Hydantoin in Heterocyclic Synthesis: Synthesis of new Imidazopyridine, Imidazotriazole, Pyrazolopurinone, Pyranoimidazole, Imidazopyridazine and Imidazopyrazole Derivatives

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Summary: A New series of imidazopyridine, imidazotriazole, pyrazolopurinone, pyranoimidazole, imidazopyridazine and imidazopyrazole derivatives were synthesized from the reaction of hydantion and its derivatives using a variety of electrophilic and nucleophilic reagents under mild conditions. The structures of the synthesized compounds were established via their elemental and spectral analyses.

Keywords*:* Hydantion; Imidazolidinedione; Immidazolopyridine; Benzamide ; Acetamide; Fused pyrazoles and Benzenesulfonamide.

Introduction

The chemistry and properties of hydantoins and their derivatives have been investigated for more than 140 years. The hydantoin moiety which is present in various biologically active compounds represents a pharmaceutical importance [1, 2]. They have a wide biological activities such as integrins and kinases inhibitors, [3, 4], anti-convulsants, anti-epileptics [5], fungicides, herbicides [6] anti-bacterial, anti-mycobacterial [7] and potent activity against the herpes simplex virus (HSV) [8], human immune deficiency virus (HIV) [9] and the leukemia subpanel [10]. Hydantoin derivatives can also be found as antiarrhythmics (azimilide), antimicrobial agents (nitrofurantoin), skeletal muscle relaxants (dantrolene) and nonsteroidal antiandrogens (nilutamide), while allantoin is used as a keratolytic, astringent, wound remedy, antacid and antipsoriatic drug [11]. Hydantoins also exhibit antidepressant, antiviral and antithrombotic activities, as well as inhibitory activity against some enzymes (human aldose reductase and human leucocyte elastase) [12]. Finally, some herbicides (spirohydantoin, thioxohydantocidin), fungicides (clodantoin) and insecticides also have the hydantoin skeleton in their structure [13, 14].

In the chemical industry various 5,5-disubstituted hydantoins constitute the basis of a new generation of weatherproof high-temperature stable epoxy resins [15]. Furthermore, hydantoin and hydantoin derivatives were used as a monomer for the synthesis of condensation polymers [16, 17]. This led us to prepare a series of the novel structural analogues of these lead compounds. Owing to the above facts and as continuation of our program of identification of new active leads that may be valuable in designing new agents [18, 19], the present work reports the synthesis of new heterocyclic compounds.

Results and Discussion

Synthesis

In the present paper we investigated the behavior of 5-[(dimethylamino) methylene] imidazolidine-2,4-dione (**1**) [19], toward some electrophilic and nucleophilic reagents,. Thus, compound **1** reacted with benzylidinemalononitrile **2a** to afford imidazo[1,5-*a*]pyridine-6-carbonitrile derivative **5a** rather than its tautomeric structure **8a** based on its spectra[l] analysis. For example, the IR spectra showed a pair of absorption band at 1636 and 1736 cm^{-1} for its carbonyl, also the IR spectra showed that the 2194 cm^{-1} is the CN absorption band. The ^{1}H-NMR revealed the presence of a pair of methyl functions at δ = 1.62 ppm, a singlet signal at δ = 4.80 ppm corresponding to 2H pyridine and a multiplet signal at ∂ = 6.96 – 7.74 ppm corresponding to aromatic protons and amino functions. The ^{13}C-NMR data of compounds **5a** showed chemical shift values at δ = 41.90 and 118.80 corresponding to the methyl and nitrile groups respectively. The MS spectrum showed that the m/z of molecular ion was 309 (M^+) in accordence with its molecular formula $C_{16}H_{15}N_5O_2$. Formation of imidazo[1,5-*a*]pyridine-6-

