Preprint Title	An Efficient Metal-free and Catalyst-free C-S/C-O Bond Formation Strategy: Synthesis of Pyrazole Conjugated Thioamides and Amides
Authors	Shubham Sharma, Dharmender Singh, Sunit Kumar, Vaishali , Rahul Jamra, Naveen Banyal, Deepika , Chandi C. Malakar and Virender Singh
Publication Date	28 Dez. 2022
Article Type	Full Research Paper
Supporting Information File 1	Supp. info Thioamide 24-12-22.docx; 4.3 MB
ORCID® iDs	Shubham Sharma - https://orcid.org/0000-0002-9657-6623; Sunit Kumar - https://orcid.org/0000-0003-3266-0217; Chandi C. Malakar - https://orcid.org/0000-0002-9478-017X; Virender Singh - https://orcid.org/0000-0003-4242-5421

An Efficient Metal-free and Catalyst-free C-S/C-O Bond Formation Strategy: Synthesis of Pyrazole Conjugated Thioamides and Amides

Shubham Sharma[1], Dharmender Singh[1,2], Sunit Kumar[1], Vaishali[1], Rahul Jamra[1,4], Naveen Banyal[1,4], Deepika[1], Chandi C. Malakar[3] and Virender Singh*[1,4]

[1]Department of Chemistry, Dr B R Ambedkar National Institute of Technology (NIT) Jalandhar, 144027, Punjab, India.

[2]Central Revenues Control Laboratory, New Delhi-110012.

[3]Department of Chemistry, National Institute of Technology (NIT) Manipur, Imphal, 795004, India.

[4]Department of Chemistry, Central University of Punjab, Bathinda, 151401, Punjab, India.

Email:- virender.singh@cup.edu.in

Abstract

An operationally simple, metal-free approach has been described for the synthesis of pyrazole tethered thioamide and amide conjugates. The thioamides were generated by employing a three-component reaction of diverse pyrazole C-3/4/5 carbaldehydes, secondary amines, and elemental sulfur in a single synthetic operation. The advantages of this developed protocol refer to the broad substrate scope, metal-free and easy to perform reaction conditions. Moreover, the pyrazole C-3/5 linked amide conjugates were also synthesized *via* oxidative amination of pyrazole carbaldehydes and 2-aminopyridines using hydrogen peroxide as an oxidant.

Keywords

Pyrazole carbaldehydes; Metal-free; C-S/O Bond Formation; Oxidative amidation; Thioamides

Introduction

During the past years, significance of pyrazole chemistry has been adequately escalated which is attributed to the discovery of their amusing biological properties. Among the heterocyclic molecules, pyrazoles are considered as privileged scaffolds for the design and construction of pharmacologically relevant scaffolds [1-3]. Their effectiveness has been witnessed in agrochemicals, chemicals, and pharmaceutical industries. Moreover, recent findings have affirmed the potential of the pyrazole nucleus as CB1 receptor antagonists [4], estrogen receptor ligands [5], A2A receptor antagonists [6], and DNA intercalating agents [7]. Importantly, pyrazole derivatives can be traced in a spectrum of well-established drug candidates of various categories with diverse therapeutic properties such as antipyretic [8], antibacterial [9], anticancer [10-12], antiviral [13], analgesic [14], antioxidants, antimicrobial [15], anti-diabetic, anticonvulsant [16], antihelminthic [17] and antiarrhythmic activities. The pyrazole nucleus is core unit in several FDA approved marketed drugs such as Sildenafil [18-20], Celebrex [21-22], Difenamizole [23], Epirizole [24], Rimonabant [25] etc. (Figure 1). Further, pyrazole derivatives occupy a prime position in material sciences owing to their tremendous applications such as brightening agents [26], semiconductors [27], organic light-emitting diodes [28], and agrochemicals [29-31]. Substituted pyrazoles are also of considerable attention because of their synthetic utilities as chiral auxiliaries [32], synthetic reagents in the multicomponent reactions [33-34], and guanylating agents [35].

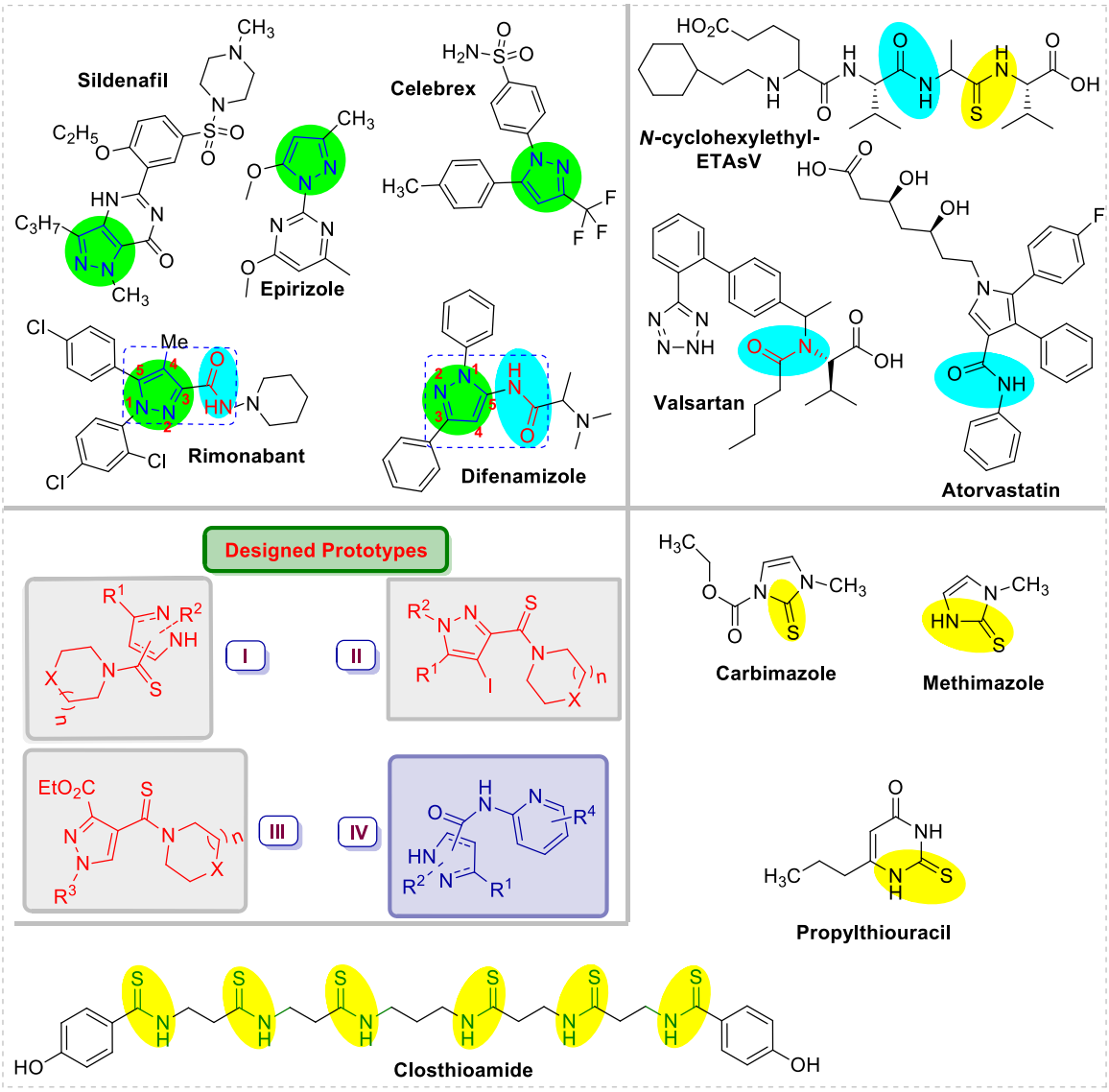


Figure 1. Representative drugs molecules based on pyrazole, thioamide and amide derivatives.

The installation of a thioamide functionality has alleged an immense attention in medicinal chemistry, due to their enormous biological activities [36-39]. Accordingly, a broad spectrum of effective and useful methods have been acknowledged in the literature for their preparation [40-42]. In this regard, a review article described by Jagodzinski *et al*. based on the examination of a massive virtual library synthesized with frequently occurring pharmacophores in the drug components concluded that the thioamide linkage establishes an intriguing class of biologically significant compounds amenable to

combinatorial chemistry [43]. This organic functional group is found in vital biological and pharmaceutical molecules such as *N*-cyclohexylethyl-ETAsV [44], Carbimazole, Methimazole, Propylthiouracil [45] and Closthioamide [46] (Figure 1). Moreover, they also find widespread applications as intermediates for the construction of five and six-membered heterocyclic compounds [47] and active pharmaceutical ingredients [48] such as fenclosic acid, fentiazac and febuxostate.

