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New eco-friendly procedure for the synthesis of 4-arylmethylene-isoxazol-5(4*H*)-ones catalyzed by pyridinium *p*-toluenesulfonate (PPTS) in aqueous medium

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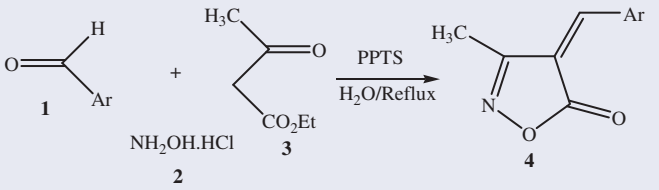
ABSTRACT

In this work we describe a new, highly efficient method for the synthesis of 3-methyl-4-arylmethylidene-isoxazol-5(4H)-one derivatives by a three-component reaction between aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride under the influence by PPTS as a low-toxicity, inexpensive, commercially available and easy to handle catalyst. The advantages of this procedure are good yields, short reaction times, simplicity of implementation, and respect of the environment.

GRAPHICAL ABSTRACT



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Aqueous media; eco-friendly method; 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones; PPTS; three-component reaction

Introduction

The ixoxazolone derivatives possess very interesting biological and pharmacological properties. They are anti-prostate tumor[1] and antimicrobial,[2] inhibitors of the factorization of tumor necrosis alpha (TNF-α),[3] potent inhibitors of PTP1B,[4] and hormone-sensitive lipase.[5] These compounds are used for the treatment of cerebro-vascular disorders and as muscle relaxants.[6] They are also used in agriculture as herbicides, plant growth regulators,[7] and fungicides.[8] Otherwise, the isoxazolone unit has also been used as the basis for the design and construction of merocyanine dyes with applications in optical recording and nonlinear optical research.[9]

On the other hand the 4-arylmethyleneisoxazol-5(4H)-ones are very useful synthesis intermediates of various heterocycles such as pyridopyrimidines,[10] imidazoles,[11]

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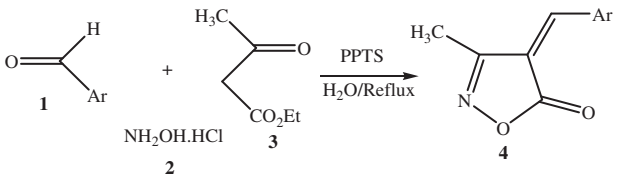


Scheme 1. PPTS-catalyzed 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones synthesis.

1,3-oxazin-6-ones,[12] and quinolines.[13] They also undergo various chemical transformations[14] such as N-methylation, alkylation, epoxidation, reduction, reduction/bromination, reduction/hydroxylation, Reformatsky reaction, and addition of organomagnesiens. Some cycloaddition reactions are also described and provide access to several polycycles types.[15]

Therefore, 4-arylmethylene-isoxazol-5(4*H*)-ones have interested the organic chemists and the review of the literature shows two main methods for the synthesis of these heterocycles. Carried out in two successive stages, the conventional process consists firstly of a reaction between ethyl acetoacetate and hydroxylamine hydrochloride to give the 3-methyl-isoxazole-5(4H)-one followed, in a second step, by a Knoevenagel condensation type with aromatic aldehydes.[16] The recent method is a one-pot three-component reaction between aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride. Catalyzed by the pyridine at reflux of ethanol, it has been reported for the first time in 2008 by Zhang et al.,[17] and now in the literature, we note the successful use of several catalysts and techniques[18] such as sodium silicate,[19] boric acid,[20] DOWEX®50WX4/H_2O,[21] sodium benzoate,[22] NaH_2PO_4,[23] sulfuric acid-modified Mesolite,[24] sodium acetate under visible light,[25] imidazole under ultrasonic irradiation[26] and Fe_2O_3, Clinoptilolite and $H_3PW_{12}O_{40}$ under microwave irradiation.[27] Some environmentally friendly catalysts such as tartaric acid,[28] sodium tetraborate,[29] sodium ascorbate,[30] citric acid[31] and sodium saccharin[32] were reported. The same reaction without catalyst in aqueous medium was also successfully performed.[33]

With a melting point of 120 °C, PPTS is an ionic complex which can be assimilated to an ionic liquid. It has been used as a catalyst in various chemical transformations such as Fisher's esterification,[34] the acetalization of α,β-unsaturated aldehydes,[35] and as a mild and efficient catalyst for the regioselective tetrahydropyranylation of indazole derivatives.[36]

For our part we have previously used PPTS as an efficient catalyst in the synthesis of 2-amino-4*H*-pyrans,[37] 1,4-benzoxazine derivatives,[38] 3,4-dihydropyrimidinones, and tetrahydroquinazoline-2,5-diones.[39]

Here, we report its use in the synthesis of 4-arylmethylene-isoxazol-5(4*H*)-ones by the reaction between aromatic aldehydes, ethyl acetoacetate and hydroxylamine hydrochloride, in an aqueous medium (Scheme 1). This is an environmentally friendly method.

