

## A FACILE SYNTHESIS OF 2-ACYLIMINO-3-BIPHENYLMETHYL-1,3,4-THIADIAZOLINE DERIVATIVES

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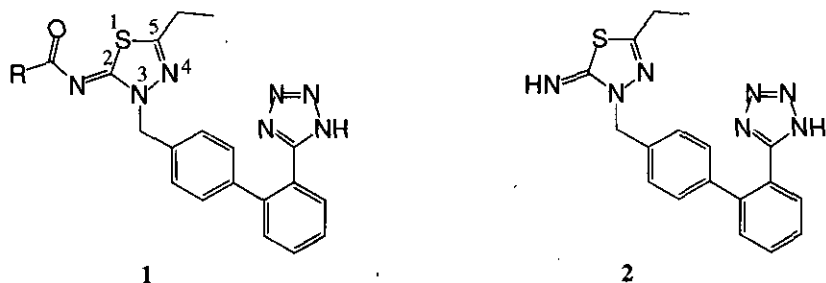
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**Abstract-** Regioselective biphenylmethylation of 2-trifluoroacetamido-1,3,4-thiadiazole (**3b**) gave 2-trifluoroacetylimino-1,3,4-thiadiazoline derivatives (**4c, d**) in good yields. Compound (**4d**) was converted to 2-(2-chlorobenzoyl)imino-1,3,4-thiadiazoline derivative (**6**), an angiotensin II receptor antagonist. This methodology was also applied to the preparation of 2-acylimino-1,3,4-oxadiazoline derivative (**8**).

Angiotensin II (AII) receptor antagonists have been promising for a novel class of antihypertensive drugs.<sup>1</sup> Recently, we have developed a new series of highly potent AII receptor antagonists (**1**) consisting of the biphenyltetrazole moiety linked to the N3 position of 2-acylimino-1,3,4-thiadiazolines.<sup>2</sup> 2-Acylimino-1,3,4-thiadiazoline derivatives (**1**) were finally prepared by acylation of a key intermediate, 2-imino-1,3,4-thiadiazoline (**2**). Although several synthetic methods for the 2-imino-1,3,4-thiadiazoline derivatives have been reported,<sup>3-6</sup> it seemed to be difficult to use their methods for the synthesis of our target compounds possessing the biphenyltetrazole moiety.

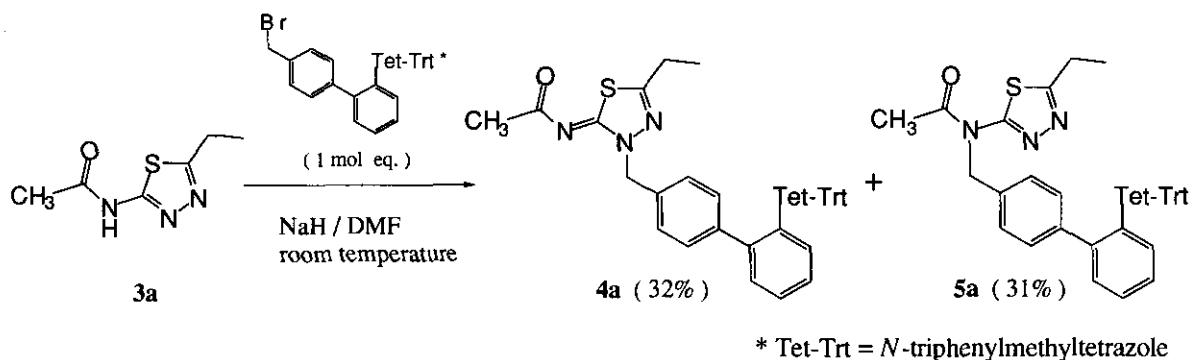
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This paper is dedicated to **Dr. Shigeru Oae**, Professor Emeritus Tsukuba University, on the occasion of his 77th birthday.



