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A novel oxidation–ring-contraction of Hantzsch 1,4-dihydropyridines to polysubstituted furans

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Abstract—A novel oxidation–ring-contraction reaction took place when 4-substituted Hantzsch 1,4-dihydropyridines were treated with Oxone. This reaction pattern provided a convenient method for the synthesis of polysubstituted furans.

The oxidation of Hantzsch 1,4-dihydropyridines (DHPs), a class of model compounds of NADH coenzyme,[1] has attracted continuing interest of organic chemists over the years. A plethora of protocols has been developed for such a purpose.[2–10] On continuance of our interest in the DHP based chemistry, we have also studied the oxidation of DHPs under different conditions.[11] With all the reported methods, DHPs are invariably transformed to pyridine derivatives via oxidative aromatization. Recently, we applied Oxone to the oxidation of DHPs, and found, unexpectedly, a novel oxidation–ring-contraction reaction took place, leading to the formation of polysubstituted furans. Herein we report this result.

Oxone, a commercially available triple salt of $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$, is an efficient and mild oxidant widely used for the epoxidation of olefins, and the oxidation of boron-, nitrogen-, phosphorus-, and sulfur-containing compounds.[12] In the initial part of this study, HEH (**1a**) was treated with 2 equiv of Oxone in CH_3CN at room temperature, and the aromatization product **2a** was generated as expected in 64%. However, when 4-phenyl DHP (**1b**) was treated with Oxone under the same condition, two products were isolated from the reaction mixture. One is the normal pyridine derivative **2b**, which was obtained in 28%. The other product, obtained in the yield of 11%, was characterized to be the four substituted furan **3b** (Scheme 1). This result was totally unexpected, as no similar result was reported before using other oxidants so far to our knowledge.

Polysubstituted furans are present as key structural units in many natural products and pharmaceuticals.[13] They are also used as versatile synthetic intermediates for the preparation of a variety of heterocyclic and acyclic organic compounds.[14] Consequently, many efforts have been devoted to the development of efficient methodology for the construction of polysubstituted furan rings.[15,16] We assumed that the oxidation of 4-substituted DHPs by Oxone might provide a convenient approach for the preparation of polysubstituted furans from the easily available 4-substituted dihydropyridines.

In light of this goal, the reaction condition was optimized to raise the yield of **3b**. Various solvent systems were tested, and the representative results are listed in Table 1. It turned out that nonpolar solvents such as toluene and CH_2Cl_2 were unfavorable for the formation of **3b**, even in the presence of phase transfer reagent n-Bu_4NHSO_4. Polar solvents such as CH_3CN, CH_3OH, and C_2H_5OH were better solvents to effect the reaction, especially in the presence of H_2O (entries 10–14). But no furan product was generated in DMF (entry 9). The best result was obtained when an aqueous solution of 1.5 equiv of Oxone (3 equiv of $KHSO_5$) was added dropwise to a stirred solution of **1b** in MeCN at refluxing temperature,[17] from which **3b** was obtained in 44%

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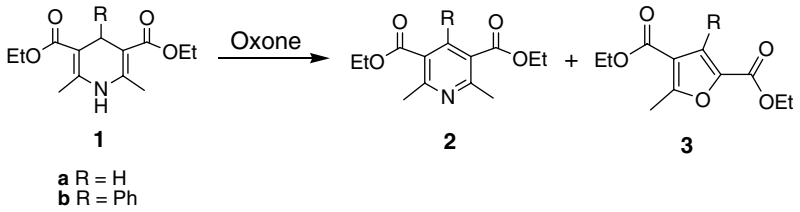


Scheme 1.