Similarly, in contemporary chemistry, the amide functionality is one of the most studied functional groups. Specifically, this moiety is vital for the formation of backbone of structural proteins and enzymes [49]. The amide linkage is present in several naturally occurring compounds and it is also one of the most productive functional groups in current pharmaceutical drugs [50-51]. As prime examples; Atorvastatin [52], Valsartan [53], *N*-cyclohexylethyl-ETAsV are successfully utilized to treat various life challenging diseases (Figure 1). Accordingly, as a part of our on-going research project, it was planned to incorporate thioamide and amide functional groups with pyrazole framework to develop new scaffolds.

An extensive literature survey revealed that several approaches are well-documented for the construction of thioamide functionality including base catalyzed Willgerodt-Kindler reaction [54], Kindler reaction in the presence of sulfated tungstate [55], thionation of amides using thionating reagents [56] and thionation of amides using TsCl (4-toluenesulfonyl chloride) or $PSCl_3$ mediated Beckmann rearrangement [57]. Although, these protocols are useful and have exhibited wide applications in organic synthesis (Figure 2); whereas, the scope of these reported methods may suffer from drawbacks such as the harsh reaction conditions, use of expensive reagents, prolonged reaction times, low product yields, and cumbersome product isolation procedures [58-61].

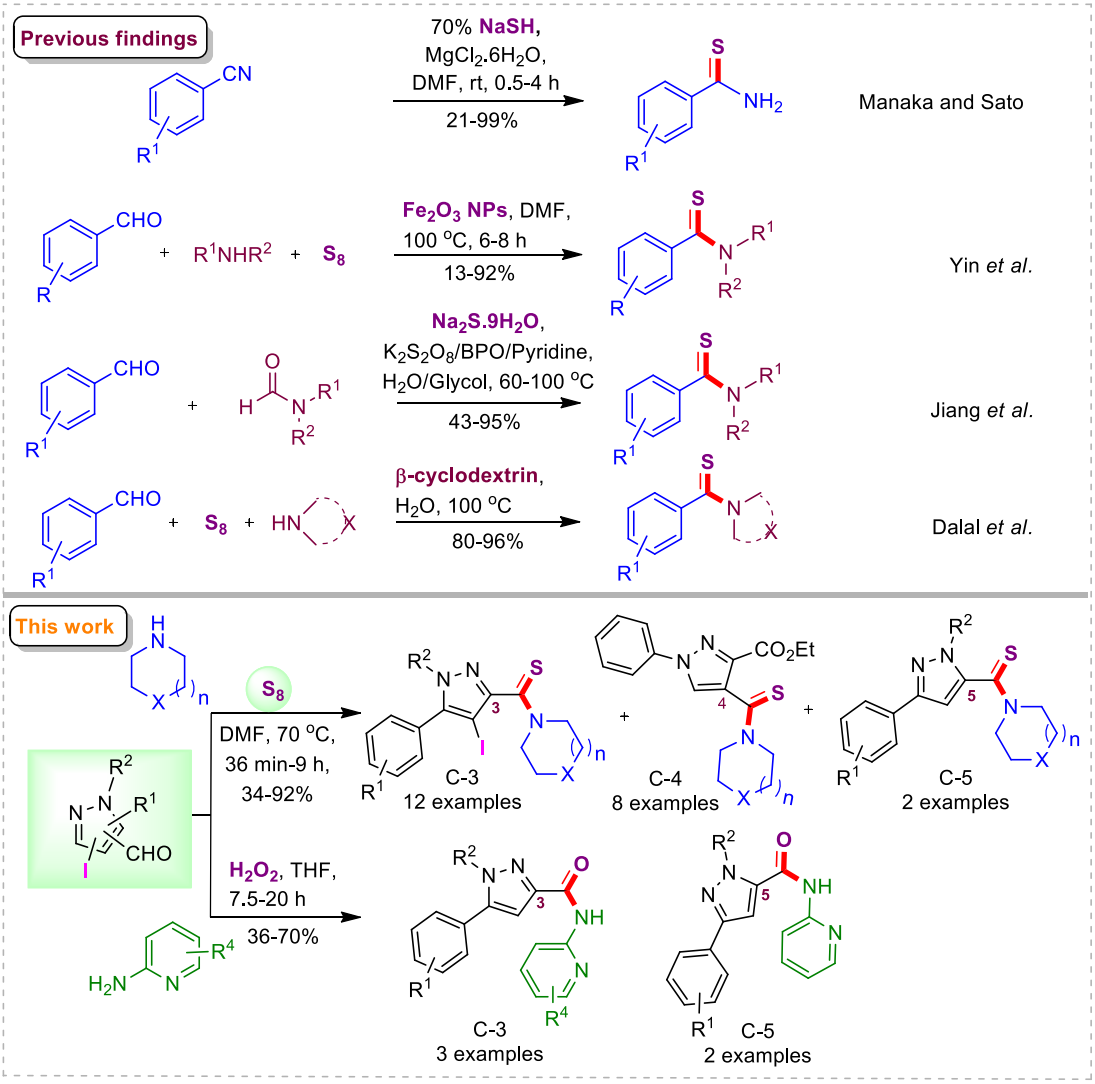


Figure 2. Previous and present findings for the synthesis of thioamide derivatives.

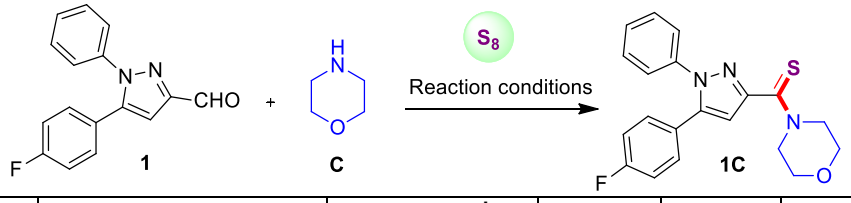
Fascinated by the immense pharmacological profiles of pyrazole, thioamide and amide derivatives, it was envisaged to develop a practical approach towards the synthesis of pyrazole-thioamide and pyrazole-amide conjugates. Elemental sulfur was explored as a sulfurating reagent for the generation of thiomides owing to its non-toxic, odourless nature and versatile reactivity profile [62-64]. To the best of our knowledge, the syntheses of pyrazole C-3/4/5 linked thioamide and amide conjugates have not been reported. Herein, we report an operationally simple one-pot procedure for the preparation of highly diversified thioamide and amide linked pyrazole analogues.

Result and discussion

Initially, the synthesis of pyrazole C-3/4/5 carbaldehydes and 4-iodo-pyrazole-3-carbaldehydes were achieved by employing the recently reported procedures [65-68]. Thereafter, the pyrazole-3-carbaldehyde **1**, morpholine (**C**) and elemental sulfur were selected as the model substrates towards the preparation of pyrazole linked thioamide derivatives. To begin with, an experiment was executed with model reactants in the presence of catalytic amounts of β-cyclodextrin (β-CD) [69] under aqueous condition at room temperature as well as under heating at 100 ^{o}C (Entries 1-2, Table 1). Unfortunately, the model reactants remained unreacted and similar observations were recorded using a mixture of H_2O:MeOH (1:4), and methanol as a reaction medium (Entries 3-4, Table 1). Moreover, it was also investigated that various organic solvents in combination with β-CD at room temperature were inactive towards accomplishment of this transformation (Entries 5-8, Table 1). Fortunately, when the reaction was performed in CH_3CN at 60 ^{o}C; a polar product was obtained, which was isolated after a short silica gel column chromatography (Entry 9, Table 1). To our delight, the spectroscopic analysis revealed the structure of the purified product as (5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)(morpholino)methanethione (**1C**), which was obtained in 64% isolated yield. Encouraged by these preliminary results, we next assembled the model reactants in DMF as a solvent in the presence of β-cyclodextrin at 60 ^{o}C. It was learned that the outcome of the reaction was slightly better (reaction time was reduced and the yield of the product **1C** was increased to 70%, Entry 10, Table 1), which indicated the superiority of DMF over other solvent. Subsequently, we examined the effects of $La(OTf)_3$ as a catalyst in combination with DMF as a solvent; however, the targeted prototype **1C** was obtained only in 20% yield at 60 ^{o}C after 24 hours of reaction time (Entries 11-12, Table 1). Next, ZnO nanoparticles were screened for the thioamidation of pyrazole-3-carbaldehyde. The desired thioamide conjugated pyrazole **1C** was afforded in 30% yield, as the starting substrates were not completely consumed even after 24 hours of reaction time (Entry 13, Table 1). On the basis of above experimental results, we concluded that CH_3CN and DMF were the ideal solvents for this transformation towards effective formation of the product. As per literature reports, K_2CO_3 shows remarkable efficacy in various organic

