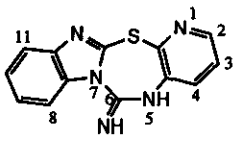
A SYNTHESIS OF 1,3,5-THIADIAZEPINE SKELETON DERIVATIVES : BENZIMIDAZO[2,1-*b*][1,3,5]PYRIDO-THIADIAZEPINE AND BENZIMIDAZO[2,1-*b*][1,3,5]-BENZOTHIADIAZEPINE DERIVATIVES

Byung-Woo Jin and Sung-Hye Cho*

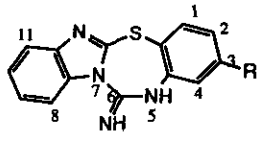
Department of Chemistry, College of Sciences, Chung-Ang University, Tong-Jak Gu, Seoul 156-756, Korea

Abstract - Pyrido and benzothiadiazepine derivatives have been successfully synthesized in good yields by the reaction of *N*-substituted thiourea **(6)** and *N*-substituted S-methylisothiourea **(7)** derivatives in the presence of DCC or potassium carbonate.

A number of *N*-substituted benzimidazoles[1] have been intensively studied for their antiparasitic, fungicidal and herbicidal properties and the various 2-substituted sulfinylbenzimidazole derivatives[2] for their antiulcer activity. During the course of study on the antiulcer agents, we have found that *N*-[2-(1*H*-benzimidazol-2-ylthio)phenyl]thiourea **(6)** or S-methylisothiourea **(7)** derivatives cyclized in the presence of dicyclohexylcarbodiimide (DCC) or anhydrous potassium carbonate to the corresponding 7-membered 1,3,5-thiadiazepine derivatives,[3] 6-imino-5*H*-benzimidazo[2,1-*b*]-[1,3,5]pyridothiadiazepine **(8a)**, 6-imino-5*H*-benzimidazo[2,1-*b*][1,3,5]benzothiadiazepine derivatives **(8b-e)**, unexpectively *via* a nucleophilic intramolecular cyclization as Scheme 1.

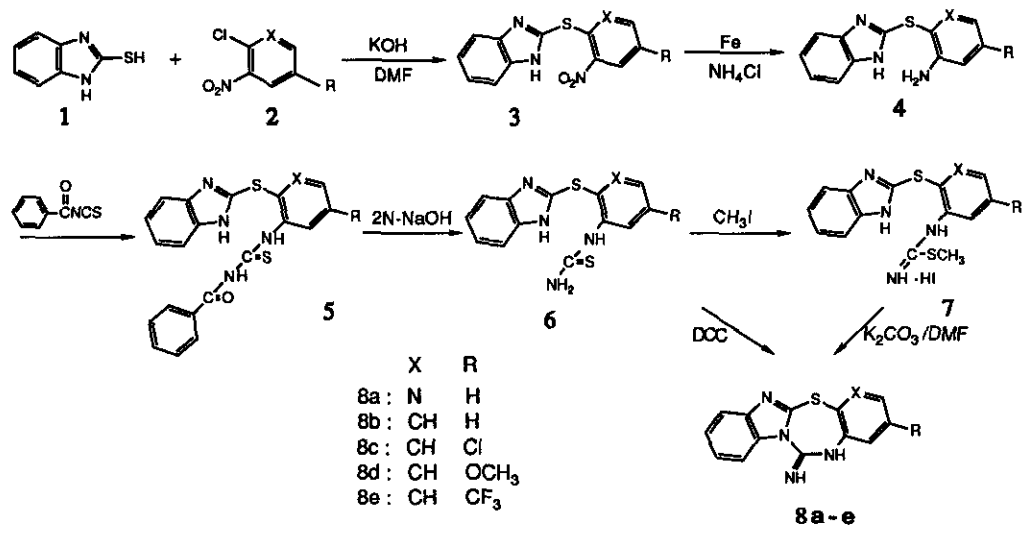


8a



8b-e

2-Mercaptobenzimidazole **(1)** reacted with 2-chloro-3-nitropyridine or 1-chloro-2-nitrobezene in the presence of anhydrous potassium hydroxide in dimethylformamide to give the nitro compounds