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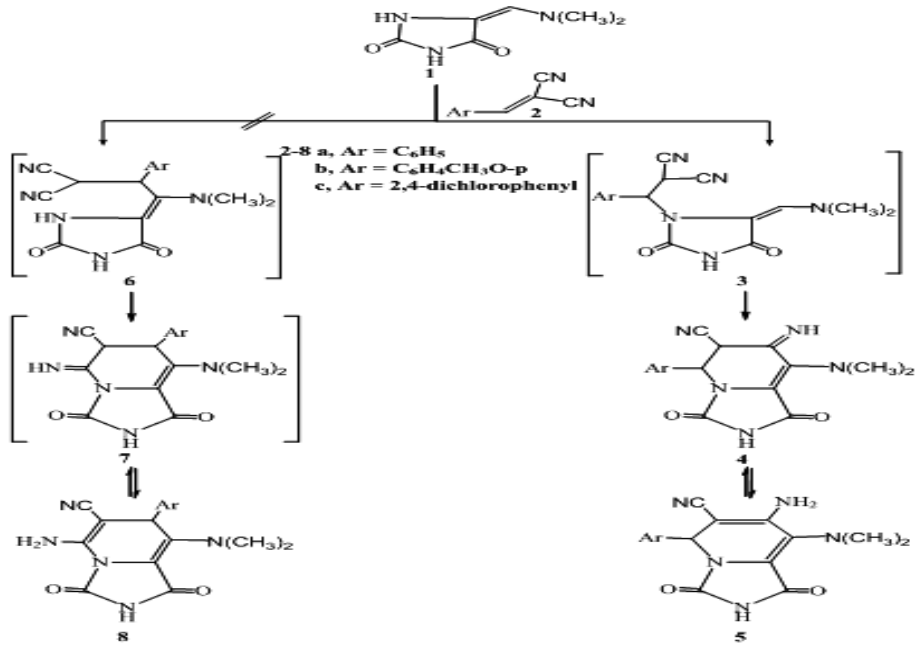
carbonitrile **5** from the reaction of benzylidine-malononitrile **2a** and imidazolidine **1** is believed to be formed via initial addition of NH group of **1** on the double bond system of benzylidinemalononitrile to give the Michael adduct **3**, which cyclizes in the same reaction condition to give **4** that tautomerizes into **5**. Similarly, imidazolidine-2,4-dione **1** reacted with arylidine-malononitrile **2b,c** to afford imidazo[1,5-*a*]pyridine-6-carbonitrile derivative **5b,c**. Establishing structure **5b,c** was based on their spectral analysis (Scheme-1).

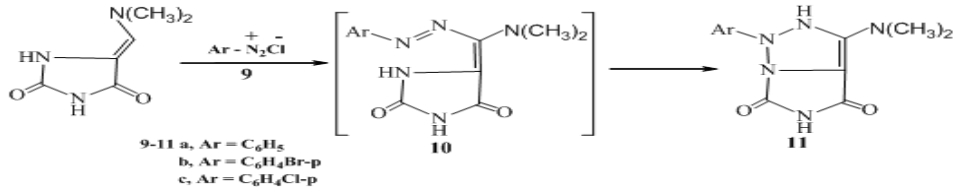
The synthetic potentiality of imidazolidine-2,4-dione **1** was also investigated through its coupling with aryl diazonium salts. Thus, when imidazolidine-2,4-dione **1** coupled with benzene diazonium chloride **9a** in ethanol and in the presence of sodium acetate, imidazo[1,5-*c*]traizole **11a** was obtained in a quantitative yield as demonstrated in Scheme-**2**. Establishing structure **11a** was based on its spectral analysis. The IR spectroscopic investigation of **11a** revealed characteristic bands at 3535, 3308 cm^{-1} (2 NH) and a pair of absorption band at 1625 and 1719 cm^{-1} for its carbonyl. The ^1H NMR showed the presence of a pair of methyl functions at δ = 1.21 ppm. The ^{13}C-NMR data of compounds **11a** showed chemical shift values conform to the suggested structure. Furthermore, the MS spectrum show that the m/z of molecular ion was 259 (M^+) confirming their molecular weight. Similarly, imidazolidine-2,4-dione **1** coupled with aryl diazonium salts **9b,c** in the same reaction condition to afford imidazo[1,5-*c*]traizole **11b,c** via intermediacy of **10** as demonstrated in Scheme-2. Furthermore the reaction of imidazolidine-2,4-dione **1** with piperidine in refluxing ethanol afforded imidazolidine-2,4-dione derivative **14** via intermediacy of **13** as demonstrated in Scheme-**3**.

