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Article

Finkelstein Reaction in Non-polar Organic Solvents: A Streamlined Synthesis of Organic Iodides

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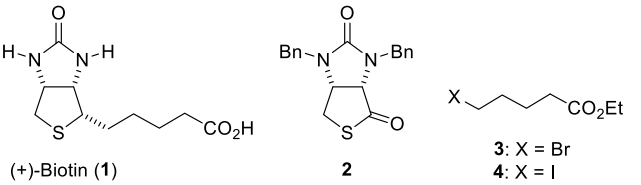
ABSTRACT: The Finkelstein reaction of organic halides was found to proceed smoothly in non-polar organic solvents other than acetone when operated in the presence of a catalytic amount of tetra-*n*-butylammonium bromide and water. The new protocol was successfully applied to a preparation of ethyl 5-iodopentanoate from the corresponding bromide which was used directly for zinc reagent formation and Fukuyama coupling to enable the formation of the (+)-biotin side chain in a streamlined manner. Rate acceleration by microwave irradiation and an application to the synthesis of trimethylsilyl iodide will be described as well.

KEYWORDS: *Finkelstein reaction, non-polar organic solvents, tetra-n-butylammonium bromide, water, microwave, trimethylsilyl iodide.*

INTRODUCTION

Organic iodides have been considered as an important class of compounds in organic synthesis due to higher reactivity than other halide analogues.[1] In particular, they have considerable importance in chemical industries and find a widespread use as reactive intermediates to install a sophisticated architecture in organic molecules.[2] For the synthesis of organic iodides, the Finkelstein reaction based on halogen exchange using iodide salts represents one of the major approaches to this important class of compounds.[3] In general, acetone or 2-butanone has been employed as a solvent to adjust solubilities of the reactant (NaI) and liberated NaX (X = F, Cl, Br, OMs, OTs).[4] However, in most cases, these solvents interfere with the subsequent reaction and exchange of the solvent is inevitably needed.

In our process development of (+)-biotin (**1**),[2a,5,9] we met a similar issue on the synthesis of ethyl 5-iodopentanoate (**4**). Iodide **4** has been used as a substrate for sensitive zinc reagent formation to install the pentanoic acid side chain of **1** to thiolactone **2**.[2a] As one of the reliable approaches to **4**, it was prepared by Finkelstein reaction of the corresponding bromide **3** in acetone. However, even a trace amount of acetone contaminated in **4** was found to considerably affect the zinc reagent formation from **4**, whereby severe in-process (IP) control in this stage was needed to attain a reproducible outcome, especially on scale. To avoid such tedious IP control and to ensure cost cutting and, more importantly, to enhance the environmental sustainability, we explored an alternative protocol and finally found out a convenient and efficient procedure of the Finkelstein reaction in inert solvents employing tetra-*n*-butylammonium bromide (TBAB) and water as catalysts.



RESULTS AND DISCUSSION

An optimization study was undertaken in the Finkelstein reaction of **3** to **4** (Table 1). To begin with, the reaction was run using a previous procedure with acetone as a solvent (entry 1). By stirring the mixture of **3** and NaI in acetone at 25 °C for 24 h, the reaction was almost completed to give iodide **4** in a 95.4% conversion along with the formation of solid NaBr. On the contrary, when non-polar toluene was used as a solvent, any detectable amount of **4** was not observed even after stirring at elevated temperature (entry 2).

In the meantime, Penso et al. reported a facile fluorination of alkyl halides using tetra-*n*-butyl fluoride in an aprotic polar solvent (CH_3CN).[6] On the basis of the reaction mechanism of the synthetic procedure, we considered it feasible that addition of a small amount of tetraalkylammonium halide could accelerate the Finkelstein reaction by converting NaI into a soluble tetraalkylammonium iodide. Thus, addition of tetra-*n*-butyl iodide (TBAI) (6 mol %) was tested, and, as expected, the reaction occurred dramatically and reached up to a 94.7% conversion by stirring at 50 °C for 73 h (entry 3). It is noteworthy that iodide **4** obtained after aqueous washing of the reaction mixture did not contain any TBAB and/or TBAI at all. To reduce the reaction time, the temperature was

