol (SCHEME 3).

Typical to the behaviour of aminopyrazoles towards some electrophiles[14], aminopyrazoles **(10a,b)** reacted with arylidenemalononitriles **(16a,b)** in ethanol and in the presence of piperidine to afford the products of addition and subsequent cyclization. These were thus formulated as the pyrazolopyrimidine derivatives **(19a-d)** and are assumed to be via intermediacy of the Michael adducts **(17a-d)** which readily cyclized into **(18a-d)** that then underwent auto oxidation and subsequent tautomerism to give **(19a-d)**. Establishing structures **(19a-d)** was based on their spectral data (SCHEME 3).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) with a Shimadzu FTIR-8201 PC spectrophotometer. ^{1}HNM spectra were obtained on a Varian Germini 200 MHz spectrometer in DMSO-d_6 as a solvent and TMS as an internal reference. Mass spectra were performed on a Shimadzu GCMS-OP 1000 Ex instrument using the direct inlet system and EI + QI MSLMRUPLR. Microanalyses were performed by the microanalytical laboratories at Cairo University.

Preparation of 1,4-dihydropyridine derivatives (6a-g)

To a solution of 3-amino-2-pentenonitrile 1 (1.92g, 0.02mol) in glacial acetic acid (50 ml), ammonium acetate (0.77g, 0.01mol) and the appropriate aldehydes **(2a-g)**. (0.01mol) were added. The reaction mixture was refluxed for 2h. then evaporated in *vacuo*. The remaining solid product was collected by filtration and washed by ethanol then crystallized from the proper solvent.

Preparation of arylhydrazoenaminonitrile (8a-c)

A solution of diaz-otized amines **(7a-c)** [prepared from appropriate aromatic amines (0.01mol) in hydrochloric acid and sodium nitrite (0.01mol) was added to 3-amino-2-petenonitrile (1) (1.92g, 0.02mol) in ethanol containing **(1g)** of sodium acetate. The reaction mixture was then stirred in ice-bath for 3h. The solid product, so-formed, was collected by filtration and washed

TABLE 1: Physical and analytical data of newly synthesized compounds

Comp. no.	Formula (Mol.weight)	m.p. (°C)	Yield (%)	Color	Solvent of Cryst.	C	H	N	Cl / Br
6a	$C_{17}H_{17}N_3$ (263)	123	70	Yellow	Ethanol	77.56, 77.33	6.4, 6.37	15.96,15.70	-
6b	$C_{17}H_{16}N_3Cl$ (297.5)	141	85	Yellow	Ethanol	68.57, 68.94	5.37, 5.30	14.11, 14.00	11.93, 11.56
6c	$C_{18}H_{19}N_3O$ (293)	165	91	Orange	Ethanol	73.72, 73.44	6.48, 6.60	14.33, 14.52	-
6d	$C_{21}H_{19}N_3$ (313)	201	74	Yellow	Ethanol	80.51, 80.25	6.07, 6.00	13.41, 13.71	-
6e	$C_{21}H_{19}N_3$ (313)	194	72	Yellow	Ethanol	80.51, 80.35	6.07, 6.03	13.41, 13.40	-
6f	$C_{15}H_{13}N_3O$ (251)	246	83	Orange	Ethanol	71.71, 71.37	5.17, 5.10	16.73, 16.66	-
6g	$C_{15}H_{13}N_3S$ (267)	198	76	Brown	Ethanol	67.41, 66.55	4.86, 5.55	15.73, 15.70	-
8a	$C_{11}H_{12}N_4$ (200)	106	75	yellow	Methanol	66.00, 66.16	6.00, 6.10	28.00, 28.15	-
8b	$C_{11}H_{11}N_4Cl$ (234.5)	153	70	orange	Ethanol	56.28, 56.16	4.69, 4.20	23.88, 23.54	15.13, 15.27
8c	$C_{11}H_{11}N_4Br$ (279)	166	65	yellow	Methanol	47.31, 47.19	3.94, 3.82	20.07, 20.00	28.67, 28.52
10a	$C_{11}H_{13}N_5$ (215)	124	60	Yellow	Ethanol	61.39, 61.20	6.04, 6.00	32.55, 32.25	-
10b	$C_{11}H_{12}N_5Cl$ (249.5)	160	75	Yellow	Ethanol	52.90, 52.95	4.80, 4.51	28.05, 28.00	14.22, 14.10
10c	$C_{11}H_{12}N_5Br$ (294)	180	71	Orange	Ethanol	44.89, 44.90	4.08, 4.10	23.80, 23.64	27.21, 27.31
11a	$C_{14}H_{15}N_7$ (281)	244	62	Yellow	Dioxan	59.78, 59.80	5.33, 5.22	34.87, 34.66	-
11b	$C_{14}H_{14}N_7Cl$ (315.5)	267	65	Yellow	Dioxan	53.24, 53.30	4.43, 4.35	31.06, 31.00	11.25, 11.40
14a	$C_{16}H_{17}N_5$ (279)	217	49	Brown	Dioxan	68.81, 68.64	6.09, 6.00	25.08, 25.10	-
14b	$C_{16}H_{16}N_5Cl$ (313.5)	198	66	Yellow	Dioxan	61.24, 61.14	5.10, 5.05	22.33, 22.19	11.32, 11.21
15a	$C_{15}H_{15}N_5O$ (281)	297	74	Yellow	Dioxan	64.05, 64.00	5.33, 5.21	24.91, 24.80	-
15b	$C_{15}H_{14}N_5OCl$ (315.5)	237	68	Yellow	Ethanol	57.05, 57.00	4.43, 4.40	22.18, 22.20	11.25, 11.10
19a	$C_{21}H_{17}N_7$ (367)	277	82	Yellow	Ethanol	68.66, 68.44	4.63, 4.53	26.70, 26.60	-
19b	$C_{21}H_{16}N_7Cl$ (401.5)	281	71	Orange	Ethanol	62.76, 62.54	3.98, 3.83	24.40, 24.42	8.84, 8.66
19c	$C_{21}H_{16}N_7Cl$ (401.5)	265	78	Yellow	Ethanol	62.76, 62.50	3.98, 3.83	24.40, 24.15	8.84, 8.52
19d	$C_{21}H_{15}N_7Cl_2$ (436)	301	69	Brown	Dioxan	57.79, 57.56	3.44, 3.26	22.47, 22.33	16.28, 16.42

