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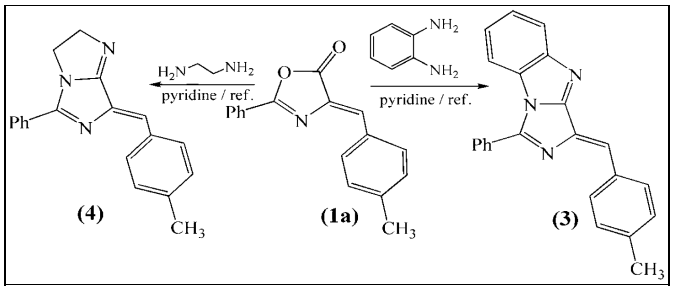

2-Phenyl-4-benzylidene-5(4*H*)-oxazolones (**1a-e**) were used as versatile starting materials for the synthesis of fused compounds such as: 4*H*-3,1-benoxazin-4-ones **(2a,b),** imidazo[4,3-*b*]benzimidazoles **(3,4),** imidazo[1,5-*b*]1,2,4-triazoles **(5a,b),** and **7**.

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INTRODUCTION

In recent years, the chemistry of oxazolones has received much attention because of their use as key starting materials for further transformations [1–11]. 5(4*H*)-oxazolone are known for their usefulness in preparing various important heterocyclic compounds [12–14]. These compounds were used as versatile reagents for the synthesis of α-keto and arylacetic acids, peptides and α-amino acids [15–17]. In continuation of this work, we reported here the synthesis of antimicrobial activity of benzoxazin-4-ones, imidazo[4,3-*b*] benzimidazoles or imidazo[1,5-*b*]1,2,4-triazoles starting with 2-Phenyl-4-benzylidene-5(4*H*)-oxazolones **1** as starting materials.

RESULTS AND DISCUSSIONS

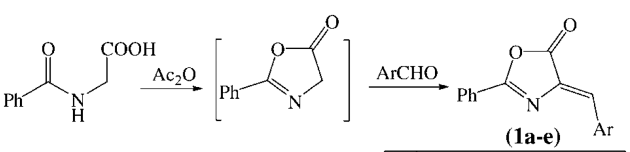
Aromatic aldehydes readily condensed with hippuric acid in the presence of acetic anhydride and sodium acetate to yield 2,4-disubstituted-5(*4H*)-oxazolones (Azlactones) [18], **1a-e**, (Scheme 1).

The newly derivatives of 2-Phenyl-4-benzylidene-5 (4*H*)-oxazolone **(1a,c)** were allowed to react with anthranilic acid in 1-butanol to give 2-substituted 4*H*-3,1-benoxazin-4-ones **2a,b,** (Scheme 2).

The IR spectrum of compounds **2a,b** showed NH bands at 3321 and 3231 cm^{-1}, two bands at 1677 and 1674, 1657 and 1653 cm^{-1} attributed to the carbonyl groups of benzoxazinone ring and amidic carbonyl group for **2a** and **2b**, respectively. ^{1}H-NMR spectrum of compound **2a** showed a broad band at 10.31 ppm for NH group, aromatic protons, and CH proton as multiplets between 8.84 and 7.10 ppm and singlet signal at 2.82 ppm for CH_3. ^{1}H-NMR spectrum of compound **2b** showed a broad band at 10.35 ppm for NH group, aromatic protons and CH proton as multiplets between 8.30 and 7.09 ppm.

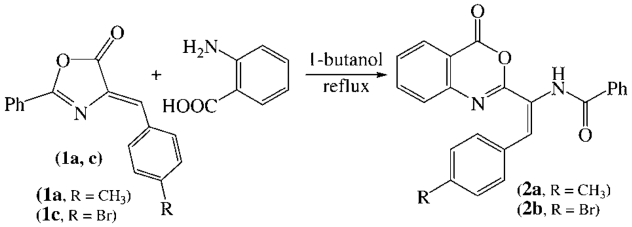
Compound **1a** was heated under reflux with *o*-phenylenediamine or ethylenediamine in pyridine for 10 hours to afford the corresponding imidazobenzimidazole derivative **3** and imidazoimidazole derivative **4** (Scheme 3).

