Improved Procedure for the Synthesis of gem-Diiodoalkanes by the Alkylation of Diiodomethane. Scope and Limitations
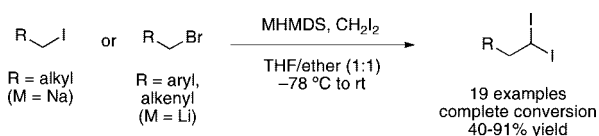
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Functionalized *gem*-diiodoalkanes are obtained in good to excellent yields by employing a convenient modified procedure for the alkylation of NaCHI$_2$ with alkyl iodides. Complete conversion to the diiodide is reliably obtained, avoiding a problematic separation of any remaining iodide starting material. Functional group tolerance toward olefins, acetals, ethers and silyl ethers, carbamates, and hindered esters is demonstrated. The use of an excess of LiCHI$_2$ allows complete conversion of allyl and benzyl bromides with minimal elimination from the diiodide product.

gem-Diiodoalkanes are valuable precursors to organometallic reagents employed in carbon−carbon bond-forming reactions. Their most notable uses include the Simmons−Smith cyclopropanation[1] and the Takai−Utimoto olefination reactions.[2] Several methods are available for preparation of alkyl-diiodides,[3−9] including the reaction of iodine with hydrazones,[3] metallated alkynes,[4] or diazo compounds (Figure 1).[5] Triflylacetals[6] and dichloroalkanes[7] can be converted to alkyldiiodides by treatment with metal iodides, and our group
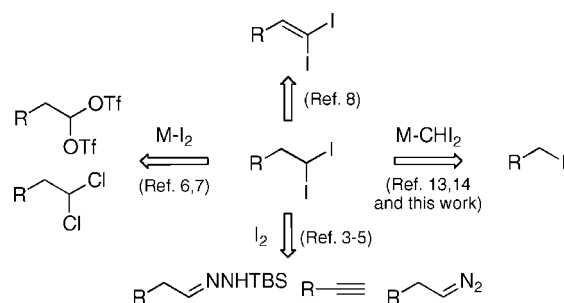

FIGURE 1. Synthetic routes to *gem*-diiodoalkanes.

recently reported a diimide reduction of 1,1-diiodoalkenes to form a range of *gem*-diiodides.[8]

Despite these available methods, the use of the *gem*-diiodides in the synthesis of complex molecules remains scarce,[10−12] and there are few examples of the preparation of highly functionalized *gem*-diiodide reagents. This is presumably due to the often low yields and low functional group tolerance in the preparation of the *gem*-diiodides or of the required precursors.

As part of our ongoing investigations into cyclopropanation methodologies, we required the synthesis of functionalized diiodide **2a**, containing a THP-protected allylic alcohol (eq 1). We chose to examine the alkylation of diiodomethane with alkyliodides, believing this would be compatible with the functionality present and allow the generation of sufficient quantities of material.[13,14] This approach was originally reported by Seyferth and Lambert, forming LiCHI$_2$ from CHI$_3$ with *n*-BuLi, at −95 °C due to the low thermal stability of the anion.[13] In 1990 Verpeaux et al. used NaHMDS to deprotonate diiodomethane, also at very low temperatures.[14] In both cases

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(8) Cloarec, J.-M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 4731–4734.

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TABLE 1. Selected Optimization for the Formation of *gem*-Diiodide 2a

entry	base (MHMDS)	equiv base/ CH_2I_2	conditions[a]	conversion (%)[b]
1	NaHMDS	2	−95 °C to rt	<5
2	NaHMDS	3	−95 °C to rt	61
3	NaHMDS	4	−95 °C to rt	80
4	NaHMDS	10	−95 °C to rt	50
5	LiHMDS	4	−95 °C to rt	55
6	KHMDS	4	−95 °C to rt	<5
7	NaHMDS	4	NaI (4 equiv), −95 °C to rt	96
8	NaHMDS	4	NaI (4 equiv), −78 °C to rt	94
9	NaHMDS	4	−90 °C, 3 h	0
10	NaHMDS	5	−78 °C to rt	>99

