Synthesis of Some New Antipyrine Derivatives

Redha I. Al-Bayati

College of Science, Al-Mustansiriyah Univ.

Iyad S. Hameed and Mustafa K. Toema

College of Education,Tikrit Univ.

(NJC)

(Recevied on 30/12/2010) (Accepted for publication 2/5/2011)

Abstract

In this work, 4-chloro acet amide derivative [2] was prepared from 4-amino antipyrine [1] and chloro acetyl chloride then converted into thiozolidine-4-one [3] on reaction with KSCN. Subsequent refluxing of compound [3] with 3-nitrobenzaldehyde in the presence of NaOAC-acetic acid gave the derivative [4]. The hydrazide derivative [5] was prepared from the 4-chloro acet amide derivative [2] and hydrazine hydrate, which upon refluxing with acetyl aceton in absolute ethanol yielded antipyrine containing pyrazol moiety [6], refluxing of compound [2] with some amines in absolute ethanol afford the corresponding acetamide derivatives [7-10]. Moreover, reaction of [1] with CS_2 and KOH afforded the salt [11], which upon reaction with hydrazine hydrate at 45-55^oC for 1hr, yielded the fused ring derivative [12].

The Schiff base [13] was prepared from 3-nitro benzaldehyde and compound [1], and then oxidized by $KMno_4$ into the acid derivative [14]. Diazotization of compound [1] with $NaNo_2$/HCl led to azo derivative [15] which is reacted with acetyl acetone to give compound [16]. Reaction of compound [[16] with hydrazine led to ring closure giving derivative with pyrazole moiety [17]. Furthermore, reaction of [1] with tetrahydrofuran in acetic acid gave derivative with pyrrolidin moiety [18].

الخلاصة

تم في هذا البحث تحضير مشتق 4-كلورو أسيتا ميدو [2] من تفاعل 4-أمينو أنتي بايرين [1] مع كلورو أسيتايل كلورايد وتم تحويلها إلى ثايازوليدين-4-أون[3] بتفاعله مع ثايوسينات البوتاسيوم.

سخن المركب [3] مع 3-نيتروبنزالديهايد بوجود أسيتات الصوديوم وحامض الخليك ليعطي المشتق [4]. حضر المشتق آلهيدرازايد [5] من تفاعل المركب [2] مع الهيدرازين والذي عند تسخينه مع الأسـيتايل أسـيتون فـي الإيثانول المطلق يعطي مشتق الأنتي بايرين الحاوي على وحدة البايرازول [6]. وعند تسخين المركب [2] مـع بعض الأمينات في الإيثانول المطلق يعطي مشتقات أسيتاميد [6-15]. وعلى كل حال تفاعل المركـب [1] مـع KOH/CS_2 يعطي الملح [11] وعند تفاعله مع الهيدرازين بدرجة حرارة 45-55° م لمدة ساعة واحدة يعطـي المشتق [12].

حضرت قاعدة شف [13] من تفاعل 3-نتروبنزالديهايد مع المركب [1] وبعدها تم أكسـدته بواسـطة $KMnO_4$ إلى مشتق الحامض[14]. دسترة المركب [1] مع $HCl/NaNO_2$ يؤدي إلى مشتق الآزو [15] والذي يتفاعل مع أسيتايل أسيتون ليعطي المشتق [16]. يتفاعل المركب [16] مع الهيدرازين يؤدي إلى غلق الحلقة معطياً مشـتق حاوي على وحدة البايرازول [17]. إضافةً إلى ذلك تفاعل المركب [1] مع نتراهيدروفيوران في حامض الخليك يعطي المشتق الحاوي على وحدة البايرولدين [18]

Introduction

4-amino antipyrine derivatives are interesting series of heterocyclic compounds, which have been shown to be diverse biological properties such as anti-inflammatory[1], analgesic[2], bactericidal[3] and antifungal[4].

