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Alcohol synthesis based on the S_N2 reactions of alkyl halides with the squarate dianion†

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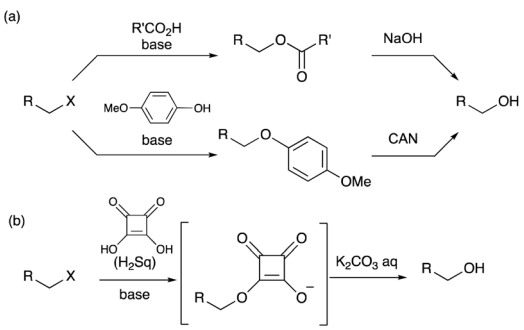
A convenient method has been developed for transforming alkyl halides into the corresponding alcohols *via* an S_N2 reaction. Treatment of an alkyl halide with the squarate dianion at high temperature produces mono-alkyl squarate, and a one-pot basic hydrolysis of the intermediate affords the alcohol in good yield.

Synthesis of alcohols from their corresponding alkyl halides is one of the most important and fundamental transformations in organic chemistry.[1] Spontaneous hydrolysis in wet polar solvents *via* an S_N1 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.[2] The S_N2 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 β-elimination reactions yielding alkenes.[3] 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_N2 reaction of an alkyl halide in high yields (Scheme 1).

Superoxide ions[4] are considered as representative nucleophiles for converting alkyl halides into alcohols,[5] but the use of hazardous reagents is a serious drawback, especially in large-scale experiments. In contrast, carboxylate anions undergo S_N2 reactions with alkyl halides to afford the corresponding esters, which can easily be converted into alcohols by saponification.[6] 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(IV) ammonium nitrate (CAN) and water.[7] 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_2Sq) 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.[8,9] The anionic charge of the squarate is completely delocalized across the four-membered ring, and the aromatic character of the conjugated π-system contributes to the exceptionally high stability of the anion.



Scheme 1 (a) Typical conversions of alkyl halides into the corresponding alcohols through S_N2 reactions with oxygen nucleophiles. (b) Conversion mechanism proposed in this work.

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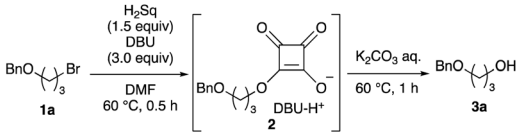
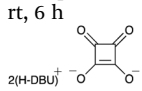
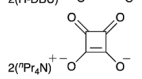
To elucidate the utility of the soft and non-basic oxygen nucleophile, we explored the S_N2 reactions of the squarate dianion (Sq^{2-}) with primary alkyl bromide **1a** under various conditions. The screening of suitable bases and solvents for the reaction revealed that the combination of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) and DMF was optimal for the *in situ* generation of Sq^{2-} from H_2Sq (see ESI-1 for details†). Bromide **1a** smoothly underwent the substitution reaction upon heating with H_2Sq (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_2CO_3 aqueous solution to obtain the desired alcohol **3a** in 89% yield (Table 1, entry 1). When i-Pr_2NEt 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_2Sq 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_2Sq from 1.5 equivalents to 0.5 equivalents because H_2Sq 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 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.[11]

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.

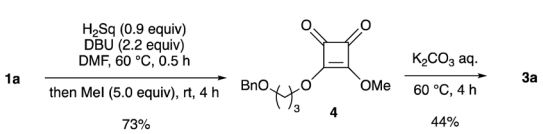
The optimized reaction conditions were applied to the transformation of several alkyl halides into their corresponding alcohols (Table 2). While a prolonged reaction time at a higher temperature was required to achieve the complete consumption of primary chloride **1b**, the desired alcohol **3a** was 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,[12] 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_N2 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 electron-withdrawing groups (entries 5–10). Cinnamyl bromide **1l** exhibited good reactivity in the S_N2 reaction of Sq^{2-}, and cinnamyl alcohol (**3l**) was obtained in 57% yield (entry 11). Additionally, allylic chlorides **1m** and **1n**, derived from isopulegol[13] and carvone,[14] 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 **1o** also afforded the corresponding alcohol **3o** in 86% yield (entry 14). Next, Sq^{2-}-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^{2-} 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

