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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 4875–4878

One-pot synthesis of *N*-allylthioureas using supported reagents

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Received 18 April 2005; revised 11 May 2005; accepted 16 May 2005
Available online 4 June 2005

Abstract—A simple and efficient method has been developed for the synthesis of *N*-allylthioureas from allylic bromides in one-pot by using a supported reagents system, $KSCN/SiO_2$–RNH_3OAc/Al_2O_3, in which allyl bromide reacts first with $KSCN/SiO_2$ and the product, allyl isothiocyanate, reacts with RNH_3OAc/Al_2O_3 to give the final product, *N*-allylthiourea, in good yield.

Polymer or inorganic solid-supported reagents have been widely used in organic synthesis. However, there are few examples using a mixture of supported reagents for synthetic purposes. Cohen et al.[1] described two-stage reactions in which a starting material was modified successively by two polymeric-transfer reagents (wolf and lamb reaction). The analogous soluble reagents would react with each other rapidly in solution, whereas they could be rendered mutually inactive on their attachment to the respective polymeric phase and therefore coexist in the same reaction vessel. While basically using the same principle, Kim and Regen[2] have realized a 'vacillating reaction', using a couple of redox reagents separately adsorbed onto inorganic solid supports. However, this concept has not been extended to reagents adsorbed on inorganic supports. Recently, we have reported novel synthetic procedures by using a couple of supported reagents.[3] For example, we have developed direct allylation of aromatic compounds using a couple of acid and base supported reagents in one-pot.[3a] The one-pot multi-step synthesis using inorganic solid-supported reagents system has also been reported.[3b–d] We realized that KSCN and NH_4OAc could not coexist in the same vessel due to interaction with each other but these reagents which were supported on separate inorganic supports, silica gel and alumina, were able to coexist and to work as a thiocyanating reagent and aminating reagent respectively in the same vessel. For instance 2-aminothiazoles were synthesized by using a supported reagents system, $KSCN/SiO_2$–RNH_3OAc/Al_2O_3, in which α-bromo ketones react first with $KSCN/SiO_2$ and the products react with RNH_3OAc/Al_2O_3 to give the 2-aminothiazoles in high yields. The halides react with potassium thiocyanate to afford thiocyanates or isothiocyanates depending on the reactivity of the halides and reaction conditions. Alkyl halides yield preferentially thiocyanates which, depending on the structure of organic residue, rearrange themselves more or less into the corresponding isothiocyanates. Allylic thiocyanates isomerize thermally with much greater ease than benzylic thiocyanates. Isothiocyanates readily react with amines to give the corresponding thioureas. Therefore, we tried to synthesize thiourea derivatives from the reaction of allylic bromide using supported reagents system '$KSCN/SiO_2$–RNH_3OAc/Al_2O_3'. Symmetrical and unsymmetrical thioureas are useful compounds in agricultural and medicinal chemistry.[4] They are also used as building blocks for the synthesis of both five- and six-membered heterocycles.[5] The common methods for the synthesis of symmetrical and unsymmetrical thioureas are the condensation of primary or secondary amines with thiophosgene[6] and isothiocyanates.[4,7] However, these methods are hazardous due to the toxic properties of both thiophosgene and isothiocyanates. On the other hand, our method does not need to handle directly isothiocyanates. Recently, several methods have been developed for the synthesis of both symmetrical and unsymmetrical thioureas involving: (a) reaction of reductive alkylation

Keywords: Thiourea; Supported reagents; One-pot synthesis.
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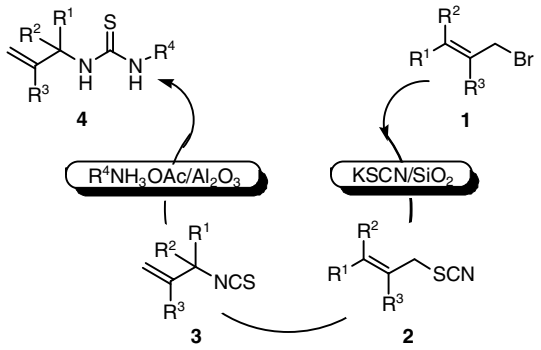
doi:10.1016/j.tetlet.2005.05.063



Scheme 1. One-pot synthesis of using supported reagents system.

