



SYNTHESIS OF ANTIBACTERIAL ETHYL 3-ARYL/ALKYL-2-(1H-TETRAZOLE-5-YL)ENOATES AND 5, 5'-(2-ARYLALKENE-1, 1-DIYL)BIS (1H-TETRAZOLES)

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ABSTRACT Aryl / alkyl ketones **1 a-c** and **5 a-b** were condensed with ethylcyanoacetate or malanonitrile afforded **3 a-c** and **7 a-b** respectively. Treatment on **3 a-c** and **7 a-b** with sodium azide and ammonium chloride in presence of dimethylformamide yielded **4 a-c** and **8 a-b** respectively. All the synthesized compounds have been characterized by the IR, NMR and Mass spectrum spectral data. Compounds **4 a-c** and **8 a-b** were evaluated for antibacterial activity.

Keywords Ethyl 3-aryl/alkyl-2-(1H-tetrazol-5-yl)enoates 5,5'-(2-Arylalkene-1,1-diyl)-bis(1H-tetrazoles) Antibacterial activity

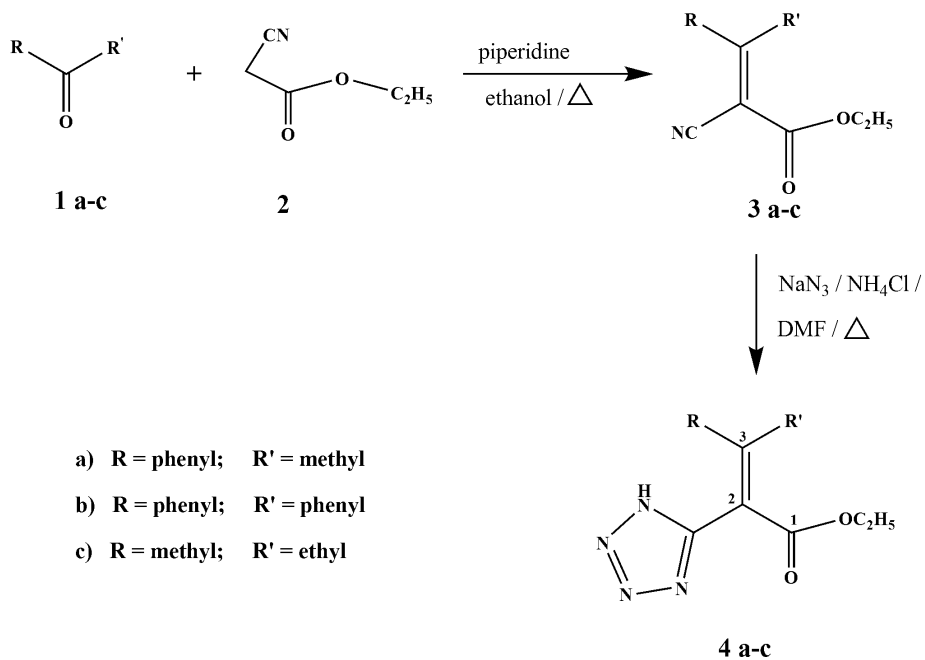
INTRODUCTION

Nitrogen-containing heterocyclic compounds are indispensable structural units for both the chemists and the biochemists. In recent years, nitrogen polyheterocycles have received increasing attention due to their potential biological properties, and considerable efforts have been undertaken to exploit synthetic routes to these compounds. In particular, the tetrazole nucleus is present in compounds endowed with analgesic [1] and antihypertensive [2]. Their derivatives possess activity in both medicinal and pharmaceutical such as antibacterial [3], antifungal [4], antiviral [5], anti-inflammatory [6], antiulcer [7] activities.

