

## Reaction of *tert*-Butyl Dibromoacetate or *N,N*-Diethyldibromoacetamide with Trialkylmanganate Providing an Alkylated Manganese Enolate

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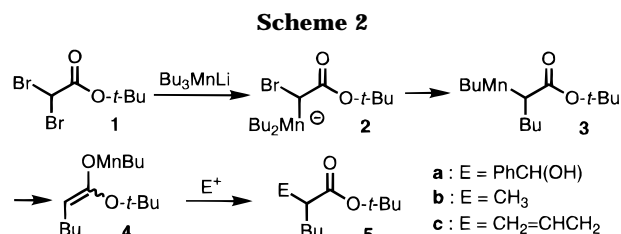
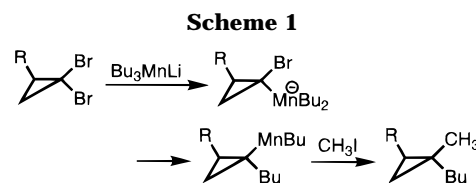
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A multiple-component coupling reaction in one pot<sup>1</sup> promoted by various organometallics represents an extremely powerful means to produce complex organic molecules. Our interest in utilizing organomanganese reagents for selective organic transformations prompted us to explore employment of trialkylmanganate for a consecutive carbon–carbon bond formation.

Recently, we have found that the treatment of *gem*-dibromocyclopropanes with trialkylmanganate followed by addition of an electrophile provided dialkylated cyclopropanes.<sup>2,3</sup> The reaction proceeds as follows: (1) the initial halogen–manganese exchange, (2) butyl migration under Br<sup>−</sup> elimination, (3) second alkylation with an electrophile such as iodomethane (Scheme 1). It then occurred to us that, if both steps of the halogen–manganese exchange and alkyl migration<sup>4</sup> should proceed well, the reaction of dibromoacetate with tributylmanganate would provide an expeditious route to butylated manganese enolate **4** (Scheme 2).<sup>5</sup> We have indeed found that treatment of *tert*-butyl dibromoacetate (**1**) with tributylmanganate followed by addition of an electrophile such as benzaldehyde afforded a three-component coupling aldol-type adduct **5a**.

A solution of *tert*-butyl dibromoacetate **1**<sup>6</sup> (1.0 mmol) in THF (3 mL) was added to tributylmanganate (1.4 mmol),<sup>7</sup> generated from MnCl<sub>2</sub> (1.5 mmol) and *n*-BuLi (4.4 mmol),



