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Alcohol synthesis based on the  $S_N^2$  reactions of alkyl halides with the squarate dianion $\dagger$ 

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A convenient method has been developed for transforming alkyl halides into the corresponding alcohols via an  $S_N^2$  reaction. Treatment of an alkyl halide with the squarate dianion at high temperature produces mono-alkyl squarate, and a one-pot basic hydrolysis of the intermediate affords the alcohol in good yield.

Synthesis of alcohols from their corresponding alkyl halides is one of the most important and fundamental transformations in organic chemistry.<sup>1</sup> Spontaneous hydrolysis in wet polar solvents via an S<sub>N</sub>1 mechanism is applicable only to highly reactive halides, such as tertiary alkyl halides. Hence, the conversion of primary and secondary alkyl halides into alcohols requires some reactions with an oxygen source.<sup>2</sup> The S<sub>N</sub>2 reaction of an alkyl halide with the hydroxide ion may provide a straightforward method for this purpose, but the "hard" property of the hydroxide ion tends to induce undesirable  $\beta$ -elimination reactions yielding alkenes.<sup>3</sup> A dialkyl ether, derived from the desired alcohol and remaining alkyl halide under basic conditions, can also be detected as a side product. Therefore, the use of oxygen nucleophiles with a "soft" property is essential for achieving the S<sub>N</sub>2 reaction of an alkyl halide in high yields (Scheme 1).

Superoxide ions<sup>4</sup> are considered as representative nucleophiles for converting alkyl halides into alcohols,<sup>5</sup> but the use of hazardous reagents is a serious drawback, especially in large-scale experiments. In contrast, carboxylate anions undergo  $S_N 2$  reactions with alkyl halides to afford the corresponding esters, which can easily be converted into alcohols by

<sup>a</sup>Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810, Japan saponification.<sup>6</sup> The delocalization of the anionic charge in a carboxylate anion makes it a "soft" nucleophile. However, the carboxylate ions barely react with the sterically hindered alkyl halides. Similarly, phenolate ions function as soft oxygen nucleophiles in the  $S_N2$  reactions with alkyl halides. *p*-Methoxyphenolate ions are widely used as reagents because alkyl *p*-methoxyphenyl ethers can be converted into the corresponding alcohols upon treatment with cerium(vi) ammonium nitrate (CAN) and water.<sup>7</sup> However, this transformation requires a two-step protocol to obtain alcohols from alkyl halides. Herein, we report that squarate dianions conveniently behave as oxygen nucleophiles that can transform primary and secondary alkyl halides. The dianion species exhibited high reactivity in  $S_N2$  reactions, and the resulting squarate monoesters readily underwent hydrolysis in one pot (Scheme 1b).

Squaric acid (H<sub>2</sub>Sq) is a strong acid ( $pK_{a1} = 0.52$  and  $pK_{a2} = 3.48$ ), comparable to trifluoroacetic acid, because of the high stability of the corresponding squarate anion.<sup>8,9</sup> The anionic charge of the squarate is completely delocalized across the four-membered ring, and the aromatic character of the conjugated  $\pi$ -system contributes to the exceptionally high stability of the anion.



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To elucidate the utility of the soft and non-basic oxygen nucleophile, we explored the S<sub>N</sub>2 reactions of the squarate dianion (Sq<sup>2-</sup>) with primary alkyl bromide 1a under various conditions. The screening of suitable bases and solvents for the reaction revealed that the combination of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) and DMF was optimal for the in situ generation of  $Sq^{2-}$  from H<sub>2</sub>Sq (see ESI-1 for details<sup>†</sup>). Bromide 1a smoothly underwent the substitution reaction upon heating with H<sub>2</sub>Sq (1.5 equiv.) and DBU (3.0 equiv.) at 60 °C in DMF, and the reaction mixture containing monoalkyl squarate 2 was treated with a K<sub>2</sub>CO<sub>3</sub> aqueous solution to obtain the desired alcohol 3a in 89% yield (Table 1, entry 1). When i-Pr<sub>2</sub>NEt was used as the base, 3a was obtained but with a dramatically reduced yield of 27% (entry 2). Investigation of the solvent effects showed that the use of MeCN resulted in good yields of 3a (entry 3), but THF led to a decreased reaction conversion to 3a (43% yield) and a recovery of 1a in 48% yield (entry 4). The absence of H<sub>2</sub>Sq prevented the formation of 3, leading to a preference for the elimination of 1a (entry 5), thereby demonstrating the role of 2 as the reaction intermediate in our system. Further examination involved changing the amount of H<sub>2</sub>Sq from 1.5 equivalents to 0.5 equivalents because H<sub>2</sub>Sq can theoretically react with two equivalents of 1a. However, this reaction resulted in the recovery of 1a in 13% yield and generation of 3a in 56% yield (entry 6), suggesting that the reactivity of 2 was lower than that of  $Sq^{2-}$ . The decrease in the amounts of DBU to 2.2 equivalents also caused the low conversion of 1a (entry 7). Although the reaction at rt required a longer time than that at 60 °C, the yield of 3a remained high (entry 8). The use of a salt prepared using  $H_2Sq$  and 2.0 equivalents of DBU led to a dramatic decrease in the yield of 3a to