Scheme 1

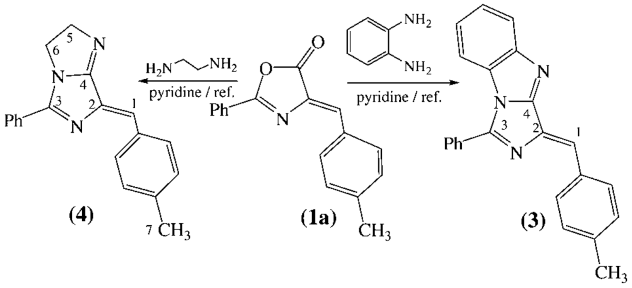


1	Ar
a	4-$CH_3C_6H_4$
b	4-ClC_6H_4
c	4-BrC_6H_4
d	3-OCH_3-4-$OCOCH_3$-C_6H_3
e	4-$OCH_3C_6H_4$

Scheme 2



Scheme 3



The reaction pathway was assumed to proceed via nucleophilic attack of amino group at the carbonyl group of oxazolone ring with ring opening followed by another nucleophilic attack of other amino group at the carbonyl group of the imidazole ring with elimination of water (Scheme 4).

The IR spectrum of compound **3** showed C=N at 1660 cm[1] and disappearance of carbonyl group. ^{1}H-NMR spectrum showed aromatic protons and CH proton as multiplets between 7.69 and 7.04 ppm, and singlet signal at 2.20 ppm for CH_3.

The IR spectrum of compound **4** showed the appearance of C=N band at 1659 and disappearance of carbonyl group bands. ^{1}H-NMR spectrum showed aromatic protons and CH proton as multiplets between 7.74 and 7.08 ppm, triplet signal at 4.09 ppm for CH_2 (C_5), and triplet signal at 2.28 ppm for CH_2 (C_6) and singlet signal at 2.24 ppm for CH_3.

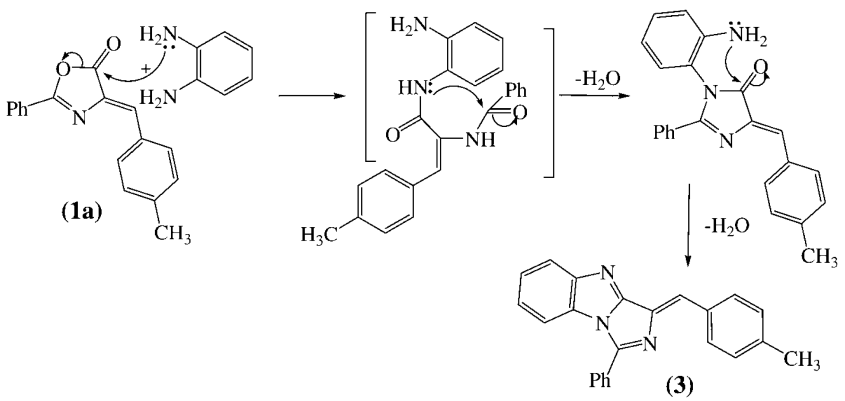
Compounds **1a,e** reacted with semicarbazide hydrochloride in refluxing pyridine to give the corresponding imidazo[1,5-*b*]-1,2,4-triazole derivatives **5a,b**. Compound **5a** was also prepared via reaction of benzoxazinone derivative **2a** with semicarbazide under the same previous condition instead of the expected (*E*)-*N*-(1-(2-oxo-2,3-dihydro[1,2,4]triazolo[1,5-*c*]quinolin-5-yl)-2-*p*-tolylvinyl) benzamide (c.f. Scheme 5).

The reaction is believed to proceed in three steps. Benzoxazinone undergone ring opening by the moisture in the reaction solvent (these compounds are easily undergone ring opening under heating in most solvents) forming *N*-acetyl anthranilic acid, followed by a nucleophilic attack of the NH_2 group at the amidic carbonyl carbon with loss of anthranilic acid molecule followed by a nucleophilic attack of NH group at the carbonyl carbon to form the intermediate imidazolone ring. Finally the nucleophilic attack of the amino amide group at the carbonyl carbon of imidazolone ring followed by cyclization with elimination of water molecule (Scheme 6).

