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# Diiodosilane. 3.[1] Direct Synthesis of Acyl Iodides from Carboxylic Acids, Esters, Lactones, Acyl Chlorides, and Anhydrides

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Diiodosilane ($SiH_2I_2$, DIS) is a very useful reagent for direct, high-yield synthesis of acyl iodides from variety of carboxylic acid derivatives, such as carboxylic acids, esters, lactones, anhydrides, and acyl chlorides. These transformations are remarkably accelerated by iodine. In the absence of iodine DIS reacts with carboxylic acids and esters, much as does iodotrimethylsilane (TMSI), to form the corresponding silyl carboxylates. However, in contrast to TMSI, DIS and iodine react further with silyl carboxylates to produce acyl iodides. This reaction, when followed by addition of an appropriate alcohol, represents an esterification and transesterification method that is useful even for sterically hindered and/or poorly nucleophilic alcohols. Lactones react with DIS to produce either silyl $\omega$-iodo carboxylates or $\omega$-iodoacyl iodides, depending on the reaction conditions. The reaction between DIS and 1 equiv of a carboxylic anhydride affords, in the presence of iodine, 2 equiv of acyl iodide.

## Introduction

Although they are highly reactive acylating agents, acyl iodides[2] are, in contrast to acyl chlorides,[3] rarely used in organic synthesis. The main approach to obtaining acyl iodides is via reaction of the corresponding acyl chlorides with various reactive iodide reagents. The first synthesis dates back to 1832 when Liebig and Wohler reported that treatment of benzoyl chloride with potassium iodide produced benzoyl iodide.[4] Later, Staudinger employed gaseous hydrogen iodide for the same purpose.[5] Hoffmann usefully modified Leibig's procedure by employing sodium iodide in acetonitrile, using a reactor–extractor apparatus.[6] Iodotrimethylsilane (TMSI) has been successfully employed for the same transformation.[7] Activated carboxylic acid derivatives other than acyl halides have also served as useful precursors for acyl iodides. Acetic anhydride, for instance, was converted into acetyl iodide using red phosphorous and iodine.[8] Ghosez utilized in situ formation of a mixed anhydride-like intermediates from carboxylic acids and tetramethyl-$\alpha$-iodo enamine, which were converted into acyl iodides.[9]

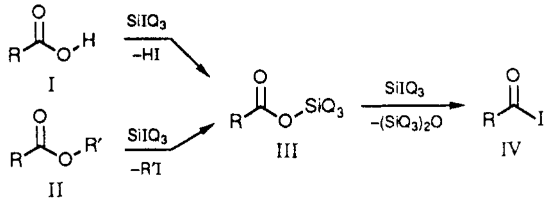
In fact, except for the latter approach, there is no other known method to obtain acyl iodides using nonactivated precursors, such as carboxylic acids and esters. It was even stated that it is impossible to prepare acyl iodides directly from carboxylic acids and inorganic iodide reagents.[7] The only reported exception to the above statements is Jung's observation that treatment of ethyl palmitate with TMSI at 75 °C for extended periods of time (several days) slowly converted the initially formed trimethylsilyl carboxylate into palmityl iodide.[10]

We report here that the inorganic reagent, diiodosilane ($SiH_2I_2$, DIS)[11] can be effectively used for direct, high-yield conversion of a variety of carboxylic acid derivatives, including free carboxylic acids, esters, lactones, anhydrides, and acyl chlorides, into acyl iodides.

## Results and Discussion

**Carboxylic Acids.** Literature precedents for the reaction of carboxylic acid derivatives with iodosilanes deal mainly with iodotrimethylsilane (TMSI).[12] A general view of the reaction of carboxylic acids and esters with TMSI is given in Scheme I (Q = $CH_3$). Carboxylic acids (I) react spontaneously, and essentially irreversibly, with TMSI to form HI and trimethylsilyl carboxylate III, which is stable under the reaction conditions.

**Scheme I**



Analogous reactions occur, although much slower, with alkyl esters (II), which are dealkylated by TMSI to produce iodoalkanes and III. Because the latter is readily hydrolyzed upon aqueous workup, this process represents a synthetically useful method for nonsaponicative hydrolysis of esters[13] and lactones.[14]

We found that DIS reacted vigorously and quantitatively with carboxylic acids, much as does TMSI, to form the corresponding silyl carboxylate III ($SiQ_3$ = $SiH_2I$). However, in sharp contrast to TMSI, DIS can react further with III to produce acyl iodide IV. The rate of the latter re-

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(7) Schmidt, A. H.; Russ, M.; Grosse, D. *Synthesis* **1981**, 216.