Scheme 1

(3) which were easily reduced by iron dust and ammonium chloride in aqueous tetrahydrofuran. *N*-Substituted thiourea derivatives **(6)** were prepared in good yields by the reaction of **4** with 1.3 equimolecular amount of benzoyl isothiocyanate in tetrahydrofuran or dimethoxyethane at room temperature within 1-2 h, and hydrolyzed to **6** by 2N NaOH aqueous solution. The final products **(8)** were synthesized by the two routes, A and B. In route A, the compounds **(6)** were treated with excess iodomethane in methanol to afford S-methylisothiouronium hydroiodide **(7)**.

The S-methylisothiourea derivatives **(7)** are unstable in acidic condition, but quite stable in the neutral or basic conditions. Thus, the cyclodesulfurization of **7** (0.05 M) was successfully performed with anhydrous potassium carbonate (0.27 M) in dimethlyformamide (60 ml) at room temperature for four days (**8b**, 85%) or 60 ℃ for 7 h (**8b**, 80%) in the presence of anhydrous potassium carbonate. It is noticeable that the compounds **(7)** were expected to react with ethylenediamine to give imidazolidine ring,[4] but the cyclization occurred preferably to form **8**, perhaps due to the configuration of **7** where the nitrogen of benzimidazole is close enough to the carbon attached to the S-methylisothiourea moiety for the cyclization. The cyclization of various *N,N'*-disubstituted thiourea derivatives with mercuric chloride, mercuric oxide[5] or DCC[6] has been described in the synthesis of several heterocyclic compounds. In route B, the thiourea derivatives **(6)** were treated with DCC in tetrahydrofuran or acetonitrile to give **8** in good yields. The results obtained are summarized in Table I.

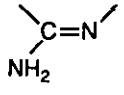
The compounds **(8)** are stable for one week incubation in 1N NaOH or 1N HCl aqueous solution

Table I. **6** or **7** $\xrightarrow[\text{or Route B (DCC)}]{\text{Route A } (K_2CO_3/DMF)}$ **8**

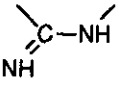
Run	Substrate	Reaction Time(h)	Reaction Temp.(℃)	Route (A,B)	Yield (%)[a]	Spectral Data
1	X=N , R=H	2	50	B	65	9a
2	X=N , R=H	7	70	A	70	
3	X=CH , R=H	3	70	B	80	9b
4	X=CH , R=H	96	25	A	85	
5	X=CH , R=H	7	60	A	80	
6	X=CH , R=Cl	96	25	A	80	9c
7	X=CH , R=OCH_3	96	25	A	80	9d
8	X=CH , R=CF_3	96	25	A	85	9e

[a]Isolated yield

and can be converted to mono- or dihydrochloric acid salts which are identified by potentiometric titration method (Ag^+ titration). The tautomeric isomers of 2-aminopyrimidine[7] have been known to exist in both amino **(I)** and imino form **(II)** through ^1H nmr study, in which the imino form **(II)** shows two distinguishable peaks for the NH protons unlike the amino form **(I)** showing one broad single peak. In the case of **8**, both forms of tautomeric isomers can be also exist. However, ^1H nmr (200, 300 MHz, DMSO-d_6) spectra show two different peaks at about 13 and 9.7 ppm which may be attributed to the NH protons in the imino form **(II)**. It was well discussed that the tautomeric isomers, amino **(I)** and imino form **(II)**, of 1-aryl-*S*-alkylisothiourea derivatives[8] can be distinguished by ir spectra. Each imino form **(II)** of **8b-e** shows a strong, sharp ν=NH stretching band at about 3300 cm^{-1} and a broad ν NH band having its center between 3247 cm^{-1} and 3047 cm^{-1} in ir spectra (KBr). In the case of **8a**, only one broad, strong band having its center at 3192 cm^{-1} is observed. Thus, the compounds **(8)** may exist predominantly as an imino form **(II)** either in a solid state or in DMSO solution. The compounds **(8)** show considerable antitumor activity in vitro.



I



II

ACKNOWLEDGEMENTS

We thank Chong Kun Dang Corp. for the generous grant to support this study and prof. Yong-Hae Kim for his helpful discussion.