**Table 1. Reaction of Dibromo Amide with Trialkylmanganate**

**6**    **a**: R<sup>1</sup> = H    **b**: R<sup>1</sup> = Me    **7**

entry	amide <b>6</b>	R <sup>3</sup> MnMtl or R <sup>2</sup> MgX	electrophile	yield (%)
1	<b>6a</b> : R <sup>1</sup> = H	<i>n</i> -Bu <sub>3</sub> MnLi	D <sub>2</sub> O	<b>7a</b> , 82
2	<b>6a</b>	<i>n</i> -Bu <sub>3</sub> MnLi	CH <sub>2</sub> =CHCH <sub>2</sub> Br	<b>7b</b> , 76
3	<b>6a</b>	<i>n</i> -Bu <sub>3</sub> MnLi	PhCHO	<b>7c</b> , 72 <sup>a</sup>
4	<b>6a</b>	<i>n</i> -Bu <sub>3</sub> MnLi	<i>n</i> -C <sub>6</sub> H <sub>13</sub> CHO	<b>7d</b> , 77 <sup>b</sup>
5	<b>6a</b>	<i>n</i> -Bu <sub>3</sub> MnLi	CH <sub>3</sub> I	<b>7e</b> , 70
6	<b>6a</b>	<i>n</i> -Bu <sub>3</sub> MnMgBr	H <sub>2</sub> O	<b>7f</b> , 80
7	<b>6a</b>	<i>n</i> -Bu <sub>3</sub> MnMgBr	PhCHO	<b>7c</b> , 84 <sup>c</sup>
8	<b>6a</b>	Et <sub>3</sub> MnMgBr	PhCHO	<b>7g</b> , 95 <sup>d</sup>
9	<b>6a</b>	Ph <sub>3</sub> MnMgBr	H <sub>2</sub> O	<b>7h</b> , 83
10	<b>6a</b>	Ph <sub>3</sub> MnMgBr	PhCHO	<b>7i</b> , 73 <sup>e</sup>
11	<b>6b</b> : R <sup>1</sup> = Me	<i>n</i> -Bu <sub>3</sub> MnLi	H <sub>2</sub> O	<b>7j</b> , 89
12	<b>6b</b>	<i>n</i> -Bu <sub>3</sub> MnLi	CH <sub>2</sub> =CHCH <sub>2</sub> Br	<b>7k</b> , 51
13	<b>6b</b>	<i>n</i> -Bu <sub>3</sub> MnLi	PhCHO	<b>7l</b> , 90 <sup>f</sup>
14	<b>6a</b>	<i>n</i> -BuMgBr	CH <sub>2</sub> =CHCH <sub>2</sub> Br	<b>7b</b> , 61
15	<b>6a</b>	<i>n</i> -BuMgBr	PhCHO	<b>7c</b> , 95 <sup>g</sup>
16	<b>6a</b>	EtMgBr	H <sub>2</sub> O	<b>7m</b> , 74
17	<b>6a</b>	EtMgBr	PhCHO	<b>7g</b> , 80 <sup>h</sup>
18	<b>6a</b>	PhMgBr	H <sub>2</sub> O	<b>7h</b> , 67
19	<b>6a</b>	PhMgBr	PhCHO	<b>7i</b> , 60 <sup>i</sup>

<sup>a</sup> Syn/anti = 65/35. <sup>b</sup> Syn/anti = 69/31. <sup>c</sup> Syn/anti = 49/51. <sup>d</sup> Syn/anti = 49/51. <sup>e</sup> Syn/anti = 49/51. <sup>f</sup> Isomeric ratio = 36/61. <sup>g</sup> Syn/anti = 45/55. <sup>h</sup> Syn/anti = 47/53. <sup>i</sup> Syn/anti = 51/49.

in THF (10 mL) at −78 °C. The mixture was warmed to 0 °C and stirred for 15 min at that temperature, and then benzaldehyde (3.0 mmol) was added to the resulting mixture. Extractive workup (AcOEt/water) followed by silica gel column purification gave β-hydroxy ester **5a** (syn/anti = 77/23)<sup>8</sup> in 46% yield. An addition of iodomethane or 3-bromopropene instead of benzaldehyde afforded the corresponding adduct **5b** or **5c** in 42% or 69% yield, respectively.

The use of *N,N*-diethyldibromoacetamide (**6a**) in place of *tert*-butyl dibromoacetate (**1**) improved the yield of the corresponding adducts.<sup>9</sup> The representative results are shown in Table 1 (entries 1–13). Several comments are worth noting. (1) Manganate reagents, derived from MnCl<sub>2</sub>

(8) The isomeric ratio of **5a** could not be improved when the aldol-type reaction was conducted under kinetic conditions (at −78 °C, 5 min).

(9) The trapping experiment of an intermediary manganese enolate from **6a** and *n*-Bu<sub>3</sub>MnLi by trimethylsilyl triflate resulted in the formation of only *N,N*-diethylhexanamide. Thus, the isomeric ratio (*E/Z*) of the enolate could not be determined.

(1) Hall, N. *Science* **1994**, *266*, 32.

(2) (a) Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1996**, *37*, 5377. (b) Kakiya, H.; Inoue, R.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 3275.

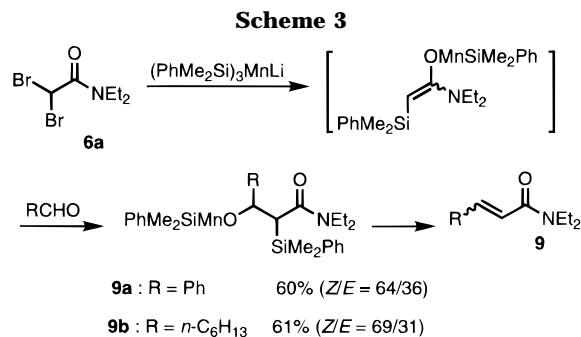
(3) The reaction of *gem*-dibromocyclopropanes with dibutylcuprate and tributylzincate has been reported. (a) Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1976**, *98*, 2362. (b) Kitatani, K.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1600. (c) Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**, *58*, 2958. (d) Harada, T.; Hattori, K.; Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6035, 6039.

