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Synthesis of oxazole derivatives using *N*-formylmorpholine as green solvent: study of antimicrobial activity

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Abstract: An efficient synthesis of oxazoles in water is described *via* reaction between arylisocyanate, and alkyl bromides in the presence of *N*-formylmorpholine. The antimicrobial activity of some synthesized compounds was studied employing the disk diffusion test on Gram-positive bacteria and Gram-negative bacteria. The results of disk diffusion test showed that these compounds prevented the bacterial growth.

Keywords: Oxazole, Ethyl bromopyruvate, NFM, Isocyanate.

Introduction

1,3-Oxazoles represent a simple heterocyclic frame which has been scarcely explored compared to the non-aromatic counterpart oxazolesstructure. Surprisingly for this simple heterocycle, only basic structures related to acetol have been converted into oxazoles [1, 2]. Syntheses of oxazoles were reported using either condensation of thiocyanic acid [3-6] or isothiocyanates [7] with an α-hydroxycarbonyl, or condensation of thiophosgen with an aminoketone [8]. The possible balance of reactivity of α-hydroxycarbonyl systems with thiocyanic acid toward the formation of either oxazolesor 1,3-oxazoline-2-thione have been recently reported [9, 10]. At present, bacteria that are resistant to drugs have generated considerable problems in the performance of many communicable diseases. Therefore, discovering new ways to extirpate these pathogens are important. For this reason, recent studies have focused on the study of the antibacterial effects of new synthesized compounds.

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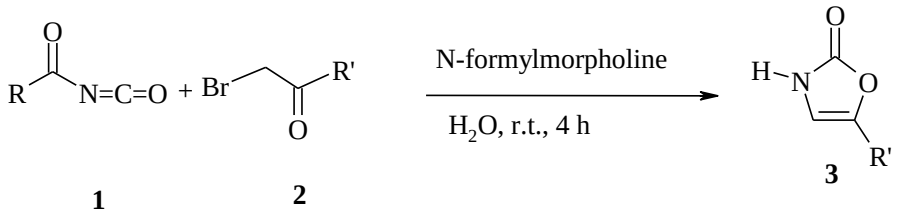
Result and disscussion

As part of our current studies on the development of new routes in heterocyclic synthesis, we report an efficient synthetic route to functionalized oxazoles. Thus, the reaction of isocyanate **1**, alkyl bromides **2** in the presence of *N*-formylmorpholine (5 mL) in water produced oxazoles **3** in good yields (Scheme **1**).

Structures of compounds **3a**–**3g** were assigned by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The ^{1}HNMR spectra of **3a**–**3g** exhibited characteristic signals for methine (δ = 7.52-7.64 ppm) protons. The ^{13}C NMR spectra of the 1,3-Oxazoline-2-thione ring system of **3a** showed signals at 118.4 (CH), 139.8 (C), 156.6 (C=O), 176.7 (C=O), and 178.1 (C=S) ppm. The mass spectra of **3a**–**3g** displayed the molecular ion peaks at appropriate *m*/*z* values.

