Tetrahedron Letters 55 (2014) 1715–1719

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A carbanion induced synthesis of highly congested pyrazole and imidazole containing heterocycles

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ARTICLE INFO

Article history:
Received 7 October 2013
Revised 20 January 2014
Accepted 22 January 2014
Available online 31 January 2014

Keywords:
Pyran-2-one
Benzo[*h*]chromene
Thiochromeno[4,3-*b*]pyran
Fluorescence
Metal sensor

ABSTRACT

An efficient approach to the synthesis of highly congested di, penta and hexacyclic pyrazoles as well as imidazole fragment containing novel heterocyclic molecule has been developed through a carbanion induced transformation of suitably functionalized 2*H*-pyran-2-ones, benzo[*h*]chromene and thiochromeno[4,3-*b*]pyrans. Due to the presence of fluorescence, we report their prime application metal sensor as off/on switching in ferric ions.

The interesting conjugation feature of nitrogen in pyrazole and its structural implications on biological and medicinal systems[1–10] has drawn attention of organic chemists towards further exploration of its chemistry. In plants, a small number of biologically active natural products[1,2] are known in which pyrazole feature is present as sub-structure. To the best of our knowledge, only four natural products are reported in the literature. The first member of this class is nigellicine (**i**) which was isolated in 1985 from the seeds of *Nigella sativa*.[1] Later on, two other pyrazole ring containing alkaloids, nigeglanine (**ii**) and nigellidine (**iii**), were isolated from *Nigella glandulifera*[2] and *Nigella sativa*,[3] respectively. Another pyrazole derivative from nature used in ancient natural remedies is bendacort (AF2071)[4] (Fig. 1).

Pyrazoles are commonly present as substructure in diversified products of therapeutic importance such as antitumor, ACE-inhibitor, antifungal, antibacterial, anti-inflammatory, antiviral, anticonvulsant and antidepressant agents.[5] These are also present as core moiety in various drugs such as celebrex (non-steroidal anti-inflammatory drug),[6] sildenafil (pulmonary arterial hypertension and erectile dysfunction drug),[7] lonazolac (non-steroidal anti-inflammatory drug)[8] and fipronil (broad spectrum insecticide),[9] Figure 2. Pyrazoles are also described as building blocks for the synthesis of complex derivatives.[10] Furthermore, pyrazole fragment containing molecules are also used in dyes and pigments for their fluorescence characteristic.[11] Recently, a poly cyclic pyrazole derivative was identified as fluorescent probe for detection of gold(III) ions in living cells.[12] Pyrazole derivatives have

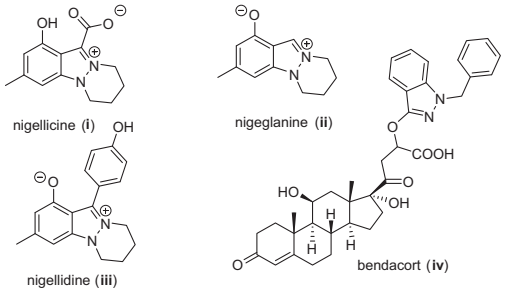

Figure 1. Naturally occurring pyrazoles.

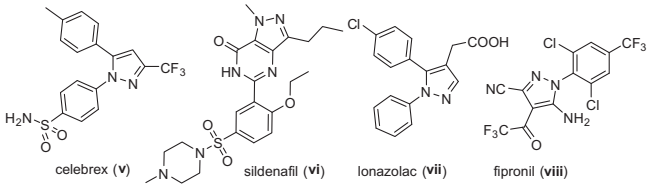

Figure 2. Pyrazole fragment containing drugs.

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http://dx.doi.org/10.1016/j.tetlet.2014.01.095
0040-4039/

been reported to be used as near-infrared cyanine dyes[13] and fluorescent sensors in material as well as in biological sciences.[14,15]

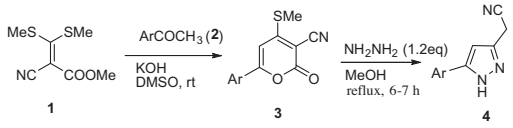
Due to their interesting chemical properties and prevalence as scaffolds in multifarious applications, we have synthesized active methylene containing pyrazoles (**4**) as a novel synthon from the suitable precursor pyrane-2-ones (**3**) using efficient chemistry and explored the synthesis of various novel di, penta and hexacyclic pyrazoles as well as imidazole fragment containing heterocycles as future aspects in medicinal and molecular imaging.

The intermediates 2-(5-aryl-1*H*-pyrazol-3-yl)acetonitrile (**4**) were synthesized from 6-aryl-4-methylthio-2*H*-pyran-2-ones (**3**),[16] whereas precursors 6-aryl-4-methylthio-2*H*-pyran-2-ones (**3**)[17] were prepared from the reaction of methyl 2-cyano-3,3-dimethylthioacrylate (**1**)[16–19] and aryl methyl ketone (**2**), Scheme 1.