REFERENCES

1. J. Bourdais and A. Mohsen M. E. Omar, *J. Heterocycl. Chem.*, 1980, **17**, 555.
2. S. P. Clissold and D. M. Campli-Richards, *Drugs*, 1986, **32**, 15.
3. L. D. Vecchia, J. Dellureficio, B. Kisis, and I. Valttas, *J. Heterocycl. Chem.*, 1983, **20**, 1287.
4. B. Rouot, G. Leclerc, and C. G. Wermuth, *J. Med. Chem.*, 1976, **19**, 1049.
5. A. Mohsen M. E. Omar, M. Ragab, A. M. Farghaly, and A. M. Barghash, *Pharmazie*, 1976, **31**, 348.
6. A. Mohsen M. E. Omar and F. A. Ashour, *J. Heterocycl. Chem.*, 1979, **16**, 1435.
7. W. W. Zobach and R. S. Tipson, 'Synthetic Procedures in Nucleic Acid Chemistry', Vol. 2, John Wiley & Sons, Inc., New York, 1973, pp. 301-306.
8. G. Tóth and L. Toldy, *Acta Chim. (Budapest)*, 1974, **80**, 349.
9. **(a)** mp 197-199 ℃; ^{1}H nmr (DMSO-d_6, δ, ppm) 12.80 (br, 1H, NH), 10.10 (br, 1H, NH), 8.77 (d, 1H, J=12.4 Hz, C_4H), 8.27-7.20 (m, 6H, PhH); ir (KBr) 3192 cm^{-1}; ms (70 eV, m/z) 267 (M^+); Anal. Calcd/Found for $C_{13}H_9N_5S$, C: 58.41/58.20, H: 3.39/3.40, N: 26.20/25.80 **(b)** mp 161-163 ℃; ^{1}H nmr (DMSO-d_6, δ, ppm) 13.10 (br, 1H, NH), 9.68 (br, 1H, NH), 8.35 (d, 1H, J=7.0 Hz, C_4H), 7.68-7.20 (m, 7H, PhH); ir (KBr) 3292 (=NH), 3047 (NH) cm^{-1}; ms (70 eV, m/z) 266 (M^+); Anal. Calcd/Found for $C_{14}H_{10}N_4S$, C: 63.14/62.99, H: 3.78/3.40, N: 21.03/20.63 **(c)** mp 217-218 ℃; ^{1}H nmr (DMSO-d_6, δ, ppm); 13.18 (br, 1H, NH), 10.02 (br, 1H, NH), 8.69 (s, 1H, C_4H), 7.82-7.33 (m, 6H, PhH); ir (KBr) 3275 (=NH), 3125 (NH) cm^{-1}; ms (70 eV, m/z) 300 (M^+); Anal. Calcd/Found for $C_{14}H_9N_4ClS$, C: 55.91/55.90, H: 3.02/3.00, N: 18.63/18.50 **(d)** mp 183-184 ℃; ^{1}H nmr (DMSO-d_6, δ, ppm) 13.09 (br, 1H, NH), 9.69 (br, 1H, NH), 8.14 (s, 1H, C_4H), 7.68-6.80 (m, 6H, PhH), 3.78 (s, 3H, OCH_3); ir (KBr); 3306 (=NH), 3247 (NH) cm^{-1}; ms (70 eV, m/z) 296 (M^+); Anal. Calcd/Found for $C_{15}H_{12}N_4OS$, C: 60.80/61.10, H: 4.08/4.15, N: 18,91/18.91 **(e)** mp 205-206 ℃; ^{1}H nmr (DMSO-d_6, δ, ppm) 13.10 (br, 1H, NH), 9.98 (br, 1H, NH), 8.86 (s, 1H, C_4H), 7.86-7.22 (m, 6H, PhH); ir (KBr) 3287 (=NH), 3105 (NH) cm^{-1}; ms (70 eV, m/z) 334 (M^+); Anal. Calcd/Found for $C_{15}H_9N_4F_3S$, C: 53.89/54.11, H: 2.71/2.76, N: 16.76/16.54.

Received, 10th January, 1994