Asian Journal of Chemistry Vol. 17, No. 4 (2005), 2233–2238

A Convenient Method for the Synthesis of New 3-Hydroxy-5(2H)-Isoxazolone Derivatives from (Chlorocarbonyl)phenyl Ketene

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The synthesis of new 5(2H)-isoxazolone derivatives has received considerable amount of attention. This class of heterocycle ring systems can undergo 1,3-dipolar cycloaddition reactions. The new derivatives synthesis was achieved by the reaction of *meso*-ionic compounds with *p*-amino thiophenol as a nucleophile.

Key Words: Synthesis, Isoxazolone derivatives.

INTRODUCTION

5(2H)-isoxazolone derivatives are being applied as extremely versatile intermediates in organic chemistry for the synthesis of different types of heterocycles such as: imidazopyridines[1], 1,3-oxazine-6-one derivatives[2], (N-O) acetal ketenes[3].

Also this kind of heterocycle rings are widely used in analytical usages, *e.g.*, extraction of ternary complexes of thorium(IV)[4], synergistic extraction of alkaline earth and alkali metals combined with trioctylphosphine oxide[5], etc.

They have also showed antimicrobial activities[6]. Therefore, the vast usages of these compounds encouraged us to pay much attention to study the new synthetical aspects of 5(2H)-isoxazolones. Hence, due to the interesting applications of different 5(2H)-isoxazolone derivatives, we were prompted to develop methods for the synthesis of these types of heterocyclic compounds.

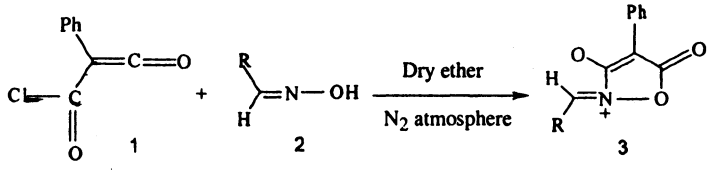
RESULTS AND DISCUSSION

As a part of ongoing interest in the study and synthesis of oxazolones and their reaction with 3,4-dithio toluene[7], we were prompted to undertake the synthesis of some new 3-hydroxy-5(2H)-isoxazolone derivatives starting with an appropriate oxime and (chlorocarbonyl)phenyl ketene.

The overall synthetic sequence to obtain isoxazolone consisted of two simple steps: (i) getting mesoionic five-membered heterocycle ring systems **(3a–f)** by the treatment of oximes **(2a–f)** with (chlorocarbonyl)phenyl ketene **(1)** and (ii)

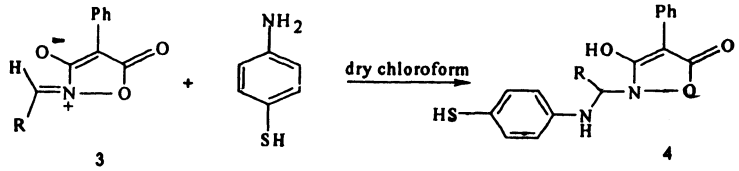
nucleophilic attack of *p*-amino thiophenol to compounds **(3a–f)** which gives **(4a–f).**

Since (chlorocarbonyl)phenyl ketene is a stable ketene and reacts with some oximes of furfural, benzaldehyde, *p*-chlorobenzaldehyde, 2,4-dichlorobenzaldehyde, *p*-N,N-dimethyl benzaldehyde and *p*-methoxy benzaldehyde, all these reactions lead to produce mesoionic five-membered heterocycles through a zwitterion as an intermediate[8] **(Scheme-1).** These zwitterionic systems are stable because the positive and negative charges are delocalized within the π-electron system.

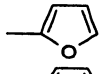
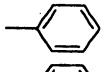
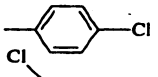
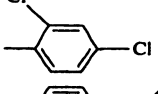
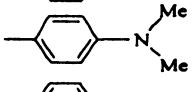
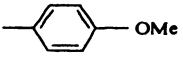


Scheme-1

It is expected that the thio group of *p*-amino thiophenol would attack as a nucleophile because it is a stronger nucleophile than the amino group, but it did not happen and an unusual attack of amino group was achieved **(Scheme-2).** The structures of new compounds **(4a–f)** are supported by different analytical spectroscopies.

