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Alkylation of ethylenethiourea with alcohols: a convenient synthesis of *S*-alkyl-isothioureas without toxic alkylating agents

Michael K. Denk* and Xuan Ye

Guelph-Waterloo Center for Graduate Studies in Chemistry, Guelph, Ontario, Canada N1G 2W1

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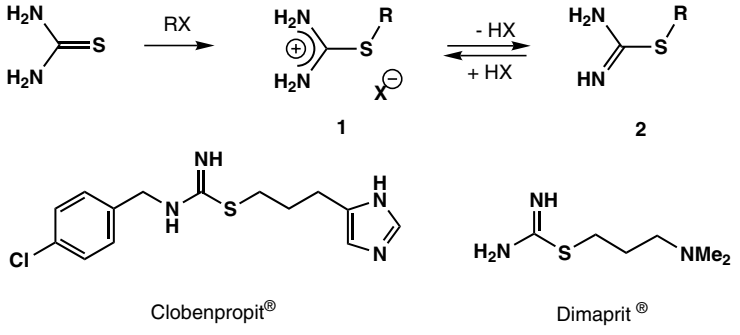
Abstract—The alkylation of ethylenethiourea with alcohols and aqueous acids (HCl, HBr, and HI) allows the synthesis of the respective *S*-alkyl-isothioureas in high yield and purity. Consistently high yields (91–98%) were obtained with 56% HI, the yields for 48% HBr (48–93%) and 37% HCl (36–85%) were lower and varied with the type of alcohol. The method is a convenient low-cost alternative to the use of alkyl iodides and an easy access to the *S*-*tert*-butyl isothiourea.

1. Introduction

S-Alkyl-isothiouronium salts **1**[1] and *S*-alkyl-isothioureas **2**[2] are starting materials for the synthesis of guanidines and heterocyclic systems.[3] In the last decade, it has been recognized that they can also serve as remarkably potent inhibitors for a whole range of enzyme systems.[4–7] Inhibition of nitric oxide synthase (NOS) has led to their use in the treatment of a range of life threatening conditions including septic shock, acute kidney failure, and organ rejection after transplantation surgery.[4] Clobenpropit®, a potent histamine H3 antagonist,[5] finds use as an anti-convulsant, while Dimaprit® is used as histamine H2 inhibitor as well as NOS antagonist.[6]

The capability of **1** and **2** to block the heart muscles Na^+/Ca^{2+} exchange system (NCX) has become a promising approach for the treatment of conditions leading to acute heart failure.[7] Preceding these exciting new findings are older studies that demonstrated the ability of **1** and **2** to protect DNA against radiation damage both in vivo and in vitro.[8]

S-Alkyl-isothioureas **2** (Scheme 1) are typically obtained by reaction of thioureas[9] with alkyl halides or other alkylating agents via the *S*-alkyl-isothiouronium salts (**1**). Tertiary alkyl derivatives is not readily accessible in this way, as solvolysis and elimination become the main reaction.



Scheme 1. Synthesis and use *S*-alkyl-isothioureas.

Keywords: Alkylation; Thiourea; *S*-Alkyl-isothiourea.
* Corresponding author. E-mail addresses: mdenk@uoguelph.ca; michaeldenk@mac.com

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The need to obtain *S*-alkyl-iso-thioureas and in particular *S*-*tert*-butyl derivatives in 100 g quantities prompted us to look for synthetic alternatives. The alkylation of thioureas with alcohols and acids, although reported as early as 1902,[9] seemed a promising approach but has subsequently been used only sporadically[10] so that the scope of the reaction has remained unclear. We have now tested this method for different combinations of alcohols and mineral acids and find that *S*-alkyl-isothioureas can be obtained in excellent yields.

2. Results and discussion

Ethylenethiourea (**3**) was chosen as substrate because the corresponding *S*-alkyl-isothioureas (**5**) are extracted more readily from aqueous solution than the rather hydrophilic isothioureas **2** (see Scheme 2).

Methanol, ethanol, isopropyl alcohol, and *tert*-butyl alcohol were included to test for primary, secondary, and tertiary alcohols. Hydriodic acid (56%), hydrobromic acid (48%), and hydrochloric acid (37%) were chosen as acids. Preliminary experiments showed that an excess of acid (up to 1.5 equiv) and alcohol (up to 3 equiv) led to improved yields of **5** and this stoichiometry was maintained for all reactions.

