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Synthesis of Isoxazolone Derivatives from (Chlorocarbonyl)phenyl Ketene with Benzhydroxamic Acids

Vajihe Nejadshafiee, Kazem Saidi,* and Mehdi Abaszadeh

*Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76169, Iran. *E-mail: saidik@mail.uk.ac.ir*
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The reaction of (chlorocarbonyl)phenyl ketene, with readily available benzhydroxamic acid derivatives, such as benzhydroxamic acid, 4-chlorobenzhydroxamic acid, 3-nitrobenzhydroxamic acid, 4-methylbenzhydroxamic acid, *N*-hydroxy-3-oxo-3-phenylpropionamide, *N*-hydroxy-2-phenylacetamide, affords isoxazolone derivatives in high yields in a one step procedure. The formation of the products proceeds by a mechanism, that involves replacement of chlorine of the ketene, by benzhydroxamic acids, followed by rapid ring closure of this intermediate to form isoxazolone derivatives.

Key Words : Ketene, (Chlorocarbonyl)phenyl ketene, Benzhydroxamic acids, Isoxazolone, Cycloaddition

Introduction

Isoxazolone derivatives formation by the reaction of a ketene with benzhydroxamic acids is of special interest because they exhibit useful biological activities. Very recently β-lactam (azetidinone) formation by *N*-propylketene [2+2] cycloaddition with imine has been reported by Tidwell and his colleagues.[1] The serendipitous discovery of diphenyl ketene by Herman Staudinger in 1905[2] is considered one of the single most important events in the history of ketenes which is a stable and isolable ketene. As reported most of the ketenes could not be isolated and detected and were described as unstable compounds. Therefore these ketenes should be generated and trapped *in-situ*.[3,4] (Chlorocarbonyl)-phenyl ketene (**1**) is an isolable and stable compound, which was prepared by dehydrohalogenation of phenyl malonyl chloride: it can be stored at cold temperature for long periods of time.[5] This ketene reacts smoothly with carbonyl groups (aldehydes and ketones),[6] oximes,[7] ethoxyacetylenes,[8] arylthioamides, thioureas,[9] arylhydrazones,[10,11] 1,3-diketones,[12] pyrazolones,[13] thiobenzamide, thioacetamide,[14] 4-hydroxyquinolin-2(1*H*)-ones and 4-hydroxy-2*H*-chromene-2-one[15] to produce synthetically valuable heterocyclic compounds. It is obvious, that many of the heterocyclic compounds have interesting physiological activities, and therefore drawn much attention. Among the heterocyclic compounds nitrogen heterocycles are of special interest because they constitute an important class of natural products, many of them exhibit useful biological activities. Isoxazolone derivatives, are in general, well known five-membered nitrogen-containing heterocyclic compounds.

Experimental

(Chlorocarbonyl)phenyl ketene **1** was prepared using the literature procedure.[5] The benzhydroxamic acid, 4-chlorobenzhydroxamic acid, 3-nitrobenzhydroxamic acid, 4-methyl benzhydroxamic acid, *N*-hydroxy-3-oxo-3-phenylpropionamide, and *N*-hydroxy-2-phenylacetamide **2a-f** were known compounds, and were prepared according to the reported procedure.[16] Solvents were dried over sodium and distilled before use. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were measured on a Mattson 1000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Bruker DRX-500AVANCE spectrometer at 500 and 125.77 MHz, respectively. Mass spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV.

General Procedure.

2-Benzoyl-3-hydroxy-4-phenyl-2*H*-isoxazol-5-one (3a): Benzhydroxyamic acid (2 mmol), was dissolved in boiling anhydrous THF (20 mL), and (chlorocarbonyl)phenyl ketene (2 mmol) was added dropwise over 2 min to the reaction mixture, which causes the color of the solution change to yellow. The reaction mixture was heated at reflux for 1/2 h, during this time it turned green. It was cooled, and the solid product was collected and recrystallized from dry *n*-hexane. Yield: Green crystals; 0.52 g, 93%; mp 141-142 °C; IR (KBr): 3364 (broad OH), 1762, 1663 cm^{-1}; MS, *m/z* (relative intensity %): 281 $(C_{16}H_{11}O_4N)^{+\bullet}$ (3) M^+ (parent peak), 105 $(PhCO)^{+\bullet}$ (base peak), 91 (19), 76 (81); ^{1}H NMR (DMSO-d_6): δ 12.20 (1H, s, OH), 7.29-8.18 (10H, m, arom); ^{13}C NMR ($CDCl_3$): δ 167.8 (C_3-enol form), 164.1 and 162.1 (2C=O), 135.22 and 130.84 (2c), 129.28, 129.01, 128.79, 127.81, 127.65,126.85 (6CH-arom), 85.82 (C).