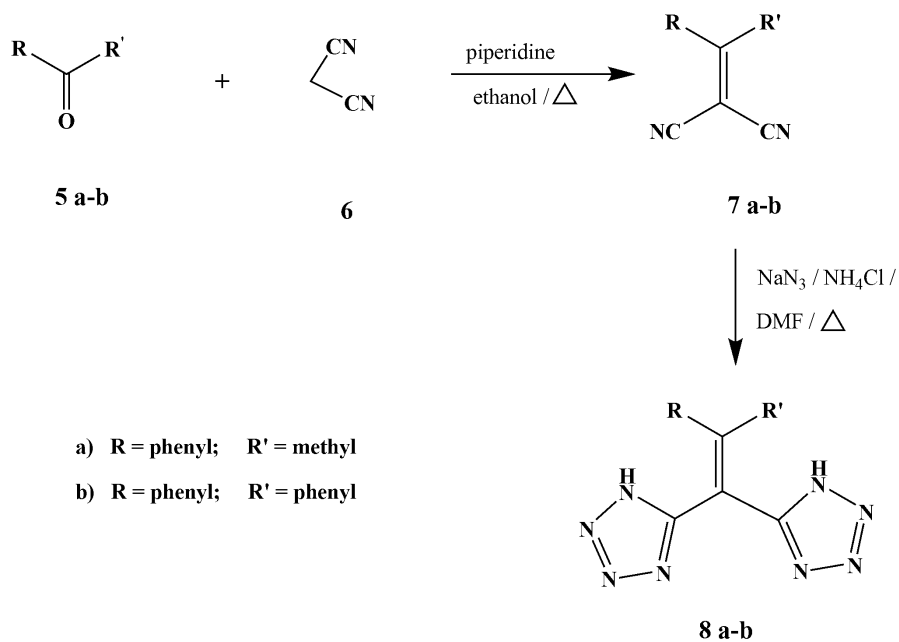
This observation prompted us to undertake the synthesis of ethyl 3-(aryl/alkyl)-2-(1H-tetrazol-5-yl)enoates **4 a-c** from ethyl 2-cyano-3-(aryl/alkyl)but-2-enoate **3 a-c** and 5,5'-(2-arylalkene-1,1-diyl)bis(1H-tetrazoles) **8a-b** from (arylalkene)malanonitrile **7a-b** and studied their antimicrobial properties.

Aryl/alkyl ketones **1 a-c** were condensed with ethylcyanoacetate **2** in presence of piperidine and ethanol afforded **3 a-c**. Treatment of **3 a-c** with sodium azide and ammonium chloride in presence of dimethylformamide yielded **4 a-c** (Scheme 1).

Similarly aryl/alkyl ketones **5 a-b** were condensed with malanonitrile **6** in presence of piperidine and ethanol afforded **7 a-b**. Treatment of **7 a-b** with sodium azide and ammonium chloride in presence of dimethylformamide yielded **8 a-b** (Scheme 2).



Scheme 1. Synthesis of compounds 4 a-c.



Scheme 2. Synthesis of compounds 8 a-b.

MATERIALS AND METHODS

All the compounds **3 a-c**; **4 a-c**; **7 a-b** and **8 a-b** gave positive test for nitrogen. The final products as well as the intermediate have been characterized by the spectroscopic data (IR and NMR & Mass spectrum). [8]

Melting points were determined on a sulphuric acid bath and are uncorrected. IR spectra were recorded on JASCO 470 FT-IR spectrometer and ¹H-NMR spectra was recorded on a 300 MHz on Bruker (Avance) NMR spectrometer using TMS as an internal standard. Mass spectra of all the synthesized compounds was performed on a JEOL JMS 600H mass spectrometer.

Experimental Procedures

General procedure for the synthesis of ethyl 2-cyano-3-aryl/alkylbut-2-enoate (**3 a-c**)

To a mixture of corresponding ketones **1 a-c** (0.10 mol), ethanol (15 mL) and ethylcyanoacetate **2** (0.10 mol) were refluxed for about 4 h. The solvent was removed *in vacuo* and the residue was poured into cold water. The product separated was filtered, dried and recrystallized with Pet. ether - Chloroform.