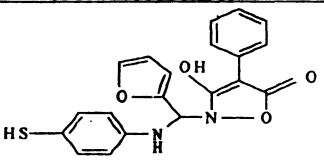
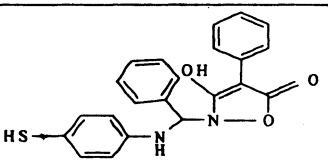
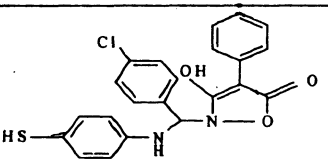
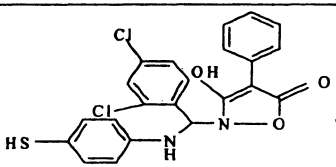
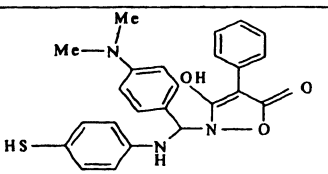
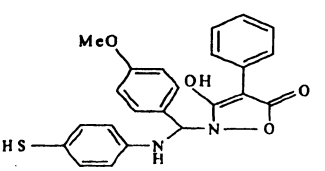


Scheme-2

Compound	R
2a,3a,4a	
2b,3b,4b	
2c,3c,4c	
2d,3d,4d	
2e,3e,4e	
2f,3f,4f	

Physical and yield data of the pure products (**4a–f**) are given in Table-1.

TABLE-1
PHYSICAL AND YIELD DATA FOR COMPOUNDS (4a–f)

Product	Compound	Melting Point °C	Yield(%)
4a		109 °C decomposed	89
4b		162 °C decomposed	91
4c		151 °C decomposed	74
4d		157 °C decomposed	83
4e		138 °C decomposed	87
4f		145 °C decomposed	84

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analysis for C, H and N was performed by National Iranian Oil Company Laboratory (Tehran) using a Heracus CHN-O-Rapid analyzer. Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer and IR spectra were obtained on a Mattson 1000 FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DRX-500 Avance spectrometer using tetramethylsilane (TMS) as an internal standard.

(Chlorocarbonyl)phenyl ketene was prepared by a procedure similar to that of Nakanishi[9]. Column chromatography was performed on silica gel 60, 0.063–0.2 mm (chloroform : hexane).

Mesoionic five-membered heterocycle ring systems[10] (3a–f)

General procedure: (Chlorcarbonyl)phenyl ketene (0.4 mmol) was added to a solution of 40 mL of dry diethylether and oxime (0.4 mmol) at 0°C under the nitrogen atmosphere. Then a crude mass product was instantly formed. The reaction mixture was filtered and the products were recrystallized from benzene.

2-[2-Furyl(4-sulfanylaninilo)methyl]-3-hydroxy-4-phenyl-5(2H)-isoxazolone (4a)

To a solution of 2-[1-(2-furyl)methylidene]-5-oxo-4-phenylisoxazol-2-ium-3(5H)-olate (0.1 mmol, 0.25 g) in 40 mL of dry chloroform was added *p*-amino thiophenol (0.1 mmol, 0.13 g) at room temperature. The mixture was stirred for 20 min, then 50 mL of cooled dry hexane was added to the reaction mixture. A violet precipitate was formed, then filtered and washed with dry chloroform. The residue was recrystallized from mixed solvent of chloroform : hexan (1 : 2) giving violet crystals.

