Tetrahedron Letters 54 (2013) 936–940

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The use of aqueous potassium dichloroiodate for the synthesis of ureas

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ARTICLE INFO

Article history:
Received 12 November 2012
Revised 3 December 2012
Accepted 5 December 2012
Available online 21 December 2012

Keywords:
Ureas
Potassium dichloroiodate
Oxidation
Halogenation

ABSTRACT

We report a straightforward and efficient reaction protocol for the syntheses of substituted ureas via treatment of thioureas with aqueous potassium dichloroiodate ($KICl_2$). By tuning the reaction condition, thioureas bearing activated *N*-aryl substituents may undergo either selective oxidation or sequential oxidation and iodination, forming iodoaryl ureas in the latter case.

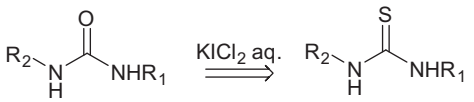
Mild and efficient methods for the synthesis of ureas have attracted a widespread interest over the years due to their diverse biological activities. Substituted ureas have been shown to have a potent inhibiting effect on HIV-1 protease enzyme,[1] as well as anticancer,[2] anticonvulsive and sedative-hypnotic activities.[3] Extensive application as agrochemicals, resin precursors and synthetic intermediates[4] has also been reported. In continuation to our research efforts devoted to the development of practical and economical organic processes,[5] herein we report an efficient and facile method for the synthesis of symmetrical and unsymmetrical ureas, bearing aryl and alkyl groups, by means of clean oxidation of the corresponding thioureas. By our approach, based upon the use of potassium dichloroiodate ($KICl_2$),[6] *N*-aryl thioureas may also undergo sequential oxidation and aryl group iodination in situ (Scheme 1). One-pot syntheses, which may involve multi-step procedures or multiple reactions in the same pot, are methodologies of choice in contemporary organic synthesis, providing, in many cases, the target compounds in high overall yields with low cost.

A number of reports in the literature deal with the oxidation of thioureas. Depending on the oxidizing agent, reaction conditions and the substitution pattern of thioureas, a variety of products may be formed, such as ureas and disulfides. Oxidative cyclization or degradation may also occur.[7]

Mishra and co-workers[7] have recently reviewed the oxidation reactions of thiourea and substituted thioureas by different reagents such as bromine water (Br_2/H_2O), bromate (BrO_3^-), peroxide in alkali, peroxide–hypochloride–bicarbonate ($H_2O_2/NaOCl/HCO_3^-$), potassium monopersulfate ($KHSO_5$) in phosphate buffer, Fe (V or VI), cetyltrimethyl–ammonium dichromate (CTADC), etc. Reagents such as lead tetraacetate,[8] manganese dioxide,[9] manganese (III) acetate[10] and tetrabutylammonium periodate[11] have also been employed. To the best of our knowledge, the reaction of thioureas with aqueous $KICl_2$ has not been previously explored.

$KICl_2$[6] is a mild oxidizing agent, convenient for iodochlorination of multiple bonds[12] and as an iodinating agent for (heterocyclic) aromatic compounds.[13] Recently, the use of related reagents, such as benzyl-triethylammonium[14]/benzyl-trimethylammonium dichloroiodate[15] and tetramethylammonium dichloroiodate[16] has been employed in aromatic iodination, but none of these studies have investigated the use of substrates functionalized with ureido/thioureido substituents.

The aqueous solution of $KICl_2$ (~2 N) can be easily prepared in the laboratory, as described by Larsen and co-workers,[6a] and it is stable at room temperature without any appreciable concentration loss for a considerably long period.



(R_1= alkyl, Ar, **I-Ar**) (R_1= alkyl, Ar and R_2= alkyl)

Scheme 1. Oxidation of thioureas with $KICl_2$ aq.

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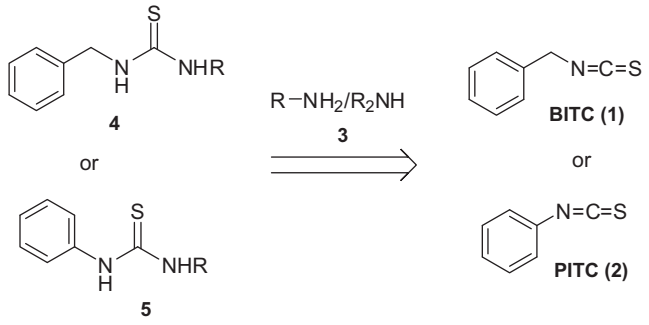
http://dx.doi.org/10.1016/j.tetlet.2012.12.045



Scheme 2. Synthesis of thioureas from BITC or PITC.