[a] Reaction performed by the addition of a solution of CH_2I_2 in THF to a solution of base in THF/ether. Deprotonation for 20−30 min before the addition of a solution of iodide **1a** in THF, all at the described temperature. Warmed slowly to rt over 12−16 h. [b] Conversion measured by ¹H NMR between CH₂I of **1a** and CHI₂ of **2a**.

only relatively simple reactive electrophiles were used. Subsequently, a modification of this approach (LiCHI₂, −110 °C) has been employed by Hoffmann and co-workers in the preparation of diiodides in the study of chiral organometallic reagents.[15,16]

(1)
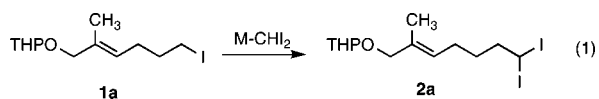
In addition to the very low temperatures, one limitation of the literature procedures is the incomplete conversion of the alkyl iodide to the *gem*-diiodide product. Although low molecular weight compounds could be purified by distillation, more complex higher molecular weight compounds are difficult to separate from the remaining iodide. Indeed, we found that the residual iodide was inseparable from the corresponding diiodide by flash chromatography *in all cases examined*. Herein we report more convenient, modified conditions for the synthesis of functionalized *gem*-diiodides in high yields providing complete conversion.

Iodide **1a** was synthesized from the corresponding primary alcohol in good yield by standard synthetic transformations.[17] Applying the conditions reported by Verpeaux et al. to form diiodide **2a** (NaHMDS, −95 °C to rt) returned mainly starting material. Initially we looked to improve the conversion by increasing the number of equivalents of the nucleophilic reagent (Table 1, entries 1−4). Increasing the number of equivalents gave increased conversions, up to 80% with 4 equiv, but the results were unreliable. More reproducible results were obtained by changing the order of addition in forming the reagent, i.e., by adding diiodomethane to a solution of the base. However, increasing the equivalents to 10 did not result in an improved level of conversion. It is important to note that the alkyl iodide substrate **1a** was completely inseparable from *gem*-diiodide

(15) (a) Hoffmann, R. W.; Knopff, O.; Faber, T. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1785–1792. (b) Müller, M.; Brönstrup, M.; Knopff, O.; Schulze, V.; Hoffmann, R. W. *Organometallics* **2003**, *22*, 2931–2937. (c) Ring opening of cyclic sulfates by LiCHI₂: Stiasny, H. C.; Hoffmann, R. W. *Chem. Eur. J.* **1995**, *1*, 619–624.
(16) (a) Müller, M.; Stiasny, H.-C.; Brönstrup, M.; Burton, A.; Hoffmann, R. W. *J. Chem. Soc., Perkin Trans. 2* **1999**, 731–736. (b) Knopff, O.; Stiasny, H. C.; Hoffmann, R. W. *Organometallics* **2004**, *23*, 705–710.
(17) See Supporting Information for further details.

TABLE 2. Scope of Modified Conditions for the Alkylation of Diiodomethane with Alkyl Iodides

entry[a]	product		yield[b,c]
1		**2a**	89%
2		**2b**	84%
3		**2c**	85% (82%)[d]
4		**2d**	65%
5		**2e**	84%
6		**2f**	91%
7		**2g**	72%
8		**2h**	55%
9		**2i**	82%
10		**2j**	88%

[a] Reaction performed on a 0.5 mmol scale. [b] Isolated yield. [c] >99% conversion in all cases. [d] Reaction performed on 4 mmol scale.

product **2a**, and upon deprotection of the THP group the products remained inseparable, limiting further studies with this compound.

Next we examined other reaction parameters to optimize for conversion of alkyl iodide **1a** to *gem*-diiodide **2a**. We found that sodium anion performed better than the lithium or potassium variants (Table 1, entries 3, 5, 6). The mixture of THF and ether was important to the conversion and gave a cleaner reaction than either solvent alone. Although additives to the reaction mixture (e.g., NaI, entries 7 and 8) resulted in an improved conversion, our optimal results came from increasing the temperature at which the reaction was performed. Indeed, at −90 °C no conversion was observed after 3 h, and hence a rise in temperature was necessary. Furthermore, we found that the deprotonation and the reaction could be performed at −78 °C, providing a much more convenient reaction setup. By employing 5 equiv of both diiodomethane and NaHMDS complete conversion to the diiodide was reliably obtained (Table 1, entry 10). The reaction proceeded cleanly providing the valuable diiodide **2a** in high yield (Table 2, entry 1).