On the other hand, it is known that alkylation of 2-acylamido-1,3,4-thiadiazoles affords a mixture of the endo *N*- and exo *N*- alkylated products because of its ambident anionic character.<sup>7-9</sup>

Our attempt to biphenylmethylation of 2-acetamido-1,3,4-thiadiazole (**3a**) also resulted in an equal amount of two products which were respectively determined to be the endo *N*-substituted compound (**4a**) and the exo *N*-substituted one (**5a**) by their <sup>1</sup>H-nmr and ir spectral data after separation on a silica gel column (Table 1). Namely, the spectral data of **5a** must be similar to those of **3a** because of the structural similarity.<sup>7</sup>



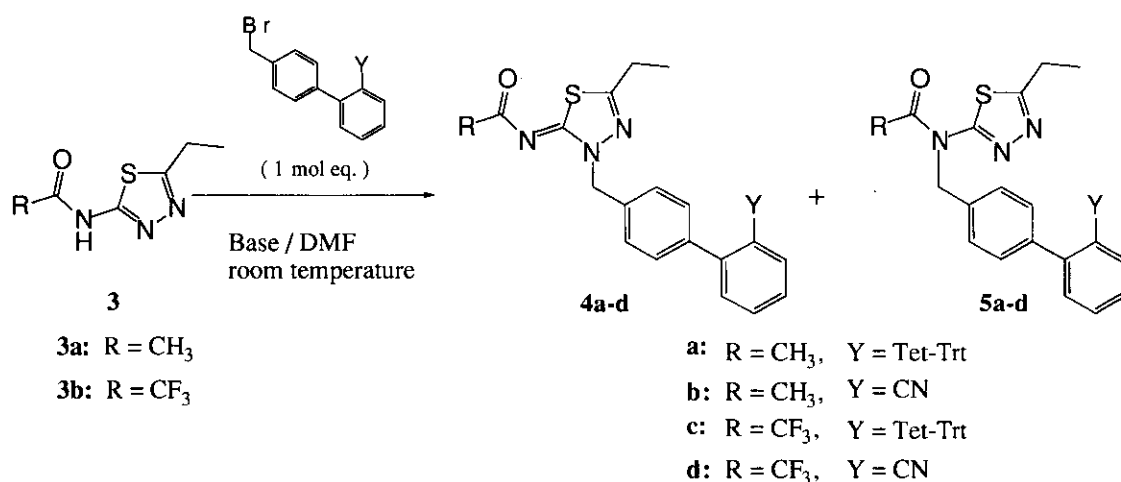
Scheme 1

Table 1 <sup>1</sup>H-nmr and ir spectral data of **3a**, **4a** and **5a**.

Compd.	<sup>1</sup> H-nmr (CDCl <sub>3</sub> )	ir
	δ ppm	ν (KBr), cm <sup>-1</sup>
	C5-CH <sub>2</sub> CH <sub>3</sub>	C = O
<b>3a</b>	3.05	1682
<b>4a</b>	2.76	1618
<b>5a</b>	3.06	1672

We anticipated that by means of the replacement of acetyl group in **3a** with trifluoroacetyl group, the

biphenylmethylation would regioselectively proceed on the endo *N*-position owing to the electron-withdrawing effect of trifluoroacetyl group. In fact, when we carried out the biphenylmethylation of 2-trifluoroacetamido-1,3,4-thiadiazole (**3b**), the endo *N*-substituted products (**4c,d**) were predominantly obtained in contrast with the case of **3a** (Table 2). Also, the trifluoroacetyl group in 2-trifluoroacetylmino-1,3,4-thiadiazoline derivatives (**4c,d**) was easily removed by treatment of alkaline solution (*e.g.*, aq. NaOH) while the acetyl group of 2-acetylmino-1,3,4-thiadiazoline derivatives (**4a,b**) was not removed under the same conditions.



