J. Fac. Pharm. Istanbul
38(1) (2005-2006)

SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW (THIOCARBAMOYLTHIO)-ACYLAMINO-1,3-THIAZOLE DERIVATIVES

Z. CESUR, N. CESUR

SUMMARY

In this study a series of novel 2-[(N,N-disubstituted thiocarbamoylthio) acylamino]-1,3-thiazole derivatives were synthesized by the reaction of potassium salts of N,N-disubstituted dithiocarbamoic acids with 2-chloro-2-phenyl-N-(1,3-thiazol-2-yl)acetamide. Structures of the compounds were confirmed by the spectral data [IR, ^{1}H-NMR and CIMS(CH_4)] and elemental analyses. The compounds were screened for agricultural insecticide and fungicide activities.

ÖZET

Bu çalışmada N,N-disübstitüe ditiyokarbamoik asid potasyum tuzlarının 2-kloro-2-fenil-N-(1,3-tiyazol-2-il)asetamid ile reaksiyonundan 2-[(N,N-disübstitüe tiyokarbamoiltiyo)açilamino]-1,3-tiyazol türevi yeni maddeler sentez edilmiştir. Maddelerin yapıları spektral veriler [IR, ^{1}H-NMR, CIMS(CH_4)] ve elementel analizler ile kanıtlanmıştır. Maddelerin tarımsal insektisid ve fungusid aktiviteleri araştırılmıştır.

Key words: 2-Amino-1,3-thiazole, carbamodithioic acid esters, agricultural insecticide activity, agricultural fungicide activity.

INTRODUCTION

N-Substituted and N,N-disubstituted carbamodithioic acid esters are known to possess antimicrobial activity (1-6), together with other biological properties (7-10). Previous publications from our laboratory have dealt with the synthesis of a series of 4-[(N,N-disubstituted thiocarbamoylthio)acyl]antipyrines, 4-[(N,N-disubstituted thiocarbamoylthio)acetamido]antipyrines and 5-aryl-2-[(N,N-disubstituted thiocarbamoyl thio)acylamino]-1,3,4-oxadiazoles, some of which exhibit significant antifungal activity (11-13). In view of these observations we synthesized some 2-[(N,N-disubstituted

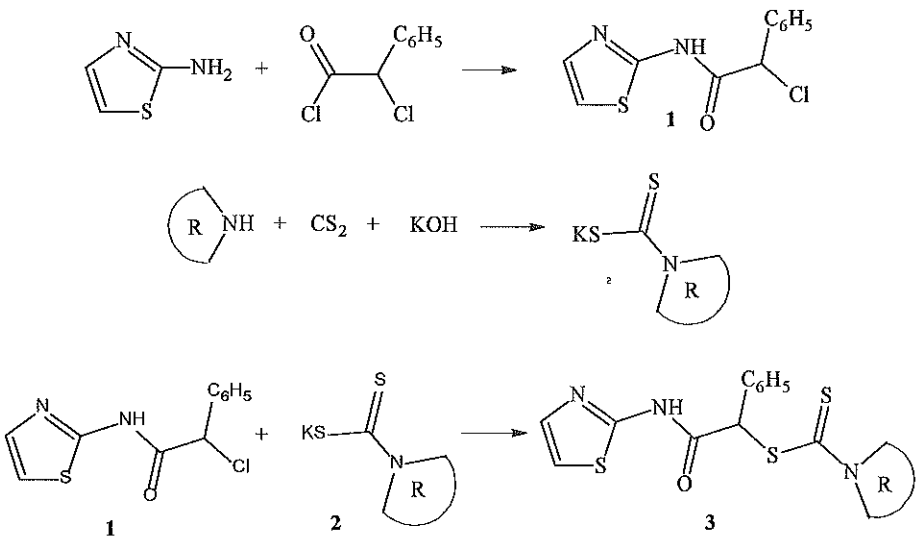
Istanbul University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry
34116 Istanbul, Turkey

J. Fac. Pharm. Istanbul
38(1) (2005-2006)

thiocarbamoylthio)acylamino]-1,3-thiazoles and tested them for agricultural fungicide and insecticide activities.

RESULTS AND DISCUSSION

The reaction of 2-chloro-2-phenyl-N-(1,3-thiazol-2-yl)acetamide **1** (14) with potassium salts of dithiocarbamic acids **2a-g** (15,16), was performed in ethanol , affording 2-[(N,N-disubstituted thiocarbamoylthio)acylamino]-1,3-thiazole derivatives **3a-g** (Scheme 1, Table).