Exploiting the versatility of enamines[20,21] for the synthesis of highly congested heterocycles such as heteroaryl-substituted α-amino- and α-hydroxy acids, fused pyridinones, pyrimidinones, pyranones and related system, we have selected enamine inbuilt heteroarenes such as 2-heteroaryl-3-dimethylamino acrylonitriles (**6**) as precursors for the preparation of novel heterocycles (**8**,**10**,**14** and **17**), which are not easily obtainable by other classical routes.

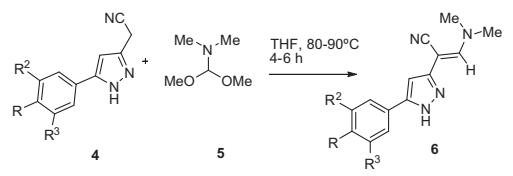
Thus, a reaction of pyrazoles (**4**) and 1.2 equiv DMFDMA (**5**) in dry THF at 80–90 °C for 4–6 h led to the formation of energetically stable Z-isomer of 3-(dimethylamino)-2-(5-aryl-1*H*-pyrazol-3-yl)acrylonitriles (**6**), Scheme 2. However, the reaction of pyrazole (**4**) with DMFDMA (**5**) under reflux in dry dioxane or DMF for 7–18 h gave a complex mixture with recovery of major amount of starting pyrazole (**4**).

In order to synthesize novel heterocycles, a model experiment was performed using **6a** and **7** as reactants in different solvent, catalyst/base, temperature and time as summarized in Table 2. As evident from Table 2, the product **8a** has not formed in ethanol, DMF or BF_3Et_2O, while in AcOH, TFA or PTSA/AcOH in EtOH the formation of product **8a** was observed in trace. Further exploration of the reaction with IRA-400 (50 mol %)/TFA or Amberlyst-15 (50 mol %)/TFA yielded the product **8a** in 19% and 23% yields, respectively, while the use of amberlyst-15 (100% mol %)/TFA improved the yield of product **8a** (36%) (Table 2). On the basis of these results, we explored the reaction of enamines (**6**) and benzamide (**7**) in TFA using amberlyst-15 as catalyst which led to the



2, 3,4	Ar	Mp (°C) of 4	yield (%) of 4
a	Phenyl	150-151	51
b	4-Methoxyphenyl	148-149	53
c	4-Bromophenyl	180-181	59
d	4-Chlorophenyl	164-165	52
e	4-Methylphenyl	158-159	50
f	4-Flurophenyl	188-189	53
g	3,4,5-Trimethoxyphenyl	159-160	74
h	3-(Trifluoromethyl)phenyl	270-271	51
i	4-Nitrophenyl	212-213	49

Scheme 1. Synthesis of pyran-2-one (**3**)[16–19] and 2-(5-aryl-1*H*-pyrazol-3-yl) acetonitrile (**4**).[16]



Scheme 2. Synthesis of 3-(dimethylamino)-2-(5-aryl-1*H*-pyrazol-3-yl)acrylonitrile (**6**) (Table 1).

Table 1
Yields of 3-(dimethylamino)-2-(5-aryl-1*H*-pyrazol-3-yl)acrylo-nitrile **6** (Scheme 2)[24]

S.N.	4/6	R^2	R	R^3	Mp (°C) of **6**	Yields (%) of **6**
1	**a**	H	H	H	221–222	85
2	**b**	H	OMe	H	213–214	79
3	**c**	H	Br	H	220–221	84
4	**d**	H	Cl	H	229–230	76
5	**e**	H	Me	H	215–216	80
6	**f**	H	F	H	249–250	69
7	**g**	OMe	OMe	OMe	171–172	51
8	**h**	CF_3	H	H	155–156	61

formation of 2-(aryl)-7-phenylpyrazolo[1,5-*c*]pyrimidines (**8a**–**b**), Scheme 3.

Probably, the reaction proceeds with elimination of NMe_2 followed by intramolecular cyclization, hydrolysis and decarboxylation, respectively. The structure of pyrazolo[1,5-*c*]pyrimidines (**8**) was identified with the help of mass, IR, 1D and 2D NMR (^{1}H NMR, ^{13}C NMR, Dept, Cosy, HMQC and HMBC). However, under similar reaction conditions, the reaction of enamine (**6**) with 2-aminopyridine (**9**) gave 3-(5-aryl-1*H*-pyrazol-3-yl)-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones (**10**) in 31–33% yield, Scheme 3.

Further, to generalize the reactions of pyrazole (**4**), reactions of **4** with **12a**–**d** in the presence of KOH/DMF at room temperature were performed, Scheme 5.