Following these results, we were interested to determine the scope of these conditions and their compatibility with functional groups and structural features. The conditions proved to be

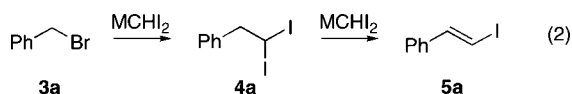**TABLE 3. Selected Optimization for the Formation of 4a from Benzyl Bromide 3a**

entry[a]	base (MHMDS)	equiv (MCHI$_2$)	conversion (%) to 4 + 5	elimination (%) from 4 to form 5[b]
1	NaHMDS	5	100	100
2	NaHMDS	1.0	61	4
3	LiHMDS	1.0	46	<1
4	LiHMDS	1.5	77	2
5	LiHMDS	1.75	88	3
6	**LiHMDS**	**2.0**	**100**	**5**
7	LiHMDS	2.5	100	11
8	LiHMDS	3.0	100	13

[a] Reaction performed on 0.5 mmol scale. [b] Percentage of the *gem*-diiodide **4a** formed that underwent elimination to **5a**.

successful for a range of substrates, all of which proceeded with full conversion (>99%) as determined by analysis of the crude reaction mixtures by ^{1}H NMR (Table 2). Simple primary alkyl chains (entries 2 and 3), internal and terminal alkenes (entries 1 and 4), and phenyl rings (entry 5) were well tolerated without elimination from the *gem*-diiodide product. The reaction was performed on a 4 mmol scale (entry 3), providing gram quantities of diiodide **2c**. Primary iodides containing TBS and benzyl ethers (entries 6 and 7) and also hindered esters and carbamates (entries 8 and 9) all gave good yields. Complex molecules containing acetals (entries 1 and 10) and internal alkynes (entry 10) could be formed in high yields.

However, methyl esters and β-aryl iodides led to decomposition presumably via attack at the carbonyl and elimination from the starting iodide respectively. Moreover, less electrophilic iodide substrates resulted in lower conversions. As such, more hindered substrates (e.g., 1-iodo-2-methylpropane, 56% conversion) and compounds containing acidic protons (e.g., free alcohols and unprotected terminal alkynes) gave incomplete conversion.

Subjecting benzyl bromide to the conditions optimized for the alkyl iodides led to conversion to the *gem*-diiodide followed by the elimination of HI to give (E)-styryl iodide **5a** in 63% isolated yield (eq 2 and Table 3, entry 1). Similar observations have been made for allyl bromide by Verpeaux et al., who also showed that reduced levels of elimination from the *gem*-diiodide product were obtained using the less basic lithium anion.[14] As above, we hoped to demonstrate that an excess of the reagent (LiCHI$_2$ in this case) could be employed to achieve complete conversion of benzyl/allyl bromides **3/6** without causing significant elimination from the products. Additionally, although the lithium anion is reported to have low thermal stability at temperatures above −100 °C, we hoped to maintain the use of the more convenient −78 °C reaction temperature.
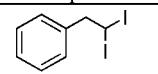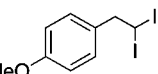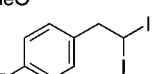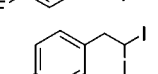
$$\text{Ph}\diagdown\text{Br} \xrightarrow{\text{MCHI}_2} \text{Ph}\diagdown\overset{\text{I}}{\underset{\text{I}}{\diagup}} \xrightarrow{\text{MCHI}_2} \text{Ph}\diagdown\diagdown\text{I} \quad (2)$$
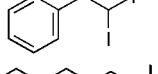
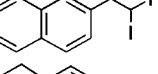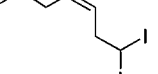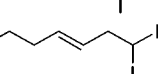**3a**   **4a**   **5a**
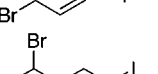
The use of 1 equiv of NaCHI$_2$ gave 61% conversion; 4% of the converted material was eliminated to styryl iodide (Table 3, entry 2). Given the requirement for an excess to achieve full conversion, we decided to concentrate on the use of the lithium anion, which gave lower levels of elimination (compare entries

(18) Achieving full conversion for the bromides **3** and **6** was also important as separation of the starting bromide and the *gem*-diiodide products remained difficult by flash chromatography.
(19) Kakiya, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2139–2147.

