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Simple and efficient methodology to prepare guanidines from 1,3-disubstituted thioureas

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ABSTRACT

Guanidinium salts were efficiently prepared by desulfurization reactions of 1,3-disubstituted thioureas using $KICl_2$ in the presence of amines. The reactions were successfully carried out at room temperature, in short reaction time, affording cyclic/acyclic guanidines (hydrochloride salts) in high chemical yields.

Guanidines are versatile organic compounds widely described by their applications[1] as strong organobases, organocatalysts, ancillary ligands, anion hosts, fluorescent molecular probes, ionic liquids, and molecular transporters. It has been reported that guanidine-containing molecules display a range of biological activities, such as anticancer,[2a] antibiotic,[2b] antiparasitic,[2c] antiprotozoal,[2d] antifungal,[2e] antiviral,[2f–i] anti-inflammatory,[2j] and others.[2k] Moreover, compounds with guanidine functionality may exhibit activities as Ca^{+2} channel blockers,[2l] apoptosis-inducing action[2m] and their salts have shown prominent ability in binding oxoanions,[1h,i] being applied in biological studies of molecular recognition.[3]

Due to the importance of cyclic/acyclic guanidines, several synthetic methods have been developed and described in the literature. Typical methods involve the reaction between primary and secondary amines (or ammonia) and a guanylating agent, such as: *N*,*N*′,*N*″-tri-Boc-guanidine, benzotriazole-1-carboxamidines, chloroformamidines, cyanamides, carbodiimides, triflylguanidines,pyrazole-1-carboximidamides, dichloroisocyanides, S-alkylisothiouronium salts, and isothioureas/thioureas.[1b,4]

Recently, bicyclic guanidines were prepared by Walker and Madalengoitia by reactions between aza-norbornenes and carbodiimides (in situ generated), through a 1,3-diaza-Claisen rearrangement.[5] Yamamoto et al. reported a one-pot synthesis of N,N′,N″-trisubstituted guanidines via a Tiemann rearrangement involving the reaction of α-chloroaldoxime *O*-methanesulfonates with alkyl amines.[6] Akamanchi and Dangate disclosed a one-pot oxidative condensation procedure using *o*-iodoxybenzoic acid and trimethylamine or ammonia as base, for the synthesis of guanidines from the reaction between both 1,3-disubstituted thioureas and amines/ammonia.[7] Apart from that, in a recent work, Looper and co-workers revealed the synthesis of bicyclic guanidines highly substituted, via a cascade silver (I)-catalyzed hydroamination/Michael addition sequence.[8]

The use of thioureas as starting material, to afford guanidines, constitutes a simple and good strategy. The advantage comes from the facile preparation of thioureas, usually obtained by the reaction of amines (aliphatic/aryl) and corresponding isothiocyanates.[9]

Guanidines are synthesized from thioureas via desulfurization reactions, mediated by reagents such as mercuric (II) chloride,[10a] *N*-iodosuccinimide,[10b] bismuth nitrate pentahydrate,[10c] Mukaiyama's reagent,[10d,e] iodine,[10f] and others.[1b,4a,d] In order to overcome drawbacks presented by classical methods such as longer reaction times, lower reaction yields and toxic or expensive reagents usage, more benign[11] and catalytic[12] approaches to prepare guanidines have been developed.

Herein, we report an efficient and straightforward method to obtain guanidinium salts **1** from 1,3-disubstituted thioureas **2** using potassium dichloroiodate ($KICl_2$) as desulfurization agent, in the presence of an amine (Route A: *Guanylation of thioureas*—Scheme 1).

$KICl_2$[13a] is a mild oxidizing agent, convenient for iodochlorination of multiple bonds[13b] and as an iodinating agent for

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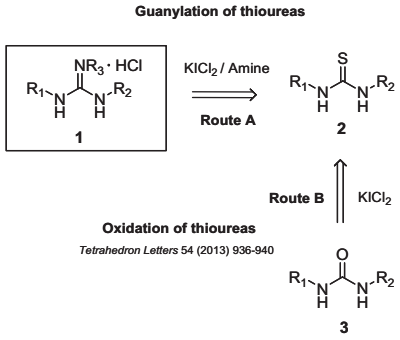


Scheme 1. Guanylation (Route A) and oxidation/iodination (Route B)[14] of thioureas with the use of $KICl_2$.

(heterocyclic) aromatic compounds.[13a,c,14] Aqueous solution of $KICl_2$ can be easily prepared in the laboratory, as described by Larsen et al.,[13a] and it is stable at room temperature without any appreciable concentration loss for a considerably long period (long shelf life >3 years).

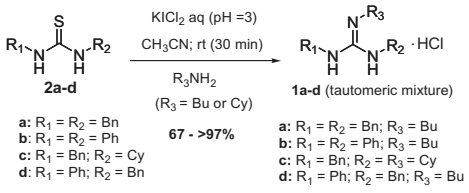
Recently, our group disclosed an efficient reaction protocol for the synthesis of substituted ureas via treatment of thioureas with aqueous potassium dichloroiodate ($KICl_2$).[14] By tuning the reaction condition, thioureas bearing activated *N*-aryl substituents may undergo selective oxidation or sequential oxidation/iodination, forming iodoaryl substituted ureas in the latter case (Route B[14]: *Oxidation of thioureas*—Scheme 1).