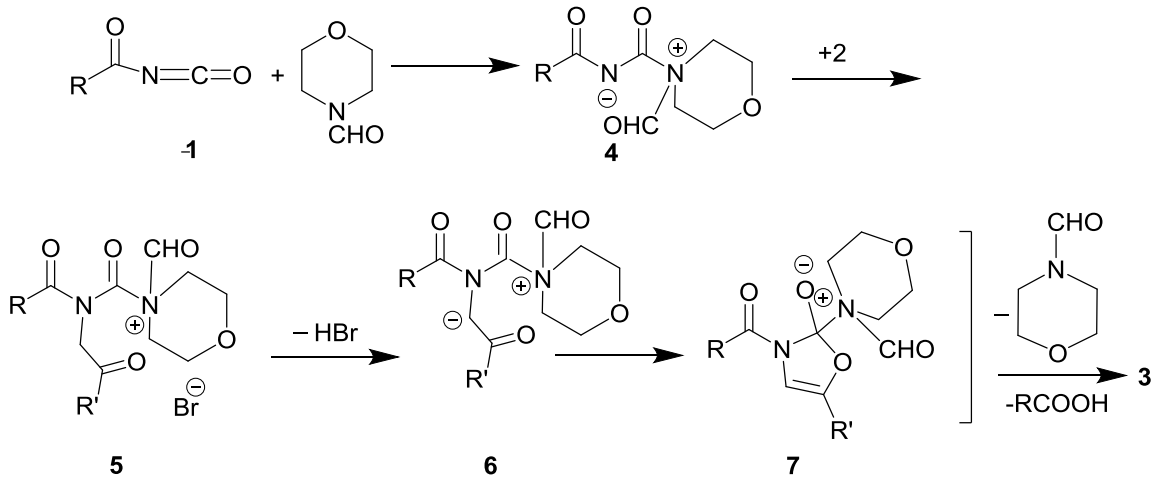
A tentative mechanism for this transformation is proposed in Scheme **2**. The reaction starts with reaction of benzoyl isothiocyanate 1 with NFM, and formation of the 1:1 adduct **4**, which is subsequently attacked by ethyl bromopyruvate to produce **5**. Intermediate **5** undergoes HBr elimination, cyclization reaction, and loss of *N*-formylmorpholine to generate **3**.



1 **2** **3**

3	R'	Yield/ % of **3**
a	Ph	78
b	p-Me-C_6H_4	80
c	P-Br-C_6H_4	75
d	p-Cl-C_6H_4	75
e	p-NO_2-C_6H_4	70
f	*t*-Bu	85
g	Et	87

Scheme 1: Synthesis of oxazol derivatives



1 **4** **5** **6** **7** **3**

Scheme 2: Proposed mechanism.

Also, a comparison between the activity of our synthesized compounds with Streptomycin and Gentamicin as standard drug was discussed. The present study indicated that the type of bacteria and concentration of compounds are effective on the diameter of the inhibition zone. It is apparent from the data listed in Table **1**, the antimicrobial activity of the most synthesized compounds **3b**, **3c**, **3e** and **3g** were good active against Gram positive bacteria and Gram negative bacteria So that the diameter of the inhibition zone of compounds has the maximum effect on *Escherichia coli*.

Table 1. The antibacterial activity of the tested compounds **4a-4g**

Compounds	Staphylococcus aureus (+)	Bacillus cereus (+)	Escherichia coli(-)	Klebsiella pneumoniae (-)
3a	8	10	9	---
3b	17	20	21	18
3c	18	22	23	17
3d	---	5	10	6
3e	15	21	23	20
3f	7	7	8	----
3g	15	21	24	20
Streptomycin	16	24	25	23
Gentamicin	19	23	24	21

Experimental Section

General

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. ^{1}H, and ^{13}C NMR spectra were obtained with a Bruker FT-500 spectrometer in $CDCl_3$, and tetramethylsilane (TMS) was used as an internal standard or 85% H_3PO_4 as external standard. Mass spectra were recorded with a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicolet Magna 550-FT spectrometer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4 % of the calculated values. All chemicals were obtained from Fluka and were used without further purification.

General Procedure for the Preparation of Compounds 3:

A mixture of isocyanate (2 mmol) and NFM (5 mL) and water as solvent stirred for 1 h. Then, alkyl bromides (2 mmol) was added gently. The reaction mixture was stirred for 4 h and extracted by Et_2O (2 x 5 mL) to afford the pure title compounds.

