J. Indian Chem. Soc.,
Vol. 82, October 2005, pp. 940-941

NOTE

Synthesis of some thiosemicarbazone and oxirane derivatives as potent antitubercular agents

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Manuscript received 13 August 2004, revised 7 July 2005, accepted 14 July 2005

Condensation of thiosemicarbazide with 1-aryl-3-(3′-chlorophenyl)-2-propene-1-ones (1a-j) afforded corresponding 4-α-(3′-chlorostyryl)-benzylidene-thiosemicarbazones (2a-j) and the compounds (1a-j) on reaction with alkaline H_2O_2 gave 3-(3′-chlorophenyl)-2-substituted benzoyl oxiranes (3a-j). All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* ($H_{37}Rv$).

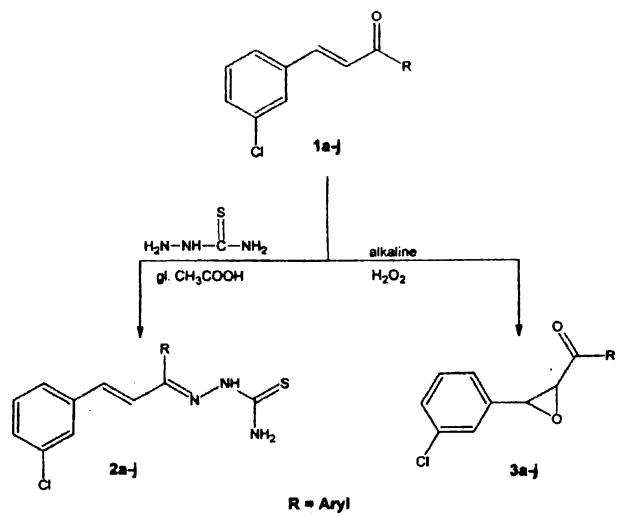
Thiosemicarbazone derivatives find wide application in medicinal use. In this present communication we have described synthesis and microbial activities of two such thiosemicarbazone derivatives.

The condensation of different aryl methyl ketones with 3-chloro benzaldehyde in presence of 40% alkali yielded corresponding l-aryl-3-(3′-chlorophenyl)-2-propene-l-ones (**1a-j**). These on condensation with thiosemicarbazide furnishes 4-α-(3′-chlorostyryl)-benzylidenethiosemicarbazones (**2a-j**) and further more chalcones (**1a-j**) reacted with alkaline hydrogen peroxide to yield 3-(3′-chlorophenyl)-2-substituted benzoyl-oxiranes (**3a-j**).

The constitution of all the products has been assigned on the basis of elemental analyses, IR, ^1H NMR and mass spectral data. All the compounds were screened for their antitubercular activity against *Mycobacterium tuberculosis* ($H_{37}Rv$) using Rifampin as standard drug and at a concentration >6.25 μg/ml.

The antitubercular evaluation of the compound was carried out at Tuberculosis Antimicrobial Acquisition Coordination Facility (TAACF), U.S.A. Primary screening of the compounds for antitubercular activity has been conducted at minimum inhibition concentration 6.25 mg/ml against *Mycobacterium tuberculosis* $H_{37}Rv$ in BACTEC 12B medium using the ALAMAR radiometric system. The antimycobacterial activity data were compared with standard drug Rifampin at 0.25 μg/ml concentration which showed 96% inhibition. Compounds having 4-bromo, 4-methyl, 4-methoxy and 4-chloro showed higher activity than the others.

The antimicrobial activity was assayed by using the cup-plate agar diffusion method[1] by measuring the zone of inhibition in mm. All the compound was screened *in vitro* for their antimicrobial activity against varieties of bacterial strains such as *E. coli, B. magaterium, S. aureus* and fungi *A. niger* at 40 μg/ml concentration. Standard drug like amoxycillin, ampicillin, ciprofloxacin, erythromycin and griseofulvin were used for the comparison purpose. It could be observed that compound **2h** (17), **3a** (15) and **3g** (20) were active against *E. coli*. Compounds **2g** (17), **3b** (20) and **3f** (18) were active against *P. vulgaris*. Compounds **2f** (16), **3c** (19) and **3i** (18) were active against *B. mega*. Compounds **2e** (14), **3b** (20) and **3f** (18) were active against *S. aureus*. Compounds **2a** (18), **3b** (21) and **3j** (18) displayed maximum activity against *A. niger*.



