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Bismuth Bromide-Catalyzed Reductive Coupling of Carbonyl Compounds and Its Application to the Synthesis of Novel Crownophanes[1]

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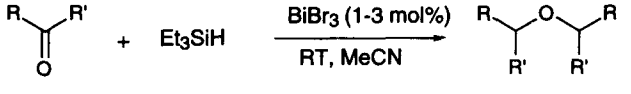
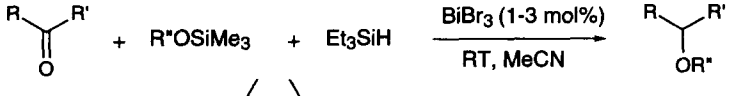
Abstract: The reductive homocoupling of carbonyl compounds and heterocoupling of a carbonyl compound with an alkoxysilane were both effected smoothly with triethylsilane in the presence of a catalytic amount of bismuth bromide (1-3 mol%) under mild conditions. This ether-forming reaction was successfully applied to the single-step preparation of novel crownophanes with olefinic or acetylenic linkages. © 1997 Elsevier Science Ltd.

In the preceding paper,[2] we have shown that bismuth bromide can efficiently catalyze the cyanation and allylation of carbonyl compounds and acetals. Herein, we describe the catalytic utility of this salt for the reductive homocoupling of carbonyl compounds (eq. 1) and heterocoupling of a carbonyl compound with an alkoxysilane (eq. 2) to afford the corresponding symmetrical and unsymmetrical ethers, respectively. Using this coupling methodology, a series of novel crownophanes with multiple bonds ($\mathbf{1}_{mn}$ and $\mathbf{2}_{n}$) were prepared in a one-pot procedure.

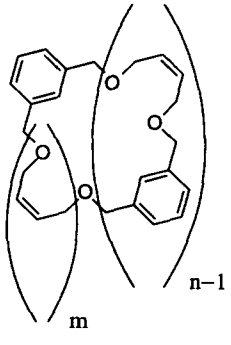
Ether linkage has been formed almost exclusively by the Williamson method in laboratory practice. The present reductive coupling procedure has an advantage over the classical method in that the reaction proceeds under non-basic conditions to form no elimination products. A few examples of this type of Lewis acid-catalyzed coupling reactions have been reported.[3] As compared to those catalysts, bismuth bromide was found to work more efficiently; 1-3 mol% of the catalyst was sufficient to complete the coupling reactions.



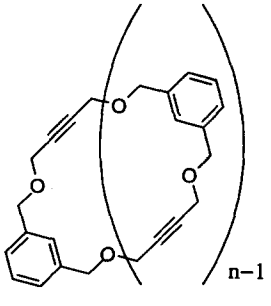
(1)



(2)



$\mathbf{1}_{mn}$ (m = 0~1, n = 2~3)



$\mathbf{2}_{n}$ (n =2~3)

The general experimental procedure is quite simple as follows: To a stirred suspension of bismuth bromide[4] (0.02-0.06 mmol), dried *in vacuo* prior to use, in dry acetonitrile (5 mL) were added successively a

carbonyl compound (2.0 mmol) and, in a case of heterocoupling alkoxysilane (1.2 equiv) in addition, then triethylsilane (1.2 equiv) *via* a syringe at room temperature under an argon atmosphere. The resulting mixture was stirred for an appropriate time, while the progress of the reaction was monitored intermittently by GLC. After usual work-up, the crude product was chromatographed on silica gel to give the corresponding symmetrical or unsymmetrical ether in the yields summarized in Tables 1 and 2.

Table 1. Synthesis of symmetrical ethers *via* the $BiBr_3$-catalyzed homocoupling reaction (eq.1).

Run	R	R'	Time	Yield (%)
1	Ph	H	< 5 min	84
2	*p*-ClC_6H_4-	H	< 5 min	93
3	*p*-BrC_6H_4-	H	< 5 min	89
4	*o*-$MeOC_6H_4$-	H	8 h	83
5	*p*-$MeO_2CC_6H_4$-	H	< 5 min	85
6	*p*-$Me_2NC_6H_4$-	H	20 h	0[a]
7	$Me(CH_2)_6$-	H	2 h	88
8	-$(CH_2)_5$-		2 h	72
9	$PhCH_2CH_2$-	Et	2 h	61
	Ph	Me	20 h	trace[a]
11	Ph	Ph	24 h	trace[a]

a) Substrate was mostly recovered.

