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One pot microwave assisted synthesis of various substituted guanidine derivatives using water as solvent: A green chemistry approach

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ABSTRACT

We are reporting an aqua mediated, one pot microwave assisted synthesis of substituted guanidine derivatives using green chemistry approach. Various substituted guanidine derivatives were prepared by reacting symmetrical and asymmetrical thiourea with different amines under alkaline condition using water as solvent under microwave irradiation (100 W) in moderate yield within 10-95 minutes. All the synthesized compounds were characterized by UV, IR, ^{1}H NMR and Mass spectroscopy.

Keywords: One pot synthesis; Green chemistry; Guanidine derivatives; Microwave irradiation.

INTRODUCTION

The importance of minimizing the impact that chemical processing produces on the environment is growing, with an increased appreciation of the need to reduce pollution and depletion of our finite environmental resources. Optimal use of material and energy and an efficient waste management can be recognized as important factors for environmental protection. In present scenario, industrial chemistry is widely adopting the concept of Green Chemistry to meet the key scientific challenges of protecting human health and the environment while simultaneously achieving commercial profitability [1,2].

Some of the important alternative tools include the use of microwave irradiation as alternative source. The short reaction times and the expanded reaction range provided by MW assisted synthesis make it ideal to meet the increased demands in industry, particularly in the pharmaceutical industry [3]. Microwave synthesis represents major breakthrough in synthetic chemistry methodologies. Conventional heating, long known to be inefficient and time consuming, has been recognized to be creatively limiting as well. Microwave synthesis gives organic chemist more time to expand their scientific creativity, test new theories and develop new processes [4].

The synthesis of guanidine derivatives has also attracted continued research interests in recent years. Many new synthetic methods and guanidinylation reagents for different classes of guanidine compounds have been reported [5-10]. Some efficient microwave assisted methods have also been reported for the synthesis of guanidine derivatives [11,12].

Generally synthesis of substituted guanidine is achieved by two step process. This involves conversion of thiourea to S-methyl derivative followed by neucleophilic substitution of S-methyl by other amines. This requires high boiling solvents like DMSO or DMF. Moreover disadvantage of this method is the generation of noxious sulfur species and

methyl mercaptan by products. Many one pot syntheses to convert thiourea directly into guanidine derivatives have been reported , which uses organic solvents and lead to evolution of dangerous gases [13,14].

Here we are reporting the synthesis of different substituted guanidine derivatives using green chemistry approach. We have modified the synthetic process by direct reaction of thiourea with various amines which removed intermediate step of S-methylation. In addition, evolution of methyl mercaptan could also be avoided. In place of organic solvent, water was used as a solvent [15] and excess of strong base (NaOH) was used to catalyze the reaction and to trap the evolved H_2S gas. In order to reduce reaction time reaction was carried out under microwave synthesizer.

EXPERIMENTAL SECTION

Chemicals and reagents

All the chemicals and solvents used for the syntheses, obtained commercially from Loba company, were of LR grade and used without further purification. Phenyl carbamodithioate was prepared according to the reported procedure [16].

Physical measurements

Thin layer chromatography was performed on aluminum plates precoated with silica gel GF_{254} and spots were visualized under UV light. Melting points of all the compounds were determined in open capillaries and are uncorrected. UV spectra were recorded in methanol on double beam UV-VIS Pharmaspec 1700 Shimadzu spectrophotometer. IR spectra of all compounds were recorded in KBr on FT-IR 8400S Shimadzu spectrophotometer. Mass spectra were recorded on Shimadzu LCMS 2010EV Mass spectrometer.^{1}H NMR spectra were obtained in $CDCl_3$ on Bruker Advance-II at 300 MHz instrument and chemical shift were measured as ppm downfield from TMS used as internal standard.

General synthetic procedure for preparation of symmetrical thiourea (1a and 1b) [17]

To a solution of potassium hydroxide 4 g in ethanol (30 mL) was added aniline or *p*-toluidine (0.2 M) and carbon disulfide (0.33 M). The mixture was refluxed on a heating mental until the crystal start separating out. Excess of organic solvent was removed by distillation under reduced pressure. The residue was filtered, washed with dil. HCl (10% v/v) followed by water. Crude products were recrystallized from ethanol.