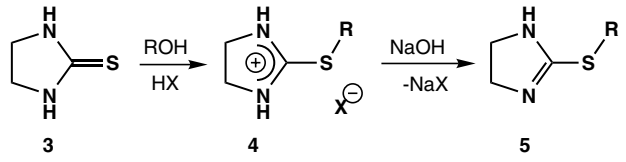
Two different reaction temperatures and two different reaction times resulting in four different sets of reaction conditions (A, B, C, D, see Table 1) were investigated.

The best yields of **5** (91–98%) were obtained for 56% HI, regardless of the type of alcohol used. The yields obtained with 48% HBr (48–93%) and 37% HCl (36–85%) were consistently lower, particularly for isopropanol.

A proper selection of the reaction time and the reaction temperature was found to be crucial to achieve good yields, the extreme example being the synthesis of **5c** with *i*PrOH/56% HI for which the yield could be increased from 17% to 99%.

Prolonged reaction times and higher temperatures led to decreased yields in some cases, as is illustrated by the *tert*-butanol/HCl combination for which the yield dropped from 64% (**A**) to 12% (**B**). Control experiments revealed that this drop in yield is due to the slow decomposition of the isothiouronium salts under acidic conditions.[11]

The excellent yields of *tert*-butyl-isothiourea (**5d**), which were obtained for both 56% HI and 48% HBr are noteworthy as the respective *tert*-butyl halides are known to give only low yields.



Scheme 2. Acid mediated alkylation of ethylenethiourea.

Table 1. Synthesis of *S*-alkyl-isothioureas **5a–d** from ethylenethiourea and alcohols

Product	Alcohol	Conditions	Yield in %		
			HI	HBr	HCl
5a	MeOH	A	95	65	60
		B	95	89	67
		C	84	86	76
		D	84	86	85
5b	EtOH	A	45	45	52
		B	98	33	34
		C	86	72	43
		D	86	73	56
5c	*i*PrOH	A	17	2	14
		B	18	10	6
		C	97	29	27
		D	99	48	36
5d	*t*BuOH	A	88	63	64
		B	91	93	42
		C	90	73	27
		D	63	40	12

Yields and reaction conditions.
A: 75 °C, 12 h.
B: 75 °C, 24 h.
C: 100 °C, 12 h.
D: 100 °C, 24 h.

Even without further purification, *S*-alkyl-isothioureas were obtained free of detectable impurities (^{1}H, ^{13}C NMR, GC–MS), a fact that is also reflected by the melting points, which generally exceeded those recorded in the literature.

3. Spectra

Trace amounts of moisture lead to qualitative changes in the NMR spectra of **5a–d**. The expected A_2B_2 spin system for the ring protons could be observed only with carefully dried samples. Trace amounts of moisture led to equivalent ring protons, most likely as a result of a rapid tautomeric equilibrium between the imine and amine nitrogen. The ^{13}C NMR signals of the isothiourea carbon in **5a–d** (165.1–162.7 ppm) showed little variation with R and appear shielded versus the thiocarbonyl group (ethylenethiourea: 185.1 ppm). The characteristic fragments in the EI mass spectra of **5a–d** correspond to the loss of the alkyl group, the loss of the thioalkyl fragment SR is not observed.

4. Conclusion

The alkylation of ethylenethiourea with alcohols and aqueous acids (HCl, HBr, and HI) allows the synthesis of the respective *S*-alkyl-isothioureas in high yield and purity. Consistently high yields (91–98%) were obtained with 56% HI, the yields for 48% HBr (48–93%) and 37% HCl (36–85%) were lower and varied with the type of alcohol. The method is a convenient low-cost alternative

to the use of alkyl iodides and an easy access to the *S*-*tert*-butyl isothiourea.

5. Synthesis of *S*-alkyl-isothioureas from ethylenethiourea and alcohols

Ethylenethiourea (20 mmol), the alcohol (60 mmol), and the respective acid (30 mmol) are heated under constant stirring (compare Table 1). The cold reaction mixture is brought to pH 11 with 40% aqueous NaOH and extracted with 3×20 mL of diethyl ether. After drying of the combined organic phases over NaOH pellets (24 h) and CaH_2 (24 h), the anhydrous 2-(alkylthio)-4,5-dihydro-1*H*-imidazoles **5** are isolated as colorless, crystalline solids.