transformations [70]. Hence, this reaction was also examined under the influences of K_2CO_3 (2 equiv.) in CH_3CN, but the reaction conditions were inactive towards the formation of pyrazole tethered thioamide **1C** (Entry 14, Table 1). Surprisingly, when the reaction was carried out in DMF at ambient temperature, the desired product **1C** was obtained in 80% yield (Entry 15, Table 1). However, the same reaction under the heating conditions at 70 ^oC, afforded the desired product **1C** in 82% yield with a drastic reduction in the reaction time to 1 hour (Entry 16, Table 1). Moreover, an increase in the amount of base had a negligible effect on the yield of the thioamide conjugate **1C** (Entries 17-18, Table 1). To check the role of K_2CO_3, we executed a model reaction in DMF without base (K_2CO_3) and it was noted that pyrazole linked thioamide **1C** was obtained in excellent yield (90%) after 2 hours of reaction time (Entry 19, Table 1). This experiment indicated that the K_2CO_3 was not mandatory for the desired thioamidation reaction. After that, DMSO and NMP were also screened as solvents in the absence of base, but longer reaction time was required for similar transformation (7 h) (Entries 20-21, Table 1). A reaction of model substrates under the neat conditions delivered the product **1C** in poor yield (Entry 22, Table 1). Based on these screening experiments, it was concluded that the reaction proceeded smoothly in DMF as the reaction medium at 70 ^oC for 2 hours, and these were considered as the optimal condition for further investigation of the scope of the developed strategy (Entry 19, Table 1).

Table 1. Screening of reaction conditions towards the formation of pyrazole conjugated thioamide[a]

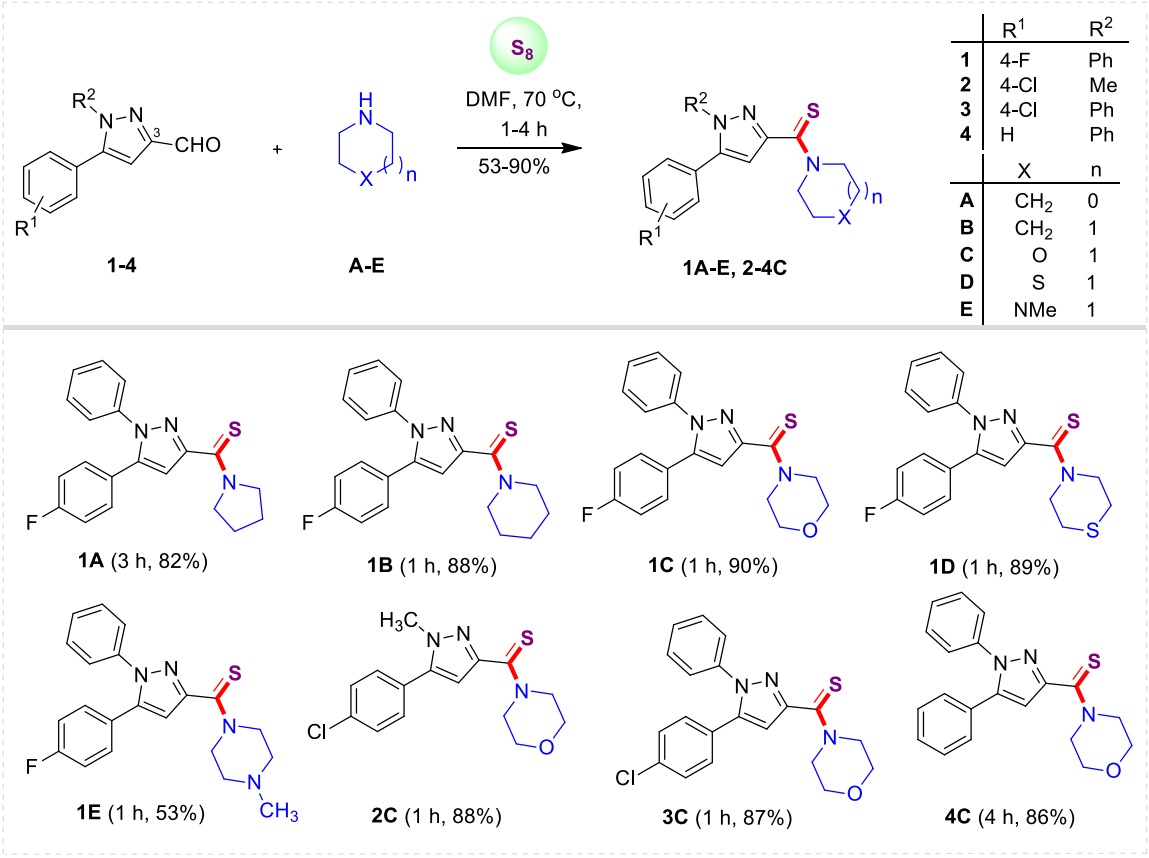


Entry	Catalyst/Reagent (equiv.)	Solvent[b]	Temp. (^oC)	Time (h)	Isolated yield[c]
1.	β-CD (0.2)	H_2O	rt	7	NR[d]
2.	β-CD (0.2)	H_2O	100	7	NR
3.	β-CD (0.2)	MeOH	rt	7	NR
4.	β-CD (0.2)	H_2O:MeOH (1:4)	rt	7	NR
5.	β-CD (0.2)	DCE	rt	7	NR
6.	β-CD (0.2)	AcOH	rt	3	NR

7.	β-CD (0.2)	CH_3CN	rt	3	NR
8.	β-CD (0.2)	toluene	rt	3	NR
9.	β-CD (0.2)	CH_3CN	60	7	64%
10.	β-CD (0.2)	DMF	60	3	70%
11.	$La(OTf)_3$ (0.1)	DMF	rt	24	NR
12.	$La(OTf)_3$ (0.1)	DMF	60	24	20%
13.	ZnO NPs (0.1)	DMF	rt	24	30% + **1**
14.	K_2CO_3 (2.0)	CH_3CN	rt	18	NR
15.	K_2CO_3 (1.0)	DMF	rt	24	80%
16.	K_2CO_3 (1.0)	DMF	70	1	82%
17.	K_2CO_3 (2.0)	DMF	70	1	80%
18.	K_2CO_3 (3.0)	DMF	70	1	79%
19.	-	**DMF**	**70**	**2**	**90%**
20.	-	DMSO	70	7	88%
21.	-	NMP	70	7	85%
22.	-	neat	70	29	13% + **1**

[a]All the reactions were optimized with 0.07 mmol (1 equiv.) of **1**, 0.08 mmol (1.1 equiv.) of **C**, 0.28 mmol (4 equiv.) of sulfur in 2 mL of solvent; [b]All the reactions were performed in anhydrous solvents (except entries 1-3); [c]Isolated yields of the purified product **1C**; [d]The model substrates remained intact; NR = no reaction.

Having established the optimal reaction condition, we explored the generality and the scope of this metal- and catalyst-free approach by employing pyrazole C-3 carbaldehydes **1-4**, secondary amines **A-E** and elemental sulfur as substrates. It was observed that the reaction conditions were compatible with different pyrazole-3-carbaldehydes and various secondary amines for the synthesis of pyrazole C-3 tethered thioamides **1A-E** and **2-4C** with the yield ranging from 53-90% (Scheme 1). Notably, 1-methylpiperazine (**E**) afforded the product in low yield (53%). The electronic nature of the substituents located at *N*-1 and C-5 position of the pyrazole ring exerted unnoticeable impacts on the yields of the desired products.