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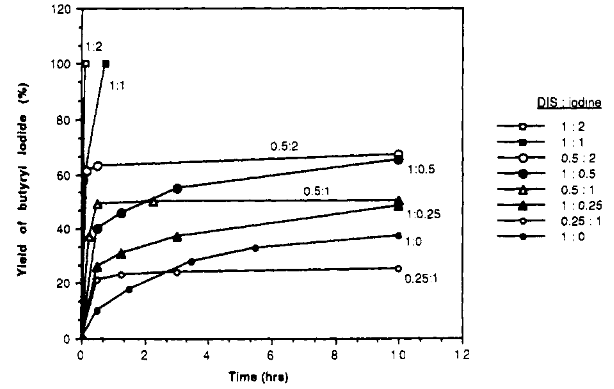


**Figure 1.** Reaction of butyric acid with DIS and iodine. Seven NMR tubes were loaded with *n*-butyric acid (8.8 mg, 0.1 mmol), $CDCl_3$ (0.5 mL), and the following amounts (mmol) of DIS and iodine, respectively: (a) 0.1, 0.2; (b) 0.1, 0.1; (c) 0.05, 0.2; (d) 0.1, 0.05; (e) 0.05, 0.1; (f) 0.1, 0.025; (g) 0.025, 0.1. The tubes were kept at 50 °C, and progress of the reaction was monitored by $^1H$ NMR.

action is accelerated remarkably by iodine. To check the optimal proportions of the two reagents in this reaction, we carried out the reaction of butyric acid with various quantities of DIS and iodine in $CDCl_3$ at 50 °C, and the appearance of butyryl iodide was monitored by NMR spectroscopy (Figure 1).

As may be concluded from Figure 1, iodine is essential for conversion of III to IV. With less than stoichiometric quantities of iodine, reactions proceed quite sluggishly. However, 1 or more equiv of iodine increases the reaction rates remarkably, leading to quantitative formation of butyryl iodide within short periods of time. With respect to the required amounts of DIS, it is clear that 1 mol of the reagent is required per mole of substrate. When 0.5 or 0.25 mol of DIS is employed, reactions stop at approximately 50 and 25% conversion, respectively. Considering the stoichiometry suggested in Scheme I, these results imply that 1 mol of DIS donates 2 mol of iodide anions in the reaction with carboxylic acid, producing 1 mol of HI and 1 mol of acyl iodide.

Thus, quantitative conversion of carboxylic acids into acyl iodides is generally achieved within 1 h at 50 °C using DIS and iodine in equimolar quantities. This procedure was tested with several aliphatic acids, including acetic, butyric, valeric, and lauric acids. With TMSI and iodine, carboxylic acids are immediately transformed into trimethylsilyl carboxylates. This product, however, does not react further to give acyl iodide in yields higher than 8% even after 15 h at 50 °C. It is noteworthy that in reactions carried out with TMSI at 50 °C in the absence of iodine, no acyl iodides were formed.

**Carboxylic Esters.** Alkyl esters and lactones are dealkylated by TMSI to produce the corresponding trimethylsilyl esters.[13,14] We compared the reactivity of DIS and TMSI toward three representative esters: isopropyl, *n*-butyl, and methyl acetates (Figure 2). All reactions were carried out in chloroform at 50 °C in the absence of iodine, using approximately equimolar quantities of ester and iodosilane. We found that both reagents react similarly under these conditions to produce silyl acetate and iodoalkane, with only minor quantities (<3%) of acetyl iodide being formed.

