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A METHOD FOR THE DESULFURIZATION OF SUBSTITUTED THIOUREAS APPLIED TO THE SYNTHESIS OF TETRAZOLE AND GUANIDINE DERIVATIVES

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Abstract: A simple yet robust set-up for the efficient desulfurization of a series of thioureas is presented, which generates the corresponding tetrazole and guanidine derivatives in moderate to high yields. This approach enabled the controlled and safe formation of the final products. In addition, we have explored the library of target products using this method.

Introduction

In recent years, desulfurization has been established on a multi-million-ton scale in down-stream oil processing towards the production of gasoline, kerosene and Diesel fuel using heterogeneous catalysts nickel, copper, cobalt, molybdenum, and tungsten etc. However, the true potential of this reaction in the lab scale total synthesis of natural products, biologically active compounds, or new materials has not been exploited yet.

Now a days heterocyclic skeletons are generally commercially available drug molecules (Figure 1).[i] They are the main building blocks in naturally occurring organic compounds.[ii] Generally heterocyclic scaffolds have been found to bearing a wide range of biological capabilities, including anti-inflammatory,[iii] anti-malarial,[iv] anti-tubercular,[v] anti-cancer,[vi] anti-asthmatic,[vii] anti-histaminic,[viii] anti-hypertensive,[ix] anti-depressant,[x] anti-microbial,[xi] anti-rheumatic,[xii] anti-diabetic,[xiii] anti-Alzheimer's, anti-Parkinson's, anti-Huntington's disease,[xiv] and many more activities[xv,xvi]. For the synthesis of diverse heterocyclic entities, the screening of suitable catalysts plays an important role.[xvii] In this regard, environmentally benign, non-volatile, non-flammable, non-corrosive, low-cost, commercially available and chemical stability Nickel catalyst is chosen for the development of method for the synthesis of tetrazoles and guanidine's through desulphurization.

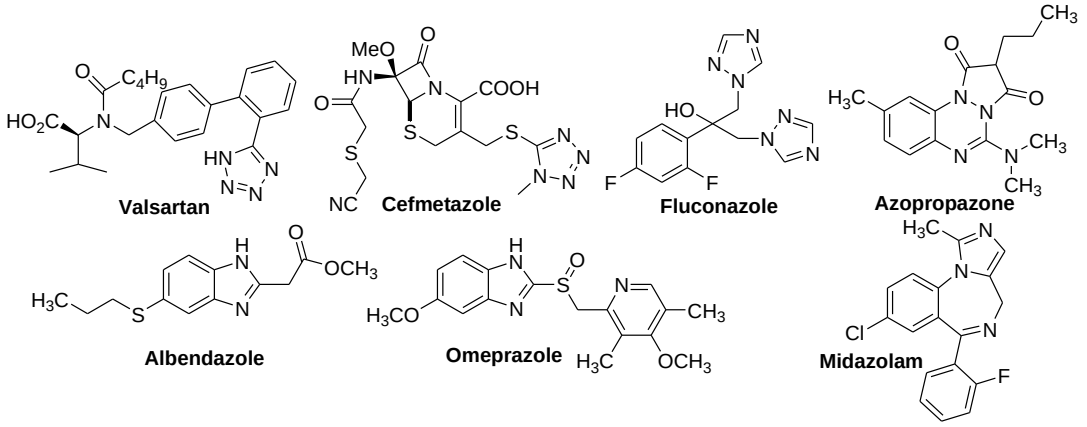


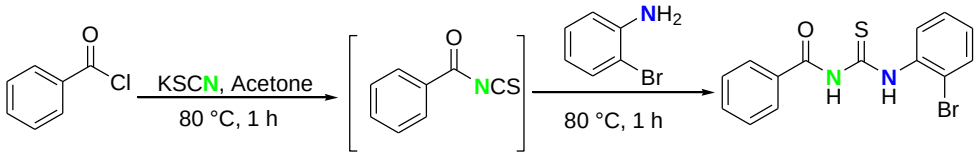
Figure 1: Examples of biologically important heterocyclic compounds

