

One-Pot Synthesis Using Supported Reagents System: Conversion of β -Dicarbonyl Compounds to α -Thiocyano- β -dicarbonyl Compounds Using $\text{CuBr}_2/\text{Al}_2\text{O}_3$ -KSCN/ SiO_2

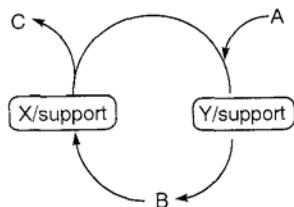
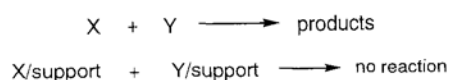
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Transformation of β -dicarbonyl compound **1** to α -thiocyano- β -dicarbonyl compounds **3** in one-pot was achieved by using supported reagents system $\text{CuBr}_2/\text{Al}_2\text{O}_3$ - KSCN/ SiO_2 , in which **1** reacts first with $\text{CuBr}_2/\text{Al}_2\text{O}_3$ and the product, α -bromo- β -dicarbonyl compound **2** reacts with KSCN/ SiO_2 to give the final product **3** in good yield.

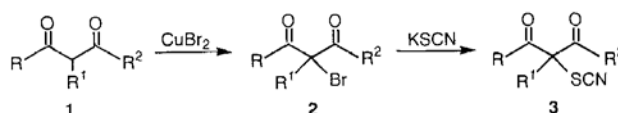
Polymer or inorganic solid supported reagents have been widely used in organic synthesis. However, there are few examples using a mixture of supported reagents for synthetic purpose. B. J. Cohen et al.¹ described two-stage reactions in which a starting material was modified successively by two polymeric 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 on the same principle, Kim and Regen² have realized a "vacillating reaction," using a couple of redox reagents separately adsorbed onto inorganic supports. However, this concept has not been extended to reagents adsorbed on inorganic supports. Recently we reported that direct allylation of aromatic compounds with allylic chloride using supported reagents system consisting of $\text{ZnCl}_2/\text{SiO}_2$ as an acid catalyst and $\text{K}_2\text{CO}_3/\text{Al}_2\text{O}_3$ as a scavenger of hydrogen chloride³. When K_2CO_3 was used as a solid base instead of $\text{K}_2\text{CO}_3/\text{Al}_2\text{O}_3$, the reaction did not proceed to a significant extent, and K_2CO_3 deactivated the catalyst. These results suggest that two reagents reacting with each other in homogenous solution are rendered mutually inactive by supporting them onto separate inorganic supports. Thus it should be possible that two-step synthesis was carried out in one-pot by using two supported reagents, in which a soluble reagent (A) react first with one supported reagent (Y) and the product (B) with the second supported reagent (X) to give the desired final product (C) as illustrated in Scheme 1.



Scheme 1.

We chose the preparation of α -thiocyano- β -dicarbonyl compounds from β -dicarbonyl compounds using supported

reagents system in one-pot in order to study the possibility of using a mixture of two inorganic solid supported reagents for synthetic purpose. α -Thiocyanatocetones are usually prepared from ketones *via* an indirect way that includes nucleophilic displacement of α -haloketones with SCN^- . Copper(II) halides are used as a halogenation reagent for ketones, and potassium thiocyanate as a thiocyanation reagent for haloketones. These reactions proceed in polar solvents such as acetonitrile and ethanol which is able to dissolve CuBr_2 and KSCN, and do not proceed in nonpolar solvent such as benzene, in which CuBr_2 and KSCN are not soluble.



For instance, diethyl 2-methylmalonate **1b** is brominated with CuBr_2 in acetonitrile to give diethyl 2-bromo-2-methylmalonate **2b** in high yield, and the brominated product is thiocyanated with KSCN under similar conditions to afford diethyl 2-methyl-2-thiocyanatomalonate **3b**. However, it is impossible to carry out the corresponding reactions in the same vessel because CuBr_2 and KSCN will interact, and thus the overall reaction must be separated into two steps: first, a reaction of **1b** with CuBr_2 , followed by a reaction of **2b** with KSCN. Both the reaction of **1b**