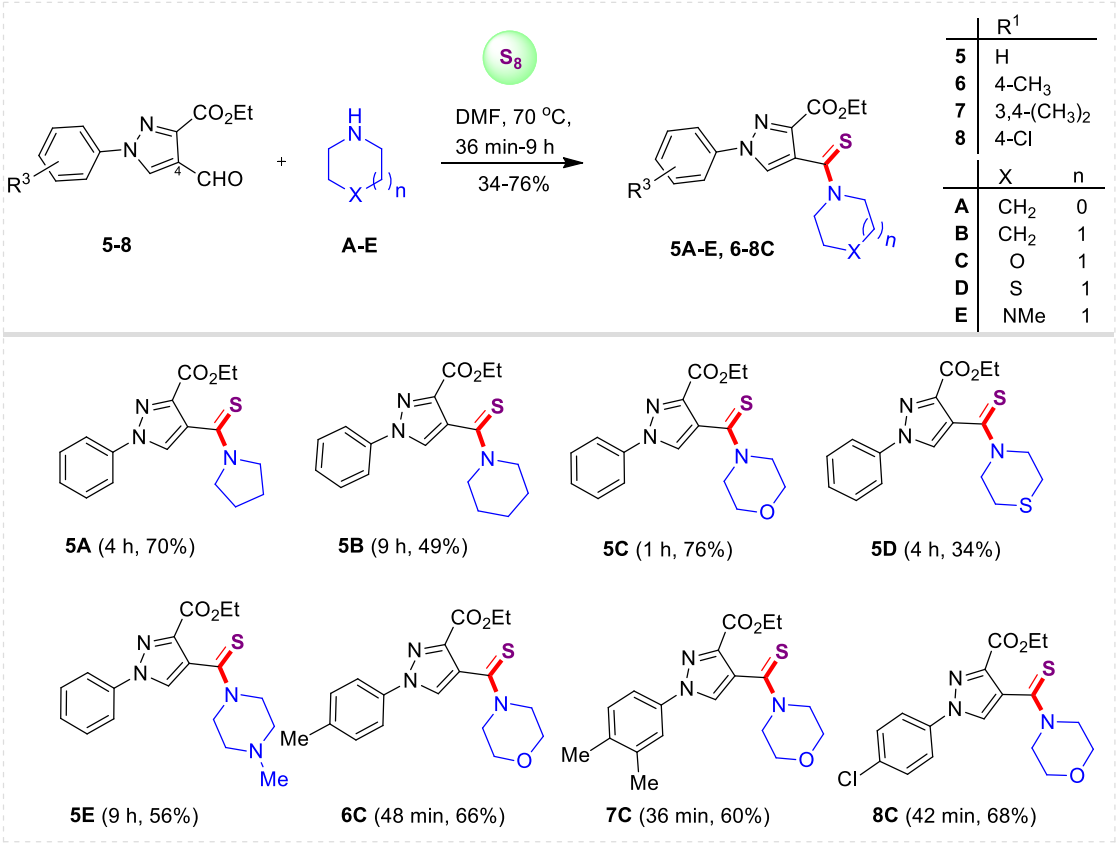


	R^1	R^2
1	4-F	Ph
2	4-Cl	Me
3	4-Cl	Ph
4	H	Ph

	X	n
A	CH_2	0
B	CH_2	1
C	O	1
D	S	1
E	NMe	1

Scheme 1. Synthesis of pyrazole C-3 tethered thioamides

Encouraged by these successful results, we further investigated the thioamidation reaction of various pyrazole-4-carbaldehydes **5-8** using the optimal conditions as illustrated in Scheme 2. The pyrazole-4-carbaldehydes **5-8** were found to be suitable substrate for this operation. It is pertinent to mention that the substrate **5** reacted with cyclic secondary amines **A-C** to yield the designed prototypes in moderate to good yield (49-76%); whereas, the thiomorpholine (**D**) delivered the thioamide conjugate **5D** in low yield (34%). During the preparation of pyrazole C-4 conjugated thioamides **5A-E** and **6-8C**; it was also noted that when the reaction was exercised with morpholine (**C**), the reaction was accomplished in lesser time (36 min-1 h) as compared to other secondary amines.

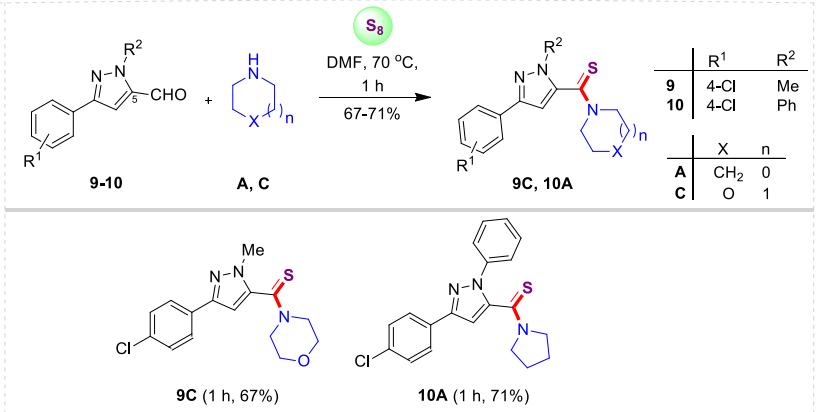


	R^1
5	H
6	4-CH_3
7	3,4-$(CH_3)_2$
8	4-Cl

	X	n
A	CH_2	0
B	CH_2	1
C	O	1
D	S	1
E	NMe	1

Scheme 2. Synthesis of pyrazole C-4 tethered thioamides

To further validate the synthetic flexibility of this methodology, we employed pyrazole C-5 carbaldehydes **9-10** for the synthesis of thioamide-conjugates. It was noted that the pyrazole-5-carbaldehydes **9-10** were more reactive as compared to pyrazole C-3 and C-4 carbaldehydes, leading to the formation of products **9C** and **10A** in high yields (67-71%) within 1 hour of reaction time as depicted in Scheme 3.

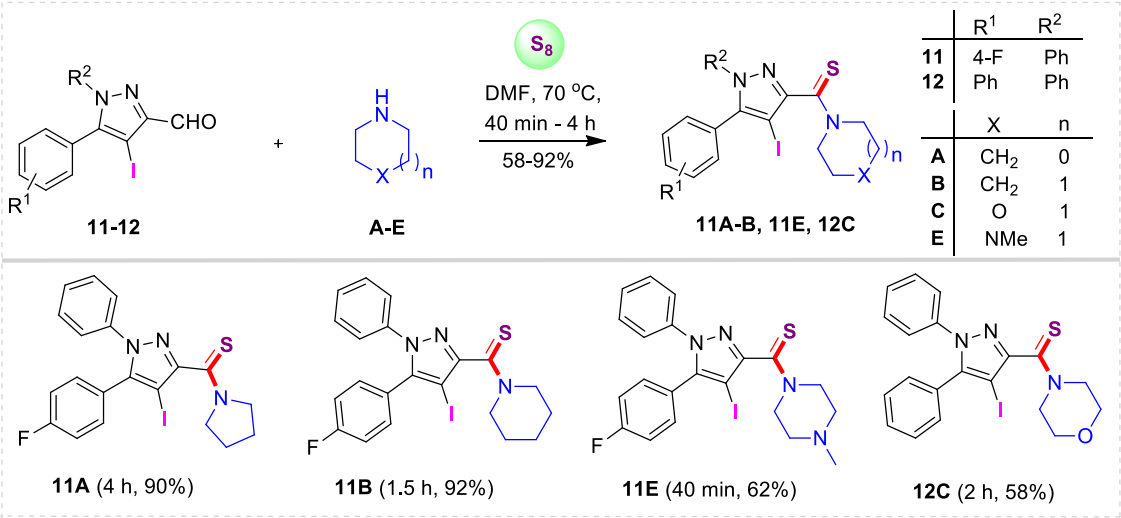


	R^1	R^2
9	4-Cl	Me
10	4-Cl	Ph

	X	n
A	CH_2	0
C	O	1

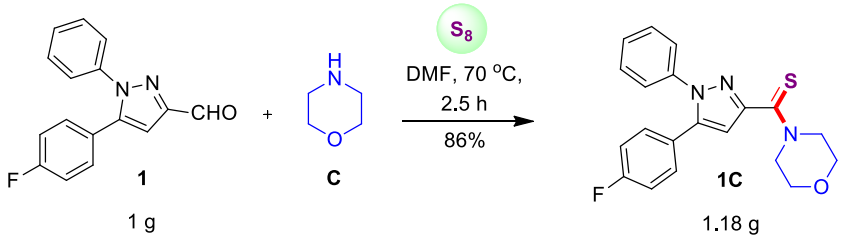
Scheme 3. Metal- and catalyst-free preparation of pyrazole C-5 linked thioamide conjugates.

Thereafter, the substrates 4-iodopyrazole-3-carbaldehydes were further investigated for this metal- and catalyst-free sulfur insertion reaction as shown in Scheme 4. It was found that 4-iodopyrazole C-3 carbaldehydes **11-12** were also tolerated well for this thioamidation process and furnished the anticipated products **11A-B**, **11E** and **12C** in good to excellent yield (58-92%) within 40 min-4 hours.



Scheme 4. Synthesis of 4-iodopyrazole C-3 tethered thioamides.

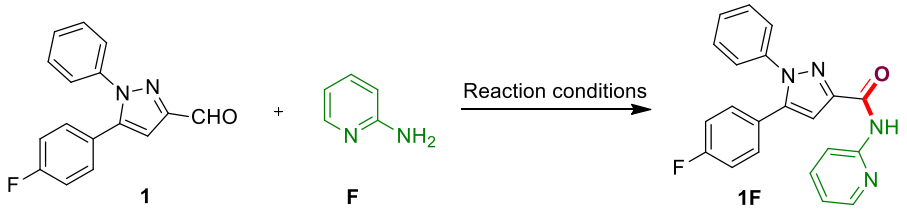
To check the industrial scope of the current protocol, we conducted a gram-scale reaction between the pyrazole-3-carbaldehyde **1**, morpholine **C** and elemental sulfur under the standard reaction conditions as depicted in Scheme 5. It was noted that this one-pot operation was completed within 2.5 hours and smoothly furnished the desired product, (5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)(morpholino)methan-ethione (**1C**) in 86% yield.