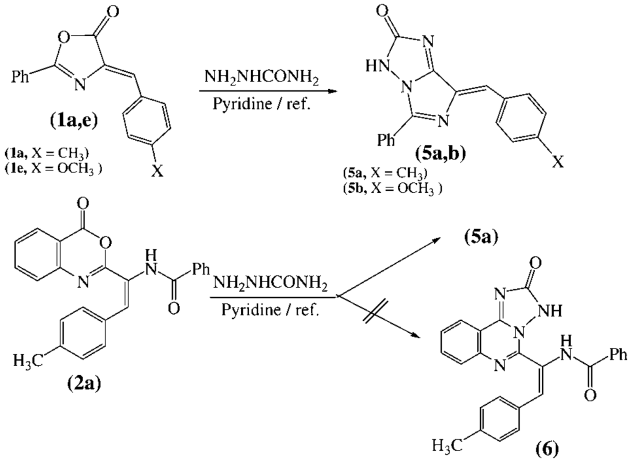
The IR spectrum of compound **5a** showed a broad band of NH group at 3342 cm^{-1} and carbonyl group at 1702 cm^{-1}. ^{1}H-NMR spectrum of compound **5a** showed aromatic protons as multiplets between 8.38 and 7.18 ppm, benzylic proton as singlet at 7.15 ppm, a broad band at 5.40 ppm for NH group and singlet signal at 2.35 ppm for CH_3. The IR spectrum of compound **5b** showed NH band at 3321 cm^{-1} and carbonyl group at 1702 cm^{-1}. ^{1}H-NMR spectrum of compound **5b** showed aromatic protons and CH proton as multiplets between 8.46 and 6.80 ppm, a broad band at 4.40 ppm for NH group and singlet signal at 3.85 ppm for OCH_3.

Refluxing of compound **1** with 2-amino benzothiazole in acetic acid containing fused sodium acetate afforded (*Z*)-*N*-(1-benzo[*d*]thiazol-2-ylamino)-1-oxo-3-p-tolylprop-2-en-2-yl)benzamide **7** (Scheme 7).

Scheme 4



Scheme 5



Antimicrobial activity evaluation. The newly synthesized compounds **1-5** were preliminary evaluated for their *in vitro* antibacterial activity against a narrow spectrum of bacterial species procured from the Laboratory of Microbial Biochemistry (Department of Chemistry, Al-Fateh University). The paper disc assay described by Cooper [19] using nutrient agar medium was applied. Suspensions of each microorganism were prepared from their 24 h-cultures to obtain $\sim 10^6$ colony forming units (cfu) per ml for plating. Paper discs (Whatman No.1) of 8 mm diameter were loaded individually with a constant amount (100 μg/disc) of the compounds to be tested. Discs were aseptically transferred and applied onto the dry surface of the inoculated plates and then incubated at 37°C for overnight (approximately 18–20 h). This assay was performed in duplicates and the mean diameters of the clear inhibition zones were recorded (mm) disregard a single colony or a faint haze caused by the inoculums. Results of the *in vitro* assay of the synthesized compounds are shown in Table 1.

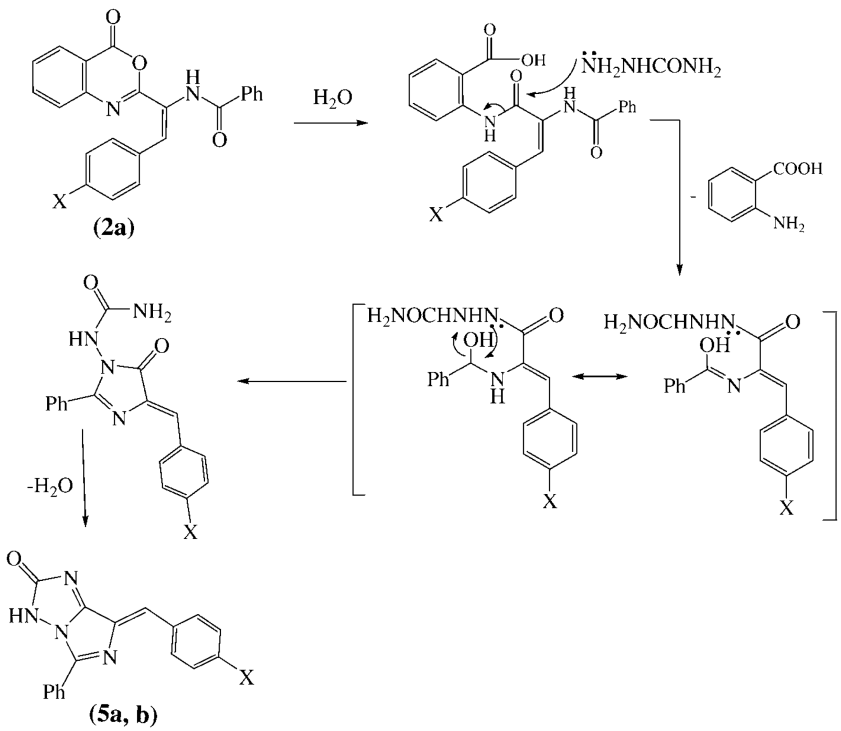
Compounds **1c**, **1d**, **1e**, and **3** showed moderate antibacterial activities especially against Gram negative bacteria, meanwhile other compounds showed no such activity.

