Concise Synthesis of Fully-Substituted Furan, Pyrrole, Butenolide, and 2-Butene-4-lactam Esters

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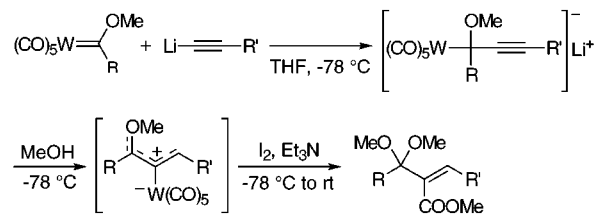
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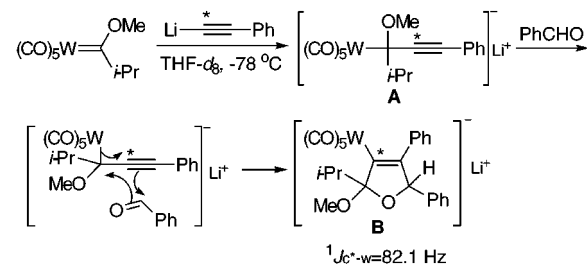
In previous papers, we reported that a new type of anionic propargyl derivative of group 6 metals is generated by the addition reaction of alkynyllithiums to Fischer-type carbene complexes and that these species react with various electrophiles such as aldehydes, imines, and so on to give trisubstituted furans, pyrroles, etc., respectively.[1,2] Also, variable-temperature (VT) NMR studies on the protonation of the propargyl tungsten species with methanol confirmed that the protonation occurs with 1,2-migration of the metal group to give a vinyltungsten intermediate, which is stable up to 0 °C. Furthermore, this new vinyltungsten intermediate was found to give a methoxycarbonylated product on oxidation with iodine (Scheme 1).[3] On the basis of these results, it was expected that the same type of 1,2-migration of the metal group would occur during the reaction of the anionic propargylmetallic species with carbon electrophiles and that the intermediates thus formed could be employed for oxidative methoxycarbonylation.[4] In this paper is described an efficient method for the preparation of fully substituted furan, pyrrole, butenolide, and 2-butene-4-lactam esters based on this strategy.

First, we carried out VT-NMR studies to confirm the structure of the intermediate formed on the reaction of the anionic propargylmetallic intermediate with an aldehyde. When the addition intermediate, derived from the isopropylcarbene complex and lithiated phenylacetylene-*2-13C*, was treated with benzaldehyde,[5] the strong peak at δ 106.1 ppm (the labeled carbon of the addition intermediate **A**) gradually disappeared at −50 to −40 °C and a strong new peak appeared at δ 163.7 ppm. This signal had a characteristic coupling with tungsten 183 with a coupling constant of 82.1 Hz, which suggests the presence of direct bonding between tungsten and the labeled carbon.[3,6] Thus, the reaction with an aldehyde is thought to proceed via a [3 + 2] cycloaddition pathway with concomitant migration of the metal group to give vinylmetallic intermediate **B** as shown in Scheme 2.[2] The intermediate **B** had remained unchanged at room temperature overnight.
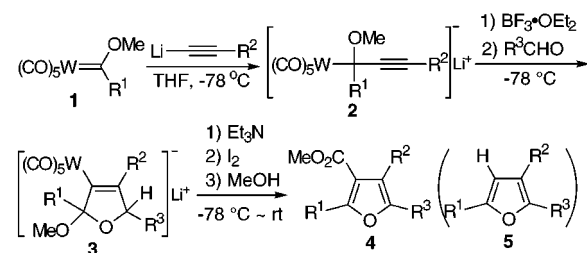
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(1) (a) Iwasawa, N.; Maeyama, K.; Saitou, M. *J. Am. Chem. Soc.* **1997**, *119*, 1486. (b) Iwasawa, N.; Maeyama, K. *J. Org. Chem.* **1997**, *62*, 1918.

(2) For the reviews of the reactions of transition metal propargylmetallic species with carbon electrophiles, see: (a) Welker, M. E. *Chem. Rev.* **1992**, *92*, 97. (b) Frühauf, H.-M. *Chem. Rev.* **1997**, *97*, 523.

(3) Iwasawa, N.; Ochiai, T.; Maeyama, K. *Organometallics* **1997**, *16*, 5137.