It has been found that 4-antipyrinyl aminoacetyl derivatives have shown considerable local anasethetic activity[5].

Various 1,2,4-triazines and its derivatives are well known to posses an array of physiological activites and are widly used in pharmaceuticals[6].

Coupling reaction of 4-amino antipyrine gave new azo compounds and the development of new structures of azo compound has been interested in the commerical application to polyester, polyamide or polyacrylic[7], where the condensation of diazo component with active methylene group of acetyl aceton afforded new component by diazotation reaction[8].

Thiazolidine derivative possess anticonsulvant, hyprotic, anticancer and have reported as novel inhibitors of the bacterial enzyme[9].

The occurance of the pyrrole nucleus in many natural and syntheitc biologically active compounds continues to contribute methadologies towards this important heterocyclic[10].

Experimental

Melting points were determined on Gallen Kamp melting points apparatus and were uncorrected. The UV spectra were performed on Hitachi-2000 Spectrophotometer. IR spectra were recorded on Shimadzu FT-IR, 8300 spectrometer as KBr disc, ^{1}H-NMR and ^{13}C-NMR were recorded at 300MHz in DMSO-d_6,on a Bruker Avance DPX-200 NMR spectrometer. The chemical shifts are reported in part per million (p.p.m.) downfield from internal tetramethyl silane (TMS) chemical shift in δ values.

Electron impact MS spectra were obtained on Shimadzu 5050A instrument. ^{1}H, ^{13}C-NMR and Mass spectra were performed at college of science, Univ. of Al-Albait-Jordan.

4-amino antipyrine [1]

Compound was supplied from BDH company as cream to pale, yellow powder, m.p. (107-109^{o}C)

Synthesis of 2-chloro-N-(4-antipyrinyl acetamide) [2][(11)]

Chloro acetyl chloride (0.04 mole) in dry benzene (20ml) added slowly to a solution of compound [1] (0.02mole) in dry benzene (60ml) with stirring then refluxed for 3hrs. The solid product was collected dried and recrystallized from ethanol to give cream solid product. M.p. (182-184^{o}C), yield 49%, U.V. (λ_{max}) : 226nm, 376nm for $\pi\rightarrow\pi^{*}$ and $n\rightarrow\pi^{*}$ respectively.

IR (cm^{-1}) : 3188 (-NH), 1691 (C=O), 761 (C-Cl) and 1600 (C=N).

^{1}H-NMR (DMSO-d_6,δ) p.p.m. : 2.1 and 3.04 (m, 6*H*,2CH_3)3.32 (S, 1*H*, NH), 4.23 (S, 2*H*,CH_2) 7.28-7.5 (m, 3*H*, aromatic protons), 9.49 (S, 1*H*, tautomeric OH).

^{13}C-NMR (DMSO-d_6, δ)p.p.m. : 11.6 and 22.98 (2C, H_3C and H_3C-N) respectively, 36.49 (CH_2Cl), 108.2, 124.2, 126.9 and 129.5 (aromatic carbons), 135.4 (H_3C-C), 152.8 (C=C) pyrazole, 162, 169.2 (C=O) amide and pyrazole ring respectively.

MS, m/z : 279.25, 265.4, 244.1, 203.2.

Synthesis of 3-(4-antipyrinyl-2-imino thiozolidin-4-one [3][(11)].

A mixture of compound [2] (0.001mole) and KSCN (0.002mole) in dry aceton (25ml) was refluxed for 3hrs, the residue washed with water and purified by column chromatography, yield 40%.

U.V. (λ_{max}) : 245 nm of $\pi\rightarrow\pi^{*}$

IR (cm^{-1}) : 3450 tautomeric OH, 3193 (-NH), 1689 (C=O) thiazole, 1622 (C=N).

Synthesis of 3-nitro-1-benzylidine-3-(4-antipyrinyl-2-imino thiozolidin -4-one). [4][(11)]. Schiff base.

