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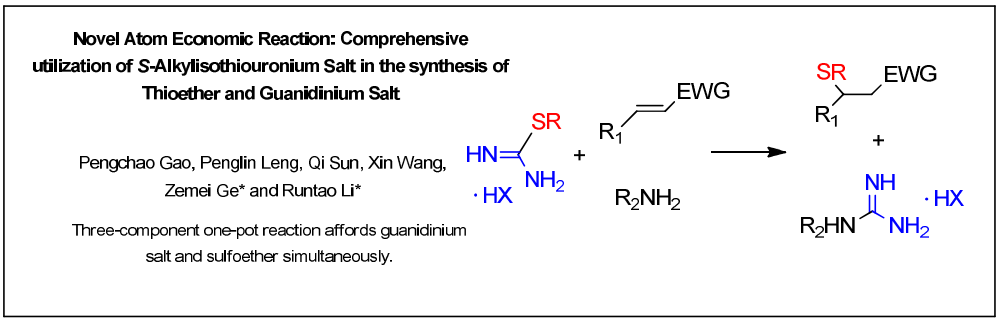
A novel atom economic three-component one-pot reaction of primary amine, *S*-alkylisothiouronium salt and Michael receptor is reported, which affords guanidinium salt and thioether simultaneously. The guanidine moiety is also involved in catalyzing the conjugated Michael addition of the mercaptan. The reaction proceeds under ambient condition using the non-toxic EtOH/H_2O mixture as the solvent, and the two products can be very easily purified. Complete atom economy is achieved by fully utilizing *S*-alkylisothiouronium salt and converting the previously wasted mercaptan by-product into the valuable thioether.



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ARTICLE TYPE

Novel Atom Economic Reaction: Comprehensive Utilization of *S*-Alkylisothiouronium Salt in the Synthesis of Thioether and Guanidinium Salt

Pengchao Gao, Penglin Leng, Qi Sun, Xin Wang, Zemei Ge* and Runtao Li*

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A novel atom economic three-component one-pot reaction of primary amine, *S*-alkylisothiouronium salt and Michael receptor is reported, which affords guanidinium salt and thioether simultaneously. The guanidine moiety is also involved in catalyzing the conjugated Michael addition of the mercaptan. The reaction proceeds under ambient condition using the non-toxic EtOH/H_2O mixture as the solvent, and the two products can be very easily purified. Complete atom economy is achieved by fully utilizing *S*-alkylisothiouronium salt and converting the previously wasted mercaptan by-product into the valuable thioether.

Introduction

The technology in organic synthesis has become so sophisticated that, given enough intellectual and economic input, almost all molecules can sooner or later be accessible in some way. However, such finesse often comes at a price that sacrifices the efficiency in material use. Although in "The Twelve Principles of Green Chemistry", "atom economy" has been advocated to maximize the utilization of materials, to date there are still limited organic reactions that can live up to such standard[1] and most reactions always involve the formation of by-products or waste. The chemical industry produces considerable amount of waste every year[2], and for chemists in the 21st century, the problem of waste reduction or even utilization is now of paramount importance.

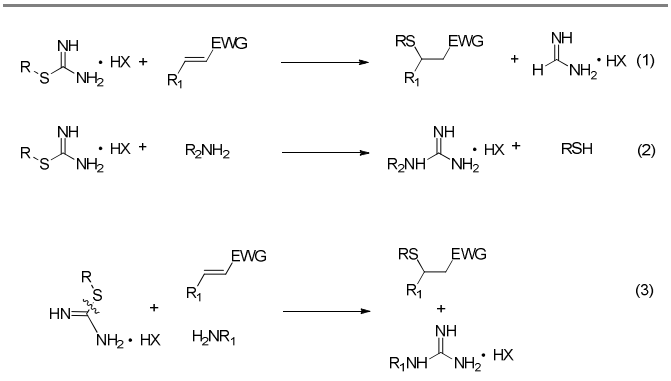
In order to solve this problem, many efforts have been focused on the reutilization of by-products[3]. Tian[4] has created the concept of "atom-economic reaction", which not only efficiently uses the reactants but also converts the by-products into useful products *in situ*. However, due to practical difficulties, this attractive idea is seldom practised. Here we report a novel three-component one-pot reaction of primary amine, *S*-alkylisothiouronium salt and Michael receptor to simultaneously afford two valuable products, thioether and guanidinum salt, with complete atom economy.

