Intramolecular Capture of Pummerer Reaction Intermediates by an Aromatic Nucleophile: Selective Construction of 1,4-Benzothiazine and Indole Ring Systems

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The simple alkyl sulfoxide 6 carrying two aromatic nucleophiles, when treated with trifluoroacetic anhydride at room temperature (Pummerer reaction conditions), underwent an intramolecular aromatic sulfenylation of the 6-exo-tet process in an exclusive manner to yield two regioisomeric 1,4-benzothiazine derivatives, 8 and 9. On the other hand, a similar reaction of the α-acyl sulfoxide 7, possessing identical aromatic nucleophiles, caused an intramolecular aromatic alkylation of the 5-exo-trig process to produce the 3-oxo-indole derivative 14 in a quantitative yield. These results demonstrate that the construction of 1,4-benzothiazine and indole ring systems can be achieved in a selective manner by proper choice of the sulfoxide side chain.

Key words  Pummerer reaction; sulfoxide; cyclization; sulfenylation; 1,4-benzothiazine; indole

Results and Discussion

The alkyl sulfoxide 6 and the α-acyl sulfoxide 7 were prepared from m-anisidine 1 and piperonal 2 in excellent overall yields, as follows. Condensation of 1 with 2 in titanium...
tetraisopropoxide followed by sodium borohydride reduction of the resulting imine gave the secondary amine 3. This amine was condensed with 2-phenylsulfanylacetyl chloride to afford the amide 4. Treatment of 4 with aluminum hydride selectively reduced the amide carbonyl to give the tertiary amine 5 in good yield. Oxidation of 5 and 4 with sodium metaperiodate in aqueous acetone afforded 6 and 7, respectively.

Treatment of the alkyl sulfoxide 6 with trifluoroacetic anhydride (TFAA) in tetrahydrofuran (THF) at room temperature (r.t.) gave two products, 8 and 9, in yields of 54% and 40%, respectively. The products were readily separated in a pure form by column chromatography over silica gel. They showed the same molecular peak at m/z 505 in their respective mass spectrum, which corresponds to the formula C_{25}H_{22}F_{3}NO_{5}S, containing the trifluoroacetate moiety. This showed that both 8 and 9 are aromatic sulfonylation products. Furthermore, the behaviors in the mass spectra and the chromatography strongly suggested that they are sulfurane derivatives with an O–S covalent bond, not a sulfonium salt.

The structures of these products were established by spectroscopic means. The assignments of NMR spectra (Fig. 1) indicated that 8 and 9 are regioisomeric compounds possessing a 1,4-benzothiazine ring system formed by the sulfonylation path (1) shown in Chart 2.

The correctness of this assignment to these products was confirmed chemically. The treatment of 8 with sodium methoxide in methanol at r.t. produced an aniline derivative 10 carrying SPh group in a quantitative yield. Similar treatment of 9 with sodium methoxide gave another aniline derivative, 11. The NMR spectra clearly indicated that they are regioisomeric to each other. The formation of the aniline derivatives can be rationalized in terms of the fission of the thiazine ring by a base catalyzed E2 elimination reaction, followed by hydrolysis of the immonium salt 13 derived from the enamine 12, as shown in Chart 4. The results confirmed that the Pummerer reaction of 6 induces a sulfonylation path (1) in an exclusive manner.

On the other hand, the α-acyl sulfoxide 7, when similarly treated with TFAA as described above, gave 14 in 99% yield. The structure of this product was established by spectroscopic means. The assignment of the aromatic protons of the 1H-NMR spectra using heteronuclear multiple bond correlation (HMBC), as shown in Fig. 2, indicated that the product has a 2-oxo-indole skeleton rather than the 3-oxo-isouquinoline one.

This assigned structure was also confirmed by chemical transformations to several indole derivatives. Reaction of 14 with NiCl₂–NaBH₄ caused the reductive desulfurization of the PhS group, to give the 2-oxo-2,3-dihydroindole 15 in 86% yield. Reduction of 14 with aluminum hydride gave the indole 16 as a major product (86%), and 2,3-dihydroindole 17 as a minor one (14%). Oxidation of 14 with NaIO₄ caused concomitant desulfurylation to give the isatin derivative 18.
Assignment of $^1$H-NMR of 8

- $6.76$ (d, $J=9$ Hz)
- $5.61$ (d, $J=2.8$ Hz)
- $5.56$ (d, $J=2$ Hz)
- $6.49$ (d, $J=2.9$ Hz)

