SYNTHESIS OF ISOXAZOLYLVINYL KETONES FROM FURAN DERIVATIVES

Olga V. Serdyuk[1], Vladimir T. Abaev[2]

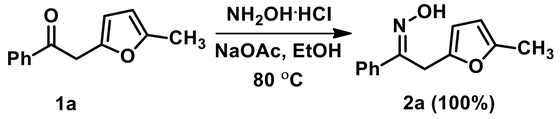
[1] Department of Chemistry and Pharmacy, Institute of Organic Chemistry I, University of Erlangen-Nuremberg, Nikolaus-Fiebiger-Str. 10, Erlangen, 91058, Germany
[2] K. L. Khetagurov North-Ossetian State University, Vatutina 43-46, Vladikavkaz, 362025, Russian Federation

Introduction

In medicinal chemistry, chalcones and their heterocyclic analogues bearing α,β-unsaturated fragments are known as important scaffolds with potent anticancer activity. In particular, isoxazolylvinyl ketones and isoxazole-chalcones demonstrate activity against lung cancer cell lines H1792, H157, A549, Calu-1,8 and prostate DU-145 cancer cell lines. We suggested that easily available furfuryl ketones **1** could serve as a starting point for the synthesis of isoxazolylvinyl ketones employing a Ring-Opening-Ring-Closure (RORC) strategy. Herein, we present a new method for the preparation of these valuable compounds.

Results and Discussions

First, we have studied the reaction of furfuryl ketone **1a** with hydroxylamine hydrochloride and sodium acetate in ethanol. However, prolonged heating of ketone **1a** at 80 °C for 24 h led exclusively to oxime **2a** instead of the expected isoxazole, presumably due to the reduced nucleophilicity of the hydroxylamino group in compound **2a** (Scheme 1).



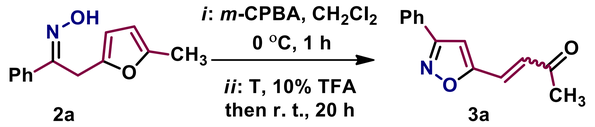
1a — 2a (100%)

Scheme 1

The target isoxazole *(E,Z)*-**3a** was obtained through the reaction of oxime **2a** with *m*-CPBA followed by treatment of the reaction mixture with TFA (Table 1). The product **3a** was isolated as a mixture of *(E,Z)*-isomers.

The isomerization of (*E,Z*)-**3a** into the stable (*E*)-isomer was easily performed under heating with catalytic 6.4 mol% of iodine.

Table 1. Synthesis of isoxazolylvinyl ketone **3a**: model reaction.

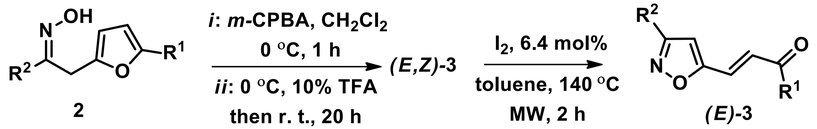


2a — 3a

Entry	Temperature, °C	Yield of **3a**, %	*E/Z*- Ratio (^{1}H NMR)
1	r. t.	56	1 : 1.0
2	0	80	1 : 30.4
3	–10	79	1 : 30.0

To illustrate the scope of the reaction, a series of oximes **2** has been synthesized and subjected to the optimized reaction conditions with *m*-CPBA and TFA. Each product **3** was prepared in a pure (*E*)-form and fully characterized (Table 2).

Table 2. Synthesis of isoxazolylvinyl ketones **3a-i**.



2

Entry	Compounds **2** and **3**	R^1	R^2	Yield of **3**, %	*E/Z*- Ratio (^{1}H NMR)
1	**a**	CH_3	Ph	82 (gram scale)	1 : 30.0
2	**b**	CH_3	4-$CH_3C_6H_4$	65	1 : 7.2
3	**c**	C_2H_5	Ph	61	1 : 4.3
4	**d**	C_2H_5	4-$CH_3C_6H_4$	60	1 : 4
5	**e**	C_2H_5	4-$CH_3OC_6H_4$	60	1: 5.2
6	**f**	C_2H_5	4-ClC_6H_4	70	1: 9.3
7	**g**	C_2H_5	4-FC_6H_4	63	1: 8.3
8	**h**	C_4H_9	Ph	50	1: 30.0
9	**i**	C_4H_9	4-FC_6H_4	63	traces : 1.0

The reaction shows relatively wide substrate scope and functional group tolerance. Importantly, the synthesis of isoxazolylvinyl ketone **3** can be performed on a gram-scale in high yields. The structure of isoxazole *(E)*-**3g** was confirmed by single-crystal X-Ray diffraction (Fig. 1).

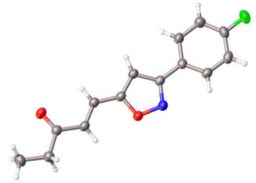
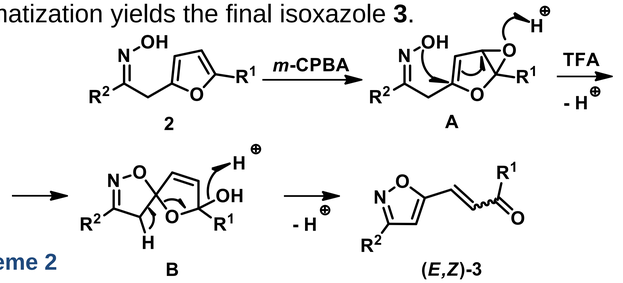


Figure 1. Structure of (*E*)-**3g**.

A proposed mechanism for the transformation **2** → **3** is presented in Scheme 2. The key step includes epoxidation of furan double bond with *m*-CPBA with formation of bicyclic epoxide **A**. Further, the treatment with TFA induces intramolecular attack of nucleophilic O-atom of hydroxylamine onto C(2) atom of the furan ring with proton-assisted epoxide ring opening giving rise to the spirocyclic intermediate **B**. The subsequent ring opening of **B** and aromatization yields the final isoxazole **3**.



Scheme 2

Acknowledgments

This work was supported by the scholarship "Promotion of Equal Opportunities for Women in Research and Teaching (FFL)" offered by the Free State of Bavaria, Germany, and the Russian Foundation for Basic Research (grant 19-03-01027).