JOC*Note*

Arylation and Vinylation of Alkenes Based on Unusual Sequential Semipinacol Rearrangement/ Grob Fragmentation of Allylic Alcohols

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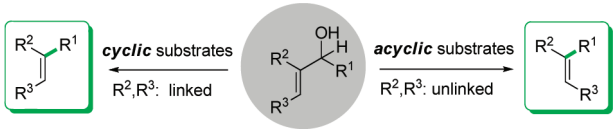
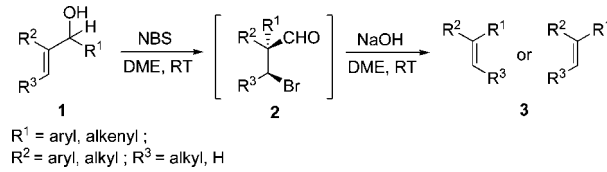


Alkenes can be stereoselectively arylated and vinylated without transition-metal catalyst under mild conditions through an interesting NBS-promoted semipinacol rearrangement and a subsequent unusual NaOH-mediated Grob fragmentation.

Many arene compounds containing vinyl moieties possess significant physiological, biological,[1] and photophysical activities[2] and are often used as building blocks in organic synthesis, particularly in the preparation of fluorescent materials.[3] Thus, arylation and vinylation of alkenes have long been one of the most important synthetic methodologies in modern organic chemistry.[4] Many endeavors have been made to discover and develop various practical methods, among which the well-known Suzuki,[5] Negishi,[6] Wittig,[7] Heck,[8] Stille,[9] and Julia[10] coupling methods have played great roles. However, those established methods generally require the related premade functionalized substrates (e.g., halides, stannanes, organoborons, and ylides), and notably, the employment of expensive transition-metal catalyst (e.g., Pd) is crucially necessary in most cases.

SCHEME 1. Sequential Semipinacol Rearrangment/Grob Fragmentation of Allylic Alcohols



In our recent investigation on tandem protocols based on the semipinacol rearrangement,[11] we interestingly found when a NBS-promoted semipinacol rearrangement of allylic alcohols **1** was performed in basic medium, the resulting β-bromo aldehydes **2** could further undergo an unusual Grob fragmentation,[12] forming aryl- or vinyl-substituted alkenes **3** (Scheme 1). To our knowledge, this kind of one-pot transformation consisting of the semipinacol rearrangement and the sequential coelimination of β-bromide and formyl group has not been reported.[13] This novel one-pot reaction provides a new efficient intramolecular arylation and vinylation method by using allylic alcohols. The main synthetic feature of this methodology lies in that an alternative arylation or vinylation of alkenes could be effectively accessed in the absence of transition-metal catalyst. Additionally, NBS and NaOH used in this transformation are cheap and easily available. Besides, the current protocol is insensitive to oxygen

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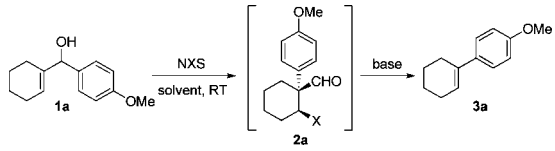
TABLE 1. Optimization of Reaction Conditions[a]



entry	NXS	solvent	base	yield[b,c] (%)
1	NBS	DME[d]		0
2	NBS	DME	Et_3N	0
3	NBS	DME	piperidine	0
4	NBS	DME	imidazole	0
5	NBS	DME	NaOAc	0
6	NBS	DME	K_2CO_3	0
7	NBS	DME	DBU[e]	0
8	NBS	DME	KOH	82
9	NBS	DME	NaOH	85
10	NBS	CH_3OH	NaOH	50
11	NBS	THF/H_2O[f]	NaOH	5
12	NBS	CH_2Cl_2	NaOH	0
13	NBS	DMF	NaOH	0
14	NBS	benzene	NaOH	0
15	NBS	CH_3CN	NaOH	0
16	NIS	DME	NaOH	64
17	NCS[g]	DME	NaOH	0

