An Efficient Methodology for Iodine-Catalyzed Synthesis of N, N' –Disubstituted Guanidines

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Abstract*: *An Iodine catalyzed multi component synthesis of N, N' –Disubstituted Guanidines in one pot three steps reaction from the reaction of benzoylchloride, ammonium thiocyanate, amine and ammonia via substitution/ addition/desulphurization under mild reaction conditions.

Index Terms*: *Iodine catalyst, desulphurization, Benzoyl Guanidines.

INTRODUCTION

Multi-Component reactions (MCRs) have become speedy growing research area and these reactions maximize the incorporation of all starting materials in final product. During this process fewer by-products were generated. This achievement makes MCRs extremely ideal and best eco-friendly reaction processes. The expected products can obtain in one-pot with fewer steps. Accordingly, MCRs have been received much attention in different research areas, such as medicinal chemistry, drug discovery programmes, combinational chemistry and natural product synthesis.[1] Guanidine, also called carbamine, is a strongly alkaline and the substituted guanidine derivatives, RN=C(NR'R")NHR'", plays a key role in numerous fields, such as pharmaceutics, organometallic, coordination chemistry and organic synthesis. Representative examples of some drugs that have guanidine structure shown below

Some representative examples of drugs that contain guanidine fragments are reported below. Trimethoprim, [2] sulfadiazine, [3] and Gleevec, [4] were found to have pharmaceutically guanidine-containing heterocycles. Rosuvastatin is used to treat high cholesterol and prevent cardiovascular disease.[5a] Guanabenz is used clinically as an antihypertensive.[5b] Imanitib is a tyrosine kinase inhibitor that is used as an anticancer drug.[5c] Cimetidine drug used to treat peptic ulcers.[5d] Zanamivir was the first neuraminidase inhibitor to be commercially developed.[5e]

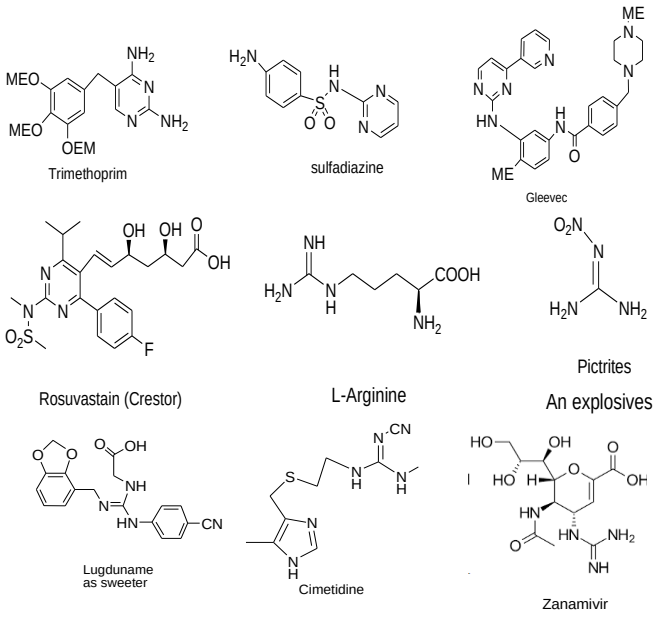


Figure 1: Selected examples of guanidine containing drugs.

The electron-rich guanidine form a stable guanidium cation $[C(NH_2)_3]^+$ by protonation[6]. The stabilization of the guanidinium cation is due to delocalization of positive charge within the Y-shaped CN_3 moiety.[7]

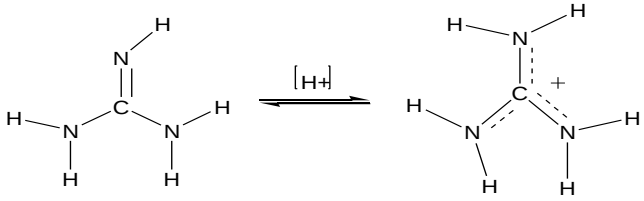
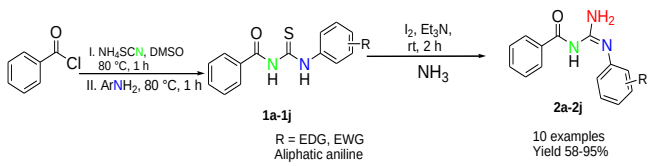


Figure 2: Resonance structures for the guanidinium cation group in the protonated form.