(4) For examples of oxidative alkoxycarbonylation of the intermediates generated by the reaction of allyl or propargyl transition-metal species with carbon electrophiles, see: (a) Shu, H. G.; Shiu, L. H.; Wang, S. H.; Wang, S. L.; Lee, G. H.; Peng, S. M.; Liu, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 530. (b) Stokes, H. L.; Ni, L. M.; Belot, J. A.; Welker, M. E. *J. Organomet. Chem.* **1995**, *487*, 95. (c) Abram, T. S.; Baker, R.; Exon, C. M.; Rao, V. B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 285. (d) Jiang, S.; Turos, E. *Organometallics* **1993**, *12*, 4280.

(5) The reaction with aldehydes is usually carried out in the presence of BF₃·OEt₂, but in this NMR study BF₃·OEt₂ was not added to avoid complications due to subsequent elimination of methanol as described in the text.

(6) Mann, B. E.; Taylor, B. F. *13C NMR Data for Organometallic Compounds*; Academic Press: London, 1981.

Scheme 1

Scheme 2[a]

$^1J_{C^*-W}=82.1$ Hz

[a] Asterisks indicate the ¹³C labeled position.

Scheme 3

As the presence of the vinylmetallic intermediate **B** was confirmed, we then carried out the iodine oxidation of this intermediate. According to the previously mentioned procedure, pentacarbonyl(1-methoxy-1-phenylmethylidene)-tungsten(0) was added to 1-octynyllithium in THF at −78 °C, and then the propargylmetallic species generated was reacted with benzaldehyde in the presence of BF₃·OEt₂ at this temperature overnight. Triethylamine (10 equiv), iodine (2 equiv), and excess methanol were added successively to the mixture at −78 °C, and the mixture was allowed to slowly warm to room temperature. Reductive workup with 10% aqueous Na₂S₂O₃ solution gave the expected methyl 4-hexyl-2,5-diphenyl-3-furancarboxylate (**4a**, R¹ = Ph, R² = *n*-Hex, R³ = Ph) in 35% yield along with trisubstituted furan **5a** in 60% yield. Formation of the protonated furan **5a** can be explained by assuming that the intermediate **3a** undergoes elimination of methanol followed by protonolysis of the carbon−tungsten bond slowly during the reaction with benzaldehyde. Next, the reaction time with benzaldehyde was examined to minimize the formation of the protonated furan **5a**. It was found that although a reaction time of 5 min was not sufficient for completion of reaction with benzaldehyde (yield of **4a**; 35%), the desired furancarboxylate **4a** was obtained in 84% yield together with a trace amount of protonated furan **5a** on carrying out the reaction for 1 h at −78 °C (Scheme 3).

We then examined preparation of various fully substituted 3-furancarboxylates **4** according to this procedure,[7] the results being summarized in Table 1. As shown in Table 1, the reaction proceeded in a similar manner employing various carbene complexes, alkynes, and aldehydes, and a wide variety of 3-furancarboxylates were obtained in good

Table 1. Preparation of Furan Esters 4[a]

R^1	R^2	R^3	yield[b] (%)
Ph	*n*-Hex	Ph	84
Ph	*n*-Hex	*i*-Pr	61
Ph	*n*-Hex	CO_2Et	60
Ph	Ph	Ph	96
i-Pr	*n*-Hex	Ph	64
i-Pr	*n*-Hex	CO_2Et	61
n-Bu	Ph	Ph	51

[a] All reactions performed in THF (12 mL) using alkynyllithium (0.6 mmol), carbene complex (0.3 mmol), $BF_3 \cdot OEt_2$ (0.6 mmol), aldehyde (0.9 mmol), triethylamine (0.5 mL), iodine (0.6 mmol), and methanol (5 mL) at −78 °C. [b] Isolated yield.

Table 2. Preparation of Pyrrole Esters 6, Butenolide Esters 7, and 2-Butene-4-lactam Esters 8[a]
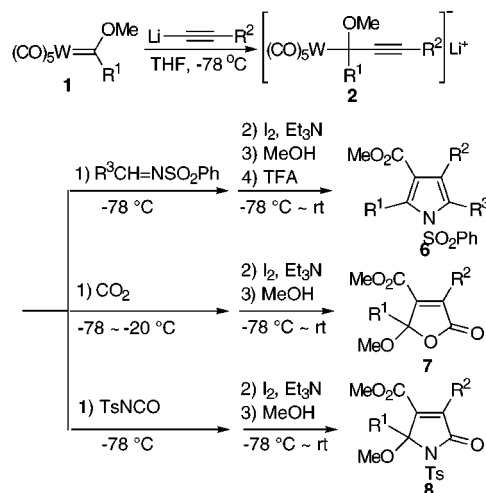
R^1	R^2	R^3	yield[b] (%) 6	7	8
Ph	*n*-Hex	Ph	76	64	74
Ph	*n*-Hex	PhCH=CH	70		
Ph	Ph	Ph		38	74
i-Pr[c]	*n*-Hex	Ph	72	48	60[d]
i-Pr[c]	*n*-Hex	PhCH=CH	70		
i-Pr[c]	Ph	Ph	70	71	66[d]
i-Pr[c]	TMS				81