Compound [3] (0.001mole) and 3-nitro benzaldehyde (0.002 mole) were added to solution of sodium acetate NaOAC (0.002mole) in acetic acid (30ml) the mixture was heated under reflux for 5hrs. The solid product was filtered, washed with water, dried and recrystallized from ethanol. M.p. (210-212^{o}C). yield 46.4%.

U.V. (λ_{max}) : 225.4 nm, 276.6 nm of $\pi \rightarrow \pi^*$.

IR cm^{-1} : 1622 (c=N), 3170 (-NH), 3055 (C-H) ar., 2960, 2845 (C-H) al. symmetrical and asymmetrical, 1352 (C-NO_2)

Synthesis of N-(4-antipyrinyl)-2-hydrazinyl acetamide. [5][(12)]

A mixture of compound [2] (0.002 mole) and hydrazine hydrate (0.01mole) in 25ml of abs. ethanol was refluxed for 3hrs. The solid product was collected washed with chloroform and filtered off and recrystallized from chloroform. m.p. (142-144^oC).

U. V. (λ_{max}) : 278.6nm, 248.4nm of $\pi \rightarrow \pi^*$

IR cm^{-1} : 3307, 3188 (NH_2NH), 1683 (C=O) amide, 1647 (C=O) pyrazole, 1591(C=N), 3421 (-OH tautomeric)

Synthesis of 2-(3,5-dimethyl-1*H*-pyrazol-1-yl)-N-4-antipyrinyl acetamide [6][(12)]

A mixture of compound [5] (0.0049 mole) and acetyl acetone (0.0049 mole) in abs. ethanol 25ml was refluxed for 6hrs. Solid product was collected, dried and recrystallized from suitable solvent. m.p. (133-135^oC), yield 52%.

U.V. (λ_{max}) : 312.6nm, 222.2nm for $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ respectively

MS, m/z : 338.2, 323.8, 297.2, 308.8, 275.4

^{13}C-NMR (DMSO, d_6-δ) p.p.m. : 10.7, 19.16, 29.3 and 36.5 (4C, $4CH_3$), 11.6 (1C, =CH), 22.98 (1C, CH_2), 97, 108.4, 123, 124, 126, 127 and 129 (5C, Ar-H), 152.4 (C=C) pyrazol, 163.5, 195.6 (C=O) pyrazole and amide respectively.

IR cm^{-1} : 3207 (-NH), 1683 (C=O) amide, 161 (C=N), 1355 (N-N).

Synthesis of N-antipyrine acetamide derivatives. [7-10][(13)]. General procedure

A mixture of an appropriate amine (0.02mole) and compound [2] (0.01mole) in abs. ethanol 10ml was refluxed for 6hrs. The residue was washed with sodium bicarbonate and water, the solid product was recrystallized from ethanol.

Compound [7] : oily, yield 50%.

U.V (λmax) : 276.2nm, 224.2nm for $\pi \rightarrow \pi^*$.

IR(cm^{-1}) : 3253(-NH), 1670(C=O) amide, 1635 (C=O) pyrazole, 3485 (-OH tautomeric), 1300 (C-N).

Compound [8] : oily, yield 38%, U.V(λmax) : 275.3, 224.8nm of $\pi \rightarrow \pi^*$.

IR cm^{-1} : 3244(-NH), 1689 (C=O) amide, 1647 (C=O) payrazole, 3493 (-OH tautomeric), 1298 (C-N)

Compound [9] : m.p. 110-112, yield 45%.

U.V (λ_{max}) : 275.6nm of $\pi \rightarrow \pi^*$.

IR cm^{-1} : 3236 (-NH), 1689 (C=O) amide, 1647 (C=O) payrazol, 3494 (-OH tautomeric), 1293 (C-N).

Compound [10] : m.p. 102-112^oC, yield 42%.

U.V. (λ_{max}) : 282.2nm of $\pi \rightarrow \pi^*$.