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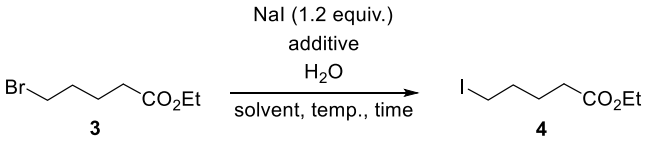
Table 1. Finkelstein Reaction of 3 to 4 in Acetone and Toluene[a]



entry	additive (mol %)	H_2O (v/w[b])	solvent (v/w[b])	temp. (°C)	time (h)	conv. (%)[c]
1			acetone (10)	25	24	95.4
2			toluene (10)	50	24	0
3	TBAI (6)		toluene (10)	50	73	94.7
4	TBAI (6)		toluene (10)	80	6.5	39.1
5	TBAI (6)		toluene (10)	80	40	86.6
6	TBAI (6)		toluene (10)	100	15	34.4
7	TBAI (6)		toluene (10)	100	40	94.0
8[d]	TBAI (6)	(0.05)	toluene (5)	100	2	99.4
9		(0.05)	toluene (5)	100	18	2.6
10	TBAB (6)	(0.05)	toluene (5)	40	20	22.2
11	TBAB (6)	(0.05)	toluene (5)	60	20	47.2
12	TBAB (6)	(0.05)	toluene (5)	80	2	99.8
13[e]	TBAB (2.5)	(0.025)	toluene (2.5)	100	2	99.7 (88)[f]
14	TBAB (2.5)	(0.05)	toluene (2.5)	100	2	99.6
15	TBAB (2.5)	(0.25)	toluene (2.5)	100	2	78.3
16	TBAB (1.5)	(0.025)	toluene (2.5)	100	2	89.2
17	TEAB[g] (3)	(0.05)	toluene (5)	100	4	18.5
18	BTMAB[h] (3)	(0.05)	toluene (5)	100	4	34.3

[a]The reaction was conducted using **3** (1 g, 4.78 mmol). [b]*v* (mL)/*w* (1 g of **3**). [c]Determined by GC. [d]Use of **3** (5 g, 23.9 mmol). [e]Use of **3** (40 g, 0.191 mol). [f]Assay yield of **4** determined by GC. [g]Tetra-*n*-ethylammonium bromide. [h]Benzyltetramethylammonium bromide.

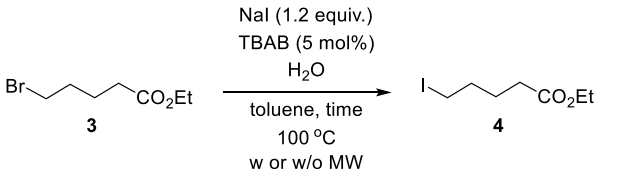
increased to 100 °C; however, an appreciable amount of **3** (6.0%) was left in the mixture even after stirring for 40 h (entry 7). It is a general idea that the need of a longer reaction time affects the entire cost due to prolonged occupancy of the facilities. To overcome this, addition of a small amount of water (0.05 v/w) was tested. To our delight, this very simple treatment has decreased the reaction time considerably (entry 8). It should be noted that in the absence of TBAB, the reaction was sluggish and gave only a trace of **4** (entry 9).

We then tested exchange of expensive TBAI to a much cheaper TBAB. Considerable temperature dependency of the reaction was again observed. Thus, while the reaction was stalled at lower temperatures (40−60 °C), it is brought to completion at 80 °C (entries 10, 11, and 12).