Table 1. Effect of solvents on the oxidation of **1a** and **1b** by Oxone[a]

Entry	Substrate	Solvent	Reaction time	Conversion[b] (%)	Products	Yield (**2a** or **2b/3b**, %)[c]
1	**1a**	Toluene[d,e]	12 h	90	**2a**	54
2	**1a**	CH_2Cl_2[d,e]	12 h	90	**2a**	68
3	**1a**	DMF[d]	6 h	100	**2a**	45
4	**1a**	Anhydrous CH_3CN[d]	6 h	95	**2a**	65
5	**1a**	$CH_3CN:H_2O = 3:2$[f]	40 min	100	**2a**	78
6	**1a**	$CH_3CN:H_2O$[17]	10 min	100	**2a**	84
7	**1b**	Toluene[d,e]	12 h	65	**2b/3b**	8/6
8	**1b**	CH_2Cl_2[d,e]	12 h	60	**2b/3b**	8/5
9	**1b**	DMF[d]	12 h	90	**2b/3b**	20/—
10	**1b**	Anhydrous CH_3CN[d]	2 h	60	**2b/3b**	28/12
11	**1b**	$CH_3CN:H_2O = 3:2$[f]	40 min	96	**2b/3b**	10/26
12	**1b**	$CH_3CN:H_2O$[17]	10 min	100	**2b/3b**	8/44
13	**1b**	$CH_3OH:H_2O$[f]	20 min	100	**2b/3b**	6/23
14	**1b**	$C_2H_5OH:H_2O$[f]	20 min	100	**2b/3b**	5/28

[a] 1.5 equiv of Oxone was used.
[b] Determined based on the recovered starting material after chromatography.
[c] Isolated yields.
[d] The reaction was carried out at room temperature.
[e] 0.1 equiv of n-Bu_4NHSO_4 was added as catalyst.
[f] The reaction was carried out under refluxing.

(entry 12). Using more Oxone did not improve the yield. Apart from **3b** and **2b**, no other products could be isolated and identified. In the case of **1a**, however, no ring contraction product was detected whatever the condition was used. Only **2a** was isolated in moderate to good yields (entries 1–6).

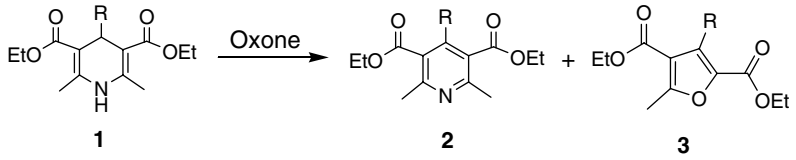
The effect of pH value of the solvent was also investigated in the hope of raising the yield of **3b**. It was found that acidic conditions were more favorable for the formation of **3b** than basic conditions, and above pH 5, the yield and conversion rate of **3b** decreased with the increase in pH value. One reason for this is probably because Oxone is labile to decomposition under heating at high pH values.[18] However, despite the attempt we made, the yield of **3b** could not be raised further.

To examine the scope of the reaction, various 4-substituted DHPs were prepared and subjected to the optimized reaction condition. As shown in Table 2, the furan products **3b–j** were generated in varying yields except for **1k**, along with a small amount of pyridine derivatives. Though the yields were generally not satisfactory, the fact that only one step was required to get access to the 2,3,4,5-four substituted furan rings from easily prepared 4-substituted dihydropyridines still makes this method a promising candidate among diverse protocols for furan synthesis.

A possible mechanism for this ring contraction rearrangement was proposed as shown in Scheme 2. Compound **1** was firstly oxidized by $KHSO_5$ to epoxide **4**, which was then transformed to **5** via an epoxide ring opening as facilitated by the adjacent N atom attack. Further epoxidation of **5** by another $KHSO_5$ molecule would give rise to **6**, from which **7** was generated by the intramolecular hydroxyl attack on the newly formed epoxide ring. Dehydration of **7**, followed by the retro-Diels–Alder type breakage of the oxygen-bridged ring, would lead to the formation of ring contraction product **3**. In the epoxidation of **5**, the epoxide ring could also be delivered cis to the OH group, but the thus formed isomer of **6** might not be transformed to **3** as OH could not attack the epoxide ring from the *anti* direction. In the case of **1a**, the dehydration of the intermediate **5a** would be a quite facile process due to the presence of an *anti* H atom adjacent to the hydroxy group, so that the second epoxidation giving **6a** could not compete, and only **2a** was obtained.

