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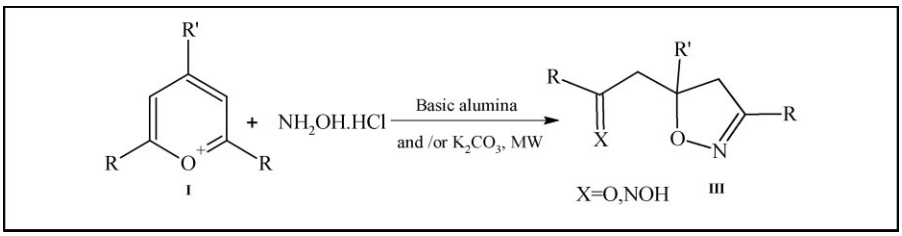

Triarylpyrylium perchlorates are readily and selectively converted into corresponding 2-isoxazolines in good yield and short reaction time using solventless conditions.

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INTRODUCTION

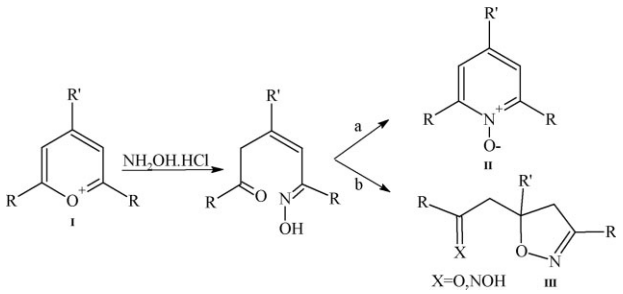
Isoxazoline heterocycles have been employed for a wide variety of uses in chemistry. These ring systems represent a class of unique pharmacophores, which are observed in many therapeutic agents and are versatile intermediates for the synthesis of complex natural products and are found in GPII/IIIa inhibitors and human leukocyte elastase inhibitors [1]. Besides being potential pharmaceutical agents, the isoxazolines have found numerous applications in synthesis through reductive cleavage of the N—O bond to give 1,3-amino alcohols [2]. Typically, 1,3-dipolar cycloaddition between nitrile oxide and alkene are used for synthesis of isoxazoline derivatives [3]. An alternative synthetic route could be offered for preparation of some 2-isoxazolines on treatment of a suspension of some 2,4,6-triarylpyrylium salts in aqueous ethanol with hydroxylamine in the presence of sodium hydroxide [4–6].

Mechanistic studies [5b,6] demonstrated that in the presence of bases the reaction proceeded, after initial attacked of the nucleophile and the ring opening to the δ-oxo-α,β-unsaturated ketoximes, not *via* path (a) but through Michael addition (path b) of two competing intramolecular cyclizations (Scheme 1). Even though this reaction is well studied in solution phase, however, solid supports procedures remain unexplored. The solvent-free use of supported reagents in combination with microwave irradiation provide ideal reaction conditions with special attributes such as reduced reaction time, easier work-up procedure, and enhanced selectivity and reactivity [7,8]. In connection with this trend and in continuation with our studies to develop selective, preparative, and synthetically useful methodology for preparation [9], application [10], and other transformation of pyrylium and thiopyrylium salts [11,12], herein, we report our results for a solvent-free microwave reaction protocol that leads to a facile preparation of 2-isoxazolines from the corresponding pyrylium salts.

