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β-Enaminonitriles in heterocylic synthesis: Synthesis of new tetrahydropyridinethione, pyridopyrimidines, pyridotriazines and dihydropyridines

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Abstract. The chemistry of enaminonitrile and enaminone derivatives has been explored for the synthesis of heterocyclic compounds. A tetrahydropyridinthione was prepared from the reaction of 2-aminocrotononitrile with cyanothioacetamide. This compound reacted with electrophilic reagents and isothiocyanates to yield a number of heterocyclic compounds.

Keywords. β-Enaminonitriles; tetrahydropyridinethione; pyridopyrimidines; pyridotriazines; dihydropyridines.

1. Introduction

β-Aminoalkenonitrile has proven to be valuable reagents in the synthesis of a wide variety of unique heterocyclic systems such as pharmaceuticals, fungicides and solvatochromatic dyes. Recently, a number of papers and patents concerning the importance of β-enaminonitriles in the synthesis of biologically active compounds, dihydropyridines analogous to nifedipine and amlodipine as potential calcium channel blockers in the treatment of angina and hypertension have been found.

2. Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) with a Shimadzu FTIR-8201 PC spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian Germini 200 MHz spectrometer in dimethyl sulphoxide-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 El + QI MSLMRUPLR. Microanalyses were performed by the microanalytical center at Cairo University.

2.1 *4,6-Diamino-1,2,3,4-tetrahydro-4-methyl-2-thioxopyridine-3-carbonitrile(**4**)*

A mixture 2-aminocrotononitrile (**1**) (0·82 g, 0·01 mol) in dioxane (20 ml) and cyanothioacetamide (1 g, 0·01 mol) was refluxed for 4 h. The solid product, so formed, was collected by filtration and crystallized from dimethylforamide as yellow crystals; m.p. > 300°C; yield (90%); IR (KBr): ν 3300 (NH_2), 3210 (NH), 2220 (CN), 1640 (CS) cm^{-1}; MS: *m/z* (%), 182 (34), 165 (100), 95 (25); ^{1}H NMR: δ 2·20 (*s*, 3H, CH_3), 3·10 (*s*, 1H, CH), 5·92 (*s*, 1H, olefinic-H), 7·24–7·30 (*br*, 5H, $2NH_2$ and NH).

Anal. calcd. For $C_7H_{10}N_4$ S : C 46·1; H 5·5; N 30·7; S 17·6%.

Found: C 46·3; H 5·8; N 31·07; S 17·8%.

2.2 *2-Amino-4-mehyl-5-cyanopyridine-6-thiol (**5**)*

A suspension of tetrahydro-pyridinethione **4** (1·8 g, 0·01 mol) in acetic acid (20 ml) was refluxed for 3 h. The solid product, so formed, was collected by

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filtration and crystallized from dioxane as yellow crystals; mp 220–222°C; yield (64%); IR (KBr): ν 3310 (NH_2), 2215 (CN) cm^{-1}; MS: *m/z* (%), 165 (65), 121 (50), 105 (100); ^1H NMR: δ 3·05 (*s*, 1H, SH), 3.20 (*s*, 3H, CH_3), 4·60 (*s*, 2H, NH_2), 6·70 (*s*, 1H, aromatic-H).

Anal. calcd. For $C_7H_7N_3S$: C 50·9; H 4·3; N 25·4; S 19·4%.

Found: C 50·6; H 4·1; N 25·1; S 19·2%.

2.3 *General procedures for the preparation of pyridopyrimidinethione (**9a,b**)*

To a solution of tetrahydro-pyridinethione **4** (1·8 g, 0·01 mol) in ethanol (20 ml) ethoxyethylene-malononitrile derivatives **6a** or **6b** (0·01 mol) and a catalytic amount of piperidine were added. The reaction mixture was refluxed for 3 h and was left to cool. The solid product, so formed was collected by filtration and crystallized from the proper solvent to give **9a,b**.

2.3a *2,8-Diamino-8-methyl-6-thioxo-7,8-dihydro-6H-pyrido[1,2-a]pyrimidine-3,7-dicarbonitrile (**9a**)*: Compound **9a** was obtained as yellow crystals (dioxane), m.p. 225–227°C; yield (70%); IR (KBr): ν 3415 (NH_2), 2205 (CN), 1640 (CS) cm^{-1}; ^1H NMR: δ 2·30 (*s*, 3H, CH_3), 3·10 (*s*, 1H, CH), 6·00 (*s*, 1H, olefinic-H), 7·30–7·42 (*m*, 5H, olefinic-H and $2NH_2$); MS: *m/z* (%), 258 (19), 179 (28), 165 (100).