An efficient and simple methodology has been demonstrated for the construction of N, N' –Disubstituted Guanidines. Iodine source was used as a desulphonating reagent.This reaction has been involved substitution / addition / desulphurization / nucleophilic substitution /electro cyclcization. In addition, functional group tolerance has been also studied.



EDG-Electron Donating Group;
EWG-Electron Withdrawing Group

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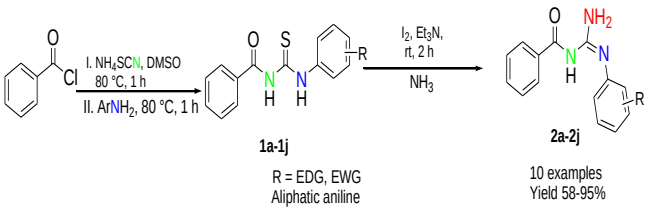
RESULTS AND DISCUSSION

The chosen method was used to check the various solvents for the above reaction. Initially, the test, experiment with acetate had a stop at N-Aryl-N-benzoyl thiourea (**1a).** So, the target product could not be reached (Table 1, entry 1). Later, when the test was tried out with CH_3CN to get better yield, but the target product was minimal with 5% yield only (Table 1, entry 2). Then, the reaction was verified with protic solvents such as EtOH and MeOH (Table 1, entries 3-4). Even this test, both solvents could not give expected results and gave only intermediate thiourea **1a** with 20% nad 30% yields respectively. During the process instead of benzoyl isothiocyanate, esters were found. During the reaction between benzoyl chloride with ammonium isothiocyanate in presence of protic solvents (nucleiophilic solvents), esters formation increased whereas the yield of benzoyl isothiocyanate is decreased. Since, the previous test results were not confirmed, the same reaction is seen with CH_2Cl_2 and $CHCl_3$ (Table 1, entry 5, 6). In order to get the intended yield, the experiment is extended further using non-polar solvents such as carbon-tetrachloride and benzene, here even the no reaction is observed (Table 1, entries 7-8). Then, when the solvent DMSO is considered for experiment. Interestingly, the target product is seen with 90% yield result (Table 1, entry 9). At the same time the test with other protic solvent DMF could give only 60% of end result (Table 1, entry 10). Finally, the reaction was tested with no solvent condition and with greenery solvent such as H_2O, no results is visible (Table 1, entry 11-12). In order to optimize the yield of the target product, the reaction was tested with both organic and inorganic bases. During the process the organic base (Et_3N) and pyridine have given the test result of 95% and 80% (Table 2, entries 1-2) respectively. But among the inorganic bases, the sodium acetate gave targeted product in better yield than others (Table 2, entry 3). Later, when it was experimented with disodium phosphate and sodium hydroxide, along with the target product spot other undetermined spots were also observed (table 2, entries 5-6). Finally, when the quantity of the catalyst is reduced, the target product could not be achieved as expected. Ultimetly , it is imposible to get the target product in the absence of the catalyst and base (Table 2, entry 7).