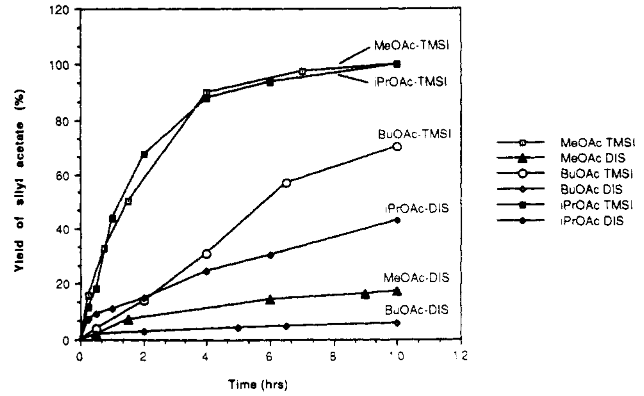


**Figure 2.** Dealkylation of alkyl acetates with iodosilanes. Iodine (0.1 mmol) and DIS (0.1 mmol) were added to a solution of alkyl acetate (0.1 mmol) in $CDCl_3$ (0.5 mL). The mixture was kept at 50 °C, and progress of the reaction was monitored by $^1H$ NMR. In reactions carried out with TMSI, 0.12 mmol of this reagent were employed together with 0.12 mmol of iodine.

**Table I. Reaction of $CH_3CO_2R$ with DIS and TMSI**[a]

| entry | R | iodosilane | time, h | III, % | IV, % |
|---|---|---|---|---|---|
| 1 | *i*-Pr | DIS | 1.50 | 32 | 66 |
| 2 | *i*-Pr | DIS | 15 | – | 100 |
| 3 | *i*-Pr | TMSI | 0.25 | 100 | – |
| 4 | *n*-Bu | DIS | 1 | 15 | 21 |
| 5 | *n*-Bu | DIS | 2.25 | 36 | 38 |
| 6 | *n*-Bu | DIS | 15 | 34 | 58 |
| 7 | *n*-Bu | TMSI | 2 | 94 | 6 |
| 8 | Me | DIS | 2.5 | 35 | 40 |
| 9 | Me | DIS | 15 | 10 | 80 |
| 10 | Me | TMSI | 1.15 | 95 | 5 |
| 11 | Ph | DIS | 2.5 | – | 76 |
| 12 | Ph | DIS | 7 | – | 82 |
| 13 | Ph | TMSI | 15 | – | – |

[a] Powdered iodine (0.1 mmol) and DIS (0.1 mmol) were added to a solution of the carboxylic acid (0.1 mmol) in $CDCl_3$ (0.5 mL) in an NMR tube. The tube was placed in a bath at 50 °C, and the reaction was monitored by $^1H$ NMR. In reactions carried out with TMSI, 0.12 mmol of this reagent was employed together with 0.12 mmol of iodine.

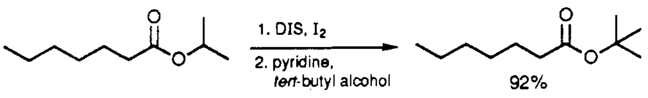
Interestingly, TMSI is clearly more reactive in these reactions than DIS. Another noteworthy observation is the relative order of reactivity of these three substrates. With respect to dealkylation with DIS, the order is iPrOAc > MeOAc > nBuOAc, which agrees with our previously reported observations on the cleavage of ethers and alcohols by DIS.[11] However, regarding dealkylation with TMSI, the order of reactivity found here, iPrOAc = MeOAc > *n*-BuOAc, contrasts with the case of ethers and alcohols, for which the order of reactivity was found to be Me ≫ *n*-Bu > iPr.[11] The unexpectedly high reactivity of the secondary ester group in this reaction probably results from the presence of substantial amounts of HI in the mixture and the relatively high temperature used.

The situation is dramatically changed upon addition of 1 equiv of iodine to the reaction mixture. Table I compares the reactivity of the above-mentioned alkyl acetates and phenyl acetate toward DIS and TMSI in the presence of iodine. It is clear that in all cases dealkylation of II to give silyl ester III is accelerated by iodine. As in the case of reactions run in the absence of iodine (Figure 2), here too, disappearance of starting material is much faster with TMSI than with DIS. With DIS, however, the silyl ester III reacts further under these conditions to give high yields of acetyl iodide IV within 15 h.

Phenyl acetate represents an interesting case in which silyl carboxylate cannot be formed with either iodosilane reagent. Expectedly, no reaction is observed with TMSI aside from formation of acetyl iodide in trace amounts (entry 13). With DIS, however, this substrate is effectively cleaved into acetyl iodide and phenylsilyl ether (entries 11, 12).