Scheme 5. Gram-scale scope of the current protocol.

The successful synthesis of pyrazole C-3/4/5 tethered thioamides inspired us to generate analogues pyrazole-pyridine conjugates having amide linkage. For this purpose, 5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-3-carbaldehyde (**1**) and 2-aminopyridine (**F**) were selected as the model reactants to explore this transformation. Initially, we conducted an oxidative amidation reaction of pyrazole-3-carbaldehyde **1** and 2-aminopyridine (**F**) in the presence of TBHP in DMSO as a solvent at 130 ^{o}C (Entry 1, Table 2). However, the reaction required longer time (20 h) for the completion, and afforded a product in 29% yield only. It was realized that the isolated product was the desired product, 5-(4-fluorophenyl)-1-phenyl-*N*-(pyridin-2-yl)-1*H*-pyrazole-3-carboxamide (**1F**), as analyzed by spectroscopic data.

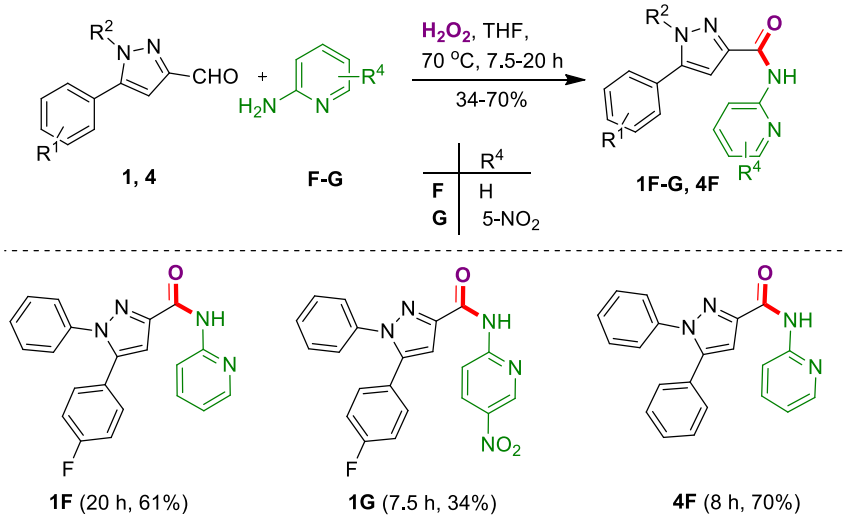
Table 2. Optimization of the reaction conditions towards the formation of pyrazole-pyridine conjugates having amide linkage[a]



Entry	Oxidant (equiv.)	Solvent[b]	Temp. (^{o}C)	Time (h)	Isolated yield[c]
1.	TBHP (3.0)	DMSO	130	20	29%
2.	TBHP (3.0)	DMF (10.0 equiv.)	130	10	35% + **1**
3.	TBHP (3.0)	CH_3CN (10.0 equiv.)	100	10	37% + **1**
4.	TBHP (3.0)	THF (10.0 equiv.)	100	9	42% + **1**
5.	TBHP (3.0)	MeOH (10.0 equiv.)	80	8	40% + **1**
6.	TBHP (10.0)	DMSO (2.0 equiv.)	**70**	18	36% + **1**
7.	H_2O_2 (25.0)	neat	rt	19	30%
8.	H_2O_2 (5.0)	DMSO	70	19	10% + **1**
9.	H_2O_2 (25.0)	DMSO (2.0 equiv.)	70	5	40%
10.	H_2O_2 (10.0)	DMSO (2.0 equiv.)	70	4	50%
11.	H_2O_2 (10.0)	DMF (2.0 equiv.)	70	8	33% + **1**
12.	H_2O_2 (10.0)	CH_3CN (2.0 equiv.)	70	5	56%
13.	H_2O_2 (10.0)	THF (2.0 equiv.)	70	7	58%
14.	H_2O_2 (10.0)	MeOH (2.0 equiv.)	70	6	45%
15.	H_2O_2 (10.0)	CH_3CN	70	4	54%
16.	**H_2O_2 (10.0)**	**THF**	**70**	**4**	**61%**

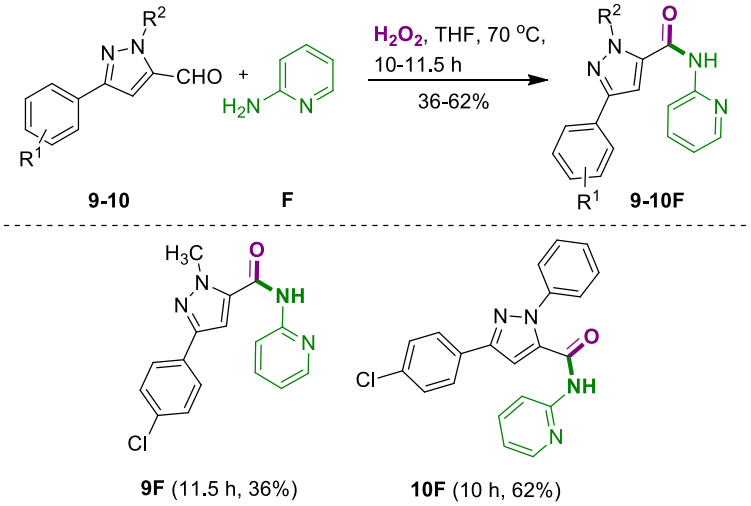
[a]All the optimization reactions were conducted with 0.07 mmol (1.0 equiv.) of **1**, 0.08 mmol (1.1 equiv.) of **F**; [b]All the reactions were examined in dry solvents (except entry 7); [c]Isolated yields of **1F**.

Next, we screened the other organic solvents including DMF, CH_3CN, THF and MeOH to improve the yield of desired product **1F**, but no improvement in the yield of the product was observed (Entries 2-5, Table 2). The oxidant TBHP (10 equiv.) failed to deliver the anticipated product in good yield (36%) (Entry 6, Table 2). Similar results were obtained with H_2O_2 (25.0 equiv.) under neat reaction conditions (Entry 7, Table 2). Next, we performed the oxidative amidation reaction with 5.0 equiv. of H_2O_2 in DMSO as a reaction medium under heated conditions; whereas, a poor yield of the product was obtained (Entry 8, Table 2). Moreover, different combinations of H_2O_2 and DMSO were examined for the oxidative amidation of pyrazole-3-carbaldehyde **1** (Entries 9-10, Table 2). Interestingly, a significant reduction in the reaction time was detected with 25 equiv. as well as 10 equiv. of H_2O_2. Next, we screened DMF, CH_3CN, THF and MeOH (2.0 equiv.) with 10.0 equiv. of H_2O_2 to increase the yield of the designed prototype **1F**. An acceptable enhancement was observed in the yield of the designed prototype (58%) **1F** (Entries 11-14, Table 2). The reactions with excess amount of solvents (CH_3CN and THF) showed a slight improvement in yield of the product **1F** (61%) in case of THF as a solvent (Entries 15-16, Table 2). From the above screening experiments, it was concluded that 10.0 equiv. of hydrogen peroxide in THF at 70 ^oC proved to be the optimal conditions for the construction of the pyrazole-pyridine conjugate with an amide linkage (Entry 16, Table 2). Having the optimized condition in hand, we employed pyrazole-3-carbaldehydes **1** and **4** for reaction with different 2-aminopyridines **F-G** towards the preparation of amide tethers as displayed in Scheme 6. The pyrazole-3-carbaldehydes **1** and **4** reacted efficiently with 2-aminopyridine (**F**) to deliver the pyrazole conjugated amides **1F** and **4F** in good yields (61-70%); whereas, in the case of 5-nitro-2-aminopyridine (**G**), the anticipated product **1G** was obtained in low yield (34%).