The starting precursor 5,6-dihydro-4-methylthio-2-oxo-2*H*-benzo[*h*]chromene-3-carbonitriles (**12a**–**b**)[22] were prepared from the reaction of 1-tetralones (**11a**–**b**) with methyl 2-cyano-3,3-dimethylthioacrylate (**1**) while 5,6-dihydro-4-methylthio-2-oxo-thiochromeno[4,3-*b*]pyran-3-carbonitriles (**12c**–**d**)[23] were prepared from the reaction of thiochromen-4-ones (**11c**–**d**) with methyl 2-cyano-3,3-dimethylthioacrylate (**1**). Compounds **12** (**a**–**d**) on amination with *sec*.amine in boiling ethanol, afforded **13**, Scheme 4.[22,23]

As evident from the topography of the lactones **12** and **13** the positions C2, C4 and C10b are electron deficient and C10b is particularly prone to nucleophilic attack because of an extended conjugation and the presence of an electron-withdrawing CN substituent at position 3. However, the reaction of an equimolar mixture of lactones **12** or **13** and pyrazole (**4**) did not deliver the expected products **15** and the reaction proceeds from the attack of nucleophile **4** at C4 position of **12** or **13** which yielded products **14**, Scheme 5. Both the lactones **12** and **13** are very useful synthons for the ring transformation reactions. The basic difference in both the lactones lies in the nature of substituent present at position 4. In case of lactone **12** the $-SCH_3$ substituent at position 4 is more labile and highly vulnerable to nucleophilic attack as compared to *sec*.amino substituent in **13**.

Therefore, various analogues **14a**–**i** have been prepared from starting the precursor **12** in good yields, Table 3. It is worthy to note that the reaction of **13a** with **4a** under similar reaction conditions yielded product **14a** only in 14% yield. Attempts were made to prepare **14a** from **12a** in improved yield by the use of different base combinations such as NaH-THF for 2 h at 40 °C and KOH-ionic liquid (ethyl methyl imidazolium chloride) for 4 h at 40 °C which yielded compound **14a** in 59% and 62% yields, respectively.

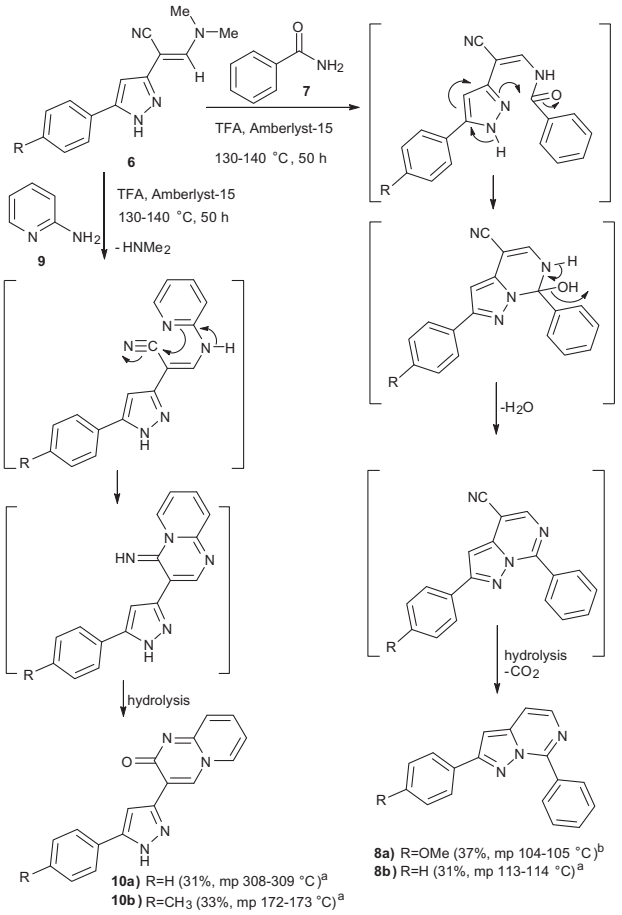
As plausible mechanism discussed in Schemes 5 and 6, the initial step in the synthesis of **14** and **17** is the attack of a carbanion, generated in situ from pyrazoles (**4**) at C4 of the lactone (**12** or **13**), followed by ring closure involving nitrogen of the pyrazole intermediate and CN function.

In order to synthesize compound **18**, we have also studied the reaction of 2-cyanomethyl-1*H*-benzimidazole (**16**) with **12a** under various reaction conditions such as NaH/THF for 2 h at 40 °C, KOH/ionic liquid (ethyl methyl imidazolium chloride) for 4 h at 40 °C and KOH/DMF which yielded compound **17** in 73%, 76% and 84%,

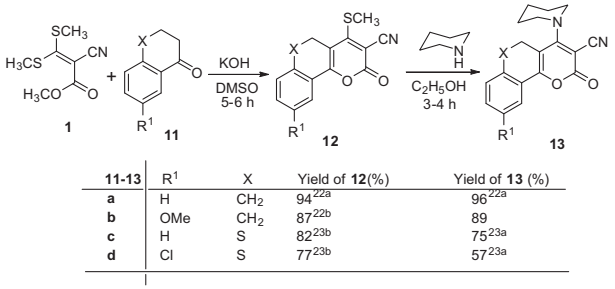
Table 2
Optimization of reaction conditions of 2-(aryl)-7-phenylpyrazolo [1,5-*c*]pyrimidine (**8a**)