After carefully examining the optimal conditions, we began to explore potential efficient catalyst conditions on the substrate scope. The phenyl gives targeted product with 85% yield (Table 4, entry 1). Furthermore, the substrate scope was extended using 4-Fluoro and 4-Chloro substrates. The target product is seen with 73% and 82% (Table 4, entries 2-3) respectively. The decrease in yield is due to contribution of strong electron-withdrawing effects. At the same time the reaction was tested with electron donating groups such as 4-methoxy and 4-methyl, substrates could give target product with 95% and 90 % yield (Table 4, entries 4-5) respectively. Then, the electron withdrawing groups such as 2- NO_2 and 4-CN groups are considered for reaction. Unfortunately, the reaction couldn't found. In order to get intended yield, the above tested reactions were extended using strong base (andhydrous K_2CO_3), and substrates give targets with 55 % and 60 % yields respectively (Table 4, entries 8[c]- 9[c]). Later, mono-methyl, di-methyl substituted aromatic rings give their respective targets with 85 % and 80 % yields (Tables 4, entries 6-7). Lastly, the substrate aliphatic anilines give target products with good yields (Table 4, entry 10).

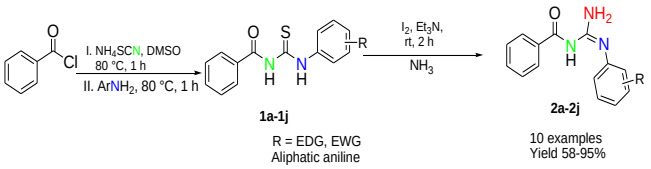
Table 1: Solvent optimization[a]



Entry	Solvent	Yield (%)[b]	
		1a	2b
1	Acetone	80	NR
2	CH_3CN	85	5
3	EtOH	20	NR
4	MeOH	30	NR
5	CH_2Cl_2	30	NR
6	$CHCl_3$	30	NR
7	CCl_4	NR	NR
8	Benzene	NR	NR
9	DMSO	5	90
10	DMF	35	60
11	H_2O	NR	NR
12	-	NR	NR

[a]The reaction used 2 mmol of *benzoyl chloride* and 1 eq. of *ammonium thiocyanate*, *DMSO*, 80°C, *RNH_2 (1 eq)*, 1h, 50 mol% of *iodide*, *Et_3N (1 eq)*, *Aq NH_3 (1 eq)*, [b]Isoated yields

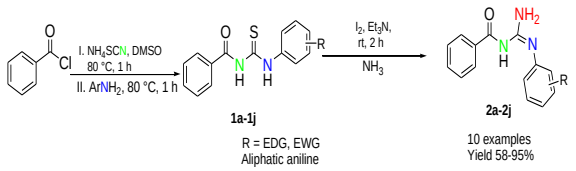
Table 2: Base optimization[a]



Entry	Base	Yield (%)[b]	
		1a	2b
1	Et_3N	10	95
2	Pyridine	10	80
3	NaOAc	20	65
4	$NaHCO_3$	25	50
5	Na_2HPO_4	10	40
6	NaOH	10	20
7	--	NR	NR

[a]The reaction used 2 mmol of *benzoyl chloride* and 1 eq. of *ammonium thiocyanate*, *DMSO*, 80°C, *RNH_2 (1 eq)*, 1h, 50 mol% of *iodide*, *Et_3N (1 eq)*, *Aq NH_3 (1 eq)*, [b]Isoated yields. [c] *K_2CO_3*(1 eq)

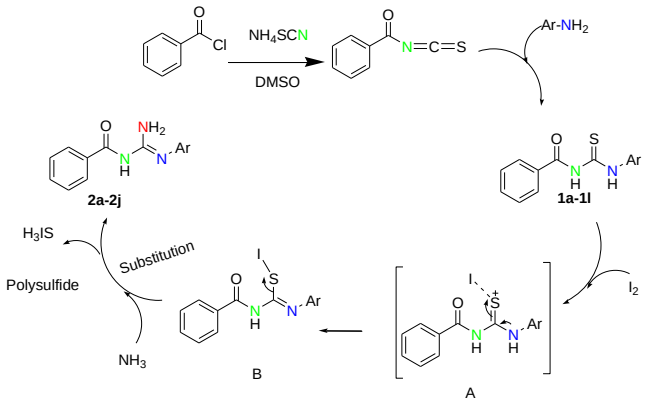
Table 4: Substrate scope of gunylation for the synthesis of N, N' –Disubstituted Guanidines [a]