The remarkable promoting effect of iodine in reactions involving iodosilanes has already been noticed in deoxy-

**Scheme II**



genation reactions.[1] Olah has also observed that cleavage of esters and ethers by TMSI is facilitated by excess iodine.[15] Of particular interest is the role of iodine in the transformation of silyl carboxylates III to acyl iodides IV. It is clear from the above-described results that the presence of 1 equiv of iodine accelerates this reaction by 1–2 orders of magnitude. Higher concentrations of iodine are even more effective. Although the exact role of iodine is not fully understood at this point, one may speculate that the phenomenon is related to the reversible formation of $I_3^-$ anion from $I_2$ and $I^-$. Triiodide anion, either free or bound to silicon, is a softer and more potent nucleophile than $I^-$ itself[16] and may facilitate conversion of III to IV.

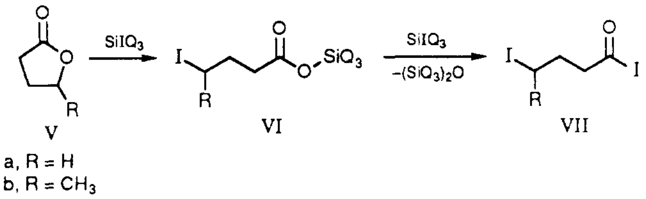
This argument, however, does not account for the difference in reactivity between TMSI and DIS. One might even predict that TMSI and iodine in sufficient amounts could convert III to IV. To verify this point we mixed *n*-butyl acetate in chloroform with an excess of TMSI (4 equiv) and iodine (2 equiv) and heated the mixture to 50 °C for 100 h. Yield of acetyl iodide did not exceed 5%, as compared to 1% in a similar reaction without iodine. To check the possible reversibility of this transformation in the case of TMSI, we dissolved hexamethyldisiloxane and acetyl iodide in chloroform and kept the mixture at 50 °C for an extended period of time. No change in the initial composition was observed even after 24 h, indicating that oxygen is irreversibly transferred from the substrate to silicon. The possibility that iodine modifies the reactivity of iodosilanes by increasing the coordination number of silicon seems unlikely, as $^1H$ NMR spectra of either TMSI or DIS in chloroform solution are not effected by addition of iodine.[1]

The major difference between the two iodosilane reagents could arise from the higher Lewis acidity and, in particular, oxyphilicity of DIS in comparison with TMSI.[1,11] A qualitative evaluation of the high oxyphilicity of DIS was provided by the following experiment. Addition of DIS to a chloroform solution of hexamethyldisiloxane at room temperature results in rapid disappearance of both compounds and concomitant formation of TMSI and hydrosiloxane oligomers (eq 1).

$$(Me_3Si)_2O + SiH_2I_2 \rightarrow 2Me_3SiI + (SiH_2O)_n \qquad (1)$$

Direct conversion of carboxylic esters into acyl iodides offers a very useful transesterification method. Due to the high reactivity of acyl iodides, they react immediately with alcohols to produce the corresponding esters. For example, the reaction of DIS with either butyric acid or any butyric ester, followed by quenching with methanol, affords methyl butyrate in high yields. Even sterically hindered and/or poorly nucleophilic alcohols are readily esterified by this approach. This is illustrated by the one-pot transformation of isopropyl heptanoate into *tert*-butyl heptanoate (Scheme II). This transformation requires addition of pyridine in order to prevent acid-promoted cleavage of the product. This method should be compared with Olah's transesterification of trimethylsilyl esters, which requires overnight reflux in chloroform and is limited to relatively nucleophilic alcohols.[15a]

**Scheme III**



a, R = H
b, R = $CH_3$

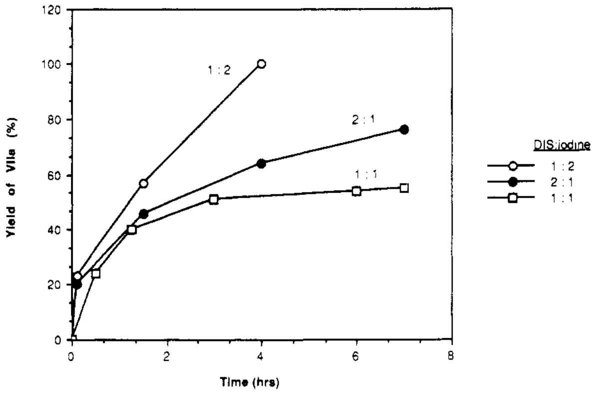


**Figure 3.** Reaction of butyrolactone (Va) with DIS and iodine. DIS and iodine were added to solutions of γ-butyrolactone (0.1 mmol) in $CDCl_3$ (0.5 mL). The mixtures were kept at 50 °C, and the reaction was monitored by $^1H$ NMR. The following amounts of DIS and iodine were used (mmoles), respectively: (a) 0.1 and 0.2, (b) 0.2 and 0.1, (c) 0.1 and 0.1.