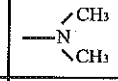
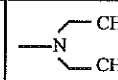
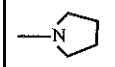
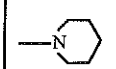
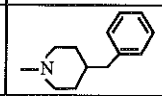
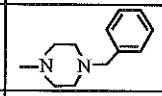
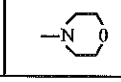
Scheme 1

Analytical and spectral data [elemental analyses, IR, ^{1}H-NMR and CIMS(CH_4)] confirmed the structures of **3a-g**. The IR spectra of **3a-g** showed bands at 3185-3090, 1690-1675 and 1270-1200 cm^{-1} indicating N-H, C=O and C=S stretchings. The ^{1}H-NMR spectral data were also consistent with the assigned structures. The COCH proton and the NH proton appeared at about 6.07-6.13 and 11.19-11.34 ppm, respectively. Aromatic, $(CH_3)_2N$, $(C_2H_5)_2N$, pyrrolidino, piperidino, piperazino and

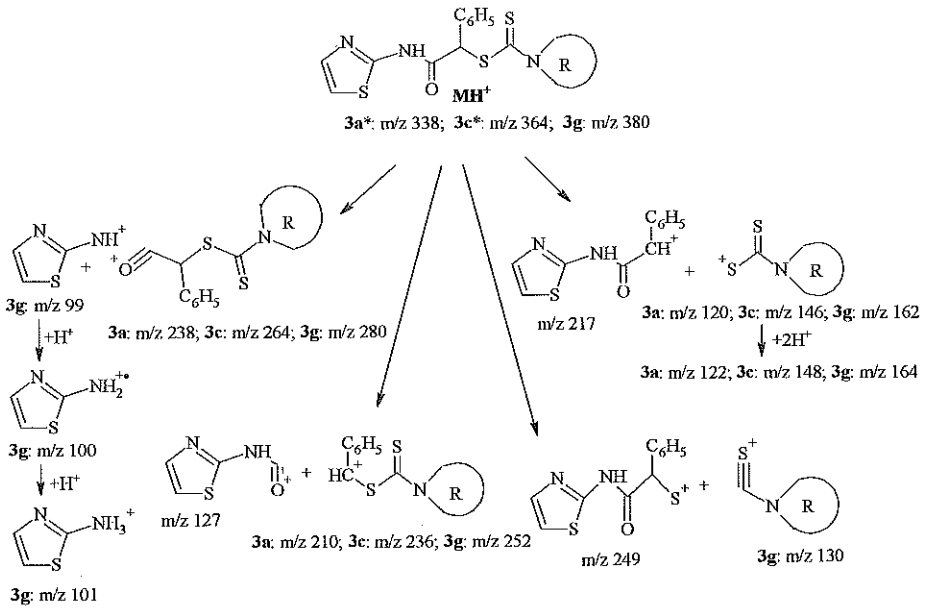
morpholino protons were observed in the expected regions (6,11).

The prototypes **3a, c** and **g** showed quasi-molecular ions (MH^+) which confirmed their molecular weights. Most of the fragments were common with some variations in intensity (Scheme 2). Spectral data of representative derivatives are given in the Experimental. The compounds were subjected to an agricultural insecticide screen (housefly, egyptian cotton leaf worm, spider mite, mosquito life cycle test) and a fungicide screen (wine downy mildew as protectant and antisporulant, wine grey mould, wheat rust, apple mildew and peanut leaf spot), but no significant activity was observed.

Table. Physicochemical data of compounds **3a-g**

Comp.	—N R	Formula (mw)	Mp (°C)	Yield (%)	Analysis (calcd./found)		
					C	H	N
3a		$C_{14}H_{15}N_3OS_3$ (337.49)	196-8	56	49.82 49.80	4.48 4.50	12.45 12.50
3b		$C_{16}H_{19}N_3OS_3$ (365.54)	173	87	52.57 52.60	5.24 5.23	11.50 11.40
3c		$C_{16}H_{17}N_3OS_3$ (363.52)	205-8	95	52.86 52.90	4.71 4.20	11.56 11.70
3d		$C_{17}H_{19}N_3OS_3$ (377.55)	188-90	93	54.08 53.07	5.07 5.35	11.13 11.42
3e		$C_{24}H_{25}N_3OS_3$ (467.67)	191-3	98	61.64 62.26	5.39 5.51	8.98 8.93
3f		$C_{23}H_{24}N_4OS_3$ (468.66)	213-5	96	58.94 59.10	5.16 5.20	11.95 11.90
3g		$C_{16}H_{17}N_3O_2S_3$ (379.52)	194-5	89	50.63 50.80	4.51 4.70	11.07 10.90

J. Fac. Pharm. Istanbul
38(1) (2005-2006)



* Ions lower than m/z 120 were not recorded.

Scheme 2

EXPERIMENTAL

Melting points were measured on a Buchi 530 melting point apparats (Flawil, Switzerland) in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin Elmer Model 1600 FT-IR spectrophotometer. ^{1}H-NMR spectra were obtained in $CDCl_3$ on a Bruker AC 200 (200 MHz) NMR spectrophotometer using TMS as internal standart. CIMS (CH_4) were recorded at the Sittingbourne Research Centre, UK. Elemental analyses were performed on a Perkin-Elmer Model 240 elemental analyzer.

General procedure for the synthesis of 3a-g

2-Chloro-2-phenyl-N-(1,3-thiazol-2-yl)acetamide (0.005 mol) and 0.005 mol of potassium salt of N,N-disubstituted dithiocarbamoic acid in 30 ml of ethanol were refluxed on a water bath for an hour. After cooling the solution was evaporated to dryness under reduced pressure and the products were washed with water and purified by recrystallization from ethanol. Physical data of compounds **3a-g** are reported in Table.

