Thioureas as Highly Active Catalysts for the Biomimetic Bromocyclization of Geranyl Derivatives

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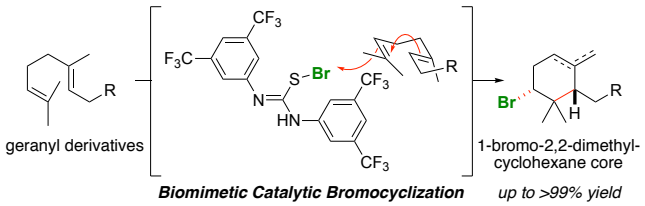
Supporting Information Placeholder

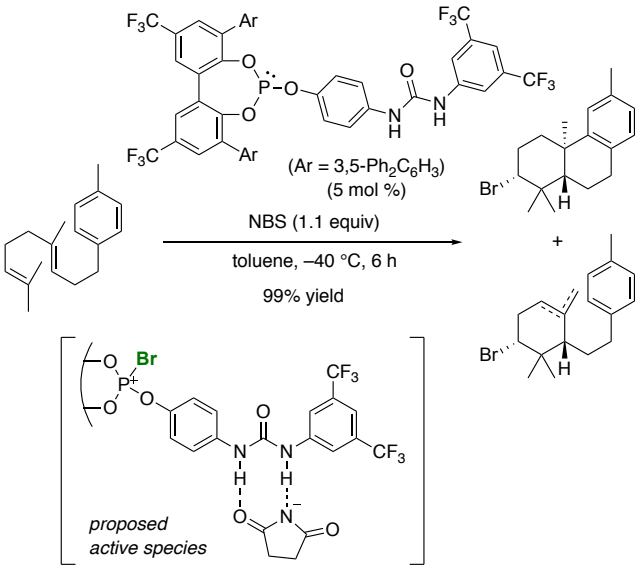


ABSTRACT: Thioureas bearing electron-deficient aryl groups show high catalytic activity in the biomimetic bromocyclization of geranyl derivatives. The reaction of geranyl derivatives with *N*-bromosuccinimide (NBS) proceeds rapidly in CH_2Cl_2 to give the corresponding bromocyclization products in high yields as a ca. 1:1 mixture of *endo*- and *exo*-isomers. The reactivity of geranyl derivatives highly depends on the terminal substituent: electron-donating substituents increase the reactivity, while electron-withdrawing substituents decrease the reactivity.

Brominated polycyclic terpenoids, which have a 1-bromo-2,2-dimethylcyclohexane core, are an important class of natural products.[1] Some of these compounds show unique biological activities such as anticancer and antiviral activities. The biosynthesis of the 1-bromo-2,2-dimethylcyclohexane core of these polycyclic terpenoids appears to involve an electrophilic bromination of acyclic isoprenoids induced by enzymes such as vanadium bromoperoxidase (V-BPO), followed by diastereoselective cyclization.[2,3] For the chemical synthesis of these bromine-containing polycyclic compounds, bromonium ion-induced biomimetic bromocyclization is the most desirable approach. Thus, considerable effort has been devoted to the development of efficient methods for the bromocyclization of acyclic isoprenoids.[4-6] For example, in 2009, Snyder and colleagues reported $Et_2SBr{\cdot}SbCl_5Br$ (BDSB) as a highly reactive electrophilic brominating reagent.[7,8] Although this method gave the corresponding bromocyclization products in high yields, a stoichiometric amount of BDSB, a rather expensive brominating agent, was required. In addition, the reaction conditions are highly acidic, and side reactions might also proceed in some cases. In 2018, Gulder and colleagues reported the halocyclization of geranyl derivatives with *N*-halosuccinimides in the presence of a stoichiometric amount of morpholine-HFIP salt in HFIP.[9]