Scheme 2

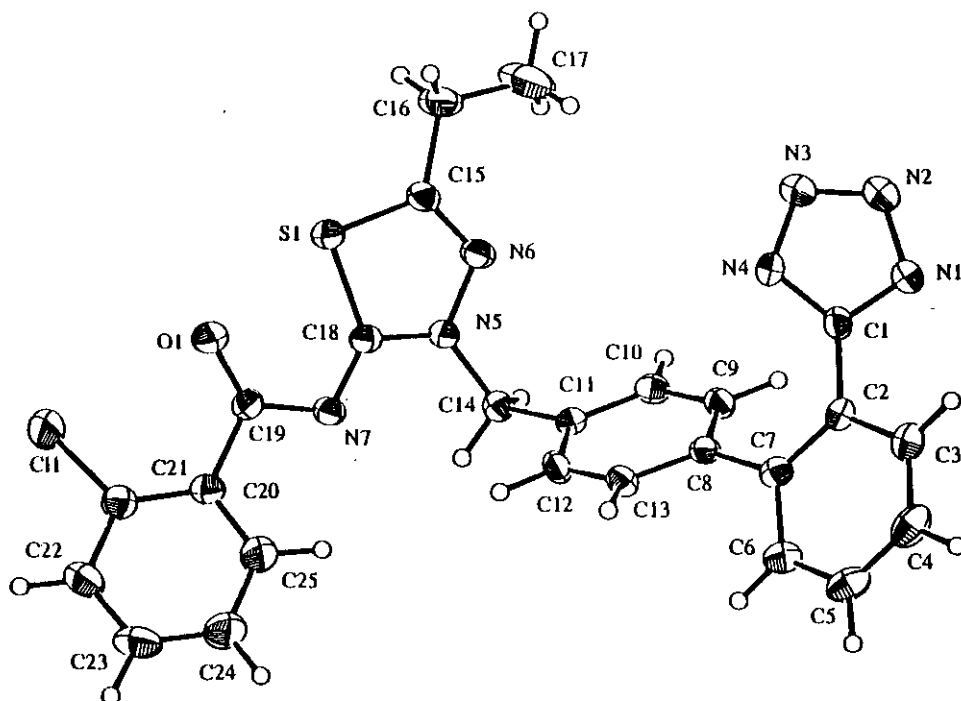
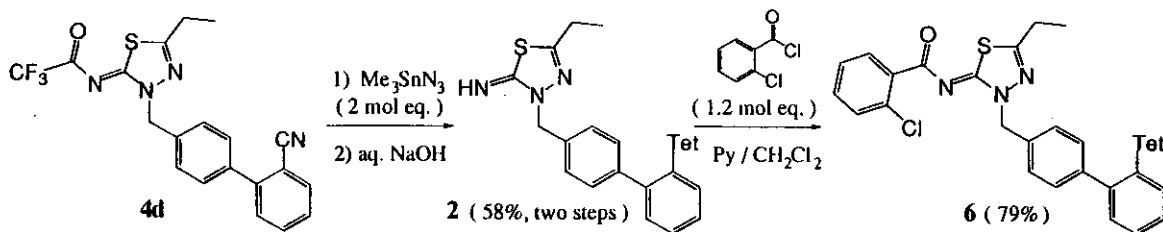
Table 2. Biphenylmethylation of 2-acylamido-1,3,4-thiadiazoles (**3a,b**).

entry	R	Y	Base	Time (h)	Yield (%) <sup>a</sup>	
					<b>4</b>	<b>5</b>
1	CH <sub>3</sub>	Tet-Trt	NaH	7	<b>4a</b> 32	<b>5a</b> 31
2	CH <sub>3</sub>	Tet-Trt	K <sub>2</sub> CO <sub>3</sub>	7	<b>4a</b> 34	<b>5a</b> 32
3	CH <sub>3</sub>	CN	K <sub>2</sub> CO <sub>3</sub>	7	<b>4b</b> 37	<b>5b</b> 34
4	CF <sub>3</sub>	Tet-Trt	NaH	5	<b>4c</b> 53	<b>5c</b> 0
5	CF <sub>3</sub>	Tet-Trt	K <sub>2</sub> CO <sub>3</sub>	7	<b>4c</b> 62	<b>5c</b> 0
6	CF <sub>3</sub>	CN	K <sub>2</sub> CO <sub>3</sub>	7	<b>4d</b> 75	<b>5d</b> 0
7	CF <sub>3</sub>	CN	K <sub>2</sub> CO <sub>3</sub>	72	<b>4d</b> 73	<b>5d</b> 0

a) Isolation yield based on the compound (**3**).

