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Dialkylation of *gem*-Dibromocyclopropanes with Trialkylmanganate and Manganese(II) Chloride-Catalyzed Reaction with Alkylmagnesium Bromide

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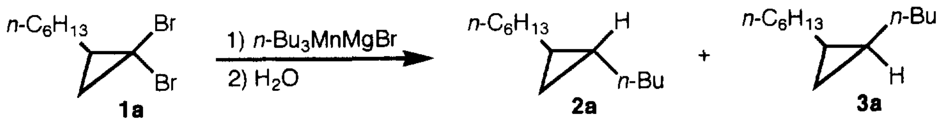
Abstract: Treatment of *gem*-dibromocyclopropanes with trialkylmanganate, derived from manganese(II) chloride and three equivalents of Grignard reagent or alkyllithium, followed by an addition of electrophiles provided dialkylated cyclopropanes in good yields. It was found the reaction with alkylmagnesium halide proceeded in the presence of a catalytic amount of manganese(II) chloride.

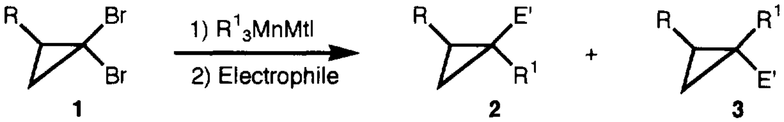
Cyclopropane derivatives are versatile synthetic intermediates. Double alkylation of *gem*-dihalocyclopropanes, which can be easily prepared by the addition of dihalocarbene to olefins, provides us with an effective route to a variety of functionalized cyclopropane derivatives. The transformation of *gem*-dihalocyclopropanes into 1-alkyl-1-butylcyclopropanes has been reported to proceed by successive treatment with dibutylcuprate[1] or tributylzincate[2,3] and several electrophiles. In this paper we describe that the reaction of *gem*-dibromocyclopropanes with trialkylmanganate[4] followed by treatment with electrophiles provides dialkylated cyclopropanes as in the case of the reaction with cuprates or zincates and also that the reaction of *gem*-dibromocyclopropanes with alkylmagnesium halides takes place in the presence of a catalytic amount of manganese(II) chloride .

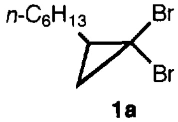
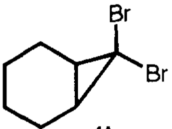
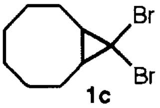
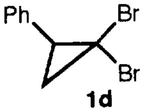
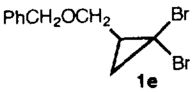
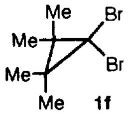
Manganese(II) chloride (151 mg, 1,2 mmol) was sonicated in tetrahydrofuran (THF, 10 ml) under argon atmosphere for 15 min. Butylmagnesium bromide (1.0 *M* ether solution, 3.6 ml, 3.6 mmol) was added to the suspension of $MnCl_2$ in THF at 0 °C. The mixture turned into a clear brown solution and then, after being stirred for 20 min at 0 °C, a part of the manganese(II) chloride precipitated as a white solid. A solution of dibromocyclopropane **1a** (0.28 g, 1.0 mmol) in THF (2 ml) was added at 0 °C and the whole was stirred at 0 °C for 1 h and then at 25 °C for 20 min. The mixture was poured into 1*M* HCl and extracted with hexane (3 x 20 ml). Purification of the products by silica-gel column chromatography gave a mixture of **2a** and **3a** (162 mg) in 89% combined yield (**2a**/**3a** = 71/29).



Various *gem*-dibromocyclopropanes were allowed to react first with trialkylmanganate, triallylmanganate or tris(phenyldimethylsilyl)manganate[5] and then with a variety of electrophiles. The results are summarized in Table 1. Among the solvent systems examined (THF, ether, DME), THF gave the best results. Several

Table 1. Stereoselective Dialkylation of *gem*-Dibromocyclopropanes[a]