Initially, we investigated the preparation of acyclic guanidines **1a–d** (Scheme 2).[15] Thioureas **2a–d** were synthesized from the reaction of benzyl (BITC) or phenylisothiocyanate (PITC) and corresponding amines, according to the literature.[9]

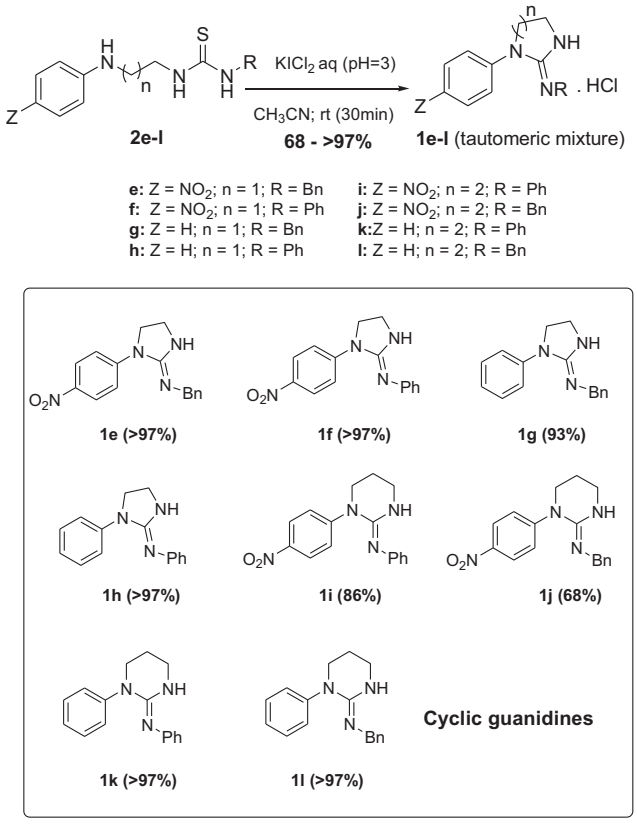
Guanylation reactions were carried out treating the thiourea/CH_3CN solutions with excess of $KICl_2$ (10 equiv; pH = 3), in the presence of butyl or cyclohexylamine. The reaction mixtures were kept at room temperature for about 30 minutes, treated with saturated aqueous $NaHSO_3$ solution, affording after isolation guanidinium salts in moderate to high yields (**1a**: >97%; **1b**: 67%; **1c**: 87%, **1d**: 90%)—Scheme 2.

Attempts to use arylamines (lower nucleophilicity), ammonium hydroxide or ammonium acetate were carried out, however guanylation was not effective and the products were obtained in very low yields. The guanidines **1a–d** were characterized by IR, NMR and HRMS. The absence of signals around 179–183 ppm (C=S) and the observation of signals at 155–160 ppm (C=NR) in ^{13}C NMR, besides the occurrence of broad absorption bands in IR spectra indicate the formation of guanidine moiety. It may be *worth mentioning* that acyclic guanidines, even on salt forms, have low stability and high tendency to hydrolyze towards their corresponding ureas, whose signals can be observed in some NMR spectra.

We have also investigated the preparation of cyclic guanidines employing the same desulfurization methodology ($KICl_2$; pH = 3), with no addition of an external amine (Scheme 3).[15] In these cases, diamines-derived thioureas **2e–l** were synthesized from aryldiamines, obtained by a methodology recently developed in our laboratory (copper oxide-catalyzed C—N cross-coupling reaction).[16]



Scheme 2. Preparation of acyclic guanidinium salts **1a–d**.

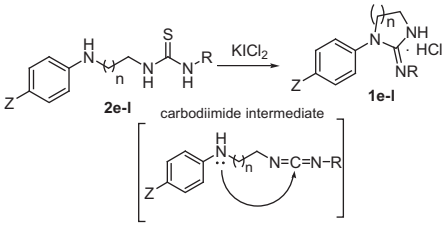


Scheme 3. Synthesis of cyclic guanidines **1e–l** from diamines-derived thioureas.