S.N.	Catalyst/base[a]	Solvent	Temp (°C)	Time	Yield[a] (%) of **8**
1	KOH	EtOH	110–120	8 h	[b]
2	KOH/basic alumina in MW (160 watt)	EtOH	—	20 min	[b]
3	KOH	DMF	80–90	24 h	[b]
4	—	AcOH	130–140	08 h	Traces
5	PTSA/AcOH	EtOH	115–120	50 h	Traces
6	—	TFA	80–90	50 h	3
7	BF_3Et_2O	—	100–110	5 h	[b]
8	IRA-400 (50 mol %)	TFA	100–110	80 h	19
9	Amberlyst-15 (50 mol %)	TFA	100–110	80 h	23[c]
10	Amberlyst-15 (100 mol %)	TFA	100–110	50 h	36[c]
11	Amberlyst-15 (200 mol %)	TFA	100–110	50 h	35[c]
12	Amberlyst-15 (300 mol %)	TFA	100–110	50 h	37[c]

[a] Separated yields.
[b] No reaction.
[c] With unseparated mixture from column chromatography.



Scheme 3. Synthesis of 2-(aryl)-7-phenylpyrazolo[1,5-*c*]pyrimidine (**8**) and 3-(5-aryl-1*H*-pyrazol-3-yl)-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (**10**),[24] [a]Amberlyst-15 (100 mol %), [b]Amberlyst-15 (300 mol %).



11-13	R^1	X	Yield of **12**(%)	Yield of **13** (%)
a	H	CH_2	94[22a]	96[22a]
b	OMe	CH_2	87[22b]	89
c	H	S	82[23b]	75[23a]
d	Cl	S	77[23b]	57[23a]

Scheme 4. Synthesis of the substituted 5,6-dihydro-2-oxo-2*H*-benzo[*h*]chromene-3-carbonitriles (**12a–b**,**13a–b**) and 2,5-dihydro-2-oxo-thiochromeno[4,3-*b*]pyran-3-carbonitriles (**12c–d**,**13c–d**).[22,23]

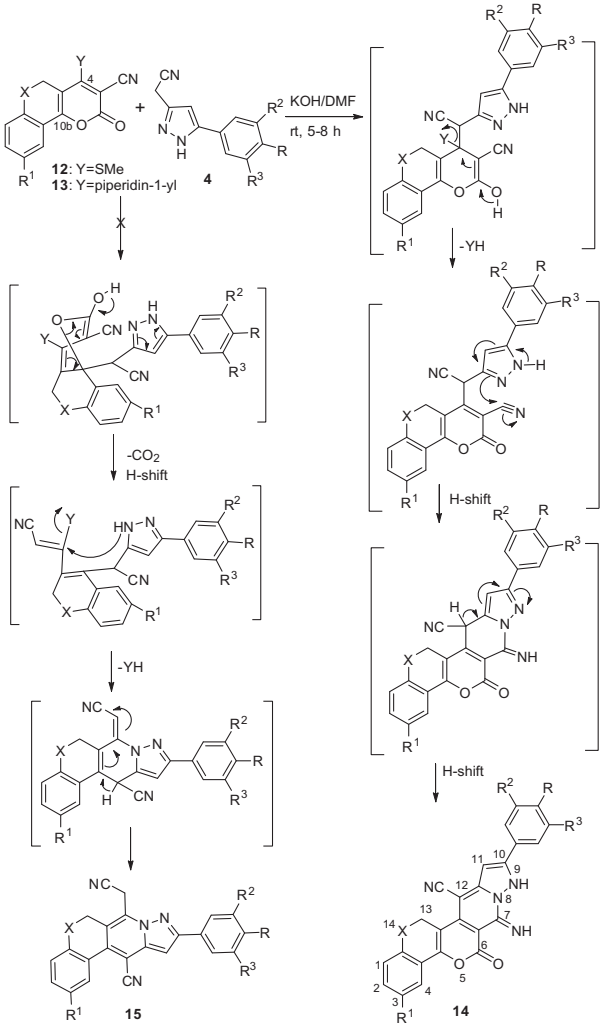
respectively instead of the product **18**. Thus, the use of KOH/DMF at 40 °C for this reaction was found to be appropriate. After optimizing reaction conditions, we have explored various reactions of lactone **12** and imidazole **16** in KOH/DMF as shown in Table 4 (Scheme 6). Under these conditions (in KOH/DMF), reaction of **13a** with **16** yielded product **17a** in 16% yield.