TABLE 1: Spectral data of newly synthesized compounds

Cpd.no.	IR (ν_{max}/cm^{-1})	^{1}H NMR (δ, ppm)	MS (relative intensity %)
6a	3398 (NH), 2198.7 (CN)	1.17 (t, 6H, $2CH_3$), 2.82 (q, 4H, $2CH_2$), 4.50 (s, 1H, 4H Pyridine), 7.00-7.64 (m, 5H, aromatic H), 9.49 (.s, 1H, NH)	263 (40), 246 (50), 186 (100)
6b	3301 (NH), 2198.7 (CN)	1.13 (t, 6H, $2CH_3$), 2.95 (q, 4H, $2CH_2$), 4.19 (s, 1H, 4H Pyridine), 7.22-7.98 (m, 4H, aromatic H), 8.79 (s, 1H, NH)	297 (10), 280 (80), 267 (44),186 (100)
6c	3300 (NH), 2200 (CN)	1.20 (t, 6H, $2CH_3$), 2.93 (q, 4H, $2CH_2$) 3.70 (s, 3H, OCH_3), 4.35 (s, 1H, 4H Pyridine), 6.87-7.88(m, 4H, aromatic H), 9.49 (s, 1H, NH)	293 (17),278 (20), 186 (100)
6d	3301 (NH), 2198.7 (CN)	1.25 (t, 6H, $2CH_3$), 2.73 (q, 4H, $2CH_2$), 3.35 (s, 1H, 4H Pyridine), 7.21-7.70 (m, 7H, aromatic H), 10.45 (s, 1H, NH)	313 (40), 283 (60), 186 (100)
6e	3300 (NH), 2198 (CN)	-	-
6f	2214.1 (CN)	1.34 (t, 6H, $2CH_3$), 3.17 (q, 4H, $2CH_2$), 7.35-7.76 (m, 3H, aromatic H)	251 (10), 196 (550), 186 (100)
6g	2214.1 (CN)	1.09 (t, 6H, $2CH_3$), 2.85 (q, 4H, $2CH_2$), 7.7.34-8.63 (m, 3H, aromatic H)	267 (40), 212 (55), 172 (39), 186 (100)
8a	3425, 3301 (NH), 2206 (CN),	1.06 (t, 3H, CH_3), 2.89 (q, 2H, CH_2), 6.94-7.52 (m, 5H, aromatic H), 10.36 (s, 1H, NH), 12.23 (s, 1H, NH)	202 (3), 201 (20), 187 (24), 159 (50), 77 (100)
8b	3271, 3270 (NH), 2214 (CN),	1.07 (t, 3H, CH_3), 2.88 (q, 2H, CH_2), 6.91-7.76 (m, 4H, aromatic H), 1033 (s, 1H, NH), 12.19 (s, 1H, NH)	235 (35), 221 (51), 193 (50),125 (100)
8c	3448, 3271 (NH), 2214 (CN)	1.06 (t, 3H, CH_3), 2.92 (q, 2H, CH_2), 7.20-7.80 (m, 4H, aromatic H), 10.45 (s, 1H, NH), 12.26 (s, 1H, NH)	281 (10), 265 (20), 239 (80), 171 (100)
10a	3410 (NH_2), 3390 (NH)	1.29 (t, 3H, CH_3), 2.85 (q, 2H, CH_2), 6.91-7.71 (m, 7H, aromatic H and NH_2), 10.35 (s, 1H, NH)	215 (90), 200 (80), 138 (100)
10b	3415 (NH_2), 3380 (NH)	1.30 (t, 3H, CH_3), 2.74 (q, 2H, CH_2), 7.21-7.70 (m, 6H, aromatic H and NH_2) 10.45 (s, 1H, NH)	249 (5), 235 (10), 193 (50), 125 (100)
10c	3400 (NH_2), 3380 (NH)	1.27(t, 3H, CH_3), 2.52 (q, 2H, CH_2), 7.21-7.73 (m, 6H, aromatic H and NH_2) 10.45 (s, 1H, NH),	294 (90), 278 (40), 201 (100)
11a	3412 (NH_2)	1.37 (t, 3H, CH_3), 3.24 (q, 2H, CH_2), 4.51 (s, 4H, $2NH_2$), 7.48-7.89 (m, 6H, arom. H and alkenyl H)	281 (10), 265 (47), 198 (50),77 (100)
11b	3410 (NH_2)	1.40 (t, 3H, CH_3), 3.20 (q, 2H, CH_2), 4.50 (s, 4H, $2NH_2$), 7.50-7.920 (m, 6H, arom. H and alkenyl H)	315 (33), 299 (10), 216 (53),112 (100)
14a	-	1.55 (t, 3H, CH_3), 2.68 (s, 6H, $2CH_3$), 3.03 (q, 2H, CH_2), 7.15-7.88 (m, 6H, aromatic H and alkenyl H)	279 (23), 264 (55), 93 (100)
14b	-	1.60 (t, 3H, CH_3), 2.70 (s, 3H, 2 CH_3), 3.10 (q, 2H, CH_2), 7.20-7.99 (m, 5H, arom. H and alkenyl H))	313 (10), 298 (25), 235 (40), 193 (40), 125 (100)
15a	3350 (NH), 1755 (CO).	1.55 (t, 3H, CH_3), 1.96 (s, 3H, CH_3), 3.12 (q, 2H, CH_2), 7.09-8.00 (m, 7H, aromatic H and NH)	281 (55), 266 (33), 105 (100)
15b	3350 (NH), 1755 (CO).	1.50 (t, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.20 (q, 2H, CH_2), 7.10-8.01 (m, 6H, aromatic H and NH)	315 (40), 300 (42), 140 (100)
19a	3400 (NH_2), 2205 (CN)	1.28 (t, 3H, CH_3), 3.00 (q, 2H, CH_2), 7.11-7.89 (m, 12H, aromatic H and NH_2)	367 (35), 217 (77), 198 (100)
19b	3405 (NH_2), 2201 (CN)	1.25 (t, 3H, CH_3), 3.10 (q, 2H, CH_2), 7.10-7.95 (m, 11H, aromatic H and NH_2)	401 (30), 217 (35), 198 (100)
19c	3390 (NH_2), 2205 (CN)	1.27 (t, 3H, CH_3), 3.09 (q, 2H, CH_2), 7.12-8.00 (m, 11H, aromatic H and NH_2)	401 (40), 247 (48), 233 (100)
19d	3395 (NH_2), 2205 (CN)	1.30 (t, 3H, CH_3), 3.10 (q, 2H, CH_2), 7.11-8.01 (m, 10H, aromatic H and NH_2)	436 (39), 247 (36), 233 (100)