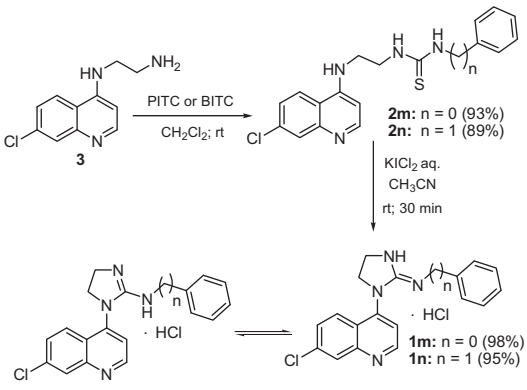
Regardless of the formed ring size, cyclic guanidines **1e–l** were also obtained in good to high chemical yields (68–>97%), with no need of purification. They could be distinguished (NMR) from their corresponding thioureas through their aliphatic methylene signals ($NCH_2(CH_2)_nCH_2N$). In ^1H NMR spectra, it was observed a different pattern for the signals of guanidines and thioureas, with all guanidines-methylene signals occurring in higher chemical shifts than the same signals in corresponding thioureas.[17]

Although no mechanistic studies have been performed, the formation of a *carbodiimide* intermediate promoted by $KICl_2$ could be implied to justify the guanidine moieties obtained (Scheme 4).[18]

Motivated by the search for new cores of polyamine-containing molecules of medicinal interest, we investigated the applicability of our new protocol to prepare 7-chloro-4-aminoquinoline-derived guanidines. The quinoline scaffold is present in several pharmacologically active synthetic/natural compounds.[19] Structure–activity relationship studies on antimalarial compounds suggest that 7-chloro-4-aminoquinoline skeleton is obligatory for the activity.[19a] It is also interesting to note that simple structure modifications have led to potent activity-bearing compounds against chloroquine-resistant strains (CQ-R) and some of these molecules are in clinical trials.[19a] With these facts in mind, we synthesized



Scheme 4. Proposed carbodiimide intermediate for synthesis of cyclic guanidines.



Scheme 5. Synthesis of guanidines derived from 7-chloro-4-aminoquinoline.

the key intermediates **2m–n** (Scheme 5) from the reaction of phenylisothiocyanate or benzylisothiocyanate with 4-(2-aminoethyl)amino-7-chloro-quinoline (**3**), prepared according to the literature.[19g]

The target cyclic guanidines **1m–n** were obtained in high yields (95–98%), using the same reaction conditions reported in Schemes 2 and 3 ($KICl_2$; rt; 30 min).[15] They were characterized by spectroscopic methods and their spectra compared to corresponding (thiourea) urea spectra, in order to certify the absence of this compound in the guanidine–tautomeric mixture. The guanidines synthesized are currently being screened for pharmacological activity.

In summary, $KICl_2$ was found for the first time to be useful for the construction of cyclic and acyclic guanidinium salts from 1,3-disubstituted thioureas. This simple protocol presents advantages such as short reaction time, high yields of products and mild reaction conditions, which makes it very useful and an attractive process for the synthesis of highly targeted compounds. In addition, the use of aqueous $KICl_2$ for the desulfurization of thioureas offers advantages in terms of safety and ease of use in comparison to other methods that often employ toxic and hazardous materials or expensive reagents usage.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.107.

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15. *General procedure for synthesis of guanidines* **1a–n**: To a solution of thiourea **2a–n** (0.5 mmol) in 5 mL of acetonitrile was added 1.3 mL (10 equiv) of an aqueous solution of potassium dichloroiodate (~2 M; pH = 3) and 0.5 mmol of butyl or cyclohexylamine (acyclic guanidines) or no external amine addition (cyclic guanidines). The mixture was stirred at room temperature for 30 min. Then, the reaction was quenched with saturated aqueous $NaHSO_3$ (15 mL). The aqueous mixture was extracted with ethyl acetate (4 × 10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give the desired product. *N,N′-dibenzyl-N″-butylguanidine hydrochloride* (**1a**). Pale yellow solid; IR (KBr): 3478, 3353, 3027, 2874, 1626, 1572, 1246, 750, 696 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 10H), 5.21 (br t, 2H), 4.31 (d, *J* = 5.8 Hz, 4H), 2.93 (t, *J* = 7.7 Hz, 2H), 1.80–1.60 (m, 2H), 1.47–1.26 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0; 139.1; 128.8; 127.4; 127.3; 44.5; 40.1; 29.3; 19.9; 13.6; HRMS-ESI: *m/z* $[M+H]^+$ calculated for $C_{19}H_{26}N_3$: 296.2121; found: 296.2120. *N-(1-(4-nitrophenyl)imidazolidin-2-ylidene)(phenyl) methanamine hydrochloride* (**1e**). Yellow solid; IR (KBr): 3258, 3040, 1660, 1600, 1545, 1504, 1321, 1111, 848, 749, 700 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ = 9.0 (br s, 2H), 8.36 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.38–7.28 (m, 5H), 4.48 (s, 2H), 4.23 (t, *J* = 8.4 Hz, 2H), 3.79 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 155.8; 145.2; 142.7; 136.3; 128.4; 127.5; 127.1; 125.2; 125.0; 50.8; 46.0; 40.7; HRMS-ESI: *m/z* $[M+H]^+$ calculated for $C_{16}H_{17}N_4O_2$: 297.1346; found: 297.1347.
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17. Comparison of NMR spectra of analogues ureas (standard compounds) were carried out in order to certify their absence in the guanidine tautomeric mixtures.
18. Acyclic guanidines should also be formed from a corresponding carbodiimide intermediate. There is no limitation for the synthesis of analogues cyclic guanidines (**1e–l)** containing electron rich N-aryl rings.
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