RESULTS AND DISCUSSION

In efforts to improve the conversion of triarylpyryliums to corresponding 2-isoxazolines, these transformations were studied on solid materials such as silica gel, basic alumina, and nontraditional solid support material, such as K_2CO_3, which couple poorly with microwaves. Before introducing general protocol, preliminary tests were carried out to survey the requisite reaction conditions and establish the modifications required for this methodology. Triphenylpyrylium perchlorate was chosen as the model compound to identify and optimize the ideal solid support. In the cases of basic alumina and K_2CO_3 as solid support 2-isoxazolines obtained as sole product in comparable yields under microwave irradiation. More importantly, isolation of the product was more simplified and environmentally acceptable especially in the case of K_2CO_3, in which only washing the reaction mixture with water gave pure product. The same reaction in the presence of silica gel showed less selectivity toward 2-isoxazoline. Other attempts in the absence of solid phases were not successful and noticeable amount of starting materials remained intact. With these experiments, we have demonstrated that the traditional solid supports with soft acidic surface is less selective and effective, whereas solid supports with soft basic surface and nontraditional ones are moderately

Scheme 1



effective and perform the high selectivity toward desired product. Following these tests, the relative molar ratio of reactants and the amounts of solid support were also optimized under suitable microwave power. For elucidating the relative importance of this method and other effects in determining the selectivity course of these conversions, we proceeded to develop the solid support route to other triarylpyrylium perchlorates which contains electron donor and withdrawing group in para position of substituted phenyl rings and the results compared with those obtain from traditional method (in EtOH solvent). The data in Table 1 clearly showed that in the all cases (**Ia–g**) the reactions exhibit high regioselectivity toward corresponding 2-isoxazolines derivatives as favored products in very short reaction times. The long reaction time (*e.g.*, 18 h for model compound) which is one of the main drawbacks of traditional method overcomes in this method. The products undergo elimination of phenacyl in presence of sodium hydroxide as base in solvent so here; any attempt to increase the rate of the reaction at elevated temperature will decrease the yields [5a]. The formation of the oximes **IIId–f** may be described by considering the fact that the completion of these reactions in the presence of extra amount of hydroxylamine need more power of microwave irradiation and also more reaction times in comparison with the others. Interestingly, unlike to those obtained from trialkyl pyrylium [6a] these oximes were obtained as single E-isomer. This is also in accordance with the general trend in oximes, namely prevalence of the configuration in which the bulkier R group is opposite to hydroxyl group [13]. Pyryliums carrying *N,N*-dimethyl substituents in para position of 4-phenyl rings (**Ih**) do not react completely and selectively with hydroxylamine under these conditions and typical reaction times.

In conclusion, a new and general procedure for the construction of 2-isoxazoline derivatives (**IIIa–g**) from readily available starting material has been developed. We believe present solvent-free procedure under microwave irradiation; provide efficient, selective, and environmentally friendly methodology for conversion of triarylpyrylium perchlorates in which desired products can be obtained by simple filtration and washings without the need for a chromatographic workup.

EXPERIMENTAL

Chemicals were purchased from Fluka, Merck, and Aldrich chemical companies. All yields refer to isolated products. Monitoring of the reactions was accomplished by TLC. A domestic Butan microwave oven (1000 W) was used. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were obtained on a Bomen.MB:102 FTIR spectrophotometer in KBr disks. ^{1}H NMR spectra were recorded on 400 MHz Brucker using $CDCl_3$ as the solvent and TMS as the internal standard.

Syntheses. All triarylpyrylium perchlorates were synthesized from the corresponding aldehydes and ketones by the

Table 1

The results for solvent-free microwave-assisted preparation of 2-isoxazoline derivatives (**III**).

					Yield (%)[b]		
Entry	R	R′	X	Time (MW power)[a]	Basic alumina	K_2CO_3	EtOH[c]
a	Ph	Ph	O	3 (300) + 0.5 (400)	84	86	74
b	Ph	4-$CH_3C_6H_4$	O	3(300)	79	85	49
c	4-$CH_3OC_6H_4$	Ph	O	3 (300) + 0.5 (400)	80	89	67
d	Ph	4-$CH_3OC_6H_4$	NOH	4.5 (300) + 1 (400)	76	81	63
e	Ph	4-$NO_2C_6H_4$	NOH	4 (300) + 1 (400)	79	81	41
f	Ph	4-BrC_6H_4	NOH	4 (300) + 1 (400)	67	80	43
g	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	O	3 (300) + 0.5 (400)	79	87	69
h	Ph	4-$(CH_3)_2NC_6H_4$	–	4.5 (300) + 1 (400)[d]	–	–	–

[a] The time and microwave power units are minute and watt, respectively.
[b] Based on the isolated products.
[c] After at least 18 h products were isolated as x = O.
[d] A mixture of unidentified products obtained.

method previously described [14,15]. The isoxazolines IIIa and IIIf were identical with samples (IR, m.p.) prepared from the pervious method [5].