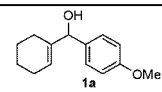
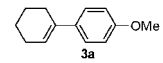
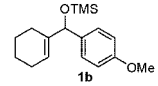
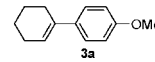
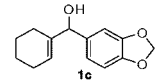
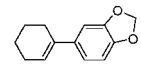
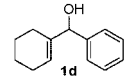
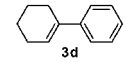
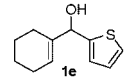
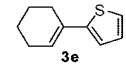
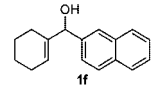
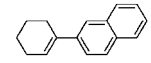
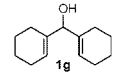
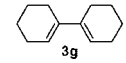
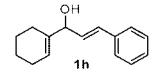
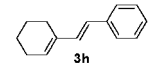
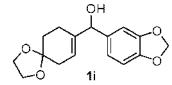
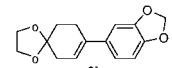
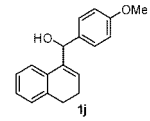
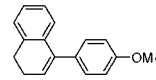
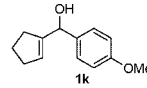
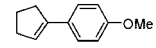
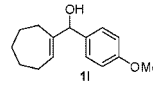
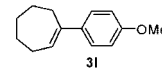
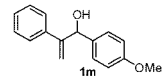
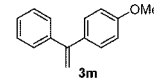
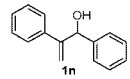
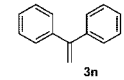
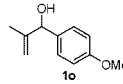
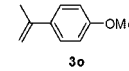
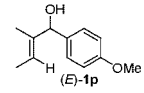
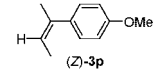
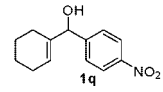
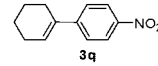
[a] Reaction conditions: allylic alcohol (1.0 mmol), NXS (1.2 mmol), solvent (2 mL), and base (2−25 mmol) at rt. [b] For entries 1−7 and 12−15, only the semipinacol rearrangement could be observed. [c] Isolated yield. [d] DME = 1,2-dimethoxyethane. [e] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene [f] THF/H_2O = 10:1. [g] No semipinacol rearrangement took place.

and moisture, leading to a very convenient experimental manipulation. Herein we present our results in detail.

The allylic alcohol substrates **1** were prepared by the addition of the corresponding vinyllithium or -magnesium to the appropriate aldehydes according to our previously reported procedure.[11] The use of **1a** as a model substrate was first investigated for optimizing the reaction condition of this semipinacol rearrangement/Grob fragmentation. The results obtained were listed in Table 1. We initially screened several organic and inorganic bases in parallel experiments (entries 1−9). Of the bases examined, we found that 25 equiv of NaOH was the best choice to form the alkene product **3a** in highest yield of 85% (entry 9). Solvent effects were examined as well (entries 9−15) in which DME was found to be the best reaction media. NCS and NIS were also tested in DME, wherein the use of NIS followed by addition of NaOH could afford the desired product in 64% yield (entry 16). Surprisingly, NCS was ineffective completely, and no semipinacol rearrangement occurred at all (entry 17). It should be noted that the reaction intermediate **2a** could be observed in the aforementioned experiments except entry 17.

On the basis of the above optimized conditions (entry 9, Table 1), the generality of this semipinacol rearrangement/Grob fragmentation was investigated by employing a series of allylic alcohols. As seen in Table 2, various cyclic allylic alcohols **1a**−**j** with the cyclohexene moiety could smoothly give the expected arylated and vinylated trisubstituted alkenes **3a**−**j** in good to excellent yields (entries 1−10), wherein the migrating group could be the aryl and the alkenyl. Remarkably, allylic alcohols containing the electron-rich aromatic ring as migrating group were the ideal substrates for this transition-metal-free one-pot arylation (entries 1−3, 9, and 10) in which the TMS-protected secondary allylic alcohol **1b** was also effective (entry 2). In addition, the thiophenyl (entry 5) and the naphthyl (entry 6) also act as good migrating groups in this reaction, although the

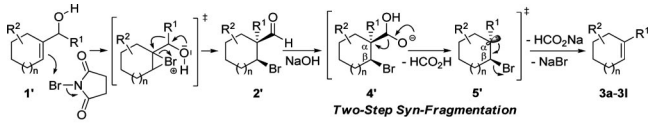
TABLE 2. Substrates Scope of the Semipinacol Rearrangement/ Grob Fragmentation of Allylic Alcohols

entry	substrate	product	yield (%)[b]
1			85
2			93
3			93
4			71
5			92
6			87
7[c]			53(65)[d]
8[c]			60(72)[d]
9			90
10			86
11			85
12			83
13			77
14			81
15			75
16			92[e]
17[f]			0

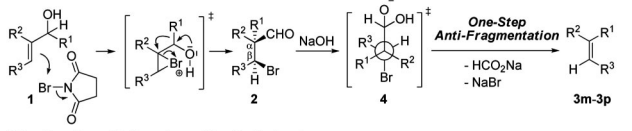
[a] General reaction conditions (unless otherwise noted): allylic alcohol (1.0 mmol), NBS (1.2 mmol), and DME (2 mL) at room temperature for 1−4 h and then NaOH (25 mmol) at ambient temperature for 12 h [b] Isolated yield. [c] Reaction time of 72 h. [d] Yield in parentheses based on the recovered starting materials. [e] Only one single isomer was isolated, and its relative configuration was determined by 1D NOE of ^1H NMR. [f] No semipinacol rearrangement could be observed, and **1q** was recovered.

alkenyl as migrating group (entries 7 and 8) showed longer reaction time (at least 72 h) and lower isolated yields (around

SCHEME 2. Proposed Mechanism of the Semipinacol Rearrangement/Grob Fragmentation



Mechanism A for Cyclic Substrates



Mechanism B for Acyclic Substrates

60%). While employing the substrate with the electron-deficient aromatic group such as **1q** (entry 17), the related semipinacol rearrangement as the first step of this kind of one-pot transformation could not proceed at all, probably due to its weak migrating capability.

