Tetrahedron Letters 51 (2010) 3678–3681

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of multisubstituted furans via copper-catalyzed intramolecular O-vinylation of ketones with vinyl bromides

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ARTICLE INFO

Article history:
Received 30 March 2010
Revised 10 May 2010
Accepted 11 May 2010
Available online 15 May 2010

ABSTRACT

With the catalysis of CuI/3,4,7,8-tetramethyl-1,10-phenanthroline, various ketones smoothly underwent the intramolecular O-vinylation with vinyl bromides leading to the efficient synthesis of the corresponding multisubstituted furans.

Furans are important structural motifs in a number of biologically active natural products and medicinal agents such as nakadomarin A[1] and Sumiki's acid.[2] They are also versatile building blocks in organic synthesis.[3] Preparations of furans have long been an important topic in organic chemistry and continue to be actively pursued.[4] Conventional methods include the Feist–Bénary reactions and the Paal–Knorr furan synthesis.[3] The recently developed transition metal (Pd, Ru, and Au)-catalyzed cycloisomerization[4b] of allenyl ketones,[5] alkynones,[6] alkynyl epoxides[7], or (*Z*)-2-en-4-yn-1-ols[8] provides atom-economic entries to the corresponding furans. However, these methods suffer from either the limited scope of application or the use of expensive catalysts. Hence, the development of mild and general synthesis of furans is still highly desirable especially in view of industrial applications. Herein, we report that the Cu(I)-catalyzed intramolecular O-vinylation of ketones with vinyl bromides or even chlorides serves as a simple and efficient method to the corresponding multisubstituted furans.

In the past decade, we have witnessed a rapid progress in the formation of aryl C–O bonds via copper-catalyzed Ullmann coupling between aryl halides and O-centered nucleophiles.[9] The high stability and low costs of the copper catalysts make these transformations attractive for industrial applications. By the appropriate choice of copper source, ligand, base, and solvent, these reactions have been developed to include a wide range of substrates under mild conditions. Ketone enolates, alcohols, and even carboxylates can be employed as the nucleophiles. This method has also been extended to the inter-[10] and intramolecular[11,12] O-vinylation reactions. Nevertheless, compared to O-arylation, the O-vinylation reactions are much less explored. We recently reported the intramolecular O-vinylation of β-ketoesters with vinyl bromides leading to the efficient formation of five-, six-, and even seven-membered cyclic alkenyl ethers.[12a] When an ordinary ketone enolate was used as the nucleophile, the corresponding furan was obtained via the in-situ isomerization of the O-vinylation product. However, the yield was very low (22%). This could be attributed to the much more difficult enolization of simple ketones than β-ketoesters. Such a phenomenon was also observed in the intramolecular O-arylation reactions.[13] Driven by our interest in copper-catalyzed intramolecular vinylation reactions,[12,14] we set out to further investigate the O-vinylation reactions of ordinary ketones in order to develop these coupling processes into a useful method for furan synthesis.

6-Bromo-1-phenylhept-6-en-3-one (**1a**) was thus chosen as the model substrate for the optimization of reaction conditions (Table 1). Compound **1a** was first subjected to the following typical conditions for Ullmann coupling: 10 mol % of CuI, 40 mol % of *N*,*N*′-dimethylethylenediamine (**L-1**),[15] 3 equiv of Cs_2CO_3 in refluxing dioxane. The expected furan **2a** was obtained in only 5% yield while most of the starting material remained unchanged (Table 1, entry 1). Changing the ligand to 2-isobutyrylcyclohexanone (**L-2**)[16] or L-proline (**L-3**)[17] did not help (Table 1, entries 2 and 3). With the use of 1,10-phenanthroline (**L-4**),[18] the yield of **2a** was slightly increased (Table 1, entry 4). When the ligand was switched to 3,4,7,8-tetramethyl-1,10-phenanthroline (**L-5**),[10a] we were delighted to find that **2a** was isolated in 57% yield (Table 1, entry 5). Extending the reaction time from 10 to 20 h led to the quantitative formation of **2a** (Table 1, entry 8). Furthermore, when the amount of **L-5** was reduced to 20 mol %, the same result was achieved (Table 1, entry 9). The effect of bases was also screened and Cs_2CO_3 turned out to be superior over K_2CO_3 and K_3PO_4 (Table 1, entries 5–7). Again, without the ligand or base, no reaction occurred (Table 1, entries 10 and 11).

