SYNTHESIS OF 2-ARYL-5,6-DIHYDRO-(1)BENZOTHIEPINO[5,4-*C*]PYRIDAZIN-3(2*H*)-ONE BY A NOVEL DEHYDROGENATION REACTION

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Treatment of 2-(4-methoxyphenyl)-4,4a,5,6-tetrahydro-(1)benzothiepine[5,4-*c*]pyridazin-3(2*H*)-one 7-oxide (**1a**) in methanesulfonic acid (MSA) gave 2-(4-methoxyphenyl)-5,6-dihydro-(1)benzothiepine[5,4-*c*]pyridazin-3(2*H*)-one (**2a**) in 80% yield. Compound **2a** was also obtained by treating **4a**, a deoxidized compound of **1a**, with dimethylsulfoxide (DMSO) in MSA, trifluoroacetic acid or HBr-AcOH. Apparently this novel dehydrogenation reaction was derived from an acid catalyzed intermolecular redox reaction, that is, a concerted elimination of 4-hydrogen, 4a-hydrogen on **1a** or **4a** and sulfinyl oxygen on **1a** or DMSO.

KEYWORDS dehydrogenation reaction; redox reaction; sulfoxide; acid catalyst; (1)benzothiepine[5,4-*c*]pyridazin-3(2*H*)-one; dimethylsulfoxide

Two ways have been reported to prepare 6-arylpyridazin-3(2*H*)-one type compounds by dehydrogenation, i.e., dehydrogenation of the corresponding 6-aryl-4,5-dihydropyridazin-3(2*H*)-ones with either bromine in acetic acid^{1,2)} or sodium *m*-nitrobenzenesulfonate in alkaline solution.^{1b)} However, the former is inapplicable to compounds which contain active substituents to bromination on the aromatic rings and the latter is not suitable for compounds which are unstable in alkaline media. In the course of studies on the synthesis of condensed pyridazine derivatives as novel anxiolytics,²⁾ we obtained information suggesting a novel synthesis pathway which overcomes these limitations.

Chart 1

In this study we attempted to remove the *O*-methyl group of 2-(4-methoxyphenyl)-4,4a,5,6-tetrahydro-(1)benzothiepine[5,4-*c*]pyridazin-3(2*H*)-one 7-oxide (**1a**)³⁾ according to the method reported by Irie et al.⁴⁾ Treating **1a** with methionine in methanesulfonic acid (MSA) gave **2a** and **3**.⁵⁾ Chart 1 shows the chemical structures of the two compounds which were elucidated mainly by spectral analyses. Moreover, **2a** was obtained exclusively in 80% yield by treating **1a** with MSA in the absence of methionine. Therefore, it appeared that the above reaction consisted of two steps, i. e., an acid-catalyzed redox-reaction in the first step and demethylation from methoxy group in the second. In this context, compound **2a** was derived from **1a** via the concerted elimination of the 7-oxygen, 4- and 4a-

hydrogen of **1a** in the first step. Compound **3** was produced at the second stage where methionine plays a role. Furthermore, application of trifluoroacetic acid (TFA) instead of MSA gave **2a** in 73 % yield. Table 1 summarizes the results of these and the following experiments. When a deoxidized compound of **1a** (**4a**)³⁾ was used, compound **4a** was recovered as an unchanged form even after a solution of **4a** in MSA was stirred at 60-65 °C for 24 h. These results prompted us to investigate the possibility of using DMSO as a source of sulfinyl oxygen (Chart 2).

Table I. Synthesis of **2a** or **2b** and the Reaction Conditions

Entry	Substrate	Reaction condition	Product	Yield(%) ^{a)}
1	1a	CH ₃ SO ₃ H, 60-65°C, 0.5 h	2a	80
2	1a	CF ₃ COOH, 60-65°C, 9 h	2a	73
3	4a	CH ₃ SO ₃ H, DMSO, 60-65°C, 16 h	2a	15
4	4a	CF ₃ COOH, DMSO, 60-65°C, 16 h	2a	55
5	4a	30% HBr-AcOH, DMSO, 20°C, 0.5 h	2a	95
6	4a	Br ₂ , AcOH, 40-45°C, 0.5 h	2a	92 ^{b)}
7	1b	CH ₃ SO ₃ H, 60-65°C, 0.2 h	2b	91
8	4b	30% HBr-AcOH, DMSO, 20°C, 0.5 h	2b	86

a) Yield : isolated yield. b) Trace amount of bromine-adduct was detected on mass spectrum.

As shown in Table I, compound **2a** was successfully obtained when DMSO was added to a solution of **4a** in MSA or TFA (entries 3, 4). Moreover, compound **2a** was afforded in good yield by treating **4a** with DMSO in 30 % HBr-AcOH at 20°C for 0.5 h (entry 5). In this reaction, the possibility of forming bromine-adduct⁷⁾ on the aromatic moiety activated with substituents, such as methoxy and thio groups, was apparent, excepting the formation of **2a**. But there was no detectable amount of the adduct in the mass spectrum, only compound **2a** was obtained. This may be attributed to the addition of equimolar DMSO in this reaction.