With the optimized conditions in hand, scale-up of the reaction was carried out using 40 g of **3** (entry 13). Despite further reduction of TBAB, water, and toluene to 2.5 mol %, 0.025 v/w, and 2.5 v/w, respectively, the reaction proceeded very well to give **4** in a 99.7% conversion (assay yield: 88%). Additional experiments where water was added more (0.5 and 2.5 v/w) on entry 13 were carried out (entries 14 and 15), and even though almost no difference of the conversion was detected for the former case, apparent reduction of conversion was found for the latter one. It should mean that addition of an increased amount of water can dissolve NaBr and retard shift of equilibrium from **3** to **4**. Reduction of the amount of TBAB from 2.5 mol % in entry 13 to 1.5 mol % was tested to result in a decreased conversion (89.2%, entry 16). For entry 13, crude **4** obtained after workup contained 10.4 wt. % of toluene as a residual solvent (see ^{1}H NMR in S3 in the Supporting Information). Nonetheless, the residual toluene did not affect the performance of the subsequent reaction since toluene is a part of the reaction solvent in the original procedure (vide infra). Finally, other phase-transfer catalysts (PTCs), tetraethylammonium bromide, and benzyltetramethylammonium bromide (BTMAB) were tested and found much less effective compared to TBAI and TBAB (entries 17 and 18).

To date, as a measure to shorten the reaction time, use of microwaves has often been carried out.[7] Thus, as a next subject for our investigation, use of microwaves was examined to accelerate the Finkelstein reaction of **3** (Table 2). For reference, conventional agitation of the reaction mixture in the presence of TBAB (5 mol %) was tested to give only a 34.7% conversion for 15 h (entry 1). In contrast, under microwave irradiation, the conversion was doubled to 62.5% for 40 min (entry 2). Further enhancement of the reaction rate was observed by addition of a small amount of water (0.05 v/w) to yield a 99.6% conversion just for 15 min (entry 3). From these results, a significant decrease in the reaction time proved to be possible by microwave irradiation.

Table 2. Finkelstein Reaction of 3 to 4 under Microwave Irradiation[a]



entry	procedure	H_2O (v/w[b])	time (min)	conv. (%)[c]
1	conventional		900 (15 h)	34.7
2	microwave		40	62.5
3	microwave	0.05	15	99.6

[a]The reaction was conducted using **3** (1 g, 4.78 mmol). [b]*v* (mL)/*w* (1 g of **3**). [c]Determined by GC.

To expand the scope of the present method, the screen of the solvent was tested (Table 3). In the presence of TBAI (6 mol %) and water (0.05 v/w), Finkelstein reaction of **3** in $CHCl_3$, 1,4-dioxane, and CH_2Cl_2 was found to occur efficiently (entries 1, 4, and 6), while use of TBME as the solvent gave only a moderate result (entry 8). As was the case for toluene, in the absence of TBAI and water, the reaction was considerably retarded in these solvents as well (entries 5, 7, and 9). Interestingly, use of tetrahydrofuran (THF) or EtOAc, even in the absence of additives, exhibited high performance (entries 2 and 3).

With a new protocol to prepare **4** in hand, we carried out the use test of **4** for the (+)-biotin synthesis (Scheme 1).[2a] Thus,

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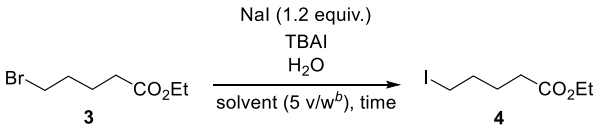
Table 3. Finkelstein Reaction of 3 to 4 in Various Solvents[a]

