Regioselective Synthesis of Benzazetines and Indoles from Alkenylanilides and Dimethyl(methylthio)sulfonium Trifluoromethanesulfonate

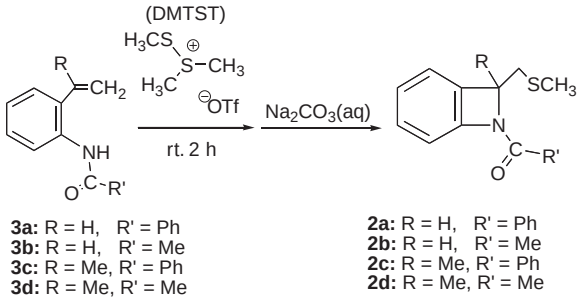
Kentaro Okuma,* Itsuki Takeshita, Takumi Yasuda, and Kosei Shioji
Department of Chemistry, Faculty of Science, Fukuoka University, Jonan-ku, Fukuoka 814-0180

(Received July 10, 2006; CL-060775; E-mail: kokuma@fukuoka-u.ac.jp)

Regioselective synthesis of benzazetines and indoles from *o*-alkenylanilides was achieved. The reaction of *o*-vinylbenzanilide with dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) gave the corresponding benzazetine in 92% yield, whereas the reaction of *o*-vinyl-*N*-*p*-toluenesulfonylanilide gave *N*-tosylindoline in 77% yield. 3-Methy-*N*-*p*-tosylindole was directly synthesized by the reaction of *o*-isopropenyl-*N*-*p*-tosylanilide with dimethyl disulfide and methyl triflate in 85% yield.

The formation of indoles (**1**) is current interest because of their synthetic and pharmacological utility. The recent methods include the intramolecular cyclization of amino-substituted Fischer chromium carbenes,[1] reaction of NBS with vinylic anilides,[2] and palladium-catalyzed intramolecular arylacylation of aryl iodide.[3] In contrast with the indole synthesis, there are relatively few reports on the synthesis of benzazetines (**2**).[4] Only the practical synthesis of **2** involves iodoamination of vinylic anilides.[5] Dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) was found to be a good reagent for the synthesis of glycosides.[6–10] Previously, we have synthesized vinylphosphonium salts by the reaction of alkenes with DMTST and triphenylphosphine.[11] However, there is no report on the synthesis of **1** or **2** by intramolecular thioamination by using DMTST. These results prompted us to investigate the synthesis of benzazetines and indoles by activating alkenes. In this communication, we would like to report a regioselective formation of indoles and benzazetines by using DMTST and *o*-alkenylanilides.

Acylated and sulfonylated *o*-vinyl- (**3a** and **3b**) and *o*-alkenylanilides (**3c**–**3i**) were synthesized by the reported procedure.[12,13] Treatment of *o*-vinylbenzanilide (**3a**) with DMTST at room temperature followed by the addition of aqueous sodium carbonate resulted in the formation of 1-benzoyl-2-methylthiomethylbenzazetine (**2a**) in 92% yield (Scheme 1). The structure of **2a** was confirmed by its spectroscopic analysis. The interesting feature of its NMR spectrum is methylene double doublet signals, which resonated at 2.85 and 3.05 ppm.[14] Another possible structure, *N*-benzoyl-3-methylthioindoline, was discarded by comparison with *N*-acetyl-3-methylindoline's *N*-methylene signals, which resonated at 3.58 and 4.21 ppm.[15] Additionally, methine carbon signal of **2a** was resonated at 75.7 ppm, which was quite different from the reported value (51.6 ppm) of methine signal of *N*-acetyl-3-(2-hydroxypropan-2-yl)indoline.[16] The result was shown in Table 1.



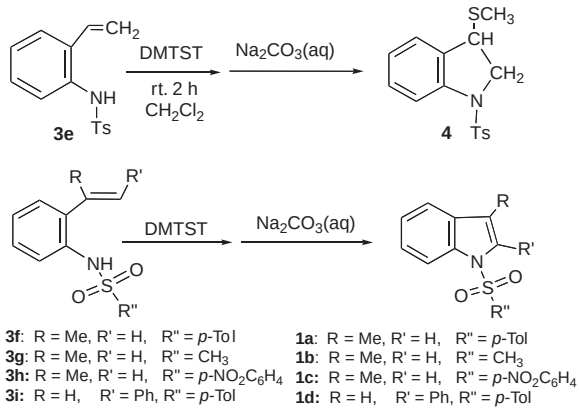
Scheme 1.