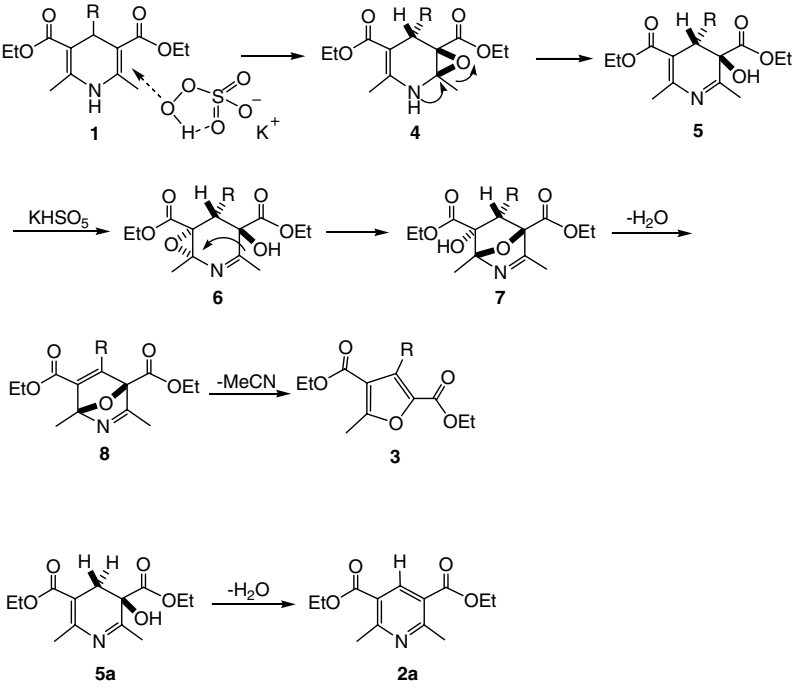
In conclusion, a novel oxidation–ring-contraction reaction taking place when 4-substituted Hantzsch 1,4-dihydrpyridines were treated with Oxone. Further studies on the mechanistic details of the reaction, and efforts to explore new reaction conditions to improve the yields of furan products are underway in this laboratory.

Table 2. Oxidation of Hantzsch 1,4-dihydropyridines by Oxone[17]



Entry	R	Substrate	Products		Yield[a] (**2**/**3**, %)
1	H	**1a**	**2a**	**3a**	84/—
2	Ph	**1b**	**2b**	**3b**	8/44
3	C_6H_4-*p*-Cl	**1c**	**2c**	**3c**	5/32
4	C_6H_4-*p*-CH_3	**1d**	**2d**	**3d**	5/40
5	C_6H_4-*p*-OCH_3	**1e**	**2e**	**3e**	6/40
6	C_6H_4-*p*-OH	**1f**	**2f**	**3f**	4/28
7	2-Furyl	**1g**	**2g**	**3g**	5/28
8	*n*-Propyl	**1h**	**2h**	**3h**	4/34
9	Styryl	**1i**	**2i**	**3i**	5/18
10	C_6H_4-*m*-NO_2	**1j**	**2j**	**3j**	5/30
11	C_6H_4-*p*-NO_2	**1k**	Complex mixtures		

[a] Isolated yields. Products **3b–j** were characterized by ^1H and ^{13}C NMR, EI-MS, and HR-MS spectra data.



Scheme 2.

Acknowledgements

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17. *General Procedure*: An aqueous solution of 3 mL Oxone (1.5 mmol) was added dropwise to a stirred solution of **1** (1 mmol) in MeCN (4 mL) at reflux temperature in 5 min. The reaction mixture was stirred under refluxing for another 5 min, and was then cooled to room temperature. The reaction mixture was quenched with 20 mL of H_2O, neutralized with saturated aqueous solution of $NaHCO_3$, and then extracted with ethyl acetate (3×10 mL). The combined organic layer was dried over anhydrous sodium sulfate, and concentrated under a reduced pressure. Products **2** and **3** were isolated from the residue by silica gel column chromatography (petroleum/acetone 15:1 to 10:1).
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