with water several times and crystallized from the proper solvent.

Preparation of aminopyrazole derivatives (10a-c)

A solution of arylhydrazoenaminonitrile **(8a-c)** (0.01mol) in ethanol (50ml) was treated with hydrazine hydrate (0.6ml, 0.01mol) The reaction mixture was refluxed for 2h, then poured onto water. The solid product, so-formed, was collected by filtration and washed with water several times and crystallized from the proper solvent.

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Preparation of pyrazolo[1,5-a]pyrimidine derivatives (11a,b)

To a solution of aminopyrazole **(10a)** or b (0.01mol) in acetic acid (30ml) malononitrile (0.66g, 0.01mol) was added. The reaction mixture was refluxed for 4h, then poured onto water. The solid product, so-formed, was collected by filtration and washed with water several times and crystallized from the proper solvent.

Preparation of pyrazolo[1,5-a]pyrimidine derivatives (14a,b and 15a,b)

To a solution of aminopyrazole **(10a)** or **(10b)** (0.01mol) in acetic acid (30ml) acetylacetone or ethylacetoacetate (0.01mol) was added. The reaction mixture was refluxed for 6h, then poured onto water. The solid product, so-formed, was collected by filtration and washed with water several times and crystallized from the proper solvent.

Preparation of pyrazolo[1,5-a]pyrimidine derivatives (19a-d)

To a solution of aminopyrazole **(10a)** or b (0.01mol) in ethanol (50ml) a catalytic amount of pipridine (1ml) and the appropriate arylidenemalononitrile **(16a,b)** (0.01mol) were added. The reaction mixture was refluxed for 3h, then evaporated in *vacuo*. The solid product, so-formed, was collected by filtration and crystallized from the proper solvent.

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