Assignment of $^1$H-NMR of 14

- $6.47$ (br d, $J=7$ Hz)
- $6.64$ (d, $J=7$ Hz)
- $5.46$ (br s)
- $6.15$ (d, $J=2$ Hz)

HH COSY of 9

- $6.6$ (H)
- $6.36$ (H)
- $5.67$ (H)
- $5.74$ (H)

NOESY of 9

Fig. 1

HMBC Cl 14

Fig. 2

Chart 4

8 or 9 $\xrightarrow{5\% \text{NaOMe, MeOH, rt, 1 h}}$ 12 $\xrightarrow{H_2O}$ 10: $R^1=H$, $R^2=\text{OMe}$

11: $R^1=\text{OMe}$, $R^2=H$

Chart 5

8

TFHAA in THF-EO

4

11

29%

15
produced by the abstraction of the sulfinylates the formation of the sulfonium ion acidic than that of the simple alkyl sulfoxide 21b the aromatic ring on the cationic carbon of the sulfonium ionimerer reaction. This process involves a nucleophilic attack of the difference in acidity of the proton attached to the sulfinyl the acylated sulfoxide species, formulated by a weak basic anion species such as trifluoroaceton-withdrawing group, is not acidic enough to be ab-
stracted by the generally accepted mechanism of the Pum-
merer reaction of the benzothiazine ring system. On the other hand, the Pummerer reaction of the
sulfur atom of 7-aromatic alkylation reaction, the process of 5-aromatic alkylation reaction, the process of 5-

The results demonstrated that the reaction path depends on the difference in acidity of the proton attached to the sulfinyl α-hydrogen.

21a, instead, the substitution reaction on the sulfur atom of 19a proceeds if the aromatic ring is highly nucleophilic.
The α-proton of the α-acyl sulfoxide 7 is apparently more acidic than that of the simple alkyl sulfoxide 6. This facilitates the formation of the sulfonium ion 21b through the ylide 20b that is formed by the abstraction of the α-proton by an anion species, thus inducing the aromatic alkylation in an exclusive manner.
The results also demonstrated that the reaction path greatly depended on the ring size formed by each cyclization; in the aromatic alkylation reaction, the process of 5-exo-trig was favored over that of 6-exo-trig, and in the aromatic sulfenylation reaction the process of 6-exo-tet was favored over that of 7-exo-tet. This observed preference coincided well with the Baldwin rule.12)

In summary, the interrupted Pummerer reaction of the simple alkyl sulfoxide 6 provided a method for constructing the benzoheterocyclic ring system. On the other hand, the Pummerer reaction of the α-acyl sulfoxide 7, as already reported by Y. Tamura et al. in the reactions of similar α-acyl sulfoxides,13) provided a method for preparing the 2-oxindole ring system.

Experimental

General Procedures  Melting points were taken on a Yanagimoto SP-M1 hot-stage melting point apparatus. Thin layer chromatography (TLC) was performed on Merck precoated Silica gel 60 F254 plates (Merck). Column chromatography was carried out with silica gel (Wakogel C-200). Medium pressure liquid chromatography (MPLC) was performed on a Kusano CIG prepurified column. IR spectra were obtained as KBr disks with a HORIBA FT-710 spectrometer and are given in cm⁻¹. NMR spectra were measured on a JEOL JNM-EX90 (1H-NMR 90 MHz, 13C-NMR 22.5 MHz) or JEOL JNM-AL 300 (1H-NMR 300 MHz, 13C-NMR 75.0 MHz) spectrom-

The formation mechanism of the products is proposed as shown in Chart 6. The process begins in a normal Pummerer reaction with activation of the sulfoxide oxygen. Attack by the neighboring electron-rich aromatic ring on the sulfur of the acylated sulfoxide species, 19a, forms a benzoazine nucleus as the sulfuran trifluorooacetates 8 and 9. On the other hand, the formation of 2-oxo-dihydroindole 14 can be rationalized by the generally accepted mechanism of the Pummerer reaction. This process involves a nucleophilic attack of the aromatic ring on the cationic carbon of the sulfonium ion 21b, which is formed via the sulfur ylide species 20b that is produced by the abstraction of the sulfinyl α-hydrogen.

The results also demonstrated that the reaction path greatly depended on the size of the sulfonium ring. In the small alkyl sulfoxide 6, the process of the conversion of 19a to the corresponding ylide 20a may be retarded, since the α-proton, because of the absence of an electron-withdrawing group, is not acidic enough to be ab-

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(42%). Thus, the Pummerer reaction of 7 induced an alkyla-
tion path (3) in an exclusive manner.