In recent decades tetrazole moiety compounds have been developed from starting precursors, for example, addition of $NaNO_2$ to aminoguanidine,[xviii] addition of NaN_3 to carbodimides or cyanamides,[xix] reaction of amines with a leaving group in tetrazoles 5-position,[xx] nucleophilic substitution by N_3^- of (a) chlorine in α-chloroformamidines[xxi] and (b) sulfur from thioureas in the presence of mercury[xxii] or lead salts[xviiic] or iodine.[xxiii] Furthermore, tetrazoles have also been prepared from the reaction between corresponding nitriles and NaN_3 via [3+2] cycloaddition using Zn (II) salts[xiv] and ZnO nanocrystal.[xxv] Recently, TBAF[xxvi] and Copper catalyst[xxvii] were also used for the synthesis of 5-substituted 1*H*-tetrazoles from the reaction between nitriles and trimethylsilyl azide. Some other reports have also been developed in recently.[xxviii] However, these methods use either toxic reagents or harsh reaction conditions such as high temperature and lack of regioselectivity.[xxix]

The synthesis of acylguanidines as potential bioactive molecules and useful building blocks for the synthesis of natural and therapeutically useful products has generated a major stimulus in academia and industry as well.[xxx] The main synthetic access to these molecular targets includes the guanylation of *N*-acylthioureas. Beside the displacement of the sulfur in the presence of ethyl-3-aminopropyl carbodiimide hydrochloride (EDCI)[xxxi] or Mukaiyama's reagent[xxxii] the most common desulphurizing agents is HgCl2.[xxxiii] It has been extensively used in the synthesis of guanidines. However, the stoichiometric utilization of mercury salts largely precludes the extended use for the synthesis of pharmaceutical relevant compounds due to their toxicity. Recently Prasad and co-workers have developed the synthesis of Guanidines and Tetrazoles using Cu catalyst[xxxiv] and stoichiometric amount of Iodine.[xxxv] Furthermore, recently Guanidines were reported with Iron catalyst,[xxxvi] however, they require moderate temperature, used high equivalent amount of base and stoichiometric amount of catalyst. In order to overcome the above said drawbacks and we would like to develop method for the synthesis of Guanidines and Tetrazoles in the presence of Nickel catalyst *via* desulphurisation/nucleophilic substitution/electro cyclization under mild reaction conditions.

Results and Discussion:

N-2-Bromophenyl *N*^{1}-benzoyl thiourea was prepared from benzoyl chloride by reacting with potassium thiocyanate and followed by nucleophilic addition with 2-bromo aniline in the presence of acetone under reflux conditions (Scheme 1).

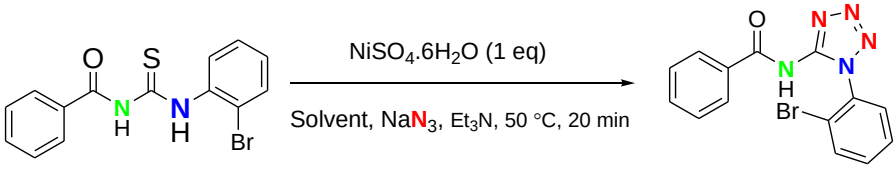


Scheme 1: The synthetic route for the synthesis of *N*-2-bromophenyl N^1-benzoyl thiourea

Initially we started the optimization with *N*-2-Bromophenyl-N^1-Benzoyl thiourea as model substrate using different solvents, bases and nickel sources at room temperature. We examined various solvents such as n-Hexane, n-Heptane, Toluene, THF, Dioxane, Acetone, DCM, $CHCl_3$, MeOH, DMSO, DMF and H_2O (Table 1, entries 1-12), and DMF was found to be the best solvent for this transformation. The conversion rate of **1a** was 100%, however, 10% product was unidentified impurity existed. The control experiment is conformed that no target product was formed in the absence of solvent (Table 1, entry 13). Later base optimization was conduced and all inorganic, organic base has produced target product in good yield (Table 2, entries 1-5), however, no reaction was proceeded in the absence of base (Table 2, entry 6). In order to effective soluability of NaN_3 and NaOH, water (0.5 mL) was added to the reaction mixture. All Nickel salts has shown same activity to wards the afford target product (Tabel 3, entries 1-4). Later the reaction was performed using 50 mol% catalyst and it gave target product in quantitative yield (Table 3, entry 5). In contrast, the yield of the final product was dramatically decreased using 25 mol% catalyst (Table 3, entry 6). Other trial like increasing temperature to 50 °C to provide target prodct in good yield within 10 min (Table 3, entry 7). The reaction was conducted in the absence of catalyst and no final product was observed (Table 3, entry 8) and the starting material is recovered intact.