IR cm^{-1} : 3246, 3196 (-NH) asym and sym, 1687 (C=O) amide, 1643 (C=O)

pyrazol, 349 (O-H) tautomeric, 1292 (C-N).

Synthesis of 1-phenyl-1,2-dihydro-4*H*-pyrazolo[4,3-*e*][1,2,4] triazine-5 (6*H*)-thione. [12](14)

(0.003mole) of potassium hydroxide was dissolved in abs. ethanol 10ml, then mixture of compound [1] disulfide CS_2 were added, kept stirring at room temp. for 1hr. and cooled. Then 1ml of hydrazine hydrate was added and heated about (45-55°C)for 1hr. The solid product was filtered, washed with ethanol. M.p. (121-123°C), yield 96%.

U.V. (λ_{max}) : 335nm for n→ π^*.

IR cm^{-1} : 3209 (-NH), 3321, 2600 (-NH, -SH tautomeric) respectively, 1508 (C=N), 1348 (C=S).

1H-NMR (DMSO, d_6-δ) p.p.m. : 2.2, 3.2 (m, 6*H*, $2CH_3$), 3.65, 3.86 (m, 2*H*, 2NH), 7.32-7.65 (m, 5*H*, Ar-H)

^{13}C-NMR (DMSO-d_6, δ) p.p.m. : 10.6 (2C, $2CH_3$) 123.5, 125.2, 126.7 and 128.8 (Ar-C), 152 (C=C) pyrazol, 138.5 (C=S).

Synthesis of 4-(3-benzylideneamino antipyrine [13](11)

The solid product was filtered after cooling at room temp., dried and recrystallized from ethanol. M.p. (183-185°C), yield 74%.

U.V. (λ_{max}) : 373.3 nm and 367.7 of n→ π^*.

IR cm^{-1} : 1614 (C=N), 1653 (C=O), 1530 (C-NO_2)

Synthesis of 4-(3-benzylidene amino antipyrine-3-carboxylic acid [14](15) Oxidation

Equimolar amount of compound [13] (0.001mole) was added to aqueous solution of $KMnO_4$ (0.001mole) and sodium carbonate (0.001mole). the mixture was heated under reflux until the color of permanganate has disappeared, then filtered off while still hot, acidified with sulphuric acid (20%) washed with a little cold water.

m.p. : 145-147°C, yield 56.3%.

U.V. (λ_{max}) : 242.4nm, 270.8nm of π→ π^*.

IR cm^{-1} : 4300 (-OH), 1635 (C=O), 1653 (C=O) payrazole, 1593 (C=N), 1536 (C-NO_2)

Synthesis of 4-(3-hydrazonopentan-2,4-dion antipyrine [16](16). Diazotization

A cold mixture of acetyl aceton (0.01mole)and sodium acetate (0.01mole) in abs. ethanol (25ml) was added dropwise with stirring to solution of diazonium deravative (15) over 10min, the stirring lasted for 30min, the reaction mixture was left about 2hrs. at room temp., red solid product then collected, m.p. (160-162°C), yield 71%.

U. V. (λ_{max}): 275nm of π→ π^*

IR cm^{-1} : 3234, 3205 (-NH) asym and sym., 1683 (C=O), 1624 (C=N), 3034 (C-H) ar. 1647 (C=O) pyrazol.

Synthesis of 4-(3,5-dimethyl-1*H*-pyrazol-4-yl)diazenyl antipyrine [17](10).

A mixture of compound [16] (0.01mole) and hydrazine hydrate (0.02mole) was heated under reflux in ethanol (25ml) for (10-12hrs), cooled and orange solid product was obtained. M.p. (176-178°C), yield 55%.

U.V. (λ_{max}) : 242nm, 272nm, of π→ π^*.

IR (cm^{-1}) : 3224, 3209 (-NH) asym and sym. 1620 (C=N), 1300 (C-N), 3034 (C-H) ar., 2905, 2850 (C-H) al., sym and asym.