Ethyl 2-cyano-3-phenylbut-2-enoate: (**3a**). Yield: 86%. IR (CHCl₃): $\nu = 3336$ (C≡N Str.), 3052, 2976, 2930, 2281, 1744 (C=O Str.), 1651 (C=C Str.), 1177, 915, 763, 699, 632 cm⁻¹. ¹H NMR (300MHZ, CDCl₃) : $\delta = 1.29$ (t, 3H, CH₂CH₃), 2.40 (s, 3H, CH₃), 3.40 (m, 2H, CH₂CH₃), 7.10 -7.91 (m, 5H, Ar-H) ppm. Mass : m/z 215.39.

Ethyl 2-cyano-3,3-diphenylacrylate: (**3b**). Yield: 74%. IR (CHCl₃): $\nu = 3337$ (C≡N Str.), 3061, 2983, 2935, 2282, 1747 (C=O Str.), 1659 (C=C Str.), 1178, 943, 920, 765, 702, 639 cm⁻¹.

Ethyl 2-cyano-3-methylpent-2-enoate: (**3c**). Yield: 87%. IR (CHCl₃): $\nu = 3331$ (C≡N Str.), 2884, 2941, 2279, 1748 (C=O Str.), 1607 (C=C Str.), 1449, 1333, 1264, 1095, 1027, 855, 778 cm⁻¹.

General procedure for the synthesis of ethyl 3-aryl/alkyl-2-(*1H*-tetrazol-5-yl)enoates (**4 a-c**)

To a solution of **3 a-c** (0.10 mol) in dry DMF (7 mL), sodium azide (0.20 mol) and ammonium chloride (0.20 mol) was refluxed for about 12 h. The reaction mixture was poured into 1:1 ice cold hydrochloric acid and the separated solid was filtered, washed with water, dried and crystallized with aq. ethanol.

Ethyl 3-phenyl-2-(*1H*-tetrazol-5-yl)but-2-enoate: (**4a**). Yield: 72%; m.p., 183°C. IR (CHCl₃): $\nu = 2924$, 2210 (C-N Str.), 1909, 1656 (C=C Str.), 1595, 1439, 1277 (N-N=N), 1150 & 1016 (tetrazole ring), 919, 761, 699 cm⁻¹. ¹H NMR (300MHZ, CDCl₃) : $\delta = 1.32$ (t, 3H, CH₂CH₃), 2.59 (s, 2H, C=C CH₃), 3.20 (q, 2H, CH₂CH₃), 7.10 (m, 5H, Ar-H) 9.11 (s, 1H, NH)ppm. Mass : m/z 258.47.

Ethyl 3,3-diphenyl-2-(*1H*-tetrazol-5-yl)acrylate: (**4b**). Yield: 53%. IR (CHCl₃): $\nu = 2922$, 2213 (C-N Str.), 1911, 1659 (C=C Str.), 1599, 1447, 1278 (N-N=N), 1151 & 1017 (tetrazole ring), 920, 764, 700, cm⁻¹. ¹H NMR (300MHZ, CDCl₃) : $\delta = 1.23$ (t, 3H, CH₂CH₃), 3.42 (q, 2H, CH₂CH₃), 7.10 (m, 10H, Ar-H) 9.32 (s, 1H, NH) ppm. Mass : m/z 320.52.

Ethyl 3-methyl-2-(*1H*-tetrazol-5-yl)pent-2-enoate: (**4c**). Yield: 68%. IR (CHCl₃): ν = 2971, 2919 (C-H Str.), 2344, 2209 (C-N Str.), 1654 (C=C Str.), 1458, 1268 (N-N=N), 1115, 1031(tetrazole ring) cm⁻¹. ¹H NMR (300MHZ, CDCl₃): δ = 1.16 (t, 3H, C=CCH₂CH₃), 1.66 (m, 3H, CH₂CH₃), 1.83 (s, 3H, C=CCH₃), 2.42 (m, 2H, C=CCH₂CH₃), 4.21 (m, 2H, CH₂CH₃), 9.10 (s, 1H, NH) ppm. Mass : m/z 210.43.

General procedure for the synthesis of 2-(arylalkene)malononitrile (**7 a-b**)

To a solution of corresponding ketones **5 a-b** (0.10 mol), ethanol (15 mL) and malononitrile **6** (0.10 mol) were refluxed for about 4 h. The solvent was removed *in vacuo* and the residue was poured into cold water. The product separated was filtered, dried and recrystallized with Pet. ether - Chloroform.