**Lactones.** Cleavage of lactones by TMSI is known to afford the corresponding silyl ω-iodo carboxylates.[14] On the basis of the above-discussed, general characteristics of open-chain esters, butyrolactones V are expected to form silyl 4-iodocarboxylates VI by reaction with either TMSI or by DIS in the absence of iodine (Scheme III). When both DIS and iodine are employed, silyl ester VI is expected to react further and produce 4-iodobutyryl iodides VII. The latter are of interest not only for preparative organic chemistry but also for the synthesis and modification of polymers.[14a]

We compared the reactivity of γ-lactone V toward DIS and TMSI in $CDCl_3$ using NMR spectroscopy. TMSI (1.2 equiv) reacts at room temperature with butyrolactone (Va) to give (trimethylsilyl)-4-iodobutyrate VIa in essentially quantitative yield within 1 h. This reaction proceeds twice as fast in the presence of iodine (1.2 equiv), complete conversion being achieved within less than 30 min. Similar rate enhancement is achieved when the temperature is increased to 50 °C. With both, iodine and increased temperature, the complete reaction occurs within 10 min. nevertheless, in all cases no further conversion of VIa into acyl iodide VIIa was observed.

The corresponding reaction of DIS with Va at room temperature produced VIa in approximately the same rate as with TMSI. Similarly, the rate of reaction is accelerated at 50 °C, leading to quantitative formation of the same product within 10 min. Interestingly, γ-valerolactone, Vb, having a secondary oxygen function, reacts slower than Va, with the primary function. Only 20% conversion into VIb were observed within 24 h at room temperature, and even at 50 °C conversion only reached 80% within 6 h. This situation contrasts the case of open-chain esters shown in Figure 2, where isopropyl ester is cleaved faster than *n*-butyl and methyl esters. This suggests that cleavage of lactones by iodosilanes is more likely to occur via an associative mechanism ($S_N2$) rather than via an $S_N1$ process.

The second step, which converts VI to VII, occurs only with DIS in the presence of iodine (Figure 3), with reaction

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[15] (a) Olah, G. A.; Narang, S. C.; Salem, G. F.; Gupta, B. G. B. *Synthesis* **1981**, 142. (b) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 612.

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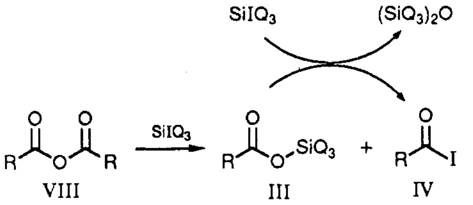
**Table II. Reaction of Acyl Halides and Anhydrides with DIS**[a]

| entry | substrate | iodosilane | temp, °C | time, min | III, % | IV, % |
|---|---|---|---|---|---|---|
| 1 | $C_2H_5COCl$ | DIS | 25 | 10 | - | 100[c] |
| 2 | $C_2H_5COCl$ | DIS[b] | 25 | 10 | - | 100[c] |
| 3 | $(C_2H_5CO)_2O$ | TMSI | 25 | 45 | 52 | 48[d,e] |
| 4 | $(C_2H_5CO)_2O$ | TMSI[b] | 25 | 15 | 55 | 45[d,e] |
| 5 | $(C_2H_5CO)_2O$ | DIS | 25 | 30 | 51 | 49[d,e] |
| 6 | $(C_2H_5CO)_2O$ | DIS | 25 | 240 | 10 | 90[e] |
| 7 | $(C_2H_5CO)_2O$ | DIS[b] | 25 | 45 | 20 | 80[e] |
| 8 | $(C_2H_5CO)_2O$ | DIS | 50 | 90 | 57 | 43[e] |
| 9 | $(C_2H_5CO)_2O$ | DIS[b] | 50 | 45 | 10 | 90[e] |

[a] DIS (0.1 mmol) was added to solution of the substrate (0.1 mmol) in $CDCl_3$ (0.5 mL) at room temperature and the reaction was monitored by $^1H$ NMR. [b] Iodine (0.1 mmol) was added prior to the addition of DIS. [c] Identical results were obtained with acetyl chloride and palmitoyl chloride. [d] No further change in this composition was observed after 24 h. [e] Identical results were obtained with acetic anhydride.