Initially, several alkyl and aryl thioureas **4** and **5** were prepared by the reaction of their corresponding amines and benzylisothiocyanate (**1**:BITC) or phenylisothiocyanate (**2**:PITC), according to the literature (Scheme 2).[5,17]

The reactions of thioureas **4** or **5** with excess of $KICl_2$ (10 equiv) were run at rt (method A) or under reflux (method B). We observed that both aryl and alkyl thioureas led to their respective ureas **6** or **7**, in high yields, when the reaction was maintained at rt, for 30 min (Scheme 3; Table 1—entries 1–3, 5–15). The reactions were complete in all cases. IR and ^{13}C NMR data confirmed the formation of ureas. On the other hand, when aryl thioureas **4e**, **4g**, **5a**–**b** and **5d** were treated by the same reagent, under reflux for 1.5 h (method B), the formed ureas could be further iodinated in situ to afford ureas **8**–**12** (Table 1). ^{13}C NMR data clearly confirmed the iodine atom introduction (δ_{C-I} = 83–85 ppm contrasting with the original δ_{C-H} = 121–122 ppm).

It is important to note that the benzyl group in 1,3-dialkyl-thioureas **4a** and **4b** was not iodinated when their reactions were maintained at reflux for longer periods of time (5 h) (Table 1, entries 16 and 17). We have also investigated the possibility of polyiodinated products. However, when 1-alkyl-3-phenyl-thiourea **5b** was maintained under reflux for a longer period (7 h), the same monoiodinated urea **9** was still obtained (Table 1, entry 19—B[c]).

The presence of an activated aryl group, as in thiourea **4h**, led to a mixture of iodinated products when the reaction was realized under method B (Table 1, entry 23).[15c] On the other hand, when the same thiourea was subjected to method A, pure non-iodinated urea **6h** was obtained in good yield (Table 1, entry 8).

These protocols proceed with high selectivity, showing the importance of electronic effects upon these reactions using this technique. Most of the produced ureas were insoluble after addition of saturated aqueous $NaHSO_3$ solution, during the work up. Therefore, they were easily isolated by a simple vacuum filtration, without the need of purification.

Further experiments were carried out to expand the scope of the methodology. Trisubstituted thioureas (**4j**–**k**, **5j**–**k**) as well as other 1,3-*dialkyl* (**4a**–**c**) and 1-*alkyl*-3-*aryl* (**4e**–**i**, **5a**–**b**) disubstituted thioureas led to good/high yields of the expected products, according to the chosen protocol (method A or B). However, as a limitation of this methodology, the oxidation of 1,3-*diaryl-thioureas* (ex. **5e**, entry 25) led to mixtures of iodinated products even when method A was applied. We have also performed studies with the *mono-substituted* thioureas **4d** and **5d**, under both conditions (method A or B). The phenyl thiourea **5d** underwent efficient one-pot oxidation and iodination to urea **12**, via protocol B (85%, entry 24). Conversely, the reactions of **4d** via method A or B and the reaction of **5d** via method A led to a mixture of unidentified products.

The oxidation/iodination of thioureas was successfully scaled-up to afford 2–4 mmol of *N*-phenyl-*N*′-butylurea (**7a**, 85%) and *N*-(*p*-iodophenyl)-*N*′-butylurea (**8**, 83%).

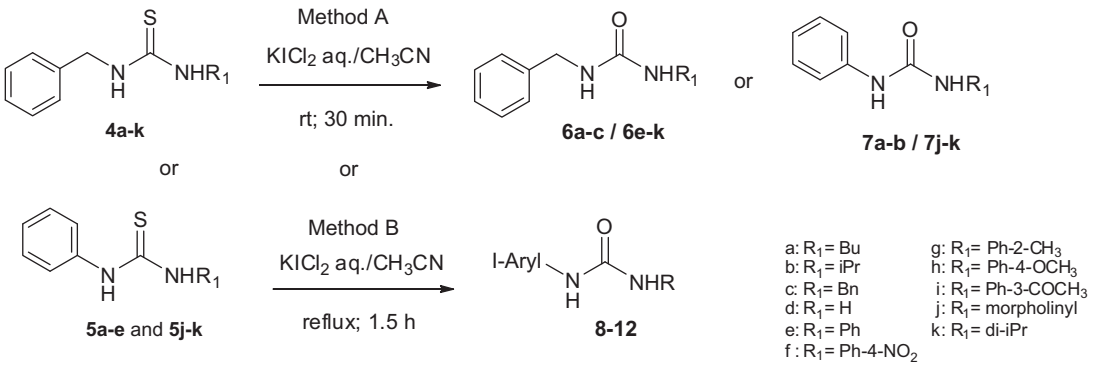
In summary, we have developed a simple procedure for the synthesis of a variety of alkyl, aryl and iodinated aryl ureas. Most products were obtained in excellent yields, not requiring purification. Contrary to the present study, most previous works focused on the reactions of thiourea itself or *N*-aryl thioureas. In a number of cases, the developed procedures intended the degradation (desulfurization) of such compounds for detoxification purposes.[7] Finally, besides allowing two sequential in situ transformations with quite a broad scope, gratifyingly, the present protocol has the advantage of being metal-free.