TABLE 4. Synthesis of *gem*-Diiodoalkanes from Benzyl/Allyl Bromides

| entry[a]	product		yield[b]
1		**4a**	86%
2		**4b**	77%
3		**4c**	78%
4		**4d**	53%
5		**4e**	65%
6		**4f**	61%
7		**7a**	70%
8[c]		**7b**	79%
9[c]		**7c**	40%

[a] Reaction performed on a 1.0 mmol scale. [b] Isolated yield following chromatography. [c] Using 3 equiv of LiHMDS/CH$_2$I$_2$ reagent.

2 and 3). Increasing the number of equivalents of LiHMDS/CH$_2$I$_2$ gave an increase in the conversion with a smaller increase in the level of elimination (entries 4−8). The use of 2 equiv was chosen to be optimal, providing complete conversion and only 5% elimination (entry 6), maintaining the −78 °C reaction temperature.

A range of substituted benzyl bromides with varying steric and electronic features were subjected to these optimized conditions to give the corresponding *gem*-diiodides in good yields (Table 4, entries 1−6). All examples resulted in the benzyl bromide being fully consumed, and any elimination product formed could be removed by flash chromatography.[18] However, the strongly electron-withdrawing 4-nitrobenzyl bromide gave poor conversion to the *gem*-diiodide with high levels of elimination, leading to only a small amount (<10%) of the desired product in the crude mixture.

Employing substituted allyl bromides (**6**) was also successful. With (Z)-1-bromohex-2-ene, 2 equiv of LiCHI$_2$ provided **7a** with good conversion and very low levels of elimination (entry 7). However, E-allyl bromides required 3 equiv of the LiCHI$_2$ reagent to achieve acceptable levels of conversion (>95%). From (E)-1-bromohex-2-ene a good yield of **7b** was obtained with low levels of elimination, but for cinnamyl bromide a lower yield of **7c** resulted as a result of increased elimination to the highly conjugated system (entries 8 and 9).

For more reactive electrophiles, fewer equivalents of diiodomethane/base could be employed. For TBSCl, a 96% isolated yield of the diiodide was achieved using 1.5 equiv of NaCHI$_2$ (eq 3).
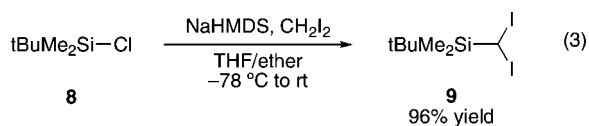
In summary, we have shown that NaCHI$_2$ and LiCHI$_2$ can be formed and used at −78 °C to generate functionalized *gem*-diiodoalkanes from alkyl iodides and benzyl/allyl bromides in high yield, providing complete conversion of the starting material. Studies into further applications of these reagents and use of the *gem*-diiodides in cyclopropanation reactions are underway.

Experimental Section

General Procedure for the Formation of Alkyl Diiodides from Alkyl Iodides Using NaHMDS/CH$_2$I$_2$. A solution of CH$_2$I$_2$ (201 μL, 2.5 mmol) in THF (0.6 mL) was added dropwise to a solution of NaHMDS (459 mg, 2.5 mmol) in THF (4 mL) and ether (4 mL) at −78 °C in a dry ice/acetone bath. After 20 min, a solution of the iodide substrate (0.5 mmol) in THF (1 mL) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature over 16 h in the dark. Water (70 mL) was added, and the mixture was extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organics were washed with water (50 mL) and dried (MgSO$_4$), and the solvent was removed under reduced pressure. **Compound 2a**. Purification by flash chromatography (100% CH$_2$Cl$_2$) afforded *gem*-diiodide **2a** as a yellow oil (255 mg, 89%). R_f 0.30 (10% ethyl acetate/hexane); IR (film)/cm^{-1} 2936, 2852, 1452, 1439, 1200, 1117, 1076, 1020, 905; ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.42 (t, J = 7.2 Hz, 1 H), 5.11 (t, J = 6.4 Hz, 1 H), 4.60 (t, J = 3.4 Hz, 1 H), 4.10 (d, J = 11.8 Hz, 1 H), 3.88 (m, 1 H), 3.85 (d, J = 11.8 Hz, 1 H), 3.51 (m, 1 H), 2.36 (m, 2 H), 2.10 (br q, J = 7.3 Hz, 2 H), 1.87−1.68 (m, 2 H), 1.66 (s, 3 H), 1.64−1.46 (m, 6 H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 133.1, 126.5, 97.5, 72.7, 62.2, 47.8, 31.5, 30.6, 25.6, 25.5, 19.5, 14.1, −25.8; HRMS calcd for C$_{13}$H$_{22}$I$_2$O$_2$Na [M + Na]$^+$ 486.9601, found 486.9597.