**Scheme IV**



rates being essentially identical for either Va or Vb. As observed in the cases of regular esters and acids, 1 equiv of DIS is sufficient to drive the reaction to completion, although excess DIS did not significantly accelerate the reaction rates. Iodine concentration, however, has a major effect on the kinetics of the reaction. With 1 equiv of iodine, the reaction proceeds quite sluggishly, but with 2 equiv the reaction is complete within 4 h.

**Acyl Halides and Anhydrides.** Acyl chlorides are the traditional source for acyl iodides. TMSI and a number of inorganic iodides have been employed for this transformation.[5] As expected, DIS transforms acyl chlorides smoothly and rapidly to the corresponding acyl iodides at room temperature. Addition of iodine does not seem to have any significant influence on this process (Table II, entries 1, 2).

A more interesting case is the reaction of carboxylic anhydrides with TMSI, which has not previously been reported. On the basis of the above results with other functional groups, anhydrides would be expected to react with TMSI to form a stable 1:1 mixture of silyl carboxylate III and acyl iodide IV (Scheme IV). This was found to be the case with or without iodine added (Table II, entries 3, 4).

With DIS, however, III may react further to form a second mole of IV, a reaction which is generally promoted by temperature and iodine, much as in the cases of carboxylic acids and esters. Indeed, in the absence of iodine DIS reacts with anhydrides to form a 1:1 mixture of III and IV with an only marginal dependence on temperature (entries 5, 8). This reaction proceeds slowly to give higher proportions of IV within several hours (entry 6). The promoting effect of iodine in this reaction is clearly seen from entries 7 and 9, where high conversions are achieved within less than 1 h.

## Conclusion

In this paper we have demonstrated that the chemical reactivity of DIS is complementary to that of TMSI. This reagent is very useful for direct, high-yield synthesis of acyl iodides from carboxylic acids, esters, lactones, anhydrides, and acyl chlorides. These reactions are accelerated remarkably by the addition of iodine.

While the remarkable promoting effect of iodine may be explained in terms of the enhanced nucleophilicity of the triiodide anion in comparison with iodide anion, the reactivity difference between DIS and TMSI is rationalized on the basis of the relatively higher Lewis acidity and, in particular, oxyphilicity of DIS. The reactivity of DIS toward other functional groups is currently being investigated in our laboratories.

## Experimental Section

**General Methods.** $^1H$ NMR spectra were recorded in deuteriochloroform at 200 or 400 MHz. Thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F-254, Art 5549). Column chromatography separations were performed on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385) under a pressure of 0.4 atm (flash chromatography). Distillations were usually performed with a Büchi Kugelrohr apparatus, the temperatures presented being pot temperatures. Chloroform was dried prior to use by passing it through an activated alumina column. Phenylsilane was prepared by reduction of trichlorophenylsilane with $LiAlH_4$, in dry ether.[17] DIS was prepared from phenylsilane and iodine, as described previously.[11] TMSI was prepared according to the literature.[18] All substrates were purchased from either Aldrich or Fluka and freshly distilled before use. The purity of all title compounds was judged to be greater than 97% by $^1H$ NMR spectral determinations.

General procedures for the preparation of acyl iodides from acids, lactones, esters, acid chlorides, and anhydrides with DIS are given in the figures and tables.

**Lauryl Iodide from Lauric Acid.** Powdered iodine (127 mg, 1 mmol) and DIS (284 mg, 1 mmol) were added to solution of lauric acid (200 mg, 1 mmol) in $CHCl_3$ (3 mL). After the initial exothermic reaction was completed, the mixture was stirred at 50 °C for 1.5 h, and then the solvent was removed by Kugelrohr distillation (30 °C/25 mm). Distillation at higher temperature (175 °C/0.5 mm) afforded lauryl iodide (285 mg, 92%), which was found to be pure by NMR analysis. NMR: $\delta$ 0.88 (t, $J$ = 7.2, 3 H), 1.26 (br s, 16 H), 1.63 (quintet, $J$ = 7.3, 2 H), 3.06 (t, $J$ = 7.3, 2 H). IR: 1800 (br, s). Anal. Calcd: C, 46.46; H, 7.47; I, 40.91. Found: C, 46.95; H, 7.86; I, 40.47.