Table 1 Change of factors under the optimized reaction conditions[a]



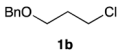
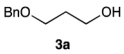
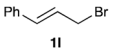
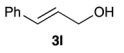
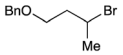
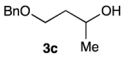
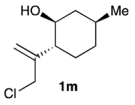
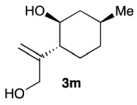
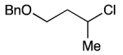
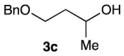
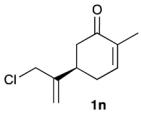
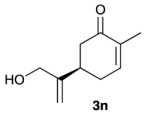
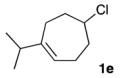
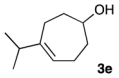
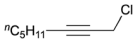
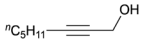
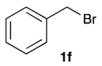
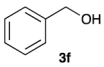
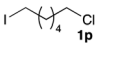
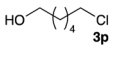
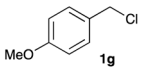
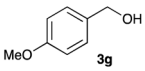
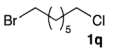
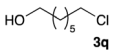
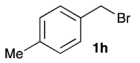
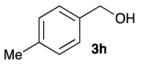
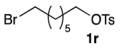
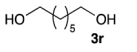
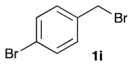
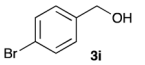
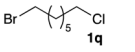
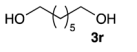
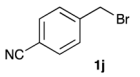
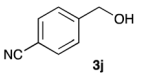
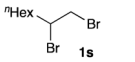
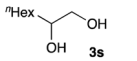
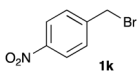
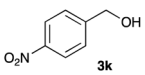
Entry	Variation from the standard conditions	Yield of **3a**[b] (%)	Recovery of **1a**[b] (%)
1	None	89	—
2	i-Pr_2NEt	27	20
3[c]	MeCN	82	—
4[c]	THF	43	48
5	Absence of H_2Sq	ND	Trace
6	0.5 equiv. of H_2Sq	56	13
7	2.2 equiv. of DBU	60	24
8	rt, 6 h	87	—
9[d]		30[f]	—
10[e]		39	—

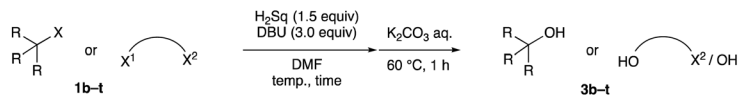
[a] 0.2 mmol scale. [b] Isolated yield. [c] 3.6 equivalents of DBU were used. [d] The reaction time was 1 h. [e] The reaction temperature ranged from 60 to 150 °C, and the reaction time was 6 h. [f] NMR yield.



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

Table 2 Substrate scope of the substitution reaction[a]