Scheme 6. H_2O_2-mediated synthesis of pyrazole-pyridine conjugates with amide tethers

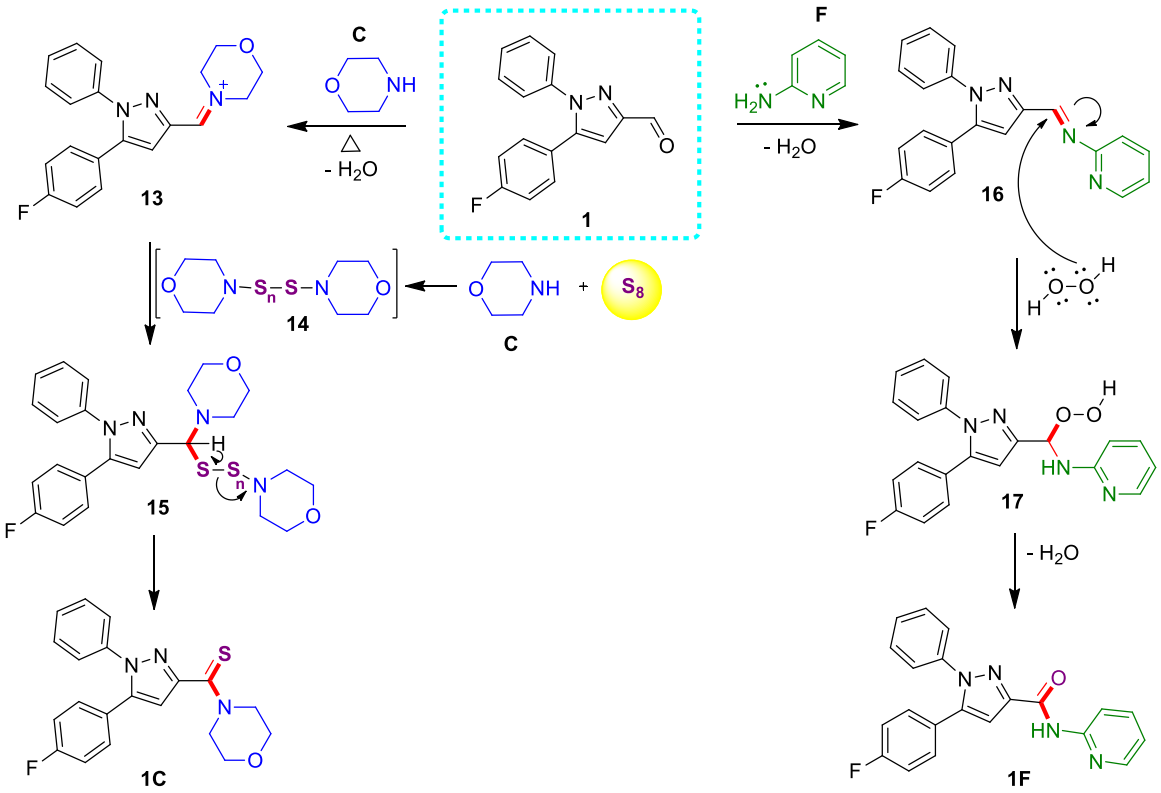
To check the synthetic versatility of this oxidative amidation approach, we tested the scope of the methodology with pyrazole-5-carbaldehydes **9-10**. Using this method, 3-(4-chlorophenyl)-1-phenyl-*N*-(pyridin-2-yl)-1*H*-pyrazole-5-carboxamide (**10F**) was produced in good yield (62%), while **9F** was generated in low yield (36%) as depicted in Scheme 7.



Scheme 7. Synthesis of pyrazole-pyridine conjugates having amide tethers.

Based on current experimental observations and literature reports [71-72] a plausible mechanistic pathway is outlined in Scheme 8 for the formation of the thioamide and amide linked pyrazole derivatives **1C** and **1F**. It is proposed that initially pyrazole-3-carbaldehyde **1** reacted with morpholine (**C**) to furnish the iminium intermediate **13**. Meanwhile, the intermediate polysulfide **14** formed by the nucleophilic attack of morpholine (**C**) on elemental sulfur may react with the intermediate **13** to afford another intermediate **14**,

which undergoes oxidation to release the thioamide tethered pyrazole **1C**. On the other hand, the pyrazole carbaldehyde **1** forms imine intermediate **16** by condensation with 2-aminopyridine. Thereafter, a nucleophilic attack of H_2O_2 on the imine carbon may afford the intermediate **17**. Finally, the loss of a water molecule from the intermediate **17** may generate the pyrazole-pyridine conjugates with amide linkage **1F**.



Scheme 8. A tentative mechanism for the formation of pyrazole conjugates with thioamide and amide linkage.

Conclusion

In summary, a simple, straightforward and efficient approach for the construction of biologically interesting highly diversified pyrazole linked thioamide and amide conjugates has been developed. The pyrazole C-3/4/5 tethered thioamide conjugates were prepared *via* a one-pot reaction between highly diversified pyrazole carbaldehydes, cyclic secondary amines, and elemental sulfur under metal- and catalyst-free conditions. The salient features of the current protocol may be attributed to the broad substrate scope, commercially available secondary amines, and operational simplicity, multicomponent

character of the reaction, easy isolation of products, short reaction time, and good to excellent yields of the desired molecules. Moreover, a practical synthetic utility of pyrazole-3/5-carbaldehydes has been explored through the formation of amide bond tethered pyrazole-pyridine conjugates. This developed methodology was successfully carried out by employing commercially available substituted 2-aminopyridines and hydrogen peroxide as an oxidant. The biological evaluation of the thioamide and amide conjugates is underway in our laboratory.

Experimental

General information

All chemicals and reagents were purchased from Sigma Aldrich, Acros, Avera Synthesis, Spectrochem Pvt. Ltd., and used without further purification. Commercially available anhydrous solvents (THF, DMF, benzene, toluene, MeOH, EtOH, and CH_2Cl_2 Spectrochem) were used in the reactions. Thin-layer chromatography (TLC) was performed using pre-coated aluminium plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). The column chromatography was performed using Spectrochem silica gel (60–120 mesh). Melting points were determined in open capillary tubes on the Precision Digital melting point apparatus (LABCO make) containing silicone oil, and the results are uncorrected. IR spectra (neat) were recorded on an Agilent FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded either on an Avance III Bruker or JEOL JNM-ECS spectrometer at operating frequencies of 200/400/500 MHz (^{1}H) and or 100/125/150 MHz (^{13}C) as indicated in the individual spectrum using TMS as an internal standard. Elemental analyses were performed on a Carlo-Erba 108 or an Elementar Vario EL III microanalyzer. The room temperature varied between 25 ^{o}C and 30 ^{o}C. The multiplicities in the ^{1}HNMR spectra are presented as s for singlet, d for doublet, dd for the doublet of the doublet, td for a triplet of doublet, t for triplet and m for multiplet. The multiplicity in the ^{13}C NMR spectra is presented as d for doublet.

Experimental section

General procedure for the synthesis of compounds 1A-E, 2-4C, 5A-E, 6-8C, 9C, 10A, 11A-B, 11E and 12C as exemplified for (5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)(morpholino)methanethione (1C): In a dry round-bottomed flask, pyrazole-3-carbaldehyde **1** (0.20 g, 0.75 mmol), morpholine (**C**; 0.072 g, 0.83 mmol), and sulfur powder (0.096 g, 3 mmol) were added in dry DMF (2 mL) at room temperature. The reaction flask was heated at 70 ^{o}C in an oil bath for 1 h. After completion of the reaction, as determined by TLC, cold water was added to the reaction mixture at room temperature which resulted in formation of precipitates of product. The product was collected via filtration under reduced pressure using a Buchner funnel and further purified by silica gel column chromatography (60-120 mesh silica gel) using hexane and ethyl acetate as an eluent (80:20, v/v) to give final product **1C** (0.247 g, 90%; R_f = 0.19, (hexane/EtOAc, 90:10, v/v).

Gram scale synthesis of (5-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-3-yl)(morpholino)methanethione (1C): A 50 mL round-bottomed flask was charged with pyrazole-3-carbaldehyde **1** (1 g, 3.74 mmol), morpholine (**C**; 0.36 g, 4.14 mmol), and elemental sulfur (0.48 g, 15 mmol) in dry DMF (10 mL) and heated the reaction mixture at 70 °C for 2.5 h. On completion of the reaction, as determined by TLC, the reaction content was cooled to room temperature and poured into ice-cold water under stirring, which resulted in the formation of precipitates. The solid was collected under vacuum using a Buchner funnel and further purified by silica gel column chromatography (60-120 mesh silica gel) using hexane and ethylacetate (80:20, v/v) as an eluent to give the analytically pure product **1C** (1.18 g from 1 g, 86%; R_f = 0.19 (hexane/EtOAc, 90:10, v/v)).

Typical procedure for the synthesis of compounds 1F-G, 4F and 9-10F as exemplified for 5-(4-fluorophenyl)-1-phenyl-*N*-(pyridin-2-yl)-1*H*-pyrazole-3-carboxamide (1F): To a stirred solution of compound **1** (0.10 g, 0.37 mmol) and 2-aminopyridine (**F**; 0.04 g, 0.42 mmol) in dry THF; H_2O_2 (0.087 mL, 3.73 mmol) was added dropwise at room temperature and the reaction was heated at 70 ^{o}C for 20 h. Upon completion of the reaction, as checked by the TLC, reaction mixture was cooled to room temperature, water was added and the product was extracted with ethyl acetate (3 x 25

mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford a crude product **1F**. This material was purified by silica gel column chromatography (60-120 mesh) using hexane and ethyl acetate as an eluent (95:05, v/v) to get the analytically pure product **1F** (0.082 g, 61%; R_f = 0.63, (hexane/EtOAc, 90:10, v/v).