Table 1	Change	of factors (	under the op	otimize	ed reacti	ion condition	sa
	BnO () Br	H <sub>2</sub> Sq (1.5 equiv) DBU (3.0 equiv)		<b>0</b> 	K <sub>2</sub> CO <sub>3</sub> aq.		

60 °C, 0.5 h

Entry	Variation from the standard conditions	Yield of $3a^b$ (%)	Recovery of $1a^{b}$ (%)
1	None	89	_
2	i-Pr <sub>2</sub> NEt	27	20
3 <sup>c</sup>	MeCN	82	_
$4^c$	THF	43	48
5	Absence of $H_2Sq$	ND	Trace
6	0.5 equiv. of $H_2\hat{S}q$	56	13
7	2.2 equiv. of DBU	60	24
8	rt, 6 h	87	_
$9^d$	2(H-DBU) <sup>+</sup> -0 -0	$30^{f}$	_
10 <sup>e</sup>	2//Pr.NI - 0 -	39	

<sup>*a*</sup> 0.2 mmol scale. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> 3.6 equivalents of DBU were used. <sup>*d*</sup> The reaction time was 1 h. <sup>*e*</sup> The reaction temperature ranged from 60 to 150 °C, and the reaction time was 6 h. <sup>*f*</sup> NMR yield. 30% NMR yield (entry 9). The bis-tetra-*n*-propylammonium salt of  $H_2Sq^{10}$  improved the yield of **3a** (entry 10), but the yield was lower than that in entry 1.<sup>11</sup>

We attempted to isolate mono-alkyl squarate 2; however, its isolation was difficult owing to its high polarity. In contrast, quenching the reaction with an excess amount of methyl iodide produced methyl alkyl ester 4, which was isolated in 73% yield (Scheme 2). Hydrolysis of 4 also occurred when using an aqueous  $K_2CO_3$  solution, but the yield of 3a was lower than that for the conversion of 1a into 3a (entry 1 in Table 1). This result suggests that the reactivity of the dialkyl squaric ester under basic hydrolysis conditions is low, and the oxyanion of 2 might accelerate the opening of the squarate moiety under the reaction conditions.

The optimized reaction conditions were applied to the transformation of several alkyl halides into their corresponding alcohols (Table 2). While a prolonged reaction time at a higher temperature was required to achieve the complete consumption of primary chloride 1b, the desired alcohol 3a was obtained in 91% yield after a one-pot hydrolysis (entry 1). Secondary halides 1c and 1d were transformed in a similar manner, giving rise to alcohol 3c in good yields (entries 2 and 3). Note that the reaction of 1c with potassium acetate in DMF at 90 °C did not yield 3c and 1c was recovered in 84% NMR yield. Although the Nozaki group reported that the direct conversion of seven-membered chloride 1e into alcohol 3e failed under various conditions,<sup>12</sup> our method facilitated this conversion when the reaction temperature was elevated to 120 °C, affording 3e in 64% yield (entry 4). These results demonstrate the usefulness of squarate dianions as oxygen-incorporating nucleophiles in  $S_N^2$  reactions. The use of benzyl halides (1g-k)enabled the formation of the corresponding alcohols (3g-k) without the influence of the electron-donating or electronwithdrawing groups (entries 5-10). Cinnamyl bromide 11 exhibited good reactivity in the S<sub>N</sub>2 reaction of Sq<sup>2-</sup>, and cinnamyl alcohol (31) was obtained in 57% yield (entry 11). Additionally, allylic chlorides 1m and 1n, derived from isopulegol<sup>13</sup> and carvone,<sup>14</sup> respectively, also efficiently induced the desired reactions, producing diol 3m and ketoalcohol 3n in 79% and 71% yields, respectively (entries 12 and 13). Propargyl chloride 10 also afforded the corresponding alcohol 30 in 86% yield (entry 14). Next, Sq<sup>2–</sup>-mediated chemoselective reactions were examined using acyclic compounds 1p-r bearing two different halides/pseudohalides. The reaction of 6-iodo-1-chlorohexane (1p) with Sq<sup>2-</sup> at rt occurred at the alkyl iodide moiety chemoselectively, which afforded 3p in 87% yield (entry 15). The subjection of 7-bromo-1-chloroheptane 1q to similar reaction conditions also induced the chemoselective



Scheme 2 Trapping of monoalkyl squarate 2 with iodomethane and trial hydrolysis of dialkyl squarate 4.

