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# SHORT COMMUNICATION An efficient and facile synthesis of flavanones catalyzed by *N*-methylimidazole

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*Abstract*: The use of *N*-methylimidazole as an efficient catalyst for the cyclization of 2'-hydroxychalcones to the corresponding flavanones in DMSO was investigated. The scope of this process was studied and various flavanones were obtained exclusively in good yields.

Keywords: 2'-hydroxychalcones; flavanones; N-methylimidazole.

# INTRODUCTION

The flavanone structure is abundant in natural products that possess a broad array of biological activity.<sup>1</sup> Due to their favorable anti-cancer, anti-estrogen and anti-inflammatory properties, flavanones have been investigated as selective estrogen receptor modulators and tumor necrosis factor (TNF)- $\alpha$  inhibitors.<sup>2</sup> Moreover, these kinds of compounds are important intermediates in the synthesis of flavanone glycosides and 2-aryl chromans.<sup>3</sup> These compounds have been synthesized by the cyclization of 2'-hydroxychalcones, that is, by an intramolecular oxa-Michael addition (Scheme 1) using various reagents, such as potassium ferricyanide,<sup>4</sup> iodine,<sup>5</sup> alkali metal carbonates<sup>6</sup> and trifluoroacetic acid.<sup>7</sup> Despite these impressive contributions, more efficient and practical catalytic systems for the synthesis of flavanones are still in high demand.

Recently, several reports referred to *N*-methylimidazole as a co-catalyst for aldol, Claisen and other reactions. Moreover, Lin reported an aza-Michael addition catalyzed by *N*-methylimidazole.<sup>8</sup> Inspired by these findings, herein the use of *N*-methylimidazole as an efficient catalyst that facilitates the cyclization of 2'-hydroxychalcones in high yields is presented.



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Scheme 1. N-Methylimidazole catalyzed cyclization of 2'-hydroxychalcones.

# RESULTS AND DISCUSSION

First, optimization experiments involving 2'-hydroxychalcone (1a) as the test substrate were performed, these focused on the determination of the effect of the solvent and the amount of *N*-methylimidazole. The results are summarized in Table I. The reaction was realized in three different solvents, *viz.*, dichloromethane, acetonitrile, and DMSO (Table I, entries 1–3). It was observed that a higher yield of the flavanone 2a was achieved in DMSO compared with those in the other two solvents, which led DMSO to be chosen for all further studies. The importance of the *N*-methylimidazole was confirmed by the fact that no product 2a was obtained in the absence of *N*-methylimidazole (Table I, entry 4). Subsequent studies indicated that 20 mol % *N*-methylimidazole was the optimal amount. The product 2a was obtained in 90 % yield after 6 h in DMSO at 80 °C, while only trace amounts of 2a were observed at room temperature (Table I, entry 7).

 TABLE I. Optimization of the solvent and the amount of N-methylimidazole

	OH DMSO, 80 °C								
	1a		2a						
Entry	Solvent	<i>N</i> -methylimidazole (equiv.)	Time, h	Yield <sup>a</sup> , %					
1	$CH_2Cl_2$	0.2	6	30					
2	CH <sub>3</sub> CN	0.2	6	75					
3	DMSO	0.2	6	90					
4	DMSO	_	6	N.R.					
5	DMSO	0.1	12	85					
6	DMSO	0.5	6	90					
7 <sup>b</sup>	DMSO	0.2	12	trace					

Ο

<sup>a</sup>Isolated yield after column chromatography; <sup>b</sup>at room temperature

0

To evaluate the scope of the substrate of this methodology, a variety of 2'-hydroxychalcones were examined in the reaction, and the results are summarized in Table II. In all cases, the optimized conditions described previously

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918

#### SYNTHESIS OF FLAVANONES

919

proved to be applicable. Good to excellent results were achieved for 4-chloro and 4-methyl substituents (Table II, entries 8 and 10). However, the 4-fluoro group significantly decreased the yield (Table II, entry 9). 4-Methoxyl and 3-nitro substitutes afforded the corresponding flavanones in good yields (Table II, entries 7 and 11). Additionally, substitutions at the  $R_1$  or  $R_2$  positions were also tolerated (Table II, entries 2–6).