Supporting Information

Supporting Information File 1:

File Name: Supp. Info

File Format: MS Word 2010

Title: An Efficient Approach towards Synthesis of Pyrazole Conjugated Thioamides and Amides using Metal Free C-S/C-O Bond Formation Strategy

Acknowledgments

S. S., S. K. and V. S. gratefully acknowledge the CIL, Central University of Punjab, Bathinda and Advanced Material and Research Centre (AMRC) at Indian Institute of Technology Mandi, HP, India for recording the spectroscopic data.

Funding

S.S. acknowledges the Ministry of Human Resource Development (MHRD), New Delhi, India, and CSIR, New Delhi for Junior Research Fellowships. S. K. and V. S. gratefully acknowledges the financial support in the form of research grants from CSIR (02 (0202) /14/EMR-II), DST (CS-361/ 2011), and DST-FIST (CSI-228/2011) New Delhi (India).

References

1. Costa, L. D.; Scheers E.; Coluccia, A.; Casulli, A.; Roche, M.; Giorgio, C. D.; Neyts, J.; Terme, T.; Cirilli, R.; Regina, G. L.; Silvestri, R.; Mirabelli, C.; Vanelle, P. *J. Med. Chem*. **2018**, *61*, 8402-8416. doi:10.1021/acs.jmedchem.8b00931
2. Karrouchi, K.; Radi, S.; Ramli, Y.; Taoufik, J.; Mabkhot, Y. N.; Al-aizari, F. A.; Ansar, M. *Molecules* **2018**, *23*, 134-220. doi:10.3390/molecules23010134
3. Nandi, G. C.; Singh, M. S.; Ila, H.; Junjappa, H. *Eur. J. Org. Chem*. **2012**, 967–974. doi:10.1002/ejoc.201101397
4. Wang, H.; Duffy, R. A.; Boykow, G. C.; Chackalamannil, S.; Madison, V. S. *J. Med. Chem*. **2008**, *51*, 2439-2446. doi: 10.1021/jm701519h
5. Naoum, F.; Kasiotis, K. M.; Magiatis, P.; Haroutounian, S. A. *Molecules* **2007**, *12*, 1259-1273. doi: 10.3390/12071259
6. Slee, D. H.; Moorjani, M.; Zhang, X.; Lin, E.; Lanier, M. C.; Chen, Y.; Rueter, J. K.; Lechner, S. M.; Markison, S.; Malany, S.; Joswig, T.; Santos, M.; Gross, R. S.; Williams, J. P.; Palomino, J. C. C.; Crespo, M. I.; Prat, M.; Gual, S.; Diaz, J. -L.; Jalali, K.; Sai, Y.; Zuo, Z.; Yang, C.; Wen, J.; Brien, Z. O.; Petroski, R.; Saunders, J. *J. Med. Chem*. **2008**, *51*, 1730-1739. doi:10.1021/jm701187w
7. Lauria, A.; Abbate, I.; Patella, C.; Gambino, N.; Silvestri, A.; Barone, G.; Almerico, A. M. *Tetrahedron Lett*. **2008**, *49*, 5125-5128. doi:10.1016/j.tetlet.2008.06.104
8. Chandra, T.; Garg, N.; Lata, S.; Saxena, K. K.; Kumar, A. *Eur. J. Med. Chem*. **2010**, *45*, 1772-1776. doi:10.1016/j.ejmech.2010.01.009
9. Abdel-Hafez, E. M. N.; Rahma, G. E. A. A. A.; Aziz, M. A.; Radwan, M. F.; Farag, H. H. *Bioorg. Med. Chem*. **2009**, *17*, 3829-3837. doi: 10.1016/j.bmc.2009.04.037

10. Lv, P. C.; Li, H. Q.; Sun, J.; Zhou, Y.; Zhu, H. L. *Bioorg. Med. Chem*. **2010**, *18*, 4606-4614. doi:10.1016/j.bmc.2010.05.034

11. Balbi, A.; Anzaldi, M.; Maccio, C.; Aiello, C.; Mazzei, M.; Gangemi, R.; Castagnola, P.; Miele, M.; Rosano, C.; Viale, M. *Eur. J. Med. Chem*. **2011**, *46*, 5293-5309. doi:10.1016/j.ejmech.2011.08.014

12. Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Baviskar, A.; Madaan, C.; Agarwal, A.; Preet, R.; Mohapatra, P. Patent 91/DEL/2011, 2011.

13. El-Sabbagh, O. I; Baraka, M. M.; Ibrahim, S. M.; Pannecouque, P.; Andrei, G.; Snoeck, R.; Balzarini, J; Rashad, A. *Eur. J. Med. Chem*. **2009**, *44*, 3746-3753. doi:10.1016/j.ejmech.2009.03.038

14. Hall, A.; Billinton, A.; Brown, S. H.; Clayton, N. M.; Chowdhury, A.; Giblin, G. M. P.; Goldsmith, P.; Hayhow, T. G.; Hurst, D. N.; Kilford, I. R.; Naylor, A.; Passingham, B.; Winyard, L. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 3392-3399. doi:10.1016/j.bmcl.2008.04.018

15. Sharshira, E. M.; Hamada, N. M. M. *Molecules* **2012**, *17*, 4962-4971. doi:10.3390/molecules17054962

16. Chimenti, F.; Bolasco, A.; Manna, F.; Secci, D.; Chimenti, P.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B.; Cirilli, R.; Torre, F. L. *J. Med. Chem*. **2004**, *47*, 2071-2074. doi:10.1021/jm031042b

17. Partridge, F. A.; Forman, R.; Bataille, C. J. R.; Wynne, G. M.; Nick, M.; Russell, A. J.; Else, K. J.; Sattelle, D. B. *Beilstein J. Org. Chem*. **2020**, *16*, 1203-1224. doi:10.3762/bjoc.16.105

18. Dale, J. D.; Dunn, J. P.; Golightly, C.; Hughes, L. M.; Levett, C. P.; Pearce, K. A.; Searle, M. P.; Ward, G.; Wood, S. A. *Org. Proc. Res. Dev*. **2000**, *4*, 17-22. doi:10.1021/op9900683
19. Dunn, J. P.; Galvin, S.; Hettenbach, K. *Green Chem*. **2004**, *6*, 43-48. doi:10.1039/B312329D
20. Ghozlan, S. A. S.; Badahdah, K. O.; Abdelhamid, I. A. *Beilstein J. Org. Chem*. **2007**, *3*, No. 15. doi:10.1186/1860-5397-3-15
21. Penning, T. D.; Talley, J. J.; Bertenshaw, S. R.; Carter, J. S.; Collins, P. W.; Docter, S.; Graneto, M. J.; Lee, L. F.; Malecha, J. W.; Miyashiro, J. M.; Rogers, R. S.; Rogier, D. J.; Yu, S. S.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Gregory, S. A.; Koboldt, C. M.; Perkins, W. E.; Seibert, K.; Veenhuizen, A. W.; Zhang, Y. Y.; Isakson, P. C. *J. Med. Chem*. **1997**, *40*, 1347-1365. doi:10.1021/jm960803q
22. Baumann, M.; Baxendale, I. R.; Ley, S. V.; Nikbin, N. *Beilstein J. Org. Chem*. **2011**, *7*, 442-495. doi:10.3762/bjoc.7.57
23. Kameyama, T.; Nabeshima, T. *Neuropharmacology* **1978**, *17*, 249-256. doi:10.1016/0028-3908(78)90108-9
24. Davie, C. -M. C.; Kositprapa, U. US Patent, **2005**, US 6,869,615 B2.
25. Kotagiri, V. K.; Suthrapu, S.; Reddy, J. M.; Rao, C. P.; Bollugoddu, V.; Bhattacharya, A.; Bandichhor, R. *Org. Proc. Res. Dev*. **2007**, *11*, 910-912. doi:10.1021/op700110b
26. Wang, M.; Zhang, J.; Liu, J.; Xu, C.; Ju, H. *J. Lumin*. **2002**, *99*, 79-83. doi:10.1016/S0022-2313(01)00204-6
27. Burschka, J.; Kessler, F.; Nazeeruddin, M. K.; Gratzel, M. *Chem. Mater*. **2013**, *25*, 2986-2990. doi:10.1021/cm400796u