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Table 2	Substrate	scope of	the substitution	reaction
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Entry	Substrate	Temp. (°C) time (h)	Product	$\operatorname{Yield}^{b}(\%)$	Entry	Substrate	Temp. (°C) time (h)	Product	Yield <sup>b</sup> (%)
1	BnOCl 1b	80 2	BnOOH 3a	91	11	Ph Br 1I	60 0.7	PhOH 3I	57
2	BnO Me 1c	80 2	BnO 3c Me	76	12	HO CI 1m	80 2	HO Me HO 3m	79
3	BnO Me 1d	90 3	BnO 3c Me	70	13		80 2	HO HO 3n	71
4 <sup><i>c</i></sup>		120 6	он Зе	64	14	<sup>n</sup> C <sub>5</sub> H <sub>11</sub>	80 1	<sup>n</sup> C <sub>5</sub> H <sub>11</sub> OH <b>30</b>	86
5	Br	60 0.5	OH 3f	71	15	I ()4 Cl 1p	rt 2	HO () <sub>4</sub> Cl 3p	87
6	MeO 1g	60 0.5	MeO 3g	96	16	Br ()_ Cl 1q	rt 6	HO () <sub>5</sub> Cl 3q	73
7	Me Ih	60 0.5	Me 3h	69	17 <sup><i>d</i></sup>	Br ( )_ OTs 1r	60 1	HO () <sub>5</sub> OH 3r	83
8	Br 1i	60 0.5	Br 3i	74	$18^d$	Br ()_Cl 1q	80 2	но () <sub>5</sub> он 3r	85
9	NC 1j	60 0.5	NC Зј	87	19 <sup>e</sup>	<sup>n</sup> Hex Br Br 1s	120 2	<sup>n</sup> Hex OH 3s	59
10	O <sub>2</sub> N Br	60 0.5	O <sub>2</sub> N OH	66					
			or X <sup>1</sup> X <sup>2</sup> 1b-t	H <sub>2</sub> Sq (1.5 equiv) DBU (3.0 equiv) DMF temp., time	K <sub>2</sub> CO <sub>3</sub> aq. 60 °C, 1 h	R OH R R Or H <b>3b-t</b>	0 Х²/ОН		

<sup>*a*</sup> The reaction was generally conducted on a 0.2 mmol scale. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> 0.1 mmol scale. <sup>*d*</sup> 3.0 equivalents of H<sub>2</sub>Sq and 6.0 equivalents of DBU were used and one-pot hydrolysis was conducted at 100 °C for 2.5 h. <sup>*e*</sup> 2.4 equivalents of H<sub>2</sub>Sq and 2.4 equivalents of DBU were used and one-pot hydrolysis was conducted at 100 °C for 1 h.

substitution with the Br group, providing 3**q** in high yield (entry 16). In contrast, the adoption of 7-bromo-1-heptyl tosylate (1**r**) to the chemoselective reaction was difficult because the eliminated bromo ion easily underwent substitution with the tosyloxy group. On the other hand, the coincident conversions of the bromo and chloro/tosyloxy groups in 1**r**/1**q** proceeded smoothly using 3.0 equivalents of Sq<sup>2-</sup> at 60–80 °C affording the same product, diol 3**r**, in 83% yield from 1**r** and in 85% yield from 1**q**, respectively (entries 17 and 18). Furthermore, the simultaneous conversion of the 1,2-dibromide moiety of 1s<sup>15</sup> was achieved *via* the exposure of 2.4 equivalents of H<sub>2</sub>Sq and DBU at 120 °C, which afforded 3**s** in 59% yield after a one-pot hydrolysis (entry 19). The E2 reaction of 1**s** competed when the proportion of DBU exceeded that of  $H_2Sq$ ; thus, we used the squarate monoanion, generated from the same equivalents of  $H_2Sq$  and DBU, as a nucleophile.