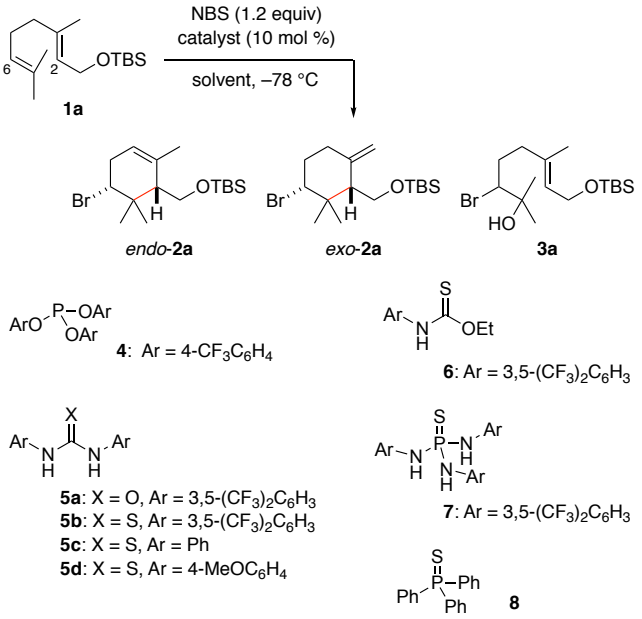
As a practical method for the biomimetic bromocyclization of acyclic isoprenoids, the use of an inexpensive and easily available brominating agent is desirable. *N*-Bromosuccinimide (NBS) is one of these desirable brominating agents, although its reactivity is low. A catalyst can be used to activate less reactive brominating agents and promote bromocyclization under mild conditions. Some catalysts that promote the bromocyclization of geranyl derivatives have recently been reported. For example, Chan and McErlean's group reported an *N*-heterocycle-flanked phosphoramidite catalyst that promoted the diastereoselective bromocyclization of a chiral geraniol derivative.[10] In 2017, Yamamoto and Samanta reported a chiral BINOL-derived thiophosphoramide catalyst that enantioselectively promoted the bromocyclization of geranyl derivatives.[11] Burns and colleagues reported enantioselective dehalogenation followed by solvolytic cyclization for the synthesis of enantioenriched 1-bromo-2,2-dimethylcyclohexane natural products.[12] Ishihara and Sakakura's group also developed phosphite–urea cooperative catalysts for the bromocyclization of geranyl derivatives.[13-15] Sterically hindered electron-deficient phosphites bearing a urea moiety successfully catalyze bromocyclization to give the corresponding products in high yields (Scheme 1). The phosphite moiety of these catalysts nucleophilically activates NBS to generate active species *in situ*. The urea moiety of the catalysts catches a succinimide anion via hydrogen bonding to promote generation of the active species. Although these catalysts show quite high activities, their structures are large and highly complex, and they require many steps to be synthesized. We report here a new method for the bromocyclization of geranyl derivatives. In this study, we focus on the development of structurally simple catalysts that can activate NBS and promote bromocyclization under weakly acidic or basic conditions at a low reaction temperature.

Scheme 1. Phosphite–urea Catalyst for the Bromocyclization of 4-Homogeranyltoluene[13]



Our study commenced with an examination of catalytic activities in the bromocyclization of geranyl TBS ether **1a** (Table 1). The reaction of **1a** with NBS (1.2 equiv) was conducted in the presence of a catalyst (10 mol%) in toluene at –78 °C. As reported previously,[13] the combined use of electron-deficient phosphite **4** and urea **5a** (1:1 molar ratio) showed better catalytic activity than the use of either **4** or **5a** alone, and the corresponding bromocyclization products **2a** were obtained in 64% yield as a ca. 1:1 mixture of *endo*- and *exo*-isomers (entries 2–4). Both *endo*- and *exo*-**2a** were generated as single diastereomers. When the reaction of **1a** was conducted in the absence of a catalyst, desired product **2a** was not obtained, and a small amount (10%) of bromohydrin **3a** was generated.

Table 1. Catalytic Activities in the Bromocyclization of 1a[a]



entry	catalyst	solvent	time (h)	yield of **2a** (%)[b]	*endo*-**2a** /*exo*-**2a**[b]
1[c]	—	toluene	19	0	—
2	**4**	toluene	19	53	1.6:1
3[c]	**5a**	toluene	19	0	—
4	**4** + **5a**	toluene	19	64	1.1:1
5	**4** + **5b**	toluene	19	58	1.1:1
6	**5b**	toluene	19	99	1:1.3
7	**5c**	toluene	19	21	1:2.7
8	**5d**	toluene	19	23	1:1.6
9[c]	**6**	toluene	19	23	1:2.2
10	**7**	toluene	19	69	1.4:1
11	**8**	toluene	19	7	1.2:1
12	—	CH_2Cl_2	1	0	—
13	**5b**	CH_2Cl_2	1	95	1.4:1
14[d]	**5b**	CH_2Cl_2	2	88	1.3:1
15	**5b**	$EtNO_2$	19	48	4.3:1
16[c]	**5b**	EtCN	19	2	1:1
17[c]	**5b**	THF	19	0	—

