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Synthetically Useful Wagner–Meerwein Rearrangement of α-Quaternary β-Bromovinyl Methyl Ethers

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A synthetically useful Wagner–Meerwein (WM) rearrangement is reported in this paper. The investigation on the design and optimization involved the substrates α-quaternary β-bromovinyl methyl ethers as well as the reaction conditions. γ-Aryl α,β-unsaturated aldehydes with versatile synthetic uses could readily be obtained through a special pathway in high yields. For example, tricyclic aromatic systems were constructed efficiently through a tandem WM rearrangement/Friedel–Crafts alkylation.

Introduction

The well-known WM rearrangement[1] is a fundamental process in organic chemistry. It involves a carbon-to-carbon 1,2-migration,[2] typically from an alkyl, vinyl, or aryl group to an adjacent carbocationic center. By applying this reaction, not only can some required functions be deposited in hard-to-access positions, but also some special and complex skeletons can be constructed, for example, in highly strained polycyclic systems.[3] Therefore, this subject has been attracting the continuous interest of chemists since Wagner's initial report in 1899.[4] However, most of the research focuses on the nature of the rearrangement intermediates,[5,6a] stereoelectronic effects or pathways of rearrangement in polycyclic systems.[6–9] In fact, the existence of many competing pathways which lead to complicated products[10] imply, to a great extent, a limitation for the practical use of this method in organic synthesis. In view of this point, our research on this subject has focused on the design of a substrate which would favor the WM rearrangement reaction and be synthetically applicable. In this report, the structure "α-quaternary β-bromo vinyl methyl ether" was designed, and it proved to be effective in the WM reaction in the presence of a Lewis acid. The important features of this WM rearrangement reaction include: (1) Introduction of the electron-rich vinyl methyl ether group would be favorable in stabilizing the carbocation, and could generate a conjugated aldehyde (-CH=CH–C=O), which is crucial to promoting the WM process. (2) The substrate structures designed here would afford interesting products if some substituents could be changed, which would generate various building blocks for the construction of some natural products. We present our preliminary investigation results here.

Results and Discussion

Our design of the substrate structure was based on the assumption that cyclopentane, hexane, and heptane were currently incorporated into many organic compounds, so they were chosen as the framework. Aromatic systems possessed high migration aptitude[11] and could be multiply functionalized, they were thus selected as the migrating group. The sterically hindered quaternary carbon center had to be introduced because of its strong promotion of group migration. As a result, the substrate α-quaternary β-bromo aldehyde **A0** (Scheme 1) was firstly prepared by a literature procedure[12] and subjected to a test WM rearrangement at 0 °C and 50 °C by using several Lewis acids [Hg(OTf)$_2$, AgBF$_4$, AgOTf etc.] as well as solvents (THF, CH$_2$Cl$_2$, EtOAc etc.). The reaction did not occur, probably because the electron-deficient aldehyde group was not beneficial to stabilizing the adjacent carbocation.[13] In view of this result, the aldehyde function was replaced by a vinyl methyl ether group (-CH=CHOMe) by the Wittig reaction[14] to give the substrate **A1**. To our great pleasure, an efficient WM rearrangement of **A1** proceeded smoothly at 0 °C and afforded γ-aryl α,β-unsaturated aldehyde **B1** in 93% yield under the promotion of Hg(OTf)$_2$. In this process, introduction of the vinyl methyl ether group not only promoted the reaction to occur smoothly in high yield, but also directed this process toward a special pathway through the stability of allylic cations.[15]

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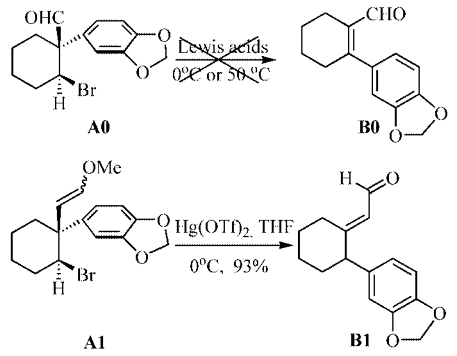
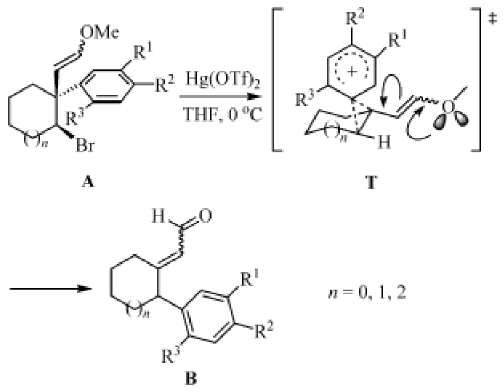


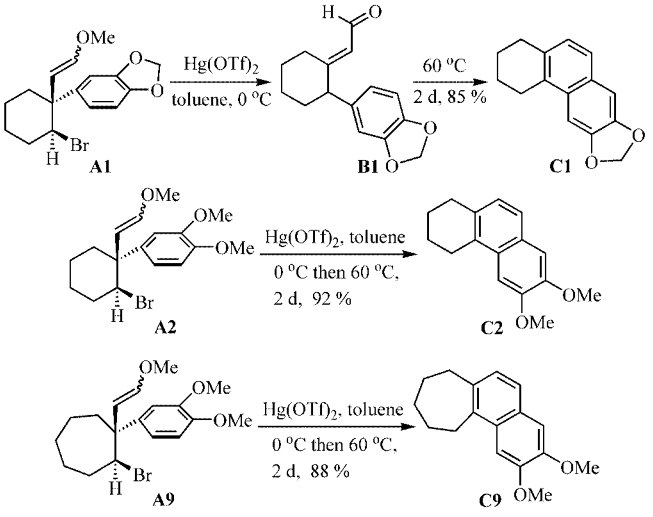
Scheme 1.