[a] All reactions performed in THF (12 mL) using alkynyllithium (0.6 mmol), carbene complex (0.3 mmol), sulfonylimine (for **6**) or tosyl isocyanate (for **8**) (0.9 mmol) or several small pieces of dry ice (for **7**), triethylamine (0.5 mL), iodine (0.6 mmol), and methanol (5 mL). [b] Isolated yield. [c] Molybdenum complex was employed. [d] In the case of the reaction of isopropylcarbene complex, a mixture of N- and O-cyclized product was obtained. O-Cyclized product was quantitatively isomerized to N-cyclized product on treatment with $EtAlCl_2$ in CH_2Cl_2 at −78 °C. Yield indicates the overall yield.

yield by the iodine oxidation of the intermediates **3**. In the case of the reaction with ethyl glyoxylate, differentiated 2,4-furandicarboxylates were obtained in good yield. It should be noted that in this reaction three carbon−carbon bond formations are performed in one sequence and that the three substituents R^1, R^2, and R^3 on the furan come from the carbene complex, alkyne, and aldehyde, respectively.

Next, we examined preparation of fully substituted pyrrole, butenolide, and 2-butene-4-lactam esters by applying the above procedure to the reaction with sulfonylimines, carbon dioxide, and tosyl isocyanate, respectively. As summarized in Table 2, the reactions proceeded as expected, and various fully substituted five-membered heterocyclic compounds were obtained in good yield by the iodine oxidation of the intermediates generated in the reaction of the anionic propargylmetallic species with these electrophiles (Scheme 4). Several points are worthy of note here. In the reaction with sulfonylimines, the iodine oxidation gave dihydropyr-

Scheme 4

role derivatives **9**,[8] which were treated with trifluoroacetic acid to give the corresponding pyrroles **6**. In the reaction with tosyl isocyanate, a mixture of N- and O-cyclized products was obtained when isopropyl carbene complex was employed. O-Cyclized product was quantitatively isomerized to N-cyclized product on treatment with $EtAlCl_2$ in CH_2Cl_2 at −78 °C.[1b] In all these reactions, tungsten complexes were usually employed due to their stability, but in some cases a molybdenum complex was employed[9] because the corresponding propargylmetals display higher reactivity toward electrophiles.

In conclusion, we have developed a highly efficient method for the preparation of a variety of synthetically useful, fully substituted five-membered heterocyclic compounds by the iodine oxidation of the intermediates produced from Fischer-type carbene complexes, alkynes, and various carbon electrophiles.

Supporting Information Available: Experimental procedures and spectral data for compounds **4** and **6**−**8** (8 pages).

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(7) **General Procedure.** To a THF (5 mL) solution of an alkyne (0.7 mmol) was added a 1.6 M hexane solution of *n*-BuLi (0.6 mmol) at −78 °C. A THF solution (2 mL) of a carbene complex (0.3 mmol) was added dropwise to the mixture, and the mixture was further stirred for 30 min at −78 °C. Then, both $BF_3 \cdot OEt_2$ (0.6 mmol) and an aldehyde (0.8 mmol) were added successively in THF solution (2 mL each) at −78 °C, and the mixture was stirred for 1 h at −78 °C. To the mixture were added triethylamine (0.5 mL) and a THF solution (1.0 mL) of iodine (0.6 mmol) at −78 °C, and after 10 min, MeOH (5 mL) was added slowly. After the mixture had been warmed to room temperature, the reaction was quenched with aqueous $Na_2S_2O_3$ solution, and the products were extracted and purified by TLC.

(8) In the previous procedure described in ref 1a, the reaction was carried out in the presence of $BF_3 \cdot OEt_2$, but the reaction was found to proceed without $BF_3 \cdot OEt_2$, and the iodine oxidation of the intermediate gave the dihydropyrrole derivative **9** as a mixture of diastereomers. Brief purification of **9** at this stage followed by trifluoroacetic acid treatment made isolation of the pyrrole derivative **6** easier.

(9) Of several molybdenum complexes prepared (phenyl, *n*-butyl, and isopropyl), only the isopropyl carbene complex was sufficiently stable to be employed at rt without the need for special handling.