Communications

Facile Synthesis of β-Ketoesters by Indium-Mediated Reaction of Acyl Cyanides with Ethyl Bromoacetate under Ultrasonication

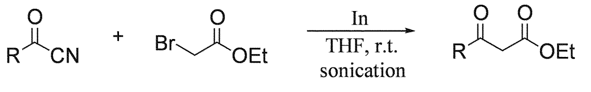
Young Sang Park, Jung Hwa Han, Byoungseung Yoo,[†] Kyung Il Choi,[‡]
Joong Hyup Kim,[‡] Cheol Min Yoon, and Byung Woo Yoo[*]

Department of Advanced Materials Chemistry, Korea University, Jochiwon, Chungnam 339-700, Korea
[*]E-mail: bwyoo@korea.ac.kr
[†]Department of Food Science and Technology, Dongguk University, Chung-gu, Seoul 100-715, Korea
[‡]Biochemicals Research Center, Korea Institute of Science and Technology, Cheongryang, Seoul 130-650, Korea

Received February 17, 2005

Key Words : β-Ketoester, Indium, Acyl cyanide, Ethyl bromoacetate

The Reformatsky reaction between α-haloester and a carbonyl compound constitutes one of the most useful methods for carbon-carbon bond formation in organic synthesis.[1] It offers the advantages of regioselective enolate formation under nearly neutral conditions. However, the classic method employing zinc dust as a reductant can be plagued by extended reaction times and byproduct formation.[2] To address these concerns, besides the classical zinc enolate, various metal enolates have been examined so far, of which indium enolate was first introduced to organic synthesis in 1975.[3] The scope of the Reformatsky reaction has progressed through the years and is the subject of several reviews.[4] It has recently been reported that organoindium reagents, prepared from α-haloester and metallic indium, readily react with aldehydes and ketones to give β-hydroxy esters.[5] However, to the best of our knowledge, the indium-mediated Reformatsky type reaction has never been applied to acyl cyanides as carboxylic acid derivatives. It was found that acyl cyanide can act as an electrophile in the indium-mediated Reformatsky type reaction to give β-ketoesters in good yields. Herein we wish to report the first example of Reformatsky type reaction of α-haloesters with acyl cyanides mediated by indium.

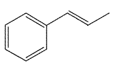
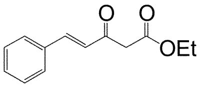
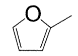
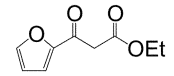
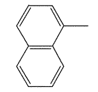
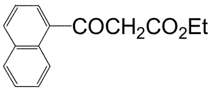


(1)

1 **2** **3**

Reaction of acyl cyanides **1** with ethyl bromoacetate **2** in the presence of indium metal under sonication[6] produced β-ketoesters **3** (eq. 1). Under the optimum conditions, the coupling reaction proceeds efficiently with good yields. To determine the optimum conditions, the reaction was performed under several reaction conditions. Particularly, the choice of the solvent is critical in the indium-mediated reaction. Thus, the reaction was carried out in several solvents but failed in THF/H_2O, DMF, DMF/H_2O, CH_3CN, and water. Among the solvents tested in this study, THF has been found to be the most suitable solvent for the reaction in terms of reaction time and yield. It is noteworthy that practically no reaction occurred in the absence of sonication. Thus, ultrasonic irradiation is necessary to accelerate the reaction. The rate enhancement under sonication may be attributed to the cavitation and the activation of the metal surface by sonic waves.[7] It was also observed that 1 : 1.5 : 2 ratio of acyl cyanide, indium metal, and ethyl bromoacetate was found to be the best ratio. Various acyl cyanides were

Table 1. Indium-mediated reaction of acyl cyanide with ethyl bromoacetate

Entry	Acyl Cyanide R	Product[a]	Time (h)	Yield (%)[b]
1	Ph	$PhCOCH_2CO_2Et$	2	88
2	2-$CH_3C_6H_4$	2-$CH_3C_6H_4COCH_2CO_2Et$	2	82
3	4-$CH_3C_6H_4$	4-$CH_3C_6H_4COCH_2CO_2Et$	3	90
4	4-tert-BuC_6H_4	4-tert-Bu$C_6H_4COCH_2CO_2Et$	3	92
5	4-$CH_3OC_6H_4$	4-$CH_3OC_6H_4COCH_2CO_2Et$	2	79
6	4-BrC_6H_4	4-Br$C_6H_4COCH_2CO_2Et$	2	82
7	2-ClC_6H_4	2-Cl$C_6H_4COCH_2CO_2Et$	2	85
8			3	85
9			3	90
10			2	87
11	$CH_3(CH_2)_8$	-	12	0
12	Cyclohexyl	-	12	0

