Mar.Üniv.Ecz.Der.,
10 (1), 11 – 16 (1994)

J.Pharm.Univ.Mar.,
10 (1), 11 – 16 (1994)

BAZI SUBSTİTUE 1,3,4- TİYADİAZOL TÜREVLERİNİN SENTEZLERİ

SYNTHESIS OF SOME SUBSTITUTED 1,3,4- THIADIAZOLE DERIVATIVES

N. Nehir GÜLERMAN* - Sevim ROLLAS* - Mert ÜLGEN*

SUMMARY

Treatment of 1- aroyl - 4- substituted thiosemicarbazides with concentrated sulphuric acid quickly leads to cyclization to stable 5-[p- (benzoylamino) phenyl] - 2 - substituted amino-1,3,4- thiadiazoles in high yields at ambient temparature. The structures and purity of these compounds were confirmed using spectrometric and spectroscopic techniques ie UV, IR, MASS, together with their melting point and elemental analyses.

ÖZET

1- aroil -4- substitue tiyosemikarbazidlerin konsantre sülfürik asidle muamelesi, oda temparatüründe iyi bir verimle hızlı bir şekilde stabil 5- [p- (benzoilamino) fenil] -2- substitüe amino-1,3,4- tiyadiazolleri verdi. Bu maddelerin yapıları ve saflığı, erime dereceleri ve elementel analizlerinin tayinine ilaveten UV, IR ve küle spektroskopisi yöntemleri ile aydınlatıldı.

* University of Marmara, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 81010, Haydarpaşa- Istanbul, TURKEY.

INTRODUCTION

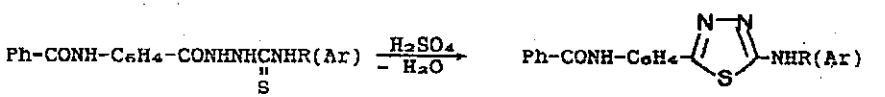
It has been previously reported that treatment of certain azo derivatives with hydrazine hydrate resulted in reductive cleavage of azo function to give the 2- substituted -5-[p-[benzoy (amino) phenyl]-1,3,4-thiadiazoles (1,2,3) which required a multistep synthesis. The fact that a wide variety of pharmacological properties ie hypoglycaemic (4), antitumor (5), antiviral (6) activities have been shown to be associated with substituted 1,3,4 - thiadiazoles has led us to find out convinient methods for the preparation of these and other thiadiazole derivatives. An initial attempt was made to prepare these compounds by the reaction of p - (benzoylamino) benzoyl hydrazine (II) with various isothiocyanates to form the intermediate 1- [p-aminobenzoyl]-4- alkyl / arly thiosemicarabzides. The aim was to react these thiosemicarbazides with sulphuric acid to prepare the desired 5- [p - (benzoy (amino) phenyl] - 2- substitutedamino - 1,3,4- thiadiazoles. However, this method yielded multiple reaction products as it probably proceeded from the free primary aromatic amino moiety in the molecule. Therefore, the protection of free amino group of II was planned by introducing the benzoyl moiety into the structure. The thought was that the benzoyl group would undergo the hydrolysis to form the free amino moiety in the molecule during the reaction or following the treatment with concentrated sulphuric acid or sodium hydroxyde solutions. This would allow us to further process with these products of free amine group by active carbonyl compounds to design pharmacologically active products. The p- (benzoylamino) benzoyl hydrazine (II) was prepared by the addition of p-(benzoylamino) benzoate to hydrazine hydrate and reacted with certain alkyl / arly isothiocyanates to give the corresponding 1- aroyl-4- alkyl / aryl thiosemicarbazides previously perapered (7).

MATERIALS AND METHODS

Materials and instruments : Hydrazine hydrate were obtained from Sigma. All other parent compounds and solvents were purchased from Merck Chemical Company. Melting points (capillary tubes) are uncorrected. IR spectra were taken on a Shimadzu - 435 spectrophotometer as KBr pellets. UV spectra were taken on a Shimadzu- 260 spectrophotometer. The samples were prepared as 10^{-3} molar solutions in ethanol. Mass spectra were determined by direct insertion of samples in methanol on a VG12F mass spectrometer with a 70 ev ionisation po-

tential, source temparature 200 - 240° . C, H, N analyses were carried out on a model 240XY Control and 1106 Carlo Erba equipments, Tubitak - Mae Instrumental Analysis Lab, Gebze, Turkey.