Table 1. Reaction of alkenylanilide **3a**–**3d** with DMTST

3	Solvent	Time/h	Products (%)
3a	CH_2Cl_2	2	**2a**: 92
3a	CH_3CN	12	**2a**: 91
3b	CH_3CN	2	**2b**: 90
3c	CH_2Cl_2	2	**2c**: 90
3d	CH_3CN	3	**2d**: 93

When *o*-vinyl-*N*-*p*-tosylanilide (**3e**) was chosen as a substrate, 3-methylthio-*N*-tosylindoline (**4**) was obtained in 77% yield. The structure was confirmed by its NMR spectrum.[14] A typical AB_2 pattern (4.2, 3.9, and 4.2 ppm) was observed at *N*-methylene and methine region of its proton NMR spectrum, which was similar to that of *N*-acetyl-3-methylindoline (3.52, 3.58, and 4.21 ppm).[15] Additionally, when *o*-isopropenyl-*N*-*p*-tosylanilide (**3f**) was chosen as a substrate, 3-methyl-*N*-tosylindole (**1a**) was directly formed in 95% yield. Other substituted alkenyl-*N*-*p*-tosylamides (**3f**–**3i**) also reacted with DMTST at room temperature to afford the corresponding *N*-tosylindoles (**1b**–**1d**) in good yields (Scheme 2). The result was summarized in Table 2. Thus, regioselective thioamination was achieved for the synthesis of benzazetines and indoles from *o*-alkenylanilides and DMTST.

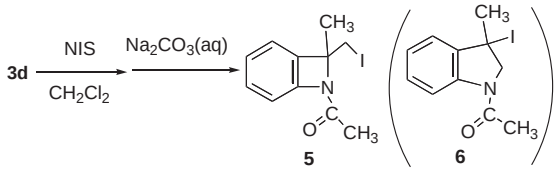
Recently, Kobayashi et al. have reported that the reaction of *o*-isopropenylacetanilide (**3d**) with iodine followed by the addition of aqueous sodium carbonate gave 2-iodomethyl-*N*-acetyl-



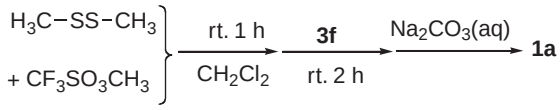
Scheme 2.

Table 2. Reaction of alkenylanilide **3e–3i** with DMTST

3	Solvent	Time/h	Products/%
3e	CH_2Cl_2	3	**4**: 77
3f	CH_2Cl_2	3	**1a**: 95
3g	CH_2Cl_2	2	**1b**: 86
3h	CH_2Cl_2	2	**1c**: 92
3i	CH_2Cl_2	12	**1d**: 68



Scheme 3.



Scheme 4.

benzazetine (**5**) in good yield.[5] However, Arisawa et al. reported the synthesis of 3-iodomethyl-*N*-acetylindoline (**6**) from *N*-iodosuccinimide (NIS) with **3d**.[2] They did not mention the reason for the difference. Since both reagents might provide three-membered cyclic iodonium intermediates, we have interested in the difference in the reactivity between iodine and NIS. When the reaction of **3d** with NIS was carried out under the condition Arisawa et al. stated,[2] the obtained product was not indoline **6** but benzazetine **5**. The structure of **5** was confirmed by comparing its spectral data to the one reported by Kobayshi et al. (Scheme 3).[5] As already shown in Scheme 1, anilide **3d** reacted with DMTST followed by the addition of aq Na_2CO_3 to afford benzoazetine **2d**, suggesting that Kobayashi's result is more plausible.

How do we account for the difference in the reactivity between the formation of benzazetine **2** and indoline **4**? We first thought that the bulkiness of *N*-acyl and *N*-sulfonyl groups plays an important role for the difference. However, *o*-isopropenyl-*N*-methanesulfonylanilide (**3g**) gave *N*-mesyl-3-methylindole (**1b**) in 86% yield, suggesting that bulkiness might be less effective for the difference in the selectivity. We then thought that the basicity of substituted anilines plays an important role for the difference. Since *N*-ethylmethanesulfonamide ($pK_a = 6.0$[17]) and benzenesulfonamide ($pK_a = 10.0$[18]) are more acidic than acetamide and benzamide ($pK_a = 17$[18]), less nucleophilic amide attacked terminal carbon to afford five-membered cyclic heterocycles.

Additionally, the present reaction did not require the isolation of DMTST. For example, when anilide **3f** was added to a solution of dimethyl disulfide and methyl triflate, 3-methylindole **1a** was obtained in 85% yield (Scheme 4). Similarly, **2b** and **1b** was obtained in 84 and 83% yields, respectively.