Anal. calcd. For $C_{11}H_{10}N_6S$: C 51·2; H 4·9; N 32·5; S 12·4%.

Found: C 51·0; H 3·7; N 32·2; S 12·1%.

2.3b *Ethyl 2,8-diamino-7-cyano-7,8-dihydro-8-methyl-6-thioxo-6H-pyrido[1,2-a] pyrimidine-3-carboxlate (**9b**)*: Compound **9b** was obtained as orange crystals (dioxane), m.p. 250–252°C; yield (74%); IR (KBr): ν 3415 (NH_2), 2205 (CN), 1640 (CS) cm^{-1}; ^1H NMR: δ 2·30 (*s*, 3H, CH_3), 3·10 (*s*, 1H, CH), 6·00 (*s*, 1H, olefinic-H), 7·30–7·42 (*m*, 5H, olefinic-H and $2NH_2$); MS: *m/z* (%), 258 (19), 179 (28), 165 (100).

Anal. calcd. For $C_{13}H_{15}N_5SO_2$: C 51·1; H 5·0; N 22·9; S 10.5%.

Found: C 50·8·0; H 5·3; N 22·6; S 10·3%.

2.3c *General procedures for the preparation of pyridopyrimidinethione (**13a–f**)*: To a solution of tetra-hydropyridinethione **4** (1·8 g, 0·01 mol) in ethanol (20 ml) arylidine-malononitrile or arylidine-cyanothioacetamide derivatives **8a–f** (0·01 mol) and a catalytic amount of piperidine were added. The reaction mixture was refluxed for 4 h and then was left to cool. The solid product so, formed was collected by filtration and crystallized from the proper solvent to give **13a–f**.

2.3d *2,8-diamino-8-methyl-4-phenyl-6-thioxo-7,8-dihydro-6H-pyrido[1,2-a] pyrimidine-3,7-dicarbonitrile (**13a**)*: Compound **13a** was obtained as yellow crystals (dioxane), m.p. 231–233°C; yield (60%); IR (KBr): ν 3390 (NH_2), 2200 (CN), 1645 (CS) cm^{-1}; ^1H NMR: δ 1·35 (*s*, 3H, CH_3), 3·10 (*s*, 1H, CH), 6·00 (*s*, 1H, olefinic-H), 7·15–7·91 (*m*, 9H, aromatic-H and $2NH_2$); MS: *m/z* (%), 334 (24), 317 (39), 165 (100).

Anal. calcd. For $C_{17}H_{14}N_6S$: C 61·6; H 4·2; N 25·1; S 9·6%.

Found: C 50·8; H 5·3; N 22·6; S 10·3%.

2.3e *2,8-diamino-8-methyl-6-thioxo-4-(4-chloro-phenyl)-7,8-dihydro-1Hpyrido[1,2-a] pyrimidine-3,7-dicarbonitrile (**13b**)*: Compound **13b** was obtained as yellow crystals (dioxane/ehanol), m.p. 280–282°C; yield (60%); IR (KBr): ν 3390 (NH_2), 2200 (CN), 1645 (CS) cm^{-1}; ^1H NMR: δ 1·35 (*s*, 3H, CH_3), 3·10 (*s*, 1H, CH), 6·00 (*s*, 1H, olefinic-H), 7·15–7·91 (*m*, 9H, aromatic-H and $2NH_2$); MS: *m/z* (%), 334 (24), 317 (39), 165 (100).

Anal. calcd. For $C_{17}H_{13}N_6SCl$: C 55·4; H 3·6; N 22·8; S 8·7; Cl 9·6%.

Found: C 55·7; H 3·9; N 22·6; S 8·4; Cl 9·4%.

2.3f *2,8-diamino-8-methyl-6-thioxo-4-p-tolyl-7,8-dihydro-1H-pyrido[1,2-a] pyrimidine-3,7-dicarbonitrile (**13c**)*: Compound **13c** was obtained as brown crystals (dioxane/ehanol), m.p. 290–292°C; yield (64%); IR (KBr): ν 3390 (NH_2), 2205 (CN), 1640 (CS) cm^{-1}; ^1H NMR: δ 1·35 (*s*, 3H, CH_3), 2·70 (*s*, 3H, CH_3), 303 (*s*, 1H, CH), 5·95 (*s*, 1H, olefinic-H), 7·10–7·66 (*m*, 8H, aromatic-H and $2NH_2$); MS: *m/z* (%), 348 (29), 257 (35), 165 (100).