^{1}H-NMR (DMSO-d_6,δ ppm : 2.07-2.7 (m, 12H, $4CH_3$), 3.85 (S, 1*H*,NH), 7.05-7.6 (m, 5*H*, Ar-H)

^{13}C-NMR (DMSO-d_6, δ) ppm : 10.2-35.54 (4C, $4CH_3$), 56.7, 58.1 (2C, -C-CH_3), 94.5 (-C-N=N),v121, 124.6, 125.4 and 127.69 (4C, aromatic pyrazole carbons), 148.8 (C=C) pyrazol, 159.6 (C=O) pyrazole ring.

MS, m/z : 311.5, 296, 270.7, 202.2.

Synthesis of 4-pyrrolidinyl antipyrine [18](17).

Equimolar amounts of compound [1] (0.015mole) and tetrahydrofuran (0.015mole)in glacial acetic acid (15ml) were refluxed about (8hrs), the solid product then collected, cooled and recrystallized from benzene. Oily, yield 63%.
U. V. (λ_{max}) : 244.4nm, 275 nm of $\pi \rightarrow \pi^*$.
IR (cm^{-1}) : 3032 (C-H) ar., 2929, 2862 (C-H) al. sym and asymmetrical, 1292 (C-H), 1653 (C=O) pyrazol.

Results and Discussion

The new 4-amino antipyrine derivatives with various moieties at 4-position were prepared following the reaction sequences depicted in schemes 1 &2. The starting material for the synthesis of the titled compounds [3-10] is 4-chloro acetamido antipyrine [2] which was prepared by the reaction of 4-amino antipyrine [1] with chloro acetyl chloride in boiling dry benzene. The IR spectrum showed the NH stretching absorption band near $3188cm^{-1}$ and the C=O stretching one at 1691 cm^{-1}.reaction of compound [2] with KSCN in dry aceton lead to ring closure giving 3-(4-antipyrinyl)-2-imino thiazolidin-4-one [3]. The IR spectrum display a C=O stretching band at 1689 cm^{-1} and C=N stretching band at 1622 cm^{-1}, in addition to the band at $3450cm^{-1}$ for tautomeric OH. Condensation of compound [3] with 3.nitro benzealdehyde in the presence of NaOAC in acetic acid gave derivative [4] whose structure was confirmed the presence of bands at $3170cm^{-1}$, $1622cm^{-1}$ and 1352, $1540cm^{-1}$ for NH, C=N and NO_2 stretching vibrations respectively.