In our previous work, *S*-alkylisothiouronium salt has been successfully used to replace thiol in the thia-Michael addition to afford various thioethers (Scheme 1, eq 1).[5] The foul smell and toxicity of thiols are thus effectively avoided. However, this method is not atom economic because the amidine segment of the *S*-alkylisothiouronium salt is abandoned as by-product.

Interestingly, guanidinum salts are most often prepared through the reaction of *S*-alkylisothiouronium salt with primary amine (Scheme 1, eq 2)[6,7]. In this reaction, only the amidine segment of *S*-alkylisothiouronium salt is used, and the malodorous mercaptan is released as waste, which can seriously contaminate the environment.

Both thioethers[8] and guanidines[9,10] have interesting potentials in medicinal applications. Thioethers are known to have anti-fungal[9] and anti-hepatitis activities, whereas guanidines are known to have antifibrinolytic[11], anti-cancer[12], anti-HIV[13], anti-viral[14], anti-adipogenic[15] activities, *etc.* Inspired by Tian's concept of atom-economic reaction in green chemistry, we envisioned that the *S*-alkylisothiouronium salts can be used efficiently if the above two reactions can be combined into one reaction (Scheme 1, eq 3). In this way, two valuable products, thioether and guanidine, are obtained in one pot in a way that much better meets the requirement of green chemistry.

Thus, we initially examined the reaction of *S*-benzylisothiourea with benzylamine and methyl acrylate as the model to explore this possible consecutive reaction under a variety of conditions.



Scheme 1. The design of the atom-economic reaction.

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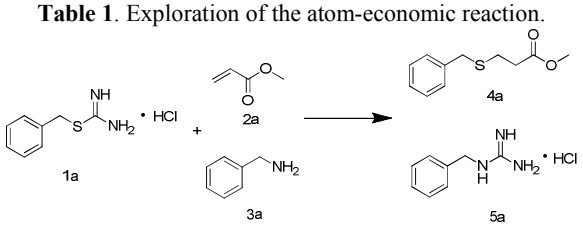
Table 1. Exploration of the atom-economic reaction.



Entry[a]	Solvent	Base	Temp/°C	Time/h	Yield of 4a (%)[b]	Yield of 5a (%)[b]
1	DMSO	TEA(0.1 equiv)	30	3	Trace	0
2	H_2O	TEA(0.1 equiv)	30	3	58	38
3	EtOH	TEA(0.1 equiv)	30	3	35	31
4	EtOH/H_2O(1:1)	TEA(0.1 equiv)	30	3	65	43
5	Acetone	TEA(0.1 equiv)	30	3	Trace	0
6	*i*-PrOH	TEA(0.1 equiv)	30	3	Trace	Trace
7	DMF	TEA(0.1 equiv)	30	3	Trace	<10
8	Ethyl Acetate	TEA(0.1 equiv)	30	3	Trace	0
9	CH_2Cl_2	TEA(0.1 equiv)	30	3	Trace	0
10	CH_3OH	TEA(0.1 equiv)	30	3	17	21
11	CH_3OH/H_2O(1:1)	TEA(0.1 equiv)	30	3	39	17
12	EtOH/H_2O(1:2)	TEA(0.1 equiv)	30	3	31	40
13	EtOH/H_2O(2:1)	TEA(0.1equiv)	30	3	48	34
14	EtOH/H_2O(1:1)	NaOAc(0.1 equiv)	30	3	53	41
15	EtOH/H_2O(1:1)	DIEA(0.1 equiv)	30	3	63	53
16	EtOH/H_2O(1:1)	DBU(0.1 equiv)	30	3	68	53
17	EtOH/H_2O(1:1)	NaOH(0.1 equiv)	30	3	63	47
18	EtOH/H_2O(1:1)	No base	30	3	36	21
19	EtOH/H_2O(1:1)	TEA(0.5 equiv)	30	3	57	50
20	EtOH/H_2O(1:1)	TEA(1.0 equiv)	30	3	65	48
21	EtOH/H_2O(1:1)	TEA(2.0 equiv)	30	3	61	48
22	EtOH/H_2O(1:1)	TEA(1.0 equiv)	0	3	0	0
23	EtOH/H_2O(1:1)	TEA(1.0 equiv)	50	3	66	46
24	EtOH/H_2O(1:1)	TEA(1.0 equiv)	70	3	68	42
25	EtOH/H_2O(1:1)	TEA(1.0 equiv)	90	3	57	50
26	EtOH/H_2O(1:1)	TEA(1.0 equiv)	30	1	35	33
27	EtOH/H_2O(1:1)	TEA(1.0 equiv)	30	6	68	51
28	EtOH/H_2O(1:1)	TEA(1.0 equiv)	30	12	62	45
29[c]	EtOH/H_2O(1:1)	TEA(1.0 equiv)	30	6	73	54
30[d]	EtOH/H_2O(1:1)	TEA(1.0 equiv)	30	6	73	51