In addition the behavior of **1** toward heterocyclic amines was also investigated. Thus, when **1** is allowed to react with aminopyrazole **15a** afforded pyrazolo[5,1-*b*] purinone **17a** via elimination of dimethylamine and subsequent cyclization. The structure of the product **17a** was deduced from their ^1H NMR, ^{13}C-NMR, mass, IR spectra, and elemental analysis. For example The IR spectra exhibited absorption bands at 1715 cm^{-1} assignable to C=O stretching vibrations and characteristic bands at 3200 and 3369 cm^{-1} corresponding to (NH) and (NH_2) groups respectively. In addition, the ^1H-NMR spectrum of **17a** revealed the presence of a singlet signal at δ = 2.31 ppm corresponding to methyl function, a multiplet signal at δ = 7.17-7.58 ppm corresponding to aromatic protons and amino group and a singlet signal at δ = 10.68 ppm corresponding to NH group. The MS spectrum showed that the m/z of molecular ion was 308 (M^+), according with its molecular formula $C_{14}H_{12}N_8O$. Similarly, imidazolidine-2,4-dione **1** reacted with aminopyrazole **15b** in the same reaction condition to give **17b** as demonstrated in Scheme-3.

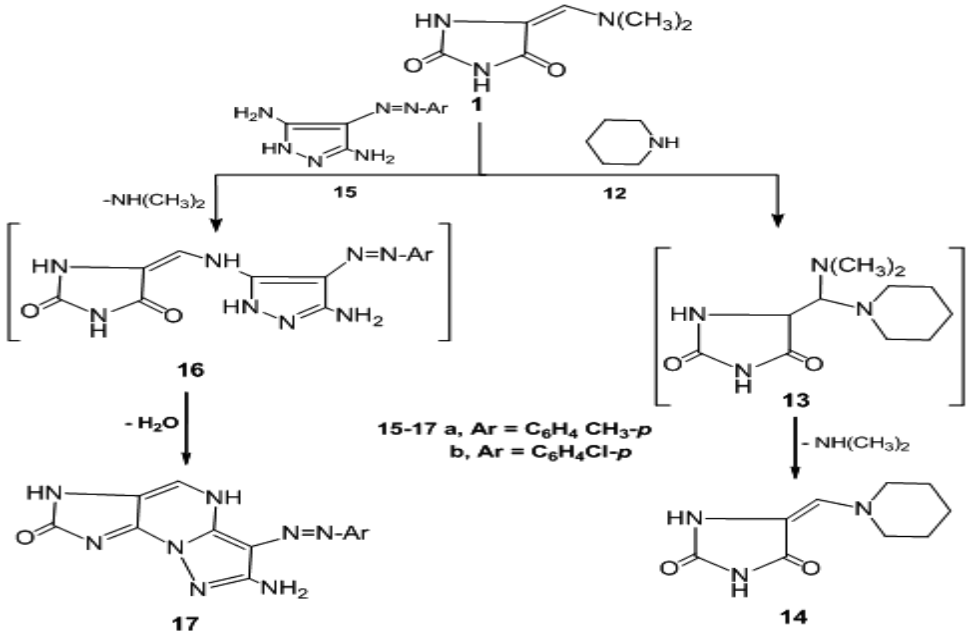
The reactivity of imidazolidine-2, 4-dione **1** toward some active methylene reagents was also investigated. Thus, when **1** is allowed to react with malononitrile **18a** in refluxing ethanol, a compound with molecular formula $C_9H_{11}N_5O_2$ = 221 was obtained. This was considered to be the pyrano[2,3-*d*]imidazole-6-carbonitrile **21** based on its spectral analysis. Thus, the IR spectroscopic investigation of **21** revealed characteristic bands at 1730 cm^{-1} (C=O) and 2201 cm^{-1} (C≡N), in addition, the ^1H-NMR of **21** revealed the presence of a singlet signal at δ = 1.22 ppm corresponding to methyl function, a singlet signal at δ = 4.14 ppm corresponding to H-4 pyran, a pair of signals at δ = 7.07 ppm and δ = 7.70 ppm corresponding to a pair of NH groups and a singlet signal at 8.36 ppm corresponding to NH_2 group. The mass spectrum of compound **21** is in accordance with the proposed structure. Thus, it showed a very intense molecular ion peak at 221 (M^+), and a number of fragments agree with the proposed structure. Formation of **21** from the reaction of **1** and malononitrile is believed to be formed via initial addition of the active methylene group of malononitrile on the double bond system of **1** to give the non-isolable intermediate **19** which cyclizes readily to give **20** that tautomerizes into **21** as demonstrated in Scheme-4. Similar to the behavior of malononitrile with **1**, ethyl cyanoacetate reacted with **1** in the same reaction condition to give pyrano[2,3-*d*]imidazole-6-carbonitrile **24** (Scheme-4). Establishing structure **24** was based on its spectral analysis. For example, IR showed the presence of a pair of carbonyl groups at 1717, 1635 cm^{-1} and CN at 2201 cm^{-1}. The ^1H-NMR of **24** revealed the presence of a pair of singlet doublets at δ = 2.96 and 3.84 with coupling constant J = 8.3 Hz, corresponding to H-3 pyrane and H-4 pyrane. The ^{13}C-NMR spectrum of (**24**) showed three distinct resonances arising from $2CH_3$, CN and C=O at δ = 31.70, 116.20, 164.20 respectively.



