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One-pot synthesis of 2-aminothiazoles using supported reagents

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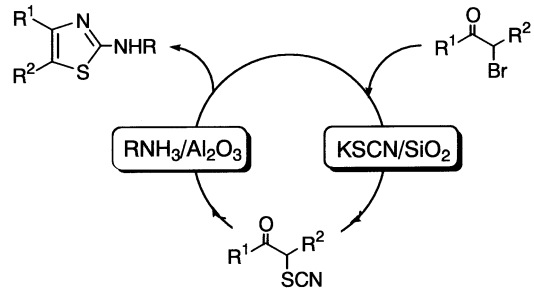
Abstract—A simple and efficient method has been developed for the synthesis of 2-aminothiazoles from α-bromo ketones in one-pot using a supported reagents system, $KSCN/SiO_2$–RNH_3OAc/Al_2O_3, in which α-bromo ketone reacts first with $KSCN/SiO_2$ and the product, α-thiocyano ketone, reacts with RNH_3OAc/Al_2O_3 to give the final product, 2-aminothiazole, in high 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. B. J. 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 reported transformation of β-dicarbonyl compounds to α-thiocyano-β-dicarbonyl compounds by using a supported reagents system consisting of $CuBr_2/Al_2O_3$ as a bromination reagent and $KSCN/SiO_2$ as a thiocyanation reagent in one-pot.[3] When $CuBr_2$ and KSCN were used instead of the supported reagents, the reaction did not proceed to a significant extent. These results suggest that two reagents reacting with each other in homogenous solution are rendered mutually inactive by supporting them onto separate inorganic supports.

We chose the preparation of 2-aminothiazoles from readily available α-halo ketones using the supported reagents system in one-pot in order to study the possibility of using a mixture of two inorganic solid-supported reagents for synthetic purposes. The 2-aminothizole ring system is a useful structural element in medicinal chemistry and has found broad application in drug development for the treatment of allergies,[4] hypertension,[5] inflammation,[6] and bacterial infections.[7] Typically, 2-aminothiazoles are prepared either by the condensation of α-halo ketones with monosubstituted thioureas or by the reaction of α-thiocyanato carbonyl compounds with aromatic or aliphatic amine hydrochlorides.[8] α-Thiocyanato carbonyl compounds can be obtained from the reaction of α-halo ketones with potassium thiocyanate. The reaction proceeds in a polar solvent such as ethanol and acetonitrile which is able to dissolve KSCN, and does not proceed in a non-polar solvent such as benzene, in



Scheme 1.

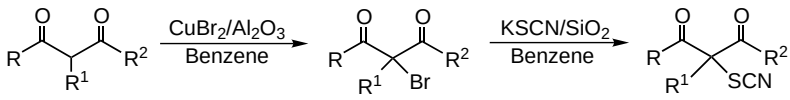


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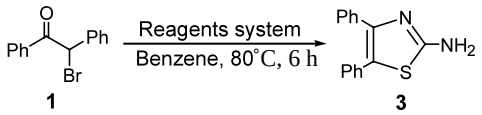
Table 1. Reaction of **1** with various reagents systems



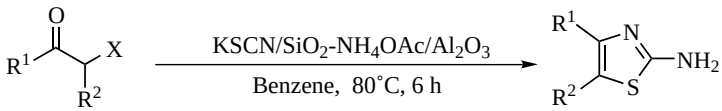
1 **3**

Reagents system	Yield of **3** (%)
$KSCN/SiO_2–NH_4OAc/Al_2O_3$	87
$KSCN–NH_4OAc$	Trace
$KSCN/SiO_2–NH_4OAc$	11
$KSCN–NH_4OAc/Al_2O_3$	53