Anal. calcd. For $C_{18}H_{16}N_6S$: C 62·1; H 4·6; N 24·1; S 9·2%.

Found: C 62·0; H 4·9; N 24·4; S 9·0%.

2.3g *2,8-diamino-4-(3,4,5-trimethoxyphenyl)-7-cyano-8-methyl-6-thioxo-7,8-dihydro-6H-pyrido[1,2-a] pyrimidine-3-carbothioamide (**13d**)*: Compound **13d** was obtained as yellow crystals (ethanol/dioxane), m.p. 250–252°C; yield (66%); IR (KBr): ν 3450 (*br*, NH_2), 2205 (CN), 1650 (CS) cm^{-1}; ^1H NMR: δ 1·35

(*s*, 3H, CH_3), 2·15 (*br*, 2H, $CSNH_2$), 2·90 (*s*, 1H, CH), 3·95 (*s*, 9H, $3OCH_3$), 5·80 (*s*, 1H, olefinic-H), 7·00–7·79 (*m*, 6H, aromatic-H and $2NH_2$); MS: *m/z* (%), 458 (19), 178 (43), 165 (100).

Anal. calcd. For $C_{20}H_{22}N_6S_2O_3$: C 52·4; H 4·8; N 18·3; S 14·0%.

Found: C 52·1; H 4·9; N 18·5; S 13·6%.

2.3h *2,8-Diamino-4-(4-chlorophenyl)-7-cyano-8-methyl-6-thioxo-7,8-dihydro-6Hpyrido[1,2-a] pyrimidine-3-carbothioamide (**13e**):* Compound **13e** was obtained as brown crystals (dioxane), mp 233–235°C; yield (62%); IR (KBr): ν 3445 (*br*, NH_2), 2200 (CN), 1647 (CS) cm^{-1}; 1H NMR: δ 1·35 (*s*, 3H, CH_3), 2·15, (*br*, 2H, $CSNH_2$), 2·95 (*s*, 1H, CH), 5·90 (*s*, 1H, olefinic-H), 7·10–7·75 (*m*, 8H, aromatic-H and $2NH_2$); MS: *m/z* (%), 402 (26), 169 (100).

Anal. calcd. For $C_{17}H_{15}N_6S_2Cl$: C 50·7; H 3·8; N 20·9; S 15·9; Cl 8·8%.

Found: C 50·3; H 3·9; N 20·5; S 15·6; Cl 9·1%.

2.3i *2,8-Diamino-4-(4-methylphenyl)-7-cyano-8-methyl-6-thioxo-7,8-dihydro-6H-pyrido[1,2-a]pyrimidine-3-carbothioamide (**13f**):* Compound **13f** was obtained as brown crystals (dioxane), mp 241–243°C; yield (72%); IR (KBr): ν 3400 (*br*, NH_2), 2225 (CN), 1645 (CS) cm^{-1}; ^{1}H NMR: δ 1·35 (*s*, 3H, CH_3), 2·00, (*br s*, 2H, $CSNH_2$), 2·35 (*s*, 3H, CH_3), 2·50 (*s*, 3H, CH_3), 2·99 (*s*, 1H, CH), 6·10 (*s*, 1H, olefinic-H), 7·15–7·90 (*m*, 8H, aromatic-H and $2NH_2$); MS: *m/z* (%), 402 (26), 207 (37), 165(100).

Anal. calcd. For $C_{18}H_{18}N_6S_2$: C 56·5; H 4·7; N 22·0; S 16·8%.

Found: C 56·2; H 4·3; N 21·6; S 16·6%.

2.4 *General procedures for the preparation of pyridotriazine derivatives (**16a,b**)*

To a solution of either benzoylisothiocyanate or acetyl isothiocyanate (0·01 mol) [was prepared by refluxing eiher benzoylchloride or acetylchloride (0·01 mol) with ammonium thiocyanate (0·76 g, 0·01 mol) in dry acetone] in dry acetone (50 ml), tetrahydropyridinethione **4** (1·8 g, 0·01 mol) was added. The reaction mixture was refluxed for 2 hrs and then poured onto water. The solid product, so formed was collected by filtration and crystallized from the proper solvent to give **16a–b**.