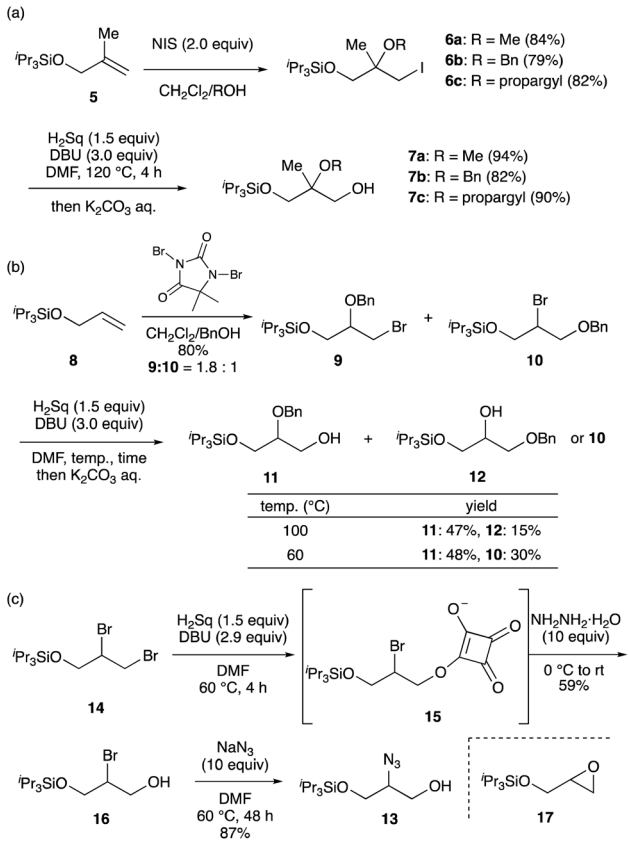
Entry	Substrate	Temp. (°C) time (h)	Product	Yield[b] (%)	Entry	Substrate	Temp. (°C) time (h)	Product	Yield[b] (%)
1	 **1b**	80 2	 **3a**	91	11	 **1l**	60 0.7	 **3l**	57
2	 **1c**	80 2	 **3c**	76	12	 **1m**	80 2	 **3m**	79
3	 **1d**	90 3	 **3c**	70	13	 **1n**	80 2	 **3n**	71
4[c]	 **1e**	120 6	 **3e**	64	14	 **1o**	80 1	 **3o**	86
5	 **1f**	60 0.5	 **3f**	71	15	 **1p**	rt 2	 **3p**	87
6	 **1g**	60 0.5	 **3g**	96	16	 **1q**	rt 6	 **3q**	73
7	 **1h**	60 0.5	 **3h**	69	17[d]	 **1r**	60 1	 **3r**	83
8	 **1i**	60 0.5	 **3i**	74	18[d]	 **1q**	80 2	 **3r**	85
9	 **1j**	60 0.5	 **3j**	87	19[e]	 **1s**	120 2	 **3s**	59
10	 **1k**	60 0.5	 **3k**	66					



[a] The reaction was generally conducted on a 0.2 mmol scale. [b] Isolated yield. [c] 0.1 mmol scale. [d] 3.0 equivalents of H_2Sq and 6.0 equivalents of DBU were used and one-pot hydrolysis was conducted at 100 °C for 2.5 h. [e] 2.4 equivalents of H_2Sq 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 **3q** in high yield (entry 16). In contrast, the adoption of 7-bromo-1-heptyl tosylate (**1r**) 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 **1r**/**1q** proceeded smoothly using 3.0 equivalents of Sq^{2-} at 60–80 °C affording the same product, diol **3r**, in 83% yield from **1r** and in 85% yield from **1q**, respectively (entries 17 and 18). Furthermore, the simultaneous conversion of the 1,2-dibromide moiety of **1s**[15] was achieved *via* the exposure of 2.4 equivalents of H_2Sq and DBU at 120 °C, which afforded **3s** in 59% yield after a one-pot hydrolysis (entry 19). The E2 reaction of **1s** 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.

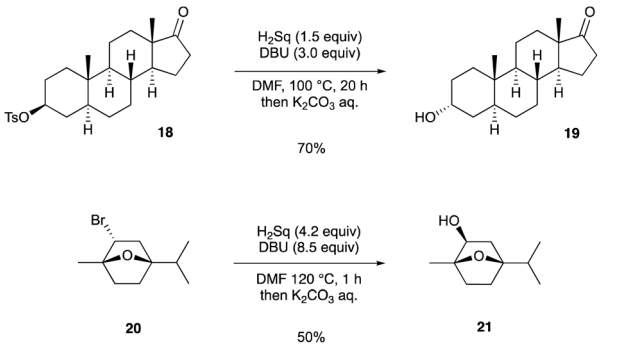
To demonstrate another application of squarates, we explored the synthesis of highly functionalized alcohol, namely glycerol (Scheme 3). In the presence of a primary alcohol, triisopropylsilyl ether **5**[16] was reacted with *N*-iodosuccinimide (NIS) to afford iodoether **6** in good yields. The use of methanol, benzyl alcohol (BnOH), and propargyl alcohol resulted in the formation of ethers **6a**, **6b**, and **6c**, respectively. Upon heating with Sq^{2-} 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**[17] 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).[18] The primary bromo group in dibromide **14**, prepared from **8** *via* bromination, underwent a chemoselective reaction upon treatment with 1.5 equivalents of H_2Sq and 2.9 equivalents of DBU. Although this reaction proceeded smoothly to produce **15**,[19] the subsequent one-pot hydrolysis of **15** using aqueous K_2CO_3 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 the bromo group with an azido group allowed the conversion 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 α-alcohol **19** in 70% yield. Although the application of bicyclic compound **20**[20] required an excess amount of Sq^{2-} and a higher reaction temperature than that required for **18**, β-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_N2 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.