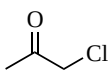
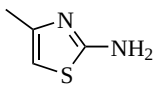
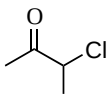
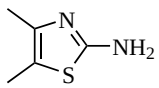
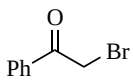
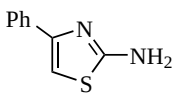
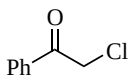
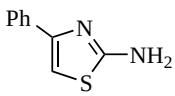
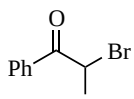
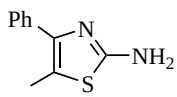
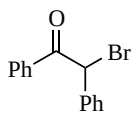
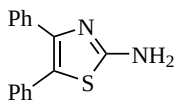
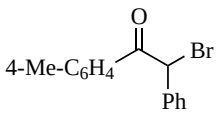
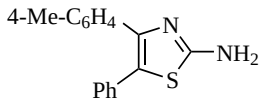
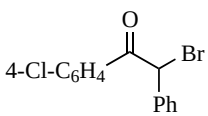
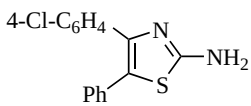
which KSCN is not soluble. α-Thiocyanato carbonyl compounds react with amine hydrochlorides in ethanol to give 2-aminothiazoles in high yield. However, it is impossible to carry out the two reactions in one-pot because KSCN and amine will interact, and thus the overall reaction must be separated into two steps: reaction of α-halo ketone with KSCN, followed by reaction of the resulting α-thiocyanate with amine hydrochloride.

Herein we report a convenient, highly efficient method for the one-pot synthesis of 2-aminothiazoles from α-bromo ketones by treating with a supported reagents system, silica gel-supported potassium thiocyanate ($KSCN/SiO_2$)–alumina-supported amino acetate (RNH_3OAc/Al_2O_3) (Scheme 1). Both the reactions of 2-bromo-2-phenylacetophenone **1** with KSCN and 2-thiocyano-2-phenylacetophenone **2** with NH_4OAc did not proceed in benzene at 80°C. In contrast, reaction with **1** with $KSCN/SiO_2$ in benzene proceeded at 80°C to give **2** in 87% after 5 h. Reaction of **2** with NH_4OAc/Al_2O_3 occurred also in benzene under similar conditions and afforded 2-amino-4,5-diphenylthiazole **3** in 90% yield. If

Table 2. Preparation of substituted 2-aminothiazoles[a]

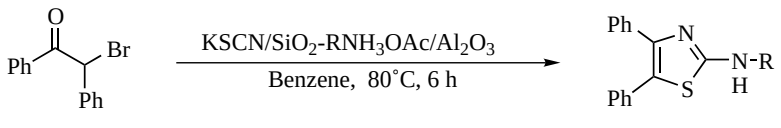


4 **5**

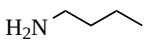
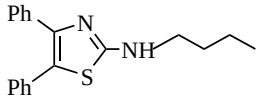
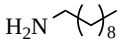
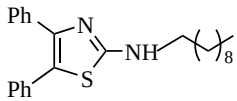
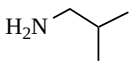
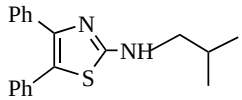
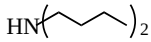
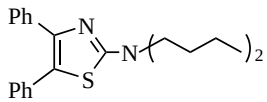
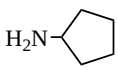
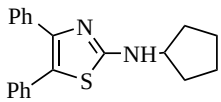
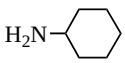
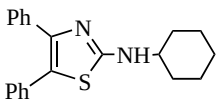
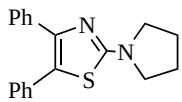
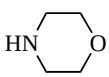
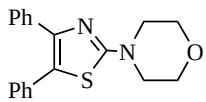
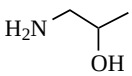
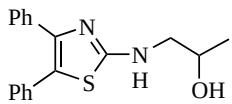
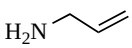
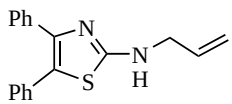
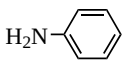
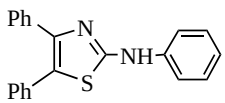
Entry	Ketone **4**	Product **5**	Isolated yield (%)
1			83
2			58
3			83
4			80
5			46
6			87
7			90
8			92

[a] α-halo ketone : 1 mmol, $KSCN/SiO_2$: 5 mmol, NH_4OAc/Al_2O_3: 6 mmol.