Anal. Calcd. for $C_{16}H_{11}NO_4$: C, 68.32; H, 3.91; N, 4.98%. Found: C, 68.08; H, 3.65; N, 5.08%.

2-(4-Chlorobenzoyl)-3-hydroxy-4-phenyl-2*H*-isoxazol-5-one (3b): Yield: Light green crystals; 0.59 g, 90%; mp 107-111 °C; IR (KBr): 3360 (broad OH), 1767, 1666 cm^{-1}; MS, *m/z* (relative intensity %): 279 $(C_{16}H_{10}O_4N)^{+\bullet}$ (2), 139 (47), 104 (30), 90 $(C_7H_6)^{+\bullet}$ (100) (base peak); ^{1}H NMR

Dedicated with respect and admiration to Professor William T. Brady a leading pioneer in the development of haloketene chemistry, including fluoro, chloro and bromo derivatives.

(DMSO-d_6): 7.07-7.94 (9H, m, arom); ^{13}C NMR: δ (DMSO-d_6): 170.78 (C_3-enol form), 170.26 and 166.40 (2C=O), 137.74 (C-Cl), 131.29, 130.34 (2C), 129.36, 128.94, 128.19, 127.47, 124.47 (5CH-arom), 79.49 (C).

Anal. Calcd. for $C_{16}H_{10}$ Cl NO_4: C, 60.95; H, 3.17; N, 4.44%. Found: C, 60.69; H, 3.26; N, 4.62%.

3-Hydroxy-2-(3-nitrobenzoyl)-4-phenyl-2*H*-isoxazol-5-one (3c): Yield: Yellow crystals; 0.55 g, 85%; mp 97-99 °C; IR (KBr): 3354 (broad OH), 1694, 1604 cm^{-1}; MS, *m/z* (relative intensity %): 325 $(C_{16}H_9O_6N_2)^{+\bullet}$ (3) $(M\text{-}1)^{+\bullet}$, 279 (3), 121 (41), 91 (93), 75 (58), 65 $(C_5H_5)^{+\bullet}$ (100) (base peak); ^{1}H NMR (DMSO-d_6): δ 13.33 (1H, s, OH), 8.60-7.23 (9H, m, arom); ^{13}C NMR (DMSO-d_6): δ 169.96 (C_3-enol form) and 165.48, 147.88 (2C=O), 135.33 (C-NO_2), 134.20, 132.44 (2C), 130.51, 129.30, 128.16, 127.48, 127.30, 126.53, 123.65 (7CH-arom), 57.57 (C_2).

Anal. Calcd. for $C_{16}H_{10}N_2O_6$: C, 58.89; H, 3.06; N, 8.58%. Found: C, 58.68; H, 3.17; N, 8.39%.

3-Hydroxy-2-(4-methylbenzoyl)-4-phenyl-2*H*-isoxazol-5-one (3d): Yield: Light green crystals; 0.56 g, 95%; mp 119-121 °C; IR (KBr): 3358 (broad OH), 1765, 1666 cm^{-1}; MS, *m/z* (relative intensity %): 295 $(C_{17}H_{13}O_4N)^{+\bullet}$ (5) $M^{+\cdot}$ (parent peak), 149 (2), 135 (27), 119 $(C_8H_9O)^{+\bullet}$ (100) (base peak), 105 (15), 90 (42); ^{1}H NMR (DMSO-d_6): δ 12.4 (1H, s, OH), 8.04-6.87 (9H, m, arom), 2.36 (3H, s, CH_3); ^{13}C NMR δ (DMSO-d_6): 168.29 (C_3-enol form), 164.61 and 163.84 (2C=O), 141.83 (C-CH_3), 135.70, 132.47 (2C), 130.75, 129.69, 128.50, 127.91, 125.22 (5CH-arom), 79.64 (C), 21.59 (CH_3).

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.40; N, 4.74%. Found: C, 68.95; H, 4.15; N, 4.67%.

