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

Terukage Hirata,[a,c] Motoo Shiro,[b] and Yoshimitsu Nagao[c]*

[a] Institute for Medical Research, Wakunaga Pharmaceutical Co., Ltd., 1624 Shimokotachi, Koda-cho, Takata-gun, Hiroshima 739-11, Japan

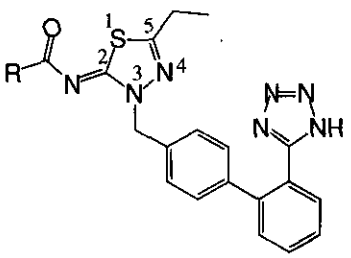
[b] Rigaku Corporation, 3-9-12 Matubara-cho, Akishima, Tokyo 196, Japan

[c] Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770, Japan

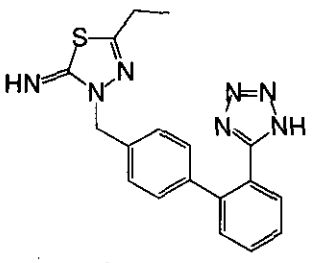
Abstract- Regioselective biphenylmethylation of 2-trifluoroacetamido-1,3,4-thiadiazole (**3b**) gave 2-trifluoroacetylimino-1,3,4-thiadiazoline derivatives (**4c,d**) in good yields. Compound (**4d**) was converted to 2-(2-chlorobenzoyl)imino-1,3,4-thiadiazoline derivative (**6**), an angiotensin II 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.[1] 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.[2] 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,[3-6] it seemed to be difficult to use their methods for the synthesis of our target compounds possessing the biphenyltetrazole moiety.

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



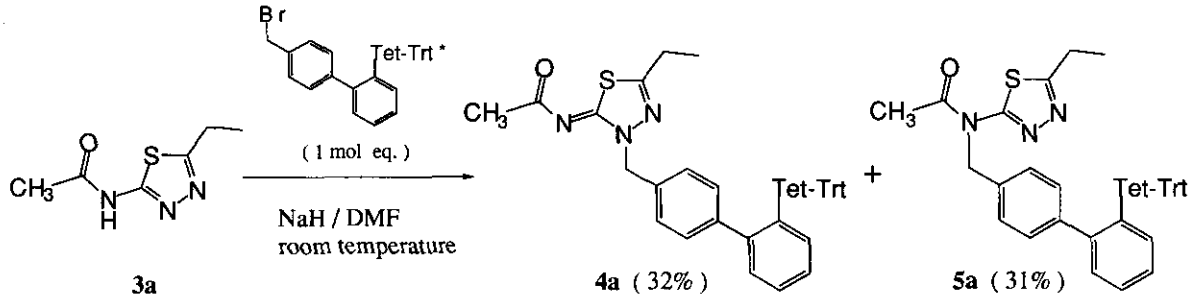
1



2

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.[7-9]

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 ^{1}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.[7]



3a **4a** (32%) **5a** (31%)

* Tet-Trt = *N*-triphenylmethyltetrazole

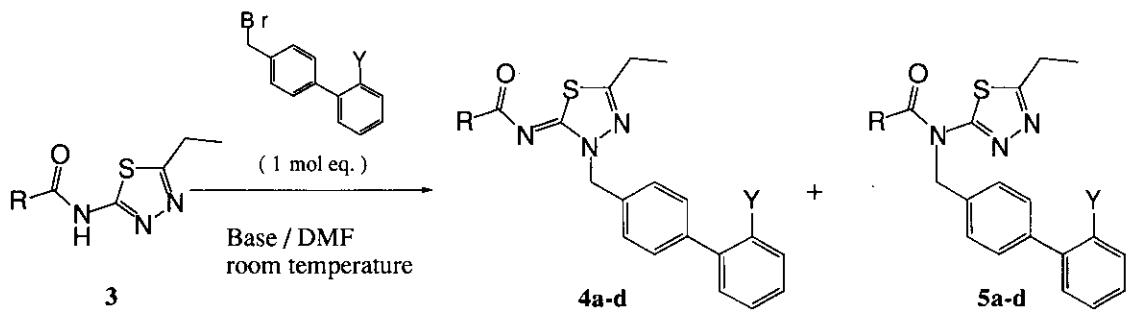
Scheme 1

Table 1 ^{1}H-nmr and ir spectral data of **3a**, **4a** and **5a**.

