

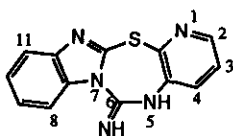
A SYNTHESIS OF 1,3,5-THIADIAZEPINE SKELETON DERIVATIVES : BENZIMIDAZO[2,1-*b*][1,3,5]PYRIDO-THIADIAZEPINE AND BENZIMIDAZO[2,1-*b*][1,3,5]-BENZOTHIADIAZEPINE DERIVATIVES

Byung-Woo Jin and Sung-Hye Cho*

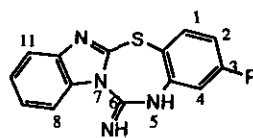
Department of Chemistry, College of Sciences, Chung-Ang University,
Tong-Jak Gu, Seoul 156-756, Korea

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 benzimidazoles¹ have been intensively studied for their antiparasitic, fungicidal and herbicidal properties and the various 2-substituted sulfinylbenzimidazole derivatives² 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), unexpectedly *via* a nucleophilic intramolecular cyclization as Scheme 1.

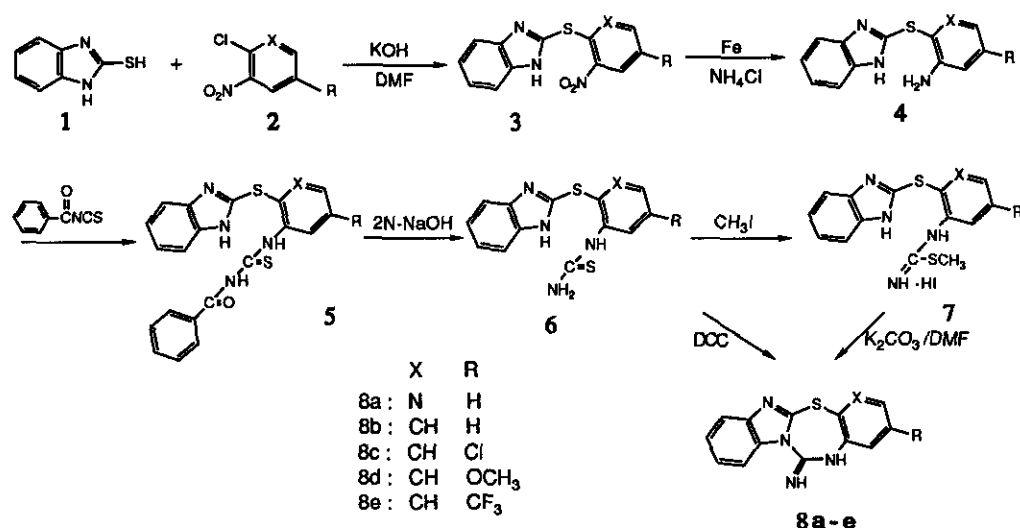


8a



8b-e

2-Mercaptobenzimidazole (1) reacted with 2-chloro-3-nitropyridine or 1-chloro-2-nitrobenzene 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*-methylisothiuronium hydroiodide (7).

The *S*-methylisothiurea 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 dimethylformamide (60 ml) at room temperature for four days (8b, 85%) or 60 °C 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*-methylisothiurea moiety for the cyclization. The cyclization of various *N,N'*-disubstituted thiourea derivatives with mercuric chloride, mercuric oxide⁵ or DCC⁶ 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.

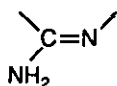
The compounds (8) are stable for one week incubation in 1N NaOH or 1N HCl aqueous solution

Table I. 6 or 7 $\xrightarrow[\text{or Route B (DCC)}]{\text{Route A (K}_2\text{CO}_3\text{/DMF)}}$ 8

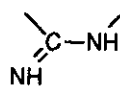
Run	Substrate	Reaction Time(h)	Reaction Temp.(°C)	Route (A,B)	Yield (%) ^a	Spectral Data
1	X=N , R=H	2	50	B	65	9a
2	X=N , R=H	7	70	A	70	
3	X=CH , R=H	3	70	B	80	9b
4	X=CH , R=H	96	25	A	85	
5	X=CH , R=H	7	60	A	80	
6	X=CH , R=Cl	96	25	A	80	9c
7	X=CH , R=OCH ₃	96	25	A	80	9d
8	X=CH , R=CF ₃	96	25	A	85	9e

^aIsolated 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-aminopyrimidine⁷ 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-d₆) 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-alkylisothiurea derivatives⁸ 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.

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9. (a) mp 197-199 °C; ^1H nmr (DMSO- d_6 , δ , ppm) 12.80 (br, 1H, NH), 10.10 (br, 1H, NH), 8.77 (d, 1H, $J=12.4$ Hz, C₄H), 8.27-7.20 (m, 6H, PhH); ir (KBr) 3192 cm^{-1} ; ms (70 eV, m/z) 267 (M^+); Anal. Calcd/Found for C₁₃H₉N₅S, C: 58.41/58.20, H: 3.39/3.40, N: 26.20/25.80 (b) mp 161-163 °C; ^1H nmr (DMSO- d_6 , δ , ppm) 13.10 (br, 1H, NH), 9.68 (br, 1H, NH), 8.35 (d, 1H, $J=7.0$ Hz, C₄H), 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 C₁₄H₁₀N₄S, C: 63.14/62.99, H: 3.78/3.40, N: 21.03/20.63 (c) mp 217-218 °C; ^1H nmr (DMSO- d_6 , δ , ppm); 13.18 (br, 1H, NH), 10.02 (br, 1H, NH), 8.69 (s, 1H, C₄H), 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 C₁₄H₉N₄ClS, C: 55.91/55.90, H: 3.02/3.00, N: 18.63/18.50 (d) mp 183-184 °C; ^1H nmr (DMSO- d_6 , δ , ppm) 13.09 (br, 1H, NH), 9.69 (br, 1H, NH), 8.14 (s, 1H, C₄H), 7.68-6.80 (m, 6H, PhH), 3.78 (s, 3H, OCH₃); ir (KBr); 3306 (=NH), 3247 (NH) cm^{-1} ; ms (70 eV, m/z) 296 (M^+); Anal. Calcd/Found for C₁₅H₁₂N₄OS, C: 60.80/61.10, H: 4.08/4.15, N: 18.91/18.91 (e) mp 205-206 °C; ^1H nmr (DMSO- d_6 , δ , ppm) 13.10 (br, 1H, NH), 9.98 (br, 1H, NH), 8.86 (s, 1H, C₄H), 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 C₁₅H₉N₄F₃S, C: 53.89/54.11, H: 2.71/2.76, N: 16.76/16.54.

Received, 10th January, 1994