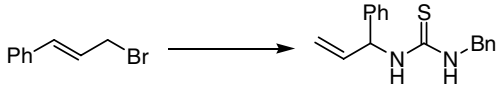
of thioureas;[8] (b) reaction of carbon disulfide and amine in the presence of MCM-41-TBD;[9] (c) reaction of amine and benzotriazole-1-carbothioic acid derivatives;[10] (d) reaction of 1-(methyldithiocarbonyl)imidazole and amine;[11] (e) solid phase reaction using peptide coupling reagents.[12] Herein, we report a simple, efficient and safety method for the one-pot synthesis of *N*-allylthioureas using a combination of supported reagents (Scheme 1).

For example, a mixture of cinnamyl bromide (1 mmol), $KSCN/SiO_2$[13] (5 mmol) and $BnNH_3OAc/Al_2O_3$[3c] (3 mmol) was stirred in benzene (10 mL) at 80 °C for 6 h, and then the used supported reagents were removed by filtration. The filtrate was evaporated to leave crude product, which was purified by column chromatography to give *N*-α-phenylallyl-*N*′-benzylthiourea[14] in 78% yield. Allylic halides react readily with KSCN to produce allylic thiocyanates, which isomerizes with allyl rearrangement into isothiocyanate. Allylic thiocyanates isomerize thermally with much greater ease than other thiocyanates, for example, benzyl thiocyanate. Benzyl bromide did not give the corresponding thiourea under similar reaction conditions.

Several solvents were tested for the reaction with cinnamyl bromide by using the combination of $KSCN/SiO_2$ and RNH_3OAc/Al_2O_3. Among the solvents tested, benzene and toluene were suitable solvents for the reaction. The reaction in polar solvents such as THF gave the product in moderate yield (44%) (Table 1).

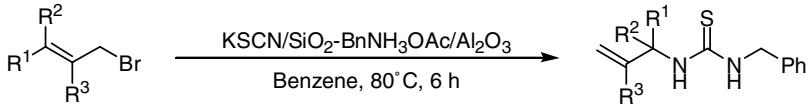
As shown in Table 2, various allylic bromides reacted with $KSCN/SiO_2$ and $BnNH_3OAc/Al_2O_3$ in one-pot to afford the corresponding thioureas. The reaction of crotyl bromide and of 1-bromo-3-methyl-2-butene gave the desired products, **4c**[15] and **4d**, in excellent yields. Cinnamyl bromide and 1-bromo-2-methyl-2-butene were also converted into the products in good yields under the same conditions. When cinnamyl chloride was used instead of cinnamyl bromide for the reaction, the yield of **4b** was lower than that of cinnamyl bromide.

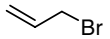
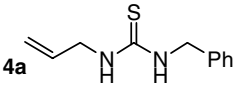
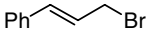
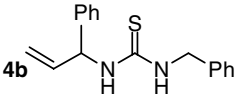
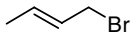
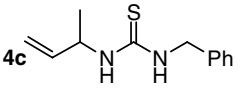
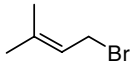
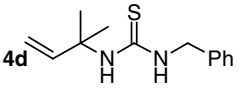
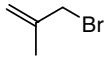
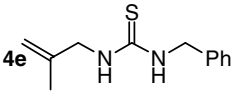
Table 1. Synthesis of *N*-α-phenylallyl-*N*′-benzylthiourea in various solvent



Solvent	Yield (%)
Benzene	78
Toluene	75
Xylene	57
Cyclohexane	Trace
THF	44

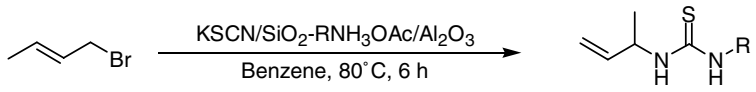
Table 2. One-pot synthesis of *N*-allyl-*N*′-benzyl thioureas[a]