Compd.	^{1}H-nmr ($CDCl_3$) δ ppm	ir υ (KBr), cm^{-1}
	C5-CH_2CH_3	C = O
3a	3.05	1682
4a	2.76	1618
5a	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-trifluoroacetylimino-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-acetylimino-1,3,4-thiadiazoline derivatives (**4a,b**) was not removed under the same conditions.



3a: R = CH_3
3b: R = CF_3

a: R = CH_3, Y = Tet-Trt
b: R = CH_3, Y = CN
c: R = CF_3, Y = Tet-Trt
d: R = CF_3, Y = CN

Scheme 2

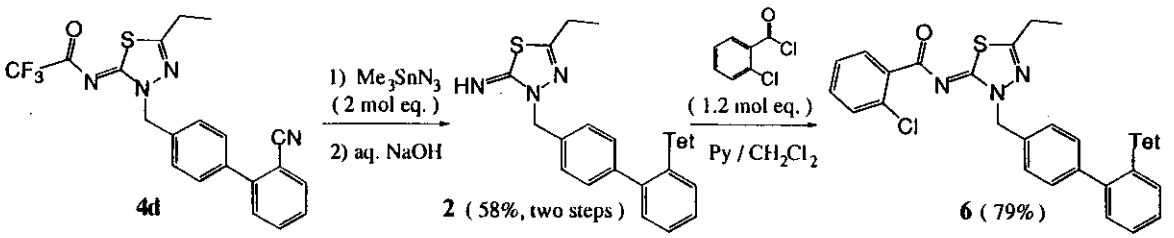
Table 2. Biphenylmethylation of 2-acylamido-1,3,4-thiadiazoles (**3a,b**).

entry	R	Y	Base	Time (h)	Yield (%)[a] 4	5
1	CH_3	Tet-Trt	NaH	7	**4a** 32	**5a** 31
2	CH_3	Tet-Trt	K_2CO_3	7	**4a** 34	**5a** 32
3	CH_3	CN	K_2CO_3	7	**4b** 37	**5b** 34
4	CF_3	Tet-Trt	NaH	5	**4c** 53	**5c** 0
5	CF_3	Tet-Trt	K_2CO_3	7	**4c** 62	**5c** 0
6	CF_3	CN	K_2CO_3	7	**4d** 75	**5d** 0
7	CF_3	CN	K_2CO_3	72	**4d** 73	**5d** 0

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

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

derivatives, was synthesized. The cyano group of 2-trifluoroacetylimino-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.