As shown in Table 1, the homocoupling reaction of benzaldehyde (run 1) and derivatives bearing an electron-withdrawing substituent at *para* position (runs 2, 3 and 5) was complete within five minutes, while the reaction of aliphatic aldehyde (run 7) and *ortho*-substituted benzaldehyde (run 4) needed longer time. The amino-substituted benzaldehyde (run 6) did not give the desired product. Alicyclic and aliphatic ketones afforded the coupling products in moderate yields (runs 8 and 9), but phenyl ketones resulted in almost no reaction (runs 10 and 11).

Table 2. Synthesis of unsymmetrical ethers *via* the $BiBr_3$-catalyzed heterocoupling reaction (eq.2).

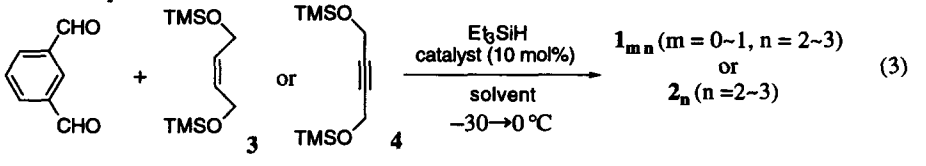
Run	R	R'	R"	Time	Yield (%)
1	Ph	H	$PhCH_2$-	< 5 min	84
2	$Me(CH_2)_6$-	H		< 5 min	86
3	*trans*-MeCH=CH-	H		2 h	76
4	*t*-Bu	H		< 5 min	58
5	*p*-MeO_2C-C_6H_4-	H		1 h	83
6	-$(CH_2)_5$-			< 5 min	89
7	Ph	Me		20 h	trace[a]
8	$Me(CH_2)_5$-	Me		1 h	96
9	$HOCH_2$-	Et		1 h	b)
10	CH_2=CH-	Me		20 h	trace[a]
11	Ph	H	Ph	1 h	0[c]
12	Ph	H	2-octyl	1 h	81
13	$PhCH_2$-	Et		1 h	88

a) Substrate was mostly recovered. b) A complex mixture resulted.

c) Dibenzyl ether was the only product obtained.

Table 2 shows that benzyl and 2-octyl trimethylsilyl ethers coupled smoothly with various aldehydes (runs 1-5, and 12), and alicyclic and aliphatic ketones (runs 6, 8, and 13), while acetophenone was mostly recovered intact (run 7). A similar trend was observed in the homocoupling reaction as mentioned above. These marked contrasts indicate that $BiBr_3$ can discriminate phenyl ketones from alicyclic and aliphatic ones, which is characteristic of $BiBr_3$ as compared with the previously reported Lewis acids, TMSOTf and trityl perchlorate.

As an extension of this coupling methodology, we have tried to prepare novel macrocyclic ethers with multiple benzyl allyl or benzyl propargyl ether linkages in a single step.[5] The coupling of isophthalaldehyde with (*Z*)-1,4-bis(trimethylsiloxy)-2-butene (**3**) and 1,4-bis(trimethylsiloxy)-2-butyne (**4**) (eq. 3) led to a series of crownophanes ($\mathbf{1}_{mn}$ and $\mathbf{2}_n$) in the yields listed in Table 3. Pure macrocycles were obtained by subjecting the crude product successively to silica gel column chromatography and gel permeation chromatography, and were identified by MALDI-TOF-MS spectra coupled with conventional analyses.[6] The structures of the 2:2 coupling products $\mathbf{1}_{12}$ and $\mathbf{2}_2$ were elucidated by X-ray analyses (Fig. 1).[7] Interestingly, the 2:1 and 3:2 coupling products $\mathbf{1}_{02}$ and $\mathbf{1}_{03}$ were obtained along with the 2:2 and 3:3 coupling products in run 2, indicating that the homocoupling occurred in parallel with the heterocoupling during the macrocycle construction. Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was superior to $BiBr_3$ as catalyst for the synthesis of $\mathbf{1}_{mn}$. In the coupling with **4**, however, a larger macrocycle was obtained in somewhat better yield with $BiBr_3$, which might be attributed to the template effect of the bismuth atom.[8]



(3)

Table 3. Synthesis of crownophanes ($\mathbf{1}_{mn}$ and $\mathbf{2}_n$) *via* the $BiBr_3$ or TMSOTf catalyzed heterocoupling reaction (eq.3).

