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A New Coupling Reaction of Alkyl Iodides with α,β -Unsaturated Esters Using $\text{Ni}_2\text{B}(\text{cat.})$ -BER in Methanol

Tae Bo Sim, Jaesung Choi, and Nung Min Yoon*

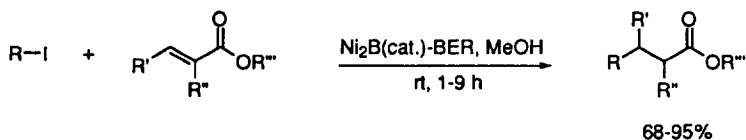
Department of Chemistry, Sogang University, Seoul 121-742, Korea

Abstract: Alkyl iodides can be coupled with α,β -unsaturated esters using $\text{Ni}_2\text{B}(0.05\text{-}0.2 \text{ eq})$ -BER(3 eq) in methanol at room temperature. Products (68-95%) are conveniently isolated, simply filtering the resin and evaporating the excess enoates and methanol. Copyright © 1996 Elsevier Science Ltd

Carbon-carbon bond formation *via* radical reactions is one of the most important synthetic steps in the construction of organic molecules. Accordingly several methods for the addition of alkyl radicals to alkenes have been worked out.¹ Among them, the coupling of alkyl halides with electron-deficient alkenes has been successfully carried out by using tributyltin hydride.² However, this method must be carried out under nitrogen atmosphere, needs high temperature initiators or photolytic conditions, and is troublesome in the purification of the products from trialkyltin halides,^{1(c),3} although a partial solution to this problem has been devised by using polymer-supported organotin compounds.^{3(a),4} Recently, we have reported borohydride exchange resin (BER)- Ni_2B in methanol is an excellent reagent for the selective reduction of alkyl halides.⁵ In the course of this study, it has been observed that not only secondary and tertiary bromides are readily reduced in comparable rate as primary bromides, but also 1-phenethyl bromide is coupled to 2,3-diphenylbutane (30%) beside the expected reduction to ethylbenzene (70%) by this system. These strongly suggested an involvement of a radical intermediate. We report here a new radical coupling reaction of alkyl iodides with α,β -unsaturated esters using $\text{Ni}_2\text{B}(\text{cat.})$ -BER in methanol (Scheme 1).⁶


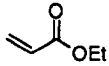
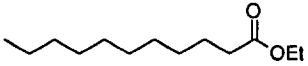

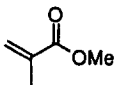
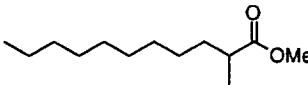

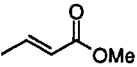
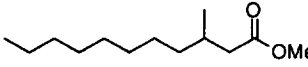
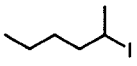
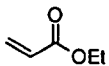
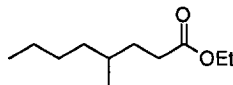
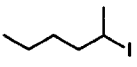
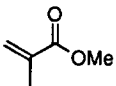
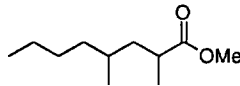
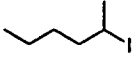
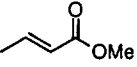
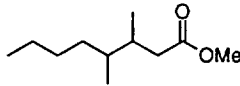

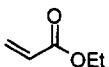
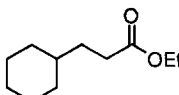

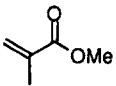
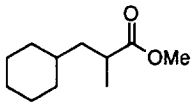

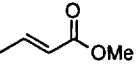
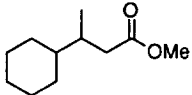
The results are summarized in Table 1. As shown in Table 1, 1-iodooctane, 2-iodohexane, and iodocyclohexane were smoothly coupled with methyl methacrylate and methyl crotonate in methanol in 1-9 h

Scheme 1



R = 1° alkyl, 2° alkyl, cyclohexyl, R', R'' = H, alkyl, R''' = methyl, ethyl

Table 1. Coupling Reaction of Alkyl Iodides with α,β -Unsaturated Esters Using Ni₂B(cat.)-BER in Methanol at Room Temperature (20 °C)^a

entry	alkyl iodide	enoate	Ni(OAc) ₂ (eq) time(h)		product	yield(%) ^b
1			0.05	20		45
			0.2	3		86
2			0.05	9		88
			0.2	1		80
3			0.05	9		68, 52 ^c
			0.2	1		42
4			0.2	1		92
5			0.05	6		91
			0.2	1		88
6			0.05	6		74
7			0.05	6		83
			0.2	3		95
8			0.05	9		93
			0.2	1		93
9			0.05	6		85
			0.2	1		60