IR (KBr, cm^{-1}) ν_{max} 1691 ν(C=O), 2625–3056 ν(OH), 3354 ν(NH); ^{1}H-NMR (DMSO-d_6): δ 3.39 (s, 1H, SH), 6.44 (s, 1H, CH), 6.55–6.86 (m, 3H, furyl), 7.05–7.92 (m, 9H, arom.), 8.14 (s, 1H, NH), 8.29 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (65.1), (79.5), (122.2–136.7), (171.1), (172.2); MS, m/e (%): 77(7), 204 (100), 256 (60), 313 (20), 380 (10, M^+), 382 (3, $(M+2)^+$). Anal. (%) Calcd. for $C_{20}H_{16}N_2O_4S$ requires: C, 63.16; H, 4.21; N, 7.37; Found: C, 63.30; H, 4.40; N, 7.30.

3-Hydroxy-4-phenyl-2-[phenyl(4-sulfanylaninilo)methyl]-5(2H)-isoxazolone (4b)

In an Erlenmeyer flask containing 40 mL of dry chloroform, 5-oxo-4-phenyl-2-[1-phenylmethylidene]-isoxazol-2-ium-3(5H)-olate (0.1 mmol, 0.27 g) was dissolved. *p*-Amino thiophenol (0.1 mmol, 0.13 g) was added to this solution. When a white precipitate was formed, the product was filtered and washed with dry chloroform and recrystallized from chloroform : hexane (1 : 2). IR (KBr, cm^{-1}) ν_{max}: 1706 ν(C=O), 2656–3098 ν(OH), 3375 ν(NH); ^{1}H-NMR (DMSO-d_6) δ 3.85 (s, 1H, SH), 6.86 (s, 1H, CH), 7.05–7.93 (m, 14H, arom), 8.10 (s, 1H, NH), 8.11 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (72.1), (79.8), (118.3–43.3), (171.2), (172.4); MS, m/e (%): 77 (15), 214 (100), 266 (40), 313 (50), 390 (10, M^+), 392 (0.7%, $(M+2)^+$). Anal. (%) Calcd. for $C_{22}H_{18}N_2O_3S$ requires: C, 67.69; H, 4.61; N, 7.18; Found: C, 67.60; H, 4.70; N, 7.10.

2-[(4-Chlorophenyl)(4-sulfanylanilino)methyl]-3-hydroxy-4-phenyl-5(2H)-isoxazolone (4c)

To a stirring solution of 30 mL of dry chloroform containing 2-[1-(4-chlorophenyl)methylidene]-5-oxo-4-phenylisoxazol-2-ium-3(5H)-olate (0.1 mmol,

0.30 g), *p*-amino thiophenol (0.1 mmol, 0.13 g) was added. Immediately yellow precipitate was formed. After washing the product with dry chloroform, filtration and purification process with column chromatography (hexane : chloroform, 2 : 1), light yellow crystals of **(4c)** were obtained.

IR (KBr, cm^{-1}) ν_{max}: 1691 ν(C=O), 2610–3081 ν(OH), 3347 (NH); ^{1}H-NMR (DMSO-d_6) δ 3.54 (s, 1H, SH), 6.86 (s, 1H, CH), 7.05–7.67 (m, 13H, arom.), 7.92 (s, 1H, NH), 8.12 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6) δ (77.5), (79.3), (122.1–136.9), (171.1), (172.3); MS, m/e (%): 77 (10), 189 (10), 248 (100), 250 (38), 300 (50), 424 (4, M^+), 426 (1.5, $(M+2)^+$). Anal. (%) Calcd. for $C_{22}H_{17}N_2O_3SCl$ requires: C, 62.26; H, 4.00; N, 6.60; Found: C, 62.40; H, 3.90; N, 6.30.

2-[(2,4-Dichlorophenyl)(4-sulfanylanilino)methyl]-3-hydroxy-4-phenyl-5(2H)-isoxazolone (4d)

To a solution of 2-[1-(2,4-dichlorophenyl)methylidene]-5-oxo-4-phenylisoxazol-2-ium-3(5H)-olate (0.1 mmol, 0.34 g) in 40 mL of dry chloroform was added *p*-amino thiophenol (0.1 mmol, 0.13 g). The mixture was stirred for 25 min, then 30 mL of cooled hexane was added to the reaction mixture. A yellow precipitate was formed, then filtered and washed with dry chloroform. The residue was purified by using column chromatography (hexane : chloroform, 3 : 1); the final product were yellow crystals.