Results and discussion

The selected model, an equimolar mixture of 4-hydroxybenzaldehyde, ethyl acetoacetate, hydroxylamine chloride, and PPTS (10 mol%), was subjected to various solvents and temperatures such as H_2O at room temperature and reflux, EtOH, EtOH/H_2O (1/1),

CH_2Cl_2, and CH_3CN at reflux. The results are summarized in Table 1 (Entries 1–7). We note that the best result has been obtained in refluxing H_2O. The reaction in water without catalyst was found more effective than the reaction without solvent and in the presence of the catalyst (Table 1, entries 8 and 1). This is probably due to a better solvation of the different reagents and a larger contact area. In addition, the water is a polar solvent and the temperature is higher for the entry 8 and these conditions facilitate this procedure. The combination of the effect of H_2O and the catalyst makes the method more efficient (Table 1, entry 9).

In a second step, and in order to determine the optimum amount of catalyst, we worked with increasing amounts of 0, 5, 15, 20, 30, and 50 mol% in refluxing H_2O (Table 1, entries 8–13). The best yield of 80% was observed with 5 and 10 mol%. Therefore, the optimum conditions of the PPTS catalyzed 3-substituted-4-4-arylmethylideneisoxazol-5(4*H*)–ones synthesis are 5 mol% of catalyst in refluxing H_2O.

The optimum conditions are applied to a variety of differently substituted aldehydes. The results obtained are summarized in Table 2. We notice that whatever the nature of the substituent and its position yields remain moderate to very good and vary between 50 and 80% (Table 2, entries 1–8): The best result is obtained with 4-hydroxybenzaldehyde (80%) while the worst with 3-metoxybenzaldehyde (50%). Moreover, it is observed that the heteroaromatic aldehyde (Table 2, entry 9) leads to a good yield of 63%.

In Scheme 2, we suggest a plausible mechanism for the formation of 4-arylmethyleneisoxazol-5(4*H*)-ones (**4**). The first step is a condensation reaction between the

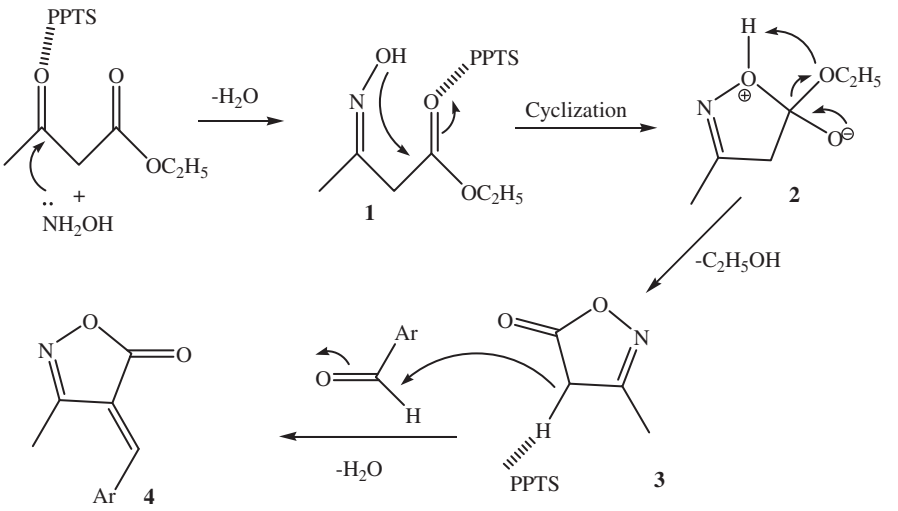
Table 1. Optimization of reaction conditions.

Entry	Solvent	Catalyst (mol%)	Time (h)	Temp. (°C)	Yield (%)
1	–	10	1	80 °C	42
2	H_2O	10	24	r.t	79
3	H_2O	10	1	Reflux	80
4	EtOH	10	3	Reflux	Traces
5	EtOH/H_2O	10	4	Reflux	40
6	CH_2Cl_2	10	1	Reflux	–
7	CH_3CN	10	1	Reflux	Traces
8	H_2O	0	1	Reflux	63
9	H_2O	5	1	Reflux	80
10	H_2O	15	1	Reflux	69
11	H_2O	20	1	Reflux	76
12	H_2O	30	1	Reflux	76
13	H_2O	50	1	Reflux	73

Table 2. PPTS-catalyzed 3-methyl-4-arylmethylene-isoxazol-5(4*H*)-ones synthesis (**4a-i**).