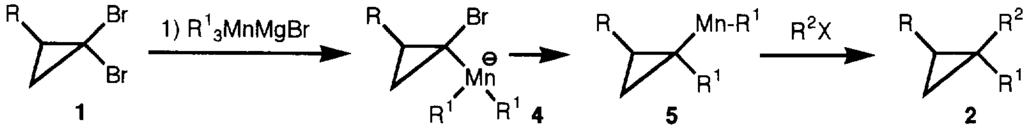


Entry	Substrate **1**	R^1_3MnMtl	Electrophile	Yield (%)	Isomeric Ratio of **2**/**3**
1	 **1a**	Me_3MnLi	H_2O	65	82/18
2		n-Bu_3MnLi	$EtOH^b$	53	68/32
3		n-$Bu_3MnMgBr$	H_2O	89	71/29
4		n-$Bu_3MnMgBr$	$CH_2=CHCH_2Br$	77	89/11
5		n-$Bu_3MnMgBr$	MeI	65	94/6
6		n-$Bu_3MnMgBr$	PhCOCl	72	83/17
7		n-$Bu_3MnMgBr$	I_2	54^c	72/28
8		n-$Bu_3MnMgBr$	$CH_2=CHBr^d$	58	99/1
9		n-$Hex_3MnMgBr$	H_2O	61	86/14
10		n-$Hex_3MnMgBr$	$CH_2=CHCH_2Br$	69	88/12
11		$(PhMe_2Si)_3MnLi$	H_2O	84	58/42
12	 **1b**	n-Bu_3MnLi	H_2O	56	87/13
13		n-$Bu_3MnMgBr$	H_2O	82	97/3
14		n-$Bu_3MnMgBr$	$CH_2=CHCH_2Br$	88	97/3
15	 **1c**	n-$Bu_3MnMgBr$	H_2O	64	87/13
16		n-$Bu_3MnMgBr$	PhCOCl	75	84/16
17		$(CH_2=CHCH_2)_3MnMgBr$	H_2O	64	83/17
18	 **1d**	n-$Bu_3MnMgBr^e$	H_2O	78	87/13
19		n-$Bu_3MnMgBr^e$	$CH_2=CHCH_2Br$	50	92/8
20	 **1e**	n-$Bu_3MnMgBr$	H_2O	75	88/12
21		n-$Bu_3MnMgBr$	$CH_2=CHCH_2Br$	66	88/12
22	 **1f**	$(PhMe_2Si)_3MnLi$	H_2O	62	——

a) The reactions were performed at 0 °C unless otherwise stated. b) Quenching the reaction with EtOH or H_2O gave the same results (yield and isomeric ratio of **2**/**3**). c) See Ref 6. d) $Pd(PPh_3)_4$ (10 mol%) was added. e) The reaction was performed at –48 °C.

comments are worth noting. (1) In contrast to the reaction with cuprate or zincate which has been performed at –48 °C or –85 °C, the reaction with manganate could be performed conveniently at 0 °C. The reaction of **1a** with *n*-Bu_3MnLi at –78°C for 30 min provided 1-bromo-2-hexylcyclopropane[7] (*cis*/*trans* = 1/2) in 65% yield in addition to an isomeric mixture of 1-butyl-2-hexylcyclopropane (**2a**/**3a** = 76/24, 30% yield). Moreover, treatment of **1a** with *n*-$Bu_3MnMgBr$ at –78 °C for 30 min resulted in almost complete recovery of **1a**. (2) Tributylmanganesemagnesium bromide, derived from $MnCl_2$ and three equivalents of butylmagnesium bromide, afforded better yields of butylated cyclopropanes **2** and **3** than tributylmanganeselithium generated from butyllithium (Entry 2 *vs* 3, 12 *vs* 13). (3) Triphenylmanganate $Ph_3MnMgBr$ or Ph_3MnLi gave phenylated cyclopropane in 34% or 30% yield, respectively, upon treatment of **1a**. (4) $(CH_2{=}CH)_3MnMgBr$ and $(Me_3Si\text{-}C{\equiv}C)_3MnMgBr$ gave a minimal amount of the corresponding alkenyl- or alkynylcyclopropanes (<5%). Manganates having secondary and tertiary alkyl ligands such as *i*-$Pr_3MnMgBr$ and *t*-$Bu_3MnMgCl$ gave 1-bromo-2-hexylcyclopropane in 50–55% yield along with an unidentified complex mixture which did not contain the desired isopropylcyclopropane or *tert*-butylcyclopropane. (5) The intermediary cyclopropylmanganese reagents **5** could be trapped by acid chloride,[8] iodine, and vinyl bromide (in the presence of $Pd(PPh_3)_4$ (10mol%))[9] as well as methyl iodide and allyl bromide. (6) 1,1-Dichlorocyclopropane such as 9,9-dibromobicyclo[6.1.0]nonane was found to be unreactive.

We are tempted to assume a similar reaction mechanism to the reaction with cuprate and zincates: (1) the initial halogen-manganese exchange at the less hindered bromine to afford **4**, (2) alkyl migration under Br^- elimination producing **5** (inversion on the cyclopropane carbon), (3) the second alkylation by R^2X with retention of the configuration. The stereoselective formation of **2** might be attributed to the bulkiness of the manganese reagents which attack the less hindered halogen selectively.