Run	Silyl ether	Catalyst	Solvent	Product (yield (%))			
1	**3**	$BiBr_3$	CH_2Cl_2 + MeCN	$\mathbf{1}_{12}$ (<1)			
2	**3**	TMSOTf	CH_2Cl_2	$\mathbf{1}_{02}$ (4)	$\mathbf{1}_{12}$ (8)	$\mathbf{1}_{03}$ (3)	$\mathbf{1}_{13}$ (3)
3	**4**	$BiBr_3$	CH_2Cl_2 + MeCN		$\mathbf{2}_2$ (7)		$\mathbf{2}_3$ (3)
4	**4**	TMSOTf	CH_2Cl_2		$\mathbf{2}_2$ (10)		$\mathbf{2}_3$ (1)

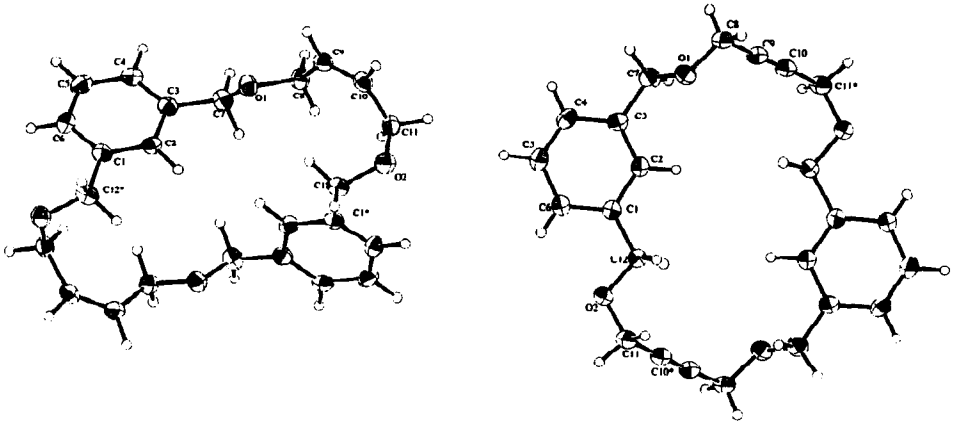


Figure 1. ORTEP perspective views of $\mathbf{1}_{12}$ (left) and $\mathbf{2}_2$ (right).

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References and Notes

1 Part of this work was presented at the 1995 International Chemical Congress of Pacific Basin Societies (PACIFICHEM '95), Honolulu, Hawaii, in December 1995 and the XXI International Symposium on Macrocyclic Chemistry (ISMC-21), Montecatini Terme, Italy, in June 1996.

2 Komatsu, N; Uda, M; Suzuki, H. the preceding paper.

3 (a) Hatakeyama, S.; Mori, H.; Kitano, K.; Yamada, H.; Nishizawa, M. *Tetrahedron Lett.* **1994**, *35*, 4367. (b) Sassaman, M. B.; Kotian, K. D.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1987**, *52*, 4314. (c) Kato, J.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1985**, 743. (d) Doyle, M. P.; West, C. T.; Donnelly, S. J.; McOsker, C. C. *J. Organomet. Chem.* **1976**, *117*, 129.

4 Commercial BiBr3 is recommended to be stored in a desiccator to avoid humidity.

5 Homocoupling reaction catalyzed by TMSOTf was successfully applied to the one-pot serial synthesis of oxa[3$_n$]cyclophanes; see, Komatsu, N.; Suzuki, H. submitted for publication.

6 $\mathbf{1_{02}}$: pale yellow oil, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.03 (d, J = 4.3, CH_2C=, 4H), 4.54 (s, CH_2Ar, 8H), 5.78 (t, J = 3.4, HC=, 2H), 7.27 (m, Ar, 8H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 65.68, 70.96, 72.22, 127.40, 127.63, 128.42, 129.39, 138.22, 138.32; MALDI-TOF-MS (pos) calcd for $C_{20}H_{22}O_3Na$ (M+Na$^+$): 333.15, found: 333.62.