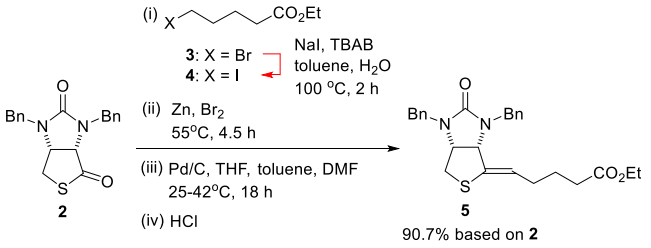


3 4

entry	solvent	TBAI (mol %)	H_2O (v/w[b])	temp. (°C)	time (h)	conv.[c] (%)
1	$CHCl_3$	TBAI (6)	(0.05)	50	24	99.8
2	THF	TBAI (6)		50	3.5	99.5
3	EtOAc			50	20	99.1
4	1,4-dioxane	TBAI (6)	(0.05)	50	19	91.8
5	1,4-dioxane			50	20	1.9
6	CH_2Cl_2	TBAI (6)	(0.05)	50	24	81.0
7	CH_2Cl_2			40	20	0.35
8	TBME	TBAI (6)	(0.05)	50	19	40.1
9	TBME			50	20	1.1

[a]The reaction was conducted using **3** (1 g, 4.78 mmol). [b]*v* (mL)/*w* (1 g of **3**). [c]Determined by GC.

Scheme 1. Application of the Finkelstein Reaction to the Synthesis of the (+)-Biotin Intermediate

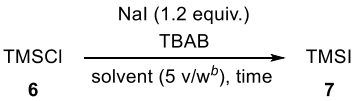


the crude iodide **4** (toluene content: 10.7%, see ^{1}H NMR in S3 in the Supporting Information) prepared according to the standard conditions (Table 1, entry 13) was added to a suspension of activated zinc dust at 55 °C; to our delight, it resulted in a smooth zinc reagent formation (a 98.6% conversion) and after reaction with thiolactone **2** gave the desired coupling product **5** in an excellent yield (90.7%). Notably, the procedure was reproducible even in a much higher scale employing 400 g of **3**, which unequivocally confirmed robustness of the present protocol.

As another application of the present method, the synthesis of trimethylsilyl iodide (TMSI) **7** from trimethylsilyl chloride (TMSCl) **6** was examined (Table 4). Iodide **7** is a powerful nucleophilic reagent to be used for such transformations as cleavage of esters, lactones, and carbamates.[8] The reaction itself is quite clean and a reliable one; however, due to instability of **7**, especially to moisture, it is better to be prepared in situ and used as a solution rather than to handle the isolated pure form. Thus, preparation of a solution of **7** in various organic solvents was examined. As mentioned above, due to the instability of **7** to moisture, the reaction was carried out under absolutely anhydrous conditions.

Initially, synthesis of **7** from **6** was tested using CH_2Cl_2 as the solvent. When the reaction was run at 40 °C in the presence of TBAB (5 mol %), a 95.4% conversion (a 90.0% assay yield, see ^{1}H NMR in S5 in the Supporting Information) was obtained for 1 h (entry 3). However, at a lower temperature (25 °C) and/or in the absence of TBAB, the reaction was apparently retarded (entries 1, 2, and 4). In this reaction, use of toluene in place of CH_2Cl_2 was possible to afford **7** with an excellent conversion as well (entry 5).

Table 4. Synthesis of TMSI 7 by Finkelstein Reaction of TMSCl 6[a]



entry	TBAB (mol %)	solvent	temp. (°C)	time (h)	conv.[c] (%)
1	5	CH_2Cl_2	25	1	75.8
2		CH_2Cl_2	25	1	61.5
				2	70.1
3	5	CH_2Cl_2	40	1	95.4 (90)[d]
4		CH_2Cl_2	40	1	69.8
				2	74.4
5	5	toluene	40	1	92.3
6		toluene	40	1	66.6
				2	68.2
7	5	CH_3CN	25	1	92.0
8		CH_3CN	25	1	97.3

[a]The reaction was conducted using **6** (1 g, 9.21 mmol). [b]*v* (mL)/*w* (1 g of **3**). [c]Determined by GC. [d]Assay yield of **7** determined by ^{1}H NMR using mesitylene as an internal standard (see ^{1}H NMR in S5 in the Supporting Information).

Interestingly, when CH_3CN was employed as the solvent, **7** was also obtained efficiently even in the absence of TBAB (entry 8).

Based on the above observations, CH_2Cl_2 or a toluene solution of **7** can be prepared concisely from **6** by addition of TBAB, while in the case of CH_3CN, no addition of TBAB was needed to attain a high level of conversion.