N,N'- diphenyl thiourea (1a):
%Yield: 77; mp: 146-148ºC {Reported: 152-154ºC [17]}; MF: $C_{13}H_{12}N_2S$ (228.31)

N,N'-bis(4-methylphenyl)thiourea (1b):
%Yield: 57; mp: 174-176ºC {Reported: 176-178ºC [17]}; MF: $C_{15}H_{16}N_2S$ (256.37)

General procedure for synthesis of asymmetrical thiourea (1c and 1d)

To a solution of methyl phenylcarbamodithioate (0.05 M) in methanol (50 mL), *p*-toluidine or *p*-chloroaniline (0.05 M) was added and refluxed and monitored by TLC to confirm completion of reaction for 24-48 h. Reaction mixture was cooled at 5ºC for 2 h in refrigerator. The solid was filtered and washed with n-hexane, dried under IR lamp and recrystallized from methanol.

1-phenyl-3-*p*-tolylthiourea (1c):
%Yield: 80; mp: 138-141ºC {Reported: 141-142ºC [18]}; MF: $C_{14}H_{14}N_2S$ (242.34)

1-(4-chlorophenyl)-3-phenylthiourea (1d):
%Yield: 30; mp: 148-150ºC {Reported: 151-152ºC [19]}; MF: $C_{13}H_{11}ClN_2S$ (262.76)

General procedure for synthesis of guanidine derivatives:

A mixture of **s**ymmetrical (1a or 1b) or asymmetrical (1c or 1d) thiourea (4 mM), different aliphatic or aromatic or heterocyclic amines (8 mM), 5 mL sodium hydroxide (1N) and 5 mL water was subjected to microwave irradiation in a 150 ml beaker at 100% power (100W) for 10 to 95 minutes. After completion of reaction (monitored using TLC), the mixture was poured on ice-cold water (50 mL). Precipitated crude product was filtered, washed with dil. HCl to remove excess amine, dried and recrystallized from petroleum ether to give designed compounds in moderate yields.

1,2,3-triphenylguanidine (2a):
UV (λ_{max}, Methanol): 268 nm; IR (KBr, cm^{-1}): 3382, 3087, 3016; ^{1}H NMR ($CDCl_3$, δ): 5.50 (s, 1H, NH-Ar), 6.31 (s, 1H, NH-Ar), 7.20-7.43 (m, 15H, Ar-H); MS (ESI): *m/z* 287.9 (M^+).

(E)-1-methyl-2,3-diphenylguanidine (2b):
UV (λ_{max}, Methanol): 240.5 nm; IR (KBr, cm^{-1}): 3423, 3230, 3182, 3062, 2999; ^{1}H NMR ($CDCl_3$, δ): 2.86 (d, 3H, N-CH_3), 4.65 (d, 1H, NH-Ar), 6.31 (s, 1H, NH-Ar), 6.99-7.53 (m, 10H, Ar-H); MS (ESI): *m/z* 225.9 (M^+).

(Z)-4-methyl-N,N'-diphenylpiperazine-1-carboxamidine (2c):
UV (λ_{max}, Methanol): 257 nm; IR (KBr, cm^{-1}): 3390, 3244, 3178, 3053, 2993; ^{1}H NMR ($CDCl_3$, δ): 2.30 (s, 3H, N-CH_3), 2.38 (t, 4H, CH_2-N^4-CH_2), 3.36 (t, 4H, CH_2-N^1-CH_2), 5.50 (s, 1H, NH-Ar), 6.98 (m, 5H, Ar-H), 7.30 (m, 5H, Ar-H); MS (ESI): *m/z* 294.9 (M^+).

(Z)-1-(4-chlorophenyl)-2,3-diphenylguanidine (2d):
UV (λ_{max}, Methanol): 267 nm; IR (KBr, cm^{-1}): 3207, 3118, 3012; MS (ESI): *m/z* 321.9 (M^+), 324 (M^{+2})

(Z)-N,N'-diphenylmorpholine-4-carboxamidine (2e):
UV (λ_{max}, Methanol): 257.5 nm; IR (KBr, cm^{-1}): 3359, 3118, 3024; MS (ESI): *m/z* 281.9 (M^+).

(Z)-1,2-diphenyl-3-(5H-tetrazol-5-yl)guanidine (2f):
UV (λ_{max}, Methanol): 246 nm; IR (KBr, cm^{-1}): 3423, 3087, 3064; MS (ESI): *m/z* 279.2 (M^+).