[a] The molar ratio **1a/2a/3a** = 1:1:1 and without illustration. [b] Isolated yield. [c] The mol ratio **1a/2a/3a** = 1.1:1:1 [d] The mol ratio **1a/2a/3a** = 1.5:1:1

The reaction was first carried out at 30 °C using triethyl amine (TEA) as the catalyst to screen a variety of solvents, including polar solvents, apolar solvents, polar aprotic solvents and mixture solvents. It can be seen that polar solvents are more favorable for the reaction than apolar solvents, and the mixture solvent 1:1 EtOH/H_2O is the best, which provides the desired products benzylthioether (**4a**) and benzylguanidine (**5a**) in 65% and 43% yield (calculated based on the amine), respectively (Table 1, entries 1–13). The use of different bases was then examined by carrying out the reaction in 1:1 EtOH/H_2O at 30 °C (Table 1, entries 14–18). The inorganic bases and the organic bases give similar results. Since the use of organic base is more convenient for the separation of products (see Experimental), we selected TEA as the base because it is cheap and easy to handle, although using DBU as the base gives slightly higher yield than using TEA. Using 1.0 equiv TEA gives more satisfying yield than using other stoichiometries (Table 1, entries 19–21). Afterwards, the reaction temperature and the reaction time were examined (Table 1, entries 23–25). The reaction is best carried out at 30 °C for 6 h. Finally, we found that the best result could be obtained when the molar ratio of the reactants is **1a/2a/3a** = 1.1:1:1.

With the optimized reaction conditions (Table 1, entry 29) in hand, we then investigated the scope of this atom-economic reaction. Firstly, various *S*-alkylisothiouronium salts were reacted with benzyl amine and three kinds of Michael receptors. As shown in Table 2, all reactions proceeded smoothly to afford the corresponding thia-Michael addition products (**4**) and benzylguanidinium salts (**5**) in 59%–83% yield and 44%–75% yield, respectively.

Subsequently, we treated glycin and 2-(azepan-1-yl)ethanamine respectively with different *S*-alkylisothiouronium salts and Michael receptors to examine whether our method could simultaneously deliver the thia-Michael addition products and other kinds of valuable guanidines, such as glucocyamine[16], a new food additive for animals and an anti-myasthenia agent, and guanethidine[17] (also known as Ismelin), a potent anti-hypertension drug. As expected, glucocyamine and Ismelin can be obtained in moderate yield along with the formation of the thia-Michael addition products in good yield (Table 3).