EXPERIMENTAL

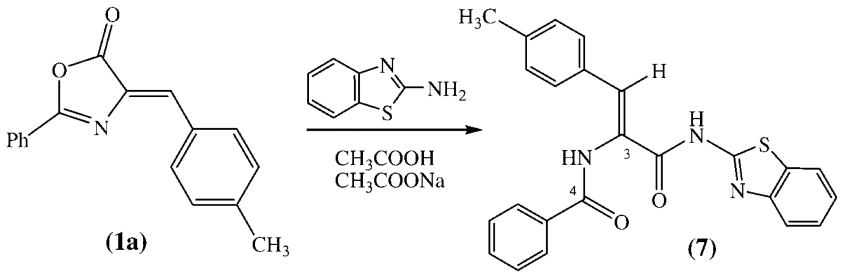
All melting points were determined on a Koffler melting points apparatus and are uncorrected. H^1-NMR spectra were recorded on a Bruker avance 300 MHz spectrometer using TMS as internal reference (chemical shift in δppm), and IR in KBr were obtained on a Bruker FTIR ISS25 spectrophotometer (λ_{max} in cm^{-1}).

2-Phenyl-4-arylidene-5(4*H*)-oxazolones (1a-e). A mixture of an aromatic aldehyde (0.05 mol), hippuric acid (0.06 mol), and sodium acetate (0.07 mol) in acetic anhydride (30 mL) was refluxed with stirring for 1 hour. The mixture was then cooled down and neutralized by sodium carbonate. The solid

Scheme 6



Scheme 7



product was separated by filtration, washed with water, dried and recrystallized from ethanol or 2-propanol.

The Characterization data of compounds (**1a,b,d**) are listed in Table 2.

N-[(E)-2-(4-methylphenyl)-1-(4-oxo-4H-3,1-benzoxazin-2-yl) vinyl]benzamide(2a), N-[(E)-2-(4-bromophenyl)-1-(4-oxo-4H-3,1-benzoxazin-2-yl)vinyl]benzamide (2b). A mixture of compound (1a, c) (0.01 mol) and anthranilic acid (0.007 mol) was refluxed in 1-butanol (50 mL) for 10 hours. The obtained solid product was filtered and recrystallized from 1-butanol as white crystals. m.p; (**2a**), 234–236°C; yield: 74%; IR(KBr): 3321–3252 (NH), 1677 (CO^4), 1657 (CO^5); ^{1}H-NMR(δppm): 10.31(br, 1H, NH), 8.84–7.10(m, 14H, aromatic, 1H, CH), 2.82 (s, 3H, CH_3). ^{13}C-NMR: 169.49 (CO^4), 166.49 (CO^5), 163.59 (C_3), 133.37(C_2), 127.81 (C_1), 141.08, 138.99, 133.74, 131.71, 131.66, 131.14, 130.92, 129.50, 129.12, 129.06, 128.34, 122.41, 119.16($C_{aromatic}$), 20.80 (C_6). Compound (**2b**); m.p; 238–240°C; yield: 71%; IR(KBr): 3314–3231 (NH), 1674 (CO^4), 1653 (CO^5); ^{1}H-NMR(δppm): 10.35(br, 1H, NH), 8.30–7.09 (m, 13H, aromatic), 7.47(s, 1H, CH). ^{13}C-NMR: 169.47 (CO^4), 166.46 (CO^5), 163.29 (C_3), 132.50(C_2), 127.85 (C_1), 140.94, 133.83, 133.53, 131.98, 131.47, 131.25, 131.14, 129.28, 129.09, 128.34, 124.86, 122.42, 122.18, 119.11($C_{aromatic}$).