28. Chou, P. -T.; Chi, Y. *Chem. Eur. J*. **2007**, *13*, 380-395. Doi:10.1002/chem.200601272

29. Yoshikawa, Y.; Katsuta, H.; Kishi, J.; Yanase, Y. *J. Pestic. Sci*. **2011**, *36*, 347-356. doi:10.1584/jpestics.G10-70

30. Numata, A.; Tanima, D.; Ando, M.; Saito, F.; Iwawaki, Y. US Patent, **2013**, US 2013/0338367.

31. Wang, M. -M.; Huang, H.; Shu, L.; Liu, J. –M.; Zhang, J. –Q.; Yan, Y. –L.; Zhang, D.-Y. *Beilstein J. Org. Chem*. **2020**, *16*, 233-247. doi:10.3762/bjoc.16.25

32. Molteni, G.; Buttero, P. D. *Tetrahedron Asymm.* **2005**, *16*, 1983-1987. doi:10.1016/j.tetasy.2005.04.014

33. Tu, X.; Hao, W.; Ye, Q.; Wang, S.; Jiang, B.; Li, G.; Tu, S. *J. Org. Chem*. **2014**, *79*, 11110-11118. doi:10.1021/jo502096t

34. Yadav, P.; Awasthi, A.; Gokulnath, S.; Tiwari, D. K. *J. Org. Chem*. **2021**, *86*, 2658−2666. doi:10.1021/acs.joc.0c02696

35. Castagnolo, D.; Schenone, S.; Botta, M. *Chem. Rev*. **2011**, *111*, 5247-5300. doi:10.1021/cr100423x

36. Bartlett, P. A.; Spear, K. L.; Jacobsen, N. E. *Biochemistry* **1982**, *21*, 1608-1611. doi:10.1021/bi00536a022

37. Yu, K. L.; Torri, A. F.; Luo, G.; Cianci, C.; Young, K. G.; Danetz, S.; Meanwell, N. A. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 3379-3382. doi:10.1016/S0960-894X(02)00761-8

38. Gannon, M. K.; Holt, J. J.; Bennett, S. M.; Wetzel, B. R.; Loo, T. W.; Bartlett, M. C.; Raub, T. J. *J. Med. Chem*. **2009**, *52*, 3328-3341. doi:10.1021/jm900253g

39. Banala, S.; Sussmuth, R. D. *ChemBioChem* **2010**, *11*, 1335-1337. doi:10.1002/cbic.201000266

40. Mahanta, N.; Kis, D. M. S.; Petersson, E. J.; Mitchell, D. *ACS Chem. Biol*. **2019**, *14*, 142-163. doi:10.1021/acschembio.8b01022

41. Kumar, K.; Konar, D.; Goyal, S.; Gangar, M.; Chouhan, M.; Rawal, R. K.; Nair, V. A. *ChemistrySelect* **2016**, **1**, 3228–3231. doi:10.1002/slct.201600601

42. Chaubey, T. N.; Borpatra, P. J.; Sharma, A.; Pandey, S. K. *Org. Lett*. **2022**, *24*, 8062–8066. doi:10.1021/acs.orglett.2c03371

43. Jagodzinski, T. S. *Chem. Rev*. **2003**, *103*, 197-228. doi:10.1021/cr0200015

44. Bach, A.; Eildal, J. N. N.; Hansen, N. S.; Deeskamp, R.; Gottschalk, M.; Pedersen, S. W.; Kristensen, A. S.; Stromgaard, K. *J. Med. Chem*. **2011**, *54*, 1333-1346. doi:10.1021/jm1013924

45. Nakamura, H.; Noh, J. Y.; Itoh, K.; Fukata, S.; Miyauchi, A. *J. Clin. Endocrinol. Metab.* **2007**, *92*, 2157-22162. doi: 10.1210/jc.2006-2135.42. Lincke, T.; Behnken, S.; Ishida, K.; Roth, M.; Hertweck, C. *Angew. Chem. Int. Ed*. **2010**, *122*, 2055-2057. doi:10.1002/ange.200906114

46. Hisano, T.; Yabuta, Y. *Chem. Pharm. Bull*. **1973**, *21*, 511-517. doi:10.1248/cpb.21.511

47. Lednicer, D. Strategies for Organic Drug Synthesis and Design; John Wiley Press: Hoboken, **2009**.

48. Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, 61, 10827-10852. doi:10.1016/j.tet.2005.08.031

49. Dunetz, J. R.; M. Javier; Weisenburger, G. A. *Org. Process Res. Dev*. **2016**, *20*, 140-177. doi:10.1021/op500305s

50. Nandi, G. C.; Samai, S.; Singh, M. S. *J. Org. Chem*. **2010**, *75*, 7785–7795. doi:10.1021/jo101572c

51. Lau, W. C.; Waskell, L. A.; Watkins, P. B.; Neer, C. J.; Horowitz K.; Hopp A. S.; Tait, A. R.; Carville, D. G. M.; Guyer, K. E.; Bates, E. R. *Circulation* **2003**, *107*, 32-37. doi:10.1161/01.CIR.0000047060.60595.CC

52. Abraham, I.; MacDonald, K.; Hermans, C.; Aerts, A.; Lee, C.; Brie, H.; Vancayzeele, S. *Vasc. Health Risk Manag*. **2011**, *7*, 209-235. doi:10.2147/FVHRM.S9434

53. Okamoto, K.; Yamamoto, T.; Kanbara, T. *Synlett* **2007**, *17*, 2687-2690. doi:10.1055/s-2007-991073

54. Pathare, S. P.; Chaudhari, P. S.; Akamanchi, K. G. *Appl. Catal., A* **2012**, *425-426*, 125-129. doi:10.1016/j.apcata.2012.03.012

55. Curphey, T. J. *J. Org. Chem*. **2002**, *67*, 6461-6473. doi:10.1021/jo0256742

56. Pathak, U.; Pandey, L. K.; Mathur, S.; Suryanarayana, M. V. S. *Chem. Comm*. **2009**, 5409-5411. doi:10.1039/B911844F

57. Manaka, A.; Sato, M. *Synth. Commun*. **2005**, *35*, 761-764. doi:10.1081/SCC-200050393

58. Xu, H.; Deng, H.; Li, Z.; Xiang, H.; Zhou, X. *Eur. J. Org. Chem*. **2013**, *31*, 7054-7057. doi:10.1002/ejoc.201301148

59. Yin, Z.; Zheng, B. *J. Sulfur Chem.* **2013**, *34*, 527-531. doi:10.1080/17415993.2013.765429

60. Wei, J.; Li, Y.; Jiang, X. *Org. Lett.* **2016**, *18*, 340-343. doi:10.1021/acs.orglett.5b03541
61. Nguyen, T. B. *Adv. Synth. Catal*. **2017**, *359*, 1066–1130. doi:10.1002/adsc.201601329
62. Nguyen, T. B. *Adv. Synth. Catal*.. **2020**, *362*, 3448-3484. doi:10.1002/adsc.202000535
63. Singh, M.; Awasthi, P.; Singh, V. *Eur. J. Org. Chem.* **2020,** 1023–1041. doi:10.1002/ejoc.201901908
64. Pathania, S.; Narang, R. K.; Rawal, R. K. *Eur. J. Med. Chem.*, **2019**, *18*, 486-508. doi:10.1016/j.ejmech.2019.07.043
65. Sharma, S.; Paul, A. K.; Singh, V. *New J. Chem*. **2020**, *44*, 684-694. doi:10.1039/C9NJ05426J
66. Devi, N.; Singh, D.; Sunkaria, R. K.; Malakar, C. C.; Mehra, S.; Rawal, R. K.; Singh, V. *ChemistrySelect* **2016**, *1*, 4696-4703. doi:10.1002/slct.201601133
67. Devi, N.; Shankar, R.; Singh, V. *J. Heterocycl. Chem*. **2018**, *55*, 373-390. doi:10.1039/C9NJ05426J
68. Nag, S.; Singh, V.; Batra, S. *Arkivoc* **2007**, 14, 185-203. doi:10.3998/ark.5550190.0008.e01
69. Mondal, R.; Mallik, A. K. *Org. Prep. Proced. Int.* **2014**, *46*, 391-434. doi:10.1080/00304948.2014.944402
70. Dheer, D.; Rawal, R. K.; Singh, V.; Sangwan, P. L.; Das, P.; Shankar, R. *Tetrahedron.* **2017**, *73*, 4295-4306. doi: 10.1016/j.tet.2017.05.081

71. Tayade, Y. A.; Jangale, A. D.; Dalal, D. S. *ChemistrySelect* **2018**, *3*, 8895-8900. doi:10.1002/slct.201801553

72. Devi, E. S.; Alanthadka, A.; Tamilselvi, A.; Nagarajan, S.; Sridharana, V.; Maheswari, C. U. *Org. Biomol. Chem*. **2016**, *14*, 8228-8231. doi:10.1039/C6OB01454B