Table 1: Solvent optimization for the preparation of Benzoylaryl-5-aminotetrazole

Entry	Solvent	Yield (%)[b]
		2a
1	n-Hexane	n.d.
2	n-Heptane	n.d.
3	Toluene	n.d.
4	THF	n.d.
5	Dioxane	n.d.
6	Acetone	n.d.
7	CH_2Cl_2	n.d.
8	$CHCl_3$	n.d.
9	MeOH	n.d
10	DMSO	45
11	DMF	90
12	H_2O	NR
13	-	NR

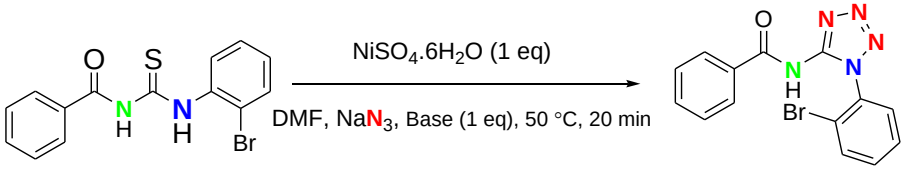


1a **2a**

[a]Reaction conditions: *N*-Benzoyl-*N'*-iodophenyl thiourea (1 mmol), $Fe_2(SO_4)_3.3H_2O$ (1 mmol), Et_3N (1 mmol), NaN_3 (1 mmol), rt, 60 min. Solvent (3 ml). [b] Isolated yield.

The effort of reaction optimization revealed that the best condition for the conversion of *N*-Benzoyl-*N'*-iodophenyl thiourea into Benzoyl-5-arylamino tetrazole is 50 mol% $NiSO_4.6H_2O$, NaN_3, and Et_3N in the presence of DMF at room temperature for 10 minutes.
Subsequently, different substituted Benzoyl-5-arylamino tetrazole were investigated under standardized conditions to exhibit the variability of this method. The substrates bearing electron donating and electron withdrawing substituents on the aryl rings and alkyl substrates were examined under the standard reaction 68-92% yield. The aryl ring having electron donating substituents like 4-Et, 4-Me and 4-OMe readily proceed the reaction to afford the target products

Table 2: Base optimization for the preparation of Benzoylaryl-5-aminotetrazole[a]



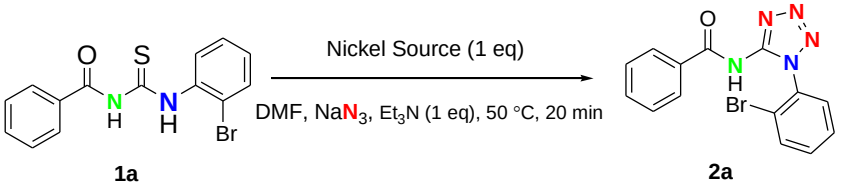
1a **2a**

Entry	Base	Yield (%)[b]
		2a
1	Et_3N	90
2	Piperidine	90
3	Na_2CO_3	90
4	$NaHCO_3$	90
5	NaOH	90
6	-	n.d.

a

Reaction conditions: *N*-Benzoyl-*N'*-iodophenyl thiourea (1 mmol), $Fe_2(SO_4)_3.3H_2O$ (1 mmol), Base (1 mmol), NaN_3 (1 mmol), rt, 60 min. DMF (3 ml). [b] Isolated yield.