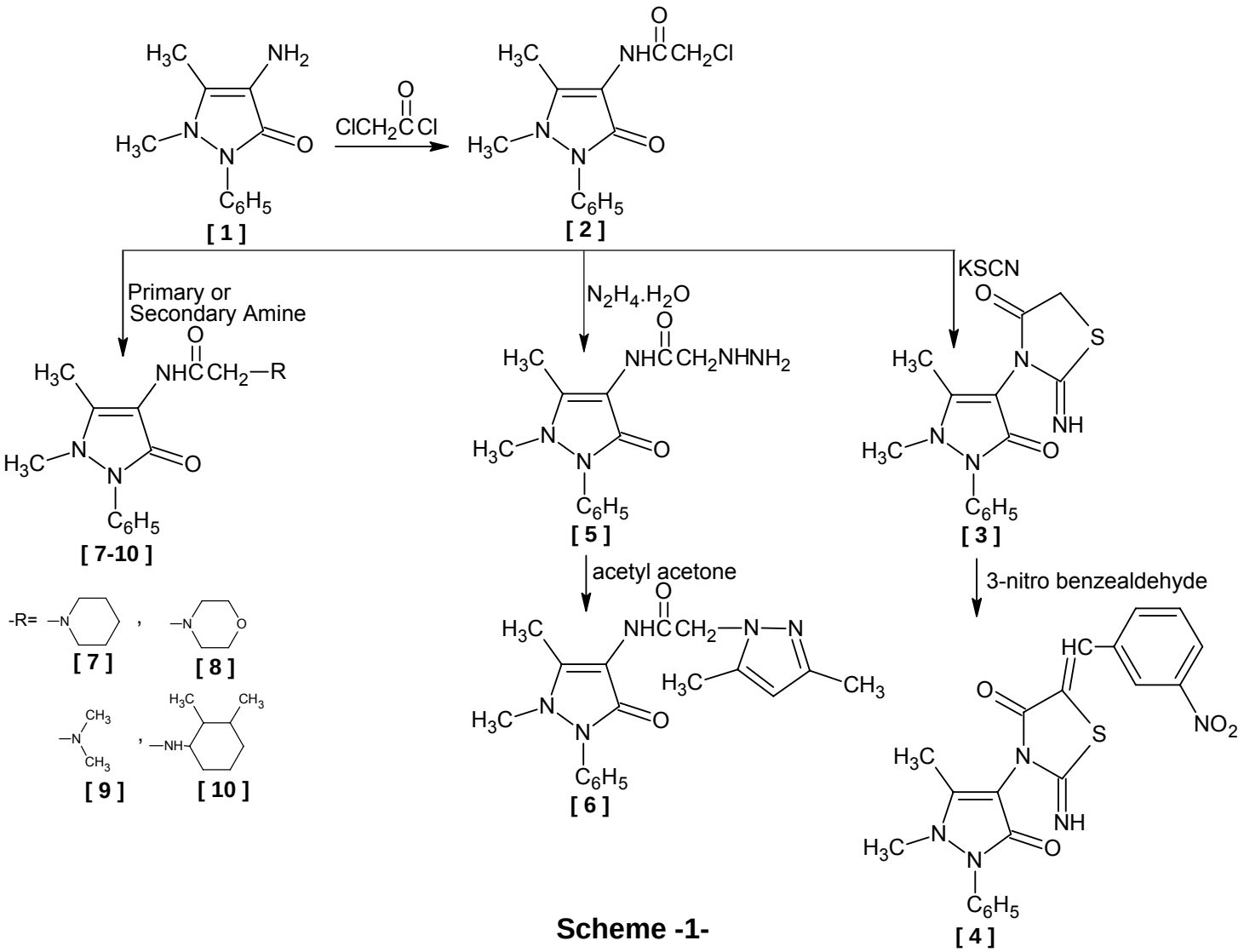
Refluxing of compound [2] with hydrazine hydrate in absolute ethanol afforded N-(4-antipyrinyl)-2-hydrazinyl acetamide [5], which comfirmed by the presence of (NH_2NH) stretching bands at 3307, 3188 and new (C=O) of amide at $1683cm^{-1}$, compound[6] was obtained in good yield from the reaction of compound [5] with acetyl acetone under reflux in abs. ethanol solution. The absorption bands at $3207cm^{-1}$,$1683cm^{-1}$ and $1616cm^{-1}$ are due to NH, C=O and C=N stretching bands respectively. In addition to the ^{13}C.NMR of compound [6] displayed the right carbon atoms in its structures, also, the mass spectra gave the right molecular ion 338.2.
Similarly, compound [2] was allowed to react with some amines (pipeidine, morpholine, N_1 N-diphenyl amine and 3,4-dimethyl aniline).
The structures of these products [7-10] were confirmed by the presence of two stretching bands of carbonyl at (1635-1647)cm^{-1} of pyrazol and (1670-1689)cm^{-1} of amide, addition other absorption bands as shown in the experimental part.