IR, ^{1}H-NMR and CIMS(CH_4) spectral data of **3a** and **3c** chosen as prototypes are as follows:

2-Oxo-1-phenyl-2-(1,3-thiazol-2-ylamino)ethyl dimethyldithiocarbamate ***(3a)***
IR (cm^{-1}) : 3180 (NH), 1690 (C=O), 1250 (C=S). ^{1}H-NMR: δ (ppm): 3.37 (3H, s, N-CH_3), 3.54 (3H, s, N-CH_3), 6.07 (1H, s, COCH), 6.97 (1H, d, J=3.5 Hz, thiazole C_5-H), 7.25-7.48 (5H, m, C_6H_5), 7.57 (1H, d, J= 3.5 Hz, thiazole C_4-H), 11.19 (1H, s, NH). CIMS(CH_4) m/z (rel.int.%): 338 (MH^+,20), 293 (1), 249 (5), 238 (100), 217 (50) , 210 (2) ,127 (20).

2-Oxo-1-phenyl-2-(1,3-thiazol-2-ylamino)ethyl pyrrolidine-1-carbodithioate ***(3c)***.
IR (cm^{-1}): 3140 (NH), 1685 (C=O), 1260 (C=S). ^{1}H-NMR δ (ppm):1.94-2.10 (4H, m, pyrrolidine $C_{3,4}$-H), 3.58-3.95 (4H, m, pyrrolidine $C_{2,5}$-H), 6.14 (1H, s, COCH), 6.97 (1H, d, J= 3.5 Hz, thiazole C_5-H), 7.31-7.48 (5H, m, C_6H_5), 8.99 (1H, d, J= 3.5 Hz, thiazole C_4-H), 11.28 (1H, s, NH). CIMS(CH_4) m/z (rel. int. %): 364 (MH^+, 18), 294 (1), 264 (90), 249 (2) , 236 (2), 217 (55), 148 (100), 146 (10),127 (72).

Acknowledgements: The screening tests and CIMS(CH_4) analyses were performed at Sittingbourne Research Centre, Sittingbourne, England. The authors thank Mr.P.Kirby and Mr.R.Davis for their collaboration.

REFERENCES

1. Alagarsamy,V., Rajasolomon,V., Ramseshu,M., Ramseshu,K.V., *Biol. Pharm. Bull.*,**28**, 1091-1094 (2005).
2. Jang,S. Y., Ha, Y.H., Ko, S.W., Lee,W., Lee, J., Kim, S., Kim, Y.W., Lee, W.K., Ha, H.J., *Bioorg. Med. Chem. Lett.*, **14**, 3881-3883 (2004).
3. Ateş, Ö., Gürsoy, A., Altıntaş, H., Ötük,G., *Arch. Pharm. Med. Chem.*, **336**,39-46 (2003).
4. Gürsoy,A., Ateş,Ö., Karalı,N., Cesur,N., Kiraz,M., *Eur. J. Med. Chem.*, **31**, 643-646 (1996).
5. Demirayak, Ş., Yamaç,M., *Acta Pharm. Turc.*, **35**, 15-19 (1993).
6. Çapan,G., Ergenç, N., Büyüktimkin, S., Yuluğ, N., *Sci.Pharm.*, **61**, 243-250 (1993).
7. Karalı,N., Apak,I., Özkırımlı,S., Gürsoy,A., Doğan Uydeş, S., Eraslan, A., Özdemir,O., *Arch. Pharm. Med. Chem.*, **332**, 422-426 (1999).
8. Marzano,C., Bettio,F., Baccichetti,F., Trevisan,A., Giovagnini, L., Fregona,D., *Chem. Biol. Interact.*, **148**, 37-48 (2004).
9. Vignaud,A., Cebrian,J., Martelly,I., Caruelle,J.P., Ferry,A., *Exp. Physiol.*, **90**, 487-495 (2005).
10. Cao,S.L., Feng,Y.P., Jiang,Y.Y., Liu,S.Y., Ding,G.Y., Li,R.T., *Bioorg. Med. Chem. Lett.*, **15**, 1915-1917 (2005).
11. Cesur,N., Ateş,Ö., Salman,A., Uzun,M., Kiraz, Kasımoğulları, Ö., Kaya,D., *Acta Pharm. Turc.*, **3**, 74-79 (1994).

J. Fac. Pharm. Istanbul
38(1) (2005-2006)

12. Ateş,Ö., Cesur,N., Güner,H., Uzun,M., Kiraz,M., Kaya,D., *Farmaco.*, **50**, 361-364 (1995).
13. Ateş,Ö., Kocabalkanlı, A., Cesur, N., Ötük,G., *Farmaco.*,**53**,541-544 (1998).
14. Cesur,Z., *Pharmazie,* **42**,716-717 (1987).
15. Clifford, A.M., Lichtry, J.G., *J.Am.Chem.Soc.*, **54**, 1163-1166 (1932).
16. Olin, J.F., Deger, T.E., US patent 2 492 314 (1949);CA, **44**, 3014p (1950).

Accepted: 27 October 2005