Scheme-1: The synthesis of imidazol[1,5-a] pyridine-6-carbonitrile derivatives (5a-c).



Scheme-2: the synthesis of imidazo[1,5-*c*][1,2,3]triazole-4,6(2*H*, 5*H*)-dione derivatives **(11a-c)**.



Scheme-3: The synthesis of 5-(piperidin-1-ylmethylene)imidazolidine-2,4-dione **(14)** and pyrazolopurinone derivatives **(17a, b).**

Experimental

Instruments

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^1H NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 at 200 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard and the coupling constants (*J* values) are given in Hz. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Thin layer chromatography (TLC) was used to monitor the course of reactions and ascertain the purity of compounds, and detection of the components was made by exposure to ultraviolet light. Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University.

Synthesis – General Procedures

Preparation of imidazo[1,5-a]pyridine **(5a-c):**

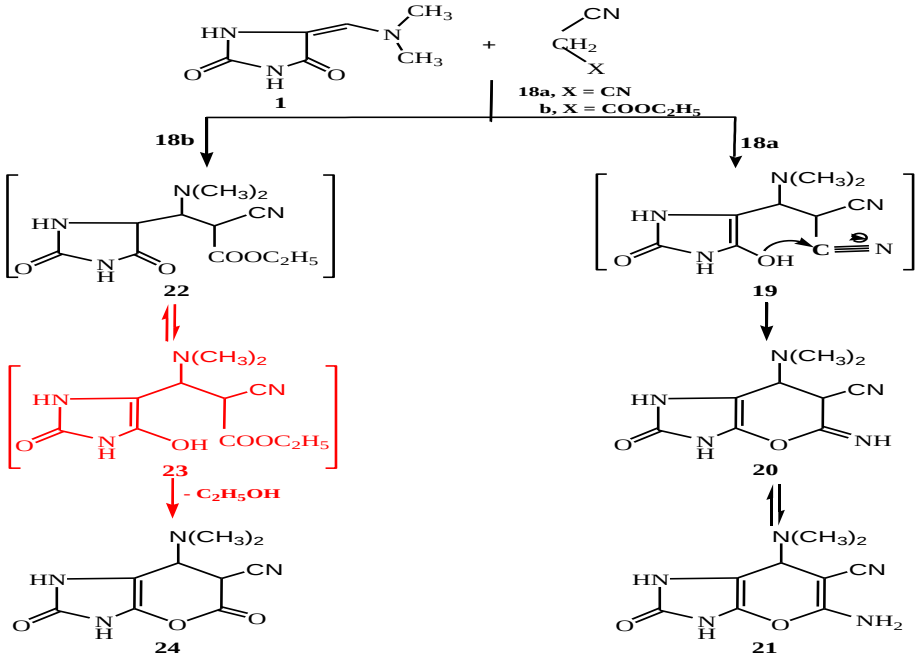
Equimolars of compound **1** (0.01 mole) and arylidinemalononitrile **(2a–c)** (0.01 mole) were mixed in ethanol (40 mL) and treated with a few drops of piperidine were refluxed for 6.0 h and poured into cold water (30 mL) and acidified with HCl. The solid product was collected and crystallized from the proper solvent.