To prepare 2-(4-chlorophenyl)-5,6-dihydro-9-methoxy-(1)benzothiepine[5,4-*c*]pyridazin-3(2*H*)-one (**2b**)⁷⁾ from **4b**,³⁾ a condition using bromine in acetic acid was applied. However, the product was a mixture of **2b** and a corresponding 10-bromine adduct. These were difficult to separate from each other for purification. Also, dehydrogenation of **4b** with sodium *m*-nitrobenzenesulfonate did not provide **2b**, because of the decomposition of the starting material. On the other hand, the target

compound **2b** was successfully prepared from **1b**³⁾ or **4b** in good yields (Entries 7, 8) under the conditions similar to those in entries 1 or 5.

From these results, it appeared that this dehydrogenation reaction resulted from a concerted elimination of 4- and 4a-hydrogen on 2-aryl-4,4a,5,6-tetrahydro-(1)benzothiepine[5,4-c]pyridazin-3(*H*)-ones and sulfinyl oxygen on **1a**, **1b** or DMSO; that is, an acid catalyzed intermolecular redox reaction occurred. The detailed mechanism of this reaction is now under investigation. Because of the simplicity of the reaction conditions, this novel reaction would be of use as an alternative method in the preparation of 2-aryl-5,6-dihydro-(1)benzothiepine[5,4-c]pyridazin-3(2*H*)-ones. We are now proceeding to apply this method for the preparation of other 6-arylpyridazin-3(2*H*)-one type compounds.

REFERENCES AND NOTES

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- 5) Compound **2a** and **3** were synthesized as follows: To a solution of **1a** (3.0 g, 0.0085 mol) in MSA was added methionine (2.5 g, 0.017 mol) and the mixture was stirred at 60-65 °C for 0.5 h. At this point, the starting compound (**1a**) was undetectable in the reaction mixture, and two spots of new products appeared on TLC. The reaction mixture was poured into ice-water and extracted with CHCl₃. The extract was washed with water, dried over MgSO₄ and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with CHCl₃ to give two fractions. We obtained 1.2 g of **2a** from the first fraction and a 0.6 g of **3** from the second. Physical data of the **2a** and **3**. **2a**: colorless needles mp 134-135 °C. *Anal.* Calcd for C₁₉H₁₆N₂O₂S: C, 67.88; H, 4.80; N, 8.33. Found: C, 67.89; H, 4.97; N, 8.25. IR_ν^{KBr}_{max}cm⁻¹: 1670 (CON). MS_{m/z}: 336 (M⁺). ¹H-NMR (CDCl₃) δ: 2.72 (2H, t, *J*=7Hz, SCH₂CH₂), 3.26 (2H, t, *J*=7Hz, SCH₂CH₂), 3.84 (3H, s, OCH₃), 6.89 (1H, s, C=CHCON), 6.97 (2H, d, *J*=9Hz, ArH), 7.35-7.43 (4H, m, ArH), 7.61 (2H, d, *J*=9Hz, ArH). **3**: colorless powder mp 312 °C (dec.). *Anal.* Calcd for C₁₈H₁₄N₂O₂S: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.12; H, 4.47; N, 8.75. IR_ν^{KBr}_{max}cm⁻¹: 3130 (OH), 1650 (CON). MS_{m/z}: 322 (M⁺). ¹H-NMR (DMSO-*d*₆) δ: 2.63- 2.77 (2H, m), 3.21-3.36 (2H, m), 6.84 (2H, d, *J*=9Hz, ArH), 7.02 (1H, s, C=CHCON), 7.42 (2H, d, *J*=9Hz, ArH), 7.52- 7.68 (4H, m, ArH).
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- 7) Physical data of the **2b**: colorless needles mp 131-132°C. *Anal.* Calcd for C₁₉H₁₅N₂O₂S: C, 61.54; H, 4.08; N, 7.55. Found: C, 61.67; H, 4.26; N, 7.55. IR_ν^{KBr}_{max}cm⁻¹: 1670 (CON). MS_{m/z}: 370 (M⁺). ¹H-NMR (CDCl₃) δ: 2.73 (2H, t, *J*=7Hz, SCH₂CH₂), 3.25 (2H, t, *J*=7Hz, SCH₂CH₂), 3.86 (3H, s, OCH₃), 6.87 (1H, s, C=CHCON), 6.97 (1H, dd, *J*=2, 9Hz, ArH), 7.40 (2H, d, *J*=8Hz, ArH), 7.52 (1H, d, *J*=9Hz, ArH), 7.68 (2H, d, *J*=8Hz, ArH).

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