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methoxyaminobenzene (5) A solution of 4 (2.0 g, 4.91 mmol) in dry EtO–OH (1:1) (20 ml) was added to a solution of AlH₃ in dry Et₂O (20 ml), prepared in situ from LiAlH₄ (500 mg) and AlCl₃ (430 mg) under an argon atmosphere. The mixture was stirred at rt. for 30 min. The reaction mixture was diluted with CHCl₃ and passed through a short column of SiO₂. The eluate was concentrated in vacuo and extracted with CHCl₃. The residue was chromato- 
graphed and eluted with ethyl acetate/hexane (1:2) to give N-(3-methoxy- 
diethylamino)phenyl)methyl-5-methoxy-2-(phenylsulfanyl)aminobenzene (11) (34 mg, 94%) as a pale yellow oil. IR: 1589, 1502, 1488. 1H-NMR (300 MHz): 1H, J = 6 Hz, ArCH₂N–), 5.61 (1H, J = 6 Hz, ArH), 5.91 (2H, s, OCH₂O), 6.10 (3H, m, PhH). 13C-NMR (75.0 MHz): 47.5 (t), 56.1 (q), 99.9 (d), 100.9 (t), 101.2 (s), 104.1 (d), 105.7 (d), 108.2 (d), 120.0 (d), 125.0 (d), 125.9 (d), 128.8 (d), 131.8 (d), 133.0 (s), 136.6 (s), 146.6 (s), 147.8 (s), 150.7 (s), 161.6 (s), LR-MS: m/z 365 (M⁺), 135 (base peak). HR-MS m/z (M⁺): C₂₃H₁₉NO₄S: 365.1085. Found: 365.1063.

Reaction of 9 with NaOMe A solution of 9 (50 mg, 0.10 mmol) in 1% 
NaOMe–MeOH (10 ml) was stirred at rt. for 2 h. The reaction mixture was concentrated in vacuo and extracted with CHCl₃. The residue was chromato- 
graphed and eluted with ethyl acetate/hexane (1:2) to give N-(3-methoxy- 
diethylamino)phenyl)methyl-5-methoxy-2-(phenylsulfanyl)aminobenzene (11) (34 mg, 94%) as a pale yellow oil. IR: 1589, 1502, 1488. 1H-NMR (300 MHz): 3.81 (3H, s, MeO), 4.25 (2H, J = 6 Hz, ArCH₂N–), 5.61 (1H, J = 6 Hz, ArH), 5.91 (2H, s, OCH₂O), 6.10 (3H, m, PhH). 13C-NMR (75.0 MHz): 47.5 (t), 56.1 (q), 99.9 (d), 100.9 (t), 101.2 (s), 104.1 (d), 105.7 (d), 108.2 (d), 120.0 (d), 125.0 (d), 125.9 (d), 128.8 (d), 131.8 (d), 133.0 (s), 136.6 (s), 146.6 (s), 147.8 (s), 150.7 (s), 161.6 (s), LR-MS: m/z 365 (M⁺), 135 (base peak). HR-MS m/z (M⁺): C₂₃H₁₉NO₄S: 365.1085. Found: 365.1063.

Pummerer Reaction of 7: TFAA (0.17 ml, 1.21 mmol) was added to a solution of 7 (100 mg, 0.24 mmol) in benzene (20 ml) at r.t. under argon 
atmosphere, and the mixture was stirred for 1 h. After removal of the solvent in vacuo, the residual oil was chromatographed and eluted with ethyl acetate/ 
hexane (1:5) to give 6 (156 mg, 54%) as a pale yellow oil. IR: 1651, 1649, 1605. UV: 281 (6800) 1H-NMR (90 MHz): 3.48 (1H, J = 14 Hz, –NCH₂CH₂S–), 1.24 (3H, m, ArH, PhH), 1.10 (2H, J = 14 Hz, ArCH₂N–), 4.88 (H, J = 14 Hz, ArH, PhH). 13C-NMR (125 MHz): 35.1 (t), 43.6 (t), 55.5 (q), 99.7 (d), 101.3 (t), 106.6 (d), 106.7 (d), 119.8 (s), 127.8 (s), 128.8 (d), 129.0 (s), 130.9 (d), 133.0 (d), 136.0 (d), 147.2 (s), 147.4 (s), 148.0 (s), 166.2 (s). LR-MS m/z: 505 (M⁺), 135 (base peak). HR-MS m/z (M⁺): C₂₃H₁₉NO₄S: 505.1171. Found: 505.1165.