2-(1-Phenylethylidene)malononitrile: (**7a**). Yield: 79%. IR (CHCl₃): ν = 3338 (C≡N), 3059, 2958, 2925, 1688, 1658 (C=C Str.), 1216, 1039, 757 cm⁻¹.

2-(Diphenylmethylene)malononitrile: (**7b**). Yield: 73%. IR (CHCl₃): ν = 3329 (C≡N Str.), 3058, 2968, 2927, 2207, 1654 (C=C Str.), 1598, 1289, 1179, 1075, 843, 697 cm⁻¹.

General procedure for the synthesis of 5,5'-(2-arylalkene-1,1-diyl)- bis(*1H*-tetrazoles) (**8 a-b**)

To a solution of **7 a-b** (0.10 mol) in dry DMF (7 mL), sodium azide (0.20 mol) and ammonium chloride (0.20 mol) were refluxed for about 12 h. The reaction mixture was poured into 1:1 ice cold hydrochloric acid and the separated solid was filtered, washed with water, dried and crystallized with aq. ethanol.

5,5'-(2-Phenylprop-1-ene-1,1-diyl)bis(*1H*-tetrazole): (**8a**). Yield: 62%; m.p., 196^oC. IR (CHCl₃): ν = 3304 (C≡N), 3261, 2957, 2925, 2270, 1968, 1658 (C=C Str.), 1394, 1279, 1214 (N-N=N), 1029 (tetrazole ring), 920, 702 cm⁻¹. ¹H NMR (300MHZ, CDCl₃): δ = 2.17 (s, 3H, CH₃), 7.14 (s, 1H, NH), 7.26 (s, 1H, NH), 7.38 (m, 5H, Ar-H) ppm. Mass : m/z 254.47.

5,5'-(2,2-Diphenylethene-1,1-diyl)bis(*1H*-tetrazole): (**8b**). Yield: 62%. IR (CHCl₃): ν = 3312 (C≡N), 3259, 2956, 2929, 2268, 1963, 1657 (C=C Str.), 1392, 1276, 1213 (N-N=N), 1027 (tetrazole ring), 918, 704 cm⁻¹. ¹H NMR (300MHZ, CDCl₃): δ = 7.11 (m, 10H, Ar-H) ppm. Mass : m/z 316.39.

RESULTS AND DISCUSSION

Antibacterial activity

Compounds **4 a-c** and **8 a-b** were evaluated for antibacterial activity by Kirby-Bauer disk-diffusion method [9] with two different concentrations (30 and 50 μ L) against *K. pneumonia*, *S. aureus*, *E. coli*, *P. aeruginosa* and *S. typhi*. All the compounds were highly active in 50 μ L concentrations. Compounds **4a** shows high activity against *K. pneumonia*, *S. aureus*, *E. coli* and *S. typhi* and compounds **8a** shows high activity against all the species at 50 μ L concentration. All other compounds possessed only moderate activity in both concentrations. The results are presented in **Table 1**.

Table 1. Antibacterial activity of Compounds 4 a-c and 8 a-b

| Compd. | Zone of inhibition (mm) | | | | | |
|--------|-------------------------|---------------------|------------------|----------------|---------------------|-----------------|
| | Conc. (µL) | <i>K. pneumonia</i> | <i>S. aureus</i> | <i>E. coli</i> | <i>P.aeruginosa</i> | <i>S. typhi</i> |
| 4a | 30 | 3 | - | 4 | - | - |
| | 50 | 13 | 10 | 9 | - | 5 |
| 4b | 30 | - | - | - | - | 8 |
| | 50 | - | 6 | - | 7 | 13 |
| 4c | 30 | - | - | 7 | - | - |
| | 50 | 9 | 4 | 10 | 6 | 9 |
| 8a | 30 | 5 | 2 | - | 6 | - |
| | 50 | 12 | 7 | 14 | 10 | 8 |
| 8b | 30 | 7 | 2 | - | 11 | 4 |
| | 50 | 9 | 4 | - | 15 | 6 |

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