CONCLUSIONS

A practical synthesis of organic iodides in non-polar organic solvents has been determined by the use of TBAB and water as the additives. The procedure can be carried out in cheap and versatile non-polar organic solvents such as toluene and does not need tedious solvent exchange for the subsequent reaction. When a quick reaction was required, use of microwave irradiation was found to be effective. As applications of the new protocol, efficient synthesis of a (+)-biotin intermediate and TMSI have been successfully worked out to substantiate the feasibility and usefulness of the present method.

EXPERIMENTAL SECTION

General. ^{1}H and ^{13}C NMR spectra (JEOL RESONANCE, 400 and 100 MHz, respectively) were recorded with tetramethylsilane used as an internal standard. Gas chromatography (GC) analyses were conducted using an Agilent 7820A. Microwave irradiation was conducted using an Anton Paar Monowave 450. Silica gel column chromatography was performed using Kieselgel 60 (E. Merck). Thin-layer chromatography was carried out on E. Merck 0.25 mm precoated glass-backed plates (60 F_{254}). Development was accomplished using 5% phosphomolybdic acid in ethanol heat or visualized by UV light where feasible. All solvents and reagents were used as received.

Ethyl 5-Iodopentanoate (4).[9] To a solution of ethyl 5-bromopentanoate **3** (40 g, 0.191 mol) and nBu$_4$NBr (1.8 g, 4.78 mmol) in toluene (100 mL) were added NaI (34.4 g, 0.230 mol) and H_2O (1 mL) at 25 °C, and the mixture was stirred at 100 °C for 2 h. After checking the conversion (99.7%) by GC analysis, the mixture was cooled down to 50

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°C and washed with H_2O (40 mL) at the same temperature to keep NaBr dissolved. Then, the mixture was further washed successively with 5% aq Na_2SO_3 (40 mL), 5% $NaHCO_3$ (40 mL), and H_2O (40 mL) at 25−30 °C. The organic phase was separated and evaporated to provide crude **4** as a light-yellow oil [48.4 g (content: 89.3%), assay yield: 88%]. The crude product was used as is in the next reaction. An analytically pure sample of **4** was obtained by distillation (bp 85−87 °C/3 mmHg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (t, J = 7.6 Hz, 2H), 3.05−3.12 (m, 2H), 2.22−2.30 (m, 2H), 1.62−1.85 (m, 4H), 1.21 (t, J = 7.6 Hz, 3H). Conditions for GC analysis: column: HP-5 (30 m × 0.32 mm × 0.25 μm), column temperature: 100−280 °C, 10 °C/min, injection temperature: 300 °C, injection volume: 0.2 μL, detector: FID, detection temperature: 300 °C, carrier gas: He (1.1 mL/min), split: 60:1.

Ethyl 5-Iodopentanoate (4) (under Microwave Irradiation).[9] To a solution of ethyl 5-bromopentanoate **3** (1 g, 4.78 mmol) and nBu$_4$NBr (77.1 mg, 0.239 mmol) in toluene (5 mL) were added NaI (860 mg, 5.74 mmol) and H_2O (50 μL) at 25 °C, and the mixture was stirred under microwave irradiation (5−10 W, 1−2 bar) at 100 °C for 15 min to give **4** in a 99.6% conversion (GC analysis).