Scheme 3

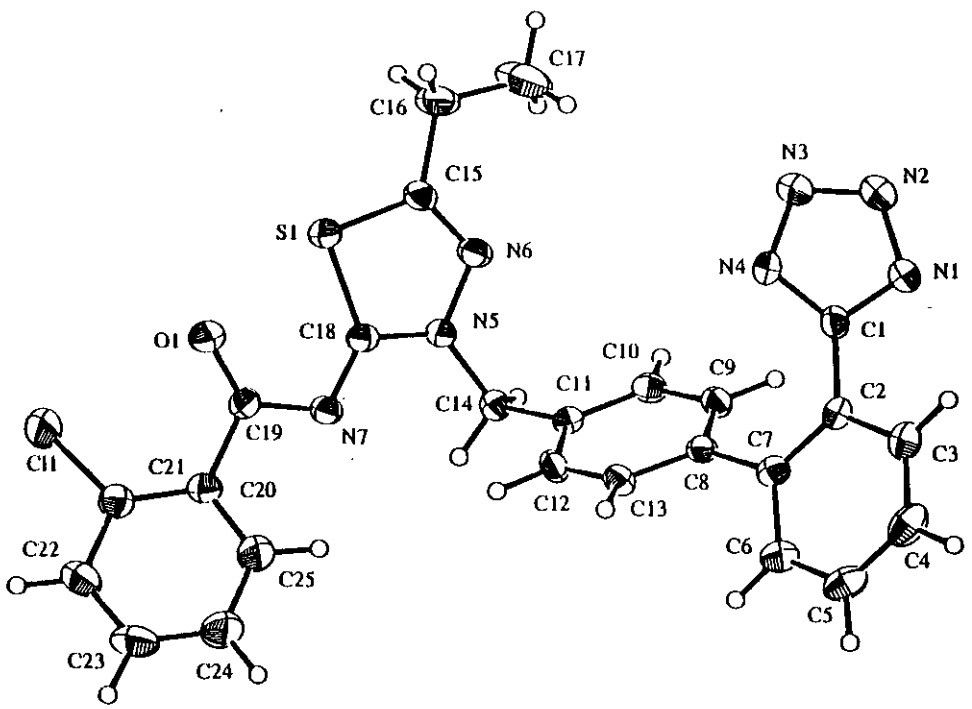
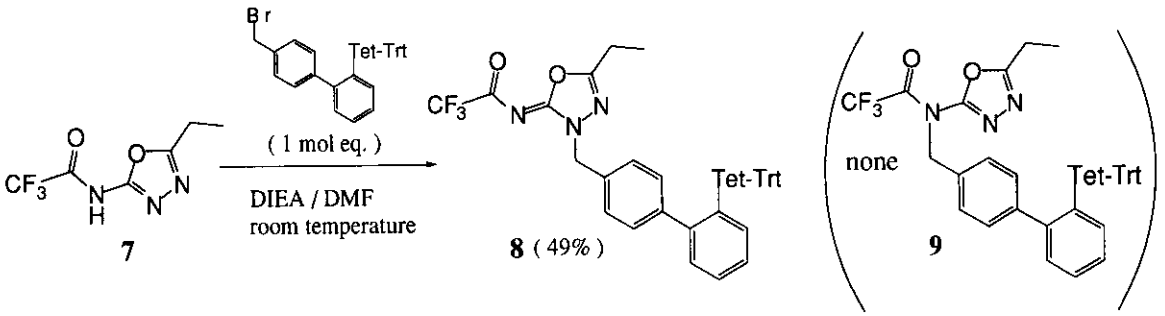


Figure 1. ORTEP drawing of the crystallographic structure of 6.

We have further examined whether this methodology can be extended to other heterocycles. Reaction of 2-trifluoroacetamido-1,3,4-oxadiazole (7)[12] with 2'-[(*N*-triphenymethyl)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.

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10. Selected analytical data. **4a**: Colorless prisms; mp 96-98 °C (AcOEt-hexane); ^{1}H-nmr (400 MHz,

$CDCl_3$) 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^{-1} (C=O) ; FABms m/z 648 $(M+H)^+$. **4d**: Colorless prisms; mp 106-107 °C (EtOH); ^{1}H-nmr (270 MHz, $CDCl_3$) 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^{-1} (CN), 1650 cm^{-1} (C=O); EIms m/z 416 M^+; Anal. Calcd for $C_{20}H_{15}N_4OF_3S$, 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); ^{1}H-nmr (400 MHz, $CDCl_3$) 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^{-1} (C=O) ; FABms m/z 648 $(M+H)^+$; Anal. Calcd for $C_{39}H_{33}N_7OS$, 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_2Cl_2-MeOH); ^{1}H-nmr (270 MHz, $CDCl_3$) 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^{-1} (C=O) ; FABms m/z 502 $(M+H)^+$; Anal. Calcd for $C_{25}H_{20}N_7OClS$, 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 = $C_{25}H_{20}N_7OSCl$, MW = 501.99, Monoclinic, C2/c(≠ 15), a = 23.869(4) Å, b = 20.332(4) Å, c = 19.981(3) Å, β = 98.48(1)°, V = 9590(2) $Å^3$, Z = 16, Dcalc = 1.391 g/cm^3, R = 0.046, Rw = 0.066.

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