Scheme 2.

On the basis of the preliminary results above, a series of α-quaternary β-bromo vinyl methyl ethers **A** were prepared to examine the generality of this WM rearrangement (Scheme 2). The results are tabulated in Table 1. The starting materials were *Z*- and *E*-isomer mixtures of vinyl methyl ethers in the various ratios determined by ^{1}H NMR spectroscopy. All reactions were completed instantaneously (within 1 min) at 0 °C, and the expected γ-aryl α, β-unsaturated aldehydes **B** were obtained in excellent yields. The *Z*/*E* ratios of the double bonds in the products changed with the size of ring systems. It is very interesting that substrates with six-membered (entries 1–6) and seven-membered (entry 9) rings, which were *Z*/*E* isomer mixtures, afforded only the *E*-isomers of the products, but the five-membered ring substrates (entries 7 and 8) afforded mixtures of *Z*- and *E*-isomers, the ratios of which are given in Table 1. These interesting stereochemical observations mentioned above have not been clarified yet. However, it is noteworthy that the *E*- and *Z*-isomer ratios of the double bonds in substrates have little effect on the stereochemistry of the product double bonds. A possibly pivotal transition state **T** is suggested in Scheme 2 according to the experimental results and the reports on the mechanism of WM rearrangement reactions.[9c,16]

An approach to the tricyclic aromatic system was developed efficiently as an example for the application of this WM rearrangement, through its sequent reaction with Friedel–Crafts alkylation (cyclization). The reaction afforded intermediate **B1** quickly at 0 °C. When substrate **A** was heated at 60 °C for two days, it was completely transformed into the tricyclic system **C**, as monitored by TLC, according to the expected sequential procedure (Scheme 3). Substrates **A1** and **A2** with six-membered rings underwent a tandem WM rearrangement/Friedel–Crafts alkylation (cyclization)



Scheme 3. The tandem WM rearrangement/Friedel–Crafts alkylation of α-quarternary β-bromo vinyl methyl ethers.

Table 1. The efficient WM rearrangement of α-quaternary β-bromo vinyl methyl ethers promoted by Hg(OTf)$_2$.[a]

Entry	Substrate A					*Z*/*E* ratio in product **B**[c]	Yield (%)[d]
	n	*Z*/*E*[b]	R^1	R^2	R^3		
1	1	45:55	OCH$_2$O		H	0:100	93
2	1	78:22	OMe	OMe	H	0:100	95
3	1	74:26	H	OMe	H	0:100	92
4	1	38:62	H	Me	H	0:100	86
5	1	77:23	H	H	H	0:100	85
6	1	64:36	OMe	OMe	CH$_2$CH(OMe)$_2$	0:100	89
7	0	86:14	OMe	OMe	H	17:83	93
8	0	70:30	OCH$_2$O		H	23:77	92
9	2	100:0	OMe	OMe	H	0:100	88

[a] All reactions were complete instantaneously at 0 °C in THF promoted by 0.5 mmol Hg(OTf)$_2$ (in a 1:1 mole ratio with the substrate). [b] The *Z*/*E* ratio was determined by ^{1}H NMR spectroscopy. [c] The stereochemistry of the double bonds was determined by 1D NOE spectroscopy. [d] Isolated yields.

to afford the corresponding tetrahydrophenanthrene[17] in 85% and 92% yields, respectively. The products obtained here include substances in a wide range of naturally occurring compounds with biological and therapeutic activities such as tanshinone,[18a] estrone,[18b] aporphine alkaloids,[18c] and morphine alkaloids.[18d] In the same way, substrate **A9** with a seven-membered ring formed a tetrahydrocyclohepta[*a*]naphthalene, the key skeleton of natural pisiferin, in 88% yield.[19] These transformations demonstrated the great potential application of our designed WM reaction in organic synthesis.

Conclusion

In summary, we have successfully developed a synthetically useful WM rearrangement reaction of α-quaternary β-bromo vinyl methyl ethers promoted by Hg(OTf)$_2$. It afforded not only an excellent method to place a aryl group at the γ-position of α, β-unsaturated aldehydes, but also a conveniently synthetic strategy to some natural skeletons with tricyclic aromatic system. Our further work about applying the reaction to total synthesis of some natural products are currently under active investigations in our laboratory.

Supporting Information (see footnote on the first page of this article): Experimental procedure, spectroscopic data, and NMR spectra of compounds.

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