General Procedure for the Formation of Alkyl Diiodides from Benzyl/Allyl Bromides Using LiHMDS/CH$_2$I$_2$. A solution of CH$_2$I$_2$ (165 μL, 2.05 mmol) in THF (0.5 mL) was added dropwise to a solution of LiHMDS (335 mg, 2.0 mmol) in THF (8 mL) and ether (8 mL) at −78 °C in a dry ice/acetone bath. After 20 min, a solution of the bromide substrate (1.0 mmol) in THF (1 mL) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature over 16 h in the dark. Water (70 mL) was added, and the mixture was extracted with ether (3 × 70 mL). The combined organics were washed with water (50 mL) and dried (MgSO$_4$), and the solvent removed under reduced pressure. **1-(2,2-diiodoethyl)-4-methoxybenzene 4b**. Purification by flash chromatography (5% ether/hexane) afforded *gem*-diiodide **4b** as an orange oil (298 mg, 77%). R_f 0.27 (5% ether/hexane). IR (film)/cm^{-1} 2993, 2931, 2903, 2832, 1608, 1583, 1509, 1462, 1439, 1427, 1303, 1247, 1177, 1079, 1032, 901, 818. ^{1}H NMR (300 MHz; CDCl$_3$): δ 7.16−7.13 (m, 2H), 6.88−6.85 (m, 2H), 5.03 (t, J = 7.4 Hz, 1H), 3.81 (s, 3H), 3.66 (d, J = 7.4 Hz, 2H). ^{13}C NMR (75 MHz; CDCl$_3$): δ 159.0, 132.1, 114.0, 55.2, 53.6, −23.3. HRMS calcd for C$_9$H$_{11}$I$_2$O [M + H]$^+$ 388.8894, found 388.8878.

Preparation of *tert*-Butyldimethyl(diiodomethyl)silane 9. A solution of CH$_2$I$_2$ (802 μL, 9.96 mmol) in THF (2.5 mL) was added dropwise to a solution of NaHMDS (1.83 g, 9.96 mmol) in THF (14 mL) and ether (14 mL) at −78 °C. After 20 min, a solution of the TBSCl **8** (1.0 g, 6.64 mmol) in THF (2 mL) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature over 18 h in the dark. Water (100 mL) was added, and the mixture was extracted with hexane (3 × 70 mL). The combined organics were washed with water (50 mL) and dried (MgSO$_4$), and the solvent was removed under reduced pressure. The residue was taken up in hexane (100 mL) and then filtered through a silica pad, eluting with hexane (50 mL). Removal of the solvent and other volatile components in vacuo afforded *gem*-diiodide **9** as a yellow oil (2.09 g, 96%). R_f 0.47 (100% hexane). IR (film)/cm^{-1} 2954, 2927, 2881, 2857, 1462, 1363, 1250, 1059, 835, 821, 808, 775. ^{1}H NMR (300 MHz; CDCl$_3$): δ 4.53 (s, 1H), 1.04 (s, 9H), 0.27 (s, 6H). ^{13}C NMR (75 MHz; CDCl$_3$): δ 27.9, 18.4, −5.0, −41.0.[19]

Supporting Information Available: Experimental and characterization data for compounds **1**, **2**, **4**, and **7** and NMR (^{1}H and ^{13}C) spectra for all *gem*-diiodides and for other novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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