Entry	Substrate (R)	Product	Yield (%)[b]
1	-C_6H_5	2a	85
2	-C_6H_4-4-Cl	2b	86
3	-C_6H_4-4-F	2c	73
4	-C_6H_4-4-OMe	2d	95
5	-C_6H_4-4-Me	2e	90
6	-C_6H_4-2-Me	2f	85
7	-C_6H_3-2,4-DiMe	2g	80
8[c]	-C_6H_3-4-CN	2h	60
9[c]	-C_6H_4-2-NO_2	2i	55
10	Benzyl	2j	85

[a]The reaction used 2 mmol of *benzoyl chloride* and 1 eq. of *ammonium thiocyanate*, *DMSO*, 80°C, *RNH_2 (1 eq)*, 1h, 50 mol% of *iodide*, *Et_3N (1 eq)*, *Aq NH_3 (1 eq)*, [b]Isoated yields. [c] *K_2CO_3*(1 eq)

Finally, the proposed mechanism for the formation of N, N' –Disubstituted guanidines from benzoyl chloride is shown in **Scheme 1**, which was propose based on experimental evidence. As we mention in **scheme 1**, benzoyl chloride reacts with ammonium thiocyanate in presence of base (amine) and solvent (DMSO) give substituted thioureas (**1a-1j**). Further, it may co-ordinate with Iodine species and remove the proton to give intermediate **B.** The intermediate **B** undergoes desulphurization (H_3IS was formed as by-product and extra sulphur might have converted into as polysulfide) and it give target product (**2a-2j)** via nucleophilic substitution with ammonia.



Scheme 1: Proposed mechanism.

EXPERIMENT

General Procedure for N, N' –Disubstituted Guanidines: To a 25ml round-bottom flask containing DMSO (4-5mL), and NH_4SCN (2 mmol, 152 mg), benzyol chloride (2 mmol, 280 mg) were added at room temperature and the whole reaction mixture was stirred for 1h, at 80 °C. Later, 5mL of respective aniline (2mmol) was added and continued the same process of heating one more hour. TLC (2% ethyl acetate with hexane) was used to monitor the thiourea derivative formation. To this, I_2 (5mole, 249 mg) was added slowly, followed by Et_3N (2mmol, 202 mg) and continued to stir the reaction mixture for 1h at room temperature. A black colour precipitate (H_3IS) was observed and it was settled at the bottom of the round bottom flask with centrifuged for 10 min by using centrifuged machine. Black colour solid precipitate was separated and it was removed. The clear solution now collected and NH_3 (2 mmol, 130 mg) was added slowly. The reaction mixture continued to stirring for 1h at room temperature. The reaction was monitored with TLC (40 % ethyl acetate with hexane). After the final product was obtained, it was washed with water (5mL) and ethyl acetate (10mL). The final crude mixture washed with brine (5mL) and water (5mL) and dried with Na_2SO_4. The residue was purified by silica-gel chromatography to get analytically pure products.

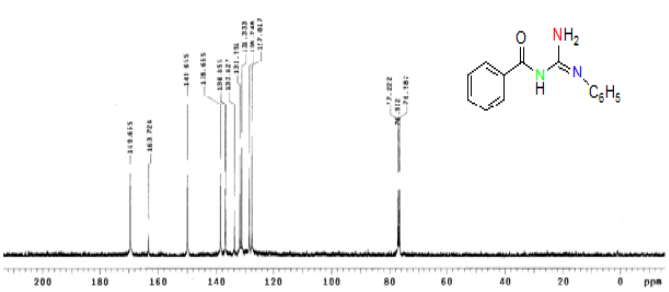


Figure 3 ^{13}C NMR spectrum of N, N' –Disubstituted guanidines (2a)

CONCLUSION

In conclusion, here we developed the synthetic method for the synthesis of of N, N' –Disubstituted guanidines from benzoyl chloride with Iodine as source of catalyst. The reactions are rapid and effortless and were carried out at moderate temperature. All the substrates could give their target products in good to excellent yields.

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