General methods

Commercially reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 200 MHz spectrometer using DMSO-d_6 as solvent. Standard Bruker software was used throughout. Chemical shifts are given in ppm (δ scale) and coupling constants (J) are given in hertz. The IR spectra were obtained on a Nicolet Magna-IR 760 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Bruker microTOF II mass spectrometer using ESI.

Experimental procedures

General method A: To a solution of thiourea **4** or **5** (0.4 mmol) in 4 ml of acetonitrile was added 2 ml (10 equiv) of an aqueous solution of potassium dichloroiodate ($KICl_2$: ~2 N).[6b] The mixture was stirred at room temperature for 30 min. Then the reaction was quenched with saturated aqueous $NaHSO_3$ (10 ml). The precipitated product was filtered, not needing further purification. When the product did not precipitate, the aqueous mixture was extracted with dichloromethane, dried over anhydrous Na_2SO_4,



Scheme 3. Synthesis of ureas with the use of aqueous potassium dichloroiodate.

Table 1
Preparation of ureas with $KICl_2$ aq

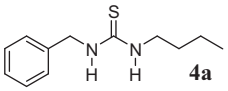
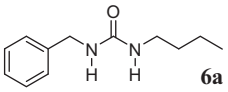
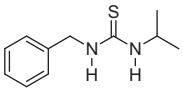
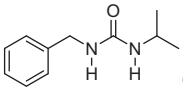
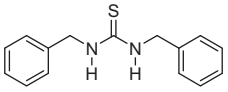
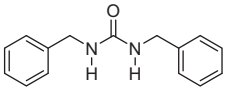
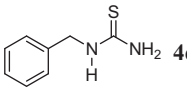
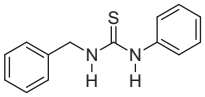
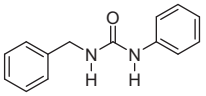
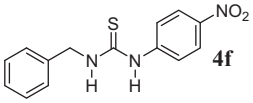
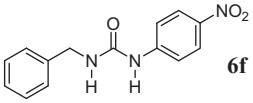
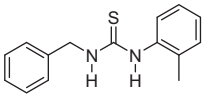
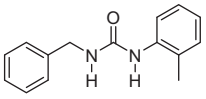
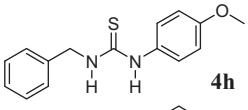
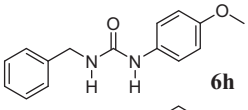
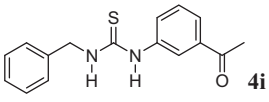
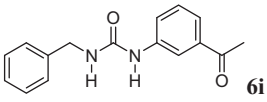
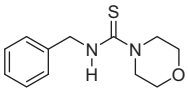
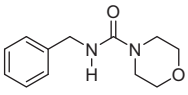
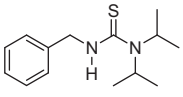
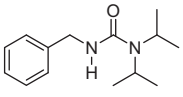
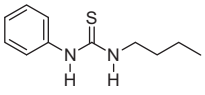
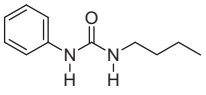
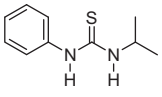
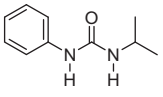
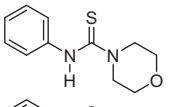
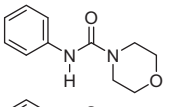
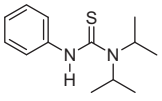
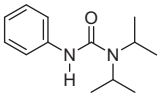
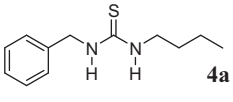
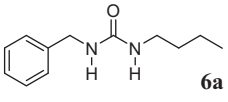
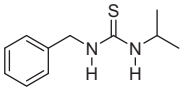
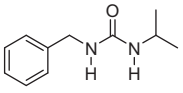
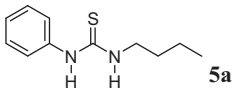
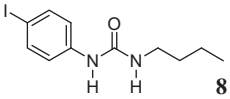
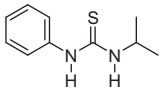
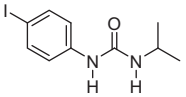
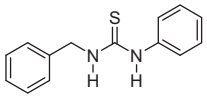
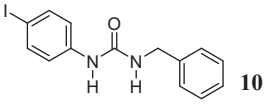
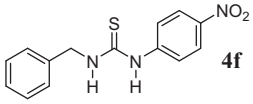
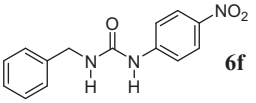
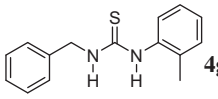
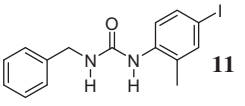
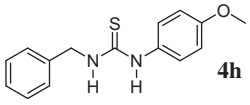
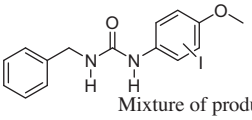
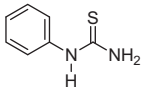
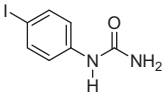
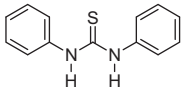
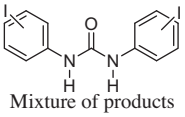
Entry	Thiourea	Method	Product[a]	Isolated yield (%)
1	 **4a**	**A**	 **6a**	>99
2	 **4b**	**A**	 **6b**	91
3	 **4c**	**A**	 **6c**	97
4	 **4d**	**A** or **B**	Mixture of products	–
5	 **4e**	**A**	 **6e**	89
6	 **4f**	**A**	 **6f**	>99
7	 **4g**	**A**	 **6g**	>99
8	 **4h**	**A**	 **6h**	77
9	 **4i**	**A**	 **6i**	>99
10	 **4j**	**A**	 **6j**	>99
11	 **4k**	**A**	 **6k**	>99
12	 **5a**	**A**	 **7a**	89
13	 **5b**	**A**	 **7b**	95
14	 **5j**	**A**	 **7j**	90
15	 **5k**	**A**	 **7k**	94
16	 **4a**	**B**[b]	 **6a**	>99
17	 **4b**	**B**[b]	 **6b**	98