1-(3-Hydroxy-5-oxo-4-phenyl-5*H*-isoxazol-2-yl)-3-phenylpropane-1,3-dione (3e): Yield: White crystals; 0.56 g, 88%; mp 118-120 °C; IR (KBr): 3447 (broad OH), 1769, 1681, 1619 cm^{-1}; MS, *m/z* (relative intensity %): 305 $(C_{18}H_{11}O_4N)^{+\bullet}$ (3), 105 $(PhCO)^{+\bullet}$ (100) (base peak), 91 (28), 76 (60), 43 (25); ^{1}H NMR (DMSO-d_6): δ 7.07-7.70 (10H, m, arom), 6.10 (2H, d, CH_2); ^{13}C NMR (DMSO-d_6): δ 163.86 (C=O), 157.69 (C_3-enol form), 153.81, 149 (2C=O), 134.43, 132.58 (2C), 130.03, 128.79, 128.31, 127.27, 126.59, 125.09 (6CH-arom), 90.71 (CH), 82.52 (C).

Anal. Calcd. for $C_{18}H_{13}NO_5$: C, 66.87; H, 4.02; N, 4.33%. Found: C, 66.57; H, 4.08; N, 4.69%.

3-Hydroxy-4-phenyl-2-phenylacetyl-2*H*-isoxazol 5-one (3f): Yield: Dark green crystals; 0.54 g, 92%; mp 130-132 °C; IR (KBr): 3446 (broad OH), 1769, 1695 cm^{-1}; MS, *m/z* (relative intensity %): 136 (21), 118 (20), 91 $(PhCH_2)^{+\bullet}$ (100) (base peak); ^{1}H NMR (DMSO-d_6): δ 11.99 (1H, s, OH), 7.34-7.22 (10H, m, arom), 3.45, 3.84 (2H, d, CH_2); ^{13}C NMR (DMSO): δ 169.40 (C_3-enol form), 167.47 (C=O), 134.83 and 133.29 (2C), 129.28, 129, 128.40, 128.22, 127.05, 126.60 (6CH-arom), 37.56 (CH_2).

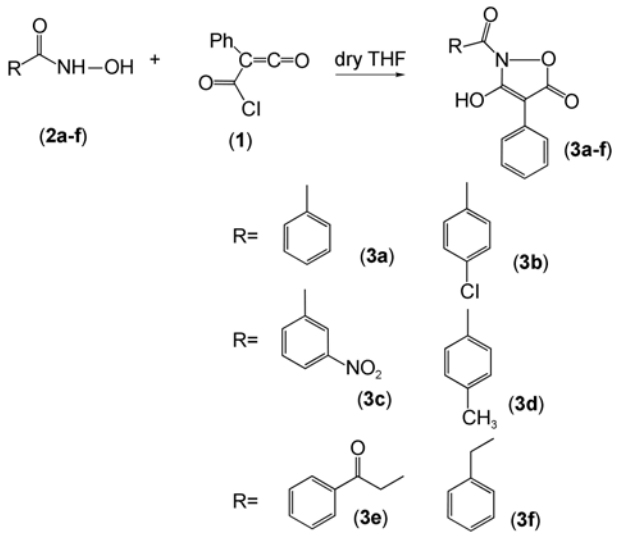
Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.40; N, 4.74%. Found: C, 68.22; H, 4.04; N, 5.06%.

Results and Discussion

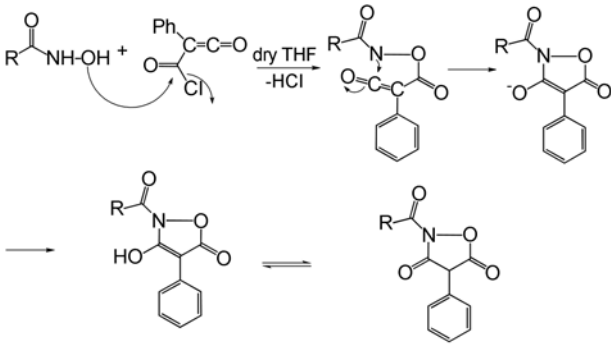
In this paper, we describe an investigation of the cycloaddition of **1** with benzhydroxamic acids to prepare isoxazolone derivatives in a one step procedure resulting in good to excellent yields (Scheme 1).