(E)-1-isopropyl-2,3-diphenylguanidine (2g):
UV (λ_{max}, Methanol): 249 nm; IR (KBr, cm^{-1}): 3425, 3184, 3066; MS (ESI): *m/z* 254.1 (M^+).

(E)-1-butyl-2,3-diphenylguanidine (2h):
UV (λ_{max}, Methanol): 256 nm; IR (KBr, cm^{-1}): 3213, 3047, 2985; MS (ESI): *m/z* 268.9 (M^+).

(Z)-N,N'-diphenylpiperidine-1-carboxamidine (2i):
UV (λ_{max}, Methanol): 256.5 nm; IR (KBr, cm^{-1}): 3392, 3245, 3172; MS (ESI): *m/z* 280.4 (M^+).

(Z)-1,2-diphenyl-3-p-tolylguanidine (2j):
UV (λ_{max}, Methanol): 267.5 nm; IR (KBr, cm^{-1}): 3382, 3209, 3116; MS (ESI): *m/z* 302.9 (M^+).

(Z)-4-methyl-N,N'-di(p-tolyl)piperazine-1-carboxamidine (2k):
UV (λ_{max}, Methanol): 265 nm; IR (KBr, cm^{-1}): 3392, 3245, 3130; MS (ESI): *m/z* 323.9 (M^+).

(E)-1-butyl-2,3-di(p-tolyl)guanidine (2l):
UV (λ_{max}, Methanol): 252 nm; IR (KBr, cm^{-1}): 3423, 3180, 3066; MS (ESI): *m/z* 294.7 (M^{-1}).

(E)-1-phenyl-2,3-di(p-tolyl)guanidine (2m):
UV (λ_{max}, Methanol): 263 nm; IR (KBr, cm^{-1}): 3207, 3033, 3012; MS (ESI): *m/z* 316.9 (M^+).

(E)-1-butyl-3-phenyl-2-p-tolylguanidine (2n):
UV (λ_{max}, Methanol): 256 nm; IR (KBr, cm^{-1}): 3392, 3245, 3016; MS (ESI): *m/z* 282.6 (M^+)

(Z)-1-phenyl-3-(5H-tetrazol-5-yl)-2-p-tolylguanidine (2o):
UV (λ_{max}, Methanol): 262 nm; IR (KBr, cm^{-1}): 3423, 3245, 3064; MS (ESI): *m/z* 294.8 (M^+).

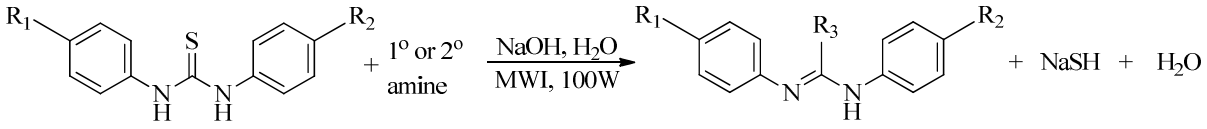
(Z)-N'-(4-chlorophenyl)-4-methyl-N-phenylpiperazine-1-carboxamidine (2p):
UV (λ_{max}, Methanol): 241 nm; IR (KBr, cm^{-1}): 3392, 3245, 3051; MS (ESI): *m/z* 329.9 (M^+).

(E)-1-butyl-2-(4-chlorophenyl)-3-phenylguanidine (2q):
UV (λ_{max}, Methanol): 257.5 nm; IR (KBr, cm^{-1}): 3207, 3116, 3012; MS (ESI): *m/z* 301.8 (M^+), 304 (M^{+2}).

RESULTS AND DISCUSSION

Synthetic approach

Targeted compounds were synthesized in moderate yield under microwave irradiation by reacting different symmetrical and asymmetrical thiourea with different types of amines using water as a solvent. The synthetic route is shown in Scheme 1.