General procedure. ***In ethanol.*** 2,4,6-Triarylpyrylium perchlorate (0.5 mmol) was suspended in ethanol (10 ml). To the stirred suspension was added an aqueous of hydroxylamine hydrochloride (2.5 mmol) and excess sodium hydroxide. The suspension was stirred for 18 h at room temperature. The products was extracted and purified by chromatography (PLC) and then recrystalized from suitable solvents.

Solvent free. Triarylpyrylium perchlorate (1 mmol) was added to 1 g of basic alumina and/or K_2CO_3 in a mortar (this ratio was optimized under our experimental condition), after homogenizing 5 mmol of hydroxylamine gradually added in portion and the mixtures were grinded for further homogenization, then irradiated in different energy and required reaction times (Table 1). The reactions were monitored by TLC using a 30:70 mixture of ether:*n*-hexane as an eluent. After completion of the reaction, the mixtures were washed with water in the case of K_2CO_3 then the products were isolated by filtration. In the case of basic alumina, the reaction mixture diluted with CH_2Cl_2 then washed with water and dried (using $MgSO_4$). Evaporation of the solvent under vacuum provided a residue which was purified by PLC to afford the desired 2-isoxazolines or their oxime derivatives.

2-(3,5-Diphenyl-4,5-dihydro-isoxazol-5-yl)-1-phenyl-ethanone (IIIa). White crystals, m.p.: 123–124°C. IR (ν max/cm^{-1}): 1340, 1370, 1450, 1680. ^{1}H NMR: 7.3–7.88 (15H, m, Ar), 4.12 (1H, d, ^2J = 17, CH_AH_B), 3.75 (1H, d, ^2J = 17, CH_AH_B), 3.74 (2H, s, $COCH_2$). *Anal*. Calcd. for ($C_{23}H_{19}NO_2$): C, 80.91; H, 5.61; N, 4.10. Found: C, 80.95; H, 5.90; N, 4.02.

1-Phenyl-2-(3-phenyl-5-p-tolyl-4,5-dihydro-isoxazol-5-yl)-ethanone (IIIb). White crystals, m.p.: 134–135°C. IR (ν max/cm^{-1}): 1340, 1370, 1430, 1450, 1680. ^{1}H NMR: 7.17–7.90 (14H, m, Ar), 4.10 (1H, d, ^2J = 17, CHAHB), 3.77 (2H, s, $COCH_2$), 3.71 (1H, d, ^2J = 17, CH_AH_B), 2.31 (3H, s, CH_3). *Anal*. Calcd. for ($C_{24}H_{21}NO_2$): C, 81.10; H, 5.95, N, 3.94. Found: C, 80.84; H, 6.02; N, 4.03.

1-(4-Methoxy-phenyl)-2-[3-(4-methoxy-phenyl)-5-phenyl-4,5-dihydro-isoxazol-5-yl] ethanone (IIIc). White crystals, m.p.: 136–137°C. IR (ν max/cm^{-1}): 1340, 1370, 1430, 1450, 1680. ^{1}H NMR: 6.90–7.80 (13H, m, Ar), 4.10 (1H, d, ^2J = 17, CH_AH_B), 3.9 (3H, s, OCH_3), 3.8 (3H, s, OCH_3), 3.70 (1H, d, ^2J = 17, CH_AH_B), 3.67 (2H, s, $COCH_2$). *Anal*. Calcd. for ($C_{25}H_{23}NO_4$): C, 74.80; H, 5.77; N, 3.49. Found: C, 74.68; H, 5.93; N, 3.69.