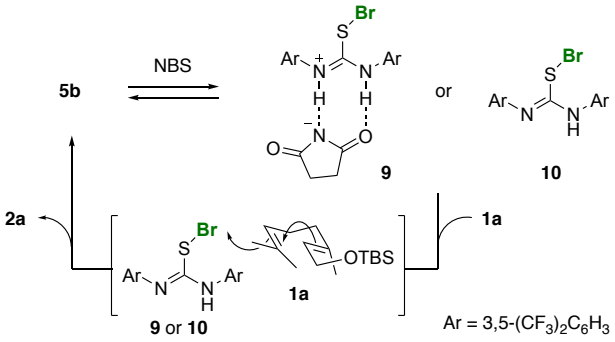
[a]The reaction of **1a** (0.1 mmol) with NBS (1.2 equiv) was conducted in the presence of a catalyst (10 mol%) in a solvent (1.5 mL) at –78 °C. [b]Evaluated by ^{1}H NMR analysis using trichloroethylene as an internal standard. [c]Bromohydrin **3a** was obtained in 10% (entries 1 and 3), 11% (entry 9), 42% (entry 15) and 22% yield (entry 16). [d]**1a** (1 mmol) was used as a substrate. *Endo*- and *exo*-**2a** was obtained in respective isolated yields of 42 and 29%.

To improve the catalytic activity, more acidic thiourea **5b** was used instead of urea **5a**. However, the combined use of **4** and **5b** (1:1 molar ratio) slightly decreased the yield of **2a** (58%, entry 5). Very interestingly, we found that when the reaction was conducted in the presence of only thiourea **5b** as a catalyst, bromocyclization product **2a** was obtained in quantitative yield (entry 6). Since thiourea **5b** showed high catalytic activity, we next examined the activities of structurally related compounds **5**–**8**. In contrast to the high activity of electron-deficient **5b**, thiourea **5c** without electron-withdrawing substituents and **5d** bearing electron-donating methoxy groups showed poor catalytic activity (entries 7 and 8). Thiocarbamate **6**, which has only one acidic proton, also gave poor results (entry 9). These results indicated that not only a nucleophilic sulfur atom but also rather acidic protons of **5b** were important for high catalytic activity. Indeed, thiophosphoric triamide **7** also showed good activity (entry 10), while triphenylphosphine sulfide (**8**)[16] was almost inert (entry 11).

The reactivity of the bromocyclization of **1a** highly depended on the solvents. When dichloromethane was used as a solvent, the reaction completed within an hour to give **2a** in 95% yield (entry 13), while the reaction did not proceed in the absence of **5b** in CH_2Cl_2 (entry 12). The reactivity in nitroethane was moderate and *endo*-**2a** was obtained as a major product (entry 15). Highly polar nitroethane might stabilize a carbocation intermediate to generate a thermodynamically stable *endo*-isomer preferentially. The use of propionitrile and THF gave poor results, and a significant amount of **3a** was generated (entries 16 and 17). The reaction of **1a** (1 mmol) under the optimized conditions also gave **2a** in 88% yield (entry 14).

Here we propose the active species generated from **5b** and NBS (Scheme 2). Based on previous reports[11,17,18] and our experimental results that the use of thioureas **5b**–**d** gave **2a** while urea **5a** was inert under the same reaction conditions,[19] it is conceivable that the sulfur atom of **5b** acted as a nucleophilic catalyst to generate cationic active species **9** or its neutral variant **10**.

