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Synthesis of oxygen heterocycles via alkynyltungsten compounds*

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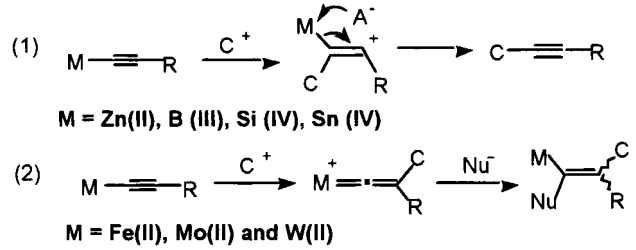
Abstract: This short review article covers some useful applications of alkynyltungsten compounds to the syntheses of complex lactones. Two types of cyclizations will be emphasized: (1) cycloalkenylation of tungsten-alkynol compounds with aldehydes to give α-alkylidene oxacarbeniums, further leading to α-alkylidene lactones and (2) intramolecular [3+2]-cycloaddition of epoxides to give bicyclic lactones. The new methodologies can provide a short synthesis of enantiopure lactones such as (–)-epilitsenolide C_2, (+)-listenolide C_1, (+)-isodihydromahubanolide A, (+)-blastmycinone, and (–)-*epi*-blastmycinone.

INTRODUCTION

The reaction of alkynylmetal complexes with organic carbonyl compounds can lead to oxygenated molecules; the regioselectivities depend on the types of metals as shown in Scheme 1 [1–2]. Alkynyl organometallics of silanes, boranes, stannanes, and zinc are not as useful as their allyl-, propargyl and allenyl species because of their low reactivities [1]. These alkynyl organometallics undergo electrophilic addition at their C_α-carbons to generate an unstable vinyl cation that is easily captured by any basic species in solution to give alkynyl derivative. Alkynyl compounds of electron-rich transition metals however show a distinct reaction pathway [2–3]. These organometallics react with carbon electrophiles at their C_β-carbons to form metal-vinylidenium intermediates which are fairly kinetically stable. Nucleophilic attack at cations of these types proceeds with regiochemistry at their C_α-carbons to effect a 1,2-addition product. Metal-vinylidenium species is also a valuable intermediate in various catalytic carbon–carbon bond formations [4]. In this study, we report two useful cyclizations based on alkynyltungsten compounds, and each reaction involves sequential bond-breaking and -forming processes.



Scheme 1

CYCLOALKENYLATIONS

Treatment of tungsten alkynols with aldehydes and $BF_3{\cdot}Et_2O$ (1.0 equiv) in diethyl ether produced tungsten-oxacarbenium salts in quantitative yields (>98%) [5]. The structures of tungsten-oxacarbeniums

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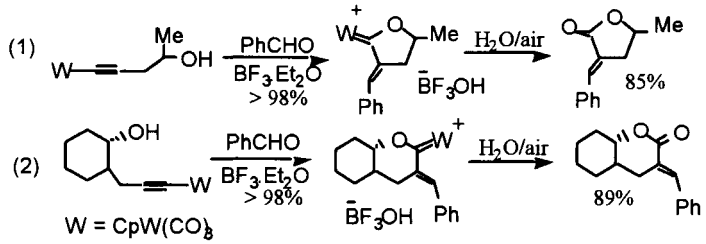
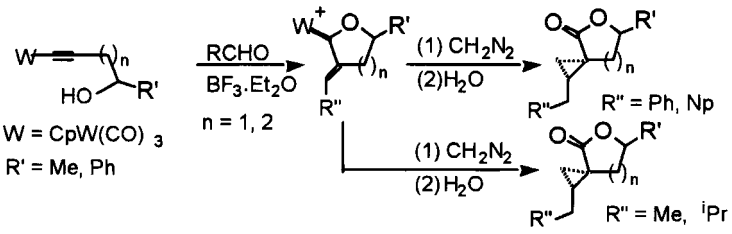
(eqs. 1–2, Scheme 2) were characterized by X-ray diffraction studies. The oxacarbenium salts were isoelectronic with neutral Group 6 Fisher carbene complexes, and easily demetallated by H_2O/air to afford α-alkylidene lactones in good yields [5]. This synthetic method is applicable to other electrophiles such as aliphatic aldehydes and trimethoxymethane to give good yields of α-alkylidene γ- and δ-lactones. This method is also effective for the synthesis of α-alkylidene γ-lactams derived from alkynyltungsten amines and aldehydes [6]. Attempts to extend this cyclization for the synthesis of larger ε-lactones and γ-lactams were unsuccessful.