METHODS



IIIa-h IVa-h

R (Ar) a: $-CH_3$, b : $-C_2H_5$, c : $-CH_2-CH=CH_2$, d : $-C_6H_{11}$,
e: $-CH_2-CH_2-C_6H_5$, f: $-C_6H_5$, g: $-C_6H_4Br$ (p), h: $-C_6H_4Cl$ (p)

Figure 1

Ethyl -p-(benzoylaminobenzoat) [I]. To a solution of benzocain (0.025 mol) in diethylether (15 ml) was added dropwise benzoylchloride. The crude product was washed with cold water, dried and recrystaallized from ethanol [mp. 136°, yield 85 %] (8).

p-(benzoylamino) benzoylhydrazine [II] . Compound [I] (0.025 mol) and hydrazine hydrate (10 mL) were heated at 130°. The precipitate formed was washed with water, filtered and dried [mp. 231 - 233°, from ethanol. Yield : 77.8%] (9).

1- Aroyl-4- alkyl / aryl thiosemicarbazide [III]. To a solution of compound [II] (0.005 mol) in ethanol (60 mL) was added isothiocyanide (0.005 mol). The reaction mixture was refluxed for 2 hours. The precipitate was filtered and recrystallized from ethanol [IIIa - h] (10).

2,5 - disubstituted - 1,3,4- thiadiazoles [IV]. To 0.005 mol [III a-h] was added dropwise concentrated sulphuric acid (3 mL, Merck). The reaction content was decanted into ice - water mixture. The precipitate [IVa- h] was first washed with sodium carbonate solution followed by washing with water. The crude product was dried and then recrystallized from ethanol (11).

RESULTS AND DISCUSSION

The required starting compound, 1 - aroyl - 4- substituted thiosemicarbazides (IIIa - h) were readly prepared in acceptable yield by reaction of isothiocyanates with II. The cyclization of (IIIa - h) in concentrated H_2SO_4 afforded the desired 5-[p- (benzoyamino) phenyl] -2-substituted amino - 1,3,4- thiadiazoles (IVa-h). The reaction time was short, 30 mins and the yield was high. All compounds were characterized by elemental analysis, UV, mass and IR spectroscopy together with their melting point analysis.

The benzoyl group did not undergo any hydrolysis during the reaction of 1- acyl/ aroyl- 4- alkyl / arylthiosemicarbazides with sulpuric acid was confirmed by elemental analysis and spectroscopic clues. Another support for this is that the molecule did not show positive results in the specific reactions for primary aromatic amines. In order to examine the cyclic products in NaOH or sulphuric acid in hot, [IVh] was chosen as a protype and no changes observed by IR spectrum following these hydrolytic reactions.

Mass spectra of compounds [lVa], [lVb] and [lIVe] revealed molecular ion peaks at m/z 310 (mw. 310.88) ; m/z 324 (mw. 324.41) and m/z 400 (mw. 400.5) respectively. In all three compounds, the main fragmentation pattern occured by removal of benzoyl moiety and gave a m / z 105 peak. This was in consistent with mass spectra other benzoylated amine compounds (8). The second fragmentation pattern was the removal of the substituent adjacent to amine function. The melting points, formulae, elemental analysis, yield, and IR spectra of synthesized compounds are given in table 1.