On the other hand the reaction of [1] with CS_2/KOH in absolute ethanol gave the salt [11], which upon ring closure with hydrazine hydrate gave the triazine-5(6*H*)thione [12] which existed in tautomeric thiol-thione equilibrium as indicated by the C=S stretching band at $1348cm^{-1}$ and S-H stretching at $2600cm^{-1}$.
^{1}H and ^{13}C.NMR spectra were also confirmed the formation of this compound.
the condensation of compound [1] with 3-nitro benzealdehyde in absolute ethanol gave the Schiff base [13]. The formation of Schiff base was indicated by the presence in its IR-spectrum of the azomethine (CH=N) stretching band at $1593cm^{-1}$, combined with the disappearance of the NH_2 stretching band. Oxidation of compound [13] with $KMnO_4$ in the presence of Na_2CO_3 resulted in compound [14] by oxidation of CH_3 group at position (3) as indicated by the OH stretching band at $4300cm^{-1}$ and band at $1635cm^{-1}$ for C=O stretching one.

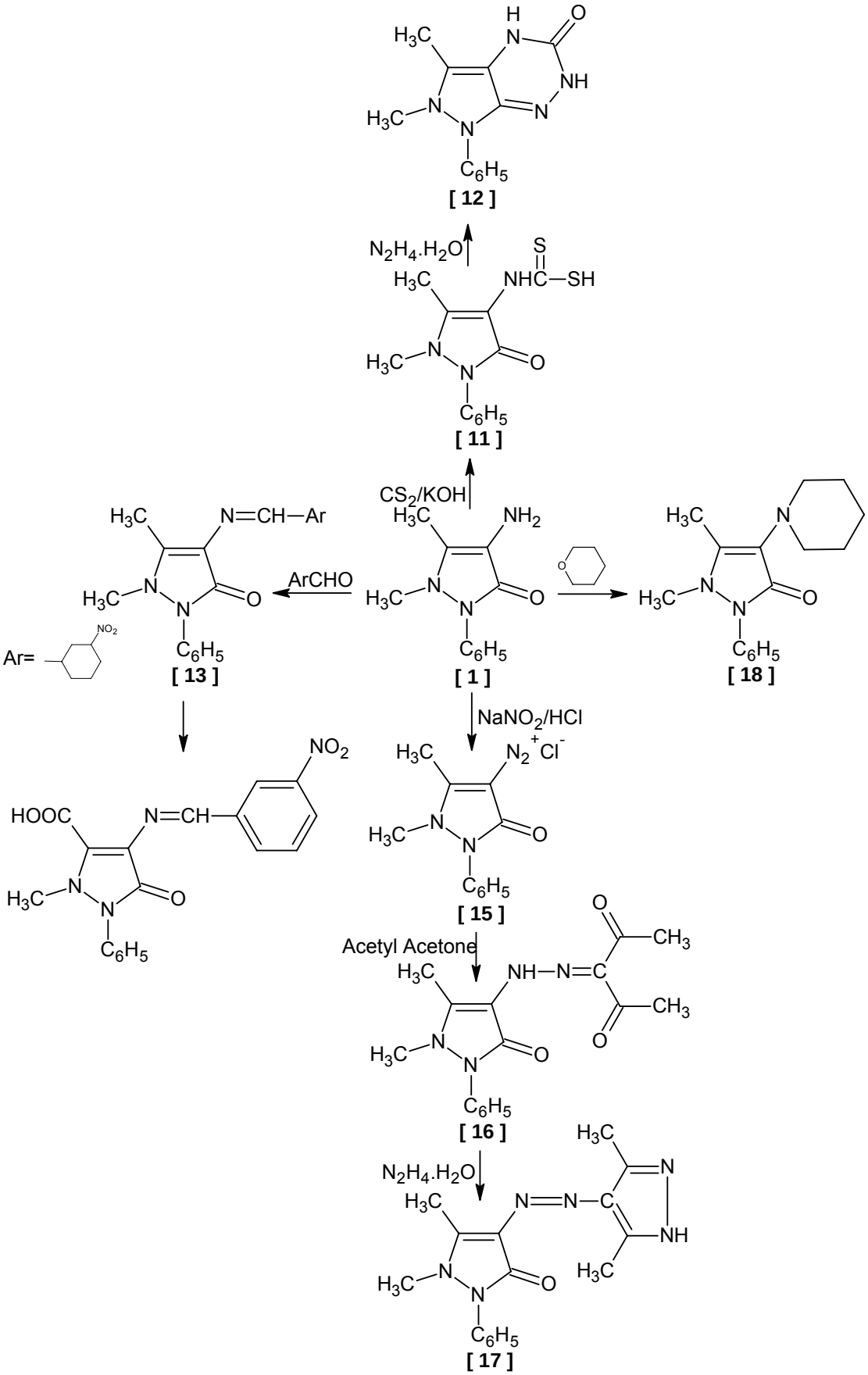
Moreover, diazotation of [1] gave the diazonium salt [15], which subsequently was coupled with active methylene compound such as acetyl acetone and resulted the azo derivative [17]. The structure of it was elucidated by the presence of absorption bands at 3205, 3234 cm^{-1} (NH), 1683cm^{-1} (C=O) and 1624 (C=N).