Table 3: Catalyst optimization for the preparation of Benzoylaryl-5-aminotetrazole[a]

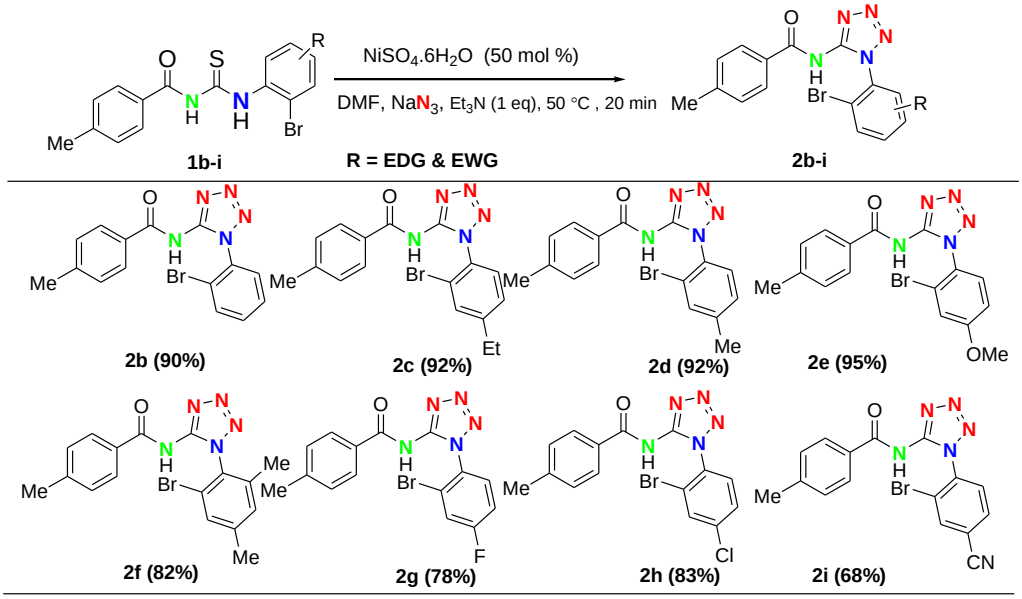


1a **2a**

Entry	Base	Yield (%)[b]
		2a
1	$NiSO_4.6H_2O$	90
2	$Ni(NO_3)_2.6H_2O$	90
3	$Ni(OAc)_2.4H_2O$	90
4	$NiCl_2$	90
5[c]	$NiSO_4.6H_2O$	90
6[d]	$NiSO_4.6H_2O$	45
7[e]	$NiSO_4.6H_2O$	90
8	-	n.d.

[a] Reaction conditions: *N*-Benzoyl-*N'*-iodophenyl thiourea (1 mmol), Iron source (1 mmol), Et_3N (1 mmol), NaN_3 (1 mmol), rt, 60 min. DMF (3 ml). [b] Isolated yield. [c] Catalyst (50 mol %) was used. [d] Catalyst (25 mol %) was used. [e] Reaction was carried out at 50 °C.

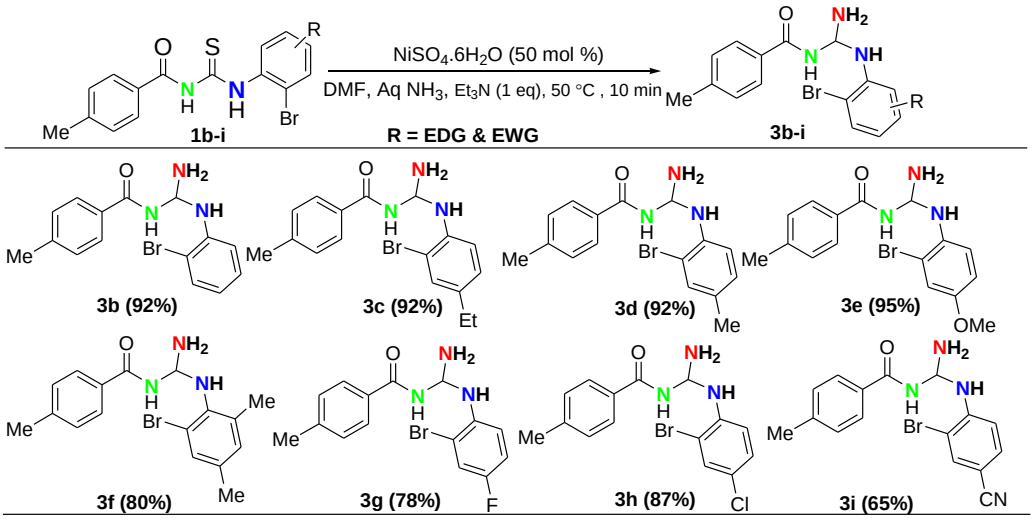
2b-d in good yield. In contrast the phenyl ring holds strong electron withdrawing group like 4-CN underwent the reaction to produce final product **2h** in lower yield. On the other hand, phenyl group bearing weak electron withdrawing groups such as 4-F and 4-Cl carried out the reaction under standardized conditions to provide the corresponding desired products **2f** in 78% yield and **2g** in 83% yield. Furthermore, phenyl ring consists of 2,4-DiMe gave the respective tetrazole product **2e** in 82% yield. The same optimized reaction conditions are applied for the construction of disubstituted guanidines and they gave the corresponding desired products (**3b-i**) in moderate to good yield.