Table 3. Reaction of 2-bromo-2-phenylacetophenone with various amines[a]



1 **5**

Entry	Amine	Product **5**	Isolated yield(%)
1			65
2			60
3			80
4			72
5			97
6			95
7			89
8			84
9			96
10			94
11			89

[a]A mixture of α-bromo ketone (1 mmol), $KSCN/SiO_2$ (5 mmol, 1.0 g) and RNH_3OAc/Al_2O_3 (6 mmol, 6.0 g) was stirred in solvent (10 ml) at 80 °C for 6 h.

1 is subjected to a mixed suspension of $KSCN/SiO_2$ and NH_4OAc/Al_2O_3 in benzene, it is strongly expected to undergo a two-step reaction in one-pot. Compound **1** will react with $KSCN/SiO_2$ to give **2**, which will further react with NH_4OAc/Al_2O_3, yielding the final product **3**. The following results demonstrate the viability of this concept **1** reacted with the supported reagents system, $KSCN/SiO_2$–NH_4OAc/Al_2O_3, to give **3** in 87% yield

(Table 1), whereas in the reaction with the unsupported reagents system the yield was a trace and in the reaction with the reagents system in which one reagent is supported on inorganic solid and the other is unsupported, the yield was lower than that with the supported reagents system.

In a typical procedure, a mixture of **1** (1 mmol), $KSCN/SiO_2$[9] (5 mmol) and NH_4OAc/Al_2O_3[10] (6 mmol) was stirred in benzene at 80°C for 6 h, and then the used solid reagents were removed by filtration. The filtrate was evaporated to leave crude products, which were purified by column chromatography over silica gel. As shown in Table 2, α-halo ketones react with $KSCN/SiO_2$ and NH_4OAc/Al_2O_3 in one-pot to produce the corresponding 2-aminothiazoles in high yields. To obtain the high yield, both supported reagents were required in large excess. Ammonium acetate was the most effective among the amine salts tested: ammonium acetate, ammonium benzoate and ammonium chloride. When α-chloro ketone was used instead of α-bromo ketone, the yield was the same as that in the reaction with α-bromo ketone. The halo ketones in which the halogen is attached to the secondary carbon afforded lower yields than that with the halo ketones in which the halogen is attached to the primary carbon (Table 2, entries 1–5). When the halo ketones in which halogen is attached to the secondary carbon were used, uncharacterized byproducts were generated along with the thiazoles. However, with the halo ketone in which the halogen is attached to the benzyl carbon, no side reactions were observed (Table 2, entries 6–8). This procedure can be efficiently applied to primary and secondary amines. The reaction of 2-bromo-2-phenylacetophenone with primary or secondary amines gave *N*-substituted-4,5-diphenyl-2-aminothiazoles in high yields (see Table 3). The yields of 2-aminothiazoles from the reaction with primary and secondary aliphatic amines (Table 3, entries 1 and 4) were lower than that with alicyclic amines (Table 3, entries 5–7). The successful use of 2-hydroxypropylamine and allylamine indicates that this procedure is unaffected by the presence of a functional group such as the C–C double bond and the hydroxyl group in an amine part.

In summary, we have developed a simple and efficient procedure for synthesizing 2-aminothiazoles in one-pot from readily available starting materials. This method may find wide application for the laboratory-scale and combinatorial synthesis of substituted 2-aminothiazoles. These experimental results demonstrate that two reagents reacting with each other in homogenous solution are rendered mutually inactive by supporting them onto separate inorganic supports, and two-step reactions are possible in one-pot by using a couple of supported reagents.

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