TABLE II. Scope of the cyclization of 2'-hydroxychalcones; the reactions were carried out with 1 mmol 2'-hydroxychalcones and 0.2 mmol *N*-methylimidazole in DMSO (1 mL) at 80  $^{\circ}$ C, 6h

Entry	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Product	Yield, %
1	Н	Н	Н	Н	2a	90
2	CH <sub>3</sub>	Н	Н	Н	2b	87
3	CH <sub>3</sub>	Н	Н	CH <sub>3</sub>	2c	76
4	CH <sub>3</sub> O	Н	Н	Н	2d	89
5	Н	CH <sub>3</sub> O	Н	Н	2e	90
6	Н	CH <sub>3</sub> O	Н	CH <sub>3</sub> O	<b>2f</b>	79 <sup>a</sup>
7	Н	Н	$NO_2$	Н	$2\mathbf{g}$	86
8	Н	Н	Н	Cl	2h	87
9	Н	Н	Н	F	2i	65 <sup>a</sup>
10	Н	Н	Н	CH <sub>3</sub>	2j	87
11	Н	Н	Н	CH <sub>3</sub> O	2k	90 <sup>a</sup>

<sup>a</sup>At 100 °C, 8 h

## EXPERIMENTAL

Commercial reagents were used as received. Analytical-grade solvents and commercially available reagents were used without further purification. For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90 °C) are used. The IR spectra were recorded on a Bruker Tensor 37 spectrophotometer as liquid film. The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were taken on a Bruker AM-300 spectrophotometer with tetramethylsilane (TMS) as an internal standard and CDCl<sub>3</sub> as the solvent. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. Electron impactmass spectrometry (EI-MS) was realized on a HP-5988 spectrometer. Elementary analyses were performed on a Vario EL III elementary analysis instrument.

### General procedure for the synthesis of flavanones

*N*-Methylimidazole (0.2 mmol) was added to a solution of 2'-hydroxychalcone **1a** (224 mg, 1 mmol) in DMSO (1 mL). After stirring the reaction mixture at 80 °C for 6 h, it was quenched by adding water and the resulting mixture was extracted with AcOEt, washed with water and brine, and dried over MgSO<sub>4</sub>. The crude product was purified by flash chromatography on silica gel to afford the desired product. The other flavanones were synthesized in a similar manner.

### Characterization of the flavanones

The structures of the synthesized flavanones were confirmed by elemental analysis and spectroscopic methods. The results are given in the Supplementary material to this paper.

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# WANG et al.

### CONCLUSIONS

In summary, a facile and efficient cyclization of 2'-hydroxychalcones using *N*-methylimidazole as a catalyst in DMSO is reported. Good yields of flavanones were obtained for a variety of 2'-hydroxychalcones. Extension of this methodology is presently under active study.

### SUPPLEMENTARY MATERIAL

Analytic and spectral data for the synthesized flavanones are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

### ИЗВОД

# ЕФИКАСНА И ЛАКА СИНТЕЗА ФЛАВАНОНА КАТАЛИЗОВАНА *N*-МЕТИЛИМИДАЗОЛОМ

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Испитана је употреба *N*-метил-имидазола као катализатора у реакцији циклизације 2'-хидроксихалкона до одговарајућих флавона у ДМСО-у као растварачу. Изучаван је домет и опсег реакција и добијени су различити флавони у одличном приносу.

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### REFERENCES

- a) L. C. Chang, A. D. Kinghorn, *Bioactive Compounds from Natural Sources: Isolation Characterisation and Biological Properties*, Taylor & Francis, London, 2001; b) Ø. M. Andersen, K. R. Markham, *Flavonoids: Chemistry, Biochemistry and Applications*, Taylor & Francis, London, 2006
- 2. M. M. Biddle, M. Lin, K. A. Scheidt, J. Am. Chem. Soc. 129 (2007) 3830
- a) K. Oyama, T. Kondo, J. Org. Chem. 69 (2004) 5240; b) J, H. Kevin Tetrahedron 61 (2005) 6860
- 4. J. K. Makrandi, S. Bala, Synth. Commun. 30 (2000) 3555
- P. D. Lokhande, S. S. Sakate, K. N. Taksande, B. Navghare, *Tetrahedron Lett.* 46 (2005) 1573
- 6. R. Mondal, A. D. Gupta, A. K. Mallik, Tetrahedron Lett. 52 (2011) 5020
- 7. G. J. Sagrera, G. A. Seoane, J. Braz. Chem. Soc. 16 (2005) 851
- 8. B. K. Liu, Q. Wu, X. Q. Qian, D. S. Lv, X. F. Lin, Synthesis (2007) 2653.

920

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