*Compound **3a:***

Pale yellow crystals; yield: 0.38 g (85%), mp 129-131°C. IR (KBr) (ν_{max}/cm^{-1}): 1724, 1631, 1585, 1518 and 1470 cm^{-1}. ^{1}H NMR: δ 1.45 (3 H, *t*, ^{3}J = 7.2, Me); 4.46 (2 H, *q*, ^{3}J = 7.2, OCH_2); 7.52 (2 H, *t*, ^{3}J = 7.8, 2 CH); 7.61 (1 H, *t*, ^{3}J = 6.1, CH); 7.65 (1 H, *s*, CH); 7.52 (2 H, *d*, ^{3}J = 6.1, 2 CH). ^{13}C NMR: δ = 14.6 (Me); 63.0 (OCH_2); 118.4 (CH); 128.9 (2 CH); 130.5 (2 CH); 133.8 (CH); 134.9 (C); 139.8 (C); 156.6 (C=O); 176.7 (C=O); 178.1 (C=O). EI-MS: 227 (M^+, 10), 121 (20), 105 (100), 77 (90), 57 (30), 51 (64); 45 (36).

Compound **3b:**

Pale yellow powder; yield: 0.55 g (95%); mp 125-127°C. IR (KBr) (ν_{max}/cm^{-1}): 1720, 1635, 1580, 1520 and 1450 cm^{-1}. ^{1}H NMR: δ 1.40 (3 H, *t*, ^{3}J = 7.2, Me); 2.41 (3 H, *s*, Me); 4.41 (2 H, *q*, ^{3}J = 7.2, OCH_2); 7.26 (2 H, *d*, ^{3}J = 8.1, 2 CH); 7.57 (1 H, *s*, CH); 8.21 (2 H, *d*, ^{3}J = 8.1, 2 CH). ^{13}C NMR: δ 14.2 (Me); 21.7 (Me); 62.4 (OCH_2); 117.8 (CH); 129.2 (2 CH); 130.2 (2 CH); 132.1 (C); 139.4 (C); 144.2 (C); 156.2 (C=O); 176.2 (C=O); 177.2 (C=O). EI-MS: 291 (M^+, 5), 172(65), 119 (100), 99 (64), 77 (80), 45 (56).

Compound **3c:**

Yellow crystals; yield: 0.53 g (75%), mp 135-137°C. IR (KBr): 1730, 1650, 1575, 1519 and 1450 cm^{-1}.^{1}H NMR: δ 1.37 (3 H, *t*, ^{3}J = 7.2, Me); 4.38 (2 H, *q*, ^{3}J =

7.2, OCH_2); 7.57 (2 H, *d*, ^3J = 8.5, 2 CH); 7.58 (1 H, *s*, CH); 8.13 (2 H, *d*, ^3J = 8.5, 2 CH). ^{13}C NMR: δ 14.2 (Me); 62.6 (OCH_2); 117.8 (CH); 128.5 (C); 131.5 (2 CH); 131.7 (2 CH); 133.6 (C); 139.6 (C); 156.0 (C=O); 175.4 (C=O); 177.9 (C=O). EI-MS: 356 (M^+, 10); 283 (45); 172 (75); 184 (100); 99 (66); 77 (64), 45 (84).

Compound **3d:**

Yellow crystals; yield: 0.43 g (70%), mp 142-144°C. IR (KBr): 1725, 1630, 1580, 1522 and 1501 cm^{-1}. ^{1}H NMR: δ 1.35 (3 H, *t*, ^3J = 7.2, Me); 4.35 (2 H, *q*, ^3J = 7.2, OCH_2); 7.56 (2 H, *d*, ^3J = 8.5, 2 CH); 7.60 (1 H, *s*, CH); 8.24 (2 H, *d*, ^3J = 8.5, 2 CH). ^{13}C NMR: δ 14.4 (Me); 62.5 (OCH_2); 118.1 (CH); 128.4 (C); 131.7 (2 CH); 132.1 (2 CH); 133.7 (C); 139.4 (C); 157.4 (C=O); 176.1 (C=O); 178.2 (C=O). EI-MS: 311 (M^+, 10); 238 (45); 172 (66); 139 (100), 77 (85), 45 (84).