$\mathbf{1_{12}}$: mp 76-77 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.96 (d, J = 5.2, CH_2C=, 8H), 4.45 (s, CH_2Ar, 8H), 5.82 (t, J = 4.0 HC=, 4H), 7.29 (m, Ar, 8H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 64.78, 71.58, 127.10, 127.21, 128.62, 129.76, 138.21; MALDI-TOF-MS (pos) calcd for $C_{24}H_{28}O_4Na$ (M+Na$^+$): 403.19, found: 403.40. Anal. Calcd for $C_{24}H_{28}O_4$: C, 75.76; H, 7.42. Found: C, 75.54; H, 7.46.

$\mathbf{1_{03}}$: pale yellow oil, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.99 (d, J = 4.1, CH_2C=, 4H), 4.01 (d, J = 4.0, CH_2C=,4H), 4.42 (s, CH_2Ar, 4H), 4.48 (s, CH_2Ar, 4H), 4.53 (s, CH_2Ar, 4H), 5.79 (t, J = 3.8, HC=, 4H), 7.27 (m, Ar, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 65.31, 65.44, 71.92, 72.04, 127.07, 127.08, 127.13, 127.17, 128.52, 129.54, 129.60, 138.22, 138.30, 138.33; MALDI-TOF-MS (pos) calcd for $C_{32}H_{36}O_5Na$ (M+Na$^+$): 523.25, found: 523.74.

$\mathbf{1_{13}}$: pale yellow oil, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.02 (d, J = 4.9, CH_2C=, 12H), 4.46 (s, CH_2Ar, 12H), 5.78 (t, J = 3.7, CH=, 6H), 7.27 (m, Ar, 12H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 65.38, 71.87, 127.02, 127.11, 128.47, 129.52, 138.17; MALDI-TOF-MS (pos) calcd for $C_{36}H_{42}O_6Na$ (M+Na$^+$): 593.29, found: 593.03.

$\mathbf{2_2}$: mp 116-117 °C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.26 (s, $CH_2C\equiv$, 8H), 4.65 (s, CH_2Ar, 8H), 7.34 (m, Ar, 8H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 57.99, 71.92, 83.10, 128.03, 128.27, 129.16, 138.15; MALDI-TOF-MS (pos) calcd for $C_{24}H_{24}O_4Na$ (M+Na$^+$): 399.16, found: 399.23. Anal. Calcd for $C_{24}H_{24}O_4$: C, 76.57; H, 6.43. Found: C, 76.49; H, 6.36.

$\mathbf{2_3}$: pale yellow oil, ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.28 (s, $CH_2C\equiv$, 12H), 4.61 (s, CH_2Ar, 12H), 7.32 (m, Ar, 12H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 57.74, 71.64, 83.14, 128.19, 128.68, 129.36, 138.03; MALDI-TOF-MS (pos) calcd for $C_{36}H_{36}O_6Na$ (M+Na$^+$): 587.24, found: 587.58.

7. Both structures were solved by direct method with the SIR92; Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Cryst.* **1994**, *27*, 435.

(a) X-ray analysis of $\mathbf{1_{12}}$: M_r = 380.48, $C_{24}H_{28}O_4$, a = 23.793(1), b = 4.885(2), c= 18.464(2), β = 106.646(7), V = 2056.0(7), Z = 4, monoclinic, C2/c (No.15), prismatic, colorless, 0.32 x 0.26 x 0.14, λ($Mo_{K\alpha}$) = 0.71069, of 2703 reflections collected, 1301 was taken as observed (I>3.0σ(I)). 128 parameters, R = 0.039, Rw = 0.056, GOF = 1.26.

(b) X-ray analysis of $\mathbf{2_2}$: M_r = 376.45, $C_{24}H_{24}O_4$, a = 8.319(1), b = 10.326(1), c= 6.3858(9), α = 91.29(1), β = 110.636(10), γ = 75.228(9), V = 495.0(1), Z = 1, triclinic, P-1 (No.2), prismatic, colorless, 0.53 x 0.42 x 0.11, λ($Mo_{K\alpha}$) = 0.71069, of 2435 reflections collected, 1150 was taken as observed (I>3.0σ(I)). 164 parameters, R = 0.037, Rw = 0.053, GOF = 1.21.

8 (a) Habata, Y.; Fujishiro, F.; Akabori, S. *J. Chem. Soc., Perkin. Trans. 1* **1996**, 953. (b) Ogawa, T.; Yoshikawa, A.; Wada, H.; Ogawa, C.; Ono, N.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1407.

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