2.4a *8-Amino-8-methyl-4-phenyl-2,6-dithioxo-1,6,7,8-tetrahydro-2H-pyrido[1,2-a] [1,3,5]triazine-7-carbonitrile (**16a**):* Compound **16a** was obtained as yellow crystals (dioxane), m.p. 271–273°C; yield (62%); IR (KBr): ν 3370 (NH_2), 2195 (CN), 1635 (CS) cm^{-1}; ^{1}H NMR: δ 1·00 (*s*, 3H, CH_3), 2·31 (*s*, 3H, CH_3), 2·80 (*s*, 1H, CH), 5·85 (*s*, 1H, olefinic-H), 7·05 (*s*, 2H, NH_2), 10·50 (*s*, 1H, NH); MS: *m/z* (%), 265 (27), 165 (100).

Anal. calcd. For $C_{15}H_{13}N_5S_2$: C 55·0; H 4·0; N 21·4; S 19·6%.

Found: C 55·4; H 4·3; N 21·6; S 19·2%.

2.4b *8-Amino-8-methyl-4-methyl-2,6-dithioxo-1,6,7,8-tetrahydro--2H-pyrido[1,2-a] [1,3,5]triazine-7-carbonitrile (**16b**):* Compound **16b** was obtained as yellow crystals (dioxane), m.p. 247–279°C; yield (66%); IR (KBr): ν 3370 (NH_2), 2195 (CN), 1635 (CS) cm^{-1}; ^{1}H NMR: δ 1·00 (*s*, 3H, CH_3), 2·31 (*s*, 3H, CH_3), 2·80 (*s*, 1H, CH), 5·85 (*s*, 1H, olefinic-H), 7·05 (*s*, 2H, NH_2), 10·50 (*s*, 1H, NH; MS: *m/z* (%), 265 (27), 165 (100).

Anal. calcd. For $C_{10}H_{11}N_5S_2$: C 45·3; H 4·2; N 26·4; S 24·5%.

Found: C 45·0; H 4·3; N 26·6; S 24·8%.

2.5 *General procedures for the preparation of thiourea derivatives (**18a,b**)*

To a solution of arylisothiocyanate **17a** or **17b** (0·01 mol) in dry acetone (20 ml) tetrahydro-pyridinethione **4** (1·8 g, 0·01 mol) was added. The reaction mixture was refluxed for 4 h then left to cool. The solid product, so formed was collected by filtration and crystallized from the proper solvent to give **(18a,b)**.

2.5a *1-(4-Amino-5-cyano-1,4,5,6-tetrahydro-4-methyl-6-thioxopyridin-2-yl)-3-ptolylthiourea (**18a**):* Compound **18a** was obtained as brown crystals (dioxane), m.p. 217–219°C; yield (55%); IR (KBr): ν 3340 (NH_2), 3350 (NH), 2200 (CN), 1655 (CS) cm^{-1}; ^{1}H NMR: δ 2·15 (*s*, 3H, CH_3), 2·35 (*s*, 3H, CH_3), 2·90 (*s*, 1H, CH), 4·50 (*br*, 2H, 2NH), 5·90 (*s*, 1H, olefinic-H), 6·81–7·10 (*m*, 7H, aromatic-H, NH_2 and NH); MS: *m/z* (%), 331 (27), 240 (52), 165 (100).

Anal. calcd. For $C_{15}H_{17}N_5S_2$: C 54·4; H 5·2; N 21·1; S 19·4%.

Found: C 54·0; H 5·3; N 21·4; S 19·8%.

2.5b *1-(4-Amino-5-cyano-1,4,5,6-tetrahydro-4-methyl-6-thioxopyridin-2-yl)-phenylthiourea (**18b**):* Compound **18b** was obtained as brown crystals

(dioxane), m.p. 210–212°C; yield (59%); IR (KBr): ν 3340 (NH_2), 3350 (NH), 2200 (CN), 1655 (CS) cm^{-1}; ^1H NMR: δ 2·10 (*s*, 3H, CH_3), 2·85 (*s*, 1H, CH), 4·60 (*br*, 2H, 2NH), 6·11 (*s*, 1H, olefinic-H), 6·81–7·15 (*m*, 8H, aromatic-H, NH_2 and NH); MS: *m/z* (%), 317 (27), 240 (52), 165 (100).

Anal. calcd. For $C_{14}H_{15}N_5S_2$: C 53·0; H 4·7; N 22·1; S 20·2%.

Found: C 53·3; H 4·3; N 22·4; S 19·8%.