Scheme 2

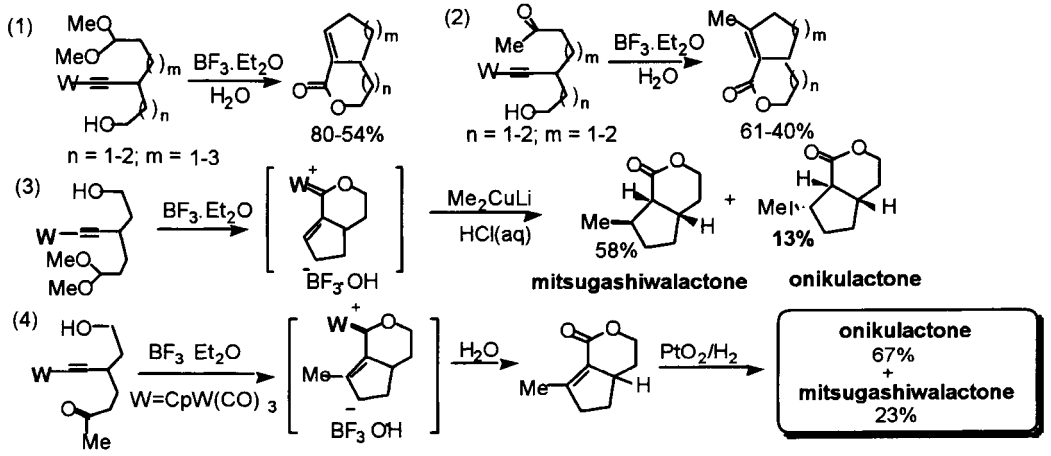
The oxacarbenium salts can undergo cyclopropanation with diazomethane to provide a one-pot synthesis of spiro-ε- and γ-lactones as depicted in Scheme 3. The reaction proceeds with high diastereoselectivities with a new cyclopropane ring trans to the phenyl or methyl substituent. Notably, there are two distinct pathways. The oxacarbenium salt bearing one alkylidene group uptakes one molecule of CH_2N_2, whereas those having an arylidene group uptake two molecules. According to isotopic labeling experiment, one of the CH_2 inserts into the Ar–C single bond of the arylidene group. The mechanism is proposed to involve a bridging phenonium ion [5].



Scheme 3

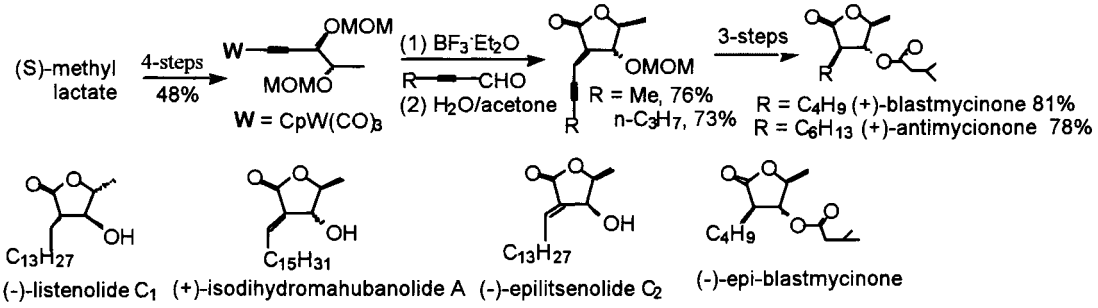
Intramolecular cycloalkenation of alkynyltungsten compounds is a useful method for the synthesis of bicyclic unsaturated lactones [7]. The sizes can be up to seven-membered carbocyclic rings fused with γ- and ε-lactones. The electrophiles include a tethered dimethoxymethane, trimethoxymethanes, and ketone group. One advantage here is that starting alkynyltungsten species bearing a tethered electrophile and alcohol were easily prepared in two steps from the alkynols $HCC(CH_2)_{n+1}OH$ and bromoalkanyl dimethoxymethane. The dimethoxymethane and trimethoxymethane derivatives gave better yields compared to their ketone analogs. An application of this method is a short synthesis of natural mitsugashilactones and onikulactone. Mitsugashilactone was selectively prepared via treatment of tungsten-pentynol (eq. 3) with $BF_3{\cdot}Et_2O$ in diethyl ether, followed by sequential treatment of oxacarbenium intermediates with Me_2CuLi and water. A similar approach gave onikulactone in reasonable yield with a different tungsten-pentynol complex (eq. 4).