To demonstrate another application of squarates, we explored the synthesis of highly functionalized alcohol, namely glycerol (Scheme 3). In the presence of a primary alcohol, triisopropylsilyl ether  $5^{16}$  was reacted with *N*-iodosuccinimide (NIS) to afford iodoether **6** in good yields. The use of methanol, benzyl alcohol (BnOH), and propargyl alcohol resulted in the formation of ethers **6a**, **6b**, and **6c**, respectively. Upon heating with Sq<sup>2–</sup> generated *in situ* in DMF at 120 °C for 4 h, followed by a one-pot hydrolysis, alcohols **7a**, **7b**, and **7c** were obtained in high yields (Scheme 3a). On the other hand, the bromoetherification of allyl silyl ether **8**<sup>17</sup> using 1,3-dibromo-5,5-dimethylhydantoin and BnOH provided



Scheme 3 (a) Synthesis of 2-methylglycerol derivatives. (b) Synthesis of doubly protected glycerols. (c) Preparation of an azidoalcohol.

a 1.8 : 1 inseparable mixture of primary bromide 9 and secondary bromide 10. This mixture was subjected to 1.5 equivalents of  $Sq^{2-}$  at 100 °C, leading to the desired  $S_N2$  reactions in both compounds. Subsequent hydrolysis resulted in the formation of primary alcohol 11 and secondary alcohol 12 in 47% and 15% yields, respectively. A decrease in the reaction temperature to 60 °C induced a selective reaction of 9, which afforded 11 in 48% yield and 10 was recovered in 30% yield (Scheme 3b). The alcohols 7, 11 and 12 are regarded as analogues of glycerol possessing two different protective groups; therefore, they are expected to be versatile building blocks for the synthesis of various complex lipids.

We further investigated the synthesis of azidoalcohol **13**, a precursor for the synthesis of sphingosine (Scheme 3c).<sup>18</sup> The primary bromo group in dibromide **14**, prepared from **8** *via* bromination, underwent a chemoselective reaction upon treatment with 1.5 equivalents of H<sub>2</sub>Sq and 2.9 equivalents of DBU. Although this reaction proceeded smoothly to produce **15**,<sup>19</sup> the subsequent one-pot hydrolysis of **15** using aqueous K<sub>2</sub>CO<sub>3</sub> solution generated bromohydrin **16** and epoxide **17** in a **1**:1 ratio. In contrast, the treatment of the reaction mixture containing **15** with excess hydrazine monohydrate suppressed the formation of **17**, affording **16** in 59% yield. The typical conditions for the replacement of **16** into **13** in 87% yield. The



Scheme 4 Inversion of the stereochemistry of secondary alkyl bromides and tosylates.

conventional protocol for synthesizing azidoalcohol **13** from olefin **8** involves 5 steps: dihydroxylation, selective protection of the primary alcohol, sulfonylation of the secondary alcohol, azidization, and removal of the protecting group. Our synthetic method of **13** from **8** can occur in 3 steps, indicating the utility of  $Sq^{2-}$  as an oxygen nucleophile.

Finally, we demonstrated the Walden inversion of secondary alkyl halides/pseudohalides with a stereogenic center (Scheme 4). The reaction of tosylate **18**, which was derived from epiandrosterone, with  $Sq^{2-}$  proceeded at 100 °C to provide  $\alpha$ -alcohol **19** in 70% yield. Although the application of bicyclic compound **20**<sup>20</sup> required an excess amount of  $Sq^{2-}$ and a higher reaction temperature than that required for **18**,  $\beta$ -alcohol **21** was obtained in 50% yield.

#### Conclusions

In conclusion, we developed a convenient method for transforming alkyl halides into the corresponding alcohols through an  $S_N 2$  reaction using  $Sq^{2-}$ . The reaction of primary- and secondary-alkyl halides with the dianion species proceeded in DMF at 60–120 °C, and the resulting mono-alkyl squarate was readily hydrolyzed by treatment with an aqueous  $K_2CO_3$  solution. Examples for the inversion of a stereogenic center were also described. Furthermore, methods for synthesizing versatile building blocks of complex lipids have also been developed. We are further exploring the utility of  $Sq^{2-}$ , a potent and safe oxygen nucleophile, in synthetic organic chemistry.

#### Data availability

All experimental procedures and spectral data are available in the ESI.†

#### Author contributions

K. T. conceived the research theme and designed the experiments. K. S., T. F., and T. T. performed the experiments and analyzed the data. K. I. and K. T. commanded this work

and wrote the manuscript. T. S. assisted in writing and editing the manuscript. All authors contributed to the discussions.

## Conflicts of interest

There are no conflicts to declare.

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