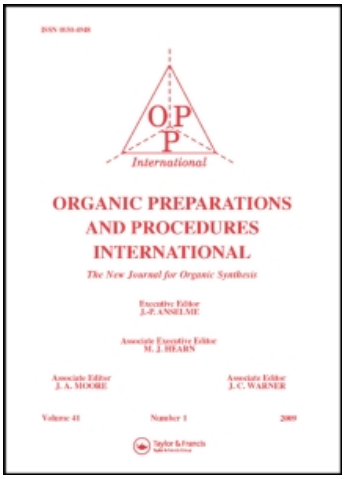

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Nobumasa Kamigata[a]; Satoshi Hashimoto[a]; Michio Kobayashi[a]
[a] Department of Chemistry, Faculty of Science Tokyo Metropolitan University, Tokyo, Japan

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AN IMPROVED METHOD FOR THE PREPARATION OF 2-SUBSTITUTED 1,2-BENZISOTHIAZOL-3(2H)-ONES. NOVEL CYCLIZATION OF N-SUBSTITUTED 2-CARBAMOYLBENZENESULFENYL BROMIDES ON ACTIVATED BASIC ALUMINA

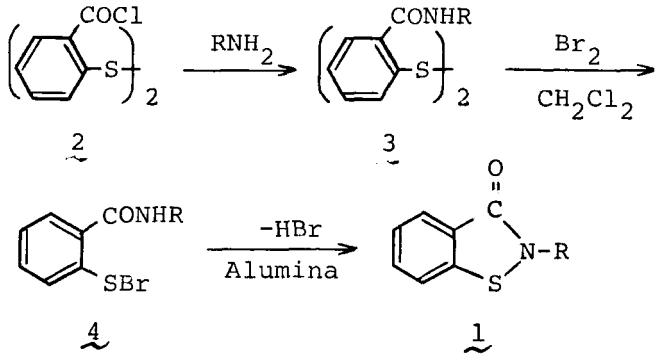
Nobumasa Kamigata*, Satoshi Hashimoto and Michio Kobayashi

Department of Chemistry, Faculty of Science
Tokyo Metropolitan University
Fukazawa, Setagaya, Tokyo 158, JAPAN

In recent years, 2-substituted 1,2-benzisothiazol-3(2H)-ones (1) have received much attention owing to their high antibacterial and antifungal properties. Although there are many reported syntheses,[1-4] they were found to be unpractical because of long synthetic steps, operational difficulties, contamination of the desired products with difficulty separable tarry material, and often low yields. For example, it is difficult to prepare benzisothiazol-3(2H)-ones possessing such base-sensitive functional groups as nitrile or ester by the method of Grivas[2] and fairly long steps are required by method of Uchida and Kozuka.[3]

This communication reports an improved method for synthesis of 1 using activated basic alumina as basic catalyst in the intramolecular cyclization reaction of N-substituted 2-carbamoylbenzenesulfenyl bromide (4). In the method reported by Reissert and Manns,[1] 2,2'-dithiobenzoyl chloride was treated with appropriate amine in carbon tetrachloride at room

temperature to give N,N'-disubstituted 2,2'-dithiodibenzamide (3). Bromination of 3 with molecular bromine gave N-substituted 2-carbamoylbenzenesulfenyl bromide (4). According to the literature above mentioned, 1 is obtained in 80% yield by treatment of 4 with water. However, in spite of repeated experiments, the isolated yield of 1 never exceeded 30% and was accompanied by the formation of resinous substances. Low yield in the formation of 1 by this method may be attributed to the intermolecular reactions of 4 to give polymeric by-products.