1a-1d **2a-2q**

1a: R_1= -H, R_2= -H
1b: R_1= -CH_3, R_2= -CH_3
1c: R_1= -H, R_2= -CH_3
1d: R_1= -H, R_2= -Cl

2a: R_1= -H, R_2= -H , R_3= -NHC_6H_5
2b: R_1= -H, R_2= -H , R_3= -$NHCH_3$
2c: R_1= -H, R_2= -H , R_3= N-methylpiperazine
2d: R_1= -H, R_2= -H , R_3= 4-Cl-C_6H_4-NH
2e: R_1= -H, R_2= -H , R_3= morpholine-
2f: R_1= -H, R_2= -H , R_3= 5-amino tetrazole
2g: R_1= -H, R_2= -H , R_3= $NHCH(CH_3)_2$
2h: R_1= -H, R_2= -H , R_3= C_6H_4-NH,
2i: R_1= -H, R_2= -H , R_3= piperidine

2j: R_1= -H, R_2= -H , R_3= 4-CH_3-C_6H_4-NH,
2k: R_1= -CH_3, R_2= -CH_3 , R_3= N-methylpiperazine
2l: R_1= -CH_3, R_2= -CH_3 , R_3= -NHC_4H_9
2m: R_1= -CH_3, R_2= -CH_3 , R_3= -NHC_6H_5
2n: R_1= -H, R_2= -CH_3 , R_3= -NHC_4H_9
2o: R_1= -H, R_2= -CH_3 , R_3= 5-amino tetrazole
2p:R_1= -H, R_2= -Cl , R_3= N-methylpiperazine
2q:R_1= -H, R_2= -Cl , R_3= -NHC_4H_9

Scheme 1 Synthetic route of compounds **2a-2q**

The following parameters were tested to optimize the reaction condition.

Role of alkali:
Thiourea reacted with different amine in the presence NaOH and KOH under microwave irradiation to obtain guanidine derivatives. With KOH reaction time was significantly increased as compared to NaOH while % yield remained almost same. (Table 1)

Table: 1 Comparison of reaction time and yield with different alkali

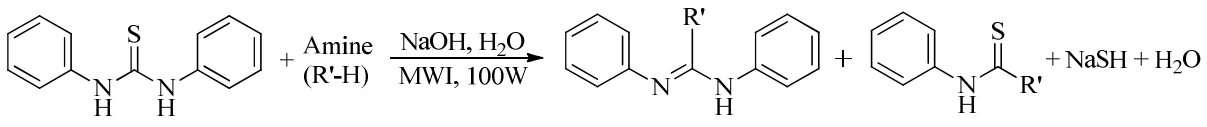
Compound	Types of alkali	Reaction time (minutes)	% Yield
2c	NaOH	10	67
2c	KOH	17	64

Exposure time:
Longer exposure times under microwave irradiation in presence of alkali resulted in to degraded product. Experiments performed at higher output power and for longer exposure time were unsuccessful, yield was not improved and decomposition products were obtained.

Temperature:
At higher temperature reaction time was reduced, but at the same time degradation of the product was also observed.

Types of amines:
All substituted amines did not react smoothly in similar conditions. Secondary amines reacted faster than primary amines. Primary aromatic amines having electron withdrawing group required more time and gave low yield.

Transamination:
In certain cases, transamination reaction was observed in which excess of primary aliphatic amines or secondary heterocyclic amines displaced aniline of symmetrical thiourea to give asymmetric thiourea as a side product (Scheme 2). Transamination reaction was not observed in case of all other thiourea.



R'= -$NHCH_3$, N-methylpiperazinyl, -$NHCH(CH_3)_2$, Morpholinyl, -NHC_4H_9,, Piperidinyl.

Scheme 2 Observed transamination reaction

All the newly synthesized compounds are white solid and air-stable except compound 2p which is semisolid and hygroscopic. They are insoluble in non-polar solvent and soluble in methanol and dichloromethane. The physicochemical data of all the newly synthesized compounds are summarized in Table 2.

Table 2 Physicochemical data of synthesized compounds (2a-2q)