With the optimized conditions (Table 1, entry 9) in hand, we then examined the generality of this method. The results are summarized in Tables 2 and 3.[19] In addition to 2,5-dialkyl-substituted furans (**2a**, **2e**, **2f**, and **2j**), 2-aryl-substituted furans **2b–d** could also be achieved in excellent yields. The reactions showed an excellent tolerance toward functional groups such as NO_2 (**1f**), Ac (**1e**),

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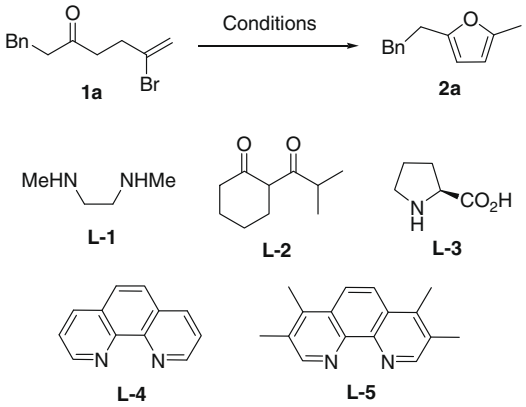
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.040

Table 1
Optimization of reaction conditions



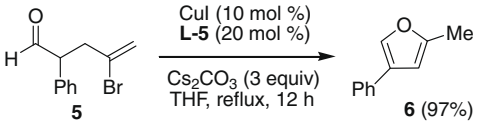
Entry[a]	Ligand (mol %)	Base	Time (h)	Yield (%)[b]
1	**L-1** (40)	Cs_2CO_3	10	5
2	**L-2** (40)	Cs_2CO_3	10	5
3	**L-3** (40)	Cs_2CO_3	10	Trace
4	**L-4** (40)	Cs_2CO_3	10	10
5	**L-5** (40)	Cs_2CO_3	10	57
6	**L-5** (40)	K_2CO_3	10	Trace
7	**L-5** (40)	K_3PO_4	10	10
8	**L-5** (40)	Cs_2CO_3	20	99
9	**L-5 (20)**	**Cs_2CO_3**	**24**	**99**
10	None	Cs_2CO_3	24	0
11	**L-5** (20)	None	24	0

[a] Conditions: **1a** (0.3 mmol), CuI (0.03 mmol), ligand, base (0.6 mmol), dioxane (10 mL), reflux.
[b] Isolated yield of **2a** based on **1a**.

or CO_2Me (**1j**). Substrates **1g** and **1h** having a 3-alkyl substituent furnished the corresponding 2,3,5-trisubstituted furans **2g** and **2h**, respectively. However, the reactions were relatively slow, presumably because of the increased steric hindrance in the enolization of ketones. As a comparison, the reaction of cyclohexanone **1i** proceeded smoothly to give the bicyclic product **2i** in a high yield.

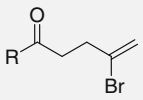
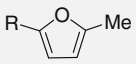
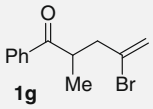
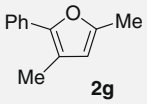
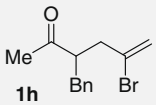
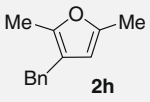
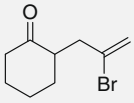
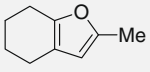
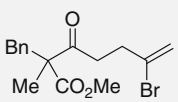
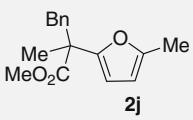
Compared to ketones **1**, substrates **3** bearing a 3-aryl group were much more reactive and the coupling proceeded at a much lower temperature (THF, reflux), as illustrated in Table 3. The enhanced reactivity of **3** should be attributed to the fact that the aryl-substitution makes the enolization of ketones **3** much easier. 3-Aryl-2,5-dialkyl-substituted furans **4a–d** were thus isolated in high yields under milder conditions. With cyclohexenyl bromide **3e** as the substrate, the tetrasubstituted furan **4e** was generated in almost quantitative yield, demonstrating the high potential of the intramolecular O-vinylation in the synthesis of multisubstituted furans.

Besides ketones, aldehydes could also be utilized in the O-vinylation reactions. As an example, the treatment of aldehyde **5** under the above-mentioned optimized conditions (Table 3) afforded the corresponding 2,4-disubstituted furan **6** in 97% yield (Eq. 1). Furthermore, vinyl chloride **7** also underwent intramolecular O-vinylation to give the expected furan such **4a** in high yield (Eq. 2).