Table 1 (*continued*)

Entry	Thiourea	Method	Product[a]	Isolated yield (%)
18	 **5a**	**B**	 **8**	83
19	 **5b**	**B**(**B**[c])	 **9**	>99 (95[c])
20	 **4e**	**B**	 **10**	91
21	 **4f**	**B**	 **6f**	91
22	 **4g**	**B**	 **11**	73
23	 **4h**	**B**[d]	 Mixture of products	–
24	 **5d**	**B**	 **12**	85
25	 **5e**	**B**	 Mixture of products	–

[a] Products were characterized by physical and spectroscopic methods.
[b] Reflux time: 5 h.
[c] Reflux time: 7 h.
[d] 25 equiv of $KICl_2$ aq was used.

filtered and concentrated under reduced pressure to give the pure product.

General method B: The same reaction mixture employed in method A was heated to reflux for 1.5 h. The same work up followed.

N-Benzyl, N′-butylurea (**6a**).[18a] White solid; mp 96–97 °C, (Lit, 98 °C); IR (KBr): 3339, 2954, 2928, 1626, 1594, 1454, 1271, 696 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ = 7.35–7.20 (m, 5H), 6.24 (br t, 1H), 5.88 (br t, 1H), 4.17 (d, J = 6.1 Hz, 2H), 2.98 (q, J = 6.1 Hz, 2H), 1.43–1.16 (m, 4H), 0.85 (t, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 158.0, 141.0, 128.1, 126.9, 126.4, 42.8, 39.4, 32.1, 19.5, 13.6.

N-Phenyl, N′-butylurea (**7a**).[18b] Pale yellow solid; mp 122–124 °C, (Lit, 123 °C); IR (KBr): 3383, 2959, 2932, 2870, 1655, 1558, 1500, 1318, 1233 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ = 8.36 (br s, 1H), 7.36 (d, J = 7.7 Hz, 2H), 7.18 (t, J = 7.7 Hz, 2H), 6.85 (t, J = 7.1 Hz, 1H), 6.08 (br t, 1H), 3.10–3.01 (m, 2H), 1.49–1.19 (m, 4H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 155.2, 140.6, 128.5, 120.8, 117.5, 39.3, 31.8, 19.5, 13.6.

N-(4-Iodophenyl), N′-butylurea (**8**). White solid; mp 178–180 °C; IR (KBr): 3329, 2953, 2930, 2867, 2862, 1633, 1587, 1561, 628, 620 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6): δ = 8.58 (br s, 1H), 7.50 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.7 Hz, 2H), 6.19 (br t, J = 5.5 Hz, 1H), 3.12–2.98 (m, 2H), 1.46–1.19 (m, 4H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-d_6): δ = 155.5, 141.1, 137.7, 120.4, 83.8, 39.1, 32.4, 20.1, 14.2; HRMS-ESI: m/z $[M-H]^-$ calcd for $C_{11}H_{15}N_2OI$: 317.0145; found: 317.0151.

Acknowledgments

The authors would like to thank CNPq, CAPES and FAPERJ for the financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.045.

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