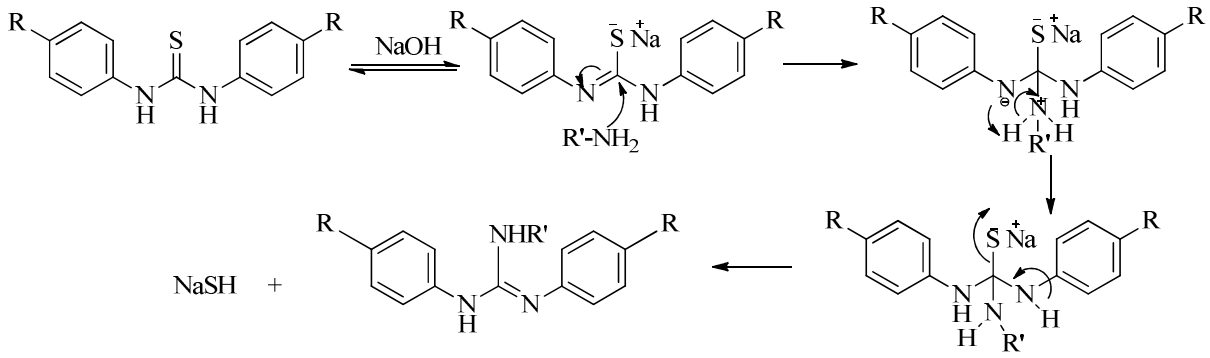
Compds	Reaction Time (min)	%Yield[#]	Melting Point (°C)	Reported mp (°C)	R_f[*]	Molecular Formula	Molecular Weight
2a	25	65	141-142	143-144 [20]	0.47	$C_{19}H_{17}N_3$	287.36
2b	20	47	105-107	108-109 [21]	0.43	$C_{14}H_{15}N_3$	225.13
2c	10	67	111-115	---	0.44	$C_{18}H_{22}N_4$	294.40
2d	45	33	130-132	133-135 [20]	0.40	$C_{19}H_{16}ClN_3$	321.80
2e	20	61	172-175	178-179 [22]	0.48	$C_{17}H_{19}N_3O$	281.35
2f	40	68	115-117	---	0.42	$C_{14}H_{13}N_7$	279.30
2g	80	36	112-114	113-115 [23]	0.42	$C_{16}H_{19}N_3$	253.34
2h	48	52	145-147	150-152 [10]	0.46	$C_{17}H_{21}N_3$	267.37
2i	22	59	145-149	---	0.46	$C_{18}H_{21}N_3$	279.38
2j	40	52	98-99	102-103 [20]	0.47	$C_{20}H_{19}N_3$	301.38
2k	20	47	82-84	---	0.44	$C_{20}H_{26}N_4$	322.45
2l	50	41	135-137	---	0.40	$C_{19}H_{25}N_3$	295.42
2m	55	55	105-107	110-112 [24]	0.40	$C_{21}H_{21}N_3$	315.41
2n	95	51	142-145	---	0.40	$C_{18}H_{23}N_3$	281.40
2o	50	57	170-175	---	0.40	$C_{15}H_{15}N_7$	293.33
2p	22	52	Hygroscopic	---	0.44	$C_{18}H_{21}ClN_4$	328.84
2q	60	47	142-145	---	0.41	$C_{17}H_{20}ClN_3$	301.81

[#] Yield refers to pure isolated product; [*]Mobile Phase: Ethyl acetate: Methanol (6:4)

Characterization

The characterization of synthesized guanidine derivatives have been achieved by satisfactory physical methods and spectral (UV, IR, ^{1}H NMR and mass) studies. UV spectra of all the synthesized compounds showed λ_{max} in the range of 240-268 nm. The IR spectrum of all the compounds shows the characteristic stretching of the secondary amino in the region of the 3400-3200 cm^{-1}. The spectrum of 2c also shows the characteristic multiple peaks of CH_2 stretching of N-methylpiperazine at 2800-3000 cm^{-1}. Further, spectrum also shows characteristic multiple peaks in aromatic region due to presence of aromatic rings. Compound 2c analyzed for ^{1}H NMR have showed multiplets near about δ 6 to 7.5 corresponding to aromatic protons. The secondary amino proton of the carboxamidine group resonates at around δ 5.5 as a singlet. Eight protons of N-methylpiperazine resonate at around δ 3.45 and δ 2.40 as triplets. Three protons of N-methyl group resonate at around δ 2.30 as sharp singlet. Mass spectra were taken in positive mode, hence shows characteristic M^+ peak. The mass spectrum also supports the proposed molecular formula of the synthesized compound. Compounds containing chlorine atom on aryl rings shows M^+ and M^{+2} peak in ratio of 3:1 due to isotopic abundance.

The probable mechanism for the synthesis of guanidine derivatives is shown in scheme 3. Alkaline condition was required to catalyze the reaction and trap *in-situ* produced hydrogen sulphide gas.



Scheme 3 Reaction mechanism for synthesis of guanidine derivatives

CONCLUSION

A new, aqua mediated, one-pot microwave assisted method has been developed to synthesize substituted guanidine derivatives using green chemistry approach. Moderate yield, shorter reaction time, easy work up procedure and trapping of dangerous H_2S gas within reaction mixture are important features of the developed method.

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