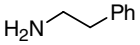
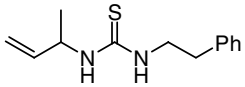
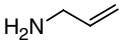
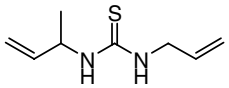
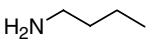
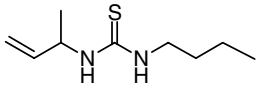
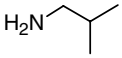
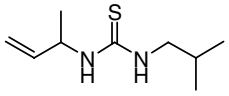
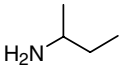
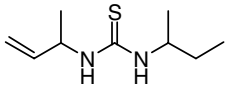
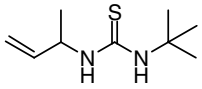
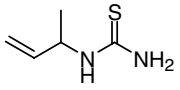
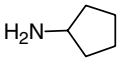
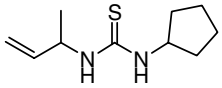
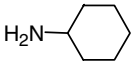
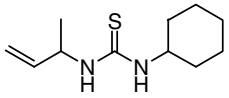
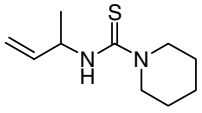


Entry	Allylic bromide	Product	Yield (%)
1		**4a** 	59
2		**4b** 	78
3		**4c** 	92
4		**4d** 	94
5		**4e** 	75

[a] Allylic bromide: 1 mmol, $KSCN/SiO_2$: 5 mmol, $BnNH_3OAc/Al_2O_3$: 3 mmol.

Table 3. One-pot synthesis of *N*-allylthioureas from crotyl bromide and various alkylammonium acetates



Entry	Amine	Product	Yield (%)
1			89
2			88
3			89
4			82
5			88
6			—
7	NH_3		—
8			92
9			90
10			47

The results of the reaction of crotyl bromide with alumina-supported alkylammonium acetates were shown in Table 3. The reactions of crotyl bromide with a series of butylammonium acetate gave the corresponding thioureas except for the reaction with *tert*-butylammonium acetate (entries 3–6). When using not only normal- and *iso*-butylammonium acetates but also *sec*-butylammonium acetate, the *N*-allylthioureas were obtained in high yields. However, *tert*-butylammonium acetate did not give the desired thiourea. Ammonium acetate also gave no expected compound (entry 7). The reactions of cycloalkyl- and allyl-ammonium acetates gave the expected thioureas in good yields (entries 2, 8 and 9). The reaction with the acetate of piperidine was also proceeded to afford expected compound in 47% yield (entry 10).

In conclusion, we have developed a simple and efficient method for the synthesis of *N*-allylthioureas in one-pot from commercially available starting materials. This method may be applicable for laboratory scale and combinatorial synthesis of *N*-allylthioureas. Further applications of this reagents system are now under investigation.

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14. *N*-α-phenylallyl-*N*′-benzylthiourea (**4b**), mp 80–81 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.55 (2H, s, CH_2), 5.06–5.18 (2H, m, CH_2=CH), 5.54 (1H, br s, CH), 5.83–5.93 (1H, m, CH_2=C*H*), 6.30 (1H, br s, NH), 6.40 (1H, br s, NH), 7.08–7.26 (10H, m, arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 48.7 (CH_2), 60.3 (CH), 117.0 (*C*H_2=CH), 127.0, 127.3, 127.6, 128.0, 128.7, 128.9, 136.5 (CH_2=*C*H), 136.8, 139.0, 181.2 (C=S). HR-MS (TOF-CI) calcd for $C_{17}H_{19}N_2S$ (MH^+): 283.1268. Found: 283.1273.
15. *N*-α-methylallyl-*N*′-benzylthiourea (**4c**), mp 68–69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (3H, d, *J* = 6.8 Hz, CH_3), 4.42 (1H, br s, CH), 4.62 (2H, s, CH), 5.02–5.10 (2H, m, CH_2=CH), 5.67–5.78 (1H, m, CH_2=C*H*), 6.08 (1H, br s, NH), 6.29 (1H, br s, NH), 7.23–7.30 (5H, m, arom). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5 (CH_3), 48.6 (CH_2), 52.0 (CH), 115.2 (*C*H_2=CH), 127.5, 127.7, 128.7, 137.0, 138.9 (CH_2=*C*H), 181.1 (C=S). HR-MS (TOF-CI) calcd for $C_{12}H_{17}N_2S$ (MH^+): 221.1112. Found: 221.1108. The NMR assignments were aided by ^{13}C DEPT, ^{1}H–^{1}H and ^{13}C–^{1}H COSY spectroscopy.