Experimental

Thin layer chromatography was used to access the reactions and purity of the compounds synthesized. The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 instrument in KBr disk and only principle sharply defined peaks are recorded, peaks (cm^{-1}) are listed. ^1H NMR spectra were recorded on Bruker AC-300 MHz FT NMR using TMS as an internal standard, chemical shift in δ ppm. Mass spectra were recorded on Jeol-D300 spectrometer.

Preparation of 4-α-(3′-chlorostyryl)-benzylidene-thiosemicarbazones (**2a-j**) :

A mixture of 1-aryl-3-(3′-chlorophenyl)-2-propene-1-ones (0.01 mol) and thiosemicarbazide (0.01 mol) in ethanol (20 ml) containing 1–2 ml glacial acetic acid was refluxed on water bath for 4 h. The reaction mixture then cooled and diluted with cold water. The separated solid was collected, washed with water and crystallized from ethanol. **2h** (79%), m.p. 106°C (Found : C, 59.01; H, 4.60; N, 12.12. Required for $C_{17}H_{16}N_3OClS$: C, 59.04; H. 4.63; N, 12.15%); ν_{max} 3290 (-NH str., amine), 1573 (C=C str., vinyl), 776 (C-Cl str.); δ 3.85 (3H, s, OCH_3), 7.63 (1H, dd, -CH=C*H*-), 7.79 (1H, dd, -C*H*=CH), 7.34–8.05 (8H, m, Ar-*H*), 8.60 (1H, s, -N*H*) ppm. *m/z* 346.

Similarly, other compounds : (**2a**) m.p. 80°, (**b**)165°, (**c**) 120°, (**d**) 145°, (**e**) 138°, (**f**) 162°, (**g**) 151°, (**h**) 106°, (**i**) 140°, (**j**) 160°, yields 72–81% were prepared.

Preparation of 3-(3′-chlorophenyl)-2-substituted benzoyl-oxiranes (**3a-j**) :

To a warm solution of 1-aryl-3-(3′-chlorophenyl)-2-propene-1-ones (**1a-j**) (0.01 mol) in ethanol (20 ml), alkaline hydrogen peroxide (0.01 mol) was added. The reaction mixture then left overnight at room temperature. The excess solvent was distilled off and the product was isolated and recrystallized from methanol. **3h**, yield 69%, m.p. 101°C (Found : C, 66.52; H, 4.48. Required for $C_{16}H_{13}O_3Cl$: C, 66.55; H, 4.50%); IR KBr (cm^{-1}) 1676 (-C=O str., ketone), 868 (C-O-C str., epoxide), 772 (C-Cl str.); ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ ppm 3.84 (3H, s, $-OCH_3$), 4.22 (1H, d, epoxide), 4.52 (1H, d, epoxide), 6.97–7.99 (8H, m, Ar-H). The mass spectrum pointed out the molecular ion peak at *m/z* 289.

Similarly, other compounds : (**3a**) m.p. 107°, (**b**) 101°, (**c**) 218°, (**d**) 250°, (**e**) 174°, (**f**) 188°, (**g**) 144°, (**h**) 101°, (**i**) 82°, (**j**) 240°, yields 68–72% were prepared.

Acknowledgement

The authors are thankful to Prof. and Head, Department of Chemistry, Saurashtra University, Rajkot for needful co-operation. Authors are also thankful to R.S.I.C., Chandigarh and C.D.R.I., Lucknow for providing spectral and analytical data. We are thankful to TAACF, Southern Research Institute, Alabama for antitubercular screening.

References

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