^aAlkyl iodides (5 mmol) were reacted with enoates (100 mmol) using Ni(OAc)₂ (0.25-1 mmol) and BER (15 mmol) at room temperature in methanol (20 mL). ^bIsolated yield. ^cReaction was carried out with 50 mmol of methyl crotonate.

at room temperature (20 °C) using 0.05 eq of Ni(OAc)₂, 3 eq of BER, and 20 eq of α,β -unsaturated esters (entries 2, 3, 5, 6, 8, and 9). Somewhat lower yields (ca. 10-20%) were observed when 10 eq of unsaturated esters were used (entry 3). In the coupling of 1-iodooctane with ethyl acrylate, a poor yield (45%) was observed in a long reaction time (20 h) under the above conditions (entry 1); however, this difficulty was readily overcome by increasing the amount of Ni(OAc)₂ (0.2 eq) (entries 1, 4, and 7). Since the double bond of ethyl acrylate is rapidly hydrogenated even at 0 °C by this system,⁷ 1-iodooctane cannot compete successfully with ethyl acrylate for the small amount (0.05 eq) of Ni₂B catalyst. On the other hand, the increase of Ni₂B brought a decrease in yields in the coupling with methyl crotonate, a hindered unsaturated ester (entries 3, 6 and 9). In this case although methyl crotonate is hydrogenated very slowly by this system under the reaction conditions,⁷ the coupling of alkyl radical with this hindered alkene must compete with the reduction of the radical to the corresponding alkanes, and the increase of Ni₂B increased the reduction. Therefore moderate to good yields were obtained with methyl crotonate in contrast to the excellent yields obtained with ethyl acrylate and methyl methacrylate. In the case of methyl methacrylate, the increase of Ni₂B increases the rate of coupling without much affecting the yields (entries 2, 5, and 8). Finally, Ni₂B(cat.)-BER in methanol has an additional advantage of simple work-up. In all cases, the simple filtration of Ni₂B-BER and the evaporation of methanol and unsaturated esters under reduced pressure gave pure products.

In conclusion, the Ni₂B(cat.)-BER in methanol is a reagent of choice for the coupling of alkyl iodides with α,β -unsaturated esters because of its good yield, mild reaction conditions, and a simple work-up procedure.

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6. *Preparation of Borohydride Exchange Resin*: An aqueous solution of sodium borohydride (1 M, 500 mL) was stirred with wet chloride-form anion exchange resin (Amberlite IRA-400 [20 - 50 mesh], 200 g) for 15 min. The resulting resin was washed thoroughly with distilled water until free from excess NaBH₄. The borohydride form anion exchange resin was then dried *in vacuo* at 60 °C for 5 h to give 102 g of dried borohydride exchange resin (BER). The dried resin was analyzed for borohydride content by hydrogen

evolution on acidification with 2 N HCl and the average hydride content of BER was found to be 3.0 mmol of BH_4^- per gram. The dried resin was stored under nitrogen in refrigerator ($\sim 4^\circ\text{C}$). The hydride content was constant over 6 weeks.

General Procedure: The preparation of ethyl undecanoate is representative. BER (5.17 g, 15 mmol) was added to a methanol solution (10 mL) of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (0.25 g, 1 mmol), and the mixture was stirred slowly at room temperature. Immediately a black coating of Ni_2B and a slow hydrogen evolution due to decomposition of BER were observed. After 1 min, ethyl acrylate (10.01 g, 100 mmol) and a methanol solution (10 mL) of 1-iodooctane (1.20 g, 5 mmol) were added, and the mixture was stirred at room temperature. After 3 h, the resin was removed by filtration, and excess ethyl acrylate and methanol were evaporated under reduced pressure to yield the pure ethyl undecanoate (0.92 g, 86%): ^1H NMR (200 MHz, CDCl_3) δ 4.13 (q, $J = 7.2$ Hz, 2 H), δ 2.29 (t, $J = 7.3$ Hz, 2 H), δ 1.69 - 0.85 (m, 22 H); MS (EI, 70 eV) m/e (relative intensity) 55 (24), 60 (18), 73 (19), 88 (100), 101 (28), 169 (9), 214 (3).