Table 1. 5-[p-(benzoylamino)phenyl]-2-alkyl/arylamino-1,3,4-thiodiazoles

[Compound] (Formula) [R(Ar)]	m.p. °C	Analysis C	H	N	Yield %	IR C=O secondary amide stretching (cm^{-1})
		Calculated (Found)				
[IVa] ($C_{16}H_{14}N_4OS.3H_2O$) [methyl]	247	52.74 (52.51	5.53 4.02	15.38 15.73)	57.4	1650
[IVb] ($C_{17}H_{16}N_4OS.2H_2O$) [ethyl]	243-245	56.65 (56.77	5.58 4.53	15.54 15.40)	45.5	1658
[IVc] $C_{18}H_{16}N_4OS.H_2O$ $.H_2SO_4$ [allyl]	236-240	47.78 (47.29	4.45 4.41	12.38 11.87)	43.3	1638
[IVd] $C_{21}H_{22}N_4OS$ [cyclohegzyl]	238-241	66.64 (66.93	5.86 6.09	14.80 13.85)	77.3	1650
[IVe] $C_{23}H_{20}N_4OS.H_2O$ [phenethyl]	190-192	65.96 (65.88	5.26 5.29	13.38 13.36)	72.3	1645
[IVf] $C_{21}H_{16}N_4OS$ [phenyl]	303-305	67.72 (66.88	4.33 4.24	15.04 14.73)	86.8	1650
[IVg] $C_{21}H_{15}BrN_4OS$ [p-bromophenyl]	303	55.88 (56.30	3.35 3.33	12.41 12.32)	86.9	1670
[IVh] $C_{21}H_{15}ClN_4OS$ [p-chlorophenyl]	307	61.99 (61.27	3.72 3.72	13.77 13.31)	39.3	1650

The formation of 2,5 - disubstituted - 1,3,4- thiadiazoles from 1-acyl/ aroyl -4- alkyl/ arylthiosemicarbazides in acid medium can be described as follows : A carbonium ion is first formed by a proton from thiosemicarbazides. This proton may come from either C = O or C = S function (13). As the sulphur atom is less electronegative than oxygene, it attacks to the carbonium ion to form a C -S bond. This result in the formation of thiadiazole ring by a number of prototropicshifts followed by elimination of one molecule of water. There are three UV absorption maxima maxima of compounds [IVa - h] ie at 203 - 204nm (aromatic E bond); 266 - 276 nm; 326 - 372 nm and a shoulder at 220 - 228 nm. The nonsubstituted 1,3,4- thiadiazoles and 2- amino -5- phenylthiodiazoles showed absorption maxima at 220 nm (14) and 252.5 nm (15) respectively. Similar compounds to the present molecules, 2- substituted

amino -5- (p - aminophanyl) -1,3,4- thiadiazoles have two maximum absorptions at 240 - 258nm and 325 - 376nm (1,3,11) respectively.

Synthetic studies on acetylated derivatives of this class of compounds by the present method using p- (acetylamino) benzoyl hydrazine as a starting product are in progress in our laboratory in order to obtain the compounds with the free primary aromatic amine group in the molecule following an hydrolytic reaction. This would help us to react the amino moiety with active carbonyl groups to be able to design pharmacologically active sythetic products.

REFERENCES

1. Rollas, S. : *J. Pharm. Univ. Mar.*, **1**, 59 (1985).
2. Rollas, S. ,Topaloglu, Y. : *J. Pharm. Univ. Mar.*, **2**, 1 (1986).
3. Özger, Y. Rollas, S. , : M. U. *J. Sci. and Tech.* , **5**, 133 (1988).
4. Hokfelt, B., Jonsson, A. : *J. Med. Pharm. Chem.*, **5**, 247 (1962).
5. Miyamoto, K., Koshiure, R., Mori, M, Yokoi, H, Mori, C., Hasegawa, T, takatori, K. : Chem. Pharm. Bull. **33**, 5126 (1985).
6. Tonew, M., Klimki, E. : *Chemotherapy*, **20**, 350 (1984).
7. Kalyoncuoğlu, N., Rollas, S., Sur - Altiner, D., Yeğenoğlu, Y., Ang, O. : *Pharmazie*, **47**, 796 (1992).
8. Coniglio, L. : *Rend. Acad. Sci.*, **36**, 56 (1930).
9. Kalyoncuoğlu, N. : *M. Sc. thesis* . University of Marmara, division of Health Sciences (1991).
10. Cesur, Z., Ergenç, N., Ilhan, E. : *Acta. Pharm.Turcica.*, **31**, 103 (1989).
11. Rollas, S. : *J. Fac. Pharm. Ist*, **18**, 3 (1982).
12. Ulgen, M. *PhD thesis*, University of London, 1992
13. Young, R. W., Wood, K. H. : *J. Am. Chem. Soc.* , **77**, 400 (1955).
14. Goerdeler, J. , Ohm, J., Tegtmeyer, O. : *Ber.*, **89**, 1534 (1956).
15. Hirayama, K. : *Handbook of Ultraviolet and visible absorption spectra of organic compounds*, 504 (1967).

(Received May 5, 1993)