(4) Alkyl migration of α-haloborate: (a) Brown, H. C.; Rogic, M. M.; Nambu, H.; Rathke, M. W. *J. Am. Chem. Soc.* **1969**, *91*, 2147. (b) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 1911. (c) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6852. (d) Brown, H. C.; Nambu, H.; Rogic, M. M. *J. Am. Chem. Soc.* **1969**, *91*, 6855. (e) Brown, H. C.; Rogic, M. M.; Rathke, M. W.; Kabalka, G. W. *J. Am. Chem. Soc.* **1968**, *90*, 818.

(5) Very recently, generation of manganese enolates from α-acetoxy carbonyl compounds with tributylmanganate has been reported: Hojo, M.; Harada, H.; Ito, H.; Hosomi, A. *J. Am. Chem. Soc.* **1997**, *119*, 5459. Other methods for the generation of manganese enolates are as follows. Deprotonation: Cahiez, G.; Figadere, B.; Clery, P. *Tetrahedron Lett.* **1994**, *35*, 3065. Transmetalation: Cahiez, G.; Figadere, B.; Clery, P. *Tetrahedron Lett.* **1994**, *35*, 3069. 1,4-Addition: Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541. Takai, K.; Ueda, T.; Kaihara, H.; Sunami, Y.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 8728.

(6) Treatment of ethyl dibromoacetate with tributylmanganate provided acetoacetate derivative **14** in 32% yield along with an unidentified complex mixture (see Scheme 6).

(7) (a) Cahiez, G. *Butyl Manganese Chloride and Related Reagents*. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, 1995; p 925. (b) Cahiez, G. *Manganese(II) Chloride*. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L., Ed.; Wiley: Chichester, 1995; p 3227. (c) Cahiez, G. *An. Chim.* **1995**, *91*, 561. (d) Corey, E. J.; Posner, G. H. *Tetrahedron Lett.* **1970**, 315. (e) Okada, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1996**, *118*, 6076. (f) X-ray of Ph<sub>3</sub>Mn<sub>2</sub>Li<sub>2</sub>; Bartlett, R. A.; Olmstead, M. M.; Power, P. P.; Shoner, S. C. *Organometallics* **1988**, *7*, 1801.



and a Grignard reagent such as *n*-BuMgBr, EtMgBr, and PhMgBr, proved to be equally as effective as lithium tributylmanganate. This result is in sharp contrast to the reaction of *tert*-butyl dibromoacetate (**1**) with tributylmanganate, generated from MnCl<sub>2</sub> and butylmagnesium bromide, which results in formation of a small amount of butylated product **5** (E = H) (<5% yield) along with a complex mixture.<sup>10</sup> (2) No products arising from attack of the  $\alpha$ -bromo enolate, BrCH=C(OMn<sup>-</sup>Bu<sub>2</sub>)NEt<sub>2</sub> (**8**), on the electrophile such as iodomethane or benzaldehyde could be detected. This indicated that the migration of the alkyl group on manganese to the adjacent carbon providing **3** occurred at a rate that was much faster than the rate of conversion of BrCH(Mn<sup>-</sup>Bu<sub>2</sub>)CONEt<sub>2</sub> (**2**) into the  $\alpha$ -bromo enolate **8**. (3) Not only *N,N*-diethyldibromoacetamide (**6a**) but also *N,N*-diethyldibromopropionamide (**6b**) reacted with trialkylmanganate easily to give the expected adducts.