On the basis of these results, compound (**6**), one of the biologically active 2-acetylmino-1,3,4-thiadiazoline

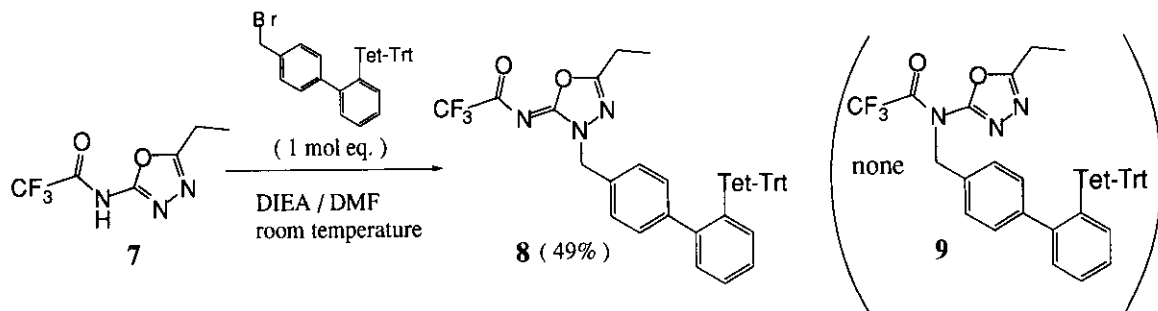
derivatives, was synthesized. The cyano group of 2-trifluoroacetylmino-1,3,4-thiadiazoline derivative (**4d**) was converted to a tetrazole group with trimethyltin azide, and then hydrolyzed with aq. NaOH to give the intermediate (**2**). Treatment of **2** with 2-chlorobenzoyl chloride provided **6** (Scheme 3). Its X-ray crystallographic analysis (Figure 1) confirmed the formation of 2-acylimino-1,3,4-thiadiazoline skeleton.



**Figure 1.** ORTEP drawing of the crystallographic structure of **6**.

We have further examined whether this methodology can be extended to other heterocycles. Reaction of 2-trifluoroacetamido-1,3,4-oxadiazole (**7**)<sup>12</sup> with 2'-[(*N*-triphenylmethyl)tetrazol-5-yl]-4-bromomethylbiphenyl in the presence of diisopropylethylamine (DIEA) gave regioselectively endo *N*-

substituted product (**8**) even in a low yield, and *exo N*-substituted product (**9**) was not obtained at all (Scheme 4).



**Scheme 4**

In conclusion, we developed a facile synthesis of 2-acylimino-3-biphenylmethyl-1,3,4-thiadiazolines *via* the regioselective biphenylmethylation of 2-trifluoroacetamido-1,3,4-thiadiazole. Further studies on extension of this methodology are in progress toward developing biologically active heterocycles.

## REFERENCES AND NOTES

1. P. B. M. W. M. Timmermans, P. C. Wong, A. T. Chiu, W. F. Herblin, P. Benfield, D. J. Carini, R. J. Lee, R. R. Wexler, J. A. M. Saye, and R. D. Smith, *Pharma. Rev.*, 1993, **45**, 205.
2. In preparation.
3. N. F. Eweiss and A. Osman, *J. Heterocycl. Chem.*, 1980, **17**, 1713.
4. A. S. Shawali and A. Osman, *J. Heterocycl. Chem.*, 1976, **13**, 45.
5. N. F. Eweiss and A. Osman, *Tetrahedron Lett.*, 1979, 1169.
6. A. S. Shawali and A. Osman, *Tetrahedron Lett.*, 1975, 165.
7. A. R. Katritzky and C. W. Rees, *Comprehensive Heterocyclic Chemistry*, Pergamon Press Inc., New York, 1984, Vol. 6, pp. 545-577.
8. D. Leppard and H. Sauter, *J. Heterocycl. Chem.*, 1980, **17**, 1469.
9. G. Weber, F. Buccheri, and N. Vivona, *J. Heterocycl. Chem.*, 1975, **12**, 841.
10. Selected analytical data. **4a**: Colorless prisms; mp 96-98 °C (AcOEt-hexane); <sup>1</sup>H-nmr (400 MHz,

