One-Pot Synthesis Using Supported Reagents System: Conversion of β-Dicarbonyl Compounds to α-Thiocyano-β-dicarbonyl Compounds Using $CuBr_2/Al_2O_3$-$KSCN/SiO_2$

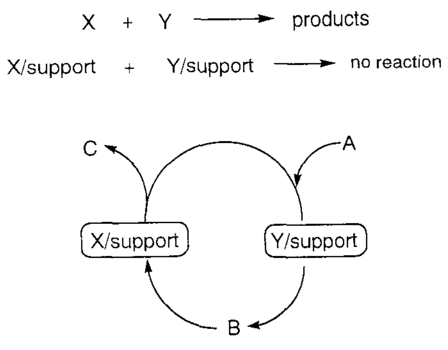
Yoshitada Suzuki and Mitsuo Kodomari*

Department of Industrial Chemistry, Faculty of Engineering, Shibaura Institute of Technology, Shibaura, Minato-ku, Tokyo 108-0023

(Received July 27, 1998; CL-980569)

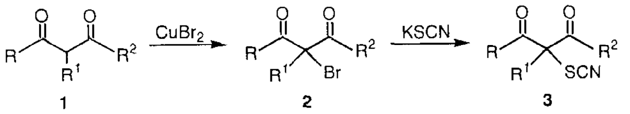
Transformation of β-dicarbonyl compound **1** to α-thiocyano-β-dicarbonyl compounds **3** in one-pot was achieved by using supported reagents system $CuBr_2/Al_2O_3$ - $KSCN/SiO_2$, in which **1** reacts first with $CuBr_2/Al_2O_3$ and the product, α-bromo-β-dicarbonyl compound **2** reacts with $KSCN/SiO_2$ 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 Regen[2] 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 $ZnCl_2/SiO_2$ as an acid catalyst and K_2CO_3/Al_2O_3 as a scavenger of hydrogen chloride[3]. When K_2CO_3 was used as a solid base instead of K_2CO_3/Al_2O_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-thiocyanato-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-Thiocyanatoketones are usually prepared from ketones *via* an indirect way that includes nucleophilic displacement of α-haloketones with ^-SCN[4]. 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 acetonitril 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.



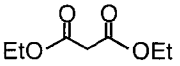
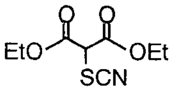
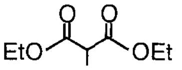
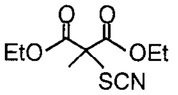
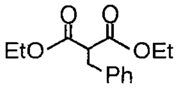
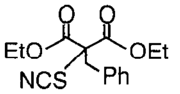
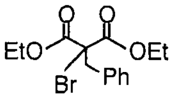
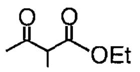
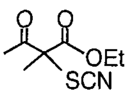
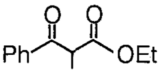
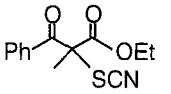
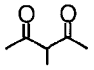
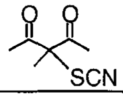
For instance, diethyl 2-methylmalonate **1b** is brominated with $CuBr_2$ in acetonitril to give diethyl 2-bromo-2-methylmalonate **2b** in high yield, and the brominated product is thiocyanated with KSCN under similar conditions to afford diethyl 2-methyl-2-thiocyanatomalonate **3b**. However, it is 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** 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) bromide[5], $CuBr_2/Al_2O_3$, in benzene proceeded at 50 °C to give **2b** in 95% yield after 1 h. Reaction of **2b** with silica gel supported potassium thiocyanate[6], $KSCN/SiO_2$, 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 $CuBr_2/Al_2O_3$ 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 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
$CuBr_2/Al_2O_3$ - KSCN	**2b**	90
$CuBr_2/Al_2O_3$ - $KSCN/SiO_2$	**3b**	83

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

Table 2. Reaction of β-dicarbonyl compounds **1** with $CuBr_2/Al_2O_3$ - $KSCN/SiO_2$ in one-pot[a]

β-Dicarbonyl compound		Product		Yield /%
	**1a**		**3a**	69
	**1b**		**3b**	83
	**1c**		**3c**	18
			**2c**	71
	**1d**		**3d**	89
	**1e**		**3e**	83
	**1f**		**3f**	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 $CuBr_2/Al_2O_3$ (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 $CuBr_2/Al_2O_3$, 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 $CuBr_2/Al_2O_3$ 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

1 B. J. Cohen, M. A. Krans, and A. Patchornik, *J. Am. Chem. Soc.*, **103**, 7620 (1981).
2 B. Kim and S. L. Regen, *Tetrahedron Lett.*, **24**, 689 (1983).
3 M. Kodomari, S. Nawa, and T. Miyoshi, *J. Chem. Soc., Chem. Commun.*, **1995**, 1895.
4 R. G. Guy, "The Chemistry of Cyanates and their Derivatives, " ed by S. Patai, John Wiley & Sons, New York (1977), pp. 819-886.
5 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.
6 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.