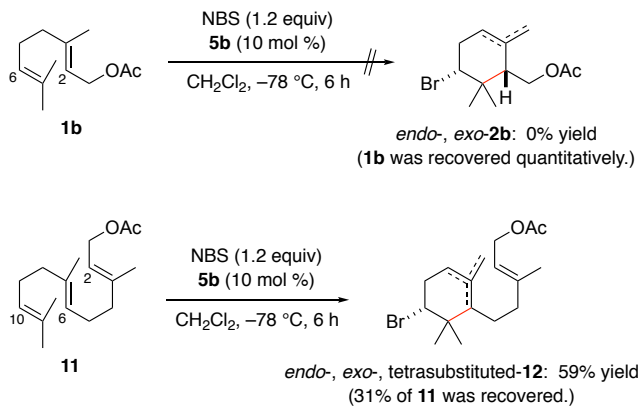
In active species **9**, succinimide anion would interact with the acidic protons of the thiourea moiety via hydrogen bonding. Active species **9** or **10** selectively reacted with the Δ6,7-double bond of **1a** to promote cyclization and give **2a** along with succinimide. Since electron-deficient thiourea **5b** showed higher activity than electron-rich **5d**, the rate-determining step would not be the formation of active species **9** or **10**, but rather bromination of the Δ6,7-double bond of **1a**.



Scheme 2. Proposed Active Species 9 and 10

The reactivity of geraniol derivatives **1** was also affected by the protecting group of the hydroxy group. For example, the reaction of geranyl acetate (**1b**) under the optimized conditions did not give any product and **1b** was recovered quantitatively (Scheme 3). In contrast to the poor reactivity of **1b**, the bromocyclization of farnesyl acetate (**11**) gave the corresponding product **12** in 59% yield under the same reaction conditions.

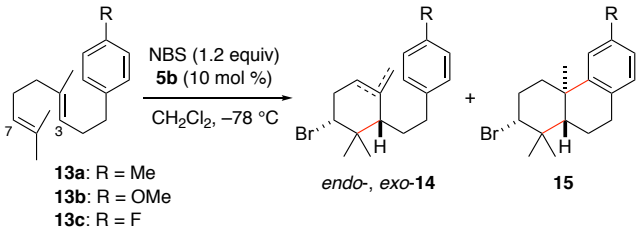
Scheme 3. 5b-Catalyzed Bromocyclization of Geranyl Acetate (1b) and Farnesyl Acetate (11)



The optimized reaction conditions could also be applied to the bromocyclization of homogeranylarenes **13**[13a] (Table 2). When the reaction of **13** with NBS (1.2 equiv) was conducted in the presence of **5b** (10 mol%), a mixture of *endo*- and *exo*-**14** was obtained along with biscyclization product **15**. Each product was obtained as a single diastereomer. Since *endo*-, *exo*-**14** could be quantitatively converted to **15** by treatment with $SnCl_4$ and trifluoroacetic acid,[13a] the combined yield of **14** and **15** was evaluated by ^{1}H NMR analysis of the crude product. As a result, the reaction of 4-homogeranyltoluene (**13a**) and 4-homogeranylanisole (**13b**), which have an electron-donating methyl or methoxy group on the aryl group, proceeded rapidly to give the corresponding products in respective yields of 100% and 92% (entries 1 and 2). On the other hand, 4-homogeranylfluorobenzene (**13c**) bearing an electron-withdrawing fluoro group required a rather long time for the reaction to complete under the same conditions (6 h, 93% yield, entry 4).

The experimental results shown in Table 1 and Scheme 3 indicated that the reactivity of **1** highly depended on the electron density of the Δ2,3-double bond. It was conceivable that cyclization would proceed via a concerted pathway, and that electron-donating interaction of the Δ2,3-double bond with the Δ6,7-double bond would be important for efficient promotion of the bromocyclization of **1** (Scheme 4). In the bromocyclization of geranyl TBS ether (**1a**), the electron-donating interaction of the Δ2,3-double bond with the Δ6,7-double bond would stabilize the transition state to promote bromination of the Δ6,7-double bond. On the other hand, the electron-donating interaction of the Δ2,3-double bond would be quite weak in the reaction of geranyl acetate (**1b**) due to the electron-withdrawing acetoxy group. This could explain why **1b** was inert under the present reaction conditions. In contrast to **1b**, the Δ6,7-double bond of farnesyl acetate (**11**) had a high enough electron density to stabilize the transition state to promote the bromocyclization.