Further reaction of [16] with hydrazine hydrate led to the introduction of cyclic C=N functionality. Thus, affording compound [17], as indicated by the strong band at 1620cm^{-1} for the C=N and other bands near 3209-3224 for NH stretching one. This structure [17] was also confirmed by ^{1}H-NMR and ^{13}C-NMR assignments, which gave the suggested structure.

Finally, refluxing of compound [1] with tetrahydrofuran in acetic acid for 8hrs. afforded 4-pyrroliyl antipyrine [18], which displayed bands at 2929, 2862cm^{-1} for cyclic C-H and 1653cm^{-1} for (C=O) of ring.


[1]
[2]
Primary or Secondary Amine
[7-10]
[7]
[8]
[9]
[10]
[5]
[6]
[3]
[4]
acetyl acetone
3-nitro benzealdehyde
KSCN

Scheme -1-



Scheme -2-

References

1. J. R. Doamaral, E. J. Blenz and F. A. ***French, J. Med. Chem***., 1969, **21**, 2.
2. Gursoy, Aysel and Demirayak chem.. abs. 93, (1988).
3. G. Shanker, R. R. Prem Kuman and S. K. Ramalingam, ***Poly Headron***, 1988, **56**, 991.
4. G. Kuschinsky and H. Lullman, "Text Book of Pharmacology", 5ht Ed., New York and London, (1973).
5. S. C. Mehra, S. Zaman and A. A. Khan, ***J. Indian Chem. Soc***., 1980, **VIII**, Aug, 829-832.
6. F. Li, Feng, Q. Meng, W. Li, W. Wang and F. Tao, ***Arkivoc***, 2007, 40-46.
7. V. H. Patel, M. P. Pratel and R. G. Patel, ***J. Serb. Chem. Soc***., 2002, **67**, 727-734.
8. G. E. Wieg and V. J. Bauer, ***J. Med. Chem,*** 1969, **12**, 943.
9. T. Li, Y. Zhao, X. Yuan, J. Zu and P. Gong, ***Molecules***, 2006, **11**, 574-580.
10. N. Diettiens, G. V. Stevens, B. Allaert and F. Verpoort, ***Arkivoc***, 2005, 92-97.
11. N. S. Cho and H. I. Shon, ***Heterocyclic Chem.***, 1991, **28**, 1725.
12. J. Mohan and A. Kumer, ***Ind. J. Heterocyclic Chem***., 2001, **11**, 71.
13. M. M. Dutta and J. S. C. Kataky, ***Ind. J. Chem.***, 1996, **6**, 69.
14. A. Fiksdahi and C. Wentrup, ***Arkivoc***, 2000, **3,** 438-444.
15. M. Pando, C. Das and Hung, ***J. Chem. Sci***., 2007, **119**, 3-9.
16. W. Horst, T. Morion and T. Emil, Chem. Abs., 92, (1980).