IR (KBr, cm^{-1}) ν_{max}: 1716 ν(C=O), 2590–3106 ν(OH), 3365 ν(NH); ^{1}H-NMR (DMSO-d_6): δ 3.25 (s, 1H, SH), 6.79 (s, 1H, CH), 6.93–7.88 (m, 12H, arom.), 8.04 (s, 1H, NH), 8.81 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (68.8), (79.7), (122.3–136.1), (170.1), (171.9); MS, m/e (%): 77 (20), 282 (100), 313 (20), 334 (30), 458 (3, M^+), 460 (2, $(M+2)^+$), 462 (0.5, $(M+4)^+$). Anal. (%) Calcd. for $C_{22}H_{16}N_2O_3SCl_2$ requires: C, 57.64; H, 3.49; N, 6.11; Found: C, 57.30; H, 3.20; N, 6.00.

2-[[4-Dimethylamino)phenyl](4-sulfanylanilino)methyl]-3-hydroxy-4-phenyl-5(2H)-isoxazolone (4e)

To a stirring solution of 30 mL of dry chloroform containing 2-{1-[4-(dimethylamino)phenyl]methylidene}-5-oxo-4-phenylisoxazol-2-ium-3-(5H)-olate (0.1 mmol, 0.31 g), *p*-amino thiophenol (0.1 mmol, 0.13 g) was added. Immediately yellow precipitate was formed. After washing the product with dry chloroform and filtration, the product was recrystallized from mixed solvent of chloroform : hexane (1 : 2) giving orange crystals.

IR (KBr, cm^{-1}) ν_{max}: 1691 ν(C=O), 2564–3081 ν(OH), 3354 ν(NH); ^{1}H-NMR (DMSO-d_6): δ 3.03 (s, 1H, SH), 3.19 (s, 6H, $2CH_3$), 6.59 (s, 1H, CH), 6.97–7.73 (m, 13H, arom.), 7.94 (s, 1H, NH), 8.96 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (40.46), (78.4), (79.8), (111.4–134.1), (171.6), (173.5); MS, m/e (%): 77 (17), 124 (10), 257 (100), 313 (30), 433 (5, M^+), 435 (3, $(M+2)^+$). Anal. (%) Calcd. for $C_{24}H_{23}N_3O_3S$ requires: C, 66.51; H, 5.31; N, 9.70. Found: C, 66.34; H, 5.20; N, 9.630.

3-Hydroxy-2-[(4-methoxyphenyl)(4-sulfanylanilino)methyl]-4-phenyl-5(2H)-isoxazolone (4f)

In an Erlenmeyer flask containing 40 mL of dry chloroform, 2-[1-(4-methoxyphenyl)methylidene]-5-oxo-4-phenylisoxazol-2-ium-3(5H)-olate (0.1 mmol, 0.30 g) was dissolved. *p*-Amino thiophenol (0.1 mmol, 0.13 g) was added to this solution. When a brown precipitate was formed, the product was filtered and washed with dry chloroform and was crystallized from chloroform : hexane (1 : 2) giving light brown crystals.

IR (KBr, cm^{-1}) ν_{max}: 1706 ν(C=O), 2610–3072 ν(OH), 3332 ν(NH); ^{1}H-NMR (DMSO-d_6): δ 3.01 (s, 1H, SH), 3.81 (s, 3H, CH_3), 6.86 (s, 1H, CH), 7.05–8.08 (m, 13H, arom.), 8.29 (s, H, NH), 8.83 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (55.3), (65.7), (76.9), (121.6–136.7), (173.5), (174.9); MS, m/e (%): 77 (28), 244 (100), 294 (70), 313 (40), 420 (5, M^+), 422 (0.3, $(M+2)^+$). Anal. (%) Calcd. for $C_{23}H_{20}N_2O_4S$ requires: C, 65.71; H, 4.76; N, 6.66; Found: C, 65.60; H, 4.90; N, 6.50 .

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(*Received*: 30 August 2004; *Accepted*: 1 June 2005) AJC-4242