Methyl 2-methylundecanoate: ^1H NMR (200 MHz, CDCl_3) δ 3.70 (s, 3 H), δ 2.46 (tq, $J = 6.9, 6.9$ Hz, 1 H), δ 1.67 - 0.88 (m, 22 H); MS (EI, 70 eV) m/e (relative intensity) 57 (20), 88 (100), 101 (25), 143 (3), 157 (3), 214 (1).

Methyl 3-methylundecanoate: ^1H NMR (200 MHz, CDCl_3) δ 3.69 (s, 3 H), δ 2.31 (dd, $J = 14.2, 6.0$ Hz, 1 H), δ 2.11 (dd, $J = 14.2, 8.2$ Hz, 1 H), δ 1.60 - 0.70 (m, 21 H); MS (EI, 70 eV) m/e (relative intensity) 55 (11), 69 (10), 74 (100), 101 (44), 157 (2), 183 (3), 214 (2).

Ethyl 4-methyloctanoate: ^1H NMR (200 MHz, CDCl_3) δ 4.13 (q, $J = 7.2$ Hz, 2 H), δ 2.34 - 2.25 (m, 2 H), δ 1.69 - 0.86 (m, 18 H); MS (EI, 70 eV) m/e (relative intensity) 55 (56), 57 (49), 73 (39), 88 (96), 101 (100), 129 (11), 141 (6), 157 (1).

Methyl 2,4-dimethyloctanoate: Diastereomer ratio was 1:1.12 as revealed by capillary GC. ^1H NMR (200 MHz, CDCl_3) δ 3.70 (s, 3 H), δ 2.67 - 2.51 (m, 1 H), δ 1.76 - 0.86 (m, 18 H); MS (EI, 70 eV) m/e (relative intensity) 57 (12), 69 (13), 73 (6), 88 (100), 101 (28), 129 (3), 143 (2), 186 (1).

Methyl 3,4-dimethyloctanoate: Diastereomers were not separated by capillary GC. ^1H NMR (200 MHz, CDCl_3) δ 3.69 (s, 3 H), δ 2.34 - 2.00 (m, 2 H), δ 1.65 - 0.77 (m, 16 H); MS (EI, 70 eV) m/e (relative intensity) 57 (25), 68 (48), 73 (100), 86 (81), 100 (68), 112 (77), 154 (8), 186 (1).

Ethyl 3-cyclohexylpropionate: ^1H NMR (200 MHz, CDCl_3) δ 4.13 (q, $J = 7.2$ Hz, 2 H), δ 2.30 (t, $J = 7.2$ Hz, 2 H), δ 1.82 - 0.79 (m, 16 H); MS (EI, 70 eV) m/e (relative intensity) 55 (83), 60 (38), 73 (43), 88 (89), 97 (43), 101 (100), 121 (16), 138 (16), 184 (1).

Methyl 3-cyclohexyl-2-methylpropionate: ^1H NMR (200 MHz, CDCl_3) δ 3.70 (s, 3 H), δ 2.50 (tq, $J = 7.0, 7.0$ Hz, 1 H), δ 1.72 - 0.80 (m, 16 H); MS (EI, 70 eV) m/e (relative intensity) 55 (35), 69 (14), 88 (100), 101 (29), 141 (20), 184 (1).

Methyl 3-cyclohexylbutyrate: ^1H NMR (200 MHz, CDCl_3) δ 3.69 (s, 3 H), δ 2.38 (dd, $J = 14.6, 5.2$ Hz, 1 H), δ 2.08 (dd, $J = 14.6, 11.9$ Hz, 1 H), δ 1.89 - 0.82 (m, 15 H); MS (EI, 70 eV) m/e (relative intensity) 55 (66), 69 (37), 74 (60), 87 (37), 101 (67), 111 (100), 141 (5), 153 (6).

7. Unpublished result: Crotonates were hydrogenated much more slowly than acrylates with BER- Ni_2B in methanol. Actually, at 0°C , acrylates were selectively hydrogenated in the presence of crotonates.