5.1. 5a. 2-(Methylthio)-4,5-dihydro-1*H*-imidazole

CAS [20112-79-2]. Colorless crystals, mp 106–107 °C, lit.[1d] 101–102 °C. ^{1}H NMR ($CDCl_3$): 2.49 [s, 3H, SCH_3], 3.48 [t, 2H, ^3J(H,H) = 9 Hz, HNCH_2], 3.85 [t, 2H, ^3J(H,H) = 9 Hz, NCH_2], 4.37 [broad, 1H, N*H*]. ^{13}C ($CDCl_3$): 13.8 [S*C*H$_3$], 46.1 [HN*C*H$_2$], 55.4 [N*C*H$_2$], 165.1 [HN*C*(N)S]. GC–MS: t_R 7.23 min, *m*/*z* (rel int.%) 116(100), 100(20), 87(25), 72(75), 59(10), 45(30).

5.2. 5b. 2-(Ethylthio)-4,5-dihydro-1*H*-imidazole

CAS [7320-60-7]. Colorless crystals, mp 62–65 °C, lit.[1d] 58–60 °C. ^{1}H ($CDCl_3$): 1.36 [t, 3H, ^3J(H,H) = 7 Hz, SCH$_2$CH_3], 3.06 [q, 2H, ^3J(H,H) = 7 Hz, SCH_2CH$_3$], 3.47 [t, 2H, ^3J(H,H) = 9 Hz, HNCH_2], 3.83 [t, 2H, ^3J(H,H) = 9 Hz, NCH_2], 4.45 [broad, 1H, N*H*]. ^{13}C ($CDCl_3$): 14.9 [SCH$_2$*C*H$_3$], 25.6 [S*C*H$_2$CH$_3$], 45.9 [HN*C*H$_2$], 55.6 [N*C*H$_2$], 164.1 [HN*C*(N)S]. GC–MS: t_R = 7.85 min, *m*/*z* (rel int.%) = 131(10) $[MH]^+$, 115(7), 102(100), 97(25), 72(38), 45(17).

5.3. 5c. 2-(Isopropylthio)-4,5-dihydro-1*H*-imidazole

CAS [99115-66-9]. Colorless crystals, mp 113–115 °C, lit.[1d] 106–108 °C. ^{1}H ($CDCl_3$): 1.39 [d, 6H, ^3J(H,H) = 7 Hz, SCH(CH_3)$_2$], 3.43 [t, 2H, ^3J(H,H) = 9 Hz, HNCH_2], 3.87 [t, 2H, ^3J(H,H) = 9 Hz, C=NCH_2], 3.79 [sept, 1H, ^3J(H,H) = 7 Hz, SCH(CH_3)$_2$], 4.28 [broad, 1H, N*H*]. ^{13}C ($CDCl_3$): 23.6 [SCH(*C*H$_3$)$_2$], 36.9 [S*C*H-(CH$_3$)$_2$], 45.2 [HN*C*H$_2$], 55.6 [N*C*H$_2$], 164.0 [N*C*S]. GC–MS: t_R = 8.18 min, *m*/*z* (rel int.%) = 145(6) $[MH]^+$, 129(8), 111(32), 102(100), 86(2), 74(30), 59(10), 45(15).

5.4. 5d. 2-(*tert*-Butylthio)-4,5-dihydro-1*H*-imidazole

Colorless crystals, mp 82–84 °C. ^{1}H ($CDCl_3$): 1.54 [s, 9H, SC(CH_3)$_3$], 3.35 [t, 2H, ^3J(H,H) = 9 Hz, HNCH_2], 3.90 [t, 2H, ^3J(H,H) = 9 Hz, NCH_2], 4.28 [broad, 1H, N*H*]. ^{13}C ($CDCl_3$): 30.8 [SC(*C*H$_3$)$_3$], 44.2 [HN*C*H$_2$] 47.6 [S*C*(CH$_3$)$_3$], 56.2 [C=N*C*H$_2$], 162.7 [HN*C*(N)S]. GC–MS: t_R = 8.38 min, *m*/*z* (rel int.%) = 159(100), 148(5), 102(50), 74(7), 57(6) 45(4). HR-MS: 158.0881 (exp.), 158.0878 (calcd for $C_7H_{14}N_2S$), deviation 2.2 ppm.

Acknowledgments

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11. In the case of **5d**, prolonged heating in 56% HI led to the formation of ethylenethiourea and isobutene.