**4-Iodobutyryl Iodide (VIIa) from $\gamma$-Butyrolactone.** DIS (296 mg, 1.04 mmol) was added to a solution of $\gamma$-butyrolactone (88.2 mg, 1.02 mmol) and iodine (260 mg, 2.05 mmol) in $CHCl_3$ (5 mL) in a 25-mL flask. The flask was sealed with a rubber septum, and the mixture was stirred for 8 h at 50 °C (bath temperature). Low-temperature Kugelrohr distillation (30 °C/25 mm) removed $CHCl_3$ and other volatile materials. Disillation at higher temperature (100 °C/2 mm) afforded 4-iodobutyryl iodide (297 mg, 91%) in the form of a bright yellow liquid. NMR: $\delta$ 3.25 (t, $J$ = 6.7, 2 H), 3.18 (t, $J$ = 7.2, 2 H), 2.44 (br quintet, $J$ = 7, 2 H).

**Propanoyl Iodide from Propanoic Anhydride.** DIS (284 mg, 1 mmol) was added to a solution of propanoic anhydride (63 mg, 0.48 mmol) and iodine (127 mg, 1 mmol) in $CHCl_3$ (5 mL). The mixture was stirred at 50 °C for 2 h and then worked up as

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described above. Kugelrohr distillation (75 °C/30 mm) afforded propanoyl iodide[6a,7] (165 mg, 88%) in the form of a slightly yellowish liquid. NMR: $\delta$ 3.11 (q, $J$ = 7.4, 2 H), 1.13 (t, $J$ = 7.4, 3 H).

**Palmitoyl Iodide from Palmitoyl Chloride.** DIS (330 mg, 1.16 mmol) was added to a solution of palmitoyl chloride (290 mg, 1.06 mmol) in $CHCl_3$ (5 mL). The mixture was stirred at 50 °C for 2 h and then worked up as described above. Kugelrohr distillation (200 °C/1 mm) afforded palmitoyl iodide[10] (338.5 mg, 87.5%) in the form of a colorless oil. NMR: $\delta$ 3.05 (t, $J$ = 6.6, 2 H), 1.64 (quintet, $J$ = 6.7, 2 H), 1.25 (br s, 24 H), 0.88 (t, $J$ = 6.5, 3 H). IR: 1800 (br, s). Anal. Calcd for $C_{16}H_{31}IO$: C, 52.46; H, 8.53; I, 34.64. Found: C, 52.81; H, 8.99; I, 34.10.

**Methyl Butyrate from Butyric Acid.** A reaction similar to the one described above was carried out with butyric acid, DIS, and iodine. After 45 min at 50 °C excess of methanol was added. The NMR spectrum taken after 1 h at room temperature showed quantitative conversion to methyl butyrate.

***tert*-Butyl Heptanoate from Isopropyl Heptanoate.** DIS (305 mg, 1.07 mmol) and iodine (135 mg, 1.06 mmol) were added to a stirred solution of isopropyl heptanoate (180.5 mg, 1.05 mmol) in $CH_2Cl_2$ (3 mL). The mixture was stirred at 50 °C for 1 h and then cooled to room temperature. Pyridine (200 mg, 2.5 mmol) and then *tert*-butyl alcohol (100 mg, 1.35 mmol) were added, and the mixture was stirred for 1 h at room temperature and then worked up with ether and water. The organic layer was washed with water and dried over sodium sulfate, and the solvent was removed under reduced pressure. Kugelrohr distillation of the residue (150 °C/30 mm) afforded *tert*-butyl heptanoate (180 mg, 92%) in the form of a colorless oil. NMR: $\delta$ 2.20 (t, $J$ = 7.6, 2 H), 1.56 (m, 2 H), 1.44 (s, 9 H), 1.30 (m, 6 H), 0.88 (t, $J$ = 6.8, 3 H).

**NMR Data. Iodosilyl Propanoate, III (R = Et, $SiQ_3$ = $SiIH_2$).** NMR: $\delta$ 2.43 (q, $J$ = 7.4, 2 H), 1.13 (t, $J$ = 7.4, 3 H).

**Iodosilyl 4-Iodobutyrate, VIa ($SiQ_3$ = $SiIH_2$).** NMR: $\delta$ 4.2 (br s, 2 H), 3.25 (t, $J$ = 6.7, 2 H), 2.60 (t, $J$ = 7.2, 2 H), 2.44 (br quintet, $J$ = 7, 2 H).