Acknowledgements

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References

1 (*a*) T. A. Hamlin, M. Swart and F. M. Bickelhaupt, *ChemPhysChem*, 2018, **19**, 1315; (*b*) V. Lankea and I. Marek, *Chem. Sci.*, 2020, **11**, 9378.

2 (*a*) E. Nakamura, T. Inubushi, S. Aoki and D. Machii, *J. Am. Chem. Soc.*, 1991, **113**, 8980; (*b*) M. Sawamura, Y. Kawaguchi, K. Sato and E. Nakamura, *Chem. Lett.*, 1997, **26**, 705; (*c*) A. Abad, C. Agulló, A. C. Cuñat and I. Navarro, *Synlett*, 2005, 3355; (*d*) B. M. Chougala, S. Samundeeswari, M. Holiyachi and L. A. Shastri, *ChemistrySelect*, 2017, **2**, 1290; (*e*) Y.-M. Cai, Y.-T. Xu, X. Zhang, W.-X. Gao, X.-B. Huang, Y.-B. Zhou, M.-C. Liu and H.-Y. Wu, *Org. Lett.*, 2019, **21**, 8479; (*f*) H. Liu, J. Liu, X. Cheng, X. Jia, L. Yu and Q. Xu, *ChemSusChem*, 2019, **12**, 2994.

3 T. Hansen, J. C. Roozee, F. M. Bickelhaupt and T. A. Hamlin, *J. Org. Chem.*, 2022, **87**, 1805.

4 (*a*) M. Hayyan, M. A. Hashim and I. M. AlNashef, *Chem. Rev.*, 2016, **116**, 3029; (*b*) D. T. Sawyer and J. S. Valentine, *Acc. Chem. Res.*, 1981, **14**, 393.

5 (*a*) R. A. Johnson and E. G. Nidy, *J. Org. Chem.*, 1975, **40**, 1680; (*b*) M. A. Brimble, G. M. Williams, R. Baker and M. James, *Tetrahedron Lett.*, 1990, **31**, 3043; (*c*) A. Matsuzawa, J. Shiraiwa, A. Kasamatsu and K. Sugita, *Org. Lett.*, 2018, **20**, 1031.

6 (*a*) S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, 1942, **64**, 2780; (*b*) R. C. Larock, *J. Org. Chem.*, 1974, **39**, 3721; (*c*) N. Ono, T. Yamada, T. Saito, K. Tanaka and A. Kaji, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 2401; (*d*) S. Yamamoto, H. Itani, H. Takahashi, T. Tsuji and W. Nagata, *Tetrahedron Lett.*, 1984, **25**, 4545; (*e*) H. A. Zahalka and Y. Sasson, *Synthesis*, 1986, 763; (*f*) J. Alexander, M. L. Renyer and H. Veerapanane, *Synth. Commun.*, 1995, **25**, 3875.

7 (*a*) Y. Masaki, K. Yoshizawa and A. Itoh, *Tetrahedron Lett.*, 1996, **37**, 9321; (*b*) L. F. Tietze and J. Görlitzer, *Synthesis*, 1998, 873; (*c*) L. He, H.-S. Byun, J. Smit, J. Wilschut and R. Bittman, *J. Am. Chem. Soc.*, 1999, **121**, 3897; (*d*) T. Toma, Y. Kita and T. Fukuyama, *J. Am. Chem. Soc.*, 2010, **132**, 10233; (*e*) W. Szeja, G. Grynkiewicz, T. Bieg, P. Swierk, A. Byczek, K. Papaj, R. Kitel and A. Rusin, *Molecules*, 2014, **19**, 7072.