Thus, one-pot and regioselective synthesis of indoles and benzazetine was achieved by using dimethyl disulfide, methyl triflate, and *o*-alkenylaniline derivatives.

References and Notes

1 B. C. G. Soderberg, J. A. Shriver, S. H. Cooper, T. L. Shrout, E. S. Helton, L. R. Austin, H. H. Odens, B. R. Hearn, P. C. Jones, T. N. Kouadio, T. H. Ngi, R. Basewell, H. J. Caprara, M. D. Meritt, T. T. Mai, *Tetrahedron* **2003**, *59*, 8775.

2 M. Arisawa, Y. Ando, M. Yamanaka, M. Nakagawa, A. Nishida, *Synlett* **2002**, 1514.

3 M. Yamaguchi, M. Arisawa, M. Hirama, *Chem. Commun.* **1998**, 1399; M. Yamane, Y. Kubota, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 331.

4 P. Beak, G. W. Selling, *J. Org. Chem.* **1989**, *54*, 5574; E. M. Burgess, L. McCullagh, *J. Am. Chem. Soc.* **1966**, *88*, 1580.

5 K. Kobayashi, K. Miyamoto, O. Morikawa, H. Konishi, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 886.

6 P. Fugedi, P. J. Garegg, *Carbohydr. Res.* **1986**, *149*, C9.

7 O. Kanie, M. Kiso, A. Hasegawa, *J. Carbohydr. Chem.* **1988**, 501.

8 K. C. Nicolaou, N. Winssinger, J. Pastor, F. DeRoose, *J. Am. Chem. Soc.* **1997**, *119*, 449.

9 S. Oscarson, F. W. Sehgelmeble, *J. Org. Chem.* **2002**, *67*, 8457.

10 S. S. Kulkarni, Y.-H. Liu, S.-C. Hung, *J. Org. Chem.* **2005**, *70*, 2808.

11 K. Okuma, T. Koike, S. Yamamoto, H. Takeuchi, K. Yonekura, M. Ono, H. Ohta, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2375.

12 D. Dopp, H. Weiler, *Chem. Ber.* **1979**, *112*, 3950.

13 P. Molina, M. Alajarin, P. Sanchez-Andrada, *Synthesis* **1993**, 225.

14 Compound **2a**: mp 51–53 °C. ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H, SMe), 2.85 (dd, 1H, $J = 5.6$, 14.0 Hz, CH_2), 3.05 (dd, 1H, $J = 7.6$, 14.0 Hz, CH_2), 5.56 (dd, 1H, $J = 5.6$, 7.6 Hz, CH), 7.09–7.55 (m, 8H, Ar), 8.18 (dd, 1H, $J = 1.2$, 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 16.86 (SMe), 40.49 (CH_2), 75.68 (CH), 124.74, 125.30, 126.60, 128.37, 128.51, 129.51, 131.72, 132.74, 139.71 (Ar), 156.56 (C=O). Compound **4**: colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.72 (s, 3H, SMe), 2.37 (s, 3H, Me), 3.90 (dd, 1H, $J = 9.6$, 12.8 Hz, CH_2), 4.18–4.25 (m, 2H, CH_2 + CH), 7.03 (t, 1H, $J = 7.6$ Hz, Ar), 7.20–7.25 (m, 5H, Ar), 7.65–7.73 (m, 3H, Ar). ^{13}C NMR ($CDCl_3$) δ 11.89 (SMe), 21.76 (Me), 43.65 (CH), 56.79 (CH_2), 114.78, 124.23, 125.77, 127.59, 129.33, 129.94, 130.93, 133.96, 142.20, 144.55 (Ar).

15 M. Dias, M. Gibson, J. Grimshaw, I. Hill, J. Trocha-Grimshaw, O. Hammerich, *Acta Chem. Scand.* **1998**, *52*, 549.

16 J. A. Murphy, F. Rasheed, S. Gastaldi, T. Ravishanker, N. Lewis, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1549.

17 J. I. G. Cadogan, S. V. Ley, G. Pattenden, R. A. Raphael, C. W. Rees, *Dictionary of Organic Compounds*, 6th ed., Chapman & Hall, London, **1996**, Vol. 1. p. 577; Vol. 5. p. 4179.

18 J. March, *Advanced Organic Chemistry*, 4th ed., John-Wiley & Sons, New York, **1992**, pp. 250–252.

Published on the web (Advance View) September 9, 2006; doi:10.1246/cl.2006.1122