CDCl<sub>3</sub>) 1.27 (t,  $J = 7.3$  Hz, 3H), 2.32 (s, 3H), 2.76 (q,  $J = 7.3$  Hz, 2H), 5.37 (s, 2H), 6.89-7.48 (m, 22H), 7.93 (dd,  $J = 6.8, 2.0$  Hz, 1H); ir (KBr) 1618 cm<sup>-1</sup> (C=O); FABms  $m/z$  648 (M+H)<sup>+</sup>. **4d**: Colorless prisms; mp 106-107 °C (EtOH); <sup>1</sup>H-nmr (270 MHz, CDCl<sub>3</sub>) 1.39 (t,  $J = 7.7$  Hz, 3H), 2.95 (q,  $J = 7.7$  Hz, 2H), 5.60 (s, 2H), 7.43-7.79 (m, 8H); ir 2208 cm<sup>-1</sup> (CN), 1650 cm<sup>-1</sup> (C=O); EIms  $m/z$  416 M<sup>+</sup>; Anal. Calcd for C<sub>20</sub>H<sub>15</sub>N<sub>4</sub>OF<sub>3</sub>S, C, 57.69; H, 3.63; N, 13.45. Found, C, 57.66; H, 3.72; N, 13.24. **5a**: Colorless prisms; mp 151-152 °C (AcOEt-hexane); <sup>1</sup>H-nmr (400 MHz, CDCl<sub>3</sub>) 1.42 (t,  $J = 7.3$  Hz, 3H), 2.17 (s, 3H), 3.06 (q,  $J = 7.3$  Hz, 2H), 5.41 (s, 2H), 6.89-7.50 (m, 22H), 7.95 (d,  $J = 6.8$  Hz, 1H); ir (KBr) 1672 cm<sup>-1</sup> (C=O); FABms  $m/z$  648 (M+H)<sup>+</sup>; Anal. Calcd for C<sub>39</sub>H<sub>33</sub>N<sub>7</sub>OS, C, 72.31; H, 5.13; N, 15.14. Found, C, 72.39; H, 5.34; N, 14.90. **6**: Colorless prisms; mp 157-158 °C (CH<sub>2</sub>Cl<sub>2</sub>-MeOH); <sup>1</sup>H-nmr (270 MHz, CDCl<sub>3</sub>) 1.38 (t,  $J = 7.8$  Hz, 3H), 3.06 (q,  $J = 7.8$  Hz, 2H), 5.58 (s, 2H), 7.19-7.57 (m, 10H), 8.02 (dd,  $J = 2.7, 8.0$  Hz, 1H), 8.06 (dd,  $J = 2.7, 8.0$  Hz, 1H); ir (KBr) 1610 cm<sup>-1</sup> (C=O); FABms  $m/z$  502 (M+H)<sup>+</sup>; Anal. Calcd for C<sub>25</sub>H<sub>20</sub>N<sub>7</sub>OCIS, C, 59.82; H, 4.02; N, 19.53. Found, C, 59.42; H, 4.07; N, 19.29.

11. The crystallographic data of compound (**6**) are as follows. MF = C<sub>25</sub>H<sub>20</sub>N<sub>7</sub>OSCl, MW = 501.99, Monoclinic, C2/c ( $\neq 15$ ),  $a = 23.869(4)$  Å,  $b = 20.332(4)$  Å,  $c = 19.981(3)$  Å,  $\beta = 98.48(1)^\circ$ ,  $V = 9590(2)$  Å<sup>3</sup>,  $Z = 16$ ,  $D_{\text{calc}} = 1.391$  g/cm<sup>3</sup>,  $R = 0.046$ ,  $R_w = 0.066$ .
12. A. R. McCarthy, W. D. Ollis, A. N. M. Barner, L. E. Sutton, and C. Ainsworth, *J. Chem. Soc. (B)*, 1969, 1185.

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