2.6 *General procedures for the preparation of dihydropyridine derivatives (**24a–e**)*

Procedure (A): To a solution of 2-aminocrotononitrile (**1**) (0·82 g, 0·01 mol) in ethanol (20 ml) a catalytic amount of piperidine and arylidinemalononitrile **19a–c** or arylidine cyanothioacetamide derivatives **19d,e** (0·01 mol) were added. The reaction mixture was refluxed for 4 h and then left to cool. The solid product, so formed was collected by filtration and crystallized from the proper solvent to give **24a–e**.

Procedure (B): To a solution of 2-aminocrotononitrile (**1**) (0·82 g, 0·01 mol) in glacial acetic acid (20 ml) the corresponding aldehyde **25a–e** (0·01 mol) was added. The reaction mixture was refluxed for 4 h and then left to cool. The solid product, so formed was collected by filtration and crystallized from the proper solvent to give **24a–e**.

2.6a *4-(2-Chlorophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarbonitrile (**24a**):* Compound **24a** was obtained as yellow crystals (dioxane), m.p. 262–264°C; yield (55%); IR (KBr): ν 3340 (NH), 2210 (CN) cm^{-1}; ^1H NMR: δ 2·08 (*s*, 6H, $2CH_3$), 4·60 (*s*, 1H, 4H-pyridine), 7·32–8·11 (*m*, 4H, aromatic-H), 9·70 (*s*, 1H, NH); MS: *m/z* (%), 269 (27), 158 (100).

Anal. calcd. For $C_{15}H_{12}N_3Cl$: C 66·8; H 4·9; N 15·9; Cl 13·1%.

Found: C 66·6; H 4·6; N 15·7; Cl 13·3%.

2.6b *1,4-Dihydro-4-(4-methoxyphenyl)-2,6-dimethylpyridine-3,5-dicarbonitrile (**24b**):* Compound **24b** was obtained as yellow crystals (dioxane), m.p. 223–225°C; yield (75%); the spectral data of this compound is compatible with the reported structure in literature.[14]

2.6c *4-(4-Bromophenyl)-1,4-dihydro-2,6-dimethylpyridine-3,5-dicarbonitrile (**24c**):* Compound **24c** was obtained as orange crystals (ethanol/dimethylforamide), m.p. 210–212°C; yield (75%); IR (KBr): ν 3340 (NH), 2205 (CN) cm^{-1}; MS: *m/z* (%), 314 (33), 159 (100); ^1H NMR: δ 2·00 (*s*, 6H, $2CH_3$), 4·60 (*s*, 1H, 4H-pyridine), 7·10–8·10 (*m*, 4H, aromatic-H), 9·53 (*s*, 1H, NH).

Anal. calcd. For $C_{15}H_{12}N_3Br$: C 57·3; H 3·9; N 13·8; Br 25·4%.

Found: C 57·5; H 3·6; N 13·7; Br 25·2%.

2.6d *1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)pyridine-3,5-dicarbonitrile (**24d**):* Compound **24d** was obtained as brown crystals (ethanol/dimethylforamide, m.p. 225–227°C; yield (60%); IR (KBr): ν 3340 (NH), 2215 (CN) cm^{-1}; ^1H NMR: δ 2·08 (*s*, 6H, $2CH_3$), 4·70 (*s*, 1H, 4H-pyridine), 7·11–8·20 (*m*, 4H, aromatic-H), 9·17 (*s*, 1H, NH). MS: *m/z* (%), 280 (23), 158 (100).

Anal. calcd. For $C_{15}H_{12}N_4O_2$: C 64·3; H 4·3; N 20·0%.

Found: C 64·0; H 4·0; N 20·3%.