7-Amino-8-(dimethylamino)-1,3-dioxo-5-phenyl-1,2,3,5-tetrahydroimidazo[1,5-a]pyridine-6-carbo-nitrile **(5a):**

It was obtained as yellow crystals from ethanol; yield 76%; mp 110–112 °C; IR (KBr, ν, cm^{-1}): 3400, 3351 (NH_2), 3200 (NH), 2926 (CH-aliph), 2194 (C≡N), 1736, 1636 (2 C=O); ^1H-NMR (DMSO-d_6) δ = 1.62(s, 6H, $2CH_3$), 4.80(s, 1H, 2H-pyridine), 6.96-7.74 (m, 8H, arom-H, NH and NH_2); ^{13}C-NMR (DMSO-d_6) δ 166.91, 155.90, 148.48, 136.0, 132.90, 131.00, 129.85, 127.15, 124.90, 118.80, 95.90, 43.55, 41.90; MS *m/z* = 309 (M^+). Anal. Calcd. (%) for $C_{16}H_{15}N_5O_2$ (309): C, 62.13; H, 4.89; N, 22.64. Found: C, 62.15; H, 4.87; N, 22.66;

7-Amino-8-(dimethylamino)-5-(4-methoxyphenyl)-1,3-dioxo-1,2,3,5 tetrahydroimidazo[1,5-a] pyridine-6-carbo nitrile **(5b):**

It was obtained as pale yellow crystals from ethanol; yield 83%; mp 118–120 °C; IR (KBr, ν, cm^{-1}): 3400, 3345 (NH_2), 3219 (NH), 2935 (CH – aliph), 2195 (C≡N), 1748 (C=O); ^1H-NMR (DMSO-d_6) δ = 1.61 (s, 6H, $2CH_3$), 3.82 (s , 3H, $-OCH_3$), 4.70 (s, 1H, H-2 pyridine), 6.96 -7.48 (m, 6H, arom-H and NH_2), 11.70 (sbr, 1H, NH); MS *m/z* = 339 (M^+). Anal. Calcd. (%) for $C_{17}H_{17}N_5O_3$ (339): C, 60.17; H, 5.05; N, 20.64. Found: C, 60.18; H, 5.08; N, 20.65.



Scheme-4: The synthesis of pyraniomidazole derivatives **(21 and 24)**.

7-Amino-5-(2,4-dichlorophenyl)-8-(dimethylamino)-1,3-dioxo-1,2,3,5-tetra-hydroimidazo[1,5-a]pyridine-6-carbonitrile **(5c):**

It was obtained as yellow crystals from ethanol; yield 57%; mp 110–112 °C; IR (KBr, ν, cm^{-1}): 3400, 3342 (NH_2), 3200 (NH), 2937 (CH aliph.), 2191 (C≡N), 1726, 1639 (2 C=O); ^{1}H-NMR (DMSO-d_6) δ = 1.52 (s, 6H, $2CH_3$), 5.18 (s,1H, H-2 pyridine), 7.20 – 8.10 (m, 6H, arom proton, NH and NH_2); MS *m/z* = 377 (M^+). Anal. Calcd. (%) for $C_{16}H_{13}Cl_2N_5O_2$ (377): C, 50.81; H, 3.46; N, 18.52. Found: C, 50.83; H, 3.48; N,18.54.

Preparation of imidazo[1,5-c]traizole derivatives **(11a-c)**

A solution of **1** (0.01 mole) in ethanol (100 mL) containing sodium acetate (2.0 g) was cooled to 0°C, stirred and treated gradually with cooled solution of aryldiazonium chloride (prepared from 0.01 mole of amine and the appropriate quantities of HCl and $NaNO_2$). The solid product formed on standing was collected and crystallized from the proper solvent.