[a]All the compounds obtained showed NMR, IR, and mass spectral data compatible with the structure. [b]Isolated yield.

screened to examine the generality of this reaction and the results are summarized in Table 1. Unfortunately, when acyl cyanide was replaced with acyl chloride, the reaction did not give any significant desired product. Although the cyano group has been reported to be a good Reformatsky acceptor,[8] our experimental results[9] suggest that the cyano group in the substrates does not react with the indium reagent. When a 1 : 1 mixture of benzonitrile and benzoyl cyanide were subjected to this reagent, the latter acted exclusively as an acceptor. This explains that the carbonyl group is more reactive than the cyano group. Although the protocal described here was also applied to reactions with aliphatic acyl cyanide, only recovered starting material was isolated (entries 11 and 12). For the aromatic acyl cyanides, the presence of various substituents, such as methyl, methoxy, bromo, chloro, and isolated double bond on the aromatic ring showed little effects on the efficiency of the reactions. Although the mechanism of the reaction is still not clarified, it is assumed that the indium enolates prepared from ethylbromoacetates and indium metal couple with acyl cyanides to afford β-ketoesters.

In conclusion, this paper describes a simple and efficient method for the synthesis of various β-ketoesters from ethyl bromoacetate and acyl cyanides using indium metal. We believe that this procedure will present an attractive alternative to the existing methodologies.

Acknowledgments. This work was financially supported by Korea Institute of Science and Technology (2E16800) and partially by Korea University.

References

1. (a) Rathke, M. W.; Weipert, P. *Zinc Enolates: the Reformatsky and Blaise Reaction* in *Comprehensive Organic Reactions*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, pp 277-299. (b) Reformatsky, S. *Chem. Ber.* **1887**, *20*, 1210. (c) Furstner, A. *Synthesis* **1989**, 571.
2. (a) Shriner, R. L. *Organic Reactions* **1942**, *1*, 1. (b) Ross, N. A.; Bartsh, R. A. *J. Org. Chem.* **2003**, *68*, 360.
3. Chao, L. C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253.
4. (a) Shriner, R. L. *Org. React.* **1942**, *1*, 1. (b) Gaudemar, M. *Organomet. Chem. Rev. A* **1972**, *8*, 183. (c) Rathke, M. W. *Org. React. (N. Y.)* **1975**, *22*, 423. (d) Rieke, R. D.; Ulm, S. J. *Synthesis* **1975**, *22*, 452.
5. (a) Araki, S.; Ito, H.;Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453. (b) Araki, S.; Katsumura, N.; Kawasaki, K.; Butsugan, Y. *J. Chem. Soc. Perkin Trans. I* **1991**, 499. (c) Araki, S.; Shimizu, T.; Butsugan, Y. *Chem. Express* **1991**, *6*, 583. (d) Bang, K.; Lee, K.; Park, Y.; Lee, P. *Bull. Korean Chem. Soc.* **2002**, *23*, 1272.
6. Sonications were carried out in a BRANSONIC ultrasonic cleaner bath, which delivered a 47 kHz wave, with a fixed electrical power of 125 Watts.
7. (a) Han, B. H.; Boudjouk, P. *J. Org. Chem.* **1982**, *40*, 6731. (b) Einhorn, C.; Einhorn, J.; Luche, J.-L. *Synthesis* **1975**, *40*, 2253.
8. (a) Blaise, E. E. C. R. *Hebd. Seances Acad. Sci.* **1901**, *132*, 478. (b) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833. (c) Krepski, L. R.; Lynch, L. E.; Heilmann, S. M.; Rasmussen, J. K. *Tetrahedron Lett.* **1985**, *26*, 981.
9. A typical procedure: Indium metal (173 mg, 1.5 mmol) was added to a solution of ethyl bromoacetate (334 mg, 2.0 mmol) in THF (3 mL) and the resulting mixture was stirred for 30 min at room temperature. A solution of benzoyl cyanide (131 mg, 1.0 mmol) in THF (1 mL) was then slowly added and the mixture was stirred for 2 h at room temperature under sonication. After complete conversion, as indicated by TLC, the reaction mixture was poured into water and extracted with ether. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to yield crude product, which was purified by column chromatography on silica gel (hexane : ethyl acetate = 6 : 1) to afford ethyl phenylacetoacetate (169 mg, 88%).