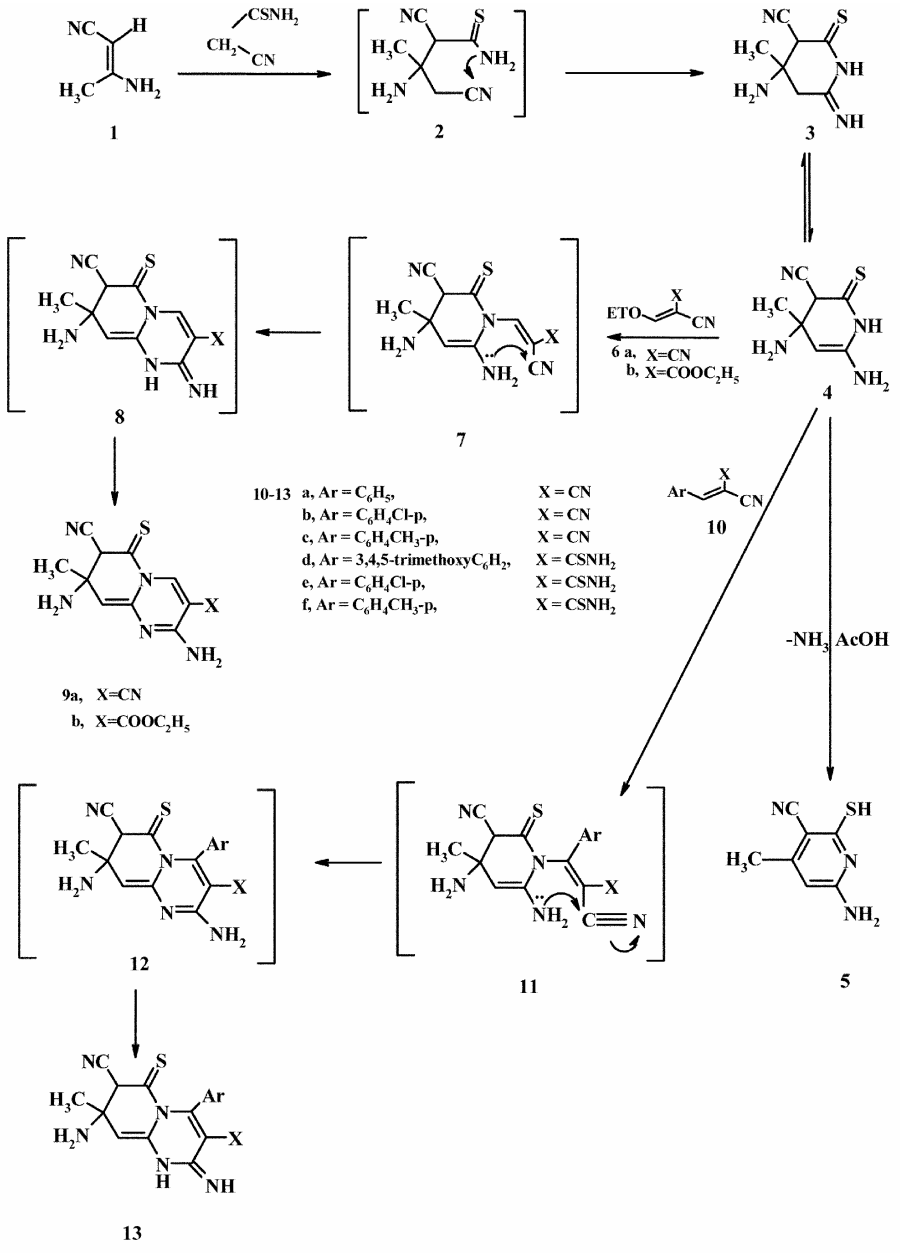
2.6e *1,4-Dihydro-4-(2,3,4-trimethoxyphenyl)-2,6-dimethylpyridine-3,5-dicarbonitrile (**24e**):* Compound **24e** was obtained as black crystals (dimethylforamide), m.p. 291–292°C; yield (60%); IR (KBr): ν 3340 (NH), 2220 (CN) cm^{-1}; ^1H NMR: δ 1·9 (*s*, 6H, $2CH_3$), 3·80 (*s*, 9H, $3OCH_3$), 7·10–8·03 (*s*, 2H, aromatic-H), 9·7 (*s*, 1H, NH). MS: *m/z* (%), 325 (40), 159 (100).

Anal. calcd. For $C_{18}H_{19}N_3O_3$: C 66·5; H 5·9; N 12·9%.

Found: C 66·3; H 5·7; N 12·7%.

3. Discussion

In our previous work from our laboratories we have explored the synthetic potentiality of β-enaminonitriles[1–3] and enaminones.[4,5] In continuation of our interest in developing the synthesis of polyfunctionally substituted heteroaromatics, we report here on the utility of 2-aminocrotononitrile (**1**) as a precursor for the synthesis of polyfunctionally substituted pyridines and pyridopyrimidines. Thus, it has been found that **1** reacted with cyanothioacetamide in refluxing dioxine to give tetrahydropyridinthione (**4**) in a quantitative yield. The structure of **4** was based on its spectral analysis. The formation of **4** from the reaction of **1** and cyanothioacetamide is believed to be via the initial addition of cyanothioacetamide to **1** to give the acyclic intermediate **2** that cyclize readily