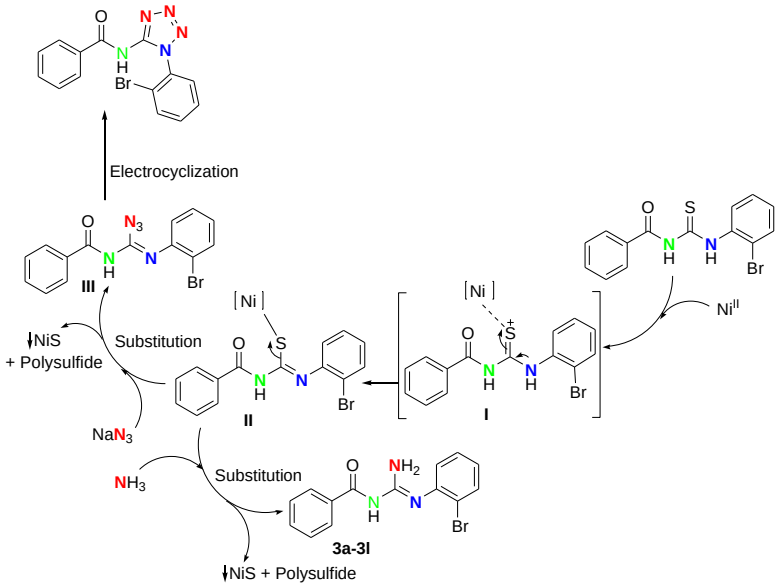
Scheme 2: Substrate scope for the synthesis of Aroyltetrazoles

Based on experimental evidence and literature reports proposed mechanism is shown in below scheme 4. Sulphur of thiourea may coordinate with Nickel (II) species (could be formed from Ni (III) salt)[xxxvii] to provide intermediate complex I. It undergoes desulphurization (NiS was formed as by-product and an extra sulphur might have converted into as polysulfide)[xxxviii] and nucleophilic substitution with NaN_3 to afford the

intermediate **III** *via* intermediates complex **II**. Electrocyclization of **III** afforded the target product tetrazole. On the other hand, desulphurization[xxxix] of intermediate **II** and followed by nucleophilic substitution with ammonia to afford the final product Guanidine. Still other mechanistic studies like conformation of NiS and others are examined in our Laboratory.



Scheme 3: Substrate scope for the synthesis of Aroylguanidines



Scheme 4: Proposed Mechanism.

Conclusions

In conclusion, we have presented a new and environmentally benign method for the synthesis of aroylguanidines and aroylaryl tetrazoles using Iron source under mild reaction conditions. Compared to other reported methods using $HgCl_2$ or $Bi(NO_3)_3.5H_2O$ the new method distinguishes itself by milder reaction conditions and shorter reaction times. Furthermore, the yields and the spectrum of accessible tetrazoles and guanidines are comparable or superior to the above mentioned methods. Further investigations concerning the optimization of the reported reaction conditions, the scope of the reaction, mechanistic studies to enlighten the role

of iron catalyst and applications towards target-orientated synthesis are currently underway in our laboratory and will be reported in the due course

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