The synthesized compounds **14** and **17** have shown partial solubility (>500 μM/mL) in various deuterated solvents such as chloroform/methanol, DMSO, TFA and D_2O. It was difficult to get ^1H NMR as well as ^{13}C NMR spectra of compounds (**10**, **14** and **17**) in these deuterated solvents because of solubility factor. Therefore, we prepared the NMR sample in dry NaOH and $(CD_3)_2SO$ and got a good quality NMR spectrum. However, it was observed that keeping the sample for longer time (>8 days) in this condition, the products were coagulated and NMR spectrum could not obtained.

Further, when we placed the solution of different pyrazole derivatives (500 μM in DMF or 3:1 $CHCl_3$/MeOH) under UV rays of long wave length (365 nm), compounds **8** and **10** displayed a white fluorescence whereas compounds **14** and **17** displayed fluorescent green colour (λ_{max} = 540–560 nm) in visual as well as long wave ultraviolet lamp (365 nm). In this context, on the basis of previously reported fluorescence sensing activities of pyrazoles analogues,[12] we focused our attention towards exploring the metal sensing activity of the pyrazoles analogue **14** which contain three nitrogen and one carbonyl oxygen for coordination with a metal ion. To pursue this goal, we prepared a 500 μM solution of pyrazole **14b** in DMF and 16 mM solution of $FeCl_3$ in DMF. Titration of 0.5 mL solution of **14b** with 16 mM solution of $FeCl_3$ showed that green colour fluorescence completely disappeared on the addition of 2 mL of $FeCl_3$ solution with formation of a non fluorescent yellow solution.

Further, our attention was to explore off/on switching sensing activity for **14b**. For this purpose, we titrated further the above non fluorescent yellow solution with 16 mM solution of EDTA in water. We observed that on addition of 2.5 mL EDTA solution, the green fluorescent colour of the compound appeared again, Figure 3. Thus, the pyrazole derivative can be explored as off/on switching sensor for metal detection.

This observation was further generalized by the use of different metal salts such as $ZnCl_2$, $CdCl_2$, CsCl, $CaCl_2$, LiCl $BF_3{\cdot}Et_2O$, $HgCl_2$, CuCl and $AgNO_3$ with compound **14b**. Among these $ZnCl_2$, $CdCl_2$, CsCl, $CaCl_2$, LiCl and $BF_3{\cdot}Et_2O$ could not stop green fluorescence,



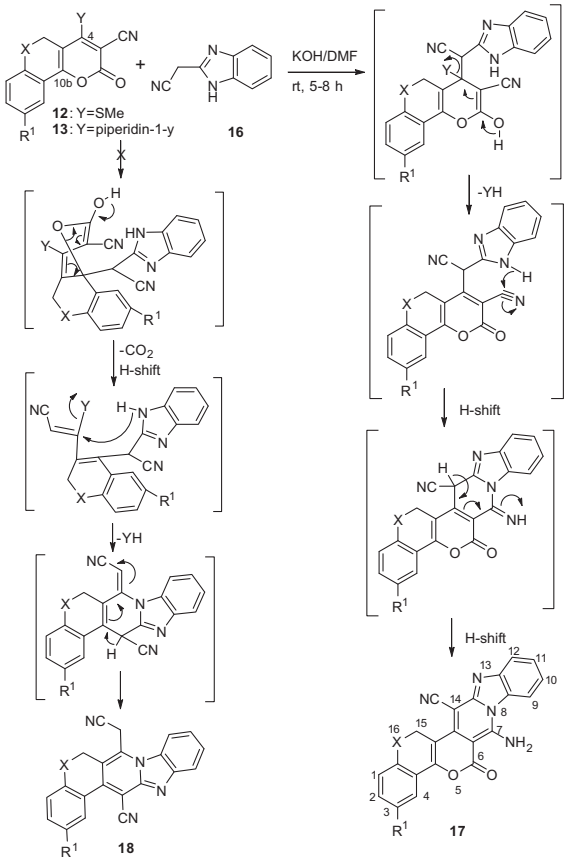
Scheme 5. Synthesis of 7-imino-6-oxo-10-aryl-6,7,9,14-tetrahydro-13*H*-benzo[*h*]chromeno[4,3-*d*]pyrazolo[1,5-*a*]pyridine-12-carbonitrile (**14a–d**)/7-imino-6-oxo-10-aryl-6,7,9-trihydro-13*H*-thiochromeno[4,3-*b*]pyrao[4,3-*d*]pyrazolo[1,5-*a*]pyridine-12-carbonitrile (**14e–i**).