Table 1. Reaction of diethyl 2-methylmalonate with various reagents system^a

Reagents system	Product	Yield/%
CuBr_2 - KSCN		no reaction
CuBr_2 - KSCN/ SiO_2		no reaction
$\text{CuBr}_2/\text{Al}_2\text{O}_3$ - KSCN	2b	90
$\text{CuBr}_2/\text{Al}_2\text{O}_3$ - KSCN/ SiO_2	3b	83

^a All reactions were carried out at 50 °C at 18 h in benzene.

with CuBr_2 and the reaction of **2b** with KSCN did not proceed in benzene at 50 °C. In contrast, reaction **1b** with alumina supported copper(II) bromide⁵, $\text{CuBr}_2/\text{Al}_2\text{O}_3$, in benzene proceeded at 50 °C to give **2b** in 95% yield after 1 h. Reaction of **2b** with silica gel supported potassium thiocyanate⁶, KSCN/ SiO_2 , occurred also in benzene under similar conditions and afforded **3b** in 87% yield after 18 h. If β -dicarbonyl compounds are subjected to a mixed suspension of $\text{CuBr}_2/\text{Al}_2\text{O}_3$ and KSCN/ SiO_2 in benzene, it was strongly expected to undergo two steps reactions in one-pot. β -Dicarbonyl compounds will react with CuBr_2 to give the

Table 2. Reaction of β -dicarbonyl compounds **1** with $\text{CuBr}_2/\text{Al}_2\text{O}_3$ - KSCN/SiO_2 in one-pot^a

β -Dicarbonyl compound	Product	Yield /%
		69
		83
		18
		71
		89
		83
		54

^a All reactions were carried out at 50 °C for 18 h in benzene. Molar ratios were **1** : CuBr_2 : KSCN = 1 : 3 : 6.

corresponding brominated products, which will further react with KSCN , yielding the final products, α -thiocyanato- β -dicarbonyl compounds. The following results demonstrate the viability of this concept (see Tables 1, 2). Diethyl 2-methylmalonate **1b** (1 mmol) was added to the suspension of $\text{CuBr}_2/\text{Al}_2\text{O}_3$ (3 mmol) and KSCN/SiO_2 (6 mmol) in benzene (10 ml), and the mixture was stirred at 50 °C for 18 h to give **3b** in 83% yield. Excess KSCN/SiO_2 was required to promote the thiocyanate formation. However, the first step, bromination with $\text{CuBr}_2/\text{Al}_2\text{O}_3$, was not

affected by the presence of excess KSCN/SiO_2 , and the used solid reagents were easily removed by filtration. Compound **1d** and **1e** as well as **1b** afforded **3d** and **3e** in high yields respectively. In the case of **1a**, the yield of **3a** was lower than that of **1b** because **1a** was brominated with $\text{CuBr}_2/\text{Al}_2\text{O}_3$ to give a mixture of mono- and dibrominated products. Diethyl 2-benzylmalonate **1c** gave **3c** in low yield along with **2c**. Although **1c** was easily brominated to give **2c** in high yield, subsequent substitution of **2c** with KSCN/SiO_2 was hard due to steric hindrance of bulky benzyl group at α -carbon. The reactivity of β -diketones such as **1f** was lower than those of β -ketoesters and β -diesters. Monoketones also reacted with the supported reagents system to give the corresponding thiocyanates. However, the yields were low because the first step, bromination, was very slow. For example, when reaction of cyclohexanone with the supported reagents system in benzene was carried out at 50 °C for 24 h, α -thiocyanatocyclohexanone was obtained in 33% yield.

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 steps reactions are possible in one-pot by using a couple of supported reagents. Efforts are being directed toward further application of this concept to other chemical transformations.

References and Notes

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- M. Kodomari, H. Satoh, and S. Yoshitomi, *Bull. Chem. Soc. Jpn.*, **61**, 4149 (1988); Alumina supported copper(II) bromide having 33% w/w on neutral alumina was used.
- M. Kodomari, T. Kuzuoka and S. Yoshitomi, *Synthesis*, **1983**, 141; Silica gel supported potassium thiocyanate having 49% w/w on silica gel was used. Silica gel (Wako Pure Chemical Industries, Wakogel C-200) and alumina (ICN Biomedicals, ICN Alumina N-Super 1) were used for preparation of the supported reagents without further purification.