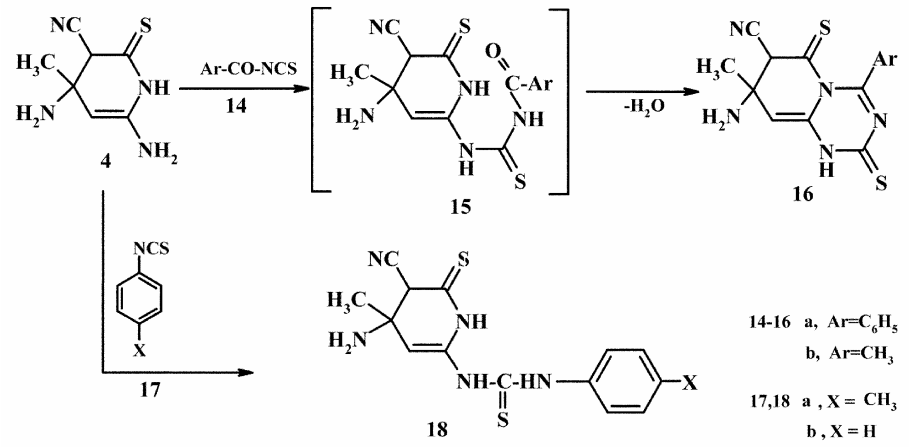


Scheme 1.

into **3** and tautomerizes into **4** (scheme 1). Heating of **4** in refluxing acetic acid for about 5 h resulted in the formation of pyridine derivative **5** via elimination of NH_3. The structure of **5** was based on its spectral data and elemental analysis (scheme 1).

Compound **4** was reacted with ethoxymethylenemalononitrile (**6a**) in refluxing ethanol/piperidine to give pyridopyrimidinthione derivative **9a**. Establishing of structure **9a** was based on its spectral data and elemental analysis. Formation of **9a** from **4** and ethoxymethylenemalononitrile (**6a**) was believed to be formed via Michael type addition of compound **4** on **6a** followed by ethanol elimination to give the acyclic intermediate **7** which is then underwent intramolecular cyclization and subsequent tautomerism to give **9a** as demonstrated in scheme 1. Similarly, compound **4** reacted with **6b** to give the corresponding pyridopyrimidinthione derivative **9b** (scheme 1).

Furthermore, the behaviour of tetrahydropyridinthione (**4**) towards some electrophilic reagents such as arylidenemalononitrile and arylidenecyanothioacetamide was also investigated. Thus, compound **4** was reacted with benzylidenemalononitrile (**10a**) in refluxing ethanol and in the presence of piperidine to give the pyridopyrimidinethione derivative **13a**



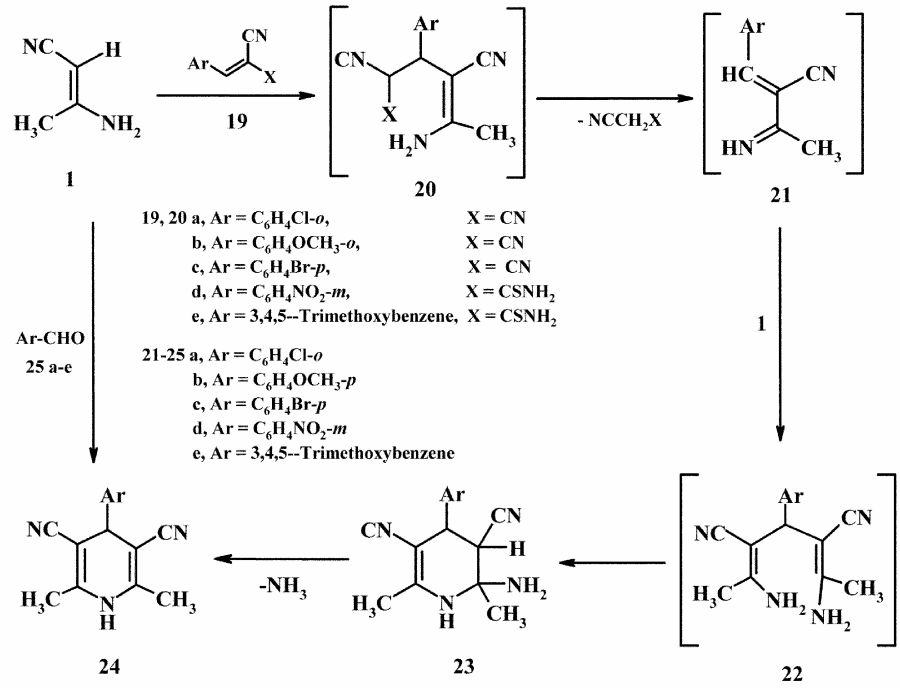
Scheme 2.