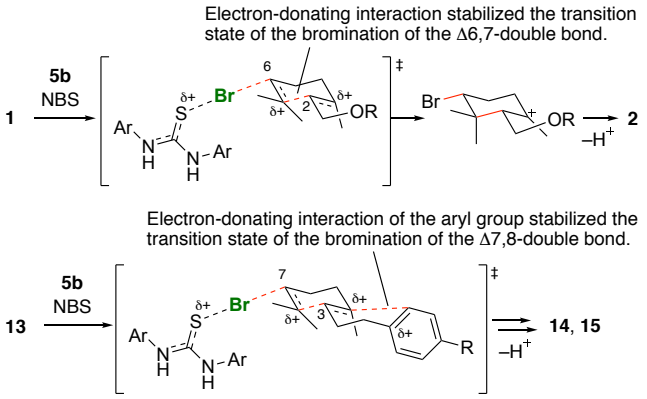
Table 2. 5b-Catalyzed Bromocyclization of Homogeranylarenes 14[a]



entry	**13**	time (h)	yield of **14** and **15** (%)[b]	**14**/**15**[b]	*endo*-**14** /*exo*-**14**[b]
1[c]	**13a**	6	0	—	—
2	**13a**	0.7	100	58:42	1:1.4
3	**13b**	0.7	92	55:45	1:1.4
4	**13c**	6	93	73:27	1:1.8

[a]The reaction of **13** (0.1 mmol) with NBS (1.2 equiv) was conducted in the presence of **5b** (10 mol%) in CH_2Cl_2 (1.5 mL) at –78 °C. [b]Evaluated by ^{1}H NMR analysis using trichloroethylene as an internal standard. [c]The reaction was conducted in the absence of **5b**.

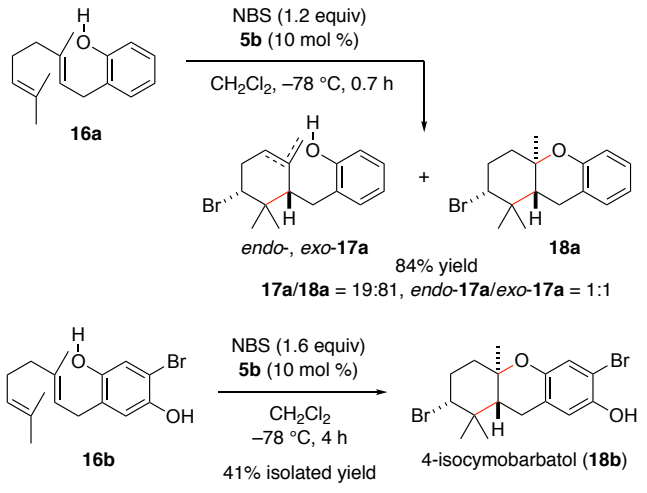
Scheme 4. Proposed Mechanism of the Bromocyclization of Geranyl Derivatives 1 and 13



The reactivities of homogeranylarenes **13** depended on the electron density of the aryl group (Table 2). These results implied that the electron-donating interaction of not only the Δ3,4-double bond with the Δ7,8-double bond but also that of the aryl group with the Δ3,4-double bond stabilized the transition state to promote the bromocyclization of **13**, even in case of the formation of monocyclization products **14** (Scheme 4).

We next examined the bromocyclization of 2-geranylphenols **16**[13b,c] (Scheme 5). The reaction of 2-geranylphenol (**16a**) proceeded rapidly to give the corresponding products **17a** and **18a** in 84% yield. Since the nucleophilicity of the phenol group was high, biscyclization product **18a** was obtained as a major product (**17a**/**18a** = 19:81). Finally, the present bromocyclization was applied to the synthesis of 4-isocymobarbatol (**18b**). Since the aryl group of **16b** was highly electron-rich and susceptible to electrophilic bromination, NBS was added in eight portions. As a result, **18b** was obtained in 41% isolated yield along with a mixture of bromination products of the aryl group of **16b** (ca. 20%).

Scheme 5. Bromocyclization of 2-Geranylphenols 16



In conclusion, we found that electron-deficient thiourea **5b** showed high catalytic activity in the biomimetic bromocyclization of geranyl derivatives. The reaction with NBS proceeded rapidly in CH_2Cl_2 even at –78 °C to give the corresponding products in high yields. The reactivity of the present bromocyclization highly depends on the terminal substituents of the substrates: geranyl TBS ether (**1a**) was rapidly converted to the corresponding product **2a**, while geranyl acetate (**1b**) was inert under the same conditions. The reactivities of 4-homogeranylarenes **13** depended on the electron density of their aryl groups. The present bromocyclization could be successfully applied to a synthesis of 4-isocymobarbatol (**18b**).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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