Encouraged by the above results, we further explored the possibility of carrying out this atom-economic reaction to afford a single functionalized molecule. Thus, we designed and synthesized the substrate **11**[18] (Scheme 2), which contains not only the Michael receptor but also a primary amine moiety. The reaction of equi-molar **11** and *S*-benzylisothiourea hydrochloride

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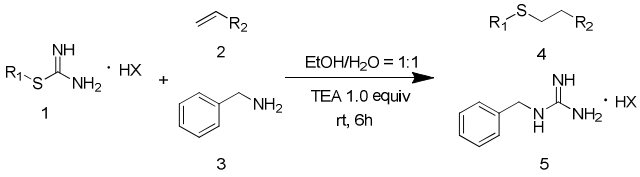
Table 2. Atom-economic reactions of substituted *S*-alkylisothiouronium salts (**1**) and Michael receptors (**2**).



1 2 3 4 5

Entry	1	2	4 (yield, %)	5 (yield, %)
1		**2a**	**4a** (73)	**5a** (54)
2	**1a**	**2b**	**4b** (82)	**5a** (64)
3		**2c**	**4c** (80)	**5a** (68)
4		**2a**	**4d** (62)	**5b**(65)
5	**1b**	**2b**	**4e** (73)	**5b** (62)
6		**2c**	**4f** (59)	**5b** (57)
7		**2a**	**4g** (68[a])	**5c** (58)
8	**1c**	**2b**	**4h** (81)	**5c** (63)
9		**2c**	**4i** (77)	**5c** (67)
10		**2a**	**4j** (68)	**5c** (54)
11	**1d**	**2b**	**4k** (76)	**5c** (61)
12		**2c**	**4l** (65)	**5c** (56)
13		**2a**	**4m** (71[a])	**5c** (51)
14	**1e**	**2b**	**4n** (83)	**5c** (57)
15		**2c**	**4o** (66)	**5c** (44)
16		**2a**	**4p** (78)	**5c** (75)
17	**1f**	**2b**	**4q** (72)	**5c** (68)
18		**2c**	**4r** (63)	**5c** (70)

[a] Performed without TEA

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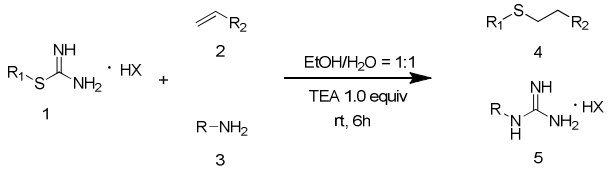
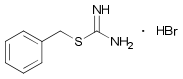
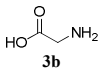
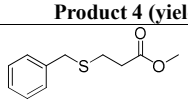
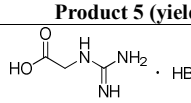
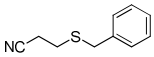
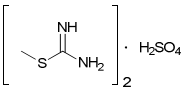
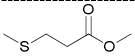
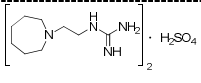
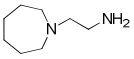
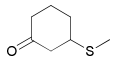
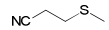
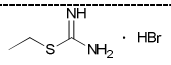
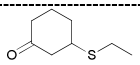
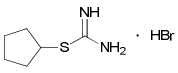
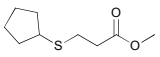
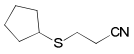
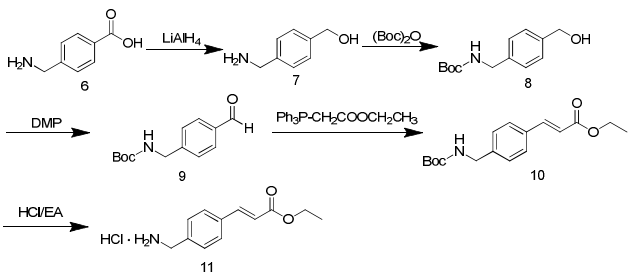
Table 3. Utilization of the atom-economic reaction to synthesize glucocyamine and Ismelin.