The cycloaddition of this isolable and stable ketene, with benzhydroxamic acids proceeds, by a simple and a one step procedure. Compounds **3a-f** were prepared in 93, 90, 85, 95, 88, and 92% yields, respectively. Thus the cycloaddition represented in Scheme 1 were accomplished by mixing the equimolar quantities of (chlorocarbonyl)phenyl ketene and benzhydroxamic acid at ambient temperature in dry tetrahydrofuran. Benzhydroxamic acid derivatives have two active sites, nitrogen and oxygen, that are capable to react with the ketene. Therefore, either the OH or NH group of benzhydroxyamic acid derivatives will attack the acyl chloride of the ketene, followed by ring closure to produce the final products. When ketene **1** was added to refluxing tetrahydrofuran solution of benzhydroxamic acid derivatives, the solution turned green, which is indicative that the reaction is occurring.

Compound **3a** was formed from the reaction of the ketene **1** with benzhydroxamic acid and shows carbonyl absorption band at 1762 and 1663 cm^{-1} in the IR spectrum. The ^{1}H NMR spectrum of **3a** indicated two kinds of proton signals with one signal quite downfield (δ 12.20 ppm) which is the proton of enol OH. This assignment is consistent with



Scheme 1



Scheme 2

Table 1. Yield of isolated products

Compound	Yield (%)
3a	93
3b	90
3c	85
3d	95
3e	88
3f	92

published literature for closely related products. The ^{13}C NMR and mass spectra are also in accordance with the proposed structure. In general, all of the spectral data supported the structures of the compounds **3a-f**.

Conclusions

In conclusion, we have shown that the condensation reaction of (chlorocarbonyl) phenyl ketene with benzhydroxamic acid derivative occurs efficiently in tetrahydrofuran, providing a convenient and rapid synthesis of isoxazolone derivatives in high yield, by a simple procedure and short experimental time. Furthermore, the products are solid and easily isolated from the reaction mixture by a simple purifications process.

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References

1. Islami, M. R.; Allen, A. D.; Vokovic, S.; Tidwell, T. T. *Org. Lett*. **2011**, *13*, 494.
2. (a) Staudinger, H. *Ber. Dtsch. Chem. Ges*. **1905**, *38*, 1735. (b) Staudinger, H. *From Organic Chemistry to Macromolecules*; Wiley: New York, 1970. (c) Tidwell, T. T. *Angew. Chem. Int. Ed.* **2005**, *44*, *5778.* Herman Staudinger von Nobel Prize in 1953.
3. Brady, W. T. *Synthesis* **1971**, *415*, 422.
4. Saidi, K.; Tidwell, T. T. *Arkivoc*. **2001**, *xii*, 100.
5. Nakanishi, S.; Butler, K. *Organic Preparations and Procedures Int*. **1975**, *7*, 155.
6. Saidi, K.; Shaterian, H. R.; Sheibani, H. *Synth. Commun.* **2000**, *30*, 2345.
7. (a) Saidi, K.; Sheibani, H. *Synth. Commun*. **2001**, *31*, 1809. (b). Tikdari, A. M.; Shokrani, A.; Hamidian, H.; Kabazzadeh, H. *J. Chin. Chem. Soc*. **2005**, *52*, 1153. (c) Potts, K. T.; Kanemass, S.; Zvillichovsky, G. *J. Am. Chem. Soc*. **1980**, 3971.
8. Brown, D. G.; Hoye, T. R.; Brisbois, R. G. *J. Org. Chem*. **1998**, *63*, 1630.
9. Padwa, A.; Coats, S. J.; Harring, S. R.; Hadjiarapoglou, L.; Semones, M. A. *Synthesis* **1995**, 973.
10. Potts, K. T.; Ehlinger, R.; Nichols, W. M. *J. Org. Chem*. **1975**, *40*, 2596.
11. Sheibani, H.; Lari, J.; Islami, M. R.; Saidi, K. *Russian Chemical Bullentin International Edition*. **2003**, *52*, 6, 1411.
12. Sheibani, H.; Islami, M. R.; Khabazzadeh, H.; Saidi, K. *Tetrahedron.* **2004**, *60*, 5931.
13. Abaszadeh, M.; Sheibani, H.; Saidi, K. *Aust. J. Chem*. **2010**, *63*, 92.
14. Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Foroughi, H.; Saidi, K. *Arkivoc*. **2005**, *XV*, 88.
15. Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Saidi, K. *Synthesis* **2005**, 435.
16. Hauser, C. R.; Renfrom, W. B. *Organic Syntheses* **1943**, *2*, 67.