(3Z)-3-(4-methylbenzylidene)-1-phenyl-3H-imidazo[1,5-a]benzimidazole(3). A mixture of compound (**1a**) (0.01 mol) and *o*-phenylenediamine (0.01 mol) in dry pyridine (30 mL) was refluxed for 10 hours, cooled and then poured onto crushed ice—HCl with stirring. The solid obtained was filtered off and washed with water, dried and recrystallized from benzene as white crystals. m.p; 176–178°C; yield, 78%; IR (KBr):

Table 1

In vitro antibacterial activity of the synthesized compounds assayed by the paper disc method.[a]

	Test compounds									
Test organisms	**1a**	**1b**	**1c**	**1d**	**1e**	**2a**	**2b**	**3**	**4**	**5a**
E. coli NRRL-3704	-ve	-ve	+ve	+ve	+ve	-ve	-ve	+ve	-ve	-ve
B. subtilis NRRL-4378	-ve	-ve	+ve	+ve	+ve	-ve	-ve	+ve	-ve	-ve

The average diameters of the clear inhibition zones (mm) induced by the subject synthesized compounds (1-5).
[a]Paper disc diameter = 8.0 mm, -ve = 8.0 mm, +ve = 10–12 mm

Table 2

Characterization data for synthesized compounds (**1a,b,d**).

Cpd	Yield (%) M. p. (°C)	IR (KBr) (ν cm^{-1})	^{1}H-NMR (δppm)	^{13}C-NMR (δppm)
1a	79 142–144	3046 (Ar—H), 2917–2850 (sp^3 C—H), 1796 (CO^3)	8.20–7.25(m, 9H, aroma), 7.23 (s,1H, CH), 2.40 (s, 3H, CH_3)	167.82 (CO^3), 163.08 (C_4), 130.95 (C_2), 128.31 (C_1), 142.11, 133.18, 132.55, 132.49, 132.07, 129.75, 128.93, 125.79 ($C_{aromatic}$), 21.80 (C_5).
1b	77 180–182	3045 (Ar—H), 1797 (CO^3)	8.21-7.40(m, 9H, aroma), 7.23 (s, 1H, CH).	167.35 (CO^3), 163.99 (C_4), 132.09 (C_2), 128.50 (C_1), 137.34, 133.72, 133.57, 133.55, 130.03, 129.28, 129.03, 125.54 ($C_{aromatic}$), 21.80 (C_5)
1d	71 192–194	3127(Ar—H), 2964–2848 (sp^3 C—H), 1796 (CO^3) 1757 (CO^5)	8.18–7.11 (m, 8H, aroma), 7.20 (s, 1H, CH), 3.95 (s, 3H, OCH_3), 2.35 (s, 3H, $COCH_3$)	168.65 (CO^5), 167.50(C_3), 163.61 (C_4), 132.41 (C_2), 128.29 (C_1), 151.34, 142.22, 133.46, 133.16, 130.90, 129.02, 126.11, 125.53, 123.18, 115.40 ($C_{aromatic}$), 55.94 (C_7) 21.80 (C_6)

1660 C═N; ^{1}H-NMR(δppm): 7.69–7.04(m, 13H, aromatic, 1H,CH) 2.20 (s, 3H, CH_3).

(7Z)-7-(4-methylbenzylidene)-5-phenyl-2,7-dihydro-3H-imidazo [1,5-a]imidazole(4). A mixture of compound **(1a**) (0.01 mol) and ethylenediamine (0.01 mol) in dry pyridine (30 mL) was refluxed for 10 hours, cooled and then poured onto crushed ice –HCl with stirring. The solid obtained was filtered off and washed with water, dried and recrystallized from 2-propanol to give brown crystals. m. p; 184–186°C; yield: 80%; IR (KBr): 1659 C═N; ^{1}H-NMR(δppm)**:** 7.74–7.08 (m, 9H, aromatic. 1H, CH), 4.09 (t, 2H, CH_2), 2.28 (t, 2H, CH_2)2.24 (s, 3H, CH_3).

(7Z)-7-benzylidene-5-phenyl-3H-imidazo[1,5-b][1,2,4]triazol-2 (7H)-ones(5a,b). *Method I.* A mixture of compounds **(1a,e**) (0.01 mol) and semicarbazide (0.01 mol) in pyridine (30 mL) was refluxed for 6 hours. The reaction mixture was cooled, poured onto crushed ice–HCl with stirring. The solid product was filtered off and washed with water, dried and recrystallized from the proper solvents as yellow crystals.

Method II. A mixture of compound **(2a**) (0.01 mol) and semicarbazide hydrochloride (0.01 mol) in pyridine (30 mL) was refluxed for 8 hours. The reaction mixture was cooled, poured onto crushed ice—HCl with stirring. The solid product was filtered off and washed with water, dried and recrystallized from 1-butanol. yield: 68 % (**5a**).