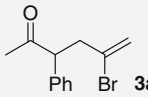
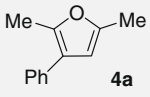
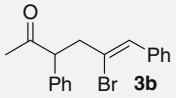
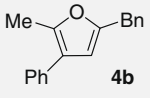
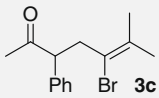
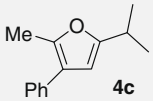
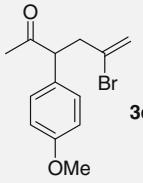
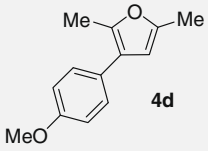
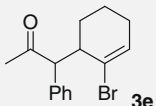
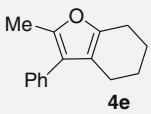
(1)

Table 2
O-Vinylation of ketones in refluxing dioxane

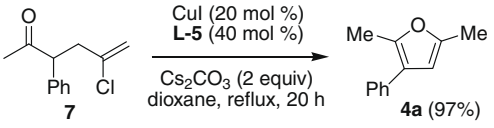
Entry[a]	Substrate	Product	Time (h)	Yield[b] (%)
				
1	**1a** (R = $BnCH_2$)	**2a**	24	99
2	**1b** (R = Ph)	**2b**	5	99
3	**1c** (R = 4-Me-C_6H_4)	**2c**	7	99
4	**1d** (R = 4-Cl–C_6H_4)	**2d**	3	82
5[c]	**1e** (R = 4-Ac-$C_6H_4CH_2CH_2$)	**2e**	12	59
6[c]	**1f** (R = 4-NO_2–$C_6H_4CH_2CH_2$)	**2f**	10	87
7	 **1g**	 **2g**	22	58
8	 **1h**	 **2h**	20	55
9	 **1i**	 **2i**	12	85
10	 **1j**	 **2j**	20	98

[a] Reaction conditions: **1** (0.3 mmol), CuI (0.03 mmol), **L-5** (0.06 mmol), Cs_2CO_3 (0.6 mmol), dioxane (10 mL), reflux.
[b] Isolated yield based on **1**.
[c] 20 mol % of CuI and 40 mol % of **L-5** were used.

Table 3
O-Vinylation of ketones in refluxing THF

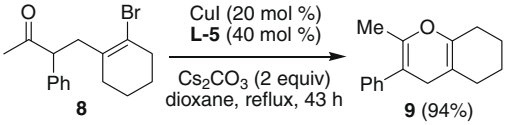
Entry[a]	Substrate	Product	Time (h)	Yield[b] (%)
1	 **3a**	 **4a**	15	99
2	 **3b**	 **4b**	24	99
3	 **3c**	 **4c**	15	99
4	 **3d**	 **4d**	11	70
5	 **3e**	 **4e**	10	99

[a] Reaction conditions: **3** (0.3 mmol), CuI (0.03 mmol), **L-5** (0.06 mmol), Cs_2CO_3 (0.6 mmol), THF (10 mL), reflux.
[b] Isolated yield based on **3**.



(2)

The above-described reactions dealt with the O-vinylation in a 5-*exo*-like mode. As an extension, the vinylation of ketone **8** in a 6-*endo*-like mode also proceeded smoothly to give the corresponding pyran **9** in 94% yield (Eq. 3).



(3)

In conclusion, the chemistry detailed above has clearly demonstrated that the Cu(I)-catalyzed intramolecular O-vinylation reactions of ordinary ketones with vinyl halides offer a convenient and efficient entry to multisubstituted furans. This should be of important application in organic synthesis.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant Nos. 20702060 and 20832006) and by the Shanghai Municipal Committee of Science and Technology (Grant No. 07XD14038).

References and notes

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19. *Typical procedure for the Cu(I)-catalyzed intramolecular O-vinylation reactions*: The mixture of ketone **1j** (102 mg, 0.30 mmol), CuI (6 mg, 0.030 mmol), **L-5** (14 mg, 0.060 mmol), and Cs_2CO_3 (0.19 g, 0.60 mmol) in dioxane (10 mL) was stirred at reflux for 20 h under nitrogen atmosphere. The resulting mixture was

cooled down to room temperature and filtered. The filtrate was then concentrated in vacuo and the crude product was purified by flash chromatography on silica gel with hexane/EtOAc (10:1, v:v) as the eluent to give the pure product **2j** as a colorless oil. Yield: 76 mg (98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (3H, s), 2.23 (3H, s), 3.21 (2H, s), 3.62 (3H, s), 5.79–5.80 (1H, m), 5.85 (1H, d, J = 3.6 Hz), 6.81–6.83 (2H, m), 7.09–7.12 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 20.6, 43.1, 48.3, 52.3, 106.2, 107.3, 126.5, 127.9, 130.3, 136.9, 151.3, 154.0, 174.6. IR (film): ν (cm^{-1}) 3209, 2951, 1737, 1605, 1562, 1496, 1454, 1377, 1238, 1219, 1101, 1024, 786. EIMS: m/z (rel intensity) 258 (M^+, 9), 199 (14), 181 (6), 167 (100), 139 (6), 118 (6), 107 (42), 91 (26), 65 (7), 43 (8). HRMS calcd for $C_{16}H_{18}O_3$ (M): 258.1256. Found: 258.1255.