**Trimethylsilyl 4-Iodobutyrate,[14a] VIa ($SiQ_3$ = $SiMe_3$).** NMR: $\delta$ 3.23 (t, $J$ = 6.7, 2 H), 2.55 (t, $J$ = 7.2, 2 H), 2.13 (br quintet, $J$ = 7, 2 H), 0.26 (s, 9 H).

**Iodosilyl 4-Iodovalerate, VIb ($SiQ_3$ = $SiIH_2$).** NMR: $\delta$ 4.2 (br s, 2 H), 4.23 (m, 1 H), 2.62 (m, 2 H), 1.98 (m, 2 H), 1.95 (d, $J$ = 6.8, 3 H).

**Trimethylsilyl 4-Iodovalerate, VIb ($SiQ_3$ = $SiMe_3$).** NMR: $\delta$ 4.20 (m, 1 H), 2.59 (m, 2 H), 1.98 (m, 2 H), 1.93 (d, $J$ = 6.9, 3 H), 0.26 (s, 9 H).

**4-Iodovaleryl Iodide, VIIb.** NMR: $\delta$ 4.16 (m, 1 H), 3.3 (m, 2 H), 1.98 (m, 2 H), 1.93 (d, $J$ = 6.8, 3 H).

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# Aldolase-Catalyzed C–C Bond Formation for Stereoselective Synthesis of Nitrogen-Containing Carbohydrates[1]

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Rabbit muscle aldolase was found to catalyze stereoselective aldol addition of dihydroxyacetone phosphate (**1**) to 3-azido-2-hydroxypropanal (**2**). The ketose 1-phosphates were isolated as barium salts, **4a**/**4b**, and hydrolyzed with acid phosphatase. The mixture of 6-azido-6-deoxy-D-fructose (**5**) and 6-azido-6-deoxy-L-sorbose (**6**) thus obtained was separated by anion-exchange chromatography. Reductive amination of **5** and **6** yielded, respectively, 1-deoxymannojirimycin (**7**) and 1-deoxynojirimycin (**8**), with high diastereoselectivity (>98:2). Analogous aldol addition of **1** to 3-azido-2-hydroxybutanal (**9**) ($E$:$Z$ = 92:8) afforded a mixture of the 6-azido-6,7-dideoxyheptuloses **12** and **13**, which contained 88% of 6-azido-6,7-dideoxy-D-*altro*-heptulose (**13**). After anion-exchange chromatography, **13** was isolated as a 18:82 mixture of the $\beta/\alpha$ anomers. Reductive amination of pure **13** gave a mixture of 2,6,7-trideoxy-2,6-imino-D-*glycero*-D-*manno*- and -D-*gluco*-heptitols (**14** and **15**) (3:2 molar ratio), which likewise was separated by anion-exchange chromatography. If a mixture of **12** and **13** was hydrogenated under identical conditions, 2,6,7-trideoxy-2,6-imino-L-*glycero*-L-*gulo*-heptitol (**16**) could be isolated besides **14** and **15**.

## Introduction

The use of rabbit muscle aldolase (EC 4.1.2.13; RAMA) in stereoselective syntheses has been reviewed by Whitesides et al.[3] and Wong et al.[4] Systematic investigations of C–C coupling reactions showed that this enzyme permits virtually no structural variation of the *C*-nucleophile, dihydroxyacetone phosphate (DHAP). The natural substrate D-glyceraldehyde 3-phosphate, on the other hand, may be substituted by various other aldehydes as *C*-electrophiles.[3,5] A broad field thus is opened up for applying this *enzymatic* reaction, particularly for the stereoselective synthesis of polyhydroxycarbonyl compounds. However, many *chemical* aldol additions have been reported in the last few years which likewise proceed with very high stereoselectivity.[6]

In our investigations on the use of enzyme-active compounds, a major objective has been the optimum combination of chemical *and* enzymatic steps. DHAP generally is obtained from D-fructose 1,6-diphosphate (FDP) by enzymatic cleavage with RAMA, and subsequent enzymatic isomerization with triose phosphate isomerase (EC 5.3.1.1; TIM).[3,4] We have developed a chemical synthesis

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[†] NMR and MS spectroscopic analyses.

[1] Part 4 of enzyme-catalyzed reactions; for Part 3, see: Ziegler, T.; Straub, A.; Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *29*, 716.

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