Entry	Ar	Product[a]	Time (h)	Yield[b]
1	C_6H_5	**4a**	3	64
2	4-MeC_6H_4	**4b**	2	62
3	4-ClC_6H_4	**4c**	3	60
4	4-$MeOC_6H_4$	**4d**	1	65
5	4-HOC_6H_4	**4e**	0.5	80
6	2-$MeOC_6H_4$	**4f**	1	72
7	$(Me)_2NC_6H_4$	**4g**	0.5	70
8	3-$MeOC_6H_4$	**4h**	3	50
9	2-Thienyl	**4i**	1	63

[a]Conditions: 1 mmol of the aldehyde, 1 mmol of hydroxylamine hydrochloride, 1 mmol of ethyl acetoacetate and 5 mol% of PPTS in 5 ml of water at reflux. [b]Isolated yields of pure products.



Scheme 2. Mechanism of formation of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones catalyzed by PPTS.

hydroxylamine and the carbonyl function of ethyl acetoacetate leading to an oxime (intermediate **1**). The second step is an intramolecular cyclization (intermediate **2**) followed by the loss of an EtOH molecule to give 3-methyl-isoxazole-5(4*H*)-one (intermediate **3**). A Knoevenagel condensation type of intermediate **3** and aromatic aldehydes leads to the final products (**4**). All the steeps were facilitated by the presence of PPTS.

Conclusions

We describe here a new, efficient process for the synthesis of 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones by a three-component reaction between aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride catalyzed by PPTS as a benign catalyst, commercially available, inexpensive, and easy to handle. The essential advantages of this method are simplicity of use, good yields, short reaction times and the use of non-toxic solvent. It is an environmentally friendly process.

Experimental

The chemicals and solvents of grade "for synthesis" have been purchased from Aldrich (USA) and Alfa Aesar (Germany) and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded as solutions in DMSO-d_6 on a BRUKER ADVANCE DPX spectrometer at 250.13 and 62.5 MHz respectively, using TMS as an internal reference. Chemical shifts are expressed in parts per million (*ppm*) and the coupling constants (*J*) in Hertz (*Hz*). IR spectra were obtained on potassium bromide (KBr) pellets with a Shimadzu FT IR-8201 PC spectrometer, ν_{max} are given in cm^{-1}. The melting points were determined in a Kofler apparatus and were not corrected.

General procedure for 3-methyl-4-arylmethylene-isoxazol-5(4H)-ones synthesis (4a-k)

1 mmol of the aldehyde, 1 mmol of hydroxylamine hydrochloride, 1 mmol of ethyl acetoacetate and 5 mol% of PPTS are mixed in a 25 ml flask equipped with a magnetic stirrer. The mixture is refluxed in 5 ml of water for the time required (Table 2), followed by TLC. When the reaction is judged to be finished, the mixture is gradually poured into ice-cold water. The stirring is maintained for a few minutes and the obtained solid is filtered and purified by crystallization from ethanol.

Spectral data for selected products

4-(4-Methylbenzylidene)-3-methylisoxazol-5(4H)-one 4b

M.p.: 148–150 °C; lit.[14] 140–142 °C;[1] H NMR: 2.3 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 7.5 (s, 1H, CH=C), 7.3 (d, 2H, J = 8.2), 8.3 (d, 2H, J = 8.2). ^{13}C NMR: 11(CH_3), 22 (CH_3-Ar), 128, 130, 140, 150 (CH=C), 162 (C=N), 169 (C=O). IR (cm^{-1}): ν_{max} = 771, 1122, 1512, 1631, 1735, 2923.

4-(4-Methoxybenzylidene)-3-methylisoxazol-5(4H)-one 4d

M.p.: 178–180 °C; lit.[23] 175–177; ^{1}H NMR: 2.35 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 7.01 (d, 2H, J = 7.5), 7.38 (s, 1H, CH=C), 8.44 (d, 2H, J = 7.5). ^{13}C NMR: 11.72 (CH_3), 55.79 (OCH_3), 114.72, 125.87, 137.06, 137.21, 149.56, 163.78 (C=N), 164.69 (C=O). IR (cm^{-1}): ν_{max} = 813, 1218, 1550, 1593, 1720, 2935.

4-(3-Methoxybenzylidene)-3-methylisoxazol-5(4H)-one 4i

M.p.: 130–132 °C; ^{1}H NMR: 3.11 (s, 3H, CH_3), 3.80 (s, 3H, O-CH_3), 7.10 (t, 1H, *J* = 6.25), 7.4 (t, 1H, *J* = 6.25), 7.70 (d, 1H, *J* = 5), 7.60 (s,1H, CH=C),8.20 (s, 1H). ^{13}C NMR:11 (CH3), 55 (CH3-O), 113.5, 120, 120.6, 150, 160.5 (C-OCH_3), 163.2 (C-CH_3), 169.2 (C=O). IR (cm^{-1}): ν_{max} = 813, 1218, 1550, 1593, 1720, 2935. HRMS (MS-ESI, m/z): $[M+H]^+$ calculated for ($C_{12}H_{12}NO_3$) 218.08117, found 218.0812.

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