Reduction of 8 with AH₂ A solution of 8 (50 mg, 0.10 mmol) in 5% 
NaOMe–MeOH (10 ml) was stirred at rt. for 1 h. The reaction mixture was 
concentrated in vacuo and extracted with CHCl₃. The residue was chromato- 
graphed and eluted with ethyl acetate/hexane (1:2) to give N-(3-methoxy- 
diethylamino)phenyl)methyl-5-methoxy-2-(phenylsulfanyl)aminobenzene (11) (34 mg, 94%) as a pale yellow oil. IR: 1600, 1508, 1488. 1H-NMR (300 MHz): 3.75 (3H, s, MeO), 4.21 (2H, J = 5 Hz, ArCH₂N–), 3.54 (1H, t, J = 5 Hz, NH), 5.90 (2H, s, OCH₂O), 6.16 (1H, d, J = 3 Hz, C6-H), 6.27 (1H, d, J = 3 Hz, C6-H). 13C-NMR (75.0 MHz): 47.5 (t), 56.1 (q), 99.9 (d), 100.9 (t), 101.2 (s), 104.1 (d), 105.7 (d), 108.2 (d), 120.0 (d), 125.0 (d), 125.9 (d), 128.8 (d), 131.5 (d). LR-MS: m/z 365 (M⁺), 135 (base peak). HR-MS m/z: M⁺: C₂₃H₁₉NO₄S: 365.1085. Found: 365.1063.
ArCH$_3$N$_2$–). 5.91 (2H, s, OCH$_2$O), 6.46 (1H, d, $J$ = 3 Hz, C3-H), 6.58 (1H, d, $J$ = 1 Hz, C2'-H), 6.63 (1H, br d, $J$ = 1 Hz, C6'-H), 6.73 (1H, d, $J$ = 8 Hz, C5'-H), 6.74 (1H, br s, C7-H), 6.78 (1H, dd, $J$ = 2, 9 Hz, C5-H), 6.99 (1H, d, $J$ = 3 Hz, C2-H), 7.50 (1H, d, $J$ = 9 Hz, C4-H).

13C-NMR (75.0 MHz): 49.9 (5), 55.7 (q), 93.5 (d), 101.1 (t), 101.6 (d), 107.4 (d), 108.3 (d), 109.3 (d), 120.2 (d), 121.5 (d), 123.1 (s), 127.1 (d), 131.3 (s), 137.0 (s), 147.1 (s), 148.1 (s), 156.3 (s). HR-MS: m/z = 281 (M$^+$), 135 (base peak). HR-MS m/z (M$^+$): Calcd for C$_{17}$H$_{15}$NO$_3$: 281.1056. Found: 281.1056.

6-Methoxy-1-(3,4-methylenedioxyphenyl)methyl-2,3-dihydropyridone (17): IR: 1620, 1498. UV: 252 (9200), 290 (7200). 1H-NMR (300 MHz): 2.89 (2H, t, $J$ = 8 Hz, C2-H), 3.30 (2H, t, $J$ = 8 Hz, C2'-H), 3.75 (3H, s, MeO), 4.13 (2H, s, ArCH$_2$N$-$), 5.94 (2H, s, OCH$_2$O), 6.10 (1H, d, $J$ = 2 Hz, C7-H), 6.18 (1H, dd, $J$ = 2, 8 Hz, C5-H), 6.7–6.9 (3H, m, ArH). 6.96 (1H, d, $J$ = 8 Hz, C4-H). 13C-NMR (75.0 MHz): 27.7 (t), 53.1 (t), 53.9 (t), 55.4 (q), 94.8 (d), 100.9 (t), 101.4 (d), 108.1 (d), 108.4 (d), 120.9 (d), 122.4 (s), 124.4 (d), 132.2 (d), 146.7 (s), 147.8 (s), 153.7 (s), 160.1 (s). LR-MS: m/z = 283 (M$^+$), 135 (base peak). HR-MS m/z (M$^+$): Calcd for C$_{17}$H$_{13}$NO$_5$: 311.0794. Found: 311.0809.

**Oxidation of 14 with NaIO$_4$** To a solution of 14 (0.1 g, 0.25 mmol) in acetone (10 ml) was added a solution of NaIO$_4$ (53 mg, 0.25 mmol) in H$_2$O (5 ml), and the mixture was stirred at r.t. for 18 h. After removal of the precipitated inorganic materials by filtration, the filtrate was concentrated in vacuo. The residue was extracted with CHCl$_3$. The product was chromatographed and eluted with ethyl acetate/hexane (1:4) to give 6-methoxy-

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**References and Notes**