Table 3
Yields and mp of 7-imino-6-oxo-10-aryl-6,7,9,14-tetrahydro-13*H*-benzo[*h*]chromeno[4,3-*d*]pyrazolo[1,5-*a*]pyridine-12-carbonitrile (**14a-d**)/7-imino-6-oxo-10-aryl-6,7,9-trihydro-*13H*-thiochromeno[4,3-*b*]pyrao[4,3-*d*]pyrazolo[1,5-*a*]pyridine-12-carbonitrile (**14e–i**) synthesized from lactone **12**, (Scheme 5)[24]

Entry	R	R^2	R^3	R^1	X	Mp (°C)	Yield (%)
14a	H	H	H	H	CH_2	303–304	67
14b	OMe	H	H	H	CH_2	280–281	60
14c	H	H	H	OMe	CH_2	305–306	79
14d	NO_2	H	H	H	CH_2	350[a]	90
14e	H	H	H	H	S	290[a]	66
14f	OMe	H	H	H	S	280[a]	61
14g	F	H	H	H	S	310[a]	63
14h	H	CF_3	H	H	S	309–310	76
14i	OMe	OMe	OMe	H	S	275[a]	65

[a] Start to decompose.

whereas $HgCl_2$, CuCl and $AgNO_3$ could diminished green fluorescence of compound **14b** and converted the solution into non fluorescence transparent solution. Thus, we report preliminary results of molecular sensing activity of pyrazole derivative **14b**.



Scheme 6. Synthesis of 7-amino-6-oxo-6,8,15-trihydro-15*H*-benzo[*h*]chromeno[4,3-*d*]pyrido[1,2-*a*]benzimidazole-14-carbonitrile (**17a–b**)/7-amino-6-oxo-6,8,15-trihydro-15*H*-thiochromeno[4,3-*b*]pyrao[4,3-*d*]pyrido[1,2-*a*]benzimidazole-14-carbonitrile (**17c–d**) (Table 4).

Table 4
9-Amino-5-chloro-8-oxo-8,9a-dihydro-1*H*-benzo[*d*]imidazolo[2,1-*g*]thiochromeno[4,3-*c*]isochromene-15-carbonitriles (**17**) synthesized from lactone **12** with yields and mp (Scheme 6)[24]

Entry	R^1	X	mp (°C)	Yield (%)
17a	H	CH_2	>315	76
17b	OMe	CH_2	>315	98
17c	H	S	309[a]	84
17d	Cl	S	312[a]	76

[a] Start to decompose.

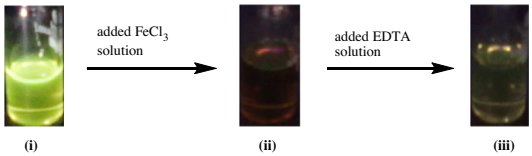


Figure 3. Change of fluorescence colour as observed in long wave ultraviolet lamp (365 nm): (i) 500 μM solution of compound **14b** in DMF, (ii) 500 μM solution of compound **14b** and 16 mM solution of ferric chloride in DMF (1:4), (iii) 500 μM solution of compound **14b**, 16 mM solution of ferric chloride in DMF and16 mM solution of EDTA in water (1:4:5).

In conclusion, we have developed an efficient method for the synthesis of enamines (**6**) and highly congested di (**8**), penta (**14**) and hexacyclic (**17**) pyrazoles as well as imidazole fragment containing novel heterocyclic molecules. In addition, this report

demonstrates the utility of the pyrazole derivative **14b** for preliminary metal sensing activity.

Acknowledgement

This work was supported by DST, New Delhi, India for financial support as DST fast track young scientist fellowship [No SR/FT/CS-20/2011] to H.K.M.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.01.095. These data include experimental data of all new synthesized compounds, scan copy of spectra, MOL files and InChiKeys of the most important compounds described in this article.