We were successful in extending cycloalkenylations to the synthesis of enantiopure natural lactones [8–10], such as (–)-epilitsenolide C_2, (+)-listenolide C_1, (+)-isodihydromahubanolide A, (+)-blastmycinone and (–)-*epi*-blastmycinone. Scheme 5 shows the key step for total synthesis of (+)-blastmycinone and (+)-antimycinone based on a modified cycloalkenylation. We employed the dimethoxymethoxy derive (Scheme 5) and alkynyl aldehydes to achieve the reaction, giving the desired



Scheme 4

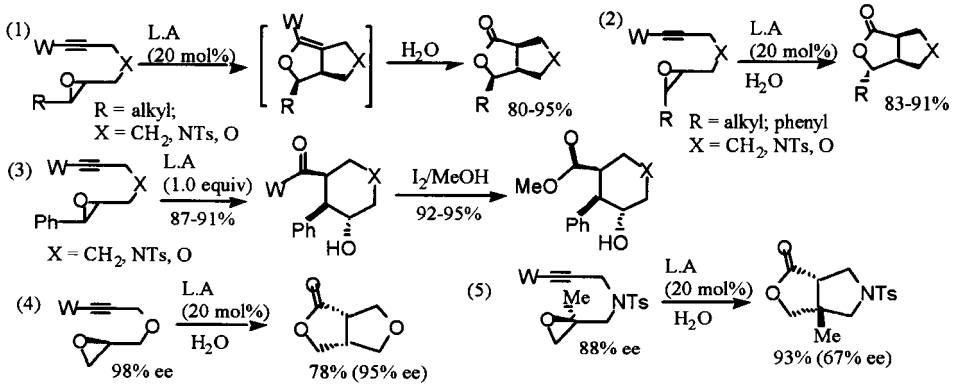
oxacarbenium salts, further leading to unsaturated lactones in good yields. Aliphatic aldehydes did not work in this case, and tungsten-furayl complexes were found as major products. The overall yield of (+)-blastmycinone and (+)-antimycinone is ca. 23–25% yields in nine steps from (S)-methyl lactate. Natural α-alkylidene γ-lactones such as (–)-epilitsenolide C_2, (+)-listenolide C_1, (+)-isodihydromahubanolide, and trisubstituted lactone (–)-*epi*-blastmycinone were also successfully prepared from this cyclization.



Scheme 5

CYCLOADDITION OF EPOXIDES

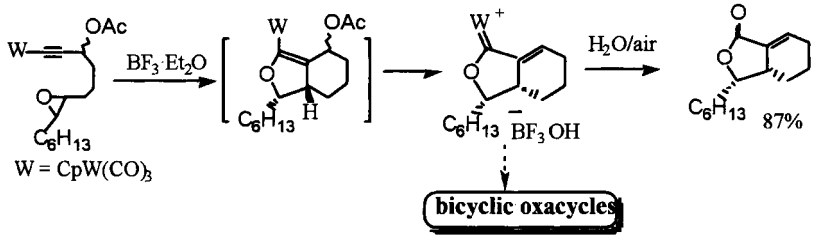
Although epoxides and aziridines are important reagents, cycloadditions of epoxides with functionalized alkynes remains unknown. [3+2]-Cycloaddition of functionalized alkenes with aziridine is reported recently [11]. We recently discovered [12] that alkynyltungsten compounds undergo smooth cycloaddition with epoxides via vinylidenium intermediates. Such [3+2]-cycloadditions proceed with high diastereoselectivities, and *trans*-epoxides gave only *cis*-lactones, whereas *cis*-epoxides gave only *trans*-lactones (Scheme 6). This implies a S_N2 mechanism for ring opening of epoxides. Only *cis*-fused isomers were formed for various bicyclic γ-lactones. In the case of a *trans*-phenyl oxide (eq. 3), the cyclization proceeds with *endo*-attack of epoxide, whereas *cis*-phenyl oxide gave cycloaddition products (eq. 2). The cycloadditions also work well for tethered *trans*-aziridines with a similar fashion. *Cis*-aziridines did not undergo cycloadditions, under conditions, and this may be attributed to steric effects that disfavor an intramolecular S_N2 process. We also prepared optically active epoxides (eqs. 4–5) to



Scheme 6

study the nature of cyclization. No significant loss of enantiopurities is observed for secondary epoxide (eq. 3), but nearly 24% loss of enantiopuritie is observed for tertiary epoxide (eq. 4).

Scheme 7 shows an instance for cycloaddition of an epoxide that can form a synthetically useful oxacarbenium if the reaction is performed in diethyl ether [13]. In principle, these cationic salts can lead to a number of oxygen heterocycles via treatment with various nucleophiles. Since optically pure epoxides are easily prepared according to literature methods [14]. It is speculated that such cycloadditions will be useful methods for synthesis of natural compounds.



Scheme 7

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