via intermediacy of Michael adduct **11a**. Formation of compound **13a** from the reaction of **4** and arylidene **10a** is believed to be formed via initial Michael addition of compound **4** on arylidene **10a** to give the acyclic non-isolable intermediate **11a** which underwent intramolecular cyclization and subsequent tautomerism to give **13a**. Establishing of structure **13a** was based on its spectral data. For example the ^{1}H NMR of compound **13a** revealed the presence of a singlet signal at $\delta = 1{\cdot}35$ ppm corresponding to CH_3, a singlet signal at $\delta = 3{\cdot}10$ ppm corresponding to sp^3 proton, a singlet signal at $\delta = 6{\cdot}0$ ppm corresponding to sp^2 proton and a multiplet signal at $\delta = 7{\cdot}15$–$7{\cdot}91$ ppm corresponding to aromatic protons and amino function. The mass spectrum of the same compound is in accordance with the proposed structure. Thus, it showed a molecular ion peak at 334. Similarly, compound **4** was reacted with arylidenmalononitriles **10b,c** in the same reaction condition to give pyridopyrimidinethione derivatives **13b,c** respectively (scheme 1).

Typical to the behaviour of arylidenemalononitriles toward **4**, arylidenecyanothioacetamide **10d–f** was reacted with **4** in refluxing ethanol and in the presence of catalytic amount of piperdine to give the pyridopyrimidinthione derivatives **13d–f** (scheme 1). Establishing of structures **13d–f** was based on their spectral data. For example ^{1}H NMR of **13d** revealed the presence of a singlet signal at $\delta = 1{\cdot}35$ ppm corresponding to methyl group, a broad signal at $\delta = 2{\cdot}15$ ppm corresponding to $CSNH_2$, a singlet signal at $\delta = 2{\cdot}90$ ppm corresponding to sp^3 proton, a singlet signal at $\delta = 3{\cdot}95$ ppm corresponding to aliphatic three methoxy groups, a singlet signal at $\delta = 5{\cdot}80$ ppm corresponding to olefinic proton and a multiplet signal at $\delta = 7{\cdot}00$–$7{\cdot}79$ ppm corresponding to aromatic protons and NH_2. The mass spectrum of the same compound further supports the proposed structure. Thus, it showed a molecular ion peak at 458, it also showed a fragment at 178.

The behaviour of **4** towards isothiocyanate reagents was also investigated to proceed typical to literature reports. Thus, benzoyl isothiocyanate **(14a)** was reacted with **4** in refluxing acetone to give the pyridotriazine derivatives **16a** via intermediacy of **15**. Similarly, acetylisothiocyanate **(14b)** reacted with **4** in refluxing acetone to give **16b** (scheme 2). Compound **4** reacted also with 4-tolylisothiocyanate **(17a)** in refluxing acetone to give the acyclic thiourea derivative **18a** whose structure was established based on its elemental and spectral data (scheme 2). Similarly, phenyl isothiocyanate **(17b)** reacted with **4** to give **18b**.

In a previous work from our laboratory[1,2] we have shown that β-enaminonitriles react readily with aliphatic, aromatic heteroaromatic aldehydes and some ketones to give pyridine and dihydropyridine derivatives analogous to a very important calcium channel blockers i.e. nifadipine drug.[6–13] In continuation of this work we investigated the behaviour of 3-aminocrotononitrile **(1)** towards some electrophilic reagents such as arylidenemalononitriles and arylidinecyanothioacetamides. Thus, it has been found that 3-aminocrotononitrile **(1)** reacted with arylidenmalononitriles **19a–c** and arylidinecyanothioacetamides **19d,e** to give dihydropyridine derivatives **24a–e**. Establishing structure **24** was based on its spectral data and authentic specimen prepared from the reaction of **1** with the corresponding aldehydes derivatives **25a–e**. Formation of **24a–e** from the reaction of **1**



Scheme 3.

and arylidene derivatives **19a–e** is believed to be formed via initial addition of **1** on the double bond of arylidene to give the Michael adduct **20** that loses either malononitrile or cyanothioacetamide to give **21**, which reacts further with one mole of **1** to give the acyclic intermediate **22** that gives the dihydropyridine **24** via cyclization and subsequent loss of NH3 (scheme 3).

4. Conclusion

The synthesis of a number of new tetrahydropyridinethiones, pyridopyrimidines, pyridotriazines and dihydropyridines was achieved by utilizing the chemistry of *β*-enaminonitriles.

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