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24. *General procedures and spectral data: General procedure for the synthesis of 3-(dimethylamino)-2-(5-aryl-1H-pyrazol-3-yl)acrylonitrile (**6**):* 2-(5-Aryl-1*H*-pyrazol-3-yl)acetonitrile (**4**, 0.02 mol) and DMFDMA (**5**, 0.03 mol) were refluxed in dry THF (50 mL) for 4–6 h. The excess THF was evaporated at reduced pressure. The crude product poured into methanol and the precipitate obtained was filtered. The obtained crude was recrystallized with methanol. *(Z)-3-(dimethylamino)-2-(5-(4-methoxyphenyl)-1H-pyrazol-3-yl)acrylonitrile (**6b**):* White crystalline solid; R_f 0.63 (EtOAc); IR (KBr): 3312 (NH), 2187 (CN) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.38 (s, 6H, NMe_2), 3.83 (s, 3H, OCH_3), 6.36 (s, 1H, =CH), 6.93 (d, 2H, J = 3.6 Hz, Ar-H), 7.36 (s, 1H, CH), 7.53 (d, 2H, J = 3.6 Hz, Ar-H), 12.12 (br s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 40.21 (2C), 54.64, 96.70, 113.47 (3C), 120.24 (CN), 126.06 (4C), 147.01, 148.68, 158.68; MS: 269.2 $(M+H)^+$; Anal. Calcd ($C_{15}H_{16}N_4O$): C, 67.15; H, 6.01; N, 20.88. Found: C, 66.98; H, 5.94; N, 20.76; *General procedure for the synthesis of 2-(aryl)-7-phenylpyrazolo[1,5-c]pyrimidine (**8**) and 3-(5-aryl-1H-pyrazol-3-yl)-2H-pyrido[1,2-a]pyrimidin-2-one (**10**):* 3-(dimethylamino)-2-(5-aryl-1*H*-pyrazol-3-yl)acrylonitrile (**6**, 3.73 mmol) and benzamide (**7**, 5.60 mmol) or 2-aminopyridine (**9**, 4.40 mmol) were refluxed in TFA (10 mL) for 50 h in the presence of 100 mol % amberlyst-15. The reaction mixture was poured in water and filtered. The sticky residue thus obtained was dried in oven and residue was dissolve in DCM. Amberlyst-15 was filtered and filtrate was concentrated and purified by silica gel column chromatography using chloroform (50–99%) in hexane; *2-(4-methoxyphenyl)-7-phenylpyrazolo[1,5-c]pyrimidine (**8a**):* Light greenish white solid, white fluorescence in long range UV; R_f 0.82 (5% MeOH/DCM); ^1H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, OMe), 6.79 (s, 1H, pyrazole ring), 6.97 (d, 2H, J = 8.4 Hz, Ar-H), 7.34 (d, 1H, J = 6.0 Hz, Ar-H), 7.58 (br s, 3H, Ar-H), 7.90 (d, J = 6.0 Hz, 1H Ar-H), 7.94 (d, J = 8.7 Hz, 2H, Ar-H), 8.62 (br s, 2H, pyrazine ring); ^{13}C NMR (75 MHz, DMSO-d_6): δ 55.74 (OMe), 94.13 (CH), 111.27 (CH), 114.59 (2 × CH), 125.56 (C), 128.46 (2 × CH), 128.69 (2 × CH), 130.80 (2 × CH), 131.45 (CH), 133.06 (C), 137.94 (CH), 144.21(C), 149.52 (C), 155.57 (C), 160.93 (C); MS: 302.2 $(M+H)^+$; Anal. Calcd ($C_{19}H_{15}N_3O$): C, 75.73; H, 5.02; N, 13.94. Found: C, 75.63; H, 4.99; N, 13.89; *3-(5-phenyl-1H-pyrazol-3-yl)-2H-pyrido[1,2-a]pyrimidin-2-one (**10a**):* Light yellowish solid, white fluorescence in long range UV; R_f 0.26 (EtOAc); IR (KBr): 1669 (C=O), 3334 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.64 (br s, 1H, NH), 7.14 (m, 1H, Ar-H), 7.22 (s, 1H, pyrazole ring), 7.26 (m, 3H, Ar-H), 7.62–7.77 (m, 4H, Ar-H), 8.04 (m, 1H, Ar-H), 9.08 (m, 1H, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 101.91, 112.72, 113.70, 116.87 (2C), 124.91, 125.78, 126.87, 127.64, 128.93 (2C), 134.94, 138.46, 144.63, 148.86, 149.15, 155.49; MS: 289.3 $(M+H)^+$; Anal. Calcd ($C_{17}H_{12}N_4O$): C, 70.82; H, 4.20; N, 19.43. Found: C, 70.71; H, 4.18; N, 19.36; *General procedure for the synthesis of 7-imino-6-oxo-10-aryl-6,7,9,14-tetrahydro-13H-benzo[h]chromeno[4,3-d]pyrazolo[1,5-a] pyridine-12-carbonitrile (**14a–d**)/ 7-imino-6-oxo-10-aryl-6,7,9-trihydro-13H-thiochromeno[4,3-b]pyrao[4,3-d] pyrazolo[1,5-a]pyridine-12-carbonitrile (**14e–i**):* A mixture of lactone **12** (1.0 mmol) and 2-(5-aryl-1*H*-pyrazol-3-yl)acetonitrile (**4**, 1.0 mmol) in DMF (9 mL) in the presence of powdered KOH (1.2 mmol) was stirred at room temperature for 5–8 h. The reaction was monitored using silica gel TLC. After