3-(dimethylamino)-1-phenyl-1H-imidazo[1,5-c][1,2,3]triazole-4,6(2H, 5H)-dione **(11a)**

It was obtained as pale yellow crystals from ethanol; yield 68%; mp 200–202 °C; IR (KBr, ν, cm^{-1}): 3535**,** 3308 (2 NH), 2950 (CH- aliph.), 1719, 1625 (2 C=O); ^{1}H-NMR (DMSO-d_6) δ = 1.21 (s, 6H, $2CH_3$), 6.92-7.78 (m, 5H, arom-H), 9.31 (S, 1H, NH), 10.62 (S, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 162.20, 151.92, 135.21, 130.95, 126.95, 124.65, 121.71, 100.60, 42,75; MS *m/z* = 259 (M^+). Anal. Calcd. (%) for $C_{12}H_{13}N_5O_2$ (259): C, 55.59; H, 5.05; N, 27.01. Found: C, 55.56; H, 5.02; N, 27.00.

1-(4-bromophenyl)-3-(dimethylamino)-1H-imidazo[1,5-c][1,2,3]triazole-4, 6(2H, 5H)dione **(11b)**

It was obtained as yellow crystals from ethanol; yield 53%; mp 260–262 °C; IR (KBr, ν, cm^{-1}): 3400**,** 3270 (2NH), 2950 (CH aliph.), 1728 (C=O); ^{1}H-NMR (DMSO-d_6) δ =1.21 (s, 6H, $2CH_3$), 6.98-7.46 (m, 4H, arom-H), 9.42 (s,1H,NH), 10.70 (s, 1H, NH); MS *m/z* = 339 (M^++1). Anal. Calcd. (%) for $C_{12}H_{12}BrN_5O_2$ (338): C, 42.62; H, 3.58; N, 20.71. Found: C, 42.65; H, 3.56; N, 20.72**.**

1-(4-chlorophenyl)-3-(dimethylamino)-1H-imidazo[1,5-c][1,2,3]triazole-4, 6-(2H, 5H) dione **(11c)**

It was obtained as Brown crystals from ethanol; yield 66%; mp 96–98 °C; IR (KBr, ν, cm^{-1}): 3418**,** 3266 (2 NH), 1732 (C=O); ^{1}H-NMR (DMSO-d_6) δ = 1.20 (s, 6H, 2 CH_3),7.04-7.88 (m, 6H, arom-H and 2 NH); MS *m/z* = 293 (M^+). Anal. Calcd. (%) for $C_{12}H_{12}ClN_5O_2$ (293): C, 49.07; H, 4.12; N, 23.84. Found: C, 49.05; H, 4.10; N, 23.81**.**

Preparation of 5-(piperidin-1-ylmethylene)imidazolidine-2,4-dione **(14)**

Equimolar amounts of compound **1** (0.01 mole) and piperidine **12** (0.01mole) in ethanol (30 mL) were refluxed for 3.0 h and poured into cold water (30 mL) and acidified with HCl. The solid product was collected and crystallized the proper solvent. It was obtained as pale yellow crystals from ethanol; yield 71%; mp 190–192 °C; IR (KBr, ν, cm^{-1}): 3350-3156 (br NH), 2759 (CH-aliph), 1776, 1724 (2 C=O); ^{1}H-NMR (DMSO-d_6) δ = 2.94 (br, 4H, $2CH_2$), 3.44 (br, 6H, $3CH_2$), 6.41 (s, 1H, alkenyl-H), 7.70 (S, 1H, NH), 10.60 (S, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 168.60, 156.85, 130.50, 115.55, 47.70, 31.60, 27.80; MS *m/z* = 195 (M^+). Anal. Calcd. (%) for: $C_9H_{13}N_3O_2$ (195): C, 55.37; H, 6.71; N, 21.52. Found: C, 55.39; H, 6.74; N, 21.55**.**

Preparation of pyrazolopurinone derivatives **(17a, b):**

A mixture of (**1**) (0.01 mole), amino-pyrazoles (**15a-b**) (0.01 mole) in ethanol (30 mL) was treated with a few drops of piperidine and heated under reflux for 12 h. The reaction mixture allowed to cool, poured into crushed ice and acidified with HCl. The solid product was filtered off and crystallized from the proper solvent.