Moreover, the reaction proceeded in the presence of a catalytic amount of manganese(II) chloride. For instance, an addition of a solution of dibromocyclopropane **1a** (1.0 mmol) to a THF solution of butylmagnesium bromide (3.0 mmol) and manganese(II) chloride (12 mg, 10 mol%) at 0 °C gave 1-butyl-2-hexylcyclopropane **2a** and **3a** in 75% combined yield after aqueous workup. In contrast, the reaction of **1a** with butylmagnesium bromide without manganese provided 1,2-nonadiene in 95% yield. The representative results of the catalytic reactions are shown in Table 2.

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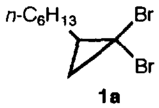
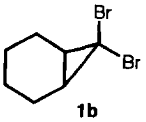
Table 2. Manganese(II) Chloride-Catalyzed Reaction of *gem*-Dibromocyclopropanes[a]

Entry	Substrate **1** (1.0 mmol)	RMtl (3.0 mmol)	Electrophile (3.0 mmol)	Yield (%)	Isomeric Ratio of **2**/**3**
1	 **1a**	*n*-BuLi	H_2O	68	66/34
2		*n*-BuMgBr	H_2O	75	79/21
3		*n*-BuMgBr	$CH_2{=}CHCH_2Br$	57	81/19
4		$CH_2{=}CHCH_2MgBr$	H_2O	79	58/42
5		$CH_2{=}CHCH_2MgBr$	$CH_2{=}CHCH_2Br$	47	——
6		$PhMe_2SiLi$	EtOH	43	79/21
7	 **1b**	*n*-BuLi	H_2O	62	85/15
8		*n*-BuMgBr	EtOH	51	93/7
9	 **1d**	*n*-BuMgBr	H_2O	51	77/23

a) The reactions were performed in the presence of 0.1 mmol of $MnCl_2$.

References and Notes

1. Kitatani, K.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1976**, *98*, 2362–2364; idem *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1600–1607; idem *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3288–3294; Kitatani, K.; Yamamoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2158–2160.
2. Harada, T.; Katsuhira, T.; Hattori, K.; Oku, A. *J. Org. Chem.* **1993**. *58*, 2958–2965; Harada, T.; Hattori, K.; Katsuhira, T.; Oku, A. *Tetrahedron Lett.* **1989**, *30*, 6035–6038, 6039–6040.
3. Cyclopropylborate has been also reported to undergo similar 1,2-migration: Danheiser, R. L.; Savoca, A. C. *J. Org. Chem.* **1985**, *50*, 2401–2403.
4. Three different types of organomanganous reagents (RMnX, R_2Mn, $R_3Mn^-Mtl^+$) have been reported. Normant, J. F.; Cahiez, G. "Organomanganous Reagents" in *Modern Synthetic Methods*, Vol. 3, pp. 173–216, 1983, Scheffold, R. Ed., Otto Salle Verlag GmbH & Co., Frankfurt am Main.
5. Fugami, K.; Hibino, J.; Nakatsukasa, S.; Matsubara, S.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1988**, *44*, 4277–4292. Fugami, K.; Oshima, K.; Utimoto, K.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 2161–2164.
6. 1-Butyl-2-hexyl-1-iodocyclopropane (*cis/trans* = 72/28): Bp 130–140°C (bath temp, 0.5 Torr); IR (neat) 3058, 2954, 2924, 2852, 1466, 1379, 1294, 1261, 1211, 1164, 1116, 1031, 942, 914, 800, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.05–0.10 (m, 0.72H), 0.32 (t, J = 6.3Hz, 0.28H), 0.68 (t, J = 6.0 Hz, 0.72H), 0.80–0.98 (m, 6H), 1.02–1.75 (m, 17.28H); ^{13}C NMR ($CDCl_3$) δ 13.98, 14.01, 21.81, 22.00, 22.51, 22.56, 22.80, 23.67, 24.02, 24.67, 28.63, 28.70, 29.01, 29.17, 30.17, 31.68, 31.77, 32.50, 36.95, 39.15, 46.00. Found: C, 50.79; H, 8.40%. Calcd for $C_{13}H_{25}I$: C, 50.66; H, 8.17%.
7. Monobromide could be obtained by quenching an intermediary manganate **4** with H_2O before being converted to **5**.
8. Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 7369–7372 and references cited therein.
9. 1-Alkylcyclopropylzincates have been reported to react with alkenyl halide in the presence of a Pd catalyst. See ref 2.

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