consumption of **12**, the crude residue was poured onto crushed ice with vigorous stirring. The aqueous suspension was neutralized with dil. HCl (if required) and the precipitate obtained was filtered, washed with water and dried. Residue was purified by silica gel column chromatography using chloroform/methanol (0–30%); *7-imino-6-oxo-10-phenyl-6,7,9,14-tetrahydro-13H-benzo[h]chrom-eno[4,3-d]pyrazolo[1,5-a]pyridine-12-carbonitrile (**14a**):* Yellow solid; R_f 0.38 ($CHCl_3$); IR (KBr): 1577, 1611, 1692 (C=O), 2203 (CN), 3259 and 3370 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.94 (t, 2H, J = 7.2 Hz, CH_2), 3.21 (t, 2H, J = 7.8 Hz, CH_2), 6.61 (s, 1H, CH), 7.28–7.48 (m, 7H, Ar-H & NH), 7.64 (m, 1H, Ar-H), 8.02 (d, 3H, J = 7.5 Hz, Ar-H); MS: 403.1 $(M-H)^+$; Anal. Calcd ($C_{25}H_{16}N_4O_2$): C, 74.25; H, 3.99; N, 13.85. Found: C, 74.12; H, 3.96; N, 13.78; *7-imino-6-oxo-10-phenyl-6,7,9-trihydro-13H-thiochromeno[4,3-b]pyrao[4,3-d]pyrazolo[1,5-a]pyridine-12-carbonitrile (**14e**):* Yellow solid; R_f 0.46 ($CHCl_3$); IR (KBr): 1586, 1690 (C=O), 2208 (CN), 3305 and 3436 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.43 (s, 2H, SCH_2), 6.65 (s, 1H, CH), 7.30–7.45 (m, 7H, Ar-H & NH), 7.74 (d, 1H, J = 7.5 Hz, Ar-H), 8.02 (d, 3H, J = 7.5 Hz, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.05, 68.76, 88.12, 95.59, 106.96, 121.48, 126.08, 127.02, 127.28 (2C), 127.87, 128.55, 129.35, 129.43 (2C), 131.17, 133.32, 134.88, 140.56, 143.05, 150.56, 153.38, 153.75, 161.72; MS: 421.1 $(M-H)^+$; Anal. Calcd ($C_{24}H_{14}N_4O_2S$): C, 68.23; H, 3.34; N, 13.26. Found: C, 68.14; H, 3.31; N, 13.20; *General procedure for the synthesis of 7-amino-6-oxo-6,8,15-trihydro-15H-benzo[h]chromeno[4,3-d]pyrido[1,2-a]benzimidazole-14-carbonitrile (**17a–b**)/7-amino-6-oxo-6,8,15-trihydro-15H-thiochromeno[4,3-b]pyrao[4,3-d]pyrido[1,2-a]benzimidazole-14-carbonitrile (**17c–d**):* A mixture of lactone **12** (1.0 mmol),2-cyanomethyl-1*H*-benzimidazole (**16**, 1.0 mmol) and powdered KOH (1.2 mmol) in DMF (9 mL) was stirred at room temperature for 5–8 h. The reaction was monitored using silica gel TLC. After consumption of **12**, the residue was poured onto crushed ice with vigorous stirring. The aqueous suspension was neutralized with dil. HCl (if required) and the precipitate obtained was filtered, washed with water and dried. The crude residue was purified by silica gel column chromatography using chloroform/methanol (0–30%); *7-amino-6-oxo-6,8,15-trihydro-15H-benzo[h]chromeno[4,3-d]pyrido[1,2-a]benzimidazole-14-carbonitrile (**17a**):* Orange solid; R_f 0.42 ($CHCl_3$:MeOH, 10:1); IR (KBr): 1563, 1612, 1692 (C=O), 2208 (CN), 3173 and 3440 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 2.93 (br s, 2H, CH_2), 3.22 (br s, 2H, CH_2), 7.11 (m, 1H, Ar-H), 7.32 (m, 4H, Ar-H), 7.49 (m, 1H, Ar-H), 7.64 (m, 1H, Ar-H), 7.89 & 9.93 (br s, 2H, NH_2), 8.79 (m, 1H, Ar-H); MS: 377.1 $(M-H)^+$; Anal. Calcd ($C_{23}H_{14}N_4O_2$): C, 73.01; H, 3.73; N, 14.81. Found: C, 72.92; H, 3.70; N, 14.73; *7-amino-6-oxo-6,8,15-trihydro-15H-thiochromeno[4,3-b]pyrao[4,3-d]pyrido[1,2-a]benzimidazole-14-carbonitrile (**17c**):* Orange solid; R_f 0.64 ($CHCl_3$:MeOH, 10:1); IR (KBr): 1556, 1603, 1691 (C=O), 2208 (CN), 3177 and 3426 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 4.48 (s, 2H, SCH_2), 7.14 (t, 2H, J = 7.5 Hz, Ar-H), 7.25–7.41 (m, 5H, Ar-H & NH_2), 7.55 (d, 1H, J = 7.8 Hz, Ar-H), 7.74 (dd, 1H, J = 1.5 & 7.5 Hz, Ar-H), 8.80 (d, 1H, J = 8.1 Hz, Ar-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 25.24, 69.31, 88.97, 107.11, 115.55, 117.50, 117.64, 121.08, 124.37, 126.29, 127.02, 127.90, 128.56, 131.32, 132.86, 135.22, 144.50, 145.41, 151.28, 151.59, 154.97, 161.31; MS: 395.1 (M^+-1); Anal. Calcd ($C_{22}H_{12}N_4O_2S$): C, 66.66; H, 3.05; N, 14.13. Found: C, 66.51; H, 3.01; N, 14.03.