8 (*a*) L. M. Schwartz and L. O. Howard, *J. Phys. Chem.*, 1970, **74**, 4374; (*b*) H. Schmidt, *Synthesis*, 1980, 961; (*c*) G. Seltz and P. Imming, *Chem. Rev.*, 1992, **92**, 1227.

9 Analogues of squaric acid or squaramide are widely used in various fields. For selected reviews see: (*a*) M. Ohno, Y. Yamamoto and S. Eguchi, *Synlett*, 1998, 1167; (*b*) J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem. – Eur. J.*, 2011, **17**, 6890; (*c*) L. A. Marchetti, L. K. Kumawat, N. Mao, J. C. Stephens and R. B. P. Elmes, *Chem*, 2019, **5**, 1398; (*d*) K. A. Agnew-Francis and C. M. Williams, *Chem. Rev.*, 2020, **120**, 11616; (*e*) J. Chasák, V. Šlachtová, M. Urban and L. Brulíková, *Eur. J. Med. Chem.*, 2021, **209**, 112872; (*f*) T. Grus, H. Lahnif, B. Klasen, E.-S. Moon, L. Greifenstein and F. Roesch, *Bioconjugate Chem.*, 2021, **32**, 1223.

10 M. G. Topuzova, S. V. Kotov and T. M. Kolev, *Appl. Catal., A*, 2005, **281**, 157.

11 We also used a di-sodium salt of H_2Sq (Q. Zhao, J. Wang, Y. Lu, Y. Li, G. Liang and J. Chen, *Angew. Chem., Int. Ed.*, 2016, **55**, 1252(8)) as the reagent, but, the reaction did not occur and **1** was recovered in 80% NMR yield.

12 A. Itoh, T. Saito, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 1456.

13 (*a*) S. G. Hegde, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver and J. Wolinsky, *Tetrahedron Lett.*, 1980, **21**, 441; (*b*) S. G. Hegde, D. Beckwith, R. Doti and J. Wolinsky, *J. Org. Chem.*, 1985, **50**, 894.

14 M. Xuan, I. Paterson and S. M. Dalby, *Org. Lett.*, 2012, **14**, 5492.

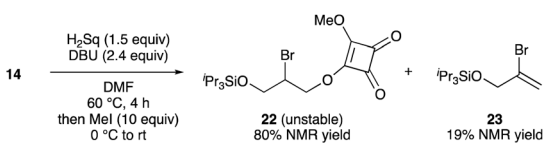
15 I. Ryu, H. Matsubara, S. Yasuda, H. Nakamura and D. P. Curran, *J. Am. Chem. Soc.*, 2002, **124**, 12946.

16 K. Zhao and R. R. Knowles, *J. Am. Chem. Soc.*, 2022, **144**, 137.

17 N. Saygili, R. J. Brown, P. Day, R. Hoelzl, P. Kathirgamanathan, E. R. Mageean, T. Ozturk, M. Pilkington, M. M. B. Qayyum, S. S. Turner, L. Vorwerg and J. D. Wallis, *Tetrahedron*, 2001, **57**, 5015.

18 (*a*) P. M. Koskinen and A. M. P. Koskinen, *Synthesis*, 1998, 1075; (*b*) R. Sridhar, B. Srinivas and K. R. Rao, *Tetrahedron*, 2009, **65**, 10701; (*c*) Y. Gao, X. He, F. Ding and Y. Zhang, *Synthesis*, 2016, 4017.

19 Reaction of **14** with H_2Sq and DBU, followed by the addition of excess amounts of MeI, provided methyl squarate **22** and vinyl bromide **23** in 80% and 19% NMR yields, respectively. Purification of the crude product *via* silica gel chromatography resulted in the decrease of the isolated yield of **22** (*ca.* 27% yield) owing to the instability of **22**.



20 R. M. Carman and B. N. Venzke, *Aust. J. Chem.*, 1973, **26**, 2235.