Recently, considerable attention has been given to selective organic synthesis carried out over inorganic supports such as silica gel and alumina.[5] If activated basic alumina is used as basic catalyst in the cyclization of 4 to 1, dehydrobromination of 4 will occur on the alumina surface and polymeric product formation is expected to be suppressed. N,N'-disubstituted 2,2'-dithiodibenzamide (3) was brominated in dichloromethane with bromine to give N-substituted 2-carbamoylbenzenesulfenyl bromide (4). To the reaction mixture containing product 4 was added activated basic alumina and the slurried mixture was stirred at room temperature. Removal of

the solvent under reduced pressure gave a pale yellow residue adsorbed on the alumina, which was transferred over an alumina column and eluted using chloroform to give pure cyclized product 1 in nearly quantitative yield. The results are summarized in the Table.

We would like to emphasize that this technique has following advantages: (a) reaction step is short, (b) applicable to compounds possessing functional groups sensitive to hydrolysis, (c) product yield is very high, and (d) the experimental operation is quite simple.

EXPERIMENTAL SECTION

Melting points were determined in open glass capillaries and are uncorrected. NMR spectra were recorded on a Hitachi R-20B instrument, using tetramethylsilane as the internal standard. IR spectra were recorded with a Hitachi 260-10 instrument. Mass spectra were obtained in a Jeol JMS-07 spectrometer.

N,N'-Disubstituted 2,2'-dithiodibenzamides (3). General Procedure.- A solution of dithiodibenzoyl chloride (2.0 g, 5.0 mmol), prepared from dithiodibenzoic acid, in dry dichloromethane (100 ml) was added dropwise at ambient temperature to a well stirred solution of desired amine (29 mmol) in the same solvent (50 ml) over a period of 15 min. The resulting mixture was stirred at room temperature for 3 hrs, then the solvent was evaporated under reduced pressure. The residue was stirred with 1 N hydrochloric acid (100 ml) for 1 hr at room temperature to remove the excess amine. The solid product 3 was collected, washed with water, and dried in a desiccator.

2-Substituted 1,2-benzisothiazol-3(2H)-ones (1). General Procedure.- A solution of bromine (1.4 g, 8.7 mmol) in dichloromethane (10 ml) was added dropwise at ambient temperature to a

TABLE 1. Data on Compounds 3 and 1

R	Yield(%)[a] 2 → 3	Yield(%)[a] 3 → 1	mp. or bp./torr(°C) of 1 found	mp. or bp./torr(°C) of 1 reported
a. p-$MeOC_6H_4$	100	96	147.5-149[b]	147-149[2]
b. p-MeC_6H_4	100	96	136-137.5[b]	135.5-136.5[3]
c. C_6H_5	100	91	141.5-142.5[b]	143-144[1]
d. p-ClC_6H_4	98	87	128.5-129[b]	129-130[2]
e. p-CNC_6H_4	100	95	184.5-185.5[c]	d
f. $C_6H_5CH_2$	100	97	86.5-88[e]	87.5-88.5[3]
g. c-C_6H_{11}	96	85	86-88[f]	87-88[3]
h. t-C_4H_9	95	90	54-55.5[f]	57-58[3]
i. C_2H_5	80	84	127-128/2	132/2.5[3]

a. Yield of pure, isolated product. b. From ethanol. c. From chloroform. d. The new compound 1e was identified by the following spectral data: IR(KBr): 2220, 1655, and 1600 cm^{-1}; NMR($CDCl_3$): δ 7.86, 8.08(4H, A_2B_2 q, 9.0 Hz) and 7.4-8.3(4H, m); Mass (20 eV): m/e 252(M^+), 105, 91, 79, 78, and 77. e. From 2-propanol. f. From ether-hexane.

well stirred suspension of desired diamide 3 (5.8 mmol) in dichloromethane (150 ml) over a period of 3-5 min and stirring was continued at room temperature for 15 hrs. Activated basic alumina (Wako Pure Chemical, 300 mesh, 20 g) was added to the reaction mixture and stirring was continued for additional 3 hrs. Removal of the solvent left a pale yellow residue which was transferred over an activated alumina column (300 mesh, 40 g) and eluted with chloroform as an eluent to give pure 1.

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