5a (X = CH_3): m.p.; 222–224°C; IR(KBr); 3342 (NH), 3045 (aromatic), 1702 (CO^5). ^{1}H-NMR(δppm): 8.38–7.18 (m, 9H, aromatic), 7.15(s, 1H, CH). 5.40 (br,1H, NH), 2.35 (s, 1H, CH_3); ^{13}C-NMR: 170.12 (CO^5), 160.59 (C_4), 140.47 (C_3), 131.46 (C_2) 128.16 (C_1), 136.42, 132.33, 132.32, 131.58, 129.39, 129.36, 128.40, 126.91 ($C_{aromatic}$), 21.18 (C_6).

5b(X = OCH_3): m.p; 190-192°C; yield: 71%; IR (KBr): 3321 (NH), 3045(aroma.), 1702 (CO^5); ^{1}H-NMR(δppm): 8.46-6.80 (m, 9H, aromatic, 1H, CH).4.40 (br,1H, NH),3.85 (s, 3H, OCH_3); ^{13}C-NMR: 170.88 (CO^5), 161.80 (C_4), 140.00 (C_3), 131.30 (C_2), 128.35 (C_1), 158.25, 134.92, 131.69, 129.73, 129.53, 128.46, 127.19, 114.93 ($C_{aromatic}$), 55.44 (C_6).

***N*-[(1Z)-3-(1,3-benzothiazol-2-ylamino)-1-(4-methylphenyl)-3-oxoprop-1-en-2-yl]benzamide(7).** A mixture of compound **(1a)** (0.01 mol) and 2-aminobenzothiazole (0.01 mol) in acetic acid 930 mL) containing fused sodium acetate was refluxed for 5 hours. The solid product was filtered off and recrystallized from ethanol. m.p; 205–208°C; yield: 54%; IR (KBr): 3243 (NH), 1658 (CO^4), 1636 (CO^3); ^{1}H-NMR (δppm): 10.15 (2NH), 8.08–7.20 (m, 13H, aromatic 1H, CH), 2.30(s, 3H, CH_3).

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REFERENCES AND NOTES

[1] Aaglawe, M. J.; Dhule, S. S.; Bahekar, S. S.; Wakte, P. S.; Shinde, D. B. J Korean Chem Soc 2003, 47, 133.
[2] Paul, S.; Nanda, P.; Gupta, R.; Loupy, A. Tetrahedron Lett 2004, 45, 425.
[3] Gelmi, M. L.; Clerici, F.; Melis, A. Tetrahedron 1997, 53, 1843.
[4] Beccalli, E. M.; Clerici, F.; Gelmi, M. L. Tetrahedron 1999, 55, 781.
[5] Cativila, C.; Garcia, J. I.; Mayoral, J. A.; Pires, E.; Brown, R. Tetrahedron 1995, 51, 9217.
[6] Abdullah, M. A.; Zayed, M. E; Shawali, A. S. Indian J Chem 2001, 40B, 187.
[7] Trcek, T.; Vercek, B. J. Arkivoc 2005, (xiv), 96–101.
[8] Aly, A. A. Tetrahedron 2003, 59, 6067.
[9] Kepe, V.; Pozgan, F.; Golobic, A.; Polanc, S.; Kocevar, M. J Chem Soc Perkin Trans 1998, 1, 2813.
[10] Kepe, V.; Polanc, S.; Kocevar, M. Acta Chim Solv 1998, 45, 455.
[11] Hishmat, O. H.; Abdel Haman, A. H.; Moawad, M. I. J Heterocycl Chem 1981, 18, 1209.
[12] Polak, M.; Vercek, B. Synth Commun 2000, 30, 2863.
[13] Trcek, T.; Vercek, B. Arkivoc 2005, 14, 96.
[14] Ozturk, G.; Alp, S.; Ergun,Y. Tetrahedron Lett 2007, 48, 7347.
[15] Mukerjee, A. K.; Kumar, P. Can J Chem 1982, 60, 317.
[16] Kumar, P.; Mukerjee, A. K. Indian J Chem 1980, 19B, 704.
[17] Badshah, A.; Khan, N. H.; Kidwai, A. R. J Org Chem 1972, 37, 2916.
[18] Carter, H. E. Org React 1946, 3, 198.
[19] Cooper, K. E. Analytical Microbiology; Kavangh, F., Ed.; Academic Press: New York, 1992.