Ethyl (3a*S*, 4*Z*, 6a*R*)-5-{Hexahydro-1,3-dibenzyl-2-oxo-4*H*-thieno[3,4-*d*]imidazol-4-ylidene}pentanoate (5).[9] Under a N_2 atmosphere, zinc dust (29.6 g, 363 mmol) was suspended in a mixture of THF (48 mL) and toluene (34 mL) and Br_2 (15.1 g, 94.5 mmol) was added dropwise at 25−30 °C over 3.5 h. Then, **4** [48.4 g (content: 89.3%), 189 mmol] was added dropwise at 55 °C over 1.5 h. The mixture was stirred at 55 °C for 3 h. After completion of the reaction (a 98.6% conversion, GC analysis), toluene (97 mL) and **2** (45.1 g, 133 mmol), followed by 10% Pd/C (dry, 1.24 g, 1.17 mmol) in dimethylformamide (12 mL), were added at 26−42 °C. The mixture was stirred at 40 °C for 3 h and at 25 °C for 15 h. After completion of the reaction, 16% aq HCl (108 mL) was added at 25 °C and the mixture was stirred at the same temperature for 1 h and filtered. The organic phase was washed successively with H_2O (93 mL, 2 × 165 mL), 5% aq Na_2SO_3 (165 mL), 10% $NaHCO_3$ (165 mL), and H_2O (93 mL) and evaporated. The residue was co-evaporated with toluene (2 × 80 mL) to give **5** as a light-yellow syrup (NET 54.4 g, assay yield: 90.7%). The crude product was used as is in the next reaction. An analytical sample of **5** was obtained by purification by silica gel column chromatography (hexane/AcOEt = 5:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.34 (m, 10H), 5.40−5.43 (m, 1H), 4.92−4.95 (m, 2H), 4.78−4.82 (m, 1H), 4.05−4.28 (m, 6H), 2.91−2.96 (m, 2H), 2.24−2.28 (m, 2H), 2.00−2.18 (m, 2H), 1.60−1.72 (m, 2H), 1.22−1.26 (m, 3H). Conditions for GC analysis: column: HP-5 (30 m × 0.32 mm × 0.25 μm), column temperature: 100−280 °C, 10 °C/min, injection temperature: 300 °C, injection volume: 0.2 μL, detector: FID, detection temperature: 300 °C, carrier gas: He (1.1 mL/min), split: 60:1. Conditions for HPLC analysis: column: L-column ODS, column temperature: 40 °C, injection volume: 10 μL, 0.01 M KH_2PO_4 (pH = 3.0) buffer/CH_3CN = 50:50, flow rate: 1.0 mL/min.

Trimethylsilyl Iodide (7). Under a N_2 atmosphere, to a mixture of **6** (1.0 g, 9.21 mmol) and TBAB (148 mg, 0.46 mmol) in CH_2Cl_2 (5.0 mL) was added NaI (1.66 g, 11.1 mmol, 1.2 equiv) and the mixture was stirred at 40 °C for 1 h. An aliquot (100 μL) of the mixture was dissolved in CH_2Cl_2 (400 μL) and subjected to GC analysis, and the conversion of the reaction was determined to be 95.4%. The assay yield of TMSI obtained was given by the following procedure: under a N_2 atmosphere, to a mixture of TMSCl (1.0 g, 9.2 mmol) and TBAB (148 mg, 0.46 mmol) in CD_2Cl_2 (5.0 mL) were added NaI (1.66 g, 11 mmol) and mesitylene (1.11 g, 9.2 mmol) and the mixture was stirred at 40 °C for 1 h. An aliquot (700 μL) of the mixture was allowed for ^{1}H NMR (CD_2Cl_2, 400 MHz) (see S5 in the Supporting Information) to calculate the assay yield of **7** (90.0%) by comparing integration of signals for the methyl group of TMSI and mesitylene. **7**: ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.55 (9H, s). Mesitylene: ^{1}H NMR (400 MHz, CD_2Cl_2): δ 6.89 (s, 3H), 2.38 (s, 9H). **6**: ^{1}H NMR (400 MHz, CD_2Cl_2): δ 0.22 (9H, s). Conditions for GC analysis: column: HP-5 (30 m × 0.32 mm × 0.25 μm), column temperature: 40−230 °C, 10 °C/min, injection temperature: 250 °C, injection volume: 0.2 μL, detection: FID, detection temperature: 300 °C, carrier gas: He (13.3 mL/min), split: 30:1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00226.

^{1}H NMR spectra of the products (PDF)

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Notes

The authors declare no competing financial interest.

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