Moreover, the allylic alcohol bearing cyclopentene or cycloheptene moiety (entries 11 and 12, Table 2) was further investigated under standard conditions, and the desired products **3k** and **3l** were readily afforded in 85% and 83% yields, respectively. To expand the substrate scope, acyclic substrates **1m**−**o** (entries 13−15) were then examined, and as expected, the reaction proceeded well, giving the *gem*-disubstituted alkenes **3m**−**o** in good yields following the standard procedure.

In order to probe the stereoselectivity of this novel semipinacol rearrangement/Grob fragmentation, one acyclic trisubstituted example was presented (entry 16, Table 2) wherein allylic alcohol (*E*)-**1p** with (*E*)-double bond was subjected to the current reaction, resulting in the formation of one alkene isomer (*Z*)-**3p** with reversed configuration of the original double bond. This interesting result shows the high stereoselectivity in the current acyclic substrate and it would be mechanistically interesting for this one-pot transformation.

According to the above results and literature reports, the reaction mechanism of this semipinacol rearrangement/Grob fragmentation was proposed as shown in Scheme 2. For the cyclic substrates (**1a**−**l**, entries 1−12 of Table 2), as shown in mechanism A of Scheme 2, first an electrophilic addition of the Br^+ released from the NBS to the allylic alcohol **1′** led to antimigration of R^1 to form β-bromoaldehyde **2′**.[11a,c] Subsequently under the basic conditions, the addition of hydroxy anion to the carbonyl of aldehyde resulted in the formation of semialdehyde intermediate **4′**. Then a two-step syn-fragmentation occurred through the sequential deformylation and debromination,[12] owing to the restraint of free rotation of $C_\alpha-C_\beta$ single bond in cyclic molecular conformation, giving the alkene product with the reserved stereochemistry of the original double bond. For the acyclic ones (**1m**−**p**, entries 13−16 of Table 2), as demonstrated in mechanism B of Scheme 2, the intermediate β-bromoaldehyde **2** generated in analogous fashion to **2′**. In contrast to the cyclic case, an energetically favorable one-step synchronous fragmentation took place,[12] due to the possibility of free rotation of $C_\alpha-C_\beta$ single bond in acyclic molecular conformation, yielding the desired alkenes with reversed configuration.

In conclusion, we have discovered a novel transition-metal-free one-pot semipinacol rearrangement/Grob fragmentation of allylic alcohols. This reaction has proved to be an effective method for arylation and vinylation of alkenes, and more widespread investigation of this novel methodology is in progress in our laboratory.

Experimental Section

General Procedure for the One-Pot Reaction. To a solution of allylic alcohol **1a** (1.0 mmol) in DME (2 mL) was added NBS (1.2 mmol) at room temperature. The resulting mixture was stirred for 3 h until the starting material disappeared by inspection of TLC. Subsequently, the NaOH powder (25 mmol) was directly added to the reaction solution, and it was further stirred overnight until TLC examination indicated the disappearance of the intermediate **2a**. The reaction mixture was diluted by addition of OEt_2 followed by addition of water. The organic layer was separated, and the aqueous phase was re-extracted with OEt_2. The combined extracts was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified by chromatography on silica gel eluting with light petroleum to yield the product **3a**. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.34-7.30 (m, 2H), 6.86−6.83 (m, 2H), 6.05−6.02 (m, 1H), 3.80 (s, 3H), 2.40−2.36 (m, 2H), 2.22−2.16 (m, 2H), 1.79−1.74 (m, 2H), 1.69−1.63 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 158.3, 135.8, 135.3, 125.9, 123.1, 113.5, 55.2, 27.4, 25.8, 23.1, 22.2. MS: *m*/*z* 188 (M^+, 100), 159 (53), 129 (40), 115 (50), 91 (38). HRMS (ESI): calcd for $C_{13}H_{16}O$ 188.1196, found 188.1194.

Acknowledgment. We gratefully acknowledge financial support from the NSFC (No. 30271488, 20911001) and the Chang Jiang Scholars Program.

Supporting Information Available: General experimental procedures, characterization data for all compounds, and 1D NOE spectra of **3p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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