7-amino-6-(p-tolyldiazenyl)-3,5-dihydro-2H-pyrazolo[5,1-b]purin-2-one **(17a)**

It was obtained as pale yellow crystals from ethanol; yield 66%; mp 250–252 °C; IR (KBr, ν, cm^{-1}): 3396 (NH_2), 3200(NH), 1715 (C=O); ^{1}H-NMR (DMSO-d_6) δ = 2.31 (s, 3H, CH_3),7.17-7.58 (m, 8H, arom-H, NH and NH_2), 10.68 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6) δ 161.45, 155.80, 149.50, 145.25, 135.20, 133.85, 128.10, 118.80, 116.80, 114.90, 114.10, 23.50; MS *m/z* = 308 (M^+). Anal. Calcd. (%) for $C_{14}H_{12}N_8O$ (308): C, 54.54; H, 3.92; N, 36.35. Found: C, 54.56; H, 3.94; N, 36.37**.**

7-amino-6-((4-chlorophenyl)diazenyl)-3,5-dihydro-2H-pyrazolo[5,1-b]purin-2-one **(17b):**

It was obtained as brown crystals from benzene; yield 66%; mp 240–242 °C; IR (KBr, ν, cm^{-1}): 3404, 3305 (NH_2), 3250 (NH), 1715(C=O);

^{1}H-NMR (DMSO-d_6) δ = 7.40-7.70 (m, 8H, arom-H, NH and NH_2), 10.76 (s, H, NH); MS *m/z* = 328 (M^+). Anal. Calcd. (%) for $C_{13}H_9ClN_8O$ (328): C, 47.50; H, 2.76; N, 34.09. Found: C, 47.52; H, 2.78; N, 34.10**.**

Preparation of pyranoimidazole derivatives **(21 and 24):**

A mixture of (**1**) (0.01 mole), active methylene reagents such as (malononitrile, ethyl cyanoacetate (**18a-b**) (0.01 mole) in ethanol (30 mL) was treated with a few drops of piperidine and heated under reflux for 12 h. The reaction mixture allowed to cool, poured into crushed ice and acidified with HCl. The solid product was filtered off and crystallized from the proper solvent.

5-amino-7-(dimethylamino)-2-oxo-1,2,3,7-tetra-hydropyrano[2,3-d]imidazole-6-carbonitrile **(21):**

It was obtained as green crystals from ethanol; yield 66%; mp 298–300 °C; IR (KBr, ν, cm^{-1}): 3339, 3214 (2 NH), 2950 (CH), 2201 (C≡N), 1730 (C=O); ^{1}H-NMR (DMSO-d_6) δ = 1.22 (s, 6H, $2CH_3$), 4.14 (s, 1H, H-4 pyrane) 7.07 (s, 1H, NH), 7.70 (s, 1H, NH), 8.36 (s, 2H, NH_2), ^{13}C-NMR (DMSO-d_6) δ 156.20, 149.00, 143.40, 115,80, 97.70, 47.65, 44.90, 43.80; MS *m/z* = 221 (M^+). Anal. Calcd. (%) for $C_9H_{11}N_5O_2$ (221): C, 48.86; H, 5.01; N, 31.66. Found: C, 48.88; H, 5.05; N, 31.65**.**

7-(dimethylamino)-2,5-dioxo-1,2,3,5,6,7-hexa-hydropyrano[2,3-d]imidazole-6-carbonitrile **(24)**

It was obtained as brown crystals from ethanol; yield 66%; mp 270–272 °C; IR (KBr, ν, cm^{-1}): 3445 (NH), 2984 (CH-aliph), 2201 (C≡N), 1717,1635 (2C=O); ^{1}H-NMR (DMSO-d_6) δ = 1.53 (s, 6H, $2CH_3$), 2.96 (d, 1H, *J* = 8.3 Hz, H-3 pyrane), 3.84 (d, 1H, *J* = 8.3 Hz, H-4 pyrane), 7.80 (s, 1H, NH), 8.94 (s, 1H , NH); ^{13}C-NMR (DMSO-d_6) δ 164.20, 156.60, 135.90, 116.20, 103.85, 52.97, 43.90, 31.70; MS *m/z* = 222 (M^+). Anal. Calcd. (%) for $C_9H_{10}N_4O_3$ (222): C, 48.65; H, 4.54; N, 25.21. Found: C, 48.68; H, 4.57; N, 25.24.

Conclusion

We achieved an efficient route for the synthesis of new synthesized unique heterocyclic compounds containing hydantion moiety by direct reaction of hydantion and its derivatives with a variety of electrophilic and nucleophilic reagents under mild conditions.

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