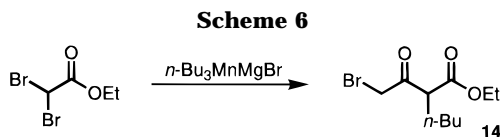
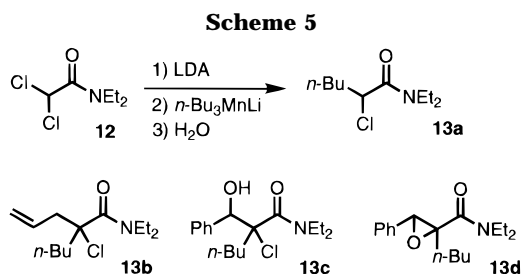
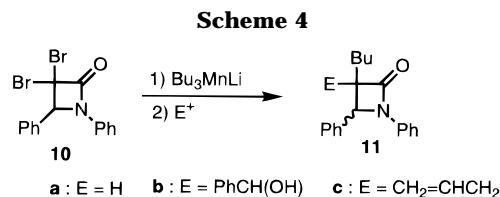
The reaction proceeded in the presence of a catalytic amount of MnCl<sub>2</sub>. For instance, treatment of **6a** (1.0 mmol) with butylmagnesium bromide (3.0 mmol) in the presence of MnCl<sub>2</sub> (0.1 mmol) followed by an addition of 3-bromopropene (3.0 mmol) provided **7b** in 61% yield. The results are also summarized in Table 1 (entries 14–19). Unfortunately, the use of **6b** (R<sup>1</sup> = Me) as a starting material in this catalytic process resulted in a formation of diethyl-2-bromopropionamide, and no butylated amide was observed.

The reaction was applied to a one-pot synthesis of  $\alpha,\beta$ -unsaturated amide.<sup>11</sup> Treatment of **6a** with (PhMe<sub>2</sub>-Si)<sub>3</sub>MnLi, derived from PhMe<sub>2</sub>SiLi<sup>12</sup> and MnCl<sub>2</sub>, followed by addition of an aldehyde provided unsaturated amide **9** in good yield as shown in Scheme 3.

(10) Treatment of **1** with triethylmanganate or triphenylmanganate, derived from MnCl<sub>2</sub> and EtMgBr or PhMgBr, gave the corresponding ethylated product or phenylated product in only 15% or 17% yield along with an unidentified complex mixture, respectively, after quenching the reaction mixture with water.

(11) From  $\alpha$ -silyl amide: Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688. Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 1947. Peterson elimination reaction: Ager, D. J. *Org. React.* **1990**, *38*, 1.

(12) Gilman, H.; Lichtemwalter, G. D. *J. Am. Chem. Soc.* **1958**, *80*, 607.



Treatment of dibromo  $\beta$ -lactam **10**<sup>13,14</sup> with tributylmanganate gave butylated lactam **11a** (trans/cis = 26/74) in 62% yield.<sup>15</sup> An addition of 3-bromopropene or benzaldehyde before quenching with water afforded **11b** or **11c** in 48% (isomeric ratio = 67/33) or 46% yield, respectively (Scheme 4).

The reaction of *N,N*-diethyldichloroacetamide (**12**) with tributylmanganate (*n*-Bu<sub>3</sub>MnLi) provided *N,N*-diethyl-2-chlorohexanamide (**13a**) in 34% yield after the reaction mixture was quenched with 1 M HCl. Thus, deprotonation of the  $\alpha$ -proton with tributylmanganate took place in preference to the chlorine–manganese exchange in this case. Treatment of **12** with lithium diisopropylamide followed by tributylmanganate improved the yield of **13a** up to 69% yield. Quenching the reaction mixture with 3-bromopropene or benzaldehyde gave allylated product **13b** or a mixture of **13c** and **13d** (**13c/13d** = 62/38) in 63% or 55% combined yield (Scheme 5).

**Supporting Information Available:** Experimental procedures and compound characterization data (7 pages).

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(13) Manhas, M. S.; Khajavi, M. S.; Bari, S. S.; Bose, A. K. *Tetrahedron Lett.* **1983**, *24*, 2323.

(14) Enolate of  $\beta$ -lactam: (a) DiNinno, F.; Beattie, T. R.; Christensen, B. G. *J. Org. Chem.* **1977**, *42*, 2960. (b) Aimetti, J. A.; Kellogg, M. S. *Tetrahedron Lett.* 1979, 3805. (c) Martel, A.; Daris, J.-P.; Bachand, C.; Menard, M. *Can. J. Chem.* **1987**, *65*, 2179.

(15) Reduced lactam, 1,4-diphenyl-2-azetidinone, was also obtained in 27% yield as a byproduct.