SYNTHESIS OF 3,4-DIHYDRO-2H-IMIDAZO-[2,1-b][1,3,4]THIADIAZINES

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Thiomethylene-active derivatives of N-imidazolylimines undergo intramolecular cyclization to give 3,4-dihydro-2H-imidazo[2,1-b][1,3,4]thiadiazines. This reaction is a new convenient method for the fusion of a dihydrothiadiazine ring to an imidazole fragment through formation of a C–C bond.

Keywords: N-alkylisatin, aminothioimidazole, imidazothiadiazine, thiobenzyl ether, thiophenacyl ether.

In previous work [1], we reported a new thermally-induced intramolecular cyclization of derivatives of N-arylimines 1, which contain S-methylene-active substituents in the ortho position, yielding spirobenzothiazines 2.

In the present communication, we report a study of this reaction using 1-amino-2-mercapto-4-R-imidazoles 3 as the heterocyclic analogs of o-aminothiophenols.

The condensation of 1-amino-2-mercaptoimidazole (3a) with benzylisatin and p-bromobenzylaldehyde gave the corresponding aldimines 4 and 5.

The alkylation of the thiol group in 4 by p-bromophenacyl halide immediately yielded spiroimidazo[2,1-b][1,3,4]thiadiazine 6.

The cyclic structure of 6 was indicated by the one-proton peaks at 6.05 and 7.75 ppm assigned to the CH and NH groups, respectively, and the lack of a two-proton signal for the methylthio group in the 1H NMR spectrum (Table 1). Furthermore, an AB quartet was observed for the prochiral methylene group of the benzylisatin fragment at 4.8 ppm, which also indicates the formation of a chiral spiran 6.
The alkylation of aldimine 5 by phenacyl halides gave imidazothiadiazines 7a,b.

The 1H NMR spectra of the obtained compounds 7 show doubling of all the signals in 68.5:31.5 ratio (for 7a) and 82.8:17.2 ratio (for 7b), which may be attributed to formation of a mixture of diastereomers in both cases.

When p-methoxyphenacyl bromide was used, the reaction stops upon formation of imidazolyl phenacyl sulfide 8, which is attributed to the decrease in acidity of the methylene protons due to the electron-donor methoxy group in the phenyl ring.

Under base catalysis conditions, sulfides 9a,b react with N-R-isatins and benzaldehydes to give imidazo[2,1-b][1,3,4]thiadiazines 10a,b, and 11a-c.

The structure of the compounds 10 was supported by the evolution of the signals of the methylene and amino groups of starting sulfide 9a to spin-coupled one-proton signals of the vicinal protons of two CH groups and an NH group of the thiadiazine ring in the 1H NMR spectra. The clear resolution of the signals for H-2 and H-3 and their coupling constants (J = 10 Hz) indicate that thiadiazines 10 are not stochastic mixtures of the four possible configurations due to the existence of two stereogenic carbon sites C(2) and C(3) but rather probably a racemates with trans arrangement of H-2 and H-3.

The 1H NMR spectra of 11a-c show two one-proton signals at 7.6 and 5.2-5.5 ppm due to NH and CH groups. The spectra of 11b,c, similar to the spectra of 6, show an AB quartet for the protons of the prochiral NCH2Ph methylene group at 4.9 ppm, indicating spirocyclization of the thiadiazine and isatin fragments.