2-[5-(4-Methoxy-phenyl)-3-phenyl-4,5-dihydro-isoxazol-5-yl]-1-phenyl-ethanone oxime (IIId). White crystals, m.p.: 150–151°C. IR (ν max/cm^{-1}): 1340, 1380, 1430, 1450, 3260 (broad), 3585. ^{1}H NMR: 8.90 (1H, oxime proton), 6.89–7.91(14H, m, Ar), 4.10 (1H, d, ^2J = 17, CH_AH_B), 3.73 (1H, d, ^2J = 17, CH_AH_B), 3.83 (1H, d, ^2J = 13.9, $COCH_AH_B$), 3.81 (1H, d, ^2J = 13.9, $COCH_AH_B$), 3.80 (3H, s, OCH_3). *Anal*. Calcd. for ($C_{24}H_{22}N_2O_3$): C, 74.60; H, 5.73; N, 7.25. Found: C, 74.48; H, 5.85; N, 7.34.

2-[5-(4-Nitro-phenyl)-3-phenyl-4,5-dihydro-isoxazol-5-yl]-1-phenyl-ethanone oxime (IIIe). White crystals, m.p.: 154–155°C. IR (ν max/cm^{-1}): 1340, 1380, 1430, 1450, 3260 (broad), 3585. ^{1}H NMR: 8.89 (1H, oxime proton), 7.20–8.20 (14H, m, Ar), 4.12 (1H, d, ^2J = 16.9, CH_AH_B), 3.83 (1H, d, ^2J = 16.9, CH_AH_B), 3.88 (1H, d, ^2J = 13.9, $COCH_AH_B$), 3.81 (1H, d, ^2J = 13.9, $COCH_AH_B$). *Anal*. Calcd. for ($C_{23}H_{19}N_3O4$): C, 68.82; H, 4.77; N, 10.47. Found: C, 68.58; H, 4.84; N, 10.71.

2-[5-(4-bromo-phenyl)-3-phenyl-4,5-dihydro-isoxazol-5-yl]-1-phenyl-ethanone oxime (IIIf). White crystals, m.p.: 164–165°C. IR (ν max/cm^{-1}): 1340, 1380, 1430, 1450, 3327 (broad). ^{1}H NMR: 9 (1H, oxime proton), 7.40–7.60 (14H, m, Ar), 3.78 (1H, d, ^2J = 16.6, CH_AH_B), 3.71 (1H, d, ^2J = 13.4, $COCH_AH_B$), 3.42 (1H, d, ^2J = 13.4, $COCH_AH_B$) 3.38 (1H, d, ^2J = 16.6, CHAHB). *Anal*. Calcd. for ($C_{23}H_{19}N_2O_2Br$): C, 63.43; H, 4.40; N, 6.44; Br, 18.36. Found: C, 64.12; H, 4.54; N, 6.12; Br, 17.82.

1-(4-Methoxy-phenyl)-2-[3-(4-methoxy-phenyl)-5-p-tolyl-4,5-dihydro-isoxazol-5-yl] ethanone (IIIg). White crystals, m.p.: 124–128°C. IR (ν max/cm^{-1}): 1340, 1370, 1430, 1450, 1680. ^{1}H NMR: 6.70–8.00 (12H, m, Ar), 4.05 (1H, d, ^2J = 16.5, CH_AH_B), 3.77 (6H, s, OCH_3), 3.70 (1H, d, ^2J = 16.5, CH_AH_B), 3.70 (2H, s, $COCH_2$), 2.37 (3H, s, CH_3). *Anal*. Calcd. for ($C_{25}H_{23}NO_4$): C, 78.17; H, 6.31; N, 3.51. Found: C, 78.20; H, 6.44; N, 3.50.

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