Compound **3e:**

Yellow crystals; yield: 0.55 g (85%), mp 133-135°C. IR (KBr): 1721, 1632, 1584, 1510 and 1469 cm^{-1}. ^{1}H NMR: δ 1.41 (3 H, *t*, ^3J = 7.1, Me); 4.43 (2 H, *q*, ^3J = 7.1, OCH_2); 7.64 (1 H, *s*, CH); 8.30 (2 H, *d*, ^3J = 8.8, 2 CH); 8.47 (2 H, *d*, ^3J = 8.8, 2 CH). ^{13}C NMR: δ 14.2 (Me); 62.7 (OCH_2); 117.7 (CH); 123.6 (2 CH); 131.0 (2 CH); 139.9 (C); 140.0 (C); 150.6 (C); 155.8 (C=O); 174.4 (C=O); 179.0 (C=O). EI-MS: 322 (M^+, 15); 249 (55); 172 (76); 150 (100), 77 (65), 45 (52).

Compound **3f:**

Yellow crystals; yield: 0.43 g (83%), mp 124-126°C. IR (KBr): 1720, 1654, 1580, 1524 and 1460 cm^{-1}. ^{1}H NMR: δ 1.18 (9 H, s, 3 Me), 1.31 (3 H, *t*, ^3J = 7.2, Me); 4.33 (2 H, *q*, ^3J = 7.2, OCH_2); 7.53 (1 H, *s*, CH). ^{13}C NMR: δ 14.1 (Me); 27.0 (3 Me), 41.5 (C), 62.3 (OCH_2); 117.7 (CH); 138.9 (C); 156.1 (C=O); 176.9 (C=O); 190.7 (C=O). EI-MS: 257 (M^+, 10); 172 (85); 85 (100), 57 (86).

Compound 3**g:**

Yellow powder; yield: 0.39 g (86%), mp 127-129°C. IR (KBr): 1729, 1654, 1587, 1524 and 1460 cm^{-1}. ^{1}H NMR: δ 1.14 (3 H, *t*, ^3J = 7.5, Me); 1.31 (3 H, *t*, ^3J = 7.2, Me); 2.62 (2 H, *q*, ^3J = 7.5, OCH_2); 4.33 (2 H, *q*, ^3J = 7.2, OCH_2), 7.52 (1 H, *s*, CH). ^{13}C NMR: δ 8.9 (Me); 14.0 (Me); 33.6 (CH_2), 62.3 (OCH_2); 117.5 (CH); 138.9 (C); 156.0 (C=O); 176.3 (C=O); 185.9 (C=O). EI-MS: 229 (M^+, 10); 224 (56); 172 (56); 57 (100), 45 (42).

Evaluation of antibacterial activity:

The antibacterial effect of synthesized compounds against Gram-positive and Gram-negative bacteria was investigated using the disk diffusion method. All microorganisms were obtained from the Persian type culture collection (PTCC), Tehran, Iran. Microorganisms were cultured for 16 to 24 h at 37°C and prepared to turbidity equivalent to McFarland Standard No. 0.5. Streptomycin and Gentamicin at a concentration 40 μg/mL, were used as standard against bacteria. The bacterial suspension was prepared to match the turbidity of the 0.5 McFarland (Approximately 1.5 × 108 CFU/mL) standards and cultured with a sterile swab on Mueller Hinton agar. All synthesized compounds were screened for their antibacterial (Gram-positive and Gram-negative) at a concentration of 25 µg/ml that was poured on sterile blank disks. The plates were incubated overnight at 37 °C for 24 h in an incubator. The result was studied by measuring the diameter of the inhibition zone and compared to with the control.

Conclusion

In conclusion, the reaction between alkyl bromide and isocyanate in the presence of *N-formylmorpholine* (20 mol%) led to functionalized 2-oxo-2,3-dihydro-1,3-oxazoles in good yields. The present procedure has the advantage that the reaction is performed under neutral conditions, and the starting material can be used without any activation or modification.

Acknowledgments

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