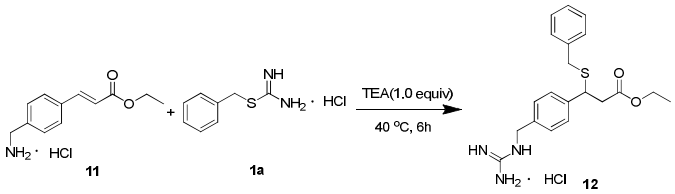
Entry	*S*-Alkylisothiouronium salt	Michael receptor	Amine (3)	Product 4 (yield%)	Product 5 (yield%)
1	 **1a**	**2a**	 **3b**	 **4a** (74)	 **5d** (57)
2		**2c**		 **4c** (83)	**5d** (59)
3	 **1b**	**2a**		 **4d** (69)	 **5e Ismelin** (66)
4		**2b**	 **3c**	 **4e** (75)	**Ismelin** (54)
5		**2c**		 **4f** (73)	**Ismelin** (53)
6	 **1c**	**2b**	**3b**	 **4h** (75)	**5d** (64)
7	 **1d**	**2a**	**3b**	 **4j** (64)	**5d** (55)
8		**2b**		 **4l** (55)	**5d** (60)

proceeded well under the optimized reaction conditions to afford the desired product **12** in 42.1% yield. This result excellently demonstrates the atom economy of the developed truly atom-economic reaction (Scheme 3).

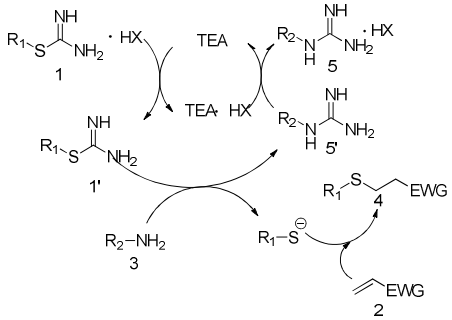
Based on the experimental observations, the possible mechanistic pathway for this atom-economic reaction is proposed in Scheme 4. *S*-Alkylisothiouronium (**1'**) is firstly released from its salt (**1**) in the presence of TEA. Then, the reaction of **1'** with the primary amine (**3**) simultaneously affords the guanidine (**5'**) and the thiolate anion, which attacks the Michael receptor (**2**) to form the thioether (**4**). The strongly basic guanidine (**5'**) captures the HX from the TEA salt to form the stable guanidinium salt (**5**), which releases TEA to participate again in the next catalytic cycle.



Scheme 2. Synthesis of ethyl 3-(4-aminomethylphenyl) acrylate **(11)**



Scheme 3. Single molecule atom-economic reaction of **11** with *S*-benzylisothiourea hydrochloride.



Scheme 4. Possible pathway of the atom-economic reaction

Conclusions

In conclusion, we have developed a novel atom economic three-component one-pot reaction of primary amine, *S*-alkylisothiouronium salt and Michael receptor to obtain both thioether and guanidinium salt in one-pot. And the two products can be easily separated by simply extraction of ethyl acetate and water. Furthermore, we realized the utilization of *S*-alkylisothiouronium salt with complete atom economy.

Experimental section

Compounds **1a-f**[5], **2a-c**[19], **3a-c**[10,17], **4a-r**[19-26], **5a-e**[15-18], **6**[28], **7**[29], **8**[29], **9**[30], **10**[31], **11**[32] are known. **12** is a new compound. Characterization data (^{1}H NMR, ^{13}C NMR, Mp, ESI-MS) are reported in Electronic Supplementary Information (ESI).

Representative experimental procedure

To the mixed solvent (10 mL, H_2O/EtOH = 1:1) was added the *S*-Alkylisothiouronium salt (4.4 mmol), the amine (4.0 mmol) the Michael receptor (4.0 mmol) and TEA (4.0 mmol). The mixture was stirred at 30 °C for 6 h, then 5 mL H_2O was added and the mixture was extracted with EtOAc (15 mL × 3). The remaining aqueous layer was concentrated under reduced pressure using a rotary evaporator and the resulting solid was washed with a small amount of ethanol, then recrystallized from hot water to give the corresponding guanidinium salt (**5**). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by column chromatography (Petroleum ether/Ethyl acetate) to afford the corresponding thia-Michael addition product (**4**).

Acknowledgements

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Notesand references

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